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Flow-mediated dilatation deficiency of the brachial artery and increased carotid intimal thickness in non-alcoholic fatty liver disease

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ABSTRACT

Aims: This study aimed to evaluate endothelial dysfunction and vascular changes in non-alcoholic fatty liver disease (NAFLD) patients by measuring carotid intima-media thickness (C-IMT) and flow-mediated dilation (FMD).

Methods: This prospective observational cohort study included 51 biopsy-proven NAFLD patients and 21 healthy controls. Endothelial function was assessed using high-resolution ultrasonography to measure brachial artery FMD and C-IMT. Patients with hepatotoxic drug use, significant alcohol consumption, or other liver diseases were excluded. Demographic data, body-mass index (BMI), and waist circumference were recorded. Statistical analyses were conducted using SPSS, with significance set at $p<0.05$.

Results: NAFLD patients showed significantly higher BMI, waist circumference, and diastolic blood pressure compared to controls. The mean C-IMT was elevated in NAFLD patients (0.67±0.09 mm) compared to controls (0.52±0.11 mm; $p<0.001$), and FMD was significantly reduced in NAFLD patients (7.3±4.8%) compared to controls (16.5±7.1%; $p<0.001$). FMD and C-IMT values were lower in NASH cases than in simple steatosis. A significant negative correlation was observed between FMD and BMI, waist circumference, and C-IMT values.

Conclusion: NAFLD patients, particularly those with NASH, exhibit significant endothelial dysfunction characterized by reduced FMD and increased C-IMT, indicating early atherosclerosis. These findings suggest that endothelial dysfunction increases with progression of NAFLD. Early recognition of vascular changes in NAFLD patients could facilitate timely interventions to reduce cardiovascular risk and disease progression.

Keywords: Non-alcoholic fatty liver disease, non-alcoholic steatohepatitis, vascular, carotid intima, liver disease

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is recognized as the most common chronic liver disease in the general population.[1-3] Due to the asymptomatic nature of most cases, the true prevalence of NAFLD remains unknown. Population-based screening studies in adults estimate the prevalence of NAFLD to be 17-33%, with rates reaching 75% in the presence of obesity. The prevalence of non-alcoholic steatohepatitis (NASH) is approximately 3%.[1-3] While the disease is more common in Western societies, its incidence is increasing significantly worldwide due to changes in dietary habits and the transition to urban lifestyles.[1] A portion of cases with simple steatosis progress to NASH. Approximately 20% of NASH cases result in progressive fibrosis and cirrhosis, and 30-40% of cirrhotic patients succumb to liver-related complications.[4,5] Furthermore, though the frequency remains unclear, subacute liver failure, hepatocellular carcinoma, and post-transplant disease recurrence are among other complications.[2,4,5] NAFLD encompasses a broad spectrum ranging from simple steatosis to NASH, fibrosis, cirrhosis, and hepatocellular carcinoma.[1]

In the etiology of NAFLD, metabolic factors such as diabetes mellitus, obesity, and hyperlipidemia play a leading role, while congenital causes, environmental factors, and certain medications may also contribute to this condition.[1-4] Insulin resistance and the factors leading to it are considered the most significant etiological contributors. Genetic predisposition, increased caloric intake, obesity (particularly central obesity), and a sedentary lifestyle are the primary risk factors for insulin resistance.[4,5]

Although some evidence has been obtained regarding the pathogenesis of hepatic steatosis, it has not yet been fully elucidated.[1,2] Why NAFLD does not develop in all obese individuals or why some individuals with simple steatosis

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develop necroinflammatory processes remains unclear.[1-3] The "two-hit" hypothesis is currently the prevailing theory in the pathogenesis of NAFLD.[3] According to this hypothesis, the first hit leads to steatosis, while the second hit initiates necroinflammatory processes, eventually resulting in NASH.[1-4]

Due to the close association between metabolic syndrome and NAFLD, diabetes and hyperlipidemia are frequently observed in affected individuals. However, it should not be overlooked that NAFLD may also occur in individuals with normal weight, without comorbidities, and even in children.[5]

The most commonly used radiological diagnostic method for NAFLD is ultrasonography (USG). USG findings include increased liver echogenicity (compared to spleen and kidney echogenicity), posterior acoustic attenuation, blurring of the margins of intrahepatic lacunar structures, and loss of clear demarcation of the right hepatic lobe and diaphragm. Similarly, computed tomography (CT) and magnetic resonance imaging (MRI) can also be effectively utilized for diagnosis.[6-8]

In our study, we aimed to evaluate differences in endothelial function in the brachial and carotid arteries of patients with NAFLD using vascular ultrasonography by measuring brachial artery flow-mediated dilation (FMD) and carotid intima-media thickness (C-IMT) levels.

METHODS

Ethics

This prospective observational cohort study was conducted with a total of 51 patients who were histopathologically diagnosed with non-alcoholic fatty liver disease (NAFLD) and admitted to the Gastroenterology and Radiology outpatient clinics of İstanbul Medeniyet University, Göztepe Training and Research Hospital between July 2010 and July 2011. The follow-up period for all patients was 24 months. The study was prepared as a specialty thesis. Ethical committee approval was not obtained. Institutional approwal was obtaned. Written informed consent was obtained from all participants. All procedures were conducted in accordance with ethical guidelines and the principles of the Declaration of Helsinki.

Exclusion Criteria

The following were used as exclusion criteria: use of hepatotoxic drugs, herbal medicines, or hormone replacement therapy; history of alcohol consumption exceeding 20 grams per day; viral hepatitis, autoimmune hepatitis, biliary diseases, malignancies, alpha-1 antitrypsin deficiency, Wilson's disease, hemochromatosis; being under the age of 18; and pregnancy.

Patients with a biopsy-proven diagnosis of NAFLD were included in the study. The healthy control group consisted of individuals with normal liver findings on sonographic evaluation and no exclusion criteria.

Clinical And Laboratory Assessment

All patients were evaluated by the gastroenterology department. Height, weight, and waist circumference (cm) were measured, and the BMI (kg/m^2) was calculated.

Carotid ultrasound (US) evaluation was performed using a 7.5 MHz transducer (Aplio, Toshiba, Tokyo, Japan). The patients were assessed in a supine position. Measurements were taken at the common carotid artery (CCA) bifurcation and the internal carotid artery. C-IMT (carotid intima-media thickness) was measured on the far wall of the CCA at a point 1 cm proximal to the bifurcation. The distance between the lumen-intima interface and the media-adventitia interface was measured. Measurements were taken from plaque-free regions. Each measurement was repeated three times for both CCAs, and the mean values were calculated. The average of the mean values from both CCAs was considered the C-IMT.

The anterior, posterior, and lateral walls of both carotid arterial systems were scanned longitudinally and transversely for the presence of plaques. Plaque dimensions, numbers, and locations were recorded.

Vascular endothelial functions were evaluated by measuring flow-mediated dilation (FMD) of the brachial artery (99). The examination was performed using a 10 MHz high-resolution linear probe (Aplio, Toshiba, Tokyo, Japan). The right brachial artery was assessed in the longitudinal axis, approximately 2 cm proximal to the antecubital fossa, with the patients in a supine position. First, baseline diameter and spectral Doppler parameters, including peak systolic velocity (PSV) and end-diastolic velocity (EDV), were measured at this location, which was marked.

A cuff was then placed on the right forearm and inflated to 250 mmHg to induce ischemia in the right brachial artery. The cuff pressure was maintained at this level for 5 minutes. Following cuff release, PSV and EDV measurements were repeated at the previously marked site 15 seconds later using spectral Doppler. One minute after cuff deflation, the brachial artery diameter was measured in the longitudinal axis for FMD assessment. FMD was calculated as the percentage change between the baseline diameter and the maximum post-ischemic diameter.

Statistical Analysis

The data were analyzed using SPSS 16.0 (SPSS Inc., Chicago, IL, USA). The student's T test (for parametric data) or the Mann-Whitney U test (for non-parametric data) was used for statistical comparison between two independent groups. For comparisons between more than two groups, one-way ANOVA was used for parametric data, and the Kruskal-Wallis test was used for non-parametric data. Correlations between variables were assessed using Spearman's correlation analysis. A p-value of <0.05 was considered statistically significant.

RESULTS

The study group consisted of 25 male and 26 female patients, with an average age of 42.8±9.8 years. A total of 21 individuals (average age: 40.5±9.7 years; 11 males and 10 females) were included in the control group. The age and gender distribution were similar between the NAFLD group and the control group. The demographic characteristics of the patients are shown in **Table 1**.

Table 1. Demographic data and arterial measurement differences in NAFLD and control groups

Parameter	NAFLD group (n=51)	Control group (n=21)	p-value
Gender (male/female)	25/26	11/10	0.440
Age (years)	42.8±9.8	40.5±9.7	0.070
BMI (kg/m²)	31.6±5.5	24.4±2.1	<0.001
Waist circumference (cm)	102.2±9.2	85.2±7.2	<0.001
Systolic BP (mmHg)	122±16.8	115.6±16.7	0.080
Diastolic BP (mmHg)	82±10.3	73.7±11.8	0.002
C-IMT (mm)	0.67±0.09	0.52±0.11	0.002
FMD (%)	7.3±4.8	16.5±7.1	<0.001

NAFLD: Non-alcoholic fatty liver disease, BMI: Body-mass index, BP: Blood pressure, C-IMT: Carotid intima media thickness, FMD: Foot and mouth disease

BMI, waist circumference, and diastolic blood pressure were significantly higher in patients with NAFLD compared to the control group. In the NAFLD group, the mean carotid intima-media thickness (C-IMT) was measured as 0.67±0.09 mm, compared to 0.52±0.11 mm in the control group, indicating a statistically significant increase (p<0.001) (Table 1).

In the NAFLD group, as shown in Table 2, eight patients (15.6%) were diagnosed with simple steatosis, 25 patients (49%) with borderline NASH, and 18 patients (35.3%) with definitive NASH.

The mean C-IMT values were 0.52±0.11 mm in the control group, 0.63±0.07 mm in patients with simple steatosis, and 0.68±0.1 mm in NAFLD cases diagnosed with either borderline or definitive NASH. The differences between these groups were statistically significant (p<0.001) and are summarized in Table 2.

No significant difference in C-IMT measurements was observed between cases with borderline NASH and those with definitive NASH (0.68±0.64 mm vs. 0.68±1.22 mm, respectively).

Atherosclerotic plaques were not detected in any individuals within the control group. However, six patients in the NAFLD group were found to have atherosclerotic plaque formation. The mean C-IMT values in patients with plaques were significantly higher compared to those without plaques (0.76±0.09 mm vs. 0.66±0.09 mm, p<0.001).

In the measurements of basal brachial artery diameter among NAFLD cases and the control group, no statistically significant differences were observed between the groups. The basal brachial artery diameters were 3.961±0.7 mm in the NASH group, 3.63±0.83 mm in the simple steatosis group, and 3.66±0.59 mm in the control group (p=0.276).

Brachial artery FMD measurements were significantly lower in NAFLD cases (7.3±4.8%) compared to the control group (16.5±7.1%) (p<0.001).

The FMD measurements of the brachial artery were recorded as 16.5±7.1% in the control group, 9.64±6.63% in the simple steatosis group, and 7.03±4.57% in NAFLD cases with NASH. The differences between the groups were considered statistically significant.

No significant differences in FMD responses were observed between patients with borderline and definitive NASH (7.9±5.8% and 6.1±2.5%, respectively).

Correlation analysis revealed a significant negative correlation between FMD measurements and BMI, waist circumference, and C-IMT measurements.

DISCUSSION

In our study, endothelial functions were evaluated in 51 biopsy-proven NAFLD patients and 21 healthy individuals in the control group using C-IMT and FMD measurements. Significant endothelial dysfunction was observed in NAFLD patients compared to the control group.

Endothelial dysfunction was more pronounced in NAFLD cases with NASH. NAFLD contributes to endothelial dysfunction, induces early atherosclerosis,[6-10] and increases the risk of cardiovascular diseases.[10] Carotid atherosclerosis, assessed by C-IMT thickness and plaque presence or frequency, was found to be increased in NAFLD patients.[6-8] Similarly, in this study, C-IMT measurements and carotid atherosclerosis were significantly increased in NAFLD patients (p<0.001).

When comparing patients with simple steatosis and those with NASH correlated with histopathological parameters, a significant increase in C-IMT measurements was detected in NASH patients.

Furthermore, FMD measurements were found to be associated with increased C-IMT values, which are another indicator of endothelial dysfunction. Previous studies have also demonstrated a significant reduction in brachial artery FMD measurements in NAFLD cases compared to those without NAFLD, and this reduction was associated with the histological progression of the disease.[9-11] Similarly, in our study, we observed that FMD measurements were significantly lower in NAFLD patients, regardless of whether metabolic syndrome was present, compared to the healthy control group (p<0.001). Additionally, the reduction in FMD measurements was more pronounced in NASH cases and in progressive NAFLD compared to simple steatosis. These findings suggest that the deterioration in endothelial function worsens with disease progression.[8,11]

Table 2. Comparison of arterial characteristics between simple steatosis, borderline NASH, and control patients

Parameter	Simple steatosis (mean±SD)	Borderline NASH (mean±SD)	NASH (mean±SD)	Control (mean±SD)	p-value*
BAD (mm)	3.63±0.83	4.1±0.9	4.09±0.72	3.66±0.6	0.060
FMD (%)	9.6±6.6	7.9±5.8	6.1±2	16.5±7.1	0.001
C-IMT (mm)	0.63±0.07	0.68±0.64	0.68±1.22	0.52±0.11	<0.001

*One-way ANOVA test results, ANOVA: Analysis of variance, NASH: Non-alcoholic steatohepatitis, SD: Standard deviation, BAD: Brachial artery diameter, FMD: Flow-mediated dilation, C-IMT: Carotid intima-media thickness

The biochemical and metabolic components underlying the relationship between NAFLD and atherosclerosis remain unclear. However, several hypotheses have been proposed. Hepatic and peripheral insulin resistance is prevalent in NAFLD patients. An impaired lipid profile may also contribute to the increased atherosclerosis risk.[7-11] Another potential mechanism is the role of increased oxidative stress, which may drive a chronic inflammatory process.[7-9]

Limitations

This study has certain limitations. The small sample size is the most significant limitation. Additionally, while endothelial-dependent vasodilation was assessed using the FMD method, endothelial-independent vasodilation was not evaluated.

CONCLUSION

In NAFLD patients, compared to healthy individuals, a reduction in flow-mediated dilation of the brachial artery and an increase in carotid intimal thickness were observed, indicating impaired endothelial function as a marker of early atherosclerosis. Moreover, endothelial dysfunction was more pronounced in patients with definitive NASH.

ETHICAL DECLARATIONS

Ethics Committee Approval

This prospective observational cohort study was prepared as a specialty thesis between July 2010 and July 2011. Ethics committee approval was not obtained at that time. Institutional approval was obtained.

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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Pain intensity, fear of movement, and fear of falling in earthquake survivors in Turkiye: a cross-sectional observational study

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ABSTRACT

Aims: On February 6, 2023, devastating earthquakes struck 11 provinces in Turkiye, leading to significant physical and psychological consequences for survivors. This study aimed to determine the frequency of pain intensity, fear of movement, and fear of falling among earthquake survivors and to examine their relationships with each other, as well as with psychological resilience and physical activity level.

Methods: This observational, cross-sectional study included 184 survivors (93 males-91 females; mean age: 34.02±10.76 years) with no pre-earthquake pain or physical trauma. Pain intensity, fear of movement, fear of falling, physical activity level, and psychological resilience were assessed using the 'Numerical Pain Scale', 'Causes of Fear of Movement Scale', 'Modified Falls Efficacy Scale', 'Short Form of the International Physical Activity Questionnaire', and 'Connor-Davidson Resilience Scale', respectively between May 02/2023 and July 30/2023. Pearson correlation analysis was performed to examine associations between these parameters.

Results: 46.7% of participants had fear of movement, 33.2% had fear of falling, and 37.7-50.5% experienced moderate to severe pain. Fear of movement was significantly associated with pain intensity, including headache ($r=0.275$, $p<0.001$), neck pain ($r=0.294$, $p<0.001$), upper back pain ($r=0.262$, $p<0.001$), and low back pain ($r=0.284$, $p<0.001$). Similarly, fear of falling (higher scores indicate lower fear) was positively associated with pain intensity, including headache ($r=0.202$, $p=0.006$), neck pain ($r=0.179$, $p=0.015$), upper back pain ($r=0.191$, $p=0.010$), and low back pain ($r=0.282$, $p<0.001$). Both fear of movement ($r=-0.243$, $p=0.001$) and fear of falling ($r=0.220$, $p=0.003$) were significantly associated with psychological resilience, while neither was correlated with physical activity level ($p>0.05$).

Conclusion: Fear of movement, fear of falling, and pain intensity are prevalent among survivors who had no prior pain and did not sustain physical trauma during the disaster. These factors are closely interrelated, independent of physical activity level. Psychological resilience plays a critical role in fear-related responses. These findings highlight the need for post-disaster rehabilitation strategies that address pain intensity, fear-related responses while considering psychological resilience.

Keywords: Earthquakes, pain, kinesiophobia, falling, psychological resilience

INTRODUCTION

On February 6th, 2023, earthquakes measuring 7.7 and 7.6 Mw. on the Richter Scale struck Kahramanmaraş in Turkiye at 04:17 A.M. and 13:24 P.M., respectively. The earthquakes resulted in considerable damage and fatalities affecting 11 provinces, including Kahramanmaraş, Hatay, Gaziantep, Osmaniye, Malatya, Adana, Diyarbakır, Elazığ, Şanlıurfa, Adıyaman and Kilis.[1] Beyond the immediate destruction, these types of major earthquakes also may increase the risk of mental and emotional disorders, including anxiety disorders,[2,3] sleep disorders[4,5] and post-traumatic stress disorder[2,6-8] as well as physical and biological complaints such as sensory and neurological disturbances.[9-16]

In a previous study analyzing pain severity, pain type, and treatment efficacy after an earthquake, hit the Abruzzi region of central Italy, one-third of the patients reported pain, and 58.8% of those reporting pain described it as severe.[17] In a study conducted in 2020, the relationship between newly-onset low back pain and preexisting musculoskeletal pain in other body regions was examined in 1,782 survivors of the Great East Japan Earthquake. During the post-disaster recovery period, the incidence of newly-onset low back pain was found to be 14.1%, and preexisting musculoskeletal pain in other body regions was identified as a related factor.[18] In 2024, post-earthquake low back and neck disability were examined

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in 291 individuals affected by the Kahramanmaraş-centered earthquakes. It was determined that 30% of the individuals had mild to moderate low back disability, while 60% had mild to moderate neck disability.[19] Although increased pain severity following earthquakes is frequently encountered, the number of studies on this topic remains limited, highlighting the need for further research.

In addition to musculoskeletal pain, earthquakes can also trigger post-earthquake dizziness syndrome,[20] and postural disorders. In a previous review study conducted in 2021, the results showed that the prevalence of balance disorders increased significantly after the major earthquakes when compared to before the earthquakes.[14] Exposure to major earthquakes and aftershocks has been shown to cause post-earthquake balance disorders by causing sensory conflicts mediated by vestibular dysfunction and/or psychological factors. In addition, that study[14] stated that this increase in the prevalence of balance disorders may also be caused by psychological factors, which is consistent with previous studies in the literature.[15,16]

The mechanisms of equilibrium dysfunction are likely to be explained by the sensory conflict theory/postural instability theory.[21,22] The basic pathology of equilibrium dysfunction is attributed to disruption of interplay between vestibular, neurological, visual and proprioceptive functions of the human body.[15] Psychological stress and maladaptive visual/somatosensory inputs caused by the earthquake may cause changes in the sense of movement, which is an important component of proprioception sense. Moreover, disruptions in the vestibular system may trigger the fear of falling, leading to decreases in physical activity capacity.

Although some previous studies reported the presence of dizziness or equilibrium disorders,[9-11,14] in survivors after the earthquake, only one study investigated the fear of movement and fear of falling.[23] In this study published in 2025, individuals affected by the Kahramanmaraş earthquake were evaluated in terms of fear of falling, balance, and fear of movement; increased age and post-traumatic stress were found to be significantly associated with fear of falling. However, this study did not address participants' physical activity levels and pain intensity.

Considering Turkiye's geographical location in a high-risk seismic zone, assessing the prevalence of increased pain severity, fear of movement, and fear of falling in earthquake-exposed individuals-along with their physical activity levels and psychological resilience-would provide valuable insights into post-earthquake disaster management by examining their interrelationships.

The present study aimed to investigate the relationships between pain intensity, fear of movement, and fear of falling in earthquake survivors without physical trauma. Additionally, we aimed to examine how these variables are associated with psychological resilience and physical activity levels. Our findings contribute to the literature by examining the interaction between pain intensity, fear of movement, and fear of falling in earthquake survivors without physical trauma, a topic that remains insufficiently explored. By adopting a multidimensional perspective that incorporates both physical and psychological aspects, this study provides new insights into post-earthquake functional impairments and supports the development of interventions aimed at facilitating the recovery process for affected individuals.

Furthermore, identifying the interaction between physical and psychological factors will enable the development of effective rehabilitation strategies for earthquake survivors without physical trauma and help shape evidence-based interventions aimed at improving long-term quality of life.

METHODS

Design of the Study

This observational and cross-sectional study received ethical approval from the Atılım University Rectorate Human Researches Ethics Committee (Date: 02.05.2023, Decision No: 604.01.02-60355), and was registered with ClinicalTrials.gov [NCT05881499]. The study was conducted per the principles stated in the Declaration of Helsinki. The participants who voluntarily agree to participate were included after obtaining written consent.

Participants

The study included 184 individuals between the ages of 18-63 who experienced the Kahramanmaraş-centered earthquakes (Adana, Adıyaman, Diyarbakır, Elazığ, Gaziantep, Hatay, Kahramanmaraş, Kilis, Malatya, Osmaniye, and Şanlıurfa) and continued to live in the above-mentioned 11 provinces.

The inclusion criteria were determined as being between the ages of 18 and 65 and having experienced the Kahramanmaraş-centered earthquakes. Exclusion criteria were as follows: the presence of pain before earthquake; the presence of physical trauma during or after earthquake, the presence of any disease that may cause falls and balance impairment or fear of movement (e.g., hemiplegia, major organ dysfunction); using any medication that may cause balance disorder (e.g., psychotropic drugs); history of severe psychiatric disorder diagnosed before the earthquake; and history of balance disorder diagnosed before the earthquake (e.g., benign paroxysmal positional vertigo) having missing responses in questionnaires, inability to cooperate and illiteracy.

Finally, a total of 184 earthquake survivors (93 males, 91 females; median age: 34.09±10.62 years; range, 18 to 63 years) were included in the study.

The flow chart was shown in **Figure**.

Data Collection

The data was gathered through local authorities at aid points in earthquake-affected cities and collected via an online survey between May and July 2023. Researchers distributed the questionnaire through social media platforms (WhatsApp, Instagram, Facebook), encouraging respondents to share it with others who had experienced the earthquake. At the beginning of the online questionnaire sent to the individuals, they expressed whether they wanted to participate in the study or not. Thus, their consent was obtained. To assess whether

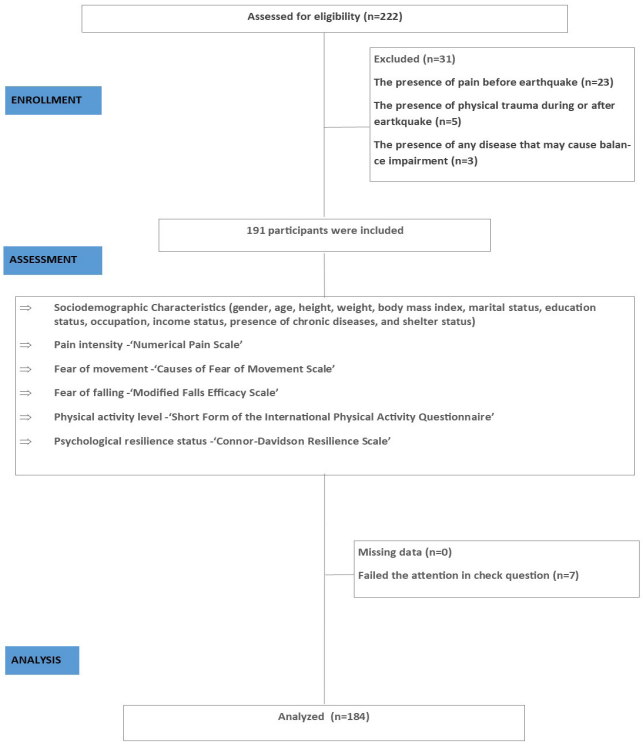

Figure. Flow chart

participants were answering the questions thoughtfully, the statement 'This question has been included to evaluate your level of attention; please select option C.' was inserted among the questions. Participants who did not select option C for this question were excluded from the study.

Sociodemographic characteristics: The sociodemographic characteristics of the participants, including gender, age, height, weight, body-mass index (BMI), marital status, education status, occupation, income status (income-expenditure relationship), presence of chronic diseases, and shelter status were recorded in a descriptive manner.

Assessment of the intensity of pain: Pain intensity was assessed using a 10 cm Numerical Pain Scale (NPS), where 0 indicated "no pain" and 10 represented "the worst pain imaginable."[24] Participants were asked to mark the level of pain they experienced on this scale, which was used to quantify their perceived pain severity. Prior to completing the questionnaire, participants were provided with a written explanation of the scale, ensuring they understood how to rate their pain. Additionally, a visual representation of the scale was included in the online form to maintain consistency in responses.

Assessment of the fear of movement: The fear of movement was assessed using the Turkish version of the Causes of Fear of Movement Scale.[25] This questionnaire, developed by Janusz Kocjan et al.[26] in 2014, consists of 20 questions and aims to diagnose and identify the causes of motor inactivity. The questionnaire is divided into two parts, biological and psychological, to determine the reasons for the fear of movement. This structure enables the identification of individual causes of fear of movement and the determination of biological and psychological causes separately. The total score obtained from the questionnaire is calculated as the average of the scores obtained from the biological and physiological sub-dimensions. In the updated version from 2018,[25] the total score ranges from 0 to 5. The scale uses a 5-point Likert scoring system (1: I totally disagree, 5: I totally agree). It has a minimum score of 0 and a maximum score of 200, with higher scores indicating greater fear of movement.

Assessment of the fear of falling: The Modified Falls Efficacy Scale (MFES) with 14 items (10 indoor and 4 outdoor activities) was used to assess fear of falling. It evaluates participants' confidence during different daily tasks and is a reliable and valid scale for estimating balance and mobility problems. The scale includes items scored between 0 (not confident) and 10 (completely confident) to assess participants' self-efficacy levels regarding falling.[27] The Turkish version developed by Çetişli-Korkmaz et al.[28] will be used in this study. Total the ratings (possible range=0-140) and divide by 14 to get each subject's MFES score. Scores of <8 indicate fear of falling. Higher scores reflect more confidence, less fear of falling. Lower scores reflect less confidence and more fear of falling.

Assessment of the physical activity level: It was assessed with the short form of the International Physical Activity Questionnaire.[29] The Turkish version of this questionnaire, was conducted by Öztürk et al.[31] The criterion in the questionnaire is that physical activities are performed for at least 10 minutes at a time. In the last 7 days with the survey; duration of vigorous physical activity, duration of moderate physical activity, walking and sitting for one day are questioned. The total physical activity score (MET-min/week) is calculated by converting vigorous, moderate activity and walking times to MET (1 MET=3.5 ml/kg/min) corresponding to the basal metabolic rate with the following calculations.

Psychological resilience status: Psychological Resilience Status was assessed using the Connor-Davidson Resilience Scale (CD-RISC-25).[31,32] It consists of 25 questions and three sub-dimensions, namely perseverance and personal competence, tolerance for negative events and spiritual tendency. The first sub-dimension, 'perseverance and personal competence,' has a maximum score of 60, the second sub-dimension, 'tolerance for negative events,' has a maximum score of 24, and the third sub-dimension, 'spiritual tendency,' has a maximum score of 16. The scale uses a 5-point Likert-type scoring system, ranging from 0-4 points, with "never true" (0 points) to "almost always true" (4 points) as response options. There is no cut-off point on the scale, and the highest possible score is 100 points, indicating a higher level of psychological resilience as the score increases.

Sample Size Calculation

The required sample size was calculated using G*Power software (Faul, Erdfelder, Lang, and Buchner, 2007) to determine the achieved statistical power for the correlation analysis of fear of movement with other variables. The correlation coefficient (r=0.242) obtained in the study was entered into the analysis with an α error probability of 0.05 and a total sample size of 184. In the post hoc power analysis, the two-tailed test revealed an achieved power (1-β) of 0.91,

indicating that the study had sufficient power to detect a significant correlation. These results suggest that the sample size was adequate to examine the relationships between fear of movement and related factors with a high probability of correctly identifying true effects.

Statistical Analysis

The statistical analyses were conducted using IBM SPSS Statistics (Version 23.0, Armonk, NY: IBM Corp.). The unit of analysis was the group. As analyses were conducted at the group level, no further adjustments were needed. Descriptive statistics of categorical variables were presented as numbers and percentages, while numerical variables were reported as means, standard deviations, and confidence intervals.

The distribution of the data was assessed using skewness-kurtosis values, histograms, and Q-Q plots. Skewness and kurtosis coefficients were considered within the acceptable range of -1 to +1, indicating a normal distribution.[33] Since the data were normally distributed, Pearson correlation analysis was applied to examine relationships between parameters.

All statistical analyses were conducted at a significance level of 0.05, and two-tailed tests were used to assess differences between groups. There was no missing data in this study.

RESULTS

The socio-demographic characteristics of the participants are presented in Table 1. The study included 184 individuals (50.5% male, 49.5% female). Most participants were married (53.8%), had a university degree (59.2%), and were employed (75.5%). The majority lived in their own houses (59.8%), and income levels were distributed as 33.7% below, 40.8% equal to, and 25.5% above expenses.

Regarding health-related parameters, 12% had chronic diseases, and 50.5% reported headaches. The prevalence of neck, upper back, and low back pain was 37.5%, 46.2%, and 44%, respectively. Additionally, 46.7% had a fear of movement (>50 points), 33.2% had a fear of falling (>8 points), and 22.5% had high psychological resilience (>94 points).

In terms of physical activity levels, 13.6% engaged in low, 24.5% in moderate, and 62% in high-intensity physical activity (>3000 MET-min/week).

Table 2 presents the descriptive statistics of the participants, including mean, standard deviation, minimum-maximum values, and 95% confidence intervals. The mean age was 34.02±10.76 years, with a BMI of 24.44±3.97 kg/m^2. The mean Numerical Pain Scale (NPS) scores for headache, neck pain, upper back pain, and low back pain were 4.43±3.41, 3.57±3.45, 3.98±3.72, and 3.89±3.68, respectively.

The total fear of movement score was 50.86±18.02, with psychological and biological sub-dimensions averaging 2.32±0.89 and 2.41±0.96, respectively. The mean fear of falling score was 6.23±2.73, and the psychological resilience status score was 94.21±19.46. The physical activity level (MET-min/week) was 6262.43±5967.37, indicating a wide range of activity levels among participants.

Table 1. Socio-demographic characteristics of the participants

		n	%
The provinces where participants experienced the earthquake	Kahramanmaraş	56	30.4
	Malatya	30	16.3
	Hatay	26	14.1
	Elazığ	20	10.8
	Kilis	17	9.2
	Adana	16	8.7
	Diyarbakır	5	2.7
	Şanlıurfa	4	2.2
	Mersin	4	2.2
	Adıyaman	3	1.6
	Gaziantep	3	1.6
Gender	Male/female	93/91	50.5/49.5
Marital status	Single/married/other	79/99/6	42.9/53.8/3.3
Education level	Elementary/secondary/high school	3/9/25	1.6/4.9/13.6
	University/postgraduate	109/38	59.2/20.7
Occupation	Employee/student/unemployed	139/32/13	75.5/17.4/7.1
Income status	Income is less than/equal to/greater than expenses	62/75/47	33.7/40.8/25.5
Type of housing	Tent/container/relative's house/own house	11/12/51/110	6/6.5/27.7/59.8
Body-mass index	Underweight/normal/overweight/obese	9/101/55/19	4.9/54.9/29.9/10.3
Presence of chronic disease	Positive	22	12
Presence of headache (NPS)	>5	93	50.5
Presence of neck pain (NPS)	>5	69	37.5
Presence of upper back pain (NPS)	>5	85	46.2
Presence of low back pain (NPS)	>5	81	44
Fear of movement	>50 points	86	46.7
Fear of falling	>8 points	61	33.2
Psychological resilience status	>94 points	25	22.5
Physical activity level	<600 MET-min/week; 600-3000 MET-min/week; >3000 MET-min/week	25/45/114	13.6/24.5/62

NPS: Numerical Pain Scale; MET: Metabolic equivalent of task

Table 3 presents the correlation analysis results, demonstrating significant associations between fear of movement, fear of falling, and pain intensity.

Fear of movement (total score) was significantly correlated with headache intensity ($r=0.275$, $p<0.001$), neck pain intensity ($r=0.294$, $p<0.001$), upper back pain intensity ($r=0.262$, $p<0.001$), and low back pain intensity ($r=0.284$, $p<0.001$), all indicating low correlations.

Table 2. Descriptive statistics

			95% confidence interval	
	x±SD	Min-max	Lower bound	Upper bound
Age (year)	34.02±10.76	13-63	32.08	35.63
BMI (kg/m^2)	24.44±3.97	16.80-39.92	23.86	25.02
Height (cm)	170.25±8.92	154-189	168.95	171.54
Weight (kg)	71.22±14.55	43-110	69.10	73.33
Headache (NPS)	4.43±3.41	0-10	3.93	4.93
Neck pain (NPS)	3.57±3.45	0-10	3.07	4.07
Upper back pain (NPS)	3.98±3.72	0-10	3.44	4.52
Low back pain (NPS)	3.89±3.68	0-10	3.36	4.43
Fear of movement-total	50.86±18.02	20-100	48.23	53.47
Fear of movement-psychological	2.32±0.89	1-5	2.18	2.44
Fear of movement-biological	2.41±0.96	1-5.25	2.27	2.55
Fear of falling	6.23±2.73	1-10	5.83	6.63
Psychological resilience status	94.21±19.46	25-125	91.38	97.04
Physical activity level	6262.43±5967.37	0-27600	5393.46	7130.40

BMI: Body-mass index, cm: Centimetre, kg: Kilogramme, kg/m^2: kilogramme/metre^2, NPS: Numerical Pain Scale

Table 3. Correlations between parameters

		Fear of movement/ total score	Fear of movement/ psychological	Fear of movement/ biological	Fear of falling	Headache	Neck pain	Upper back pain	Low back pain	Psychological resilience status	Physical activity level
Fear of movement-total score	r	1.000	.253	.162	-.080	.275	.294	.262	.284	-.243	.057
	p	.	.001*	.028*	.281	<.001*	<.001*	<.001*	<.001*	.001*	.441
Fear of movement-psychological	r	.253	1.000	.718	-.154	.038	.028	-.020	.016	-.104	.054
	p	.001*	.	<.001*	.037*	.609	.705	.793	.825	.161	.470
Fear of movement-biological	r	.162	.718	1.000	-.019	.067	.027	-.007	-.033	-.112	-.054
	p	.028	.000	.	.796	.364	.713	.926	.661	.132	.467
Decreased fear of falling	r	-.080	-.154	-.019	1.000	-.202	-.179	-.191	-.282	.220	-.020
	p	.281	.037	.796	.	.006*	.015*	.010*	<.001*	.003*	.788
Headache (NPS)	r	.275	.038	.067	-.202	1.000	.716	.676	.638	-.129	.096
	p	.000	.609	.364	.006*	.	<.001*	<.001*	<.001*	.081	.195
Neck pain (NPS)	r	.294	.028	.027	-.179	.716	1.000	.824	.782	-.131	.036
	p	.000	.705	.713	.015	<.001*	.	<.001*	<.001*	.076	.625
Upper back pain (NPS)	r	.262	-.020	-.007	-.191	.676	.824	1.000	.842	-.137	.071
	p	.000	.793	.926	.010*	<.001*	<.001*	.	<.001*	.063	.338
Low back pain (NPS)	r	.284	.016	-.033	-.282	.638	.782	.842	1.000	-.078	.058
	p	.000	.825	.661	<.001*	<.001*	<.001*	<.001*	.	.291	.435
Psychological resilience status	r	-.243	-.104	-.112	.220	-.129	-.131	-.137	-.078	1.000	.068
	p	.001	.161	.132	.003*	.081	.076	.063	.291	.	.357
Physical activity level	r	.057	.054	-.054	-.020	.096	.036	.071	.058	.068	1.000
	p	.441	.470	.467	.788	.195	.625	.338	.435	.357	.

NPS: Numerical Pain Scale

Fear of falling scale score was significantly associated with headache intensity (r=-0.202, p=0.006), neck pain intensity (r=-0.179, p=0.015), upper back pain intensity (r=-0.191, p=0.010), and low back pain intensity (r=-0.282, p<0.001), all indicating low correlations.

Pain intensity in different body regions was significantly correlated with each other. Additionally, psychological resilience status was negatively correlated with fear of movement (r=-0.243, p=0.001) and positively correlated with decreased fear of falling (r=0.220, p=0.003), both indicating low correlations.

DISCUSSION

This study is the first to comprehensively examine the relationships between pain intensity, fear of movement, and fear of falling among earthquake survivors who had no pre-existing pain and did not sustain physical trauma during the disaster. Our findings reveal that pain is a prevalent issue among survivors, despite the absence of direct physical injury, and that fear of movement and fear of falling are significantly associated with pain intensity across different body regions albeit with low correlations. Moreover, psychological resilience emerged as a key factor influencing these fear-related responses, whereas physical activity levels did not show a significant relationship with fear of movement (kinesiophobia) or fear of falling. These results highlight the unique impact of earthquakes on survivors' pain perception and fear-related behaviors, filling a critical gap in the existing literature.

A total of 184 earthquake survivors, from 11 affected provinces, participated in this study, with an almost equal distribution of males (50.5%) and females (49.5%). Notably, 46.7% of the participants reported fear of movement, while 33.2% exhibited increased fear of falling. Despite having no history of pain before the earthquake, 50.5% of the survivors experienced headaches, 37.5% reported neck pain, 46.2% suffered from upper back pain, and 44% had low back pain. These findings underscored the considerable impact of the earthquake on musculoskeletal health, even in individuals without direct physical trauma.

Previous studies have primarily focused on trauma-induced pain following earthquakes. A study conducted in 2012 examined the prevalence and trajectory of trauma-related pain in the weeks following the 2009 earthquake in the Abruzzi region of Italy.[17] That retrospective observational study analyzed pain severity, pain type, and treatment efficacy over the five weeks following the disaster.[17] Their findings indicated that 34.6% of the patients reported pain, and among them, 58.8% experienced severe pain.[17] Pain prevalence followed a biphasic pattern: in the first 15 days, pain was predominantly associated with physical trauma, then decreased before resurging around the fifth week due to rebuilding efforts.[17] Their results highlighted the significant burden of trauma-related pain in post-earthquake settings and suggested that pain intensity may fluctuate based on physical activity and environmental stressors during recovery.[17] Unlike that study, which focused on trauma-induced pain and its treatment, our research provided a novel perspective by evaluating pain intensity, fear of movement, and fear of falling in earthquake survivors who did not sustain physical injuries. This distinction is crucial, as it enables a better understanding of pain mechanisms that arise independently of direct trauma, potentially driven by psychological stress, altered postural control, or heightened central sensitization.

Another study conducted on survivors of the Kahramanmaraş-centered earthquakes examined the relationships between post-earthquake anxiety, sleep disturbances, and musculoskeletal pain.[19] That study, which included 291 participants, found that low back and neck pain were prevalent, with up to 37% of individuals exhibiting moderate to severe disability according to the Oswestry Disability Index and Neck Disability Index.[19] However, that study did not assess whether participants had sustained physical trauma, making it unclear whether pain was due to direct injury or secondary to psychological and environmental stressors.[19]

Another study investigated the development of new-onset low back pain (LBP) among survivors of the Great East Japan earthquake (GEJE), examining the role of preexisting musculoskeletal pain.[18] That longitudinal study followed 1,782 survivors who had no LBP at three years post-earthquake and reassessed them one year later.[18] The results revealed that 14.1% of participants developed new-onset LBP, and those with preexisting musculoskeletal pain were at significantly higher risk.[18] Our study complemented that research by focusing on an earlier post-disaster period (3-5 months after the earthquake) rather than years later, allowing for a more immediate evaluation of musculoskeletal pain responses in non-injured survivors.[18] Additionally, while that study examined anxiety and sleep disturbances, it did not evaluate movement-related fears such as fear of movement and fear of falling, which are critical in understanding functional limitations post-disaster.

These studies collectively demonstrated the significant impact of earthquakes on musculoskeletal health, yet they primarily focused on trauma-related pain, long-term pain trajectories, or psychological factors like anxiety and sleep disturbances. Our study provided a unique perspective by evaluating pain intensity, fear of movement, and fear of falling in non-injured survivors within the early post-disaster period, highlighted the need for early intervention strategies that addressed both physical and psychological aspects of recovery.

In our study, 46.7% of the participants reported high levels of fear of movement, indicating that nearly half of the non-injured earthquake survivors experienced significant movement-related fear despite the absence of direct physical trauma. This finding suggests that factors beyond physical injury, such as psychological distress, altered postural control, and central sensitization, may contribute to fear of movement in post-earthquake populations. Given that fear of movement is associated with activity avoidance and long-term functional impairment, its high prevalence in our sample underscores the need for early interventions targeting movement-related fears to prevent chronic disability.

A study published in 2025 was the first to evaluate post-earthquake fear of movement, fear of falling, and balance impairments in earthquake survivors.[23] Their findings highlighted the role of aging and post-traumatic stress disorder (PTSD) in fear of falling.[23] However, this study did not assess pain intensity, psychological resilience, or physical activity levels, leaving an important gap in understanding how these factors influence movement-related fears.

Unlike the previous study,[23] which focused on PTSD and aging, our study demonstrates a direct relationship between pain severity and fear of falling, highlighting the need for pain management strategies in post-disaster rehabilitation.

Furthermore, while physical activity is often considered a protective factor against falls, our findings indicated that it is

not significantly associated with fear of falling in earthquake survivors. Instead, psychological resilience appears to play a critical role, suggesting that mental health interventions aimed at enhancing resilience may be as important as physical rehabilitation programs in post-earthquake recovery efforts.

Psychological resilience plays a crucial role in post-disaster recovery, particularly in mitigating fear-related movement restrictions. Our findings showed that individuals with higher resilience reported lower levels of fear of movement and fear of falling, despite experiencing musculoskeletal pain. This suggests that resilience acts as a protective mechanism, potentially buffering against the psychological distress that often exacerbates movement-related fears. These findings highlighted the need for incorporating psychological resilience-building interventions into rehabilitation programs, as strengthening mental coping strategies may enhance physical recovery and prevent long-term disability in earthquake survivors.

Physical activity is widely recognized as a key component of musculoskeletal health and overall well-being. However, our findings indicated that physical activity levels were not significantly associated with fear of movement or fear of falling in earthquake survivors. This suggests that, in post-disaster settings, psychological factors such as fear and stress may override the protective benefits of regular physical activity. Additionally, disruptions to daily routines and limited access to exercise facilities following a disaster may contribute to reduced physical activity engagement. Future research should explore how structured physical activity programs can be effectively implemented in post-disaster rehabilitation settings to support both physical and psychological recovery.

The sociodemographic characteristics of survivors also played a crucial role in shaping post-earthquake health outcomes. The majority (59.8%) were living in their own homes, while 27.7% resided with relatives, and 12.5% were in temporary shelters such as tents or containers. These living conditions may have influenced their overall health, as individuals in unstable housing situations often reported higher pain levels and increased movement-related fears. Financial constraints were another critical factor, with 33.7% of participants stating that their income was below their expenses, which could have contributed to heightened stress and limited access to healthcare resources. Many participants were displaced from their homes and had to live in temporary shelters such as tents or containers, leading to significant environmental and psychological stressors. The lack of stable housing and reduced access to healthcare services may have exacerbated musculoskeletal pain and increased movement-related fears.

Additionally, financial constraints and loss of social support networks could have further contributed to psychological distress, reinforcing the need for targeted interventions that consider the broader social determinants of health in disaster-affected populations. Future studies should examine how living conditions and socioeconomic status influence rehabilitation outcomes in earthquake survivors.

Another notable finding was the high level of education among participants, which can be attributed to the study being conducted five months after the earthquake when essential personnel, including government employees, teachers, and other public sector workers, were required to return to duty in affected regions. This may have influenced the sample composition and should be considered when interpreting the findings. Our data indicated that 75.5% of participants were employed, while 24.5% were unemployed or unable to work due to disaster-related disruptions. Those who returned to work may have experienced additional physical and psychological stress due to occupational demands, whereas unemployed individuals may have faced financial insecurity, further exacerbating post-disaster health challenges. Additionally, individuals who resumed their professional duties in disaster-affected areas may have encountered increased workloads, logistical difficulties, and heightened emotional stress, all of which could contribute to musculoskeletal complaints and movement-related fears. Future research should explore the interplay between employment status, psychological resilience, and musculoskeletal health in disaster recovery settings to better understand the long-term implications of work-related stress and financial instability on post-earthquake rehabilitation outcomes.

Limitations

The present study has some limitations. Fear of movement, pain, and fear of falling were assessed through self-reported questionnaires, which, while validated, may not fully capture the complexity of these constructs. Additionally, as a cross-sectional study, causal relationships between pain, psychological resilience, and movement-related fears cannot be definitively established. Future studies should employ longitudinal designs to explore how these relationships evolve over time and consider objective movement analyses to further examine postural adaptations and functional limitations in earthquake survivors.

CONCLUSION

Despite these limitations, this study has several strengths. It is among the first to investigate the interplay between pain intensity, fear of movement, and fear of falling in earthquake survivors who did not sustain physical injuries. By incorporating psychological resilience as a protective factor, our study provides novel insights into how psychological factors influence post-disaster musculoskeletal health. Additionally, our findings highlight the importance of addressing movement-related fears in early rehabilitation programs to prevent long-term functional limitations. These contributions underscore the need for comprehensive rehabilitation approaches that integrate both physical and psychological components to optimize recovery in earthquake-affected populations.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Atılım University Rectorate Human Researches Ethics Committee (Date: 02.05.2023, Decision No: 604.01.02-60355).

Informed Consent

Signed and informed consent forms were obtained from all earthquake victims.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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The effect of obesity on prognosis in patients with endometrioid type endometrial adenocarcinoma

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ABSTRACT

Aims: This study sought to investigate the relationship between pre-treatment body-mass index (BMI) and established prognostic factors associated with endometrial cancer, as well as to assess its impact on survival in patients diagnosed with this malignancy.
Methods: Patients diagnosed with endometrioid-type endometrial cancer between January 2000 and June 2010 at the medical oncology clinic, and who received treatment and follow-up at our clinic, were included in the study. The patient files and the hospital electronic database were retrospectively reviewed. The patients were divided into non-obese (BMI <30 kg/m^2) and obese (BMI ≥30 kg/m^2) groups, then compared in terms of clinical characteristics, pathological results, and survival outcomes.
Results: A total of 126 patients, 44 in the non-obese group and 82 in the obese group, were included in the study. The two groups were statistically similar when classified according to demographic and clinicopathological data. Stage, tumour grade, cytology, depth of myometrial or lymphovascular invasion and lymph node metastasis were significantly associated with 5-year survival. The 5-year disease-free survival rate was 86.4% in the non-obese group and 87.8% in the obese group. When examining cause-specific survival rates, they were found to be 86.4% and 90.2%, respectively and no statistically significant association was observed between 5-years survival outcomes between both groups.
Conclusion: This study demonstrated that there was no significant relationship between obesity and the defined prognostic factors of the disease and 5-year survival results.
Keywords: Endometrial cancer, obesity, survival

INTRODUCTION

Endometrial cancer is one of the most prevalent types of gynecological cancer globally.[1] According to Globocan data, 417,000 new cases were diagnosed globally in 2020, with 97,000 deaths occurring.[2] According to the same data set, endometrial cancer ranks fourth among the most prevalent cancer types among Turkish women (incidence rate: 11.1 per 100,000). The World Health Organization also reported 5,463 new cases of endometrial cancer among Turkish women in 2018, with 1,051 deaths.[2]

Hormones are a significant factor in endometrial cancer, which occurs predominantly during the postmenopausal period.[3] Obesity contributes to endometrial carcinogenesis through mechanisms such as inflammation, hyperinsulinemia-insulin resistance, and unopposed estrogen.[4] In excessive adipose tissue, which has high aromatase activity, estrone is formed from androstenedione, and estradiol is formed from testosterone. Moreover, in obese women, the presence of hyperinsulinemia results in a decline in sex hormone-binding globulin (SHBG) levels. This, in turn, leads to an increase in free hormone levels, consequently exposing the endometrium to elevated estrogenic effects.[5,6] Hyperestrogenemia and insulin resistance, in conjunction with hyperinsulinemia, have been demonstrated to enhance the systemic availability of insulin like growth factor-1 (IGF-1). This, in turn, triggers the activation of specific pro-oncogenic pathways that affect the endometrium.[6,7] Moreover, obesity has been demonstrated to induce a state of chronic inflammation within the endometrium, featured by high levels of pro-inflammatory cytokines (IL-6, IL-8), thereby engendering a carcinogenic environment.[7]

Obesity, through the aforementioned mechanisms, has been identified as a serious threat for endometrial cancer development, with the incidence of this condition being 2-5 times higher in obese women.[5] Each 5 kg/m^2 increase in body-mass index (BMI), the risk of endometrial cancer has been demonstrated to increase by 60%.[8] Women with a BMI over 25 kg/m^2 face double the endometrial cancer risk, while those with a BMI exceeding 30 kg/m^2 can experience a threefold increase in risk.[9] Despite the clear link between elevated BMI and a heightened likelihood of endometrial cancer, research

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reveals conflicting information regarding how BMI impacts survival rates for women after diagnosis.[9-21] With the global increase in overweight and obesity, there is an urgent need for further research and awareness regarding the critical relationship between obesity and cancer outcomes. In view of the data presented, our study has two main aims. First, it aims to analyze the relationship between pre-treatment BMI and various established prognostic factors of the disease. The other is to investigate how pre-treatment BMI impacts survival outcomes for these patients.

METHODS

Approval for the present study was obtained from the Ondokuz Mayıs University Clinical Researches Ethics Committee (Date: 12.02.2016, Decision No: OMÜ-KAEK-2016/68). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The study population comprised patients diagnosed with endometrioid-type endometrial cancer at the internal medicine medical oncology clinic from January 2000 to June 2010 and whose treatment and follow-up were performed in our center. The patient files and the hospital electronic database were retrospectively reviewed. We excluded patients who had not undergone hysterectomy. Data collected from patient files included age, BMI, parity, menopause status, International Federation of Gynecology and Obstetrics (FIGO) stage, tumour grade, size, myometrial and lymphovascular invasion, cytology, pathology results (metastasis to lymph nodes etc.), and details on surgical and adjuvant treatments. Information on recurrence and mortality was also obtained.

A total of 126 patients participated in the study, which divided them into two groups as non-obese (BMI <30 kg/m^2) and obese (BMI ≥30 kg/m^2) based on their pre-treatment BMI. A comprehensive comparison was conducted between the groups concerning clinical characteristics, pathology results, and survival outcomes.

Statistical Analysis

The study used SPSS version 20 software for statistical analysis. We compared the average values of the groups using the student's T test and looked at frequency data with the Chi-square test. We calculated survival data using the Kaplan-Meier method and compared survival rates with the log-rank test. A p-value of ≤0.05 was considered statistically significant.

RESULTS

A total of 126 patients participated in the study, 44 were classified as non-obese, while 82 were classified as obese. The mean BMI for the non-obese group was 25.98 kg/m^2, with a range from 18.7 to 29.7 kg/m^2. In contrast, the mean BMI for the obese group was 36.75 kg/m^2, with a range from 30 to 56.6 kg/m^2.

The study examined various clinical characteristics of the patients, including age, BMI, parity, and menopausal status. In addition, we evaluated the pathological results that were determined to be important for the prognosis of the disease. The surgery performed and the subsequent treatment modalities were categorized for both groups. The analysis revealed no statistically significant difference between the groups (Table 1).

The average follow-up duration for the cohort was 46.7 months, with a range of 3 to 118 months. Throughout the follow-up period, 109 patients (86.5%) survived, while 17 patients (13.5%) passed away. Of these 17 patients, 14 (11.1%) died within the first 5 years following diagnosis. Additionally, 6 patients (4.8%) experienced recurrence, with 3 patients (2.4%) having a recurrence within the first 5 years. Of the 6 patients who had recurrences, 4 died, with one of these deaths occurring within the first 5 years post-diagnosis. The cohort analysis indicated that the 5-year disease-free survival rate was 87.3%, while the cause-specific survival rate was 88.9%.

When evaluating patients' clinical and pathological data with respect to 5-year survival; stage, tumour grade, cytology, myometrial invasion deeper than half, lymphovascular invasion, and metastasis to lymph nodes were statistically significant for survival, while no statistical significance was found for other parameters (Table 2).

When evaluating the effect of patients' BMI values and their classification into non-obese and obese groups on 5-year survival rates, the findings were as follows: In the non-obese group, which consisted of 44 patients, the 5-year disease-free survival rate was 86.4%. In contrast, the obese group, composed of 82 patients, had a survival rate of 87.8% and no statistically significant difference between the groups (p-value: 0.833) (Figure A). In terms of cause-specific survival, the rates were 86.4% for the non-obese group and 90.2% for the obese group, again showing no statistically significant difference (p-value: 0.545) (Figure B).

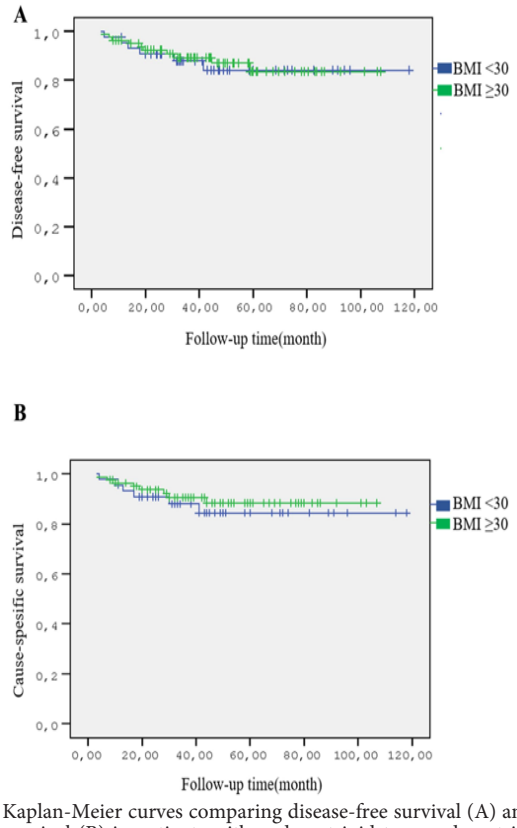

Figure. Kaplan-Meier curves comparing disease-free survival (A) and cause-specific survival (B) in patients with endometrioid-type endometrial cancer according to body-mass index

Table 1. Patients features					
		Case n (%)	Non-obese (<30 kg/m²)	Obese (≥30 kg/m²)	p-value
		126	44	82	
Age	≤50	36 (28.6)	12 (27.3)	24 (29.3)	0.813
	>50	90 (71.4)	32 (72.7)	58 (70.7)	—
Menopause	Premenopause	27 (21.4)	11 (25.0)	16 (19.5)	0.474
	Postmenopause	99 (78.6)	33 (75.0)	66 (80.5)	—
Parity	0	18 (16.2)	6 (15.4)	12 (16.7)	0.861
	≥1	93 (83.8)	33 (84.6)	60 (83.3)	—
Stage	1-2	97 (77.0)	30 (68.2)	67 (81.7)	0.086
	3-4	29 (23.0)	14 (31.8)	15 (18.3)	—
Tumour grade	1	44 (36.4)	16 (36.4)	28 (36.4)	0.972
	2	65 (53.7)	24 (54.5)	41 (53.2)	—
	3	12 (9.9)	4 (9.1)	8 (10.4)	—
Tumour size (mm)	≤20	12 (12.4)	4 (12.1)	8 (12.5)	0.616
	>20	85 (87.6)	29 (87.9)	56 (87.5)	—
Myometrial invasion	<1/2	64 (51.2)	19 (43.2)	45 (55.6)	0.128
	>1/2	61 (48.8)	25 (56.8)	36 (44.4)	—
Lymphovascular invasion	Negative	78 (75.7)	24 (66.7)	54 (80.6)	0.116
	Positive	25 (24.3)	12 (33.3)	13 (19.4)	—
Cytology	Negative	102 (95.3)	36 (94.7)	66 (95.7)	0.585
	Positive	5 (4.7)	2 (5.3)	3 (4.3)	—
Lymph node metastasis	No	96 (80.7)	33 (76.7)	63 (82.9)	0.414
	Yes	23 (19.3)	10 (23.3)	13 (17.1)	—
PLND	Not done	31 (25.6)	10 (23.3)	21 (26.9)	0.658
	Done	90 (74.4)	33 (76.7)	57 (73.1)	—
PALND	Not done	51 (42.1)	18 (41.9)	33 (42.3)	0.962
	Done	70 (57.9)	25 (58.1)	45 (57.7)	—
Adjuvant therapy	Not done	50 (39.7)	13 (29.5)	37 (45.1)	0.117
	Radiotherapy	47 (37.3)	17 (38.6)	30 (36.6)	—
	Chemotherapy	16 (12.7)	6 (13.6)	10 (12.2)	—
	CT+RT	13 (10.3)	8 (18.2)	5 (6.1)	—

PLND: Pelvic lymph node dissection, PALND: Para-aortic lymph node dissection, CT: Chemotherapy, RT: Radiotherapy

DISCUSSION

Obesity is a prevalent and significant concern among women diagnosed with endometrial cancer, as numerous studies have consistently demonstrated that obesity substantially increases the risk of developing endometrial cancer and underscored the importance of managing this risk factor.[22-24] However, the impact of obesity on the prognosis of the disease-specifically how it interacts with other critical prognostic factors-remains less clear, despite the large body of research available in the literature.[9-21,25] Undoubtedly, identifying and accurately evaluating the risk factors and clinicopathological features that adversely affect the prognosis of endometrial cancer are crucial. A deeper understanding of these factors will be critical for tailoring more effective treatment strategies and follow-up protocols, ultimately improving survival rates and patient outcomes in this common cancer type.

In our study, we evaluated clinical characteristics, such as age, parity, and menopausal status. Our findings indicated that there were no statistically significant difference between non-obese individuals (BMI <30 kg/m²) and those classified as obese (BMI ≥30 kg/m²). We conducted an assessment of pathological outcomes, which included FIGO staging, tumour grading, tumour dimensions, myometrial or lymphovascular invasion, cytological findings, lymph node metastasis, and the surgical as well as subsequent adjuvant treatment strategies employed. When each prognostic factor was assessed independently, survival outcomes were consistent with those reported in the literatüre.[26-28] Notably, however, our multivariate analysis revealed that there were no significant difference in 5-year disease-free survival or cause-specific survival rates between the groups in relation to obesity.

A thorough review of existing literature highlights a notable disparity in the findings concerning the relationship between obesity and survival outcomes. Some studies support our

Table 2. Prognostic factors and survival of patients

			Disease-free survival		Cause spesific survival	
		Case n (%)	5-year DFS (%)	p-value	5-year CSS (%)	p-value
Age	≤50	36 (28.6)	94.4	0.114	94.4	0.191
	>50	90 (71.4)	84.4		86.7	
Menopause	Premenopause	27 (21.4)	92.6	0.346	92.6	0.480
	Postmenopause	99 (78.6)	85.9		87.9	
Parity	0	18 (16.2)	83.3	0.640	88.9	0.967
	≥1	93 (83.8)	89.2		89.2	
BMI (kg/m²)	<30	44 (34.9)	86.4	0.833	86.4	0.545
	≥30	82 (65.1)	87.8		90.2	
Stage	1-2	97 (77.0)	91.8	0.005	93.8	0.001
	3-4	29 (23.0)	72.4		72.4	
Tumour grade	1	44 (36.4)	93.2	0.018	95.5	0.006
	2	65 (53.7)	87.7		89.2	
	3	12 (9.9)	66.7		66.7	
Tumour size (mm)	≤20	12 (12.4)	100	0.178	100	0.209
	>20	85 (87.6)	85.9		88.2	
Myometrial invasion	<1/2	64 (51.2)	95.3	0.004	95.3	0.015
	>1/2	61 (48.8)	78.7		82.0	
Lymphovascular invasion	Negative	78 (75.7)	89.7	0.019	92.3	0.004
	Positive	25 (24.3)	72.0		72.0	
Cytology	Negative	102 (95.3)	90.2	0.073	92.2	0.023
	Positive	5 (4.7)	60.0		60.0	
Lymph node metastasis	No	96 (80.7)	91.7	0.009	93.8	0.002
	Yes	23 (19.3)	73.9		73.9	
PLND	Not done	31 (25.6)	83.9	0.413	87.1	0.502
	Done	90 (74.4)	91.1		92.2	
PALND	Not done	51 (42.1)	84.3	0.290	86.3	0.221
	Done	70 (57.9)	92.9		94.3	
Adjuvant therapy	Not done	50 (39.7)	92.0	0.162	94.0	0.113
	Done	76 (60.3)	84.2		85.5	

DFS: Disease-free survival, CSS: Cause spesific survival, BMI: Body-mass index, PLND: Pelvic lymph node dissection, PALND: Para-aortic lymph node dissection

conclusions, demonstrating no significant association between obesity and survival rates.[15-19] Conversely, some studies suggest a troubling correlation between increased BMI and heightened mortality risk.[9-14,25] For example, Secord et al.[25] reported that a 10% rise in BMI was linked to a 9.2% increase in mortality.

While numerous studies have associated obesity with poorer survival outcomes, some studies have highlighted the so-called 'obesity paradox,' where higher BMI appears to be associated with better survival in specific patient populations.[20,21] Temkin et al.,[21] in a multicenter retrospective study, found that women with a BMI ≥30 had an average survival of 117 months, whereas those with a BMI <25 had a survival of 85 months (p: 0.003). The authors proposed several potential explanations for this paradoxical finding. One key factor is the younger age at diagnosis often seen in obese patients, which may result in a longer overall survival period. Additionally, obese individuals tend to present with lower tumour grades and earlier stages of cancer, both of which are associated with better prognoses. Another factor worth considering is the clinical tendency to administer reduced doses of postoperative chemotherapy to obese patients, which could, paradoxically, lead to improved survival outcomes due to reduced toxicity.

The findings from studies investigating the effect of obesity on survival outcomes have been inconsistent, likely due to differences in study design, patient selection, and the BMI cutoffs used for categorization. In a study by Gates et al.,[29] which involved 165 patients diagnosed with endometrioid-type endometrial carcinoma, those with a BMI greater than 25 kg/m² were found to have more favorable prognostic factors than those with a lower BMI. On the other hand, when the BMI cutoff was set at ≥35 kg/m² (class 2 obesity) or ≥40 kg/m² (morbid obesity), the more obese groups demonstrated worse prognostic factors and lower survival rates.

Limitations

Similarly, the findings of our study may have influenced by the BMI cutoff (≥30 kg/m²) employed to delineate the patient groups. Had the cutoff been set according to class 2 obesity or morbid obesity, the results might have shown a different relationship. This represents an inherent limitation of our study. Other limitations of the study include its retrospective nature, which inherently restricts the ability to draw definitive conclusions about causality; a small sample size, particularly in subgroups; a lack of data on BMI changes following treatment; the absence of data about metabolic parameters or obesity-related comorbidities; and the inclusion of single-center data, which may reduce generalizability.

CONCLUSION

In conclusion, the study demonstrates that pre-diagnosis obesity does not impact the survival of Turkish women with endometrioid-type endometrial adenocarcinoma. However, the role of obesity in the prognosis of non-endometrioid subtypes remains unclear and warrants further research to better understand its impact. Additionally, the effects of changes in BMI post-diagnosis, along with any related interventions, on long-term survival in endometrial cancer warrant further investigation. These areas could represent important opportunities for future research, particularly in understanding the potential benefits of weight management interventions in improving patient outcomes.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Ondokuz Mayıs University Clinical Researches Ethics Committee (Date: 12.02.2016, Decision No: OMÜ-KAEK-2016/68).

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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Investigation of the effects of radionuclides used in nuclear medicine on organ dose and effective dose

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ABSTRACT

Aims: The aim of this study is to investigate the effects of ^{68}Ga, ^{18}F, ^{89}Sr, ^{13}N, ^{133}Xe and ^{131}I radionuclide sources on organ doses and effective doses at different distances.

Methods: In this study, radionuclides commonly used in nuclear medicine applications were defined in the VMC dose calculation software to determine organ doses and effective dose values at varying distances. Additionally, the dose rates of each radionuclide were obtained using the Rad pro calculator online program.

Results: For different radionuclides at a 10 mCi dose, average dose rate measurements were conducted at varying distances. Specifically, ^{13}N and ^{89}Sr delivered the highest doses to certain organs, whereas ^{133}Xe ve ^{131}I resulted in lower doses. The effective doses at 100 cm for ^{68}Ga, ^{18}F, ^{89}Sr, 13N, ^{133}Xe and ^{131}I sources were determined to be 2.72 µSv, 2.94 µSv, 2.50 µSv, 2.84 µSv, 0.91 µSv, and 1.16 µSv, respectively. The effective doses at 150 cm for ^{68}Ga, ^{18}F, ^{89}Sr, ^{13}N, ^{133}Xe and ^{131}I sources were determined to be 1.56 µSv, 1.49 µSv, 1.30 µSv, 1.46 µSv, 0.14 µSv, and 0.58 µSv, respectively. As the distance increased, radiation exposure levels decreased.

Conclusion: In this study, radiation exposure decreased significantly with distance from the source, demonstrating the importance of maintaining distance and applying ALARA principles in clinical settings. Furthermore, avoiding close proximity to the radiation source and utilizing appropriate shielding methods are crucial in minimizing radiation exposure.

Keywords: Dose rate, organ dose, VMC program, ICRP female phantom

INTRODUCTION

Nuclear medicine is a rapidly evolving medical field that utilizes radioactive substances for the diagnosis, staging, and treatment planning of various diseases. Radiopharmaceuticals used in this field accumulate in specific organs or tissues, enabling imaging or therapeutic applications. Significant advancements in imaging technology, along with variations in procedures and radionuclide types used in nuclear medicine, have led to notable changes in absorbed doses over time.[1,2]

Most of these changes stem from the widespread adoption of molecular hybrid imaging procedures, such as single-photon emission computed tomography/computed tomography (SPECT/CT), positron emission tomography/computed tomography (PET/CT), and positron emission tomography/magnetic resonance imaging (PET/MRI), which provide both functional and anatomical information. These hybrid systems demonstrate high sensitivity and accuracy. Moreover, they reduce interobserver variability by enabling more precise localization and characterization of scintigraphy findings.[3,4]

New techniques and radioactive compounds are continuously being developed for the diagnosis of clinical diseases. Patients are exposed to ionizing radiation due to radioisotope injection.[5] Therefore, radiation safety is of paramount importance in nuclear medicine applications. The radiation doses received by patients and organs vary depending on the type and activity of the radionuclide used, the route of administration, the patient's physiological characteristics, and the imaging or treatment protocol. During nuclear medicine procedures, patients may receive doses ranging from 740 to 1110 MBq for bone scans, 111 to 740 MBq for renal scans, and 74 to 370 MBq for thyroid scans.[6,7]

Although nuclear medicine procedures provide undeniable diagnostic and therapeutic benefits to patients, the significant increase in radiation exposure among nuclear medicine patients and personnel has raised concerns about potential adverse health effects.[8,9] Nuclear medicine professionals are exposed to varying levels of radiation depending on the radionuclide used during imaging and therapeutic procedures. In SPECT and SPECT/CT scans, radiopharmaceuticals labeled with Technetium-99m (^{99m}Tc) are commonly used. However, with the introduction of PET/CT in nuclear medicine, a substantial increase in radiation doses among nuclear medicine personnel has been observed.[10-13]

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Among the various imaging procedures used in nuclear medicine, Fluorodeoxyglucose (^{18}F-FDG) is widely employed in oncological, neurological, and cardiological imaging. Gallium-68 prostate-specific membrane antigen (^{68}Ga-PSMA) is commonly utilized for prostate cancer imaging, while strontium-89 (^{89}Sr) is frequently administered for the relief of bone pain associated with certain cancer types. Nitrogen-13 (^{13}N) is used in myocardial perfusion imaging, whereas Iodine-131 (^{131}I) is applied in the treatment and imaging of thyroid cancer and hyperthyroidism. Additionally, Xenon-133 (^{133}Xe) is used for lung perfusion and ventilation scintigraphy.[14]

In nuclear medicine applications, the as low as reasonably achievable (ALARA) principle is implemented to minimize radiation doses to the lowest possible levels. This principle is applied by considering key factors such as time, distance, and shielding measures to ensure the safety of both patients and healthcare professionals.[15-18] According to the annual dose limits established by the International Commission on Radiological Protection (ICRP), For the lens of the eye, the annual dose limit is set so as not to exceed 20 mSv averaged over five consecutive years, with no single year exceeding 50 mSv. For the skin, the annual equivalent dose limit is 500 mSv, applied to any 1 cm^2 area of skin. Similarly, for extremities such as the hands, feet, forearms, and ankles, the annual dose limit is also 500 mSv. For other organs, there are no explicit individual limits; instead, exposure is regulated indirectly through the overall effective dose limit. With regard to effective dose, the annual limit for adult radiation workers is 20 mSv, averaged over a period of five years, with a maximum of 50 mSv in any single year.[15-17] While individual radionuclides like ^{68}Ga, ^{18}F, ^{89}Sr, ^{13}N, ^{133}Xe, and ^{131}I are widely used and studied, comparative evaluations of their organ-specific and whole-body dose distributions, particularly at varying distances, are underrepresented in the literature. However, few studies have comprehensively compared multiple commonly used radionuclides side by side in terms of how distance affects both organ level and effective dose. To our knowledge, this is the first study to systematically model and compare dose distributions for this range of radionuclides using both organ-specific and whole-body metrics over varying distances. The results provide crucial guidance for enhancing safety protocols in nuclear medicine environments.

The purpose of this study is to analyze and compare the radiation doses delivered by selected radionuclides (^{68}Ga, ^{18}F, ^{89}Sr, ^{13}N, ^{133}Xe, and ^{131}I) to various organs and the whole body at different distances using simulation software. The study aims to assess how radiation exposure varies with radionuclide type and distance, providing critical information for improving radiation protection strategies for both patients and healthcare professionals. The findings also contribute to a better understanding of dose optimization in clinical nuclear medicine practices. Additionally, ^{68}Ga, ^{18}F, ^{89}Sr, ^{13}N, ^{133}Xe, and ^{131}I radionuclide sources on organ doses and effective doses at varying distances using the visual Monte Carlo (VMC) dose calculation program. Furthermore, the dose rates of these radionuclide sources at different distances were obtained using the Rad Pro Calculator online program.

METHODS

This study did not require ethical approval as it did not involve any human subjects or animal experiments. All procedures were carried out in accordance with the ethical rules and the principles.

The properties of the radionuclides used in the study are shown in Table 1.

Table 1. Properties of radionuclids used in nuclear medicine[8,20,21]

Radionuclide	Half-life	Radiation/MeV	Production	Application
^{68}Ga	67.71 m	β^+/1.89	Generator	PET imaging
^{18}F	109.77 m	β^+/0.63	Accelerator	PET imaging
^{89}Sr	50.56 d	β^-/1.49	Reactor	β^- therapy
^{13}N	9.97 m	β^+/1.20	Accelerator	PET imaging
^{133}Xe	5.24 d	γ, β^-/0.37	Reactor	SPECT imaging
^{131}I	8.03 d	γ, β^-/0.36	Reactor	β therapy, SPECT imaging

The visual Monte Carlo (VMC) is a Monte Carlo simulation software used for radiation dose calculations. It is widely utilized in medical physics and radiation safety. VMC simulates the interactions of radiation particles, such as photons and electrons, within matter, allowing for the computation of dose distributions in various applications.[2] Equivalent and effective dose can be calculated with equations 1 and 2 below.[21,22]

$$H_T = Q \times D_T H_T = Q \times D_T \quad (1)$$

The dose equivalent is expressed in sieverts (or rems) to differentiate it from the absorbed dose, which is measured in grays (or rads). In this context, Q represents the quality factor of the type of radiation, determined by its linear energy transfer (LET) in water such as a value of approximately 1 for X-Rays. DT refers to the absorbed dose at a specific point within a tissue.

$$H_E = \sum w_T H_T H_E = \sum w_T H_T \quad (2)$$

Here, wT denotes the weighting factor assigned to a specific tissue or organ (T), while HT represents the dose equivalent received by that tissue. The effective dose, HE, is calculated by summing the products of each tissue's weighting factor and its corresponding dose equivalent across all tissues.

In this study, radionuclides commonly used in nuclear medicine were defined in the VMC dose calculation software to determine organ doses and effective dose values. Although the dose range of these radiopharmaceuticals in clinical applications varies between 4 mCi and 20 mCi, a standard 10 mCi activity level was used in the simulations to ensure accuracy in comparative analyses. The adult female reference phantom defined by the International Commission on Radiological Protection (ICRP) was selected as the phantom model. In the VMC program, ^{68}Ga, ^{18}F, ^{89}Sr, ^{13}N, ^{133}Xe and ^{131}I sources with 10 mCi activity were simulated at distances of 25 cm, 50 cm, 100 cm, and 150 cm from the ICRP adult female phantom, and organ and effective dose calculations were

performed. Additionally, the Rad Pro Calculator software was used to compute dose rates by incorporating the half-lives of these radiopharmaceuticals.

The Rad Pro calculator is a software program that performs various nuclear calculations and is particularly useful for health physicists, physicians, technicians, and other radiation physics professionals. Furthermore, it enables radioactivity unit conversions and calculates gamma emitter dose rates and activities.

RESULTS

The radiation doses received by organs at different distances are detailed in Tables 2-5. These tables present organ doses and effective doses (μSv) for various radioisotopes and distances. The data provided are crucial for radiation safety and risk assessment. The results indicate that radiation exposure to organs varies significantly depending on the type of radionuclide and the distance from the source. Figure illustrates an image obtained from the VMC program used in this study.

Table 2. Radiation dose to which organs are exposed at a distance of 25 cm

Organ doses D (T)	^{68}Ga	^{18}F	^{89}Sr	^{13}N	^{133}X	^{131}I
Red bone marrow	8.82	9.16	12.23	9.85	0.33	3.30
Colon	16.16	16.96	22.19	26.17	0.90	6.86
Lung	9.42	9.57	10.36	21.35	0.79	3.76
Stomach	11.77	13.40	20.53	29.05	0.79	4.86
Breast	18.06	18.86	20.84	12.23	1.98	8.10
Remainder	10.75	11.36	13.86	19.66	0.59	4.27
Ovaries	17.51	18.18	23.15	16.49	1.48	6.89
Bladder	16.79	18.35	24.17	16.66	0.50	7.10
Oesophagus	7.98	7.28	11.99	16.04	0.36	2.24
Liver	15.84	16.10	16.17	25.32	1.25	6.17
Thyroid	7.58	8.25	11.13	32.64	1.19	3.50
Bone surface	7.59	7.88	9.06	11.06	0.28	2.93
Brain	4.14	4.17	3.89	6.76	0.21	1.56
Salivary gland	7.43	7.87	10.29	11.40	0.78	2.88
Skin	9.46	10.13	11.30	12.89	0.68	3.86
Adrenals	7.50	9.21	12.66	20.40	0.25	3.55
Extrathor airways	7.81	7.16	8.03	16.04	0.89	3.22
Gall bladder	16.56	19.54	18.49	29.05	1.25	7.67
Heart	8.29	8.92	13.26	31.37	0.75	3.35
Kidneys	9.56	10.42	11.62	13.29	0.36	3.90
Lymphatic nodes	12.89	12.38	15.71	31.32	0.70	4.44
Muscle	9.61	10.11	11.53	11.07	0.48	3.78
Oral mucosa	8.45	10.93	8.52	6.76	0.41	2.88
Pancreas	12.50	13.63	17.49	21.57	0.65	5.32
Small intestine	16.81	17.34	24.30	24.03	0.81	6.98
Spleen	5.02	4.99	8.61	14.50	0.14	1.70
Thymus	11.03	7.86	13.12	0.00	0.57	3.41
Eye lens	9.14	9.29	7.72	24.45	0.01	0.36
Effective dose (μSv)	12.61	13.27	16.73	19.91	3.21	5.16

Table 3. Radiation dose to which organs are exposed at a distance of 50 cm

Organ doses D (T)	^{68}Ga	^{18}F	^{89}Sr	^{13}N	^{133}X	^{131}I
Red bone marrow	5.09	5.23	5.74	5.57	0.25	1.82
Colon	8.41	8.64	8.23	10.68	1.16	3.37
Lung	6.20	6.27	5.89	9.16	0.64	2.24
Stomach	6.65	7.76	7.80	11.32	0.99	2.41
Breast	9.60	10.97	12.29	4.22	1.21	4.81
Remainder	6.27	6.39	6.19	8.43	0.69	2.46
Ovaries	9.11	9.76	10.58	8.47	0.87	4.47
Bladder	7.59	9.04	9.64	9.55	0.92	3.01
Oesophagus	5.12	6.48	5.36	7.20	0.57	1.40
Liver	7.52	7.91	7.31	9.61	0.78	3.15
Thyroid	6.26	6.81	8.29	9.69	0.36	2.76
Bone surface	4.71	4.87	4.89	5.73	1.05	1.81
Brain	2.93	3.07	3.00	4.47	0.23	1.02
Salivary gland	5.17	5.75	4.84	5.83	0.40	2.37
Skin	5.54	5.81	5.85	6.54	0.96	2.20
Adrenals	4.72	6.91	4.28	5.63	0.22	1.72
Extrathor airways	5.65	5.29	5.89	7.20	0.57	2.83
Gall bladder	6.49	6.56	5.08	11.32	0.99	3.55
Heart	5.77	5.91	7.32	13.46	0.94	2.61
Kidneys	4.60	4.88	5.16	5.96	0.30	1.76
Lymphatic nodes	6.98	6.84	7.11	13.46	0.94	3.07
Muscle	5.49	5.74	5.94	5.89	0.57	2.22
Oral mucosa	4.90	6.41	5.43	4.47	0.23	1.44
Pancreas	7.08	6.89	8.28	9.59	0.75	3.23
Small intestine	8.16	8.61	9.18	9.51	0.91	3.44
Spleen	3.02	3.44	4.02	6.23	0.31	1.17
Thymus	9.16	7.42	4.60	0.00	0.00	2.44
Eye lens	0.00	3.39	0.00	28.01	4.76	0.00
Effective dose (μSv)	7.04	7.62	7.79	8.54	1.77	2.90

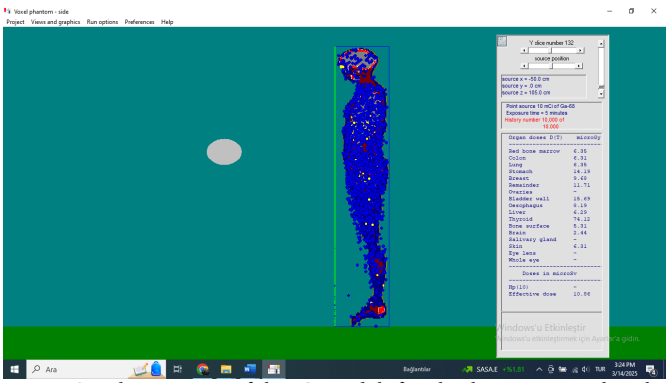

Figure. Simulation image of the ICRP adult female phantom created in the VMC program

Generally, the radiation dose received by organs significantly decreases as the distance increases. For instance, for red bone marrow, ^{89}Sr at a distance of 25 cm results in a dose of 12.23 μSv, while at distances of 50, 100, and 150 cm, this dose decreases to 5.74 μSv, 2.26 μSv, and 1.01 μSv, respectively. Similarly, for the stomach, ^{13}N delivers a dose of 29.05 μSv

Table 4. Radiation dose to which organs are exposed at a distance of 100 cm

Organ doses D (T)	^{68}Ga	^{18}F	^{89}Sr	^{13}N	^{133}X	^{131}I
Red bone marrow	2.03	2.00	2.26	2.20	0.10	0.76
Colon	3.10	3.10	3.03	3.28	0.35	1.15
Lung	2.59	2.79	2.47	3.00	0.23	1.15
Stomach	2.72	2.50	3.14	3.22	0.27	0.94
Breast	2.83	4.24	1.50	2.14	0.65	1.84
Remainder	2.36	2.64	2.32	2.96	0.24	0.93
Ovaries	3.16	3.50	4.27	3.88	0.68	1.52
Bladder	3.53	3.94	3.46	3.94	0.36	1.51
Oesophagus	1.79	2.85	2.04	2.75	0.19	1.20
Liver	2.69	2.81	2.44	3.13	0.27	1.01
Thyroid	3.56	2.85	2.08	0.60	0.70	1.08
Bone surface	2.13	2.18	2.16	2.30	0.43	0.85
Brain	1.51	1.67	1.45	2.03	0.10	0.57
Salivary gland	1.91	2.64	2.01	2.39	0.15	1.25
Skin	2.39	2.48	2.39	2.60	0.37	0.91
Adrenals	0.92	2.51	0.66	0.99	0.00	1.11
Extrathor airways	2.17	2.13	1.72	2.75	0.19	1.02
Gall bladder	2.82	2.12	1.58	3.22	0.27	0.91
Heart	2.31	3.00	2.82	4.41	0.34	1.12
Kidneys	2.08	1.92	1.79	1.91	0.14	1.23
Lymphatic nodes	2.51	2.55	2.84	4.41	0.34	0.94
Muscle	2.32	2.46	2.32	2.43	0.25	0.90
Oral mucosa	2.52	3.68	1.78	2.03	0.10	0.88
Pancreas	2.65	2.81	3.23	4.22	0.15	0.87
Small intestine	3.10	3.02	2.58	3.35	0.31	1.18
Spleen	0.98	1.38	1.65	1.95	0.12	0.26
Thymus	3.32	3.33	4.80	0.00	0.00	1.08
Eye lens	0.00	3.06	0.00	12.88	1.97	0.65
Effective dose (μSv)	2.72	2.94	2.50	2.84	0.91	1.16

Table 5. Radiation dose to which organs are exposed at a distance of 150 cm

Organ doses D (T)	^{68}Ga	^{18}F	^{89}Sr	^{13}N	^{133}X	^{131}I
Red bone marrow	1.25	1.33	1.01	1.31	0.06	0.49
Colon	1.65	1.61	1.53	1.80	0.18	0.65
Lung	1.31	1.56	1.22	1.48	0.12	0.55
Stomach	1.56	1.74	1.40	1.64	0.15	0.67
Breast	1.72	1.30	0.75	0.82	0.23	0.51
Remainder	1.27	1.41	1.26	1.43	0.13	0.57
Ovaries	2.36	1.87	2.35	1.54	0.29	0.49
Bladder	1.47	1.52	1.74	1.62	0.20	0.69
Oesophagus	1.56	1.17	1.43	1.28	0.14	0.69
Liver	1.56	1.44	1.04	1.45	0.13	0.57
Thyroid	2.39	1.17	0.29	1.63	0.18	0.72
Bone surface	1.29	1.35	0.97	1.22	0.24	0.52
Brain	0.86	1.05	0.87	1.00	0.06	0.36
Salivary gland	0.97	1.19	1.15	1.14	0.10	0.45
Skin	1.38	1.49	1.16	1.41	0.20	0.55
Adrenals	0.91	1.39	0.00	0.39	0.11	0.32
Extrathor airways	1.03	1.30	1.43	1.28	0.14	0.38
Gall bladder	1.08	1.41	1.40	1.64	0.15	0.55
Heart	1.34	1.40	1.80	2.17	0.17	0.56
Kidneys	1.02	0.95	0.83	0.98	0.05	0.34
Lymphatic nodes	1.79	1.67	1.80	2.17	0.17	0.73
Muscle	1.34	1.41	1.09	1.27	0.13	0.54
Oral mucosa	1.03	1.45	0.87	1.00	0.06	0.47
Pancreas	1.44	1.60	1.22	2.05	0.10	0.55
Small intestine	1.57	1.73	1.24	1.50	0.16	0.73
Spleen	0.91	1.19	1.07	1.12	0.06	0.45
Thymus	1.44	0.98	0.00	0.00	0.00	1.00
Eye lens	0.00	0.00	3.36	2.90	1.29	0.00
Effective dose (μSv)	1.56	1.49	1.30	1.46	0.14	0.58

at 25 cm, whereas at 50 cm, 100 cm, and 150 cm, this value decreases to 11.32 μSv, 3.22 μSv, and 1.64 μSv, respectively. In Table 2, the doses received by the ovaries when exposed to ^{68}Ga, ^{18}F, ^{89}Sr, ^{13}N, ^{133}Xe and ^{131}I sources at 25 cm are obtained as 17.51 μSv, 18.18 μSv, 23.15 μSv, 16.49 μSv, 1.48 μSv, and 6.89 μSv, respectively. Additionally, in Table 1, the doses received by the breast when exposed to ^{68}Ga, ^{18}F, ^{89}Sr, ^{13}N, ^{133}Xe and ^{131}I sources at 25 cm are found to be 18.06 μSv, 18.86 μSv, 20.84 μSv, 12.23 μSv, 1.98 μSv, and 8.10 μSv, respectively. The highest dose exposure in the ovaries and breast organs was obtained with the ^{89}Sr radionuclide. The effective doses at a distance of 25 cm for ^{68}Ga, ^{18}F, ^{89}Sr, ^{13}N, ^{133}Xe and ^{131}I sources were found to be 12.61 μSv, 13.27 μSv, 16.73 μSv, 19.91 μSv, 3.21 μSv, and 5.16 μSv, respectively.

Table 3 presents the radiation doses received by the ovaries and the mammary gland at a distance of 50 cm from various radioactive sources. The ovaries, when exposed to ^{68}Ga, ^{18}F, ^{89}Sr, ^{13}N, ^{133}Xe and ^{131}I sources, received doses of 9.11 μSv, 9.76 μSv, 10.58 μSv, 8.47 μSv, 0.87 μSv, and 4.47 μSv, respectively. At the same distance, the mammary gland received doses of 9.60 μSv, 10.97 μSv, 12.29 μSv, 4.22 μSv, 1.21 μSv, and 4.81 μSv from the same respective sources. The effective doses at 50 cm for ^{68}Ga, ^{18}F, ^{89}Sr, ^{13}N, ^{133}Xe and ^{131}I sources were determined to be 7.04 μSv, 7.62 μSv, 7.79 μSv, 8.54 μSv, 1.77 μSv, and 2.90 μSv, respectively.

Table 4 details the radiation doses received by the ovaries, mammary gland, and kidneys at a distance of 100 cm from various radioactive sources. The ovaries, when exposed to ^{68}Ga, ^{18}F, ^{89}Sr, ^{13}N, ^{133}Xe and ^{131}I sources, received doses of 3.16 μSv, 3.50 μSv, 4.27 μSv, 3.88 μSv, 0.68 μSv, and 1.52 μSv, respectively. At the same distance, the mammary gland received doses of 2.83 μSv, 4.24 μSv, 1.50 μSv, 2.14 μSv, 0.65 μSv, and 1.84 μSv from the same respective sources. The kidneys, another radiation-sensitive organ, received doses of 2.08 μSv, 1.92 μSv, 1.79 μSv, 1.91 μSv, 0.14 μSv, and 1.23 μSv from ^{68}Ga, ^{18}F, ^{89}Sr, ^{13}N, ^{133}Xe and ^{131}I sources, respectively, at a distance of 100 cm. The effective doses at 100 cm for ^{68}Ga, ^{18}F, ^{89}Sr, ^{13}N, ^{133}Xe and ^{131}I sources were determined to be 2.72 μSv, 2.94 μSv, 2.50 μSv, 2.84 μSv, 0.91 μSv, and 1.16 μSv, respectively.

Table 5 further presents the radiation doses received by the ovaries, mammary gland, and kidneys at a distance of 150 cm from the same radioactive sources. At 150 cm, the ovaries received doses of 2.36 µSv, 1.87 µSv, 2.35 µSv, 1.54 µSv, 0.29 µSv, and 0.49 µSv, respectively, while the mammary gland received doses of 1.72 µSv, 1.30 µSv, 0.75 µSv, 1.43 µSv, 0.13 µSv, and 0.51 µSv. The effective doses at 150 cm for ^{68}Ga, ^{18}F, ^{89}Sr, ^{13}N, ^{133}Xe and ^{131}I sources were determined to be 1.56 µSv, 1.49 µSv, 1.30 µSv, 1.46 µSv, 0.14 µSv, and 0.58 µSv, respectively. At 150 cm, the kidneys received doses of 1.02 µSv, 0.95 µSv, 0.83 µSv, 0.98 µSv, 0.05 µSv, and 0.34 µSv from the same radioactive sources.

Analysis of organ doses from radionuclides reveals that certain organs receive higher doses from specific radionuclides. The stomach exhibited the highest dose from ^{13}N (29.05 µSv) and ^{89}Sr (20.53 µSv). The large intestine was also exposed to elevated doses from ^{13}N (26.17 µSv) and ^{89}Sr (22.19 µSv). The gallbladder received the highest dose from ^{13}N (29.05 µSv). The thyroid gland (32.64 µSv) was among the organs receiving the highest dose from ^{13}N. The heart (31.37 µSv) and lymph nodes (31.32 µSv) also experienced significant doses from ^{13}N. These findings indicate that ^{13}N and ^{89}Sr radionuclides, in particular, induce concentrated doses in specific organs. When comparing organ doses from various radionuclides, ^{13}N and ^{89}Sr were generally identified as the radionuclides imparting the highest radiation doses. Conversely, ^{133}Xe and ^{131}I radionuclides typically exhibited the lowest doses. The doses received by the thyroid and red bone marrow from ^{133}Xe at 25 cm were 1.19 µSv and 0.33 µSv, respectively. The highest dose from ^{131}I was observed in the gallbladder (7.67 µSv), with other organs generally receiving less than 5 µSv. Notably, the radiation dose received by organs significantly decreased as distance increased. For instance, the ^{13}N dose to the stomach decreased from 29.05 µSv at 25 cm to 1.64 µSv at 150 cm. Similarly, the ^{13}N dose to the thyroid decreased from 32.64 µSv to 1.63 µSv, and the ^{13}N dose to the lymph nodes decreased from 31.37 µSv to 2.17 µSv. These values emphasize the critical importance of maintaining distance for clinical radiation safety.

In this study, average dose rate measurements were conducted at varying distances for different radionuclides at a dose of 10 mCi (Table 6). The results obtained demonstrate that the dose rate decreases inversely proportional to distance. This is an expected phenomenon and aligns with the fundamental principles of radiation physics. While the dose rate is high at close proximity to the source, it significantly diminishes with increasing distance. Notable differences were observed among the radionuclides. ^{13}N and ^{18}F radionuclides exhibited the highest dose rates across all distances, whereas the ^{89}Sr isotope displayed the lowest dose rate. This variation stems from the characteristic properties of the radionuclides. For instance, the emission of high-energy gamma rays by ^{13}N and ^{18}F contributes to their elevated dose rates, while the emission of low-energy beta particles by ^{89}Sr results in its lower dose rate.

Table 6. For 10 mCi dose, average dose rate measurements at different distances (mR/h)

	25 cm	50 cm	100 cm
^{68}Ga	10.30	2.57	0.64
^{18}F	91.22	22.78	5.68
^{89}Sr	0.076	0.019	0.004
^{13}N	94.30	23.55	5.87
^{133}X	7.76	1.94	0.48
^{131}I	32.68	8.16	2.03

DISCUSSION

In this study, the radiation doses delivered by different radionuclides to organs and the body at various distances were investigated. The results indicate that factors such as radionuclide type and distance significantly affect organ doses. These findings highlight the critical importance of radionuclide selection and distance control in radiation safety practices. Specifically, it was observed that the isotopes ^{13}N and ^{89}Sr delivered the highest doses to certain organs, whereas ^{133}Xe and ^{131}I exhibited lower dose levels. The organ doses obtained using the VMC dose calculation program were generally consistent with those reported in the literature.[23,24] For instance, ^{18}F-FDG is one of the most commonly used radiopharmaceuticals in PET imaging, particularly in oncological, neurological, and cardiological applications. Our study also demonstrated that ^{18}F resulted in significant doses in multiple organs. Similarly, ^{131}I is widely used in the treatment of thyroid cancer and hyperthyroidism, leading to high doses in thyroid tissue. Our findings confirmed that the thyroid dose of ^{131}I was higher than that of other organs. Previous studies have shown that high-energy beta- and gamma-emitting radionuclides increase organ doses.[1,2,23] Likewise, several studies have emphasized that maintaining an adequate distance is a crucial factor in reducing radiation doses.[9,23] In this context, applying the ALARA principle is essential for both patients and nuclear medicine personnel. An analysis of the dose distribution revealed that the thyroid, stomach, and lymph nodes were exposed to high radiation doses. This outcome may be attributed to the biological characteristics and vascularization levels of these organs. The literature suggests that highly vascularized organs tend to accumulate more radioisotopes.[23-25] Therefore, additional protective measures should be considered for these organs in clinical applications.

Limitations

The VMC dose calculation program and the Rad Pro Calculator online tool used in this study provided a high level of accuracy in radiation dose calculations. However, simulation-based studies have certain limitations. Firstly, these simulations were performed using idealized phantom models, which do not fully reflect individual patient variability. Additionally, environmental factors, patient metabolism, and radioisotope bioavailability can influence dose distribution in real clinical applications.

CONCLUSION

In this study, the radiation doses delivered by different radionuclides to organs and the body at specific distances were investigated. The findings indicate that radionuclide type and distance significantly affect organ doses. At a distance of 25 cm, ^{13}N gave the highest stomach dose of 29.05 µSv, while ^{13}Xe

showed the lowest dose values in most organs. At 25 cm the effective dose ranged from 3.21 μSv (^{13}Xe) to 19.91 μSv (^{13}N). At 150 cm all doses decreased significantly, with the highest effective dose being only 1.56 μSv (^{68}Ga). These quantitative findings reinforce the importance of maintaining distance and implementing protective measures in nuclear medicine environments. In particular, the isotopes ^{13}N and ^{89}Sr were found to deliver the highest doses to certain organs, whereas ^{133}Xe and ^{131}I exhibited lower dose levels. It was observed that maintaining distance significantly reduces radiation exposure levels. In this context, it was concluded that implementing the ALARA principle is of great importance, particularly for nuclear medicine personnel and patients. By providing direct dose comparisons under controlled simulation conditions, this research contributes a novel, dataset for six commonly used radionuclides in nuclear medicine. These insights can inform risk assessment, staff training, and protective measure development, leading to improved radiation safety protocols. The study's findings may contribute to the development of more effective protective measures to minimize radiation doses in clinical applications. Future studies incorporating more detailed analyses of individual patient variability and environmental factors will allow for a better understanding of radiation exposure.

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

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

Author Contributions

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

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Original Article

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A bibliometric analysis of the literature from the past to the present on the use of artificial intelligence in orthodontics and orthognathic surgery

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ABSTRACT

Aims: This study aims to investigate the publication characteristics of academic work centred around artificial intelligence (AI) in orthodontics and orthognathic surgery in detail.

Methods: In this analysis, the VOSviewer software and the Bibliometrix Biblioshiny R-package were employed for the purposes of bibliometric investigation and data visualisation.

Results: Between 1991 and 2024, 842 articles were published, averaging 12.33 citations per article. China topped the list with 200 articles, succeeded by the U.S. with 183 and South Korea with 121. Seoul National University authored the highest number of publications (47), succeeded by Peking University (36) and the University of North Carolina (34). Seoul National University (807) and the Catholic University of Leuven (567) ranked highest in citation impact. Jacobs Reinhilde was the most prolific author, with 22 publications, and alongside Dinggang Shen and Adriaan Van Gerven, had the greatest citation counts of 544, 491, and 476, respectively. The most used keywords were "artificial intelligence," "deep learning," "machine learning," "orthodontics," "convolutional neural network," "orthognathic surgery," "dentistry," "cephalometry," "CBCT," and "cephalometric analysis."

Conclusion: This bibliometric analysis illustrates that AI has swiftly become an expanding research subject in orthodontics and orthognathic surgery, attracting considerable interest from the scientific community. The thorough investigation indicates that AI is essential, especially in cephalometric evaluations, diagnostic procedures, and treatment strategies.

Keywords: Artificial intelligence, bibliometrics, orthodontics, orthognathic surgery

INTRODUCTION

Artificial intelligence (AI) refers to the capacity of machines to perform tasks that typically require human intelligence, such as learning, reasoning, and decision-making. First introduced as a concept in 1956, AI has since evolved into a transformative technology across a wide range of fields, including healthcare and dentistry.[1,2] One of AI's most powerful attributes is its ability to process and analyze vast datasets with exceptional speed and consistency.[3] In recent years, AI applications have emerged as promising tools for enhancing diagnostic accuracy, streamlining clinical workflows, and supporting decision-making in dental specialties.[4]

In orthodontics, AI has been applied to patient monitoring, skeletal age assessment, temporomandibular joint (TMJ) diagnostics, automated cephalometric landmark detection, treatment planning, and outcome evaluation.[5] These applications suggest that AI may significantly improve clinical efficiency and accuracy while reducing practitioners' administrative burdens.[6] Given the irreversible nature of many orthodontic and orthognathic procedures, which require high standards of diagnostic precision and individualized planning, AI can play a valuable role in consolidating clinical and radiographic data for more reliable assessment and treatment planning.[7,8]

Orthognathic surgery, in particular, demands comprehensive preoperative analysis due to the anatomical complexity and functional implications of the procedures involved. AI models have recently been employed in a variety of related tasks, including prediction of facial profile changes following orthognathic surgery,[9] estimation of intraoperative blood loss,[10] automated surgical planning using CBCT and intraoral scanning,[11] skeletal maturation assessment,[12] and detection of maxillofacial anomalies.[13]

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The increasing integration of AI into orthodontics and orthognathic surgery reflects the broader technological evolution across healthcare disciplines. As AI-driven research expands within these fields, there is a growing need to systematically evaluate the academic literature to understand the scope and trajectory of this emerging domain. A bibliometric study offers a rigorous method for analyzing publication trends, identifying key research themes, mapping citation patterns, and highlighting influential authors and institutions. Such an approach provides valuable insights into the current state and future directions of AI applications in orthodontics and orthognathic surgery.[14] Prior bibliometric studies in orthodontics have examined topics such as cleft lip and palate,[15] lingual orthodontics,[16] temporary anchorage devices,[17] and clear aligner treatments.[18] Alternatively, they have concentrated on the most-cited papers.[19]

The objective of the present study is to conduct a comprehensive bibliometric analysis of the literature concerning the use of AI in orthodontics and orthognathic surgery. We hypothesize that while both fields demonstrate increasing engagement with AI, orthodontics has received more research attention and integration of AI methodologies than orthognathic surgery. Through this analysis, we aim to identify publication trends, prominent contributors, and thematic developments to inform future research directions and support the clinical advancement of AI-assisted interventions in these domains.

METHODS

In accordance with the ethical standards governing research and the principles of the Declaration of Helsinki, no approval was required, as the study did not involve clinical studies or the use of patient data. That is why clinical trial number is not applicable.

In August 2024, a comprehensive literature search was conducted using the Web of Science (WoS) Core Collection database, originally established by the Institute for Scientific Information (ISI) and currently maintained by Clarivate Analytics. Prior to the final search on 1 August 2024, a screening process and a series of pilot searches were performed to optimize the search strategy. These initial searches were broadened and led to the identification of 3,069 records. The "all fields" option was selected during the electronic search to retrieve the maximum number of relevant entries. To ensure completeness, manual screening was also performed to enhance accuracy.

As a result of these pilot searches, a total of 3069 studies were found when ''artificial intelligen*'' OR ''deep learn*'' OR ''machine learn*'' OR ''convolutional neural network*'' OR ''CNN*'' OR ''Recurrent neural network*'' OR ''RNN*'' OR ''Fully Convolutional Network*'' OR ''FCN*'' OR ''artificial neural network*'' (all fields) and "orthod*" OR "cephal*" OR "craniofacial*" OR "maxillo*" OR "orthogn*" (all fields) was typed in the search bar to determine the publications to be included in the study. The document types were filtered to include "article," "proceeding paper," "review," and "early access."

Only English-language publications were considered. Titles and abstracts were screened first to assess eligibility. If eligibility could not be determined at this stage, full texts were reviewed. A single reviewer conducted article selection. Although this ensured consistency, the potential for selection bias is acknowledged. In future studies, inclusion of multiple independent reviewers is recommended.

Following the filtering and screening process, a total of 842 articles were selected for analysis. The VOSviewer software (developed by Leiden University's Centre for Science and Technology Studies) and the Bibliometrix Biblioshiny R-package (available via https://www.bibliometrix.org/home/index.php/layout/biblioshiny) were employed in this analysis for the purposes of bibliometric investigation and data visualisation.

The VOSviewer software (version 1.6.20) was downloaded on 30 September 2023 and has since been used by our team in multiple bibliometric studies. For the purposes of this particular study, the literature search and article selection were carried out in August 2024. Although the software installation predates the current study, all visualizations and analyses included in this manuscript were generated using data from the August 2024 search. This clarification is provided to address any potential confusion about the timeline of data collection and analysis.

The VOSviewer enables the production of maps of authors or journals based on co-citation data, as well as maps of keywords based on co-occurrence data. The software provides an extensive viewer for the detailed examination of bibliometric maps.[20] Bibliographic data exported in ".txt" format using a marked list were opened in Microsoft Excel (Microsoft, Inc., Redmond, Washington). We cleaned the dataset to resolve formatting issues and inconsistencies. For example, variations in author names such as "Cevidanes, Lucia," "Cevidanes, Lucia H.S.," and "Cevidanes, Lucia Soares" were merged to ensure accurate representation. Author data were cross-verified using the Web of Science and, when needed, Scopus or general web searches. Similarly, inconsistent country names-e.g., "Turkey" vs. "Turkiye"-were standardized. After these corrections, the cleaned dataset was exported again and visualized in VOSviewer.

An innovative open-source tool for the comprehensive examination of scientific networks is the Biblioshiny R-pack. The program facilitates the implementation of a proposed workflow for bibliometric analysis. The suggested tool is flexible, amenable to improvement, and compatible with other statistical R packages, given that it was created with the R programming language. Consequently, it constitutes an invaluable instrument in an ever-changing discipline such as bibliometrics.[21] The data was exported in the '.bib' file format and then subjected to processing by the program, which yielded the generation of visuals.

The Microsoft Excel program was employed for the purpose of data tabulation.

RESULTS

Growth in Publications

A total of 842 articles were obtained for review concerning the application of AI in the domains of orthodontics and orthognathic surgery. The annual growth rate of publications was relatively stable from 1991 to 2016. Nevertheless, there was an appreciable surge in the volume of publications from 2017 to 2024. From January 1 to August 1, 2024, a total of 114 articles were published (Figure 1). The articles in question have been referenced a total of 10,381 times, of which 6,029 were not self-citations. The average number of citations per article was 12.33.

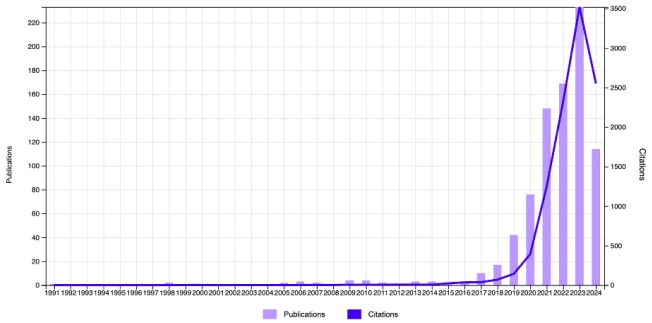

Figure 1. The quantity of publications and corresponding citations, organized by year

Countries/Regions and Institutions

A total of 73 countries or regions published at least one article on the topic of AI in orthodontics and orthognathic surgery between the years 1991 and 2024. China has published the greatest number of articles on the subject, with 200 articles, followed by the United States and South Korea, which have published 183 and 121 articles, respectively. Moreover, these countries were the recipients of the greatest number of citations. A collaboration map of countries on this subject, together with a list of the five most prolific countries, is provided in Figure 2. In terms of institutional affiliations, there were notable examples of robust collaborative relationships, including those with Seoul National University, Ulsan University, and Kyungpook National University (Figure 3A). Seoul National University published the greatest number of papers, with a total of 47, followed by Peking University and the University of North Carolina, which published 36 and 34 papers, respectively. With regard to the analysis of citation figures, Seoul National University and the Catholic University of Leuven were the most highly cited universities, with respective figures of 807 and 567. Although Seoul National University and the Catholic University of Leuven are among the most influential institutions in their respective fields, it has been observed that they do not engage in collaboration (Figure 3B). The top five most prolific institutions are represented in Figure 3C.

Authors

The author profiles extracted from the publications were subjected to analysis with the aim of identifying the most influential scholars in the field of AI in orthodontics and

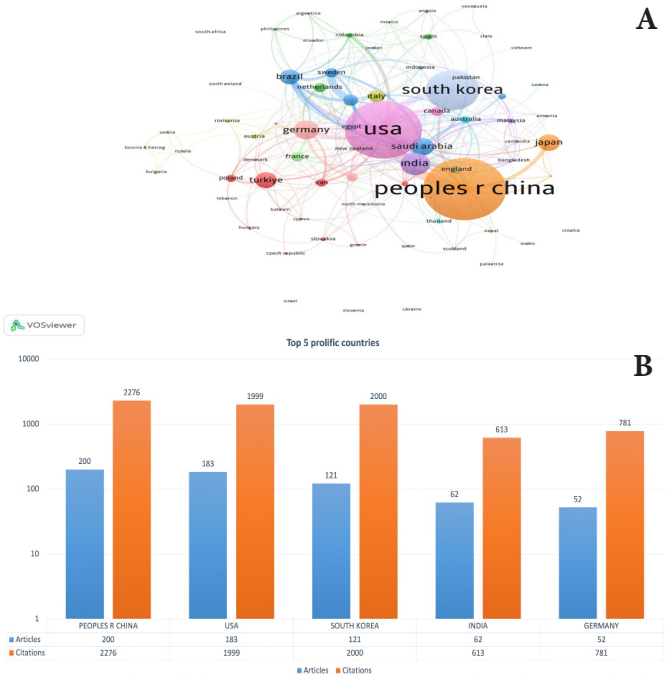

Figure 2. A) The collaboration map of countries on this subject B) The five countries with the highest rates of productivity

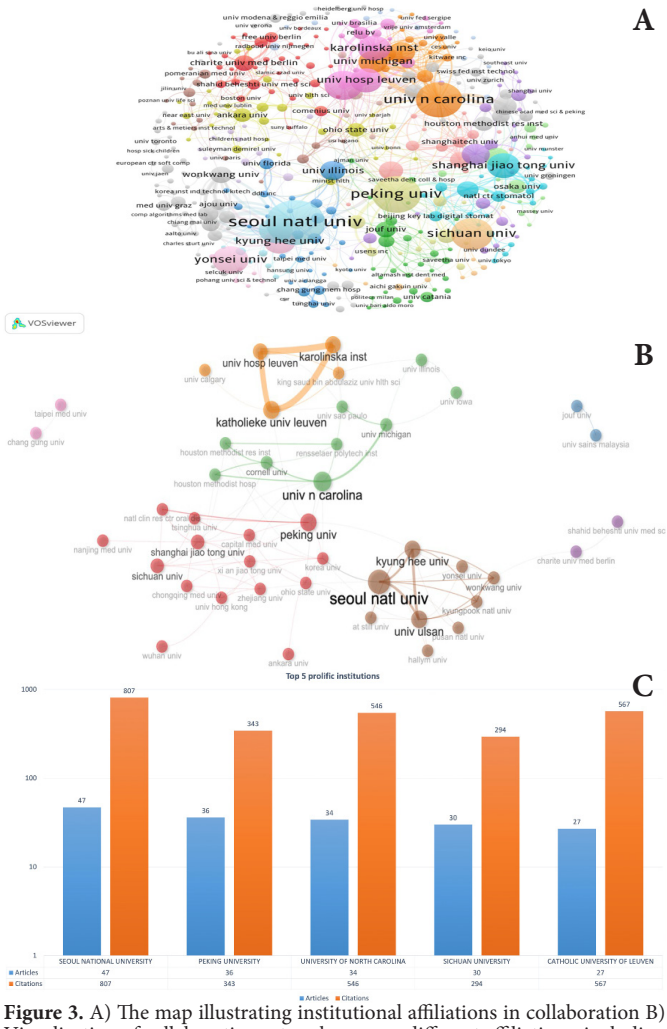

Figure 3. A) The map illustrating institutional affiliations in collaboration B) Visualization of collaborative networks among different affiliations, including Seoul National University and the Catholic University of Leuven C) The five most productive institutions

orthognathic surgery. The seven most prolific authors are presented in Figure 4A. The most prolific author was Jacobs, Reinhilde (Belgium, n. 22), followed by Xia, James J. (USA, n. 20), and Xu, Tianmin (China, n. 20). With regard to the attention paid to their work by other authors, Jacobs, Reinhilde; Shen, Dinggang; and Van Gerven, Adriaan, have had the most significant impact on this field, having been cited 544, 491, and 476 times, respectively. The findings suggest that the majority of collaborating authors were from the same country or region. A notable degree of collaboration in Figure 4B was evident between the following research teams: Xia, James J., and Deng, Hannah H; Xu, Tianmin, and Pei, Yuru; and Lucia, Cevidanes, and Jonas, Bianchi.

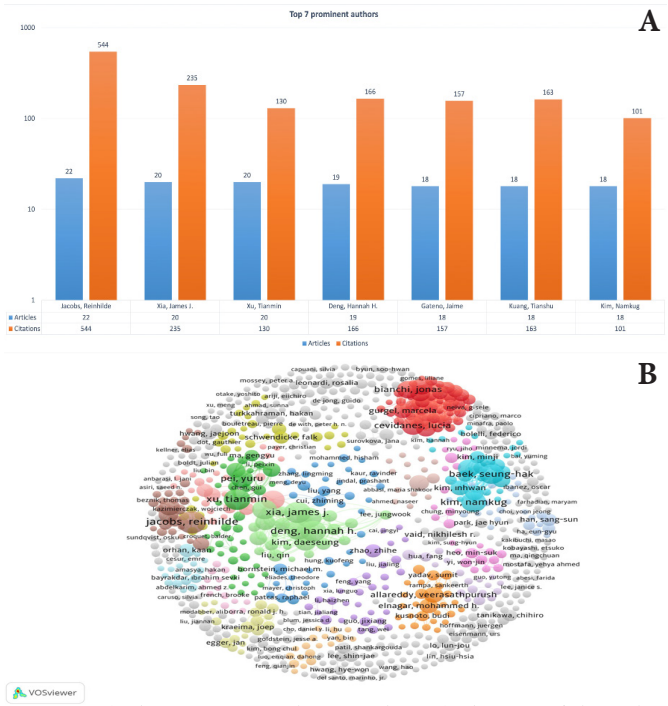

Figure 4. A) The seven top-producing authors B) The map of the author collaboration on this topic

Articles

The most highly cited publications provide readers with a comprehensive overview of the development and current status of a field of study, offering guidance to subsequent investigators and influencing the direction of ongoing research. Table presents the 25 most frequently cited papers in this context.

Journals

Figure 5 depicts the five most prolific journals, as determined by the number of publications and citations. The three journals with the highest number of publications were Scientific Reports, Orthodontics & Craniofacial Research, and Diagnostics, with respective publication numbers of 42, 40, and 30. With regard to the number of citations, the most influential journals were Medical Image Analysis, Scientific Reports, and the Journal of Dentistry, with 647, 554, and 552 citations, respectively.

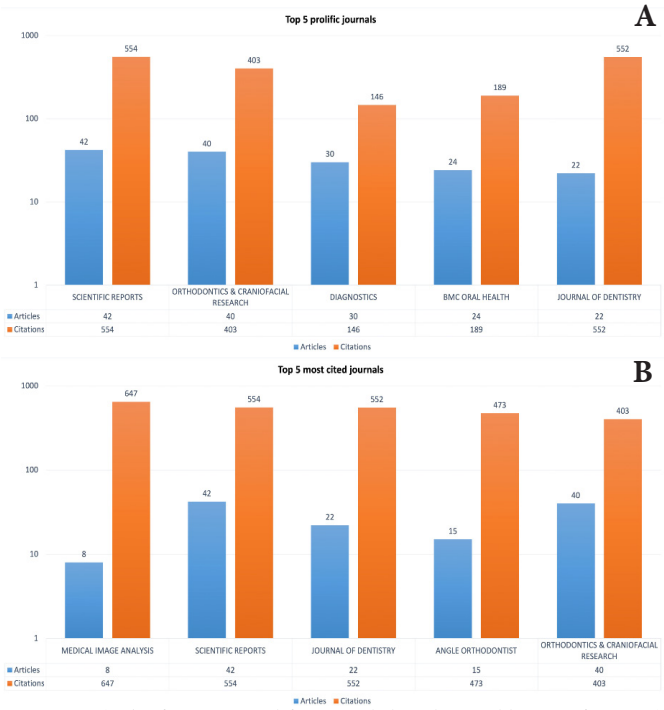

Figure 5. A) The five most prolific journals based on publication figures B) The five most prolific journals considering citation counts

Co-citation References

The co-citation network in Figure 6 displays references cited together at least 30 times. This analysis revealed key studies that have shaped interdisciplinary links between orthodontics, radiology, and AI applications. Central nodes represent foundational works frequently co-cited in the literature, highlighting their continued relevance to the field.

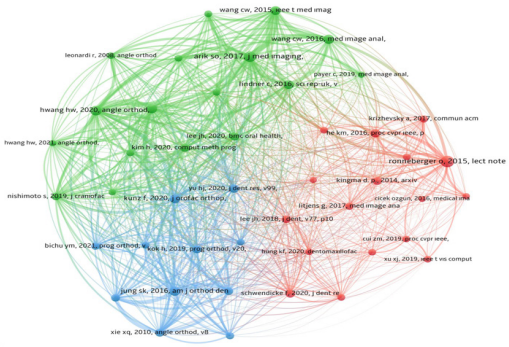

Figure 6. The co-citation reference network map of citations cited a minimum of thirty times

Keywords

The most frequently occurring keywords were "artificial intelligence," "deep learning," "machine learning," "orthodontics," "convolutional neural network," "orthognatic surgery," "dentistry," "cephalometry," "cbct," and "cephalometric analysis" (Figure 7). The results revealed that AI exhibited the highest occurrence and total link strength. In light of the recent proliferation of publications on the subject of AI in orthodontics and orthognathic surgery, particularly in the period following 2019, we present in Figure 8 a map of

Table. Top 25 most frequently cited articles

Title	Author	Sources	Publication year	Total citations	Average per year	Type of study
Deep learning for automated skeletal bone age assessment in X-Ray images	Spampinato et al.[32]	Medical Image Analysis	2017	264	33	Article
Convolutional neural networks for dental image diagnostics: a scoping review	Schwendicke et al.[33]	Journal of Dentistry	2019	192	32	Review
Integrating spatial configuration into heatmap regression based CNNs for landmark localization	Payer et al.[34]	Medical Image Analysis	2019	185	30.83	Article
Developments, application, and performance of artificial intelligence in dentistry-a systematic revie	Khanagar et al.[35]	Journal of Dental Sciences	2021	180	45	Review
Fully automated quantitative cephalometry using convolutional neural networks	Arik et al.[36]	Journal of Medical Imaging	2017	157	19.63	Article
The use and performance of artificial intelligence applications in dental and maxillofacial radiology: a systematic review	Hung et al.[37]	Dentomaxillofacial Radiology	2020	149	29.8	Review
Deep learning in medical image analysis: a third eye for doctors	Fourcade A, Khonsari RH.[38]	Journal of Stomatology Oral and Maxillofacial Surgery	2019	129	21.5	Article; Proceedings Paper
Automated identification of cephalometric landmarks: part 1-comparisons between the latest deep-learning methods YOLOV3 and SSD	Park et al.[39]	Angle Orthodontist	2019	114	19	Article
Automated identification of cephalometric landmarks: part 2- might it be better than human?	Hwang et al.[40]	Angle Orthodontist	2020	108	21.6	Article
Artificial intelligence in orthodontics evaluation of a fully automated cephalometric analysis using a customized convolutional neural network	Kunz et al.[41]	Journal of Orofacial Orthopedics	2020	106	21.2	Article
3D tooth segmentation and labeling using deep convolutional neural networks	Xu et al.[42]	IEEE Transactions on Visualization and Computer Graphics	2019	101	16.83	Article
Artificial neural network modeling for deciding if extractions are necessary prior to orthodontic treatment	Xie et al.[43]	Angle Orthodontist	2010	92	6.13	Article
Automated skeletal classification with lateral cephalometry based on artificial intelligence	Yu et al.[44]	Journal of Dental Research	2020	87	17.4	Article
A fully automatic AI system for tooth and alveolar bone segmentation from cone-beam CT images	Cui et al.[45]	Nature Communications	2022	86	28.67	Article
Automated cephalometric landmark detection with confidence regions using Bayesian convolutional neural networks	Lee et al.[46]	BMC Oral Health	2020	80	16	Article
Deep geodesic learning for segmentation and anatomical landmarking	Torosdagli et al.[47]	IEEE Transactions on Medical Imaging	2019	80	13.33	Article
Applying artificial intelligence to assess the impact of orthognathic treatment on facial attractiveness and estimated age	Patcas et al.[48]	International Journal of Oral and Maxillofacial Surgery	2019	78	13	Article
Impact of artificial intelligence on dental education: a review and guide for curriculum update	Thurzo et al.[49]	Education Sciences	2023	77	38.5	Review
Towards a fully automated diagnostic system for orthodontic treatment in dentistry	Murata et al.[50]	2017 IEEE 13th International Conference on E-Science (E-Science)	2017	77	9.63	Proceedings Paper
Bone age assessment with various machine learning techniques: a systematic literature review and meta-analysis	Dallora et al.[51]	PloS One	2019	76	12.67	Review
Deep multi-scale mesh feature learning for automated labeling of raw dental surfaces from 3D intraoral scanners	Lian et al.[52]	IEEE Transactions on Medical Imaging	2020	74	14.8	Article
Usage and comparison of artificial intelligence algorithms for determination of growth and development by cervical vertebrae stages in orthodontics	Kök et al.[53]	Progress in Orthodontics	2019	74	12.33	Article
Automatic classification and segmentation of teeth on 3D dental model using hierarchical deep learning networks	Tian et al[54]	IEEE Access	2019	74	12.33	Article
Orthodontic treatment planning based on artificial neural networks	Li et al.[55]	Scientific Reports	2019	73	12.17	Article
TSegNet: an efficient and accurate tooth segmentation network on 3D dental model	Cui et al.[56]	Medical Image Analysis	2021	72	18	Article

CNNs: Convolutional neural networks, YOLOV3: You only look once version 3, SSD: Solid state disk, AI: Artificial intelligence, CT: Computed tomography

the co-occurrence network of keywords used on this topic, as well as a word cloud of keywords. Additionally, we utilized a longitudinal visual associated with the keywords in **Figure 9**, as evaluating trend topics related to keywords is crucial in identifying potential research gaps or areas for future exploration.

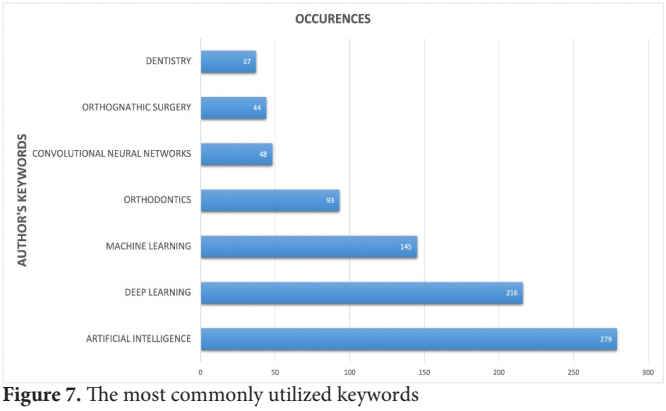

Figure 7. The most commonly utilized keywords

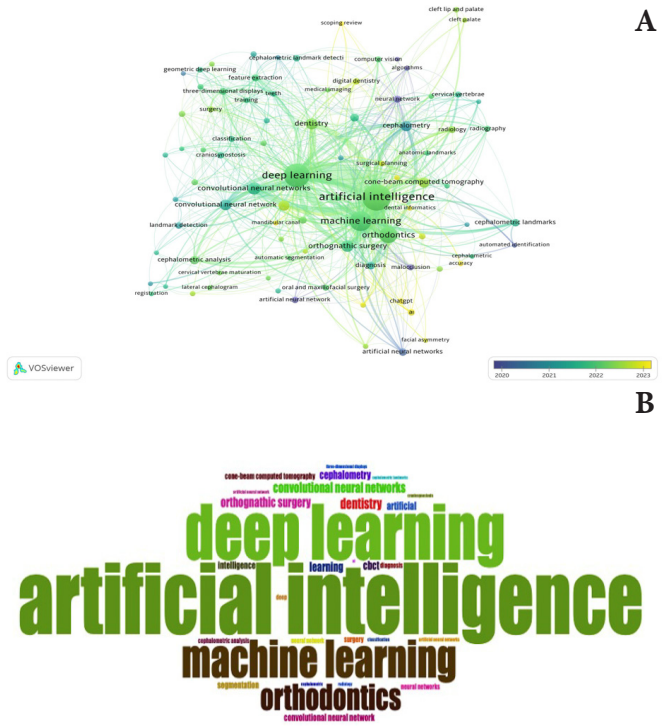

Figure 8. A) The co-occurrence network map of keywords B) The word cloud of keywords

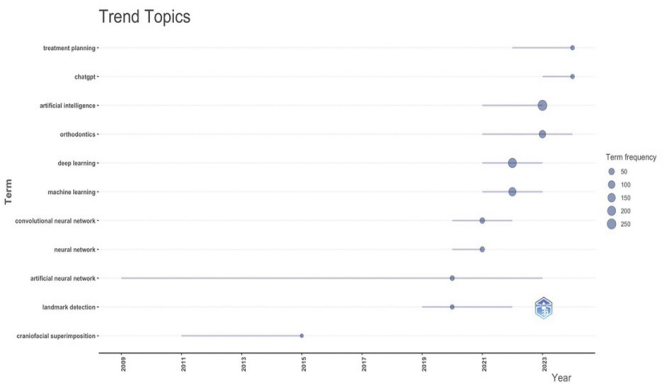

Figure 9. A longitudinal visualization of keyword trends

Thematic Map

Thematic mapping, shown in **Figure 10**, identified the main conceptual clusters within the literature. These clusters reflect core research areas such as diagnostic imaging, treatment planning, and cephalometric analysis.

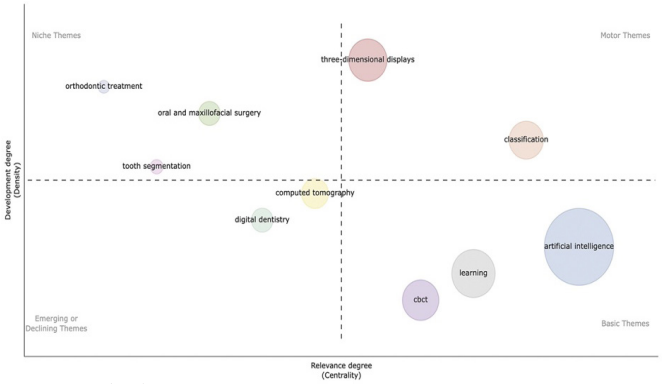

Figure 10. The thematic map

DISCUSSION

This bibliometric study provides meaningful insights into the expanding role of AI in orthodontics and orthognathic surgery. The marked increase in AI-related publications after 2017 suggests a shift from theoretical exploration to more mature, clinically focused applications. AI systems-particularly those using machine learning algorithms-have been employed in various tasks such as automatic cephalometric analysis, dental segmentation, and three-dimensional (3D) imaging.[22] In addition, they support automated anatomical landmark detection and growth and development assessment,[23] as well as evaluations of upper airway obstruction, decision-making for extractions, remote consultations, and clinical documentation.[24] More recent applications involve treatment outcome prediction, including postoperative facial profile and symmetry, determination of surgical necessity, perioperative blood loss estimation, and surgical simulation.[25]

By evaluating the publication patterns, research focuses, and methodological approaches in the literature, this bibliometric study contributes to a better understanding of how AI technologies are shaping clinical workflows and advancing treatment planning in orthodontics and orthognathic surgery.

This bibliometric analysis reveals notable shifts in the trajectory of research on AI in orthodontics and orthognathic surgery. Between 1991 and 2016, the relatively modest growth in publications suggests that AI applications in these fields were largely in an exploratory phase. However, the surge in research output from 2017 onward signals a transition toward clinically oriented and evidence-driven investigations. This increased scholarly interest parallels broader advancements in AI capabilities, including improvements in diagnostic precision, treatment simulation, and prognosis prediction.[26-28] These developments underscore AI's growing status as a supportive tool in dental practice, capable of transforming traditional workflows and enhancing clinical efficiency.

Several factors likely contributed to this post-2017 escalation in publications. First, technological innovations-particularly in deep learning and big data processing-have made AI tools more accessible and adaptable for dental professionals.[29] Second, the increasing availability of large-scale annotated datasets and high-performance computing has enabled the

development of more sophisticated and generalizable models. Finally, the widespread integration of AI across other medical disciplines may have encouraged researchers in dentistry to explore its utility in orthodontic and surgical contexts.

The citation analysis reinforces the scientific impact of this body of work. With a total of 10,381 citations and an average of 12.33 citations per article, the literature demonstrates both depth and influence. Notably, 6,029 of these were non-self-citations, suggesting that AI-focused studies are being actively referenced by independent researchers, further affirming their contribution to the advancement of knowledge and practice.[30] These findings reflect a growing consensus within the dental community regarding the value of AI not only in research but also in real-world clinical integration.

The distribution of publications from 1991 to 2024 in the field of AI in orthodontics and orthognathic surgery highlights important geographical and institutional patterns. Contributions from 73 countries demonstrate the global reach and growing international relevance of AI in dental research. Among them, China, the United States, and South Korea stand out as the most prolific, publishing 200, 183, and 121 articles, respectively. This productivity reflects not only their scientific infrastructure but also strategic investments in AI-driven healthcare innovation. China's leadership may be attributed to national policy initiatives, public-private collaboration networks, and a strong emphasis on digital transformation in healthcare.[31] The United States has similarly benefited from robust research ecosystems and sustained federal and private funding. South Korea's position reinforces its commitment to integrating AI technologies across healthcare sectors through coordinated efforts among academia, government, and industry.

Institutional analysis reveals that Seoul National University is the most productive institution, with 47 publications. It is followed by Peking University (36 publications) and the University of North Carolina (34 publications). These institutions have distinguished themselves not only through output but also through influence, as seen in high citation counts-807 for Seoul National University and 567 for the Catholic University of Leuven. The prominence of these institutions suggests their central role in shaping the research agenda and advancing methodological innovations in the use of AI within orthodontics and orthognathic surgery. However, the findings also highlight limited cross-institutional collaboration, which represents an opportunity for greater knowledge exchange and interdisciplinary synergy on a global scale.

Among the most influential studies identified in this bibliometric analysis, several have significantly shaped the application of AI in orthodontics and orthognathic surgery. One of the top-cited works by Spampinato et al.[32] applied deep learning techniques for skeletal bone age assessment in radiographic images. The study demonstrated that AI could improve diagnostic accuracy and reproducibility in growth evaluation, a key consideration in pediatric orthodontics.

Another important contribution is the scoping review by Schwendicke et al.,[33] which synthesized research on convolutional neural networks (CNNs) for dental image diagnostics across multiple domains, including endodontics, periodontology, and radiology. The review highlighted the versatility of CNNs and their growing role in image interpretation and clinical decision-making.

Additionally, the work by Payer et al.[34] introduced a heatmap-based CNN architecture for anatomical landmark localization using small datasets. This approach demonstrated strong performance in cephalometric applications, suggesting that AI can achieve high accuracy even under data constraints-a common challenge in medical image analysis.

Several high-impact studies identified in this analysis further illustrate the expanding scope of AI applications in dentistry and orthodontics. Khanagar et al.[35] conducted a comprehensive systematic review of AI technologies in dental practice, highlighting their use in diagnosis, treatment planning, and outcome prediction across diverse specialties. This study emphasized that AI has become a central component of clinical decision support systems, particularly due to its accuracy and reproducibility.

Arık et al.[36] explored the use of deep CNNs for fully automated cephalometric analysis. Their findings underscore the utility of CNNs in identifying anatomical landmarks and performing quantitative assessments of craniofacial structures, a crucial task in both orthodontics and orthognathic surgery.

In another systematic review, Hung et al.[37] examined AI applications in dental and maxillofacial radiology. Their work summarized evidence from 50 studies covering tasks such as osteoporosis detection, cephalometric landmark localization, and the segmentation of cysts and tumors. The review reinforced AI's potential to streamline diagnostic workflows and enhance radiological precision.

Further contributions to the field underscore the evolving precision and clinical utility of AI-driven diagnostic tools. Fourcade and Khonsari[38] emphasized the transformative role of deep learning in medical imaging, presenting it as a "third eye" that enhances visual diagnosis, particularly in complex fields such as radiology and pathology. Their work highlights how CNNs can augment diagnostic accuracy and support clinicians in visually intensive tasks.

In the domain of cephalometric analysis, Park et al.[39] compared two advanced object detection algorithms, YOLOv3 and SSD, for automated landmark identification. Their study demonstrated that both models could perform cephalometric landmark detection with a high degree of accuracy, offering a fast and reproducible alternative to manual tracing. Expanding on this, Hwang et al.[40] evaluated whether these AI systems could outperform human experts. Their results showed that the YOLOv3 model achieved performance levels comparable to experienced clinicians, suggesting AI's strong potential as a reliable assistant in orthodontic diagnostics.

Moreover, Kunz et al.[41] developed a fully automated cephalometric analysis tool using a customized CNN architecture. The model's performance was benchmarked against that of human specialists, revealing comparable levels of precision. Their findings support the feasibility

of integrating AI-driven tools into routine orthodontic workflows, offering efficiency gains without compromising diagnostic quality.

Together, these studies illustrate the significant strides made in AI-assisted imaging, particularly in cephalometric assessment-an area that demands high anatomical precision. As accuracy, reliability, and speed continue to improve, AI systems are poised to become indispensable components of modern orthodontic and surgical planning processes.

In evaluating the dissemination of AI-related research within orthodontics and orthognathic surgery, journal analysis reveals key publication and citation trends. Among these, Medical Image Analysis emerged as the most highly cited journal, amassing 647 citations from only 8 publications. This suggests a high citation density and reflects the journal's strong influence, particularly in areas such as medical imaging and AI-based diagnostic systems. In contrast, Scientific Reports was the most prolific journal by output, publishing 42 articles on the topic. While its total number of publications is higher, the average citations per article are notably lower compared to medical image analysis, indicating that while scientific reports plays a critical role in quantity, medical image analysis holds a greater qualitative impact in terms of scholarly recognition. These findings highlight the importance of both high-volume and high-impact publication venues in shaping the discourse around AI in dental specialties.

Figure 9 illustrates the longitudinal evolution of thematic trends in AI research within orthodontics and orthognathic surgery, offering insight into how publication focus has shifted alongside technological developments. Between 2009 and 2015, dominant keywords such as "artificial neural network" and "craniofacial superimposition" reflect early foundational efforts focused on digital image processing and craniofacial mapping-paving the way for AI's entrance into dental diagnostics.

From 2016 to 2020, the emergence of terms like "deep learning," "convolutional neural network," and "landmark detection" highlights a shift toward more advanced computational methods. This period coincides with major breakthroughs in CNN architectures, enabling automated and precise identification of cephalometric landmarks-crucial for treatment planning and outcome assessment in orthodontics.

Since 2021, the focus has increasingly turned to clinical applicability. Keywords such as "treatment planning," "artificial intelligence," and "orthodontics" suggest growing efforts to translate algorithmic models into real-world workflows. The rise of "transfer learning" underscores efforts to overcome limitations in labeled datasets by adapting pre-trained models to dental tasks. Notably, the appearance of "ChatGPT" in 2023 signals a nascent but rapidly growing interest in conversational AI, particularly for enhancing patient communication, education, and clinical decision support.

This longitudinal keyword analysis also uncovers emerging research frontiers and critical gaps. One particularly promising area is predictive modeling, reflected by recurring terms such as "deep learning" and "treatment planning." These applications highlight AI's growing role in forecasting clinical outcomes and tailoring personalized treatment strategies in orthodontics. However, despite its promise, predictive modeling remains largely theoretical. Few studies have validated these models in real-world clinical settings, limiting their current applicability. Expanding external validation efforts across diverse patient populations is essential to ensure their generalizability and clinical relevance.

An equally important observation is the relative underrepresentation of orthognathic surgical planning in AI literature. The lack of domain-specific keywords or clusters points to a significant gap in research. Given the complexity and irreversible nature of orthognathic procedures, AI-based simulation tools and outcome prediction models could offer valuable decision support. Future studies should prioritize this area to balance the orthodontics-dominant focus observed in current literature.

Finally, the parallel rise of key technologies-particularly CNNs and transfer learning-correlates strongly with the accelerated growth of AI research in dental specialties. These innovations have enabled automated diagnostics and robust model development even with limited datasets. Moving forward, the integration of generative AI, multimodal models, and real-time feedback systems may further enhance clinical workflows, offering not only precision but also adaptability across diagnostic and treatment contexts.

Limitations

This study has several limitations that should be considered when interpreting the results. The bibliometric analysis was limited to the Web of Science Core Collection (WoSCC), which may have excluded relevant studies indexed in other major databases such as Scopus or PubMed. As a result, the overall representation of global research output may be incomplete. Additionally, while the article selection process was carefully conducted, the involvement of a single reviewer, as noted in the methodology, may introduce a degree of selection bias. Furthermore, the analysis relied on author affiliations and keyword metadata, which may not fully capture the nuances of interdisciplinary contributions or evolving terminologies in the field.

CONCLUSION

This bibliometric study highlights the significant and accelerating role of AI in orthodontics and orthognathic surgery. Technological advancements-particularly in deep learning and transfer learning-have driven a surge in publications, especially after 2017, marking a shift from foundational research to clinical application. Orthodontics has received the bulk of AI-related attention, while orthognathic surgery remains an underrepresented but promising frontier. Institutions such as Seoul National University and high-impact journals like medical image analysis have shaped the discourse through influential contributions. Moving forward, expanding AI research into orthognathic surgical planning, improving interdisciplinary collaboration, and validating AI tools in real-world settings will be crucial. Emerging technologies such as generative AI and multimodal models offer exciting opportunities to enhance diagnosis, treatment

planning, and patient care. These developments signal a paradigm shift, positioning AI as a core component of future clinical and academic practice in dental specialties.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study is a bibliometric analysis based on publicly available scientific literature and does not involve human participants, clinical trials, patient data, or any interventions requiring ethical 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.

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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Factors affecting response to relapse treatment in multiple sclerosis patients

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ABSTRACT

Aims: Relapses, a hallmark of multiple sclerosis, often lead to functional loss and a decline in quality of life. While the accelerating effect of intravenous methylprednisolone treatment on the recovery from multiple sclerosis relapses is well established, the rates of recovery can vary between relapses. This study aimed to evaluate the responses to intravenous methylprednisolone treatment administered during relapses in multiple sclerosis patients and to investigate the clinical factors and imaging characteristics influencing these responses.

Methods: Patients diagnosed with relapsing-remitting multiple sclerosis who presented within the first 3 weeks of the onset of relapse symptoms were included in the study. Along with the patients' demographic information, disease characteristics, Expanded Disability Status Scale scores during relapses, affected functional systems, and brain and spinal cord magnetic resonance imaging findings were recorded. As relapse treatment, patients were administered 1000 mg/day of intravenous methylprednisolone for 5 days. Expanded Disability Status Scale scores were calculated on the 5th, 15th, and 30th days of treatment. Patients were compared in terms of disease characteristics and imaging findings based on changes in Expanded Disability Status Scale scores before and after treatment on the 30th day.

Results: A total of 50 relapsing-remitting multiple sclerosis patients (13 men and 37 women, mean age 32.5±9.2 years, mean disease duration 4.7±5.3 years) were included in the study. Improvements of varying degrees were observed in half of the patients by the 5th day of treatment and in all patients by the 15th and 30th days. The mean Expanded Disability Status Scale score of the patients before treatment was 3.2±1.0, which decreased to 1.4±0.9 on the 15th day and 0.4±0.6 on the 30th day after intravenous methylprednisolone treatment. In the group with greater improvement (≥3-point reduction in Expanded Disability Status Scale) on the 30th day compared to the group with less improvement (<3-point reduction in Expanded Disability Status Scale), the following were observed: higher pre-treatment Expanded Disability Status Scale scores ($p<0.001$), more frequent involvement of the pyramidal system during relapses ($p<0.001$), a higher number of patients with cerebellar demyelinating lesions on brain magnetic resonance imaging ($p=0.01$), and more frequent infratentorial lesion locations ($p=0.04$).

Conclusion: Our findings demonstrated that symptom improvement on the 30th day of intravenous methylprednisolone treatment was greater than on the 15th day, suggesting that evaluating recovery from relapses before one month may be misleading. Furthermore, it was observed that improvement was more pronounced in relapses accompanied by pyramidal symptoms, which were more severe and disabling.

Keywords: Multiple sclerosis, relapse, methylprednisolone, disability

INTRODUCTION

Multiple sclerosis (MS) is a disease characterized by demyelination, inflammation, and axonal damage in its pathogenesis, exhibiting heterogeneity in various aspects, including histopathology, clinical course, neuroimaging features, and treatment responses. Relapses are a hallmark of MS, and most patients experience a relapsing-remitting course (relapsing-remitting MS, RRMS), which is classified as an active type of disease according to the newly defined classification.[1-3] MS relapses are the clinical manifestation of newly developed demyelinating activity in any segment of the central nervous system or the reactivation of pre-existing demyelinating lesions.[4,5] Relapses often lead to functional impairment and a decrease in the quality of life for patients.

The natural course of most MS relapses include a repair period following the relapse, which achieves clinical remission. The repair phase is slower than the inflammatory phase, with relapses followed by a gradual and variable recovery process lasting weeks to months.[6,7] Especially in the early stages of the disease, the resolution of inflammation and the occurrence of remyelination can result in the complete resolution of relapse-related symptoms. However, in some cases, repeated relapses may lead to limited remyelination and subsequent

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neurodegeneration, resulting in residual deficits and a stepwise progression of disability.[3]

The treatment of MS relapses is important for reducing the recovery time of disability that develops during the relapse and for minimizing the risk of developing permanent disability. Key objectives of relapse treatment include accelerating recovery, alleviating disability, influencing subsequent disease activity, achieving long-term improvement, and minimizing side effects.

In the treatment of MS relapses, the general approach is that mild relapses typically do not require treatment, whereas moderate to severe MS relapses with disabling symptoms are treated with high-dose systemic corticosteroids.[4,5] The efficacy of high-dose intravenous methylprednisolone (IVMP) in treating MS relapses has been well established, and it is recommended as the first-line treatment.[8-10] Corticosteroid therapy has been shown to accelerate the rate of recovery, shorten the duration of relapses, reduce the permeability of the blood-brain barrier, and suppress contrast enhancement in magnetic resonance imaging (MRI).[9,11] While these findings suggest that corticosteroid treatment contributes to a faster resolution of the pathophysiological mechanisms responsible for clinical relapses, data on the degree of recovery remain insufficient. Moreover, information about the characteristics of patients who benefit most from relapse treatment is limited.

This study aimed to evaluate the responses to IVMP treatment administered during relapses in RRMS patients and to identify the clinical and imaging characteristics that influence these treatment responses.

METHODS

Ethical Considerations

The study was initiated with the approval of the Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Researches Ethics Committee (Date: 23.03.2015, Decision No: 21/09). Written consent was obtained from all the patients participating in this study. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Fifty consecutive patients who fulfilled diagnosis of RRMS based on the 2010 McDonald criteria, with pre-relapse EDSS scores ≤1, and who presented within the first 3 weeks of the onset of relapse symptoms, were prospectively included in the study. Patients with a diagnosis of secondary or primary progressive MS, those with mild relapses not requiring treatment, those with contraindications to corticosteroid therapy, and those with neurological disorders other than MS were excluded from the study.

Patients were included after confirming that their symptoms met the definition of a relapse, which includes new or worsening symptoms lasting at least 24 hours, arising acutely or subacutely, without fever or infection, and accompanied by typical objective findings of MS.

Data Collection

The demographic information of the patients was recorded, including age at disease onset, disease duration, total number of relapses, annual relapse rate, time from relapse onset to initiation of IVMP treatment, EDSS scores during relapse, and the affected functional systems (pyramidal, cerebellar, brainstem, sensory, bowel-bladder, visual, mental). The relapses were categorized as mono- or polysymptomatic.

Findings from contrast-enhanced brain and spinal cord MRI were documented, including plaque locations and contrast enhancement. Demyelinating lesions detected on T2 and FLAIR images were classified by location as juxtacortical, deep white matter, periventricular, corpus callosum, brainstem, cerebellar, or spinal cord. Locations of contrast-enhancing MRI lesions were identified as deep white matter, periventricular, callosal-pericallosal, brainstem, cerebellar, or spinal cord.

Treatment Protocol and Evaluation

All patients received 1000 mg/day IVMP for 5 days, and the time between relapse onset and initiation of treatment was recorded. Patients were assessed on the 5th day of treatment and during follow-up on the 15th and 30th days, with EDSS scores calculated at each evaluation. Patients were compared in terms of disease characteristics and imaging findings based on the changes in their EDSS scores before treatment and on the 30th day post-treatment.

Statistical Analysis

The statistical analysis was performed using the SPSS 22.0 software (Statistical Package for the Social Sciences, version 22.0 for Windows, SPSS Inc., Chicago, IL). The normality of the distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. Descriptive statistics for continuous variables were presented as mean±SD or median (minimum-maximum), and categorical variables were expressed as numbers (%).

For comparisons between groups, the student's T test or Mann-Whitney U test was used for continuous variables, while the Pearson chi-square test was employed for categorical variables. A p-value of <0.05 was considered statistically significant.

RESULTS

Fifty RRMS patients (37 females, 13 males; mean age 32.4±9.2 years) were included in the study. The mean disease duration was 4.7±5.3 years. MRI of the brain and spinal cord during the relapse revealed contrast-enhancing lesions in 46 patients (92%). The mean duration from symptom onset to initiation of IVMP treatment was calculated as 9.7±6.2 days. By the 5th day of IVMP treatment, a reduction in EDSS scores was observed in 25 patients, and by the 15th and 30th days, all patients showed a decrease in EDSS scores. The mean EDSS score was 3.2±1.0 before treatment, which decreased to 1.4±0.9 on the 15th day and 0.4±0.6 on the 30th day (**Table 1**).

Comparison of patients based on EDSS score changes (**Table 2**):

By the 30th day, 21 patients showed <3 points reduction in EDSS, while 29 patients had ≥3 points reduction. The group with greater improvement had higher pre-treatment EDSS

Table 1. Demographic and clinical characteristics, brain and spinal cord imaging findings	
	n=50
Age (years)	32.5±9.2
Gender (female/male)	37 (74%)/13 (26%)
Age at disease onset (years)	27.8±7.15
Disease duration (years)	4.7±5.3
Total number of relapses	3.5±2.6
Annualized relapse rate	2.2±2.35
Pre-IVMP EDSS score	3.2±1.0
EDSS score on day 15 post-IVMP	1.4±0.9
EDSS score on day 30 post-IVMP	0.4±0.6
Time from relapse onset to IVMP (days)	9.7±6.2
MRI T2-FLAIR lesion locations	
Juxtacortical	18 (36%)
Deep white matter	31 (62%)
Periventricular	44 (88%)
Corpus callosum	43 (86%)
Brainstem	25 (50%)
Cerebellar	26 (52%)
Spinal cord	32 (64%)
Patients with contrast-enhancing MRI lesions	46 (92%)
Contrast-enhancing lesion locations	
Deep white matter	20 (40%)
Periventricular	25 (50%)
Callosal-pericallosal	6 (12%)
Brainstem	11 (22%)
Cerebellar	8 (16%)
Spinal cord	14 (28%)

IVMP: Intravenous methylprednisolone, EDSS: Expanded Disability Status Scale, MRI: Magnetic resonance imaging

scores (p<0.001), more frequent involvement of the pyramidal system during the relapse (p<0.001), and a higher prevalence of cerebellar demyelinating lesions on brain MRI (p=0.01) and infratentorial lesion localization (p=0.04). Although cerebellar system involvement and total relapse numbers were more frequent in this group, the differences were not statistically significant. No significant differences were observed in the localization of contrast-enhancing MRI lesions between the groups.

The remaining variables, including supratentorial, spinal cord lesions, and contrast-enhanced lesion localizations, showed no significant differences.

DISCUSSION

In our study, all patients demonstrated varying degrees of improvement in relapse symptoms and findings by the 15th and 30th days of IVMP treatment. This could be attributed to most patients being in the early stages of the disease and the natural course of MS, which tends to result in relapse recovery with minimal or no deficits.[6] Additionally, nine patients had disease durations exceeding 10 years but maintained EDSS scores below 3, suggesting they might have a benign form of MS, potentially contributing to better responses to relapse treatment.

The effectiveness of corticosteroid treatment for MS relapses has shown variability across studies. Factors such as individual differences, the definition of recovery, methods and scales used to quantify recovery, and the timing of evaluations significantly influence these results. A meta-analysis reported that patients treated with high-dose steroids had a 0.76-point reduction in EDSS scores after 5-7 days and a 0.85-point reduction after 2-4 weeks compared to placebo.[8] Another meta-analysis noted that high-dose steroids reduced the non-recovery rate by 0.2 at five weeks post-treatment compared to placebo.[9] The NARCOMS study, which retrospectively evaluated 4,238 patients through self-reporting, found that one month after corticosteroid treatment, 40% of patients reported improvement, 25% noted no change, and 35% experienced worsening of symptoms. Among those treated with IVMP, 51% reported improvement compared to 47% in the oral corticosteroid group.[12]

In our study, EDSS score reductions were greater on the 30th day of IVMP treatment compared to the 15th day. While improvements were observed in half of the patients by the 5th day, these changes were less pronounced compared to the subsequent evaluations. These findings suggest that evaluating relapse recovery at one month may provide a more accurate assessment than earlier evaluations at 15 days. However, the extent to which spontaneous remission influenced our results remains uncertain. Most MS relapses, regardless of treatment, exhibit varying degrees of spontaneous recovery. This natural course, combined with the heterogeneity of relapse phenotypes, makes it challenging to distinguish the specific contributions of any given treatment.[6]

The duration of maximum improvement and recovery processes after relapses have been investigated in various studies. It has been reported that at least a one-point reduction in EDSS scores occurred in 44% of patients by the 1st month, 56% by the 3rd month, and 52% by the 6th month following corticosteroid treatment.[13] Another study found recovery rates of 78% at three months and 86% at six months post-relapse.[14]

In our study, no correlation was found between the duration from relapse onset to the initiation of IVMP treatment and treatment response. Although earlier treatment (within one week of symptom onset) is generally considered more effective, there is no direct evidence supporting this. Some studies suggest that treatment initiated within 1-2 months of relapse onset can still be effective.[4,13]

Patients with higher EDSS scores during relapses demonstrated greater improvement by the 30th day of IVMP treatment. This aligns with previous findings indicating that moderate to severe relapses are more likely to show significant recovery after corticosteroid treatment.[13] Our study also found that patients with pyramidal system involvement during relapses experienced greater improvement, suggesting that this could be a predictor of better treatment response.

Interestingly, while pyramidal, brainstem, cerebellar, and sphincter involvement are associated with poor prognosis,

Table 2. Comparison of demographic and clinical characteristics, MRI findings based on EDSS score changes			
	EDSS reduction <3 points (n=21)	**EDSS reduction ≥3 points (n=29)**	**p**
Age	33.2±10.2	32.0±8.6	0.67
Gender (female/male)	16 (76.2)/5 (23.8)	21 (72.4)/8 (27.6)	0.86
Age at disease onset (years)	28.9±8.7	27.1±5.8	0.40
Disease duration (years)	2 (1-16)	3 (1-23)	0.47
Total number of relapses	2 (1-14)	3 (1-10)	0.06
Annualized relapse rate (n/disease duration)	2 (0.5-8)	1.3 (0.25-12)	0.42
Pre-IVMP EDSS score	2 (2-3.5)	3.5 (3-6)	<0.001
Post-IVMP day 30 EDSS score	0 (0-2)	0.5 (0-2)	0.16
Duration from relapse onset to IVMP initiation (days)	10 (2-20)	7 (2-20)	0.72
Functional systems affected during relapse			
Pyramidal	10 (47.6)	25 (86.2)	<0.001
Cerebellar	4 (19)	13 (44.8)	0.06
Brainstem	7 (33.3)	8 (27.6)	0.66
Sensory	14 (66.7)	21 (72.4)	0.66
Bowel-bladder	7 (33.3)	11 (37.9)	0.74
Visual	5 (23.8)	9 (31)	0.57
Mental	4 (19)	7 (24.1)	0.67
Relapse symptoms			
Monosymptomatic	6 (28.6)	3 (10.3)	0.10
Polysymptomatic	15 (71.4)	26 (89.7)	
MRI T2-FLAIR demyelinating lesion locations (number of patients)			
Juxtacortical	8 (38.1)	10 (34.5)	0.79
Deep white matter	13 (61.9)	18 (62.1)	0.39
Periventricular	18 (85.7)	26 (89.7)	0.5
Corpus callosum	18 (85.7)	25 (86.2)	0.64
Brainstem	8 (38.1)	17 (58.6)	0.15
Cerebellar	6 (28.6)	20 (69)	0.01
Spinal cord	12 (57.1)	20 (69)	0.39
Supratentorial MRI lesions	21 (100)	29 (100)	-
Infratentorial MRI lesions	11 (52.4)	23 (79.3)	0.04
Spinal cord MRI lesions	12 (57.1)	20 (69)	0.39
Number of patients with contrast-enhancing MRI lesions	19 (90.5)	27 (93.1)	0.74
Contrast-enhancing MRI lesion locations (number of patients)			
Deep white matter	8 (42.1)	12 (44.4)	0.88
Periventricular	8 (42.1)	17 (63)	0.16
Callosal-pericallosal	2 (10.5)	4 (14.8)	0.67
Brainstem	7 (36.8)	4 (14.8)	0.09
Cerebellar	2 (10.5)	6 (22.2)	0.3
Spinal cord	6 (31.6)	8 (29.6)	0.89
Supratentorial contrast-enhancing lesion	14 (73.7)	23 (85.2)	0.33
Infratentorial contrast-enhancing lesion	8 (42.1)	10 (37)	0.73
Spinal cord contrast-enhancing lesion	6 (31.6)	8 (29.6)	0.89

MRI: Magnetic resonance imaging, IVMP: Intravenous methylprednisolone, EDSS: Expanded Disability Status Scale

sensory and visual system involvement is linked to better prognosis.[17] This highlights that the effects of IVMP on relapse remission may differ from these prognostic factors. Prognostic factors such as age, gender, disease duration, annualized relapse rate, and mono- or polysymptomatic findings did not correlate with treatment responses in our study.

MRI findings were also evaluated in relation to relapse recovery. Patients with greater improvement on the 30th day of IVMP treatment had more frequent cerebellar demyelinating lesions and infratentorial lesion localization. This suggests that patients with higher infratentorial lesion loads may respond better to relapse treatment. However, no significant relationship was found between contrast-enhancing lesions or their locations and recovery.

Our findings highlight that evaluating relapse recovery before one month may be misleading, as greater improvements were observed on the 30th day compared to the 15th day. Additionally, more severe and disabling relapses, particularly those with pyramidal symptoms, demonstrated greater recovery. Prognostic factors such as age, gender, disease duration, and annualized relapse rate were not associated with treatment responses.

Limitations

Our study has several limitations. First, the patient group evaluated in this study had relatively low pre-attack EDSS scores and mild disability levels, which may have contributed to the generally favorable treatment responses observed during attacks. Another limitation is that treatment responses were assessed only within the first 30 days following an attack; therefore, we could not evaluate long-term treatment outcomes. Additionally, we were unable to assess the impact of spontaneous recovery following an attack on treatment responses. Future studies with larger patient populations may provide more detailed insights into factors influencing treatment response during attacks.

CONCLUSION

This study revealed three key findings on high-dose IVMP for relapses in RRMS. First, although EDSS scores began to improve by day 5, the largest improvements occurred by day 30, showing that assessing recovery before one month may be inaccurate. Second, patients with more severe relapses, indicated by higher pre-treatment EDSS scores and pyramidal involvement, showed greater improvements by day 30, despite having more disabling symptoms at onset. Third, individuals with cerebellar and infratentorial lesions on MRI had better treatment responses. In contrast, age, disease duration, annual relapse rate, and mono-versus polysymptomatic presentations did not significantly affect outcomes. Clinically, these findings underscore the value of evaluating relapse recovery at or beyond one month and highlight that severe relapses and specific MRI features (pyramidal involvement, infratentorial lesions) may predict stronger responses to steroid treatment. Further research could refine our understanding of these patterns and optimize relapse management.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Dışkapı Yıldırım Beyazıt Training and Research Hospital Clinical Researches Ethics Committee (Date: 23.03.2015, Decision No: 21/09).

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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Asymptomatic malaria in selected rural health facilities in Vihiga County, Western Kenya

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ABSTRACT

Aims: Malaria is still a devastating health challenge in the world. In 2022, Africa accounted for 93.6% of all malaria cases with 95.4% deaths globally. Kenya recorded about 3.5 million new malaria cases with a mortality of 12,011 deaths while Vihiga County had a prevalence of 20% for all symptomatic outpatients. Asymptomatic malaria infection in Kenya was reported as 42% and 10% from two malaria endemic areas. Asymptomatic patients never visit health facilities for treatment but remain Plasmodium falciparum reservoirs in the community. This study assessed the occurrence of asymptomatic malaria around five rural health facilities in a malaria endemic Vihiga County, Western Kenya.

Methods: This was a cross-sectional survey targeting 336 participants and running between April 2022 and March 2023. CareStart malaria HRP2 (Pf) was used for sample diagnosis as per manufacturer's instructions. Demographic and other laboratory parameters of study participants were taken.

Results: Chi-square was used to analyse this data. Average percentage prevalence for asymptomatic malaria was 8.3%; (95% CI; 5.3%-10.8%, $p<0.05$). Age category of below five years had a prevalence of 2.5% (95% CI: 0.6%-9.5%, $p>0.05$), between five and seventeen years was 10.6% (95% CI: 5.8%-15.2%, $p<0.05$) and above seventeen years was 9,6% (95% CI: 4.7%-14.6%, $p<0.05$). Females had a prevalence of 9.6% (95% CI: 5.5%-13.7%, $p<0.05$) while males had 6.9% (95% CI: 3.5%-11.0%, $p<0.05$). High quarterly rainfall of 249.7 mm had 12.2% prevalence while low rainfall of 12 mm had 1.2% prevalence of asymptomatic malaria respectively

Conclusion: This study demonstrated the presence of asymptomatic malaria participants in Vihiga County, Western Kenya. There were more asymptomatic cases during rainy than dry seasons. This study underscores the need for continued surveillance and treatment of the malaria asymptomatic cases to reduce its spread.

Keywords: Malaria, asymptomatic malaria, mRDT, Pfhrp2/3

INTRODUCTION

Malaria is a devastating health challenge in the world. It is caused by five species of the malaria causing parasites in human beings namely *Plasmodium vivax, Plasmodium malariae, Plasmodium ovale, Plasmodium knowlesi* and *Plasmodium falciparum*.[1,2] The most prevalent of the species is the *Plasmodium falciparum*.[3] Out of 234 million malaria cases in the world 70% were recorded in Africa.[4] In Kenya, there have been efforts made to reduce the spread of malaria however; it still records 6.7 million cases annually with 4000 deaths most of who are children.[3,5] In 2022, Vihiga County which is found in a malaria endemic Lake Victoria basin, recorded a malaria prevalence of 20% of all outpatient to the health facilities.[6] Asymptomatic malaria refers to a condition where an individual is *infected Plasmodium falciparum* but does not show any symptoms of malaria, such as fever, chills, headache, or fatigue. Its infection in Kenya has been reported as 42% and 10% from two malaria endemic areas respectively. Since asymptomatic patients do not freely come for treatment, they are never treated therefore, they remain as parasite reservoirs in the community which is a set-back to malaria eradication strategies.[7,8]

Malaria does manifest itself with symptoms like fever, headache, hypoglycaemia, respiratory distress, nausea, jaundice among others which can be confirmed by diagnostic tests, however, it may fail to show any of these signs but test positive on diagnosis hence said to be asymptomatic.[8,9] Asymptomatic malaria refers to the presence of asexual parasites in the peripheral blood which can be confirmed by diagnosis.[9,10] Due to high mortality caused by malaria, WHO has recommended rapid diagnostic tests (RDTs) targeting the *Plasmodium falciparum* to mitigate against deaths caused by the parasites.[2,11,12] Most of the malaria prevalence reports from various studies may be less accurate as they rely on data from hospital visits by symptomatic patients. Malaria symptomatic cases are not documented and consequently are not planned

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for. Unfortunately, such like patients become malaria parasite reservoirs since they do not show any malaria signs but become sources of transmission between infection cycles in the community.[10,11]

There are three methods that are used in malaria diagnosis namely microscopy, molecular method by use of polymerase chain reaction (PCR) and the rapid diagnostic test (RDT).[2,7,12] In Vihiga County, the use mRDT to detect *Plasmodium falciparum*-specific rich histdine rich proteins (Pfhrp 2/3) is broadly used for diagnosis, especially in malaria surveillance studies.[12] Research has shown that Pfhrp2/3 is not necessarily an essential gene for the growth of the parasite but it's a bio-marker antigen for the presence of *Plasmodium falciparum* in hosts' blood circulation.[2,7,12]

The prevalence of asymptomatic malaria varies with different areas of study in world. In Uganda, the prevalence of asymptomatic cases reported was 34.7% while Tanzania recorded an average prevalence of 37.3%.[7,13,14,15] In Ghana, asymptomatic cases were recorded at 8% while Webuye and Ajigo areas in Western part of Kenya had an asymptomatic percentage prevalence of 10% and 42% recorded respectively.[7,16] On an extreme end, there was a site in Kenya called Kapsisywa which had only two (2) cases and Kipsamoite which did not record any asymptomatic case.[7,16,17]

To control the spread of malaria, World Health Organization (WHO) has recommended testing, treating and tracking of the disease as a disease management protocol.[18] If Malaria is diagnosed early and effectively treated, it reduces the spread of the parasite in the community. However, malaria control is faced with many challenges of improper diagnosis, inadequate resource allocation, inexperienced technical personnel, poor tracking of cases and lack of clinical confidence in diagnostics which is manifested in the lack of accuracy some test-results.[19] Other determinants that control the dynamics of spread of malaria and accurate diagnosis includes spatio-temporal distribution of the malaria cases, intensity of infection, method of diagnosis and the presence of asymptomatic malaria cases.[7,20,21] Studies on malaria prevalence in Vihiga County have concentrated on suspected malaria visits to the health facilities and attention has been on children under five years and pregnant mothers; the two populations that are considered most vulnerable to malaria infection.[8,10,17,22] No study has reported on asymptomatic status in this region hence this study assessed the prevalence of asymptomatic malaria cases around the selected health facilities in Vihga County, Western Kenya.

METHODS

Ethical Approval

This study was approved by the Maseno University Scientific Ethics Committee (Date: 06.06.2022, Decision No: MUSERC/01047/22) and The National Commission of Science, Technology and Innovation, in Kenya (Date: 01.07.2022, Decision No: NACOSTI/P/22/18417) which provided the research permit. The Vihiga County Commissioner, Vihiga County Director of Education and the County government of Vihiga also approved data collection in the County. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design

This was a community based cross- sectional survey carried out in the catchment area of five rural health facilities between April 2022 and March 2023 among the 336 in Vihiga County Western Kenya. Apparently, it targeted healthy participants of all ages recruited by way of consenting and signing a questionnaire and it was designed to run through dry and wet period through the twelve months. The p-value for the significant difference between the rainy and non-rain will be computed. Vihiga County has the highest population density in Kenya of 1,094 persons per square kilometre, way above the national average of 66 persons per square kilometre.[9] The neighbouring Counties of Nandi, Kakamega, Siaya and Kisumu have high transmission rate, especially, during the long rainy season.[22,23] Entomological inoculation rate (EIR) varies with specific location from 6.000-0.145 infective bites/person/night.[24,25] In Vihiga County, malaria is endemic and with mosquito bites of over 300 per month. Malaria is experienced throughout the year with peaks of transmission both during long rains (april, may and july) and short rains (october, november and part of december). Most people in this County live in the villages which are densely populated.[6,23] Blood samples were collected from consenting patients using a finger-prick for Care startTM rapid diagnostic tests. Thick and thin blood smears were prepared and Giemsa stained for microscopy. Dried blood spots on whatman filter paper for use during molecular analysis by polymerase chain reaction were also prepared.[25,26]

The Study Area

Vihiga is located $0^0$17'N, $34^0$74'E, and receives rainfall ranging between 1800mm-2000mm with distinct long and short rainy seasons. The mean temperature is 23^0C, ranging between 14^0-32^0C. The altitude varies between 1300m and 1500m above sea level.[6] Vihiga County has five sub counties and the study purposefully sampled one rural (furthest from the main sub county hospitals) health facility per Sub County. These health facilities mainly relied on mRDTs as the main malaria diagnostic method. Microscopy and PCR methods are not in use in these facilities for lack of infrastructure (electricity, Reagents, equipment) and well-trained staff for reading and interpreting the results.[26-28] These health facilities were Ekwanda health centre in Luanda Sub County, Musunguti Dispensary in Vihiga Sub County, Bugina health centre in Sabatia Sub County, Kaptis Dispensary in Hamisi Sub County and Esiarambatsi Health centre in Emuhaya Sub County.

Sample Size Determination

The sample size was determined by Charan J. and Biswas T. (2013) formular:[30]

$$n = \frac{Z^2 p(1-p)}{d^2}$$

Where; n is the expected sample population, Z is the score of the confidence level (95%)=1.96, p is expected population at a

prevalence of 32.4%[29] and d is the margin of error=5% (0.05). This formula yielded a sample population of 337 of which, one dropped off from the study giving final sample population of 336.

Inclusion and Exclusion Criteria

In this study, there was no restriction on age limit and were stratified in three categories of 1 (below five years), 2 (between 5 and 17 years) and 3 (more than seventeen years). All participants or their guardians (for the under age) had the fill a consent form for enrolment into this study. They were also allowed freedom to withdraw from the study whenever they deemed fit without any prejudice of missing out on treatment if they were mRDT positive for malaria. Other participants that did not consent to the study and those that had malaria symptoms were excluded from the study.

Blood Collection and Processing

Trained phlebotomists collected finger prick blood samples from volunteers from the sampled rural hospitals of the five sub-counties of Vihiga County. The finger prick produced about 0.5mL of blood from each volunteer. The study used an immunochromatographic rapid diagnostic test that targets the Pfhrp2/3 protein.[26,28,31] The testing process involved putting blood in the capillary tube which was used to put a drop of blood in a sample well from which the specimen migrates through the nitrocellulose membrane by capillarity. Two drops of the buffer assay were added to the buffer well. The test pad is coated with monoclonal antibodies specific for the Pfhrp2/3 malaria parasite antigens. The test results showed either presence or absence of the colour bands as compared to the control colour band that should and must show for accurate test interpretation. The results were read after 20 minutes.[12] The sensitivity of the RDT (for true positive results) is placed at 98% and the specificity (ability to detect true negative) is 97.5%. The reliability and validity of the test mRDT outcome was ensured by following the methods manual for product testing of mRDT, version seven, 2018.[11] The people who turned out to be positive (even if they did not show any symptoms) for the Plasmodium falciparum parasites were subjected to treatment with artemether lumefantrine (Coartem) anti-malaria drugs[18]. Whole blood was preserved by spotting the dry blood spot (DBS) paper for future processing and analysis as recommended by WHO.[18]

Instruments of Data Collection

The interviews were conducted either in English, Kiswahili or local language (Luhya) for inclusivity. Interpretation as positive mRDT outcome used the WHO guidelines for both faint and clear thick visible bands.[18] The clinic form was designed to capture gender, age, location (area of stay), the malaria history and symptoms if any. The participants diagnosed for malaria around the five health facilities were later categorised in to two tables segregated by sex and age as shown in **Table 1, 2**. The age brackets (x) applied in this section are: 1 which is x≤5 years, 2 is 5<x≤17 years and 3 is x>17 years.

Table 1. Asymptomatic mRDT positive cases within Vihiga County based on age categories and sex

The health facilities	Infection status		Age categories			Sex	
	Positive	Negative	(1) x≤5 years	(2) 5 years <x≤17 years	(3) x>17 years	Male	Female
Ekwanda (n=49)	4	45	0/15	3/23	1/11	1/22	3/27
Esiarambatsi (n=178)	13	165	2/45	6/78	5/55	6/86	7/92
Bugina (n=46)	4	42	0/7	1/20	3/19	2/25	2/21
Musumguti (n=31)	3	28	0/7	2/15	1/9	0/13	3/18
Kaptis (n=32)	4	28	0/5	3/6	1/21	3/13	3/19
Totals	28/336	308	2/79	15/142	11/115	11/159	17/177
Asymptomatic Prevalence	8.30%		2.50%	10.6%	9.60%	6.90%	9.60%
95% Confidence interval	5.3%-10.8%		0.6%-9.5%	5.8%-15.2%	4.7%-14.6%	3.5%-11.0%	5.5%-13.7%
p-value (≤0.05)	<0.001		0.787	<0.001	<0.001	<0.001	<0.001

Table 2. Average monthly Rainfall against positive asymptomatic malaria rapid diagnostic test participants in Vihiga County, Western Kenya

Year	2021									2022		
Months	Apr	May	Jun	Jul	Sep	Aug	Oct	Nov	Dec	Jan	Feb	Mar
Monthly Rainfall (mm)	312	320	177	132	259	360	180	198	247	0.8	0.2	35
n=336	39	37	26	29	32	22	19	24	38	19	24	27
Positive Asymptomatic malaria (28)	6	5	2	2	3	4	1	1	3	0	0	1
Percentage (%) prevalence	15.4	13.5	7.7	6.9	9.4	9.1	5.3	4.2	7.9	0	0	3.7
Average quarterly Rainfall (mm)	249.7			250.3			208.3			12		
Average quarterly asymptomatic malaria % ages (Q)	Q2=12.2%			Q3=8.5%			Q4=5.8%			Q1=1.2%		

Statistical Analysis

A total of 336 participants consented for enrolment and were subjected to Pfhrp2/3 mRDT. The positive cases were identified and categorised as per their ages and sex which were critical parameters for this study. Data was analysed using frequency counts and percentages with the help of STATA package version 18.0. The findings were presented in tables and discussed. Both descriptive and inferential statistics were used in the analysis. For inferential statistics, Chi-square test of associations was used at a $p<0.05$ statistical significant, which indicated 95% confidence interval. Positive asymptomatic mRDT cases were analysed by age and sex to establish any associations between the parameters and the mRDT outcome. The positive cases were counted recorded, analysed and presented in **Table 1**. Moreover, confidence intervals were calculated to show the percentage range within which the cases would fall from all expected cases at 95% confidence interval.

RESULTS

In a duration of twelve (12) months spanning two (2) years divided in 4 quarters (of 2nd, 3rd and 4th quarters in 2021 and 1st quarter for 2022), community Health workers went round within catchment areas of the five health facilities and engaged the public on malaria transmission and testing. They recruited the volunteers who accepted to be part of the study. The participants were recruited on signing the informed consent form. Their ages and gender were critical parameters for inclusion. In this study, a *Plasmodium falciparum* histidine rich protein 2/3 (Pfhrp2/3) test was performed as the results were availed to the participants positive cases were commenced on malaria treatment.

Asymptomatic mRDT Positive Cases within Vihiga County Based on Age Categories and Sex

The age categories stratification of the asymptomatic malaria cases within the study area of the five health facilities are illustrated in **Table 1**.

n; represents the total number of participants in each health facility. Positive were asymptomatic participants who tested positive using mRDT. (1); Age below 5 years. (2): Ages between 5 years and 17 years. (3): Ages above 17 years. For the age categories, the numerators were the test outcome while the denominators were the samples diagnosed from that age group. M represents male and F female' the p-values were considered significant at $p\leq0.05$. Values in bold are significant p-values at a cut off of $p\leq0.05$.

Ekwanda health centre had a total of forty nine (49) participants diagnosed for malaria using mRDT. Four (4) out of forty nine (49) tested positive. There was no asymptomatic malaria for the age bracket of below 5 years while there were three (3) and one (1), positive asymptomatic malaria among the age categories between 5 and 17 years and above seventeen (17) years, respectively. Out of the four positive asymptomatic participants at Ekwanda health centre, one (1) was a male while three (3) were females, Esiarambatsi health centre had a total of one hundred and seventy eight (178) participants out of which thirteen (13) tested positive for malaria using mRDT. Of the thirteen (13), two (2) out of forty five (45) participants diagnosed from the first age category of below five (5) years were positive for malaria.,From the second category of between five (5) and Seventeen (17) years, six (6) were out of seventy eitght (78) diagnosed in that category were positive. The final age category of more than seventeen years had five (5) out of fifty five (58) being positive for malaria. Esiarambatsi had six (6) out of eighty six (86) males and seven (7) out of Ninety two (92) femaleas positive for malaria when diagnosed using mRDT. Bugina health centre had a total of forty six (46) participants out of which four (4) tested positive for malaria using mRDT. None (0) out of seven (7) participants from the first age category of below five (5) years was positive for malaria. The second category of between five (5) and Seventeen (17) years had only one (1) out of twenty (20) being positive for malaria. The final age category of more than seventeen years had three (3) out of nineteen (19) being positive for malaria. Bugina had two (2) out of twenty five (25) males and two (2) out of twenty one (21) females being positive for malaria when diagnosed using mRDT. Musunguti dispensary had a total of thirty one (31) participants out of which three (3) tested positive for malaria using mRDT. None (0) out of seven (7) participants from the first age category of below five (5) years was positive for malaria. The second category of between five (5) and Seventeen (17) years had two (2) out of fifteen (15) being positive for malaria. The final age category of more than seventeen years had only one (1) out of nine (9) being positive for malaria. Musunguti had none out of thirteen (13) males and three (3) out of eighteen (18) females being positive for malaria when diagnosed using mRDT Kaptis dispensary had a total of thirty two (32) participants out of which four (4) tested positive for malaria using mRDT. None (0) out of five (5) participants from the first age category of below five (5) years was positive for malaria. The second category of between five (5) and Seventeen (17) years had three (3) out of six (6) being positive for malaria. The final age category of more than seventeen years had only one (1) out of twenty one (21) being positive for malaria. Musunguti had three (3) out of thirteen (13) males and three (3) out of nineteen (19) females being positive for malaria when diagnosed using mRDT.

In **Table 1**, the asymptomatic malaria infection status from the three hundred and thirty six (336) participants was twenty eight (28). a prevalence of 8.3% (95% CI. 5.3%-10.8%, $p<0.05$). The first age category of 1 (below five years) had two (2) asymptomatic malaria positive out of seventy nine (79) participants. This was a prevalence of 2.5% (95% CI. 0.6%-9.5%. $p>0.05$). The second category of 2 (between five and seventeen years) had fifteen (15) asymptomatic malaria positive out of one hundred and forty two (142) participants. This was a prevalence of 10.6% (95% CI. 5.8%-15.2%. $p<0.05$). The last category of 3 (over seventeen years) had eleven (11) asymptomatic malaria positive out of one hundred and fifteen (115) participants, a prevalence of 9.6% (95% CI. 4.7%b-b14.6%. $p<0.05$). Out of the three hundred and thirty six (336) participants with twenty eight (28) asymptomatic malaria positive; the number of male participants was one hundred and fifty nine (159) from which eleven (11) were malaria positive, a prevalence of 6.9% (95% CI. 3.5%-11.0%. $p<0.05$). The female participants were one hundred and seventy seven

(177) out of which, seventeen (17) were asymptomatic malaria positive. This was a prevalence of 9.6% (95% CI. 5.5%-13.7%. p<0.05).

The effect of seasonality on the prevalence of asymptomatic malaria in Vihiga County, Western Kenya

Transmission of malaria depends on various human activities and climatic conditions. Rainfall is a key climatic factor that influences breeding patterns of the mosquito vector.

The study ran for twelve months between April 2021 and March 2023, Daily amount of rainfall was recorded and its monthly average computed in mm. n (336) was the total number of participants that were tested using mRDT kit of which twenty eight (28) were found to be asymptomatic malaria positive. Malaria positive participants had been detected in all but two (2) months of january and february. Percentage prevalence was calculated for each of the ten months that reported malaria positive participants. The Average quarterly Rainfall (mm) was assessed alongside average quarterly (Q) percentage prevalence for asymptomatic malaria participants.

The study was designed to run for twelve months between April 2021 and March 2023. Daily amount of rainfall was recorded and was used to compute monthly average in mm as shown in **Table 2**. n (336) was the total number of participants that were subjected to mRDT tests of which 28 were found to be malaria positive. Malaria positive participants had been detected in all but two (2) months of january and february. Percentage prevalence was calculated for the eleven months that reported malaria positive participants. The average quarterly rainfall (in mm) were 249.7, 250.3. 208.3 and 12.0 were assessed alongside average quarterly (Q) prevalence of 12.3%, 8.5%, 5.8% and 1.2% for asymptomatic malaria participants (**Table 2**).

DISCUSSION

Vihiga County is found in a malaria endemic Lake Victoria region of Western part of Kenya with an infection prevalence of between 13%-15% of all outpatients visiting the health facilities. Asymptomatic malaria infection in Kenya has been reported by various studies albeit inconsistencies in prevalence.[7,8] Since these asymptomatic patients are never identified and treated, they become *Plasmodium falciparum* reservoirs in the community hence a hindrance to malaria eradication processes. This study used malaria rapid diagnostic test (mRDT) to assess the occurrence of asymptomatic malaria participants in the catchment areas of the five rural health facilities in Vihiga County, Western Kenya which is a malaria endemic zone. The study established the presence of malaria asymptomatic cases with a prevalence of 8.3% (p<0.05) from the sample population of 336. This prevalence was less than the 42% found in Ajigo and 10% found in Webuye which are two endemic areas to malaria in Kenya. Ghana had previously recorded a prevalence of 8% which was slightly less than the 8.3% found in Vihiga County.[7,17] This value was consistence with the 8% value obtained in Ghana[7] but was less than 19% reported in Nigeria and 34.7% reported in Uganda.[8,10,29]

This study was designed to establish the occurrence and percentage prevalence of malaria asymptomatic participants in Vihiga County. It was informed by variations in values reported for malaria occurrence and prevalence for studies undertaken by different researchers but in the same area. Therefore, malaria prevalence has always been underestimated since some malaria cases which are asymptomatic status are not identified in the community. This is caused by presence of patients that do not show any of the malaria symptoms hence are never identified consequently; they are not part of the plans for malaria treatment and control.[32] Malaria management and control can be effective if there is focus not only on case visits to the health facilities but on asymptomatic people in the community as well.

The dynamics of malaria infection is controlled by many factors which can be broadly categorised as human hosts, the nature of parasite subspecies, the agents of transmission and the geographical influence caused by rainfall and other environmental factors. This study considered demographics of human hosts and the rainfall patterns at the time. It aimed at finding out if the sex and age of an individual can influence the occurrence of asymptomatic malaria cases in the population. The sexes were defined as either male (M) or female (F) and the ages were categorised in three categories of five (5) years and below, between five (5) years and seventeen (17) years (included) and lastly more than seventeen years. This research finding revealed that the two parameters of sex and age have significance influence to occurrence of asymptomatic malaria infections in the populations in Vihiga County as previously reported as 10% in Webuye, Western Kenya.

The age group which had least infections of asymptomatic malaria was that belonging to (1) 'below five years' which recorded two (2) positive subjects out of a total 336 participants (**Table 1**). Their history indicated that they had been exposed to anti-malarial drugs in the recent past prior to random testing. In this category, the prevalence of asymptomatic malaria was not statistically significant (p>0.05). This implied that this category does not have risk of experiencing asymptomatic malaria and can be attributed to various factors that are associated with participants in this age category as reported in other studies.[7,33] They have not developed naturally acquired immunity to malaria yet, which normally results from several entomological bites by the vector causing many inoculations of the parasites; they are immunologically naïve to infections.[34,35] Lack of natural immunity also makes them very vulnerable to parasite exposure with resounding symptoms that are easily detected for treatment and control. The participants in this category frequent antenatal clinics from where they are introduced to the malaria vaccines which has slowed down malaria infection in this population.[32] Sensitization on the adverse effects of malaria coupled up with advocacy for- and the use of long lasting treated mosquito nets has helped in controlling the spread of malaria.[32,36]

There is shift in asymptomatic malaria participants from the under five years to the other age groups reported in this study and it is in consistent with other reports from other studies.[31] The highest prevalence was noted in the middle age bracket of 2 with a value of 10.6%. It represents a big reservoir for asymptomatic malaria parasites. The adult category (ages of above 17 years) had the second highest prevalence

(9.6%) of asymptomatic participants. The two categories of 2 [between five (5) to seventeen (17) years] and 3 [more than seventeen an (17) years] both had a p<0.05. The occurrence of asymptomatic malaria was significant to the two age bracket. These categories of participants have been exposed to very many malaria parasite inoculations brought about by a long period of exposure-time to mosquito bites of the participant.[27] This has made them develop naturally acquired immunity which makes them resistant to the presence of the parasite hence do not present themselves to the health facilities as malaria infected.[10]

Heavy rains and warm temperature increases malaria transmission status since there will be proliferation of the malaria parasite vectors.[11] This, consequently, increased spread of the symptomatic malaria but also showed high prevalence of asymptomatic patients during high rainfall periods as shown in **Table 2**. The high average rainfall experienced in the quarter 2 (249.7 mm) and 3 (250.3) of 2021 was marched with high prevalence of 12.2% and 8.2%. This showed positive relationship between high rainfall and occurrence of asymptomatic malaria cases. High rainfall increases pools of water and hence the breeding sites for the parasite vectors.[37,38]

The prevalence of asymptomatic malaria was 8.3% of which, the prevalence of males was 6.9% (p<0.05) while that of the females was 9.6% (p<0.05). There was significance influence of the sexes to the occurrence of asymptomatic malaria in this region. The females had a higher prevalence of asymptomatic malaria than their male counterpart. This could be attributed to their evening activities of cooking in the open, and other household chores, mostly done outside their houses exposing the m to malaria mosquito vectors.[6] Female were also generally more willingly to participate in the study than their male counterpart.

Stakeholders in health matters have increased efforts in malaria control in the children less than five years of age because of their naive immunity to malaria parasites, which if not abetted, may result to high mortality. The source of danger to the community is the middle age bracket (between 5 and 17 years). They have a high percentage of asymptomatic malaria cases and if they are not identified out through constant surveillance and treatment commenced, they will remain the source of the parasites for the vectors and hence an impediment to malaria management and control strategies. It therefore calls for increased cross-sectional surveys in malaria endemic regions to help point out malaria asymptomatic victims for treatment. This will help eradicate malaria parasites from the less addressed reservoir of asymptomatic individuals.

The malaria management strategy in most health facilities in Vihiga County is testing, treating and tracking of those patients visiting the facilities. Therefore the prevalence reported is based on case visits to the health facilities; rarely does it capture malaria parasite reservoirs in asymptomatic subjects. Since asymptomatic malaria cases help transcend parasite between malaria infection residents. This report, therefore, advises on regular community malaria surveys to target asymptomatic cases and make referrals for treatment and follows ups as a malaria control.

Limitations

- Low parasite density which makes detection by standard methods (microscopy) difficult
- Underrepresentation of some categories of people during sampling for example mobile people were not considered but may also be asymptomatic cases among them
- Testing of people who are not sick may elicit ethical issues and therefore make follow ups sessions difficult
- Lack of information on the actual people who progress from asymptomatic from symptomatic malaria.

CONCLUSION

This study showed an asymptomatic malaria prevalence of 8.3% distributed, albeit not uniformly, between the sexes and throughout the three age categories of young, middle and old age. The middle age category had the highest prevalence of the malaria cases. There were more asymptomatic malaria participants during rainy season as compared to the dry season. This calls for all-inclusive malaria control strategies with reference to age stratification, gender disparity and seasonal changes so that asymptomatic malaria cases are detected and treated off the community.

Recommendations;

- Regular malaria epidemiological surveys targeting asymptomatic populations should be carried out to help manage challenge caused by malaria.
- Large scale studies using highly sensitive diagnostics procedure should be conducted to help flag out asymptomatic cases for treatment and advice on policy direction on malaria management.
- Introduction of free malaria treatment as an incentive to those asymptomatic subjects who voluntarily seek diagnosis for malaria.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Maseno University Scientific Ethics Committee (Date: 06.06.2022, Decision No: MUSERC/01047/22).

Informed Consent

Written consent was obtained from the patients or Guardians of the under age patients participating in this study.

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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Psychometric evaluation of the Turkish language Person-Centered Climate Questionnaire-family version

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ABSTRACT

Aims: This report aims to evaluate the Turkish validity and reliability of the Person-Centered Climate Questionnaire-family version (PCQ-F) and contribute to the literature.

Methods: This methodological study included 177 participants who applied to the hospital emergency department (ED). The validated English version of the PCQ-F was translated into Turkish and subsequently translated back into English to assess the alignment between the two versions. Experts then reviewed the Turkish translations, making necessary semantic and grammatical adjustments to finalize the Turkish version. Confirmatory factor analysis was employed to evaluate construct validity. The factorability was evaluated using the Kaiser-Meyer-Olkin measure and Bartlett's test of sphericity. The reliability of the Split Half method was assessed using the Spearman-Brown and Gutman coefficients, alongside the calculation of Cronbach's alpha. Additionally, the Item Discrimination Index was evaluated using Mann-Whitney U test.

Results: The confirmatory factor analysis indicated the presence of three distinct factors within the scale. The Split Half reliability results were found to be 0.980 and 0.976. The internal consistency analysis was determined to be 0.940 and 0.988 based on Cronbach's alpha. The presence of floor and ceiling effects was deemed absent.

Conclusion: The analysis of the PCQ-F Turkish version showed that this is a valid and reliable. The PCQ-F serves as a tool for evaluating the perceived psychosocial environment within healthcare, and can also assess the similarities and differences in experiences between families and patients across various healthcare contexts.

Keywords: Climate, family, person-centered care, psychometrics, questionnaire

INTRODUCTION

Patient- and family-centered care represents a model for the organization, provision, and assessment of health care services that emphasizes collaborative relationships among health care providers, patients, and their families.[1] This approach has been associated with improved health outcomes, enhanced experiences for patients and families, increased satisfaction among clinicians and staff, and more efficient use of resources.[1,2]

Disease management is a multifaceted process occurring across diverse environments, including homes, hospitals, and communities. In all these contexts, the involvement of family is crucial, as it can significantly impact family dynamics. The presence of illness extends beyond the individual, often resulting in alterations to the entire family's lifestyle. Family members frequently assume roles that encompass both physical and emotional support, such as preparing meals, administering medications, facilitating physical activity, and assisting with emotional resilience, all aimed at aiding the patient's recovery and illness management.[3]

Trends towards family-centered care in medicine have increased over the last decade, and there has been an increasing recognition of the significant role that patient families have in clinical practice. In the literature, there is an increasing number of studies emphasizing the importance of family functioning in all age groups, from newborns and infants who need intensive care treatment, to elderly people who need medical and social support due to various chronic diseases and increased frailty, or people with various chronic diseases such as spinal cord injury, cancer, heart and kidney failure, or mental illnesses.[4-8]

Family members frequently play a crucial role for patients, particularly in instances of acute or critical illness. From a holistic perspective that encompasses biological, psychological, and social dimensions, families serve as vital resources for both patients and healthcare providers. Rather than viewing them as passive recipients, engaging patients and their families as active participants in decisions regarding follow-up, treatment, or care can enhance health outcomes

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and elevate satisfaction levels for both patients and their families.[9] In order to ensure the best communication and cooperation between healthcare professionals and patients' relatives, methods have been researched and scales have been tried to be put forward.[9,10] To evaluate experiences within the healthcare environment, two distinct scales were developed, one targeting patients (PCQ-P)[11] and the other focusing on staff (PCQ-S).[12] These scales were initially Swedish and were designed, assessed, and validated. A family version of the PCQ (PCQ-F) was then developed to determine the extent whereby individuals within the family assessed the care environment.[9] The PCQ-P has three sub-dimensions to measure the experience of safety, everyday life and hospitality. A safe environment is established when personnel are approachable, demonstrate proficiency, and communicate in clear, comprehensible language. Additionally, maintaining cleanliness and providing areas that allow for both privacy and social interaction are crucial components of this environment. When positive distractions are provided in an environment where patients and their families can feel comfortable and think about things other than the disease and treatment, a daily living environment is provided. A hospitable atmosphere is established when the surroundings communicate that individuals' needs are fulfilled, alongside an impression of care and attention that surpasses anticipated standards.[11,12] PCQ-F addressed the previously unexamined aspect of evaluating family members' perceptions of the care environment in terms of person-centeredness.[9]

In Turkiye, there is a lack of instruments to measure how family members view the caring environment in terms of person-centeredness. As a result of the aforementioned considerations, this research endeavor was meticulously designed with the primary objective of evaluating both the validity and reliability of the PCQ-F instrument specifically within the unique socio-cultural and psychological context of Turkiye, while simultaneously aiming to contribute substantially to the existing body of scholarly literature that addresses this pertinent topic in depth.

METHODS

The Process of Translation and the Subsequent Adaptation to Cultural Contexts

The researchers responsible for the development of the PCQ-F survey were contacted through email to obtain necessary permissions for utilizing the scales in this study. Prior to conducting the validity and reliability assessment, approval was secured from the Ankara University Faculty of Medicine Clinical Researches Ethics Committee (Date: 20.06.2023, Decision No: 106-394-23). This investigation was carried out in compliance with the principles outlined in the Declaration of Helsinki. Each participant furnished written informed consent for the use of their data in the research.

The Turkish adaptation of the PCQ-F was performed by three linguists and two subject matter experts to ensure linguistic validity. Two forward translators worked independently (double-blind) and translated the original PCQ-F into Turkish. The Turkish version was back translated into English by two independent translators and compared to the original scale. These two independent translators are the independent individuals unfamiliar with the original scale. The PCQ-F was finalized based on the feedback of a Turkish linguist who reviewed the English and Turkish meanings of the scale items.

After the translation process, the scale was first applied to a group of 24 people and the answers to the questions were analyzed to check the comprehensibility and applicability of the questions in the scale. Since the answers were logical and evenly distributed, it was concluded that the scale was applicable to the target group.

Participants and Data Collection

This methodological research involved 177 participants admitted to the emergency department between July 1 and October 31, 2023. Inclusion criteria; being over 18 years of age, having at least literacy level education, volunteering to answer the survey questions presented on the online-tablet. Exclusion criteria: obvious signs of cognitive impairment and/or depression, known to be receiving serious neurological or psychiatric treatment, such as dementia or schizophrenia, vision/hearing problems (reported or perceived).

In validity and reliability studies, having at least 10 times the number of scale items is considered sufficient for the evaluation of the scale.[13] In our study, a minimum sample size of 170 people was found sufficient for 17 questions.

Statistical Analysis

Data analysis was conducted using SPSS 11.5 and AMOS 24.0 software. Descriptive statistics included mean±SD (standard deviation) and median (min-max) for quantitative variables, while qualitative variables were represented by the number of individuals (percentage). The Mann-Whitney U test evaluated statistically significant distinctions between pairs of qualitative variables, while the Kruskal-Wallis H test was utilized for qualitative variables encompassing more than two categories, owing to the infringement of normality assumptions. Construct validity was evaluated through confirmatory factor analysis, with factorability tested using the Kaiser-Meyer-Olkin measure and Bartlett's test of sphericity. Reliability was assessed using the Spearman-Brown and Gutman coefficients for Split Half reliability, alongside the calculation of Cronbach's alpha. Additionally, the Mann-Whitney U test was applied to determine the Item Discrimination Index. A p-value that is determined to be lower than the threshold of 0.05 is regarded as indicative of statistical significance, suggesting that the observed results are unlikely to have occurred by random chance alone and thereby warrant further investigation and consideration within the context of the research findings.

RESULTS

Validity

Content validity: Content validity in this research was assessed by 15 experts who classified 17 items using a three-tier rating system: "essential," "useful, but not essential," and "not necessary." The minimum CVR for the group of 15 experts was determined to be 0.49. The CVR is computed using the formula CVR=[E/(N/2)]-1, where E represents the

number of experts who rated an item as "essential," and N denotes the total number of experts. According to the CVR values presented in Table 1, it was determined that all items should remain in the item pool, as the CVR for each item exceeded the threshold of 0.49.

Table 1. CVR and CVI values of items

Items	Essential	Useful, but not essential	Not necessary	CVR	CVI
I1	15	0	0	1.000	
I2	15	0	0	1.000	
I3	14	1	0	0.867	
I4	13	1	1	0.733	
I5	15	0	0	1.000	
I6	14	1	0	0.867	
I7	15	0	0	1.000	
I8	15	0	0	1.000	
I9	15	0	0	1.000	0.867
I10	15	0	0	1.000	
I11	12	2	1	0.600	
I12	13	1	1	0.733	
I13	14	0	1	0.867	
I14	12	1	2	0.800	
I15	14	1	0	0.867	
I16	13	2	0	0.733	
I17	14	1	0	0.867	

CVR: Content validity ratio, CVI: Content Validity Index

The CVI for the scale is determined by calculating the average Content Validity Ratio CVR of the items included in the item pool. In this study, the CVI was computed as CVI=(1.000+1.000+0.867+…+0.867)/17=0.867. Since the CVI of 0.813 exceeds the threshold of 0.67, it was concluded that the scale demonstrates statistical significance.

Logical validity: The scale demonstrated logical validity by accurately measuring the key components and delivering the desired information with precision.

Testing of factorability: The KMO test was utilized as a statistical measure to ascertain the appropriateness and adequacy of the sample being analyzed in relation to its suitability for conducting factor analysis. A KMO value that surpasses the threshold of 0.80 is widely recognized as a clear indication of a robust and reliable foundation for performing factor analysis, thereby suggesting that the underlying data structure is indeed conducive to such analytical endeavors. In the context of this particular study, an impressive KMO value of 0.981 was achieved, which serves to definitively confirm that the sample utilized was not only adequate but also remarkably suitable for the intended factor analysis. Moreover, in addition to the KMO test, Bartlett's test of sphericity was meticulously performed in order to rigorously evaluate the adequacy of the correlation matrix for the purposes of factor analysis, which yielded a statistically significant result ($p<0.001$), thus reinforcing the validity of the correlations observed within the data. This comprehensive assessment highlights the robustness of the sample and the analytical methods employed, ensuring that the results derived from the factor analysis are both reliable and meaningful. Consequently, the findings of this research are underpinned by a solid methodological foundation, rendering them not only credible but also of substantial value to the broader field of study.

Construct validity: The current study employed confirmatory factor analysis, building on a Turkish validity and reliability assessment of a scale that had previously demonstrated validity and reliability in its original language. Table 2 presents the factor loadings for the scale's items categorized by subscales, revealing that all items exhibited factor loadings exceeding 0.7, thereby confirming construct validity for the subscales. The Chi-square to degrees of freedom ratio ($\chi 2/df$) was determined to be 1.487, which is well below the acceptable threshold of 3 ($p<0.001$). Additionally, the study reported RFI, CFI, TLI and GFI values of 0.958, 0.988, 0.986 and 0.963 respectively, all surpassing the acceptable benchmark of 0.9. The RMSEA value was calculated at 0.053, which is also below the acceptable limit of 0.08. Overall, the findings affirm the construct validity based on the established criteria.[14] The path diagram for construct validity is given in Figure.

Table 2. Item factor loadings by subscales

Items	Safety	Everydayness	Hospitality
I1	0.936		
I2	0.927		
I3	0.922		
I4	0.932		
I5	0.908		
I6	0.912		
I7	0.904		
I8	0.926		
I9	0.894		
I10	0.899		
I11		0.915	
I12		0.940	
I13		0.932	
I14		0.946	
I15			0.923
I16			0.893
I17			0.938

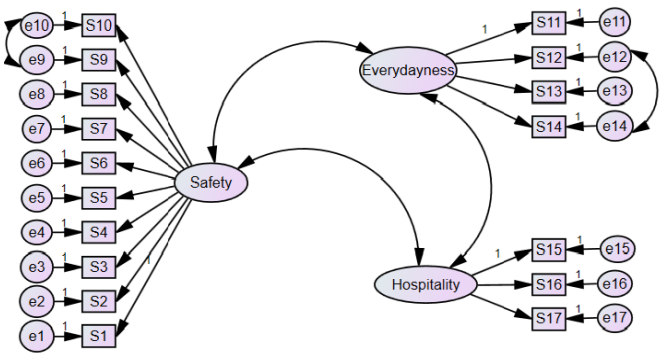

Figure. Path diagram of the Person-Centered Climate Questionnaire-family version

Reliability

Split half reliability: This scheme was used because there was not enough time to re-test the patients and it was difficult to reapply the scale because most of the patients were discharged in a short time. In this method, the items of the scale are divided into two halves and the calculation is based on the correlation between the total scores obtained from these items. The most commonly used Spearman-Brown and Gutman statistics for this method were used in the study. The coefficients for Spearman-Brown and Gutman methods were 0.980 and 0.976, respectively. The results indicated that the scale demonstrated reliability.

Cronbach's alpha: Upon conducting a thorough analysis of the data, the computed values of Cronbach's alpha demonstrated an exceptionally high level of reliability across the various subscales, revealing values that reached an impressive 0.981 for the subscale dedicated to Safety, 0.961 for the subscale pertaining to everydayness, and 0.940 for the subscale associated with hospitality, while the overall total score for the PCQ-F was recorded at an outstanding 0.988. Thus, it can be inferred that both the scale and its respective subscales demonstrate strong internal consistency.

Comparison of top-bottom 27% groups (Item Discrimination Index): A significant difference was observed between the upper and lower 27% groups for the safety, everydayness, and hospitality subscales ($p<0.001$, $p<0.001$, and $p<0.001$), as well as for the overall PCQ-F total score. The analysis determined that the scale possesses a sufficient Item Discrimination Index.

Analysis of ceiling and floor effects within the measurement instrument: The safety subscale in the study had a minimum score of 0 and a maximum score of 50. There were 1 (0.6%) participant who scored 0 and 2 (1.1%) subjects that recorded 50. The everydayness subscale had a minimum score of 0 and a maximum score of 20. Eight (4.5%) participants scored 0, and 4 (2.3%) participants scored 20. The hospitality subscale had a minimum score of 0 and a maximum score of 15. Four (2.3%) participants scored 0, and 7 (4.0%) participants recorded a 15. The entire scale had a minimum score of 0 and a maximum score of 85. One (0.6%) participant scored 0, and 1 (0.6%) participant scored 85. The findings indicate the absence of ceiling or floor effects in both the overall scale and its individual subscales.

Descriptive Statistics

The comprehensive statistical data pertaining to the overarching scale as well as its distinct subscales are meticulously delineated in Table 3, which specifically pertains to the cohort of physicians who actively participated in the study. Upon conducting a thorough analysis of the data, it was ascertained that there were no statistically significant variations or discrepancies in the scores obtained from the scale when evaluated across the various examined demographic and clinical variables that were taken into consideration during the research process. This finding underscores the relative uniformity of the scale scores among the participating physicians, suggesting a consistent response pattern that spans the different subgroups analyzed within the study framework.

Table 3. Comparisons of descriptive variables for subscale scores and total score

Variables		Safety		Everydayness		Hospitality		PCQ-F score	
		Mean±SD	Median (min-max)	Mean±SD	Median (min-max)	Mean±SD	Median (min-max)	Mean±SD	Median (min-max)
Age	≤42	22.35±12.39	20.00 (2.00-49.00)	8.07±4.88	7.50 (0.00-20.00)	6.75±3.83	6.50 (0.00-15.00)	37.16±20.63	34.50 (3.00-83.00)
	>42	24.78±13.31	26.00 (0.00-50.00)	9.26±5.53	10.00 (0.00-20.00)	7.45±4.03	8.00 (0.00-15.00)	41.48±22.54	45.00 (0.00-85.00)
	p-value		0.192[a]		0.128[a]		0.228[a]		0.176[a]
Gender	Female	24.98±13.41	26.00 (0.00-50.00)	9.17±5.43	9.00 (0.00-20.00)	7.51±4.11	8.00 (0.00-15.00)	41.66±22.56	41.00 (0.00-85.00)
	Male	20.86±11.42	19.00 (2.00-48.00)	7.68±4.71	7.00 (0.00-17.00)	6.32±3.50	7.00 (0.00-15.00)	34.86±19.18	33.00 (3.00-80.00)
	p-value		0.063[a]		0.109[a]		0.073[a]		0.068[a]
Marital status	Single	23.69±12.89	24.00 (2.00-47.00)	8.47±4.78	8.00 (0.00-17.00)	7.09±3.78	7.50 (1.00-15.00)	39.24±21.04	40.00 (3.00-78.00)
	Married	23.40±12.91	24.00 (0.00-50.00)	8.75±5.51	9.00 (0.00-20.00)	7.08±4.05	7.00 (0.00-15.00)	39.23±22.08	40.00 (0.00-85.00)
	p-value		0.842[a]		0.859[a]		0.908[a]		0.945[a]
Educational status	Elementary	24.29±14.79	25.00 (1.00-50.00)	9.27±6.21	9.00 (0.00-20.00)	7.39±4.39	8.00 (0.00-15.00)	40.95±25.01	41.00 (2.00-85.00)
	High school	26.35±11.52	26.50 (3.00-48.00)	9.83±4.46	9.50 (0.00-20.00)	8.00±3.73	8.00 (0.00-15.00)	44.19±19.35	45.00 (3.00-80.00)
	University	22.18±12.60	18.50 (0.00-48.00)	8.03±5.02	7.00 (0.00-19.00)	6.66±3.85	6.00 (0.00-15.00)	36.87±20.96	32.00 (0.00-81.00)
	Postgraduate	20.23±12.07	21.00 (2.00-50.00)	6.88±4.89	7.00 (0.00-19.00)	5.92±3.50	5.50 (1.00-15.00)	33.04±20.16	34.50 (3.00-84.00)
	p-value		0.073[b]		0.148[b]		0.067[b]		0.110[b]
Patient's relative before	No	23.02±12.53	21.00 (2.00-49.00)	8.37±4.75	8.00 (0.00-19.00)	7.01±3.82	7.00 (1.00-15.00)	38.40±20.76	37.00 (5.00-83.00)
	Yes	24.01±13.25	25.50 (0.00-50.00)	8.91±5.67	9.00 (0.00-20.00)	7.16±4.06	8.00 (0.00-15.00)	40.08±22.53	41.50 (0.00-85.00)
	p-value		0.571[a]		0.574[a]		0.773[a]		0.590[a]

SD: Standard deviation, Min: Minimum, Max: Maximum, a: Mann-Whitney U test, b: Kruskal Wallis H test

DISCUSSION

The PCQ-F scale offers an innovative approach to examine how family members perceive psychosocial care and the extent to which it is regarded as person-centered. This scale aims to contribute to the literature by providing more information on how various care settings are perceived by family members. Through the scale, knowledge can be increased in the psychosocial context and person-centered care can be developed in relevant areas, taking into account the well-being of all individuals involved in the study. In this research, the assessment of the validity and reliability of the Turkish adaptation of the PCQ-F scale was conducted.

he initial version of the scale represents the sole research in the existing literature that has evaluated its validity and reliability. The original study indicated that construct validity was confirmed through a three-factor structure. Lindahl et al.[9] did not conduct exploratory factor analysis in their study; however, they indicated that a three-factor structure was suitable. In the current research, confirmatory factor analysis was executed based on this three-factor framework, although it was not validated. Evaluation was made based on the total score of 17 questions and the single-factor structure was provided by confirmatory factor analysis.

In evaluations, a scale is deemed more dependable when its Cronbach's alpha approaches 1. The initial research on the scale revealed Cronbach's alphas of 0.95 for the safety subscale, 0.88 for the everydayness subscale, and 0.75 for the hospitality subscale.[9] In the current investigation, the Cronbach's alpha for the PCQ-F total score was determined to be 0.988. Additionally, the test-retest (split half reliability) correlation coefficients for the PCQ-F total score were recorded at 0.980 and 0.976 using two different methods. These findings suggest that the scale demonstrates a high level of reliability for use.

Limitations

The study's limitation lies in the fact that the scale was administered to relatives of patients within the high-stress context of an emergency room. Because in such an environment, people tend to complete the scale by answering quickly without reading. The limitation was addressed by incorporating a control question into the survey, aimed at discouraging random responses from participants. Those who failed to select the appropriate response to the control question, which asked them to indicate that they had read and understood the instructions, were excluded from the study. As a result, 17 people were removed from the study. The study was completed using the data of the remaining people, thus creating a more reliable study.

CONCLUSION

The findings from the study indicate that the Turkish adaptation of the PCQ-F is both valid and reliable. This instrument can effectively evaluate perceptions of the psychosocial climate within healthcare environments and its potential impact on outcomes. Additionally, it serves to analyze the similarities and differences in experiences between families and patients across various healthcare contexts.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Ankara University Faculty of Medicine Clinical Researches Ethics Committee (Date: 20.06.2023, Decision No: 106-394-23).

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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Investigation of traditional and complementary medicine use among oncology patients: a cross-sectional analysis

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ABSTRACT

Aims: The aim of this study was to determine the prevalence of traditional and complementary medicine (T&CM), sociodemographic characteristics, methods used, attitudes towards this medicine and the main factors affecting its use in oncology patients.

Methods: This cross-sectional study was conducted between June 1 and July 31, 2024, involving patients receiving treatment at the Medical Oncology Service of Ankara Etlik City Hospital who agreed to participate in the study. Data collection was carried out through a questionnaire, and statistical analysis was performed using the Chi-square test, with a significance level set at $p<0.05$.

Results: While 40.8% of the 179 patients used T&CM before cancer diagnosis, this rate decreased to 28.4% afterwards. While there was a significant correlation between education level and T&CM use ($p=0.03$), no correlation was found between gender and age. Phytotherapy was the most frequently used method (66.7%). T&CM was mostly used for cure (66.7%), but only 3.9% of patients reported complete benefit. It was observed that 76.5% of the patients did not consult their physician or ask for information about T&CM. The most common reason for this is lack of patient knowledge. Only 11.7% of patients reported receiving adequate information about T&CM from their physicians.

Conclusion: It was found that patients did not have enough information about T&CM and doctors did not provide enough information on the subject. Accurate information for patients can be provided by increasing the awareness of doctors about T&CM methods. In this way, patient-doctor communication can be strengthened, patients' reservations can be reduced and a more open exchange of information can be provided.

Keywords: Traditional and complementary medicine, phytotherapy, oncology

INTRODUCTION

The World Health Organization (WHO) describes traditional and complementary medicine (T&CM) as a body of knowledge, skills, and practices that are used across different cultures for the prevention, diagnosis, and treatment of both physical and mental conditions. These practices are based on cultural beliefs, experiences, and theories, some of which may have scientific explanations while others do not. A number of alternative therapies are currently accepted in our country, including phytotherapy, leech treatment, larva application, cupping, mesotherapy, apitherapy, prolotherapy, acupuncture, hypnosis, ozone application, music therapy, homeopathy, reflexology, osteopathy and chiropractic.[1,2]

Cancer patients have to cope with both the symptoms of the disease itself and the negative effects of oncological treatments at the same time. The challenges encountered in this endeavour prompt patients to explore alternative therapeutic avenues beyond the conventional medical interventions. It is clear that interest in T&CM methods is increasing, both in our country and globally.[3,4] The primary objectives of employing T&CM methodologies are to mitigate the adverse effects associated with conventional oncological therapies, enhance appetite, provide effective pain management, and bolster the immune system.[5]

Despite the high prevalence of T&CM methods in cancer treatment, there is a notable deficit in communication between doctors and patients regarding the use of these methods. In a survey conducted by the 'American Society of Clinical Oncology (ASCO)' in 2014, it was shown that most of the oncologists surveyed did not have sufficient knowledge about T&CM methods and could not communicate effectively with their patients.[6] This may be attributed to the fact that T&CM methods are not adequately incorporated into oncology guidelines.

The aim of our study is to determine the prevalence of traditional and complementary medicine (T&CM), its

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sociodemographic characteristics, methods of application, perceptions, and the main factors influencing its use. For this purpose, the responses of patients admitted to the Medical Oncology Service of Ankara Etlik City Hospital to a questionnaire based on a literature review on T&CM were evaluated. The objective of the study is to enhance physicians' awareness of T&CM, provide patients with comprehensive information, strengthen patient-physician communication, and prevent patients from giving incorrect or incomplete statements due to fear of physicians' reactions.

METHODS

This study utilized a descriptive and cross-sectional design to examine the use of T&CM methods, the reasons behind their use, influencing factors, patient satisfaction, and whether physicians were informed by patients hospitalized in the Medical Oncology Service of Ankara Etlik City Hospital. This study was approved by the Ankara Etlik City Hospital Scientific Researches Evaluation and Ethics Committee (Date: 22.05.2024, Decision No: AEŞH-BADEK-2024-485). All procedures in this study adhered to the principles outlined in the Helsinki Declaration, including its subsequent revisions or other equivalent ethical guidelines.

After obtaining the necessary ethical committee approval, the study included the first 200 patients admitted to the Medical Oncology Service for any reason between June 1, 2024, and July 31, 2024, who voluntarily agreed to participate in the survey. Patients were permitted to terminate their participation in the survey at any point. A total of 21 patients were excluded from the study for this reason. Patients were asked to provide verbal consent, and the questionnaires were conducted via face-to-face interviews.

The questionnaire comprised 10 questions pertaining to the sociodemographic characteristics and oncological status of the patients. Furthermore, the questionnaire comprised a total of 30 questions, including 20 items designed to ascertain whether the participants had applied T&CM to their patients, the methods they had employed if they had done so, whether they had informed their physicians, whether the physicians had informed the patients about T&CM, and patient satisfaction following the application of T&CM.

The data obtained in this study were analyzed using SPSS 30 (Statistical Package for the Social Sciences, version 30). The chi-square test was employed for statistical analysis. The level of statistical significance (p-value) was determined based on the applied tests, with a threshold of $p<0.05$ considered statistically significant.

RESULTS

The study analyzed 179 cancer patients, with a median age of 61 years (19-92) and a male predominance (58.6%). The most frequently observed comorbidities were hypertension (33.5%) and diabetes mellitus (30.0%). Lung (21.8%), gastric (15.1%), and pancreatic (11.2%) cancers were the most frequent types, with 63.2% of cases being metastatic. Nearly half (49.2%) were diagnosed within six months. The primary hospitalization reason was oncological treatment continuation (32.4%), followed by infections (17.9%) and nutritional support (16.2%). Other causes included electrolyte imbalance (11.7%), blood transfusion (5.6%), and interventional procedures (16.2%). Table 1 summarizes the clinical and demographic characteristics.

Table 1. Demographic and clinical characteristics of the patients (n=179)

Parameters	n (%)
Age median (range)	61.0 (19.0-92.0)
Sex n	
Female	74 (41.4)
Male	105 (58.6)
Education level	
Illiterate	33 (18.4)
Primary education	69 (38.6)
High school	45 (25.1)
University	32 (17.9)
Comorbidity	
Yes	99 (55.4)
No	80 (44.6)
Comorbidity	
Diabetes mellitus	55 (30.0)
Hypertension	60 (33.5)
Hypothyroidism	6 (3.3)
Chronic obstructive pulmonary disease-asthma	11 (6.1)
Neurological diseases	13 (7.2)
Others	10 (5.5)
Type of cancer	
Lung	39 (21.8)
Gastric	27 (15.1)
Pancreas	20 (11.2)
Jinecological (over-endometrium-cervix)	19 (10.6)
Colorectal	16 (8.9)
Breast	14 (7.8)
Head and neck	13 (7.3)
Sarcoma (soft tissue-bone)	9 (5.0)
Biliary tract	6 (3.4)
Bladder	4 (2.2)
Others	12 (6.7)
Stage	
Metastatic	113 (63.2)
Non-metastatic	66 (36.8)
Time after diagnosis (months)	
<6	88 (49.2)
6-12	42 (23.5)
>12	49 (27.3)
Cause of hospitalisation	
Electrolyte imbalance	21 (11.7)
Infection	32 (17.9)
Blood transfusion necessity	10 (5.6)
Oncological treatment continued	58 (32.4)
Nutrition and support	29 (16.2)
Other interventional procedures etc	29 (16.2)

As demonstrated in Table 2 and Figure, the majority of patients (69.3%) reported that their physicians had not provided them with any information regarding T&CM. Only 11.7% of patients indicated that they had been adequately informed. It was observed that 76.5% of patients did not consult their doctor about T&CM, nor did they request information from their doctor. The most common reason for this was a lack of information available to the patients. Despite this, 23.5% of patients actively sought a doctor's opinion on T&CM, yet physician recommendations remained limited, with only 4.8% endorsing its use, while 78,6% explicitly advised against it. Following a cancer diagnosis, 28.4% of patients used T&CM, a decrease from 40.8% who had used it before diagnosis (Table 2 and Figure).

Table 2. Patients' knowledge and utilisation of T&CM

Parameters	n (%)
Doctor's provision of information about T&CM	
Adequate information	21(11.7)
Inadequate information	34(19.0)
No information at all	124(69.3)
Have you asked for a doctor's opinion-recommendation about TCM?	
Yes	42(23.5)
No	137(76.5)
Doctor's response to patients inquiring about T&CM	
Recommended	2(4.8)
Did not recommend	33(78.6)
No comment	7(16.6)
Use of T&CM before diagnosis of cancer	
Yes	73(40.8)
No	106(59.2)
After diagnosis of cancer	
Yes	51(28.4)
No	128(71.6)
Would you consider using T&CM in the future?	
Yes	17(9.5)
No	125(69.8)
Undecided	37(20.7)

T&CM: Traditional and complementary medicine

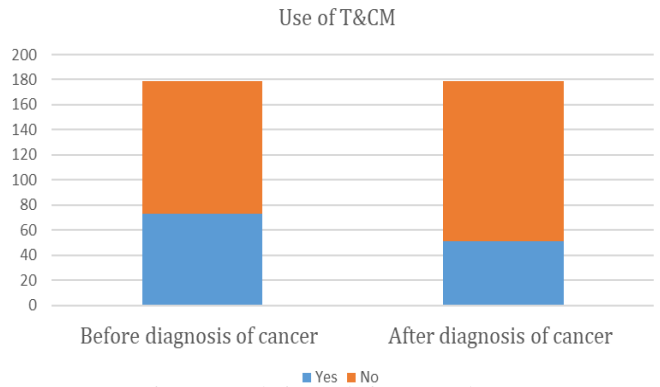

Figure 1. Rates of T&CM use before and after cancer diagnosis

T&CM: Traditional and complementary medicine

The majority of patients (52.9%) were encouraged by their families, while 19.6% were influenced by social media to use T&CM. The primary reasons for T&CM use were seeking a cure (54.9%), appetite improvement (23.6%), and pain control (21.5%). The most commonly used method was phytotherapy (66.7%), followed by cupping therapy (15.7%) and religious practices (13.7%). However, only 3.9% of patients reported experiencing complete benefit. Recommendations, methods, and outcomes of T&CM use after a cancer diagnosis are summarized in Table 3.

Table 3. Reasons, tools, results of using T&CM after diagnosis of cancer

Parameters	n (%)
Who recommended T&CM use after cancer diagnosis?	
Her/hisself	1 (2.0)
Family	27 (52.9)
Neighbor	7 (13.7)
Friend	6 (11.8)
Social media	10 (19.6)
Applied T&CM tools	
Phytotherapy (herbal treatment)	34 (66.7)
Shrine-prayer religious orientation	7 (13.7)
Hacamat (cupping)	8 (15.7)
Leech treatment	2 (3.9)
Satisfaction status of T&CM users (results)	
Benefited	2 (3.9)
Some benefit	17 (33.3)
No benefit, no harmed	24 (47.0)
Harmed	8 (15.8)
Reasons for using TCM n (%)	
For cure	28 (54.9)
For appetite	12 (23.6)
For pain control	11 (21.5)

T&CM: Traditional and complementary medicine

T&CM users and non-users showed no important differences in age (p=0.08), sex (p=0.75), cancer stage (p=0.94), or time since diagnosis (p=0.72). However, education level significantly differed (p=0.03), with T&CM users having a higher proportion of high school and university graduates. Lung (25.4%) and gastric (17.6%) cancers were more common among T&CM users, but cancer type was not statistically significant (p=0.25). Table 4 summarizes the characteristics associated with T&CM use after cancer diagnosis.

DISCUSSION

Patients undergoing treatment for cancer must contend with the clinical manifestations of the disease while simultaneously grappling with the adverse effects of oncological therapies. The challenges encountered in this endeavour often prompt patients to explore alternative avenues of treatment beyond the conventional medical paradigm. There is a growing interest in T&CM methodologies, not only in our country but also globally.[3,4]

Table 4. Analysis of T&CM use after cancer diagnosis

Characteristics	T&CM users n (%)	T&CM non-users n (%)	p
Age (years)			
<40	7 (13.7)	9 (7.0)	
40-60	23 (45.1)	44 (34.4)	0.08
>60	21 (41.2)	75 (58.6)	
Sex n (%)			
Female	22 (43.1)	52 (40.6)	0.75
Male	29 (56.9)	76 (59.4)	
Education level			
Illiterate	7 (13.7)	26 (20.3)	
Primary education	14 (27.5)	55 (43.0)	0.03*
High school	15 (29.4)	30 (23.4)	
University	15 (29.4)	17 (13.3)	
Stage			
Metastatic	32 (62.7)	81 (63.3)	0.94
Non-metastatic	19 (37.3)	47 (36.7)	
Type of cancer			
Lung	13 (25.4)	26 (20.3)	
Gastric	9 (17.6)	18 (14.1)	
Pancreas	3 (5.9)	17 (13.3)	
Jinecological	3 (5.9)	16 (12.6)	
Colorectal	3 (5.9)	13 (10.2)	
Breast	6 (11.8)	8 (6.2)	0.25
Head and neck	5 (9.8)	8 (6.2)	
Sarcoma (soft tissue-bone)	3 (5.9)	6 (4.7)	
Biliary tract	2 (3.9)	4 (3.1)	
Bladder	0 (0.0)	4 (3.1)	
Others	4 (7.9)	8 (6.2)	
Time after diagnosis (months)			
<6	23 (45.1)	65 (50.8)	
6-12	12 (23.5)	30 (23.4)	0.72
>12	16 (31.4)	33 (25.8)	
Use of TCM before diagnosis of cancer			
Yes	24 (47.1)	49 (38.3)	0.28
No	27 (52.9)	79 (61.7)	

T&CM: Traditional and complementary medicine, *p<0.05 indicates statistical significance

In the course of our investigation, we observed that 28.4% of the patients in question had resorted to the use of T&CM methods subsequent to receiving a diagnosis of cancer. In a study conducted by Keene et al.[3] the frequency of applying T&CM methods was found to be 51%, while in a study by Hill et al.[7] this rate was reported to be 54.5%. In a study reported by Ulusoy et al.[9] in Turkiye in 2021, T&CM's prevalance application was reported as 33.3%. In a study involving 75 patients with head and neck cancer in nine countries in Europe, the prevalence of T&CM application was reported as 22.7%.[8] A review of the literature reveals that the use of T&CM is more prevalent, particularly in Asian countries.[10] These findings indicate that the prevalence of T&CM use varies significantly across different geographic regions, influenced by cultural structures and healthcare systems. A review of the literature showed that the rate of using T&CM methods increased following a cancer diagnosis. In contrast, our study demonstrated that the rate was higher prior to a cancer diagnosis.[8] This may be attributed to the fact that patients did not perceive the anticipated benefits from T&CM applications prior to their utilisation.

Various factors such as age, gender, educational attainment, tumor type and stage, geographical location, and socioeconomic status influence the adoption rate of T&CM practices. Studies conducted by Keene, Hill, Mwaka, and Molassiotis have reported that the use of T&CM is most frequently observed among younger individuals, females, those with higher levels of education and income, and individuals with prior experience using T&CM methods.[3,5,7,12] While the existing literature suggests significant associations between these demographic and socioeconomic variables and T&CM use, several studies have also failed to confirm such relationships.[13-15] In our study, a statistically significant relationship was found only between educational level and the frequency of T&CM use, whereas no significant association was identified with gender or age. There may be several explanations for the greater tendency of highly educated individuals to utilize T&CM methods. As the level of education increases, individuals are more likely to access health-related information and possess the skills to critically evaluate it. This may enhance their inclination to explore alternative approaches alongside conventional treatments. Moreover, highly educated individuals tend to adopt a more proactive and autonomous role in healthcare decision-making, which may facilitate the use of self-directed practices such as T&CM.

Phytotherapy is the most prevalent T&CM method in the majority of studies referenced in the literature.[13,16-18] This study, phytotherapy was identified as the most frequently employed T&CM method. Visiting holy sites was reported to be the most commonly used T&CM method among cancer patients in a study conducted in Iran. The diverse socioeconomic, cultural and geographical characteristics of countries have resulted in the implementation of a multitude of T&CM methods.[19]

The T&CM methods are employed by patients for a variety of purposes, including the pursuit of a cure, the alleviation of symptoms, the stimulation of appetite, and the management of pain. As is the case in a large number of studies published in the literature, the most common reason for the use of T&CM in our study was to facilitate the healing process.[20,21]

The findings of our study indicate that 76.5% of patients did not seek consultation with their physician regarding T&CM and did not request information from their doctor. In our study, the most significant reason for patients failing to consult their doctor about T&CM was the absence of information and a lack of awareness about T&CM. The fact that the majority of our patients are primary school graduates or illiterate may be a factor that causes this situation. Nevertheless, numerous studies in the literature have demonstrated that the primary reason why patients who undergo T&CM do not provide information to their physicians is due to apprehension about the potential response from the medical practitioner.[5,22,23]

It is important to note that this may present a challenge in accurately determining the prevalence of T&CM use.

Another important factor for underreporting of T&CM is the lack of adequate knowledge of physicians on this subject. In addition, the current state of communication between patients and physicians is inadequate, which prevents the disclosure of T&CM to healthcare professionals.5,24 The proportion of patients who stated that they received adequate information about T&CM was very low (11.7%) in our study.

An analysis of the distribution of individuals who recommend T&CM methods reveals that friends, relatives, and neighbours represent a significant proportion.[8,12,25-27] The Internet and social media play an integral role in this distribution process.[14,28] Our study is similar to the studies in the literature.

The majority of studies in the literature indicate that patients derive benefit from T&CM methods.[16,29,30] In contrast to the majority of studies in the literature, our study revealed that only a small proportion of patients who applied T&CM methods fully benefited (3.9%). The discrepancy in outcomes may be attributed to the heterogeneous expectations of patients, their advanced disease stages, and the variations in the implementation of T&CM methods across different centres and frequencies.

Limitations

This study has several limitations. Firstly, its single-center and cross-sectional design restricts the generalizability of the findings. Since all participants were recruited from a single institution, regional sociocultural variations that might influence the use of T&CM could not be assessed. Secondly, the data were collected through self-reported questionnaires, which may be subject to recall bias, particularly in relation to patients' prior use of T&CM. In addition, some patients may have refrained from disclosing their use of T&CM due to concerns about their physicians' potential reactions, which could have led to underreporting. Moreover, the study relied solely on survey-based data and did not include objective clinical outcomes related to T&CM practices. These limitations underscore the need for future multi-center, prospective studies that incorporate both qualitative and quantitative methods to obtain a more comprehensive understanding of T&CM utilization among cancer patients.

CONCLUSION

It was observed that patients lacked sufficient knowledge about T&CM, physicians did not adequately inform them, and patients often did not disclose their use of T&CM to their doctors. Contrary to our findings, most studies in the literature suggest that patients tend not to inform their physicians about T&CM use due to concerns over potential negative reactions. This presents a challenge in accurately determining the true prevalence of T&CM use. Therefore, improving patient awareness and strengthening physician–patient communication is essential. To achieve this, integrating basic T&CM education into medical school curricula, providing in-service training for healthcare professionals, and developing evidence-based clinical guidelines are recommended. Physicians equipped with communication strategies that encourage openness may facilitate more accurate information sharing and support the safer integration of T&CM into oncological care.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Ankara Etlik City Hospital Scientific Researches Evaluation and Ethics Committee (Date: 22.05.2024, Decision No: AEŞH-BADEK-2024-485).

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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Prognostic importance of PET score obtained from IMPeTUs criteria in multiple myeloma

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ABSTRACT

Aims: Multiple myeloma (MM) is a clonal plasma cell malignancy that infiltrates the bone marrow, bone, and sometimes extramedullary sites. Reliable staging and prognostic factors are essential for patient management. Imaging modalities, especially 18F-FDG PET/CT, are essential for the assessment of disease extent. This study evaluates a scoring system based on the IMPeTUs criteria for predicting progression-free survival (PFS) in MM.

Methods: This study included 35 newly diagnosed, treatment-naive MM patients (13 females, 22 males). Baseline ^{18}F-FDG PET/CT scans were obtained within one month of diagnosis. Five different assessments were performed. The PET score is a scoring system adapted from the previously established IMPeTUs to provide a more nuanced assessment of PET scan results in newly diagnosed patients. This system incorporates the DS (Deauville score), a standardised measure of treatment response in lymphoma, together with an assessment of the number of lesions seen on the PET scan.

Results: The mean age of the cohort was 65 years. Ig G kappa was the most common MM type (37.1%). Diffuse bone marrow uptake and focal lesions were observed in 37.2% and 57.2% of patients, respectively, DS ≥4. The PET score cut-off of 6.5 predicted PFS with 61.5% sensitivity and 72.7% specificity (AUC 0.715). Median PFS was significantly different between patients with PET score <6.5 and ≥6.5 (35±4.1 months vs. 23.6±4.03 months, p=0.027).

Conclusion: The PET score cut-off value of 6.5 serves as a potential prognostic tool for MM, aiding in patient stratification and treatment decisions.

Keywords: Multiple myeloma, positron-emission tomography, neoplasm staging

INTRODUCTION

MM is a clonal plasma cell malignancy that infiltrates the bone marrow, bone and sometimes extramedullary sites. This disease may vary over time depending on factors such as genetics and stage; survival and clinical features may vary from a few months to more than ten years. Therefore, reliable staging and identification of prognostic factors are important. In fact, many clinical-laboratory parameters, imaging modalities and cytogenetics have been proposed to improve staging and prognosis of the disease.[1] Currently used staging systems for myeloma patients are Durie and Salmon, International Staging System (ISS) and Revised International Staging System.[2] One of the most important factors in assessing the prognosis of MM patients is the extent of the disease, and imaging modalities are of critical importance. Bone survival, traditionally used in the Durie and Salmon system, has been replaced by more advanced imaging modalities such as CT, 18F-2-fluoro-2-deoxyglucose ^{18}F-FDG positron emission tomography/computed tomography (PET/CT) and magnetic resonance imaging (MRI). Recent studies have shown that ^{18}F-FDG PET/CT and MRI are useful for prognostic staging of MM patients based on the presence and number of focal lesions and diffuse bone marrow infiltration.[3,4] In addition to its role in staging, ^{18}F-FDG PET/CT has a role in evaluating treatment response and monitoring minimal residual disease in MM. The metabolic activity of myeloma lesions visualised by PET/CT can provide early information on the efficacy of treatment. This makes PET/CT an important tool not only in initial staging but also in the ongoing management of myeloma.[5] Whole-body ^{18}F-FDG PET/CT has the advantage of assessing both medullary and extramedullary disease and identifying metabolically active lesions before and after treatment.[3] However, due to the variable pattern of bone marrow involvement in MM, standardisation of ^{18}F-FDG PET/CT reports can be difficult.[6] Most standardisation studies are based on the assessment of ^{18}F-FDG uptake by SUVmax values, while others are based on visual assessment or a combination of both method.[7,8] The Italian Myeloma PET Usage (IMPeTUs) have recently been developed to standardise

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the interpretation of ^{18}F-FDG PET/CT images.[9-11] These criteria allow visual assessment of ^{18}F-FDG uptake using the Deauville 5-point scoring (5-PS), widely used in lymphoma patients, and identification of the metabolic status of the bone marrow and target lesion.[12] The location and number of focal bone lesions, the number of lytic lesions and the presence of possible paramedullary lesions, extramedullary lesions and fractures are also reported. PET/CT has also been effective in identifying high-risk myeloma patients. Patients with high SUVmax values or persistent PET-positive lesions after initial treatment have been shown to have a worse prognosis.[13] In this study, we present the scoring system we developed to easily calculate IMPeTUs criteria in clinical practice and its adequacy in predicting progression-free survival according to these criteria.

METHODS

The study was carried out with the permission of the Gazi Yaşargil Training and Research Hospital Clinical Researches Ethics Committee (Date: 03.03.2023, Decision No: 339/2023). We obtained an informed consent form from all patients for procedure. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. This study was conducted at Gazi Yaşargil Training and Research Hospital and was designed as a retrospective study covering the period between March 2019 and June 2023. A total of 35 patients (13 women and 22 men) diagnosed with multiple myeloma were included in the study. Inclusion criteria were as follows: presence of previously untreated newly diagnosed active myeloma requiring induction therapy and eligible for transplantation; age ≤70 years; baseline ^{18}F-FDG PET/CT available within maximum 1 month after diagnosis of MM requiring treatment. All patients participating in the study received three or four cycle bortezomib-cyclophosphamide-dexamethasone treatment followed by autologous stem cell transplantation. Multiple myeloma type, ISS stage, date of diagnosis, chemotherapy regimens, number of lines of treatment, date of autologous stem cell transplantation, date of relapse if any, follow-up period and date of excitus if any were recorded. Bone marrow Deauville 5-PS, number of bones with focal bone involvement, Deauville 5-PS in focal bone involvement, number of lytic bones, number of paramedullary and extramedullary involvement, and Deauville 5-PS in these areas were recorded at diagnosis on ^{18}F-FDG PETCT. In this study, we developed and established a novel PET scoring system specifically designed to provide a more refined assessment of PET scan results in newly diagnosed MM patients. Our scoring system, referred to as the IMPeTUs-derived PET score, is an adaptation of the previously validated IMPeTUs criteria, incorporating both the DS and the number of lesions observed on PET scans.

Image Acquisition Protocol

All patients were asked to fast and discontinue intravenous (IV) glucose for at least 6 hours prior to scanning. Patients' blood glucose levels were confirmed to be ≤140 mg/dl using the finger-stick method, and 3.5-5.5 MBq/kg of ^{18}F-FDG was administered intravenously. One hour after injection, CT images (120 kV, 80 mAs/slice, 700 mm transaxial field of view (FOV), no gap, 64x0.625 mm collimation, pitch 1.4, 0.5s rotation time, 3.3 mm slice thickness, 512x512 matrix) were acquired from the vertex to mid-thigh in the supine position using the Discovery IQ 4 ring 20 cm axial FOV PET/CT unit (GE Healthcare, Milwaukee, WI, USA). PET images were then acquired over 2.5 min per bed position [3D FOV 20 cm, ordered subset expectation-maximisation algorithm (OSEM) 5 iterations/12 subset, full width at half maximum (FWHM) 3 mm]. Intravenous non-ionic contrast was administered at a dose of 1.5 ml/kg to all patients with no contraindications. All ^{18}F-FDG PET/CT images were reviewed on an AW 4.7 workstation (Advantage Workstation software version 4.7; GE Healthcare, Milwaukee, WI, USA). PET/CT scans acquired from whole body and evaluated by two experts with at least 10 years of FDG-PET/CT experience. The IMPeTUs are largely based on visual assessment to minimise interpretation variability. However, in addition to visual assessment, lesion-background SUVmax measurements at interval thickness times were used. Five different assessments were performed. The PET score is a scoring system adapted from the previously established IMPeTUs to provide a more nuanced assessment of PET scan results in newly diagnosed patients. This system incorporates the DS, a standardised measure of treatment response in lymphoma, together with an assessment of the number of lesions seen on the PET scan.

PET scoring according to DS:

- DS 1: Scored as 0 point.
- DS 2-3: Scored as 1 point.
- DS 4-5: Assigned as 3 points.

PET scoring according to number of lesions:

- 0 lesions: Assigned 0 point.
- 1-3 lesions: Scored as 1 point.
- More than 3 lesions: Assigned 2 points (**Figure 1, Table 1**).

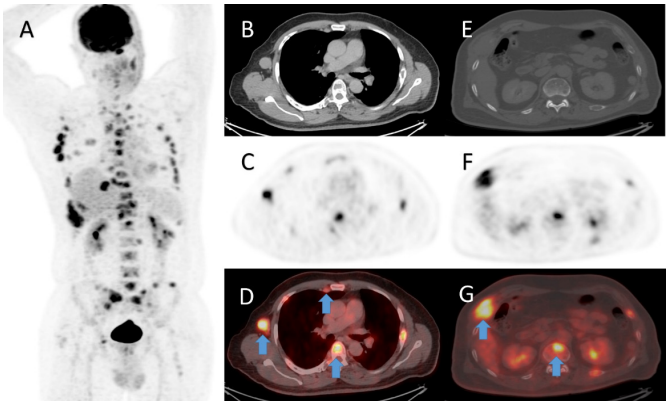

Figure 1. A 65-year-old male patient's imaging

A 65-year-old male patient with multiple myeloma underwent FDG PET/CT imaging before treatment. According to the impetus; diffuse BM DS 2, focal lesion score 4, focal lesion DS 5, lytic lesion score 4, EM present, EM DS 5, PM present. However, it was found as 11 according to the PET score we developed. The PFS of the patient was 15.7 months.

A; MIP B; CT, C; PET and D; Fusion images: right axilla and parasternal lymph node involvement (PM, blue arrow) and lytic bone lesions (blue arrow), E; CT, F; PET and G; Fusion images; bone lesion destructing the right 6th costa (EM, blue arrow) and lytic bone lesions (blue arrow).

FDG: Fluorodeoxyglucose, PET: Positron emission tomography, CT: Computed tomography, BM: BM: Bone marrow, DS: Deauville score, PFS: Progression-free survival, MIP: Maximal inspiratory pressure

Table 1. IMPeTUs criteria vs PET score	
IMPeTUs criteria	**PET score**
DS of diffuse BM uptake	
No uptake at all	0
≤ mediastinal blood pool uptake	1
> mediastinal blood pool uptake, ≤ liver uptake	
> liver uptake +10%	2
>> liver uptake (twice or more)	
Number of focal lesion	
No lesion	0
1 to 3 lesions	1
4 to 10 lesions	2
>10 lesions were scored	
DS of focal lesions	
No uptake	0
≤ mediastinal blood pool uptake	1
> mediastinal blood pool uptake, ≤ liver uptake	
> liver uptake +10%	2
>> liver uptake (twice or more)	
No of lytic lesions	
No lesion	0
1 to 3 lesions	1
4 to 10 lesions	2
>10 lesions were scored	
DS of extramedullary lesions	
No uptake	0
≤ mediastinal blood pool uptake	1
> mediastinal blood pool uptake, ≤ liver uptake	
> liver uptake +10%	2
>> liver uptake (twice or more)	
Extramedullary	
0	0
1	1
Paramedullary	
0	0
1	1

IMPeTUs: Italian myeloma criteria for PET use, PET: Positron emission tomography, DS: Deauville score, BM: Bone marrow

Statistical Analysis

SPSS 26.0 (IBM Corporation, Armonk, NY, United States of America) was used to analyse the variables. The Kolmogorov-Smirnov test was used to determine whether univariate data were normally distributed. Kaplan-Meier (product-limit method) log-rank analysis was used to examine the effect of factors on death and survival. The PFS cut-off value to differentiate MM patients was performed by ROC curve analysis. Quantitative variables were expressed as mean±SD (standard deviation) and median (interquartile range), while categorical variables were expressed as n (%). Variables were analysed with 95% confidence interval and $p<0.05$ was considered significant.

RESULTS

Thirty-five MM patients, 13 (37%) females and 22 (63%) males, were included in our study. The mean age of the patients was 65 years, with a minimum of 46 and a maximum of 70 years. Regarding the types of multiple myeloma, 8 (22.9%) of the patients had Ig G lambda, 13 (37.1%) had Ig G kappa, 4 (11.4%) had Ig A lambda, 4 (11.4%) had Ig A kappa, 3 (8.6%) had lambda light chain and 3 (8.6%) had kappa light chain. ISS stage 1 disease was present in 28.6%, ISS stage 2 disease in 37.1% and ISS stage 3 disease in 34.3% of the patients. 2 patients were excitus. Only one patient had t (4;14) and 13q del mutation, the others had no mutation about myeloma. The number and percentages of patients in terms of metabolic state of the bone marrow according to Deauville 5-PS, number of focal PET-positive lesions, presence of extramedullary and paramedullary disease, number of lytic lesions are given in the Table 2. The presence of extramedullary disease (EMD) was observed in 29 patients (82.9%), while it was absent in 6 patients (17.1%). Similarly, paramedullary disease (PMD) was present in 20 patients (57.1%) and absent in 15 patients (42.9%). Diffuse bone marrow uptake was observed in 37.2% of patients, while focal lesions were present in 57.2%, both with a Deauville score (DS) of 4 or higher. ROC curve analysis identified a PET score cutoff value of 6.5, which showed a sensitivity of 61.5% and a specificity of 72.7% for detecting progression-free survival (PFS) in multiple myeloma (MM), with statistical significance (area under the curve (AUC): 0.715±0.091, p=0.036) (Figure 2). The median PFS was 35±4.1 months (95% CI, 26.9-43.1) for patients with PET score <6.5 and 23.6±4.03 months (95% CI, 15.7-31.5) for patients with PET score ≥6.5 (Table 3). The 1-year rate of PFS was 100% for patients with PET score <6.5 and 68.1% for patients with PET score ≥6.5. The 3-year rate of PFS was 57.8% for patients with PET score <6.5 and 37.2% for patients with PET score ≥6.5 (Figure 3).

Table 2. Number and percentages of patients according to the IMPeTUs criteria										
	Diffuse BM DS		**F**		**FS**		**L**		**EM DS**	
Valid*	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
1	1	2.9	16	45.7	9	25.7	8	22.9	32	91.4
2	9	25.7	11	31.4	1	2.9	4	11.4	1	2.9
3	12	34.3	-	-	5	14.3	2	5.7	-	-
4	11	31.4	8	22.9	12	34.3	21	60	1	5.7
5	2	5.7	-	-	8	22.9	-	-	-	-

*Valid numbers are Deauville scores, IMPeTUs: Italian myeloma criteria for PET use, PET: Positron emission tomography, BM: Bone marrow, DS: Deauville 5-point Scale, F: Focal bone lesions, FS: Hotest focal bone lesion Deauville 5-PS, L: Lytic lesions, EM: Extramedullary

Table 3. Relapse frequency according to PET score			
PET score	**Total number**	**Number of relapse**	**Percentage**
<6.5	21	5	76.2%
≥6.5	14	8	42.9%
Overall	35	13	62.9%

PET: Positron emission tomography

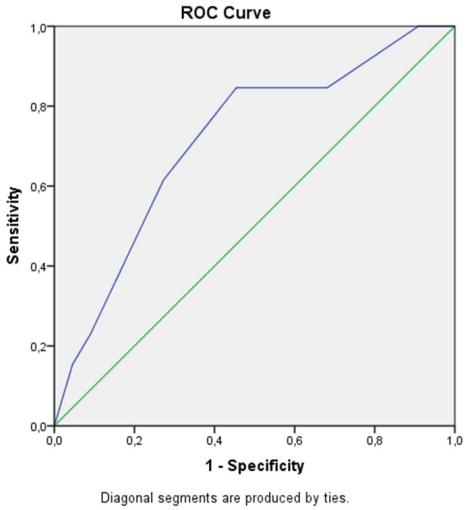

Figure 2. ROC curve

The PET score cut-off value of 6.5 had a sensitivity of 61.5% and a specificity of 72.7% for the detection of PFS in MM and was statistically significant (AUC 0.715)

ROC: Receiver operating characteristic, PET: Positron emission tomography, PFS: Progression-free survival, MM: Multiple myeloma, AUC: Area under the curve

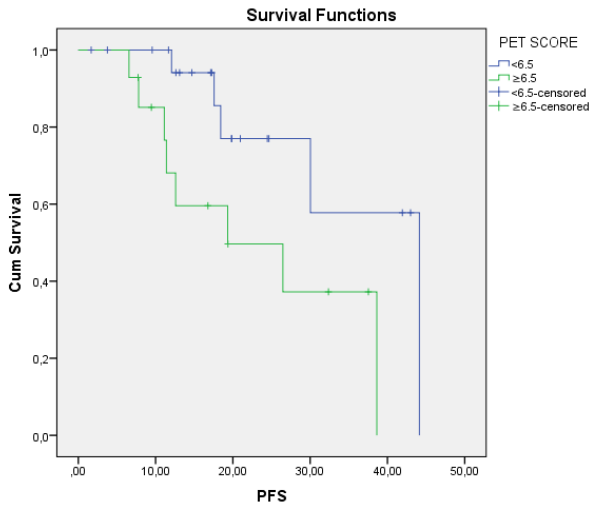

Figure 3. Kaplan meier test for patients with PET score <6.5 and ≥6.5

PET: Positron emission tomography

DISCUSSION

^{18}F-FDG PET/CT is a highly valuable diagnostic tool for patients with both newly diagnosed and relapsed or refractory MM. It offers high sensitivity and specificity in assessing bone damage, detects extramedullary proliferative sites of clonal plasma cells, and provides crucial prognostic information. However, ^{18}F-FDG PET/CT may be difficult to interpret in some patients. In MM-associated anemia, there is a significant increase in BM tracer uptake, resulting in a hot background in the bone. Since FDG uptake varies, a baseline study is essential for reference. New fractures may appear as false positives and metallic bone implants can cause significant artefacts in the images.[3] Most importantly, response criteria have not been defined. Due to the need for standardised interpretation criteria for the evaluation of ^{18}F-FDG PET/CT scans in MM, IMPeTUs criteria were developed.[9] It should be noted that in order to apply the IMPeTUs criteria to the clinical management of MM patients, it is necessary to determine the limits of positivity for each defined parameter and to reduce the number of non-prognostic parameters. Our study included 35 patients with newly diagnosed MM who received first-line treatment with bortezomib-cyclophosphamide-dexamethasone followed by autologous stem cell transplantation. 13 (37%) were women and 22 (63%) were men, aged between 46 and 85 years, with a mean age of 65 years. The cohort represented a diverse spectrum of MM types and stages, with Ig G kappa being the most prevalent type (37.1%) and ISS stage 2 being the most common stage (37.1%). A significant finding of our study was the presence of diffuse bone marrow uptake in 37.2% of patients and focal lesions in 57.2%, with a DS greater than or equal to 4 in both cases. This indicates a high level of metabolic activity in a substantial proportion of the cohort, which is consistent with the aggressive nature of MM. Also, the demographic characteristics, MM type distribution and imaging findings of our study are consistent with those previously reported in the literature.[7,12] The presence of diffuse and focal bone marrow involvement with high SUVmax values is an important finding that is consistent with published data and demonstrates that our results are within the expected range for MM patients. Analysis of the PET score by ROC curve analysis revealed a cut-off value of 6.5, which had a sensitivity of 61.5% and a specificity of 72.7% for predicting PFS in MM patients. This was statistically significant with an area under the curve (AUC) of 0.715. Median PFS was significantly different between patients with PET score below and above 6.5. Patients with a PET score of less than 6.5 had a median PFS of 35±4.1 months, compared to 23.6±4.03 months for patients with a PET score of 6.5 or higher (p=0,027). This significant difference highlights the potential utility of PET score as a prognostic marker in MM. In the study by Fonti et al.,[6] there were no statistically significant differences in visual parameter values between patients with or without progression, except for the number of lytic lesions that was significantly different in patients with progressive disease as compared to those without progression (p=0.022). Additionally, the SUVmax value was significantly different between patients with or without progression (p=0.04). The study by Zamagni et al.[8] demonstrated that PET/CT parameters, including the number of focal lesions (FLs), SUV, and extramedullary disease (EMD), were strong prognostic indicators in multiple myeloma. Specifically, the presence of at least three FLs (≥3 FLs), an SUV >4.2, and EMD at baseline were associated with poorer 4-year progression-free survival (PFS) rates (50%, 43%, and 28%, respectively). Furthermore, SUV >4.2 and EMD were linked to reduced overall survival (OS) rates (77% and 66%, respectively). In the study by Deng et al.,[14] DS plus stage III (p=0.021) and Deauville bone marrow score equal to or above 4 (p=0.031) were found to be reliable prognostic factors in newly diagnosed MM patients. Individual parameters may not be predictive in IMPeTUs. Combined PET scoring system may provide a more comprehensive assessment of disease prognosis. The statistically significant result obtained at the PET score cut-off value of 6.5 reinforces the importance of a comprehensive approach in the interpretation of PET scan in MM. In Deng's study they found that Durie-Salmon Plus staging system based on IMPeTUs stage III and the Deauville score of bone marrow ≥4 were independent prognostic

factors associated with OS.[14] Similar to that study, our results showed a significant relationship between the PET score, which we developed based on IMPeTUs scoring, and survival prediction. However, the lack of a significant correlation between individual IMPeTUs criteria and PFS in our study suggests that further refinement of these criteria may be necessary. Furthermore, the discordance with the study by Sachpekidis,[15] who found no significant association between the presence of PMD and PFS, suggests that further research is needed to confirm these findings in different patient cohorts.

Limitations

The limitation of our retrospective design and evaluation in a selected group of patients is the following; the clinical utility of our scoring system should be evaluated in studies with a larger number of patients grouped according to ISS stage. The strength of our study is that we evaluated in a homogenous patient group.

CONCLUSION

The PET score, derived from IMPeTUs criteria, cut-off value of 6.5 could serve as a valuable prognostic tool in clinical practice, aiding in the stratification of patients. Future studies with larger cohorts and longer follow-up periods are warranted to further validate these findings and refine the prognostic criteria for MM.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Gazi Yaşargil Training and Research Hospital Clinical Researches Ethics Committee (Date: 03.03.2023, Decision No: 339/2023).

Informed Consent

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

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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The role of elevated monocyte and high-density lipoprotein cholesterol ratio in endothelial dysfunction and cardiovascular risk in acromegaly patients

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ABSTRACT

Aims: This study aimed to investigate the role of the monocyte-to-high-density lipoprotein ratio (MHR) as an indicator of endothelial dysfunction and cardiovascular risk in patients with acromegaly.

Methods: The study group consisted of 125 patients diagnosed with acromegaly, while the control group included 123 healthy individuals who visited the endocrine clinic due to pituitary incidentaloma but had no acromegaly diagnosis. Medical and laboratory records of all participants were reviewed retrospectively.

Results: The average MHR in patients with acromegaly was found to be statistically significantly higher than that in the healthy control group. In the acromegaly group, systolic blood pressure, glucose, HbA1c, lipids (total cholesterol, LDL, triglycerides), sedimentation rate, CRP, and neutrophils were significantly higher to the control group. The optimal MHR cutoff for acromegaly was 12.01, with 85.1% sensitivity, 85% specificity, and an AUC of 0.64.

Conclusion: MHR, a potential biomarker considered an indicator of inflammation, was significantly higher in patients with acromegaly compared to the healthy control group. This finding suggests that MHR may serve as a useful marker for assessing cardiovascular risk and endothelial dysfunction in patients with acromegaly.

Keywords: Acromegaly, monocyte to HDL cholesterol ratio, cardiovascular risk, cardiovascular markers

INTRODUCTION

Acromegaly is a chronic endocrine disorder caused by persistently elevated levels of growth hormone (GH) and insulin-like growth factor-1 (IGF-1). These hormonal imbalances can lead to widespread effects on various organ systems, particularly the cardiovascular system.[1,2] Regardless of the underlying cause, patients with acromegaly have an increased risk of developing metabolic complications such as dyslipidemia, hypertension, and insulin resistance. All of these conditions are closely related to an increased risk of cardiovascular disease.[3-5]

The monocyte-to-HDL cholesterol ratio (MHR) has emerged as a novel and accessible biomarker for predicting systemic inflammation and cardiovascular risk.[6] Monocytes play a key role in atherosclerotic plaque formation, while HDL cholesterol is known for its anti-inflammatory and cardioprotective properties. A high MHR reflects an imbalance between pro-inflammatory and anti-inflammatory mechanisms, making it a valuable prognostic marker for cardiovascular complications.[7]

The health of the endothelium, a thin layer of cells lining the blood vessels, is critical for overall vascular function. Endothelial cells regulate blood flow, manage coagulation processes, and modulate immune and inflammatory responses.[8] When these cells are damaged or dysfunctional, a range of issues can arise, including the onset and progression of atherosclerosis.[9] Endothelial dysfunction is increasingly recognized as one of the earliest markers of cardiovascular disease. It directly contributes to the development of serious events such as hypertension, plaque accumulation in arteries, heart attacks, and strokes. In this context, the assessment of markers like MHR becomes increasingly important, as they reflect the underlying inflammatory state that can lead to endothelial damage.[10,11]

MHR is rapidly becoming a valuable biomarker in cardiovascular research and clinical practice.[12] By dividing the monocyte count by HDL cholesterol levels, healthcare providers can quickly assess a patient's inflammatory and lipid profile.[13] A high MHR is associated with an increased risk of cardiovascular events, particularly in individuals with chronic illness or those with ambiguous traditional risk factors.[14] This is especially relevant in populations such as acromegaly patients, who are already facing increased metabolic and cardiovascular stress. In these patients, traditional lipid

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panels may not fully reflect the inflammatory burden or may be insufficient in predicting future complications. MHR can serve as an additional tool that may enhance early diagnosis and better inform treatment decisions.[5,14-16]

Relationship between MHR and endothelial dysfunction: Monocytes (a type of white blood cell) play an important role in the body's immune and inflammatory responses. When their levels rise (as captured in MHR), they can damage the endothelial cells that line our blood vessels.[17-19] This damage impairs the normal functions of the endothelium, such as controlling blood flow and vascular tone. When the endothelium is constantly under inflammatory stress, it creates a favorable environment for the development of atherosclerosis. Atherosclerosis is the buildup of plaques in the arteries and is one of the underlying factors behind heart attacks and strokes. Simply put, higher monocyte levels mean more inflammation, which damages blood vessels and increases the risk of serious cardiovascular issues.[13]

Underlying Mechanisms Behind the Relationship between MHR and Cardiovascular Risk

Inflammation plays a central role in the pathogenesis of cardiovascular diseases. Monocytes, as a significant component of the immune system, initiate and sustain inflammatory responses.[20-22] In acromegaly, chronic inflammation resulting from excessive growth hormone secretion can lead to increased monocyte counts, resulting in endothelial damage and elevated cardiovascular risk.[23,24]

Cholesterol Metabolism and MHR

HDL cholesterol helps remove excess cholesterol from the blood by preventing plaque buildup in the arteries. However, in patients with acromegaly, HDL cholesterol levels are typically low, disrupting the balance between monocytes and HDL cholesterol. This imbalance contributes to the increase in MHR and cardiovascular risk.[25,26]

Acromegaly Increases Cardiovascular Risk

In acromegaly, the body produces excessive amounts of GH, and this excess affects not only height or physical characteristics but also has significant effects on the cardiovascular system. GH can lead to arterial stiffness (vascular rigidity or atherosclerosis), reducing the elasticity of blood vessels and making it difficult for the body to regulate blood pressure.[27,28] Additionally, GH alters the body's lipid profile, often leading to abnormal cholesterol levels and hypertension. These changes accelerate the development of cardiovascular diseases and increase the risk of life-threatening events such as heart attacks and strokes.[28]

Besides GH, other factors commonly seen in acromegaly patients, such as insulin resistance, obesity, and dyslipidemia, further exacerbate cardiovascular risk.[5] These metabolic abnormalities worsen endothelial dysfunction, facilitating the progression of cardiovascular diseases.

In the context of acromegaly, the effects of GH and IGF-1 levels on MHR have not yet been fully elucidated. This study aims to investigate potential differences in MHR among acromegaly patients and assess its relationship with cardiovascular risk. Thus, it seeks to provide a deeper understanding of the role of MHR as a prognostic marker for cardiovascular diseases associated with GH and IGF-1 levels.

Understanding the potential role of MHR in predicting cardiovascular risk in acromegaly patients may contribute to the development of early intervention strategies for this population. In this context, large-scale and long-term studies in the future could provide further evidence to support the clinical utility of MHR.

METHODS

Ethical Considerations

Ethical approval was obtained from the Akdeniz University Faculty of Medicine Human Researches Ethics Committee (Date: 30.01.2025, Decision No: TBAEK-131). All procedures comply with the provisions of the Declaration of Helsinki.

Study Design

Retrospective medical records of acromegaly patients (72 women and 53 men) were used. These patients were admitted to the Akdeniz University Faculty of Medicine Endocrinology outpatient clinic between 2014 and 2024 due to symptoms of acromegaly or incidental pituitary adenomas.

Dataset Profile

We collected the following parameters from the medical records and laboratory archives; age, sex, any chronic/systemic disease, CRP, total cholesterol (TC), triglyceride (TG), LDL cholesterol, HDL cholesterol, glycosylated hemoglobin A1c, serum creatinine.

The study group comprised of 125 patients with acromegaly (72 females, 53 men, with a mean age of 56.51±13.04 years) randomly selected from the Endocrinology referral center of the Hospital of Clinics of the Akdeniz University of Antalya. The control group comprised of an approximately 1:1 sample of 123 ambulatory patients without acromegaly (71 females, 52 males 56±13 years) who were matched for age, sex and CV disease risk factors, namely hypertension, diabetes mellitus, dyslipidemia, body-mass index (BMI) and smoking.

All participants underwent a thorough physical examination, including measurement of BMI and blood pressure (BP), according to standard methods.[29,30] All medications in use were recorded. Framingham's global CV risk score (FRS) was estimated for all of them.[31] Risk factors evaluated for the FRS were age, total cholesterol and HDL cholesterol, systolic BP, hypertension, and diabetes status.[31] Acromegaly was diagnosed based on the presence of clinical features in addition to biochemical evidence of GH excess: IGF-1 levels above age-adjusted reference range and lack of suppression of GH to <1 μg/L following documented hyperglycemia during an oral glucose load.[32]

Study Design and Population

This cross-sectional, comparative study was conducted to investigate the relationship between the MHR and cardiovascular risk across acromegaly. Patients diagnosed with acromegaly. A total of (number) patients who met the inclusion criteria were included in the study.

Inclusion and Exclusion Criteria

Patients were included if they were aged 18 years or older, had a confirmed diagnosis of acromegaly based on biochemical and radiological findings, and provided informed consent. Exclusion criteria included the presence of active infections, chronic inflammatory diseases (e.g., rheumatoid arthritis), recent steroid use (unrelated to Cushing's syndrome), pregnancy, or severe organ dysfunction (e.g., end-stage renal or hepatic disease).

Data Collection and Laboratory Measurements

Demographic and clinical data, including age, sex, BMI, and blood pressure, were recorded. Blood samples were collected after an overnight fast for biochemical analyses.

Monocyte count: Monocyte levels were measured using an automated hematology analyzer (model and manufacturer).

HDL cholesterol: HDL cholesterol levels were measured using an enzymatic colorimetric method (specific kit and manufacturer).

MHR calculation: The MHR was calculated by dividing the monocyte count by the HDL cholesterol level (mg/dl).

Other laboratory parameters, such as fasting blood glucose, total cholesterol, triglycerides, C-reactive protein (CRP), and sedimentation rate, were also measured to assess metabolic profiles.

Cardiovascular Risk Assessment

Cardiovascular risk was assessed using clinical and laboratory markers such as blood pressure, lipid profiles, and glucose metabolism parameters.

Statistical Analysis

All statistical analyses of this study were performed with SPSS for Windows 22.0 package program (SPSS Inc., Chicago, IL). The Kolmogorov-Smirnov test was used to test normality of distribution. Pearson's Chi-square test was performed for categorical data analyses. We compared parametric values among groups by student's T test. Comparisons of non-parametric values among groups were performed by the Mann-Whitney U Test. Receiver operating characteristic (ROC) curve analysis was used to compare the prognostic powers of the MHR for DRP. $p<0.05$ was considered statistically significant.

RESULTS

Patients Demographics

One hundred twenty-five acromegaly patients (72 females and 53 males) who had were eligible for the study. Similarly, 123 control patients (71 females and 52 males) without acromegaly healthy subjects determined as control groups. Patients with acromegaly were regarded as Group 1, healthy subjects were regarded as group 2. The mean age of patients was 56.51±13.04 years in acromegaly patients, and 56.10±10.87 years in healthy subjects. There were no statistical differences between the two groups in terms of age and gender (p=0.725 and p=0.999, respectively).

All laboratory parameters (monocyte counts, HDL cholesterol, and MHR) are summarized in **Table**. The monocyte counts were significantly different between two groups (p=0.043). While monocyte counts were significantly higher in acromegaly patients.

During follow-up, five patients with acromegaly were reported as deceased. Among them, four deaths were attributed to cardiovascular complications, while one patient succumbed to post-Whipple surgery due to malignancy associated with acromegaly.

Compared to the control group, systolic blood pressure, glucose, HbA1c, and lipid parameters (total cholesterol, LDL cholesterol, and triglycerides), as well as sedimentation rate, CRP, and neutrophil levels, were found to be significantly elevated. In contrast, the acromegaly group's HDL cholesterol and hemoglobin levels were significantly lower. However, diastolic blood pressure, creatinine, lymphocyte count, and platelet levels showed no statistically significant differences between the two groups.

Table. Demographic characteristics of the patients

	Control group, n: 123	Acromegaly n: 125	p
Age	56.10±10.87	56.51±13.04	0.725
Female/male	71 (57.7%)/52 (42.2%)	72 (57.6%)/53 (42.4%)	0.999
Acromegaly duration (years)	-	14.6±8.10	
Diabetes mellitus	-	73 (58.4%)	
Hypertantion	-	33 (26.4%)	
Hyperlipidemia	-	55 (44%)	
Smoking	16(125)	20 (125)	0.625
BMI (kg/m^2)	24.7±4.1	26.17±4.9	0.001
Systolic BP mmHg	116.22±12.66	125.05±13.37	<0.001
Diastolic BP mmHg	76.82±8.12	77.84±9.07	0.352
Growth hormone	0.35±6.6	6.50±7.70	<0.001
IGF-1	115±25.66	430±252.94	<0.001
Glucose (mg/dl)	92±13	142.65±83.73	<0.001
HbA1c (%)	5.40±1.10	6.75±1.66	<0.001
Creatinin (mg/dl)	0.83±0.17	0.86±0.50	0.410
Total cholesterol (mg/dl)	185.01±27.01	211.25±44.04	0.001
LDL-C (mg/dl)	113.04±24.06	128.11±35.31	0.001
Trigliserit (mg/dl)	143.21±50.60	206.28±125.55	<0.001
HDL-C (mg/dl)	47.85±72.81	44.70±11.82	0.004
Monocyte (/L)	496±0.15	523.56±150.34	0.043
MHR	10.37±4.21	12.43±4.64	0.001
ESR (mm/h)	7.02±3.02	21.45±14.38	0.001
CRP (mg/dl)	1.30±1.61	8.21±24.66	0.002
Hemoglobine (g/dl)	13.32±1.42	12.80±1.76	0.022
WBC (/L)	7321.81±1685.21	7327.91±2000.22	0.973
Neutrophil (/L)	4610.21±1300.68	4280.00±1714.78	0.033
Lenfosite (/L)	2100.82±0.71	2317.82±801.21	0.060
Platelate (×10^3/L)	261.54±63.80	257.55±73.82	0.547

BMI: Body-mass index, BP: Blood pressure, IGF-1: Insulin-like growth factor-1, WBC: White blood cell, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, HbA1c: Glycated hemoglobin, HDL: High-density lipoprotein, MHR: Monocyte count to HDL ratio

The optimal cutoff value of MHR for acromegaly was 12.01 with 85.1% sensitivity and 85% specificity and an area under the ROCs curve was 0.64, as shown in Figure.

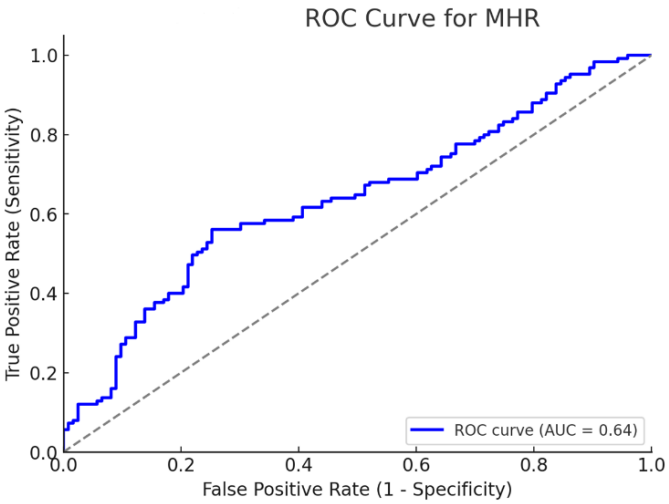

Figure. ROC analysis of MHR for acromegaly

ROC: Receiver operating characteristic, MHR: Monocyte count to HDL ratio, HDL: High-density lipoprotein

DISCUSSION

In this study, we evaluated the MHR and various laboratory parameters in patients with acromegaly compared to healthy controls. Our findings indicate that MHR is significantly elevated in acromegaly patients, suggesting a potential connection between chronic inflammation and lipid metabolism dysregulation in this population.

A key finding of our study is that the optimal cutoff value for distinguishing acromegaly patients from healthy individuals was determined to be 12.01, with a sensitivity of 85.1% and a specificity of 85%. The area under the curve (AUC) of 0.64 suggests a moderate diagnostic value for MHR in acromegaly, which aligns with previous studies that highlight its role as an inflammatory marker in a range of endocrine and metabolic disorders.

Acromegaly is known to be associated with increased cardiovascular risk, as reflected in our results. Monocyte counts, a marker of systemic inflammation, were significantly higher in acromegaly patients compared to the control group (p=0.043). Additionally, levels of systolic blood pressure, glucose, HbA1c, and lipid parameters (total cholesterol, LDL cholesterol, and triglycerides) were significantly elevated in acromegaly patients, while HDL cholesterol levels were lower. These findings indicate a pro-inflammatory and atherogenic state in acromegaly, likely contributing to the increased cardiovascular morbidity and mortality observed in this population.

Importantly, among the acromegaly patients in our study, five were reported deceased, with four deaths attributed to cardiovascular complications. This underscores the necessity of early detection and management of cardiovascular risk factors in patients with acromegaly. Given that MHR is emerging as a marker of inflammation and cardiovascular risk, our findings suggest it could serve as a useful tool for risk stratification in this population.

As there are no prior studies examining the relationship between acromegaly and MHR, we could not make direct comparisons. This study is the first to establish an association between acromegaly and MHR. Monocytes play a crucial role in inflammatory reactions, as they are responsible for secreting pro-inflammatory and pro-oxidant cytokines. Conversely, HDL cholesterol possesses antioxidant and anti-inflammatory properties, including reducing macrophage accumulation, inhibiting monocyte transmigration, increasing nitric oxide synthase expression in endothelial tissues, and protecting endothelial cells.[35]

Recent research has identified the MHR as a promising new marker for inflammation in diabetes and its complications. For example, Gökçay Canpolat et al.[36] observed that MHR levels were higher in diabetic patients with neuropathy compared to those without, although the difference wasn't statistically significant. Karatas et al.[16] found a more noticeable result MHR levels were significantly higher in patients with diabetic nephropathy compared to both diabetics without kidney issues and healthy individuals. Similarly, Onalan et al.[37] reported that MHR levels were significantly elevated in diabetics with kidney damage versus those without it. In our own study focusing on acromegaly patients, we found a specific cutoff value for MHR: 12.01. This value showed a strong ability to detect cardiovascular risk, with a sensitivity of 85.1% and specificity of 85%. The AUC was 0.64, which suggests that MHR has a moderate but meaningful diagnostic value in identifying cardiovascular risk among acromegaly patients.

Interestingly, while monocyte counts, lipid parameters, and inflammatory markers (CRP, sedimentation rate, and neutrophil levels) were elevated in acromegaly patients, no significant differences were observed in diastolic blood pressure, creatinine levels, lymphocyte counts, or platelet levels between the two groups. This suggests that the inflammatory response in acromegaly may be more closely related to monocyte activation and alterations in lipid metabolism rather than generalized immune activation.

Overall, our findings highlight the potential utility of MHR as a biomarker for inflammation and cardiovascular risk in acromegaly. Future studies with larger sample sizes and longitudinal follow-up are warranted to better understand the prognostic significance of MHR and its role in guiding therapeutic strategies for acromegaly patients.

Limitations

Our study has several potential limitations that should be acknowledged. The first limitation is the relatively small sample size and the retrospective design of the study, which may restrict the generalizability of our findings and introduce potential biases. The second limitation is the incomplete data regarding the medications used by the patients, which precluded an evaluation of the potential effects of pharmacological treatments on the observed outcomes. The third limitation pertains to the presentation of monocyte count as a numerical value, which does not provide information on monocyte activation status. Monocyte activation, which plays a critical role in the pathogenesis of diabetic complications, could offer

deeper insights into the underlying mechanisms but was not assessed in this study. These limitations highlight the need for future prospective studies with larger cohorts, comprehensive medication data, and more detailed assessments of monocyte activation to further elucidate the relationships explored in this research.

CONCLUSION

Our study shows that the MHR is significantly higher in patients with acromegaly than in healthy individuals. This suggests that inflammation and disrupted lipid metabolism play an important role in the cardiovascular risks linked to acromegaly. MHR may be a useful biomarker for identifying acromegaly patients at greater risk of heart disease. The increase in MHR appears to reflect the impact of excess growth hormone and IGF-1 on cholesterol balance and inflammation. Understanding how inflammation and cholesterol issues interact in acromegaly can lead to earlier diagnosis and more targeted treatments to prevent heart complications. While more research is needed, MHR could become a valuable tool for managing cardiovascular health in acromegaly patients.

ETHICAL DECLARATIONS

Ethics Committee Approval

This research received approval from the Akdeniz University Clinical Researches Ethics Committee (Date: 30.01.2025, Decision No: TBAEK-131).

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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COPD and eosinophils: a perspective from the intensive care unit

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ABSTRACT

Aims: Chronic obstructive pulmonary disease (COPD) is a progressive respiratory disorder characterized by airflow limitation and chronic airway inflammation. Various biomarkers have been investigated to better guide the treatment and predict the prognosis of COPD patients, among which blood eosinophil levels have received particular attention. Unlike many previous studies, our investigation specifically focuses on COPD patients in the intensive care unit (ICU), where disease severity is markedly higher

Methods: Data from 141 COPD patients admitted to the ICU over a one-year period were retrospectively analyzed. The patients were classified into two groups based on their blood eosinophil counts; a low eosinophil group (0-100 cells/μl) and a moderate-high eosinophil group (>100 cells/μl). These groups were compared in terms of clinical scoring systems, laboratory parameters, and ICU-related clinical outcomes.

Results: Patients with low eosinophil levels had higher levels of infection-related biomarkers, including procalcitonin, neutrophil-to-lymphocyte ratio, and platelet-to-lymphocyte ratio. Additionally, a weak positive correlation was observed between increasing eosinophil levels and partial carbon dioxide pressure. However, no statistically significant associations were found between eosinophil levels and outcomes such as mortality, tracheostomy requirement, or the need for inotropic support.

Conclusion: In addition to its established role in predicting response to corticosteroid therapy, the peripheral blood eosinophil count may serve as a potential biomarker for guiding treatment strategies and prognostic evaluation in COPD exacerbations managed in the ICU. It should be noted that in COPD patients with higher eosinophil levels requiring intensive care follow-up, non-infectious exacerbations -such as those triggered by environmental exposures, medication nonadherence, or underlying airway inflammation- may be more prominent.

Keywords: COPD, eosinophil, intensive care, mortality, respiratory disease

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a respiratory condition characterized by chronic airflow limitation, combined with inflammation of the airways. The illness is progressive and highly prevalent in most regions of the world. Acute exacerbation of COPD represents an important clinical issue in that exacerbation not only worsens the course of the disease itself but also increases hospitalization rates and healthcare expenditure associated with COPD.[1,2] These exacerbations, particularly those severe enough to require intensive care unit (ICU) admission, may have a strong impact on patient outcomes. Thus, the identification of reliable biomarkers predictive of the severity and clinical consequences of COPD exacerbations has become an important research priority.

One biomarker of interest is blood eosinophil count, which has been investigated for its role in the management of COPD. Eosinophils are a specific white blood cell subtype that is intimately related to inflammation and have been reported to correlate with some exacerbation phenotypes in COPD.[3] High levels of eosinophils have been reported to be associated with a good response to corticosteroid therapy and may thus impact on clinical outcomes such as length of stay (LOS) in the hospital and overall mortality.[4,5] However, the value of blood eosinophils for the prediction of clinical outcomes such as LOS in the ICU, mortality, acidotic respiratory failure, or infectious exacerbation in ICU-admitted COPD exacerbation patients is still understudied.[6]

Severe exacerbations of COPD are usually characterized by respiratory acidosis, probably as a consequence of the worsening of gas exchange and increase in respiratory workload. This condition often requires treatment in ICUs and impacts significantly on patients' outcomes. Although of clinical importance, the potential correlation of respiratory acidosis with eosinophils has not been specifically investigated up to now. Moreover, understanding the behavior of eosinophils in infectious versus non-infectious COPD exacerbations may be useful in developing personalized therapeutic approaches.[7] Such analyses, when done in the ICU setting, may have

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important implications for improving current prognostic models and guiding individualized management.

In this retrospective study, we retrospectively analyzed the data of 141 admitted COPD exacerbation patients to the ICU within one year. Our objective was to elucidate the association between the blood eosinophil counts with major clinical outcomes, which included ICU LOS, mortality, respiratory acidosis, and infectious exacerbations. This study will contribute to the current understanding of the role of eosinophils in the management of COPD, particularly in critically ill patients, and add to the evolving evidence in this field. Unlike many previous studies, our investigation specifically focuses on COPD patients in the ICU, where disease severity is markedly higher.

METHODS

The study was performed in accordance with the Helsinki Declaration. After obtaining ethical approval from the Ankara Sanatorium Training and Research Hospital Clinical Researches Ethics Committee (Date: 11.12.2024, Decision No: 2024-BÇEK 185), the study commenced. All patients hospitalized in a tertiary-level ICU, predominantly treating respiratory diseases, were screened over a one-year period from January 2022 to January 2023. Informed consent forms were obtained from patients and/or their legal guardians prior to accessing patient information. A total of 387 patient files were reviewed, of which 149 were identified as being admitted to the ICU with a diagnosis of COPD exacerbation.

Before initiating our study, we ensured that the informed consent forms, which we routinely obtain from patients and/or their legal guardians in our ICUs, were fully completed and approved. These forms grant permission for the use of patients' clinical and radiological data in scientific research.

Among these, 8 patients were excluded as they had died within the first 24 hours of ICU admission. These exclusions were made because it was not possible to rule out causes of mortality unrelated to COPD. Consequently, 141 patients were included in the study (Figure 1). Demographic data, including age and sex, were recorded. The included patients were then divided into two groups based on their peripheral blood eosinophil absolute counts.

- **Group 1:** Comprised patients with blood eosinophil levels between 0-100 cells/µl and was defined as the low eosinophil group.
- **Group 2:** Included patients with blood eosinophil levels ≥100 cells/µl and was defined as the moderate-high eosinophil group (Figure 1).

For both groups, initial ICU admission measurements of C-reactive protein (CRP), procalcitonin, D-dimer, white blood cell count (WBC), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR) were recorded as markers of infection and inflammation. Additionally, partial carbon dioxide pressure (pCO_2) levels at ICU admission were documented, and patients were classified according to respiratory failure subtypes.

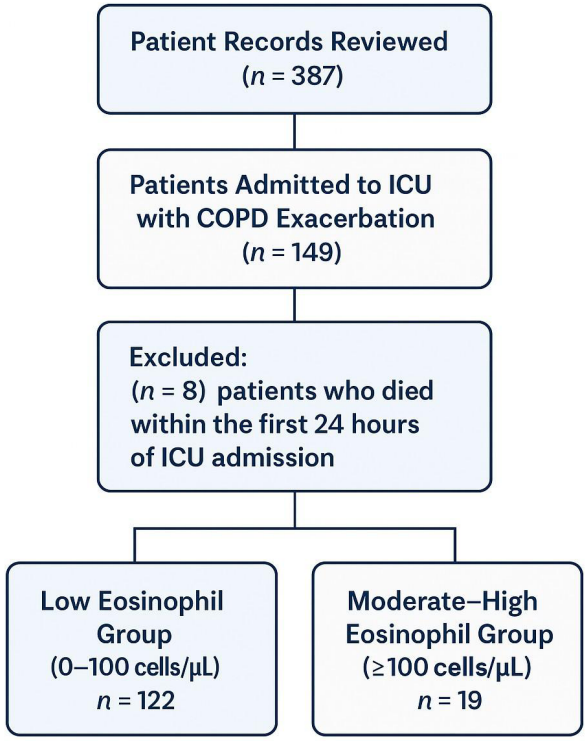

Figure 1. Flowchart of patient selection and eosinophil-based grouping

Further data collected included ICU length of stay (LOS), ICU mortality, and the need for intubation. To compare comorbidity profiles, mortality risk, and infection severity between the groups, the Charlson Comorbidity Index, APACHE II scores, and SOFA scores were also recorded at ICU admission.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics Version 27 (IBM Corp., Armonk, NY, USA). Categorical nominal variables were summarized as frequencies and percentages (n, %). Ordinal variables and numerical data that did not follow a normal distribution were reported as medians with their corresponding ranges (min-max). Numerical data with a normal distribution were expressed as mean±standard deviation (SD). In the patient groups, for categorical variables, the Chi-square test was used if each cell contained more than 5 patients. If any cell contained fewer than 5 patients, Fisher's exact test was applied.

Numerical data were analyzed using the student's T test when normally distributed, and the Mann-Whitney U test when not. The normality of numerical data was assessed using Kolmogorov-Smirnov and Shapiro-Wilk tests, skewness and kurtosis values, histograms, and proximity of outliers to each other. For bivariate correlation analyses, Spearman's correlation test was applied if at least one of the variables did not follow a normal distribution, while Pearson's correlation test was used if both variables were normally distributed.

A confidence interval of 95% was adopted for all statistical tests, with a significance threshold set at $p<0.05$. For normally distributed numerical variables with significant differences between means, effect sizes were calculated using Cohen's d.

RESULTS

Among the 141 patients included in the study, 91 were male and 50 were female. Of these, 122 were assigned to the low eosinophil group, while 19 were categorized into the moderate-high eosinophil group. The average age in the low eosinophil group was 71.13±0.87 years, compared to 68.42±2.05 years in the moderate-high eosinophil group. No significant differences were identified between the two groups in terms of age, APACHE II scores, SOFA scores, Charlson Comorbidity Index (CCI), or glasgow coma scores (GCS) (Table 1).

When comparing infective parameters, patients in the low eosinophil group had significantly higher neutrophil counts, NLR, PLR, and procalcitonin levels, while their lymphocyte counts were significantly lower (p-values: 0.009, <0.001, <0.001, 0.026, and 0.002, respectively). However, no significant difference was observed between the groups in terms of CRP levels (p: 0.461) (Table 1).

Additionally, among patients admitted to the ICU with COPD exacerbation, no significant differences were identified between the low eosinophil and moderate-high eosinophil groups in terms of sex, mortality, intubation requirement during ICU stay, inotropic support, or tracheostomy needs (p-values: 0.892, 0.365, 0.574, 1, and 1, respectively, based on Chi-square or Fisher's exact test as appropriate).

Correlation analyses conducted between eosinophil levels and other quantitative variables across both groups revealed a moderate, significant negative correlation between eosinophil levels and both PLR and NLR (p<0.001, r: -0.300, 95% CI: -0.448 to -0.137; p<0.001, r: -0.330, 95% CI: -0.474 to -0.169, respectively, Spearman) (Figure 2, 3). Additionally, a moderate, significant positive correlation was observed between eosinophil levels and lymphocyte counts (p<0.001, r: 0.311, 95% CI: 0.149 to 0.457). Furthermore, a weak but significant positive correlation was identified between eosinophil levels and partial carbon dioxide pressure (pCO_2) (p: 0.004, r: 0.238, 95% CI: 0.071 to 0.392, Spearman). Similarly, eosinophil levels exhibited a weak but significant positive correlation with ICU length of stay (p: 0.016, r: 0.203, 95% CI: 0.034 to 0.361, Spearman). Among all variables, intubation duration showed the strongest positive correlation with ICU length of stay (p<0.001, r: 0.511). However, when partial correlation analysis was performed by controlling for intubation duration, the correlation between eosinophil levels and ICU LOS was no longer significant (p: 0.220) (Table 2).

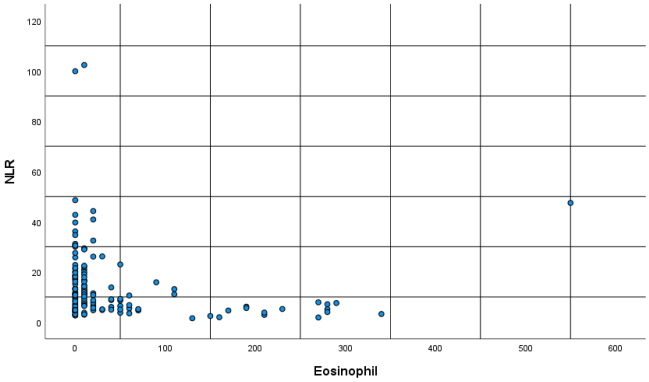

Figure 2. Correlation between eosinophil and NLR

NLR: Neutrophil/lymphocyte ratio

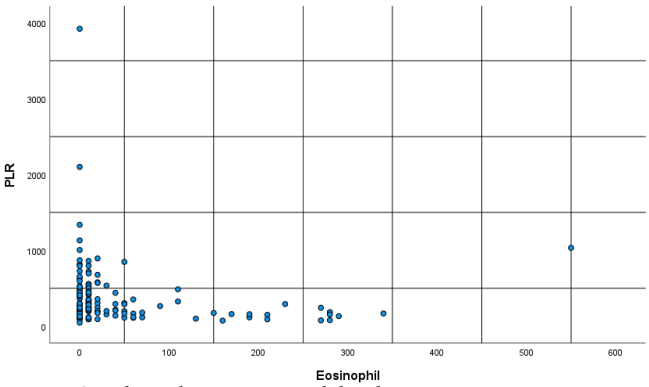

Figure 3. Correlation between eosinophil and PLR

PLR: Platelet/lymphocyte ratio

DISCUSSION

COPD represents a heterogeneous group of disorders, and over the years, efforts have been made to define its subtypes based on distinct clinical and pathological characteristics. Identifying these subtypes is crucial for developing personalized

Table 1. Comparison of quantitative values between patient groups

Parameter	Low eosinophil group [mean±SD or median (min-max)]	Moderate-high eosinophil group [mean±SD or median (min-max)]	p-value
Age (years)	71.13±0.87	68.42±2.05	0.253[a]
APACHE II score	17.3±6.9	15.7±6.9	0.373[a]
SOFA score	4.5±3.5	4.2±3.2	0.784[a]
CCI	3.8±1.5	3.8±2.4	0.969[a]
GCS	15 (3-15)	15 (3-15)	0.713[a]
Lymphocyte count (cells/µl)	894±571	1557±796	0.002[a*]
Neutrophil count (cells/µl)	9786±4954	7374±3258	0.009[a*]
Procalcitonin (ng/ml)	6 (1-155)	4 (1-21)	0.026[b*]
Neutrophil/lymphocyte ratio	11.22 (2.6-102.3)	5.09 (1.5-47.4)	<0.001[b*]
Platelet/lymphocyte ratio	284.8 (47.01-3921.3)	157.8 (74.06-1033.3)	<0.001[b*]

[a]: Student's T test, [b]: Mann-Whitney U test, *: Significant values at 95% confidence interval, SD: Standard deviation, min: Minimum, max: Maximum, APACHE: Acute physiology and chronic health evaluation, CCI: Charlson Comorbiditiy Index, GCS: Glaskow coma score, SOFA: Sequential organ failure assessment

Table 2. Correlation analysis of eosinophil levels with clinical and laboratory variables				
Variables	**Correlation coefficient (r)**	**p-value**	**95% CI**	**Test type**
Eosinophil-PLR	-0.3	<0.001	-0.448 to -0.137	Spearman
Eosinophil-NLR	-0.33	<0.001	-0.474 to -0.169	Spearman
Eosinophil-lymphocyte count	0.311	<0.001	0.149 to 0.457	Spearman
Eosinophil-pCO_2	0.238	0.004	0.071 to 0.392	Spearman
Eosinophil-ICU LOS	0.203	0.016	0.034 to 0.361	Spearman
Intubation duration-ICU LOS	0.511	<0.001	0.373 to 0.627	Spearman
Eosinophil-ICU LOS (Partial, controlled for intubation duration)	0.104	0.220		Partial Spearman

CI: Confidence interval, PLR: Platelet/lymphocyte ratio, NLR: Neutrophil/lymphocyte ratio, pCO_2: partial carbondioxide pressure, ICU: Intensive care unit, LOS: Length of stay

treatment strategies in disease management. For instance, beyond the classical subtypes such as chronic bronchitis and emphysema, recent years have seen the emergence of phenotypic variations like Asthma-COPD Overlap Syndrome (ACOS) and eosinophilic COPD. The recognition of these subtypes is not only essential for understanding the natural course of the disease but also plays a pivotal role in optimizing therapeutic responses.

In recent years, studies have explored the relationship between peripheral blood eosinophil levels and COPD exacerbations, as well as their impact on treatment response. A study by Pavord et al.[8] demonstrated that COPD patients with higher eosinophil levels significantly benefitted more from inhaled corticosteroid (ICS) therapy. By analyzing various eosinophil thresholds, the study highlighted that eosinophil levels above 300 cells/µl were particularly associated with higher response rates to treatment.

In patients monitored in the ICU due to COPD exacerbation, eosinophil levels have been reported to yield differing outcomes in terms of infectious and inflammatory processes. A retrospective study conducted by Singh et al.[9] involving 200 ICU patients observed that those with low eosinophil levels (<100 cells/µl) were more frequently associated with infectious causes and required mechanical ventilation for longer durations. In our study, while no significant difference was found between the groups in terms of ICU length of stay, a weak but significant positive correlation was identified between eosinophil count and ICU length of stay across all patients. In our analysis, where the need for mechanical ventilation was determined to be the most significant factor prolonging ICU stays, partial correlation analysis neutralized this effect, revealing that eosinophil levels had no independent impact on ICU length of stay. The imbalance in sample sizes between the two patient groups emerged as a limitation of our study. This imbalance may have contributed to findings that, while inconsistent with the literature, were deemed coincidental. In a study by Christenson et al.[10] involving 120 patients, it was demonstrated that those with the ACOS phenotype had significantly higher eosinophil levels and responded better to corticosteroid therapy. These findings underscore the potential impact of phenotypic differentiation on tailoring individualized treatment strategies.

Analyses based on low, moderate, and high eosinophil levels provide valuable insights into the treatment and prognosis of COPD patients. For instance, in the WISDOM study by Watz et al., it was observed that discontinuing ICS therapy in patients with eosinophil levels >300 cells/µl significantly increased the risk of exacerbations.[11] These findings suggest that eosinophil levels may serve not only as a predictor of treatment response but also as an effective biomarker for forecasting clinical outcomes.

In our study, we found that as eosinophil levels increased, the partial carbon dioxide pressure (pCO_2) measured at ICU admission also rose significantly. This finding could indicate that higher eosinophil counts in patients are associated with more severe inflammatory processes, potentially leading to greater bronchoconstriction. Similarly, a prospective study by Wang et al.,[12] conducted on 300 ICU-admitted COPD exacerbation patients, reported that low eosinophil levels (<100 cells/µl) were associated with higher mortality rates. However, in our study, no significant differences in mortality rates were observed between the groups.

One of the most notable findings of our study is the observation that patients with lower peripheral blood eosinophil levels exhibited significantly higher levels of infection-related inflammatory markers such as NLR, PLR, and procalcitonin. This finding strongly supports the hypothesis that non-eosinophilic COPD exacerbations may be primarily driven by infectious etiologies. Several studies in the literature have suggested that eosinopenia in critically ill patients reflects acute physiological stress and impaired immune response, and is associated with worse prognosis.[13] In the context of COPD, low eosinophil levels may indicate infection-related exacerbations and suggest that this phenotype may require a different treatment approach than eosinophilic exacerbations.[14,15] Moreover, previous research has shown that ratios such as NLR and PLR are significant predictors of 30-day mortality in patients with severe COPD exacerbations requiring intensive care.[16]

In the 2018 review by Kostikas et al.,[17] it was discussed that blood eosinophil count can influence treatment strategies in both asthma and COPD. In asthma, elevated blood eosinophil levels have gained importance in identifying patients who may be candidates for biologic therapies. In COPD, higher eosinophil counts have been associated with a better response to inhaled corticosteroid (ICS) therapy, particularly in patients with frequent exacerbations. While a cut-off value of 300 cells/µl is generally accepted in asthma to define eosinophilia, there is still no consensus on a universal threshold or optimal measurement frequency for blood eosinophils in COPD.

Recent studies increasingly recommend the use of blood eosinophil levels as a biomarker in patients with COPD. Their value is progressively recognized both in guiding treatment decisions and in predicting treatment response.[18,19] When evaluated alongside the findings of our study, the admission of a patient with a COPD exacerbation and elevated eosinophil levels to the ICU should prompt the ICU physician to consider the following questions:

- Could this exacerbation likely be non-infectious in nature?
- Does the patient currently use inhaled corticosteroids? Have they discontinued them? How is their treatment adherence?
- Is a favorable response to treatment likely? Should anti-inflammatory therapies be prioritized?

Considering all these aspects, we believe that in critically ill COPD patients admitted to the ICU with acute exacerbations, in addition to leukocyte, neutrophil, lymphocyte, and platelet counts in complete blood count, eosinophil levels should also be taken into account to develop more personalized and phenotype-specific treatment strategies.

Future Research Recommendations

Future studies should aim to validate the findings of this study in larger, prospective, and multicenter cohorts to improve generalizability and statistical robustness. In particular, further research should focus on the longitudinal behavior of blood eosinophil levels during different phases of COPD exacerbation and recovery, as well as their dynamic relationship with infectious markers and respiratory function. Moreover, incorporating data on prior corticosteroid use, treatment adherence, and environmental exposures could offer deeper insight into the pathophysiological basis of eosinophilic versus non-eosinophilic exacerbations. A more refined phenotypic classification of COPD patients in the ICU setting may facilitate the development of personalized therapeutic strategies and improve clinical outcomes.

Limitations

This study has several limitations that should be acknowledged. First and foremost, there was a notable imbalance in group sizes, with a considerably larger number of patients in the low eosinophil group (n=122) compared to the moderate–high eosinophil group (n=19). This disproportion may have reduced the statistical power of group comparisons and limited the generalizability of the findings. Additionally, due to the retrospective design, potential confounding factors such as prior corticosteroid use, medication adherence, and the precise etiology of exacerbations (e.g., bacterial vs. viral) could not be fully assessed.

CONCLUSION

Although peripheral blood eosinophil levels are not yet a primary determinant in decision-making models for managing and predicting prognosis in patients admitted to the ICU with a diagnosis of COPD exacerbation, they should undoubtedly be considered in clinical practice. In our study, we did not evaluate parameters such as the use of ICS or treatment adherence prior to ICU admission. However, future ICU-based studies should focus on these factors to better understand the triggers of COPD exacerbations between ICU admissions. Large-scale prospective studies are needed to analyze the relationships between ICS usage, treatment adherence, blood eosinophil levels, and infectious processes to improve patient outcomes.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Ankara Sanatorium Training and Research Hospital Clinical Researches Ethics Committee (Date: 11.12.2024, Decision No: 2024-BÇEK 185).

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.

Use of Artificial Intelligence

Artificial intelligence was utilized for English grammar checking after the manuscript was written.

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Original Article

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Comparison of creativity and critical thinking among female students of selective and public high schools

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ABSTRACT

Aims: This study is conducted to provide comparison between female students of selective and public high schools (PHS) in Urmia city in Iran, using creativity and critical thinking measures.
Methods: Statistical randomized-sampling technique is used in selection of 90 students from one selective high school (SHS) and 260 students from three PHS. The Torrance creativity and California critical thinking inventories were used for data collection.
Results: A causal-comparative strategy is used in the analysis, while one-way ANOVA test and T test between independent groups were used to test the hypothesis regarding the difference between students in SHS and PHS. Results showed that there is a significant difference between SHS and PHS groups (fluidity, expansion, initiative, and flexibility).
Conclusion: It is concluded that while considering the critical thinking, no significant difference exists between the components of deductive and inductive analysis. But, differences between selected groups was observed when considering the analysis and inference components. According to the results obtained for creativity, a meaningful relationship between all of the elements in both of the selected groups with $p<0.001$ is observed.
Keywords: Critical thinking, creativity, female students, public high school, selective high school

INTRODUCTION

Creativity and critical thinking are among the most essential capabilities for collaborative and social relationships. Creative thinking can be considered as the ability to produce idea,[1] generating alternative solutions,[2] and helping individuals confront different problems with ease. Juliantine[3] believed that creativity in individuals can be improved through education, resulting in humans with superior creative abilities. Amabile concluded that, based on the componential theory of creativity, individual-specific skills, cognitive processes that leads to creativity, and intrinsic motivation of the individual can be considered as the pivotal components of creativity for each person.[4] The structure of an educational system exerts a profound influence on the cultivation of students' creative and critical thinking abilities. In the Iranian context, traditional educational practices are predominantly shaped by exam-centric, memorization-based methodologies that prioritize standardized assessment over cognitive exploration. Such approaches tend to constrain the development of creativity and higher-order thinking by valuing rote reproduction rather than original thought. In contrast, contemporary pedagogical paradigms-such as student-centered, collaborative, and project-based learning-have been shown to significantly enhance students' creative capacities by fostering active engagement and problem-solving. As Girgin and Akcanca[5] argued, the integration of the collaborative creativity model within educational settings equips learners with the ability to generate, assess, and implement innovative solutions to complex, real-world challenges, thereby nurturing a more dynamic and adaptable cognitive skillset.

Recently, Matraeva et al.[6] suggested that creativity can be evaluated based on the degree of accuracy, authenticity, flexibility, and Guilford fluency in a person. It is believed that creativity in students is more related to the personal characteristics, attitude, supervisory technique, and administrative behavior of the teacher in charge. Hence, it is not surprising that the educational system of any country plays a key role, in the students' skills and competencies within creativity context. Creativity is also associated with the originality of ideas, openness to new experiences, willingness for new things, willingness to take risks (i.e. thoughts and actions), and sensitivity to the beauty of the ideas. Likewise, Gülel[7] and Kanli[8] addressed creativity in Turkish students with consideration to different educational backgrounds and their demographic properties. Agnoli et al.[9] showed that the level of creativity for any student is related to several factors most of which are related to the environmental variables that take place inside or outside the school. Also, Gralewski and Karwowski[10] stated that the socio-economic status of

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the family and/or the any extrinsic support positively affects students' creativity during childhood, but loses its impact in adulthood.

On the other hand, the critical thinking obviously has a great effect on the students' performance. Lipman[11] defined critical thinking, as a type of thinking that has a fundamental characteristic based on several criteria and self-corrective tendency towards its context or theme. Santrock[12] showed that we are able to create critical idea by patterning and motivating the behaviors and our skills. In today's world, acquisition of skills for critical thinking is more about the undeniable necessity in labor market, facing material and spiritual questions, evaluation of viewpoints, individuals' policy, institutions, and facing with social problems. According to Brodin and Frick[13] any person needs to be mentored to turn this process into an academic skill, while Adriansen[14] believed that rationality, analytical thinking, evaluative perspective, and selectivity are the concepts of which are needed to improve critical thinking. More recently, Saputro et al.[15] conceptualized the critical thinking as a bi-dimensional act that includes dispositions and skills, and therefore its dispositional aspects are broad-mindedness, truth-bearing, and self-confidence.

Paul and Elder[16] have examined the connection between critical and creative thinking. They argued that creativity influences both the production and critique processes, which in turn affect how we evaluate and make judgments. They also believed that the best way to develop critical thinking is through Socratic questioning-the method of asking and answering questions to stimulate deeper thoughts. Unlike Marzano,[17] Paul and Elder[16] did not see critical and creative thinking as separate. They believed these two types of thinking are closely related and often function as one. Creative thinking involves generating or producing ideas, while critical thinking involves evaluating or judging them.

Even the definition of "creative" includes a critical aspect, such as imagination and intellectual originality. When someone is engaged in deep, meaningful thinking, the mind both creates and evaluates ideas at the same time. So, creativity and critical thinking work together to generate and assess outcomes. Good thinking requires both imagination and strong intellectual standards. In theory, creativity and critical thinking can be separated, but in practice, they are part of the same mental process. Thought becomes systematic when it follows a clear path to the end, but it can also rely on intuition when no clear plan or strategy is present.

A creative mind sets standards for what it creates. No effective mind lacks judgment, precision, or clarity. A weak mind would rely on vagueness, irrelevance, or inconsistency. Therefore, a capable mind produces valuable ideas because it holds itself to high standards and cares about both how and what it creates.[18] Numerous studies have been conducted on creativity and critical thinking skills. But, many of them have focused on either one of the constructs in isolation, or within limited socio-cultural contexts. Furthermore, a considerable portion of the existing literature predominantly examines creativity and critical thinking at the university level, overlooking the developmental period of adolescence, particularly within high school settings. In addition, prior studies have rarely addressed the influence of school type-especially the distinction between selective and public high schools-on students' creativity and critical thinking abilities. The impact of familial background, and specifically maternal education level, on these cognitive skills has also not been extensively explored in relation to school environments. These gaps highlight the need for a comprehensive investigation that considers both individual and environmental factors simultaneously.

As outlined, critical thinking and creativity play a pivotal role in educational planning and the formulation of long-term policies aimed at fostering a more progressive and resilient society. However, in developing countries such as Iran, there remains a noticeable scarcity of systematically conducted and well-documented studies that address these dimensions within the educational context. To the best knowledge of the authors, there is no comprehensive study regarding the role of educational differences and creativity among students in Urmia city, Iran. Hence, this study investigates the cognitive differences between students in elite and public schools in Urmia through a multidimensional lens. Given that elite schools in Iran admit students via competitive exams and maintain rigorous academic standards, the research critically evaluates whether these conditions translate into enhanced cognitive abilities. It further examines how differing educational environments-such as resource availability, class size, and academic focus-affect student development. By comparing students from similar socio-economic backgrounds, the study also addresses issues of educational equity. Moreover, the findings offer practical implications for policymakers and educators while contributing original insights to the underexplored educational context of Urmia city. This study also investigates the role of mothers' education level (called as the parents' education level here after) on creativity and critical thinking of the students.

METHODS

Ethics

The study was conducted in accordance with the Declaration of Helsinki, and approved by the I.R.I. Ministry of Education Ethics Committee (Date: 23.04.2013, Decision No: 551/41/27700, documented in Farsi).

Participants

As detailed previously, this study provides a comparative look between creativity and critical thinking skills among female students that are studying either in public or selective high schools in Urmia city, Iran. Since there exist only two selective high school (SHS) and seven public high schools (PHS) with similar socio-economic background in the city of Urmia, we have decided to get our samples from one SHS and three of PHSs. Then, a random sampling technique is used and sample sets with 90 students from the SHS and 260 students from three PHSs are used in the conducted analysis. It is noteworthy that the number of students at SHS (i.e. 90 students) were considered to be fewer than those who study in PHS (i.e. 260 students) due to lower number of attendees and highly selective nature of the SHSs in Iran. Additionally,

in distribution of the inventories, students with similar economic and social background were preferred to reduce the effect of external factors and bias in the study.

Measures Used

Multiple-choice paper-and-pen test of Torrance creativity: The multiple-choice paper-and-pen inventory test also called as the Torrance creativity test, is developed based on the definition of Torrance for creativity in human being.[18-20] In Iran, the test is also known as the Torrance creativity (TC), which is briefed and standardized by Abedi[21] and continuously applied in studies conducted by Iranian researchers. In this respect, the TC test evaluates four elements of critical thinking namely fluidity, innovation, flexibility and development. Abedi concluded that the perpetuity coefficient of fluidity section is about 85%, while the remaining criteria including innovation, flexibility and development sections respectively have 82%, 85%, and 80% effect.

California Critical Thinking Skills Test: California critical thinking skills test of form B (CCTST-FB) contains 34 multiple choice questions[22] with one correct answer in the field of cognitive skills of critical thinking (analysis, evaluation, inference, deductive and inductive reasoning) for specific measurement of the level of critical thinking skills in the post high school stages. For this, one score is given to every correct answer and the total sum of the correct answers is considered as the total score (maximum 34 scores). In this respect, the correct answer is the one which is correctly selected in concordance with the test key. The participant(s) during the test has 45 minutes to answer 34 questions out of 200 questions, while the test results, finally reveals the validity and reliability along with a choice for distinguishing the degree of difficulty in the test. For this reason, it was assumed that the CCST-FB provides more comprehensive results than the remaining tools for assessment of critical thinking.

In this regard, the range of the questions include cases which measures the conceptual analysis from one sentence to a more complex integration of critical thinking. Hence, some answer to the CCST-FB test needs explicating a correct inference from a case's needs by evaluation and rational justification of a conclusion. It is noteworthy that the validity of the CCST-FB test has been reported to be between 68%-70% with utilizing the Kuder-Richardson method. Eslami also has reported a validity of 78% for this test when utilizing the retesting method.[23] Similarly, Bigdeli reported that the validity of perpetuity for CCST-FB test is about 73% when using 15-day retesting method.[24]

In conclusion, and based on the posterior studies it was concluded that both of the TC and CCTST-FB tests are eligible, credible, and would eventually provide reasonable results in evolution of the hypothesis of the study, which are detailed in the following section.

Hypothesis

The credibility of the hypotheses from a deductive aspect is tested using one-way ANOVA test and T test of independent groups. In this respect, the following hypothesis are used to make a comparison based on creativity and critical thinking among the selected groups.

- **Hypothesis 1:** There is difference between creativity of female students of SHS and PHS.
- **Hypothesis 2:** There is difference between critical thinking of female students of SHS and PHS.
- **Hypothesis 3:** There is a relation between critical thinking and/or creativity with the education level of mothers for female students attending for SHS and PHS.

Yet, as the calculated Cronbach's-alpha coefficients for estimation of perpetuity of creativity and critical thinking scales are considered to be 82% and 51% respectively (to be de-tailed in the results), all the perpetuity coefficients in case of removing the question are less than these values. Therefore, the questions of the tests are suitable for evaluating the considered variables and could be utilized in the analysis and reasoning with acceptable perpetuity.

RESULTS

Initially, the data acquired from the TC and CCTST-FB tests are evaluated using Statistical Package for the Social Sciences (SPSS) software. To ensure the comparability of two unequal groups, homogeneity of variance and normality of the samples are tested. Table 1 details the obtained results for TC and CCTST-FB tests, while the Table 2 details the

Table 1. Statistics related to the obtained results of TC and CCTST-FB tests

Test	Variable	n	Max	Min	μ	σ	γ	k
TC	Fluidity	22	44	11	27.72	5.75	-0.03	-0.05
	Development	11	21	3	12.94	3.41	-0.14	-0.28
	Innovation	16	32	6	19.71	4.46	-0.08	-0.24
	Flexibility	11	21	5	14.48	3.20	-0.30	-0.43
	Creativity (overall)	60	113	37	74.85	12.98	0.11	-0.29
CCTST-FB	Analysis	9	38	9	24.14	4.38	-0.20	0.94
	Evaluation	14	52	14	35.70	5.21	-0.32	1.40
	Deduction	11	40	11	29.14	4.66	-0.61	1.19
	Deductive reasoning	17	56	17	41.34	5.73	-0.29	0.59
	Inductive reasoning	14	52	14	37.01	5.32	-0.72	2.00
	Critical thinking (overall)	34	115	35	88.97	10.37	-0.61	2.00

TC: Torrance reativity, CCTST-FB: California critical thinking skills test of form B, n: The number of questions related to each variable in the test, Max: The maximum grade obtained from the collected questionnaires, Min: The minimum grade obtained from the collected questionnaires, μ: The average grade obtained from the collected questionnaires, σ: Standard deviation, γ: Skewness, k: Kurtosis of the collected samples

Kolmogorov-Smirnov test of normality of the conducted tests. Since the p-value (i.e. k-s) is bigger than the significance level, it can be concluded that the measured variables for creativity and critical thinking is normally distributed and can be used for further analysis. This is also illustrated in Figure, which depicts the probability distribution function (PDF) of samples for creativity and critical thinking separately. It can roughly be concluded that the samples are normally distributed which confirms the results of Kolmogorov-Smirnov in Table 2.

Table 2. Kolmogorov-Smirnov test of normality for the TC and CCTST-FB tests

Test	Variable	k-s	Sig.	n
TC	Fluidity	0.88	0.42	350
	Development	1.28	0.07	350
	Innovation	0.99	0.27	350
	Flexibility	1.73	0.005	350
	Creativity (overall)	0.83	0.50	350
CCTST-FB	Analysis	1.09	0.18	350
	Evaluation	1.14	0.15	350
	Deduction	1.43	0.03	350
	Deductive reasoning	0.88	0.41	350
	Inductive reasoning	1.49	0.02	350
	Critical thinking (overall)	1.02	0.25	350

TC: Torrance creativity, CCTST-FB: California critical thinking skills test of form B, k-s: Score of the test, Sig: Significance

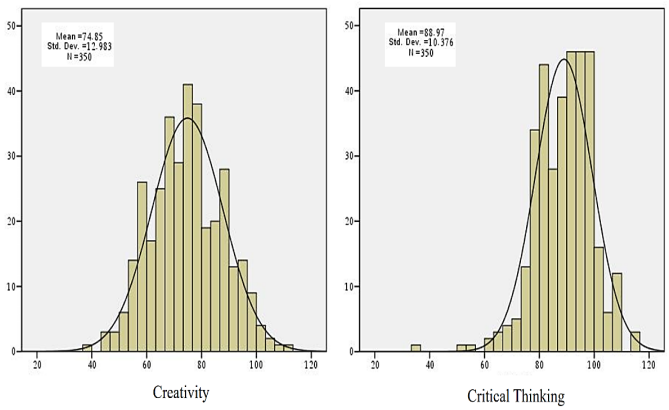

Figure. The PDF and the histogram of samples taken for creativity and critical thinking

PDF: Probability distribution function

It is also noteworthy that the deviations in flexibility, deduction, and deductive reasoning (Table 1) can be neglected due to the small skewness and kurtosis together with the large sample size of the experiment. Additionally, by applying the Cronbach-alpha it can be assured about the concordance between components of the tests. In this respect, Table 3 details the results of Cronbach-alpha for the conducted tests. Since the Cronbach-alpha for creativity and critical thinking respectively are 0.82 and 0.51, perpetuity coefficients in case of removing the question are less than these values. Therefore, the questions are suitable for measuring the desired variables and the tests used in the study have acceptable reliability.

Table 3. The Cronbach's alpha value for the conducted tests

Parameter	Index	Value
Creativity	A	0.82
	Number of questions	60
	Sample size	350
Critical thinking	A	0.51
	Number of questions	34
	Sample size	350

After the initial data analysis were conducted, to test the first hypothesis of the study regarding the difference between creativity of female students of PHS and SHS, T test is used among two independent groups of students. As given in Table 4, it can be concluded that with 99% confidence ($p<0.01$), there is a meaningful difference between the variable of creativity (overall) of female students of PHS and SHS, while the reasons may lie within the capacity and/or the facilities provided by the school to the students which attend SHSs. It can also conclude that creativity levels significantly differ between female students in PHS and SHS.

Table 4. Results of T test for the first hypothesis, regarding the difference between creativity and its elements in PHS and SHS

Variable	School	M	t	Df	Sig.
Fluidity	Public	26.27	-8.76	348	0.001
	Selective	31.85			
Development	Public	12.54	-3.79	348	0.001
	Selective	14.09			
Innovation	Public	19.04	-4.88	348	0.001
	Selective	21.62			
Flexibility	Public	13.81	-7.07	348	0.001
	Selective	16.40			
Creativity (overall)	Public	71.66	-8.52	348	0.001
	Selective	83.95			

PHS: Public high schools, SHS: Selective high school, Df: Degrees of freedom, Sig: Significance

Then, to test the second hypothesis of the study regarding the difference between the critical thinking of female students of SHS and PHS, once again the T test was used among two independent groups. Results are given in Table 5, indicating that there is no meaningful difference between the elements of evaluation, deductive, and inductive reasoning. However, there is difference between the elements of analysis and deduction between both groups. So, it can be concluded that the element of critical thinking is different between two groups which is the source of creativity and therefore requires higher level of cognitive complexity.

Likewise, Table 6 depicts the mothers' level of education that is later used in evaluation of the effect of mother education on creativity and critical thinking of students. Additionally, to test the third hypothesis of the study regarding the relation between the critical thinking or creativity with the education level of students' mothers, one-way ANOVA test is used (Table 7). According to the result of the one-way ANOVA test, it can

Table 5. Results of T test for the second hypothesis, regarding the difference between critical thinking and its elements in SHS and PHS

Variable	Type	M	t	Df	Sig.
Analysis	PHS	23.84	-1.95	135	0.05
	SHS	24.98			
Evaluation	PHS	35.82	0.75	348	0.45
	SHS	35.34			
Deduction	PHS	29.42	1.95	348	0.05
	SHS	28.32			
Deductive reasoning	PHS	41.66	1.75	348	0.08
	SHS	40.44			
Inductive reasoning	PHS	37.08	0.45	348	0.65
	SHS	36.79			
Critical thinking (overall)	PHS	89.09	0.33	139	0.74
	SHS	88.64			

SHS: Selective high school, PHS: Public high schools, Df: Degrees of freedom, Sig: Significance

be concluded that there is meaningful relation between the average variable of critical thinking and the level of mothers' education.

Table 7. Results of the one-way ANOVA test for third hypothesis, regarding the relationship between creativity and critical thinking related to the mothers' education

Variable		SD	Df	MS	F	Sig.
Creativity	Intergroup	1049.76	6	174.96	1.05	0.39
	Intragroup	55652.96	336	165.43		
	Overall	56702.72	342			
Critical thinking	Intergroup	2597.49	6	432.91	4.35	0.001
	Intragroup	33422.85	336	99.47		
	Overall	36020.34	342			

ANOVA: Analysis of variance SD: Standard deviation, Df: Degrees of freedom, Sig: Significance

DISCUSSION

This study makes an original contribution by exploring factors influencing creative and critical thinking development among Iranian high school students, addressing the scarcity of comparative research between selective and public schools. Findings reveal that students in selective schools exhibit stronger cognitive skills, underscoring the influence of educational settings.

Results obtained for the first hypothesis indicate that there is a significant difference between the average creativity between female students of PHS and SHS, while findings are in line with the result obtained by Chan.[25] Selective high schools, by virtue of their superior resources and instructional strategies, cultivate an educational environment that is highly conducive to the development of students' creative and critical thinking abilities. Through individualized guidance, problem-based learning, and cognitively stimulating pedagogies, such institutions foster originality, cognitive flexibility, and advanced problem-solving skills-key components of creative potential. Hence, it is assumed that the SHS are well equipped with educational and upbringing equipment in comparison with other schools. As a results, there is a probability that can be expressed in which school type would not present the creativity level of the students, given that they have been provided with conditions facilitating creativity, school type may not fully determine students' creativity levels. Yet, according to some studies the students who study at schools in which encourage innovation, creativity, and value the creativity of their students would encounter more creative students in comparison to the students who study at schools that focus only on the educational performances.

Result achieved for the second hypothesis is also in concordance with the conducted result of previous studies such as those conducted by Alborzi and Ostovari.[28] In this respect, it can be concluded that critical thinking components, such as deduction and analysis, differ significantly between the two groups, which is the outcome for creativity and therefore requires higher level of cognitive complexity and for this, processing complex information is needed. Therefore, the fact which is also confirmed by most of the experts is that the critical thinking skills develops in discussions, exchanging opinions and solving problems.

Since the Cronbach's alpha values for the creativity and critical thinking components are 0.82 and 0.51 respectively, it is evident that internal consistency for creativity falls within the acceptable and desirable range. In contrast, while the alpha coefficient for critical thinking appears lower than the generally accepted threshold of 0.68-0.78,[26] its acceptance can be justified under certain empirical and methodological considerations. Specifically, the perpetuity coefficients observed upon item deletion remained below the reported alpha value, suggesting that none of the individual items disproportionately weakened the overall scale reliability. Moreover, in exploratory or pilot-phase studies-particularly those involving abstract constructs such as critical thinking-lower alpha values may still be considered tolerable, especially when the construct comprises heterogeneous dimensions or when the number of items is limited (limited number of SHS and PHS in this study). As noted in the psychometric

Table 6. Demographic information regarding the mothers' level of education

School		PHD	BSc	MSc	Post-high school	High school	Guidance school	None
PHS	Number	4	18	67	34	90	28	14
	Percent	1.2	5.2	19.5	9.9	26.2	8.2	1.4
SHS	Number	1	8	43	15	18	3	0
	Percent	0.3	2.3	12.5	4.4	5.2	0.9	0

PHD: Philosophiae Doctor, BSc: Bachelor of Science, MSc: Master of science, PHS: Public high schools, SHS: Selective high school

literature (e.g., Cortina;[26] Schmitt[27]), a Cronbach's alpha around 0.50 can be considered adequate for preliminary investigations or newly adapted scales in educational and behavioral research, provided the instrument demonstrates conceptual validity and the items capture different facets of a multifaceted cognitive domain. Therefore, although the alpha value for critical thinking is below ideal expectations, its interpretability and utility remain valid within the contextual and methodological scope of this experimental study.

Results obtained for the third hypothesis indicate that there is relation between the variable of critical thinking and mother's education level, while our results are in line with the conducted analysis of Ghasemi and Oghlidos.[29] Generally speaking, the role of parents' education in upbringing kids and growth of creativity and critical thinking or adaptation of creative thinking in life is undeniable, constructive, and crucial. Based on the results obtained, there is no significant relationship between the mean of the creativity variable and the mother's level of education. However, there is a significant relationship between the mean of the critical thinking variable and the mother's level of education. Therefore, parents are an effective role-model for their children, whereas in this course of age, the level of dependency and relation of female teenagers with parents especially mothers are more and therefore are influenced by their thoughts and opinions.

To brief the discussion, it can be said that we deal with a process rather than a consequence or an output, both for creativity and critical thinking. In total agreement with the results of Mohseni et al.,[30] there is a significant difference between the students who attend PHS and SHS in terms of motivation for progress, creativity and its components, and can conclude that the gifted students have higher creativity and critical thinking abilities. Yet, creativity involves generating original ideas and redefining existing values through systematic and reflective thinking, a process that inherently requires critical evaluation. Due to the conceptual overlap between creativity and critical thinking, growth in one often reinforces the other, which is in line with the preliminary studies of Paul and Elder[16] and in oppose with Marzano[17] that the critical and creative thinking should be considered as one. Additionally, by studying the classification of bloom from educational purposes in cognitive environment, for reaching up to combination level, mostly used as equivalent to creativity, we must have successfully passed the analysis level which is considered to be one of the elements of critical thinking. According to Bloom's taxonomy, achieving creativity (synthesis) requires successfully passing the analysis level, a key element of critical thinking. This emphasizes that creativity relies on the prior development of critical thinking, particularly analytical reasoning. Within this framework, the educational system and maternal education serve as key factors in shaping cognitive growth. Mothers with higher educational backgrounds often cultivate intellectually enriched home environments, reinforcing analytical skills essential for creative thinking. Thus, the combined influence of supportive schooling and maternal intellectual engagement significantly enhances female students' capacity for both critical and creative thought.

Limitations

This study is limited by its focus on female students from Urmia, restricting the generalizability of the results. Additionally, the reliance on TC and CCTST-FB scales captures only momentary cognitive performance, potentially overlooking long-term development. The absence of controls for socio-economic status, un-even sample size, instructional practices, and individual variability further constrains the findings. Future research should incorporate broader, more diverse samples and longitudinal approaches to address these limitations comprehensively.

CONCLUSION

This study addresses creativity and critical thinking abilities between female students who were randomly selected from selective and public high schools of Urmia city in Iran. For this, the TC and CCTST-FB inventories are used among 90 students selected from one SHC and 260 students from three PHS randomly selected for this aim. Then, three hypotheses are used to test the difference between creativity and critical thinking among the selected students. The hypotheses were tested by means of T test and one-way ANOVA test. Results showed that;

- Creativity between the female students of PHS and SHS are not the same.
- There is statistically significant difference between the elements of evaluation, deductive, and inductive reasoning in students of PHS and SHS.
- A significant relationship exists between critical thinking skills and mothers' education levels.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the I.R.I. Ministry of Education Ethics Committee (Date: 23.04.2013, Decision No: 551/41/27700, documented in Farsi).

Informed Consent

Informed consent was obtained from all subjects involved in the study.

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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The sleep-muscle axis: how poor sleep quality predicts probable sarcopenia in the older adults

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ABSTRACT

Aims: Investigate whether there is a link between the quality of sleep and the likelihood of developing sarcopenia in older adults.
Methods: Among the 498 patients over 65 who enrolled in the internal medicine geriatrics clinic between December 2024 and March 2025, 74 patients with poor sleep quality (group 1) and 110 patients with good sleep quality (group 2) were included in the study. The remaining 314 patients were excluded from the study. Demographic characteristics, body measurements, comprehensive geriatric assessments, potential sarcopenia assessments, and Pittsburgh sleep quality measurements were conducted.
Results: The average age of group 1, consisting of a total of 74 people, is 73.5±5.1 years, and the average age of group 2, consisting of 110 people, is 71.6±5.2 years. A statistically significant difference was detected between the groups in terms of average age distribution (p=0.03). The average body-mass index (BMI) value of group 1 patients was statistically significantly lower than that of group 2 patients (p=0.038). When the comprehensive geriatric evaluation was compared between the groups, the rate of possible sarcopenia was 81 percent in group 1 and 17 percent in group 2 (p<0.034).
Conclusion: Findings suggest a potential link between sleep quality and probable sarcopenia in older adults.
Keywords: Sleep quality, sarcopenia, older adults

INTRODUCTION

The world population gradually ages due to rising life expectancy and decreased fertility.[1] The growing aging of individuals has resulted in an enormous rise in the overall amount of people who will require care in the future.[2] Sleep is crucial for preserving one's health and standard of living. Despite the physiological changes in sleep-wake cycles and structure of sleep that occur during aging, older adults experience the repercussions of a range of difficulties linked to sleep length, difficulty beginning and sustaining sleep, and breathing problems during sleep.[3] Older adults are more likely to suffer from sleep disorders like insomnia and poor sleep quality. About ten percent of aged people have often sleep problems in their habitual existences. This raises older adult's risk of dying as well as lowering their quality of life.[4] Sleep disturbances can trigger a variety of pathways, including sympathetic activation, metabolic abnormalities, and a pro-inflammatory state, they all have a part in sarcopenia evolution.[5,6]

Sarcopenia, which was recently classified as muscular failure, is distinguished by Low muscle mass and strength combined, or changed muscle quality, which raises the risk of death, hospitalization, fractures, falls, and disability.[7,8]

Because sarcopenia and sleep problems share pathophysiology, studying their interactions may help us better understand the mechanisms at work.

Sarcopenia is estimated to affect around the world, 10-16% of older adults.[9] Age-related modifications to the structure of muscles may be a major contributing factor to several poor health outcomes in older adults, such as fractures, falls, cognitive decline, and death.[9,10] To facilitate prompt management and early identification of those at risk for sarcopenia, the Asian Sarcopenia study group (AWGS) 2019 consensus introduced the concept of "probable sarcopenia".[11] Loss of muscle mass or poor physical function, which can be assessed with low-cost, easily applicable techniques for population screening and clinical practice, is referred to as sarcopenia. Therefore, additional studies are needed to determine the etiology and complications associated with sarcopenia. Various factors contribute to the pathogenesis of sarcopenia. Of these; other risk factors should be taken into account, including hormone fluctuations, cardiovascular disease, inflammatory cytokines, resistance to insulin, activity level, gender, heredity, and nutritional condition.[12,13]

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Negative health outcomes in older adults, such as dementia, diabetes, cardiovascular disease, coronary heart disease, obesity, and mortality, are linked to either too little or too much sleep.[14-16] Prior research has connected many aspects of skeletal muscle injury to short sleep duration and poor sleep quality.[17-19] Unbalances in sleep balance have also been linked in recent studies to increased cortisol levels, which can impact muscle, decreased growth hormone and testosterone synthesis, and an increased risk of insulin resistance,[20] lack of sleep can alter the circadian cycle, which can result in abnormalities in the metabolism of skeletal muscles.[21]

An increasing amount of data points to the potential role that sleep disturbances may play in mediating the onset of sarcopenia Compared to sarcopenia, "probable sarcopenia" is a relatively recent term, and its diagnostic standards are less strict. Older adults may be able to prevent and reduce their risk of developing "probable sarcopenia" sooner if the idea is introduced and its relationship to sleep length is examined. In addition, there is presently debate regarding the connection between the length of sleep disturbances and potential sarcopenia in older adults. Verifying this connection could aid in establishing healthy sleep habits and offer practical intervention techniques outside of dietary and physical activity changes.

METHODS

Ethics

The Ankara Bilkent City Hospital Non-interventional Clinical Researches Ethics Committee of our university granted clearance for this investigation (Date: 25.12.2024, Decision No: TABED-2 24-733). All subjects gave their agreement because the study was prospective. The Declaration of Helsinki was followed when conducting the study.

Study Population

The demographic characteristics, body measurements, comprehensive geriatric assessments, probable sarcopenia assessment, and Pittsburgh sleep quality measurements were performed. Patients under the age of 65, those who smoked, had alcohol or drug addiction, Volunteers using prescription antidepressants were also excluded from the study due to the effects of antidepressants on sleep and those who used sleeping pills were excluded from the study. Among 498 patients over the age of 65 who applied to the internal medicine geriatrics outpatient clinic between December 2024 and March 2025, 184 patients who agreed to participate in the study were included in the study. Patients with poor sleep quality (PSQI >5) (group 1) consisted of 74 patients, and patients with good sleep quality (PSQI <5) (group 2) consisted of 110 patients. BMI was calculated as weight/height (kg/m^2). Waist circumference (WC, cm) was calculated by measuring the circumference of the circle passing through the middle of the lines perpendicular to the 10th rib and the anterior superior iliac spine on both sides. Functional status was assessed using the Lawton-Brody instrumental activities of daily living (IADL) and Katz activities of daily living (ADL) scales.[22,23] Nutritional status was evaluated using the Mini-Nutritional Assessment Short Form (MNA-SF).[24] Polypharmacy was defined as the use of ≥5 medications.[25] The same experienced doctor evaluated patients' frailty state using the Clinical Frailty Scale (CFS). Clinical frailty is defined by CFS using a score system that ranges from 1 (extremely fit) to 9 (terminally ill), both living with frailty (CFS ≥4) and being non-frail/robust (CFS <4).[26,27]

Assessment of Sleep Quality

The Pittsburgh Sleep Quality Index (PSQI), offers measures of seven domains: (1) subjective sleep quality, (2) sleep latency, (3) sleep duration, (4) disturbances in sleep, (5) sleep effectiveness, (6) use of sleep aids, and (7) daytime impairment scores, was used to assess the quality of sleep.[28] A 3-point ascending scale is used to rate these domains; a score of 0 indicates optimal sleep quality and a score of 3 indicates subpar sleep quality. The calculation was made using the global PSQI score, which goes from 0 (the highest sleep quality) to 21 (the poorest sleep quality). Over a month, the PSQI evaluates typical sleep patterns, including sleep quality and disruptions. Instead of assessing sporadic episodes of prolonged sleep latency, the PSQI survey assesses regular protracted sleep latency. The questionnaire gives a score between 0 and 3 depending on how long it takes to fall asleep each night (0: falls asleep in ≤15 min, 1: falls asleep in 16-30 min, 2: falls asleep in 31-60 min, and 3: falls asleep in >60 min). A single-item question on the PSQI about the usual length of sleep was used to determine sleep length; sleep length of less than seven hours per night was classified as unhealthy.[29] Poor sleep quality was indicated by a global PSQI score of more than 5, which is in line with established guidelines.[28]

Assessment of Probable Sarcopenia

To measure the muscle strength of the patients, Utilizing the Takei grip strength dynamometer, HGS was measured. For males and women, respectively, poor muscular strength (probable sarcopenia) was defined as HGS <27 kg and <16 kg.[7]

Statistical Analysis

Version 23 of the SPSS software package was used to perform the statistical analyses. Using both analytical (Kolmogorov-Smirnov test) and visual (histograms, probability charts) methods, the variables were assessed for normal distribution. The use of median (IQR) for non-normally distributed numbers, mean±standard deviations (SD) for regularly distributed variables, and percentages for categorical variables marked the introduction of descriptive studies. The study used the chi-square test to evaluate differences between the two types of data and the Mann-Whitney U test to compare continuous variables. Two-sided testing was used to compare each published p-value to a significance level of 5%. Using logistic regression and multivariable binary analysis, the association between sleep quality and probable sarcopenia was demonstrated.

RESULTS

A total of 74 group 1 patients with a mean age of 73.5±5.1 years and a total of 110 group 2 with a mean age of 71.6±5.2 years were included in the study. A statistically significant difference was found between the groups in terms of mean age

distribution (p=0.03). The mean body-mass index (BMI) value of the patients in sleep was 28.2±6.3, statistically significantly lower than the patients in good sleep 30±5.9 (p=0.038). Other demographic and body measurements did not differ significantly between groups (p>0.05) (Table 1).

Table 1. Baseline characteristics of the research population by group. Two groups were created from the study sample groups who poor sleep quality and groups who good sleep quality

	Group 1 (n=74)	Group 2 (n=110)	p
Age, years, mean±SD	73.5±5.1	71.6±5.2	0.03
Marital status, married, n (%),	44 (59)	67 (61)	0.5
Education level, n (%)			
0	34 (46)	65 (59)	
1	21 (28.5)	28 (25)	0.10
2	19 (25.5)	16 (14)	
Height, cm, IQR	158 (10)	15 (11)	0.78
Sex, female, n (%)	46 (62)	69(62)	0.54
Weight, kg, IQR	71.2 (18)	73.5 (20)	0.33
Waist circumference, cm, IQR	96.7 (12)	99.9 (18)	0.53
Hip circumference, cm, IQR	103 (13)	106.5 (13)	0.30
BMI, kg/m^2, mean±SD	28.2±6.3	30±5.9	0.038

*Variables are presented as n (%), mean±SD or median (IQR), BMI: Body-mass index, cm: Cantimeter, kg: Kilogram; kg/m^2: Kilogram/square meters

The components of the CGA are presented in Table 2. In patients group 1, the median Katz ADL score was recorded as 5.0 (1.0), whereas it was 6.0 (1.0) in those group 2, this difference was statistically significant (p=0.02). The median IADL score was recorded as 6.0 (1.0), whereas it was 8.0 (1.0) in those group 2, this difference was statistically significant (p=0.01). The proportion of patients who are frail according to CFS was 90% in patients with group 2 and 72% in patients with group 1 (p=0.001). Furthermore, the median CFS score was 5.0 (1.0) in patients group 1 and it was 3.0 (1.0) in those group 2 (<0.001).

Table 2. Study participants' geriatric syndromes based on their sleep quality

	Group 1 (n=74)	Group 2 (n=110)	p
Katz ADL, median (IQR)	5 (1.0)	6 (1.0)	0.02
IADL, median (IQR)	6 (1.0)	8 (1.0)	0.01
MNA-SF, median (min-max)	12 (6-13)	14 (10-14)	0.001
MNA-SF, categorized, n (%)	56 (75)	41 (37)	<0.001
Handgrip Strength, kg, median (IQR)	17.0 (3.0)	18.0 (6.0)	0.001
Probable Sarcopenia, n (%)	60 (81)	17 (17)	0.034
CFS, median (IQR)	5 (1.0)	3 (1.0)	<0.001
CfS categorized, n (%)	67 (90)	80 (72)	0.001
Incontinence, n (%)	59 (80)	22 (20)	0.002
Polypharmacy, n (%)	61 (82)	24 (21)	0.001

*Variables are presented as n (%), mean±SD or median (IQR), Cm: Cantimeter, kg: Kilogram, ADL: Activities of daily living, CFS: Clinical Frailty Scale, IADL: Instrumental activities of daily living, MNA-SF: Mini nutritional assessment short form

The median score of low muscle strength differed between the two groups [p=0.001, 17.0 (3.0) vs 18.0 (6.0)] in patients with group 2 and group 1, respectively). The median score of MNA-SF was 12 (1.0) in patients group 1 and 14 (1.0) in patients group 2 (p=0.001).

While the incontinence rate was 80 percent in those with group 1, it was 20 in those group 2(p=0.002). Polypharmacy and GDS were also significantly higher between both groups and were respectively (p=0.001, p=0.001).

The binary logistic regression analysis is displayed in Table 3, possible factors affecting sleep. Since there was no difference in univariate analysis, these factors were determined with known factors. Sleep was associated with changes in age, incontinence, and handgrip.

Table 3. Analysis of the sleep using binary regression

	Odds ratio	95% CI	p
Age, years	0.933	0.875-0.994	0.031
Sex	1.179	0.583-2.385	0.647
Married	0.798	0.397-1.602	0.525
MNA-SF	0.188	0.93-0.378	0.001
CFS	0.010	1.353-9.625	0.10

*OR: Odds ratio, CI: Confidence interval, MNA-SF: Mini nutritional assessment short form, CFS: Clinical Frailty Scale

DISCUSSION

This study aimed to look at the connection between sleep quality and probable sarcopenia in older adults. Our findings suggest a strong correlation between inadequate sleep and the higher prevalence of probable sarcopenia in geriatric patients. Specifically, the group with poor sleep quality had a significantly higher percentage of patients diagnosed with probable sarcopenia compared to those with good sleep quality. Moreover, our analysis revealed that sleep quality was associated with other geriatric syndromes, including frailty, functional limitations, and polypharmacy. This may be explained by the high probability of geriatric syndromes in this group, as the most important risk factor for these syndromes is, as expected, advancing age. These results underline the importance of considering sleep quality as a potentially modifiable risk factor for managing and preventing sarcopenia in older adults.

The observed relationship between sleep and sarcopenia in our study aligns with the growing body of evidence suggesting that sleep disturbances may contribute to muscle dysfunction in aging populations.[30,31] Older adults frequently suffer from sleep issues such as insomnia and poor sleep quality and are known to exacerbate various age-related conditions, including sarcopenia.[32,33] The biological mechanisms underlying this connection are multifaceted. Sleep deprivation has been shown to alter the secretion of growth hormone and testosterone, both of which are crucial for maintaining muscle mass and strength. Additionally, disrupted sleep can lead to increased cortisol production, which may promote muscle catabolism and contribute to the loss of muscle mass.[34,35,7]

Our study found that individuals with poor sleep had significantly lower BMI and higher rates of frailty, which is consistent with previous research suggesting that poor sleep may accelerate the decline in physical function and muscle strength.[36,37] The role of frailty, which is often considered a precursor to sarcopenia, is noteworthy in our study. We observed that patients with poor sleep were more likely to be classified as frail, and frailty was strongly associated with the presence of probable sarcopenia. This finding supports the concept that sleep quality may influence both the onset and progression of sarcopenia by contributing to frailty, further emphasizing the importance of addressing sleep in geriatric care.[38,39]

In terms of functional capacity, we found that patients with poor sleep had significantly lower scores on the Katz and Lawton-Brody activities of daily living (ADL and IADL), indicating a greater level of dependency. This finding is in line with research that has shown that poor sleep is associated with decreased physical functioning and an increased risk of disability in older adults.[40,41] Furthermore, our study highlights the impact of poor sleep on handgrip strength, a widely acknowledged indicator of strength of muscles and a key component in diagnosing sarcopenia. The lower handgrip strength observed in patients with poor sleep further reinforces the link between inadequate sleep and muscle dysfunction.

Polypharmacy and incontinence were also significantly more prevalent in the poor sleep group, which may represent an added layer of complexity in managing geriatric patients. The high rate of polypharmacy observed in the poor sleep group may reflect the use of medications, such as sedatives and antidepressants, that can negatively impact sleep quality and potentially worsen sarcopenia. Similarly, incontinence, which is more common in individuals with poor sleep, is another geriatric syndrome that can further impair quality of life and functional independence.[42-44]

Limitations

This study contributes insightful information on the possible processes that connect inadequate sleep to sarcopenia. Perhaps the most important limitation is that we evaluated probable sarcopenia, not sarcopenia. Other methods and physical performance indicators required for a definitive definition of sarcopenia were not evaluated. However, it is important to acknowledge several limitations. First, the study's cross-sectional methodology makes it impossible to establish a causal link between sleep quality and sarcopenia. Longitudinal studies are needed to determine the temporal effects of sleep disturbances on muscle health over time. Additionally, while the Pittsburgh Sleep Quality Index (PSQI) is a widely used tool for assessing sleep quality, it is based on self-reported data, which might be biased. Future studies using objective measures of sleep, such as polysomnography or actigraphy, would provide a more comprehensive understanding of the link between sarcopenia and sleep.

CONCLUSION

In conclusion, our research shows that a higher frequency of likely sarcopenia and other geriatric disorders, including frailty and functional impairments, is linked to poor sleep quality. These findings suggest that improving sleep quality in older adults may be an important strategy for preventing or mitigating the progression of sarcopenia. Future studies ought to investigate the underlying mechanisms of this relationship and investigate whether interventions aimed at improving sleep could help prevent or treat sarcopenia in aging populations. Interventions such as medications, cognitive-behavioral therapy for insomnia (CBT-I), and lifestyle changes that promote better sleep hygiene could hold promise in improving both sleep and muscle health in older adults.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of Ankara Bilkent City Hospital Non-interventional Clinical Researches Ethics Committee (Date: 25.12.2024, Decision No: TABED-2 24-733).

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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A decade of SGLT2 inhibitors in cardiovascular science: a bibliometric review

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ABSTRACT

Aims: Sodium-glucose cotransporter 2 (SGLT2) inhibitors have gained significant attention in cardiovascular science due to their cardioprotective and Reno protective effects beyond glucose control. Over the past decade, research in this field has expanded rapidly. This study aims to conduct a bibliometric analysis of global research trends on SGLT2 inhibitors in cardiovascular diseases from 2014 to 2024, evaluating publication output, citation impact, influential contributors, keyword trends, and international collaboration networks.

Methods: A bibliometric analysis was performed using the Web of Science (WoS) Core Collection database, focusing on articles published between January 1, 2014, and December 31, 2024, within the "cardiac cardiovascular system" category. VOSviewer software was utilized to visualize author collaborations, institutional affiliations, keyword co-occurrence, and citation distributions.

Results: A total of 1,271 articles were analyzed. Research output has increased significantly, particularly after 2020, aligning with key clinical trials on SGLT2 inhibitors. The most prolific journals included Cardiovascular Diabetology, Journal of the American College of Cardiology, and European Journal of Heart Failure. Leading institutions such as Harvard Medical School, University of Toronto, and University of Groningen were identified as major contributors. Citation analysis highlighted high-impact studies on SGLT2 inhibitors' cardiovascular and renal benefits. Keyword co-occurrence analysis showed that heart failure, diabetes mellitus, and renal protection were dominant themes. The United States, Germany, and China emerged as major players in global collaborations, shaping the research landscape.

Conclusion: The bibliometric findings suggest that research on SGLT2 inhibitors in cardiovascular diseases is rapidly evolving, with increasing global contributions and high-impact publications shaping clinical applications. Future studies should focus on long-term cardiovascular and renal outcomes, mechanistic insights, and comparative effectiveness research to further establish SGLT2 inhibitors' role in cardiovascular medicine.

Keywords: SGLT2 inhibitors, cardiovascular diseases, heart failure, bibliometric analysis, citation impact

INTRODUCTION

Cardiovascular diseases (CVDs) continue to be the most common disease today, especially in people with diabetes and chronic kidney disease (CKD).[1] The relationships between these conditions are understood because processes of metabolism and hemodynamics are recognized as risk factors for the development of cardiovascular events.[2]

Sodium-glucose cotransporter 2 (SGLT2) inhibitors represent a new pharmacological class that goes beyond glucose control to include cardiovascular and renal protection.[3] Landmark trials like EMPA-REG OUTCOME study first showed the clear evidence of the cardiovascular protective effect of SGLT2 inhibitors by documenting the reduction of cardiovascular death and hospital admissions for heart failure.[4] These outcomes were confirmed in subsequent meta-analyses and systematic reviews that reported a reduction in major adverse cardiac events (MACE) and the preservation of renal functions in various populations.[5,6]

With the development of new literature, the role of SGLT2 inhibitors in cardiovascular diseases is gaining attention, as a bibliometric analysis already provides an overview of some key contributors and research focus changes in this area.[7] Some studies have defined important and leading publications of interest along with the increase in international attention towards this area of research.[8] There is no existing literature that provides a detailed bibliometric examination concerning the scope of SGLT2 inhibitor research in the field of cardiovascular medicine.

This study will help fill this gap by performing a bibliometric study of all literature published on SGLT2 inhibitors and cardiovascular diseases within the time frame of January 1,

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2014, to December 31, 2024, using WoS. In particular, this analysis intends to:

- Evaluate temporal trends in research output and citation dynamics.
- Identify key contributors, institutions, and influential journals in this field.
- Assess the impact of high-citation studies and emerging research themes.
- Explore keyword co-occurrence networks and research clusters.
- Examine global collaboration networks and institutional affiliations.

By systematically mapping the academic landscape of SGLT2 inhibitors in cardiovascular diseases, this study aims to provide valuable insights for researchers, clinicians, and policymakers interested in the future directions of this evolving therapeutic area.

METHODS

Ethical Considerations

Since this research is a bibliometric study, it did not require ethics committee approval. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Data Collection

Data for this bibliometric analysis were obtained from the Web of Science (WoS) core collection, a widely used database containing high-quality, peer-reviewed scientific publications. The study focused on the topic of "SGLT2 inhibitors" within the field of "cardiac cardiovascular system" and examined studies published between January 1, 2014, and December 31, 2024. The search query applied the keyword "SGLT2 inhibitors" with the "topic" filter and restricted the results to the "cardiac cardiovascular system" category in WoS categories.

As a result of the initial search, 1271 articles were identified. The titles, abstracts, and keywords of the articles were carefully reviewed, 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 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 Temporal Distribution of Scientific Publications on SGLT2 Inhibitors

Figure 1 presents the annual distribution of studies obtained from the Web of Science dataset.

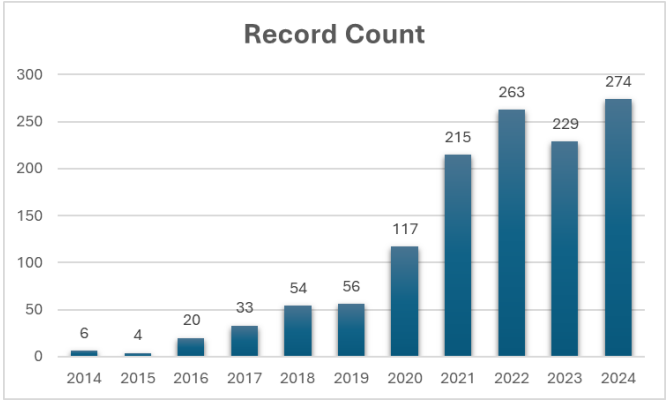

Figure 1. Annual distribution of publications on SGLT2 inhibitors

Based on the analysis conducted using Web of Science data, the distribution of studies on "SGLT2 inhibitors" within the "cardiac cardiovascular system" field from 2014 to 2024 is presented below;

In 2014, only six studies were published, and this number decreased to four in 2015. Starting in 2016, a gradual increase in the number of studies was observed, reaching 54 in 2018 and 56 in 2019. A significant rise occurred in 2020, with 117 studies published, followed by 215 studies in 2021 and 263 in 2022. In 2023, the number of studies reached 229, and in 2024, it peaked at 274 publications, marking the highest number of studies within the analysis period.

Overall, these data indicate a remarkable increase in scientific research on SGLT2 inhibitors in the field of "cardiac cardiovascular system" in recent years. This trend highlights the growing significance of SGLT2 inhibitors in cardiovascular health and the increasing academic interest in this topic.

Journals with the Highest Number of Publications on the Topic

The distribution of journals that have published the most studies on "SGLT2 inhibitors" within the field of "Cardiac Cardiovascular System" in the Web of Science database is presented in Table 1.

Table 1. Distribution of journals by number of publications and percentage

Publication titles	Record count	% of 1271
Cardiovascular Diabetology	135	10.622%
Journal of the American College of Cardiology	82	6.452%
European Journal of Heart Failure	76	5.980%
European Heart Journal	70	5.507%
Circulation	53	4.170%
Frontiers in Cardiovascular Medicine	52	4.091%
Esc Heart Failure	43	3.383%
Heart Failure Reviews	40	3.147%
Cardiovascular Drugs and Therapy	35	2.754%
Jacc Heart Failure	34	2.675%
Others	651	51.219%

According to Table 1, research on SGLT2 inhibitors in the cardiac cardiovascular system field is concentrated in specific journals. Cardiovascular Diabetology leads with 135 publications (10.62%), followed by the Journal of the American College of Cardiology (82, 6.45%), European Journal of Heart Failure (76, 5.98%), and European Heart Journal (70, 5.50%).

Other notable journals include Circulation (53, 4.17%), Frontiers in Cardiovascular Medicine (52, 4.09%), ESC Heart Failure (43, 3.38%), Heart Failure Reviews (40, 3.15%), Cardiovascular Drugs and Therapy (35, 2.75%), and JACC Heart Failure (34, 2.67%).

Additionally, 651 articles (51.22%) appeared in various other journals, reflecting the broad academic scope of this research. However, Cardiovascular Diabetology, Journal of the American College of Cardiology, and European Journal of Heart Failure emerge as key contributors, emphasizing the growing significance of SGLT2 inhibitors in cardiovascular health.

Analysis of Highly Cited Studies; Authors, Article Titles, Journals, Publication Years, and Citation Counts

Table 2 presents detailed information on these influential studies, including authors, article titles, journal names, publication years, and citation counts.

The most cited study, Heidenreich et al.,[9] published in the Journal of the American College of Cardiology, received 1261 citations. This study is a clinical practice guideline issued by the American College of Cardiology (ACC) and American Heart Association (AHA) for managing heart failure, making it a key reference in the field.

Cherney et al.[10] scrutinized the renal hemodynamic impacts of SGLT2 inhibitors on patients with type 1 diabetes and published their findings in the Circulation journal which has been cited 984 times.

Heerspink et al.[11] concentrated on the cardiovascular and renal effects of SGLT2 inhibitors, their mechanisms, and clinical usage for which they received 927 citations in Circulation.

Mcguire et al.[12] conducted an SGLT2 inhibitors meta-analysis regarding the cardiovascular and renal impacts on type 2 diabetes patients and published their findings in JAMA Cardiology, which has 732 citations.

Lopaschuk & Verma[13] shed light on the mechanistic insights of SGLT2 inhibitors on the cardiovascular system and received 533 citations in JACC; Basic to Translational Science.

Table 2. Highly cited articles on "SGLT2 inhibitors" in the "cardiac cardiovascular system" field

No	Author(s)	Article title	Journal name	Publication year	Citation count
1	Heidenreich et al.[9]	2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines	Journal of the American College of Cardiology	2022	1261
2	Cherney et al.[10]	Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus	Circulation	2014	984
3	Heerspink et al.[11]	Sodium glucose cotransporter 2 inhibitors in the treatment of diabetes mellitus: cardiovascular and kidney effects, potential mechanisms, and clinical applications	Circulation	2016	927
4	McGuire et al.[12]	Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes a meta-analysis	Jama Cardiology	2021	732
5	Lopaschuk GD, Verma S.[13]	Mechanisms of cardiovascular benefits of sodium glucose co-transporter 2 (SGLT2) inhibitors A state-of-the-art review	JACC-Basic to Translational Science	2020	533

These studies relate to SGLT2 inhibitors since they were the most cited ones that pertain to its focus on cardiovascular and renal mechanisms, outcomes, and even treatment guidelines. This suggests that SGLT2 inhibitors have functions apart from diabetes management such as in the prevention and treatment of cardiovascular disease. The phenomenon of increasing citation rates denotes the increasing concern and interest in the role of SGLT2 inhibitors in cardiovascular medicine.

Statistical Evaluation of Publications from the Most Cited Institutions

The institutions contributing towards research with "SGLT2 Inhibitors" within the "cardiac cardiovascular system" subfield structure of the WoS database are provided along with their corresponding publication and citation counts in the Table 3.

Table 3. Most cited institutions and number of publications according to Web of Science data

Organization	Documents	Citations
University of Toronto	57	6348
Harvard Medical School	68	4267
University of Groningen	39	2845
University of Glasgow	45	2517
Brigham and Women's Hospital	37	2292

The presentation of the data in Table 3 is the justification of the most productive institutions with regard to the "SGLT2 inhibitors" in the "cardiac cardiovascular system" field and most importantly, their publication activity "output."

As previously considered, the academic impact of the University of Toronto is unparalleled, where the 57 articles published from the university have received 6,348 citations. Following in 2nd place is Harvard Medical School with 68 publications and 4,267 citations. The University of Groningen comes in 3rd with 39 articles and 2,845 citations, signifying the importance of SGLT2 inhibitor's politics on cardiovascular science productivity.

In addition to that, the University of Glasgow has published 45 studies capturing 2,517 citations which demonstrates their impact in the field. Brigham and Women's Hospital also stands out as one of the leading institutions in this field are with 37 publications and 2,292 citations.

The latter two institutions with the highest impact are mainly medical schools and cardiovascular research centers. This suggests that SGLT2 inhibitors are gaining clinical and academic interest, and that leading research institutions are undertaking studies in this area.

Trends in the Use of Keywords in Scientific Publications

The most frequently used keywords related to "SGLT2 inhibitors" in the Web of Science database and the connections between these keywords are visualized in Figure 2.

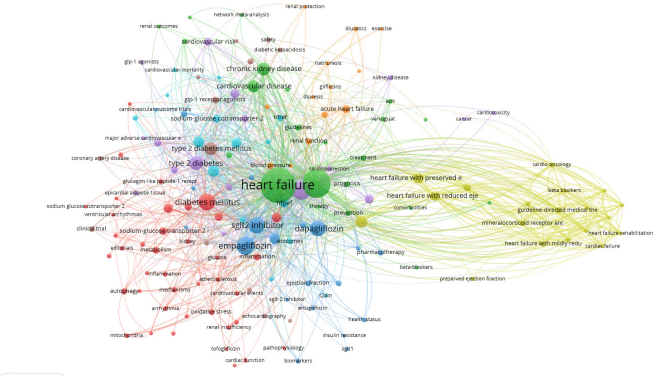

Figure 2. Co-occurring keywords and their frequency of use

The bibliometric analysis was conducted using VOSviewer software, with a minimum threshold value of 5. This threshold ensured that only keywords appearing five times or more were included in the analysis, allowing the study to focus on the most commonly used terms.

Although a total of 1,629 different keywords were identified in the analysis, only 159 keywords met the specified criteria and were included. This method aims to highlight the most prominent keywords in research on SGLT2 inhibitors and the relationships between them.

The analysis results identified the most frequently used keywords with the strongest interconnections, categorizing them into eight distinct clusters. A total of 2,021 connections were mapped, providing valuable insights into the terminology within this research field. Figure 2 visually represents the academic publications on "SGLT2 inhibitors" in the "cardiac cardiovascular system" field and highlights the most frequently used keywords, showcasing the key concepts in this area of research.

According to the documents provided, the most frequently used term is "heart failure", which is reported to have occurred 153 times. This suggests that heart failure occupies a significant portion in the literature pertaining to SGLT2 inhibitors.

The second most frequently used keyword "SGLT2 inhibitors" with 130 occurrences suggests this class of drugs is widely researched in terms of its cardiovascular impact. The words "diabetes" (105 times) and "diabetes mellitus" (80 times) indicate that SGLT2 inhibitors are mostly regarded in the context of diabetes, which is the primary focus of these studies.

Specific names of the drugs like "empagliflozin" (94 times) and "dapagliflozin" (79 times) suggest a greater interest in some SGLT2 inhibitors particular research areas, which tends to focus on the clinical effects of these drugs.

These results clearly show the overlap relevance of SGLT2 inhibitors to cardiovascular disease and diabetes. Keyword frequency is an important metric of literature research and understanding these fields. Besides, many times the same term is mentioned to help scientists comprehend the role SGLT2 inhibitors diabetes clinical and covered pharmaceutical issues.

Ultimately, his explain the relationships between SGLT2 inhibitors, cardiovasculars diseases and diabetes. Most of all, the word usage frequency tells us what issues need to be focused on when doing research.

Analysis of Institutional Collaboration Networks

SGLT2 inhibitors in the field of cardiac cardiovascular system: the network of collaborations and affiliations was explored in detail. Such exploration reveals the collaborations patterns and relationships, where the findings of the analysis are presented visually in Figure 3.

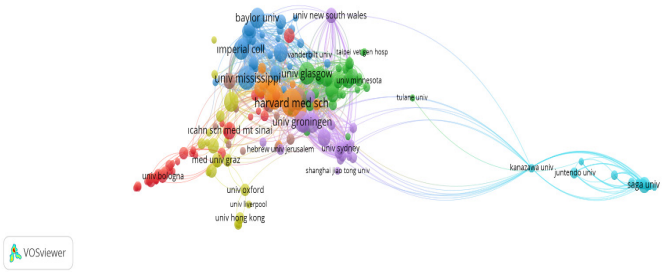

Figure 3. Bibliometric visualization of institutional scientific collaboration networks

SGLT2 inhibitors research within cardiac systems is only 1 part of the research: This work utilizes VOSviewer software. In the collaboration network analysis, colors denote thematic or regional groups, while connections are a reflection of academic partnerships. The thicker the connections, the more intense the collaborations are, and the higher the level of research activity. This visualization reveals the institutional balance of SGLT2 inhibitors research focused on the cardiac cardiovascular system, revealing existing partnerships and possibilities for future research collaborations.

The results from this analysis indicate that SGLT2 inhibitors research in the cardiac cardiovascular system is done by a few institutions. One of the most central institutions, Harvard Medical School, with 104 connections makes central institution of academic collaboration networks and is a leader in SGLT2 inhibitors research with multiple other institutions.

Likewise, University of Toronto (89 connections) and University of Groningen (86 connections) have numerous collaboration relations which are proportional to their scientific productivity. Though Brigham and Women's Hospital (82 connections) and University of Mississippi (75 connections) have comparatively lower, these are still significant academic institutions in the area who support research through institutional collaborations. University of Glasgow (73 connections) also deserves note as a highly connected university.

In any case, the analysis results suggest that the work combining SGLT2 inhibitors and the cardiovascular system is done in a particular set of universities and research institutes. These studies not only reveal a certain way in which collaboration is structured, but they also reveal a particular strategical way in which further collaboration may be useful for the achievement of goals.

Analysis of Author Collaboration Networks

The study examined published papers for the term "SGLT2 inhibitors" from Web of Science in cardiac cardiovascular system. The collaboration networks among researchers were analyzed and the participants within such networks were portrayed with results describing the academic interrelation and the growth patterns of scientific cooperation. Figure 4 depicts this Eck data visually, examining the collaboration networks further.

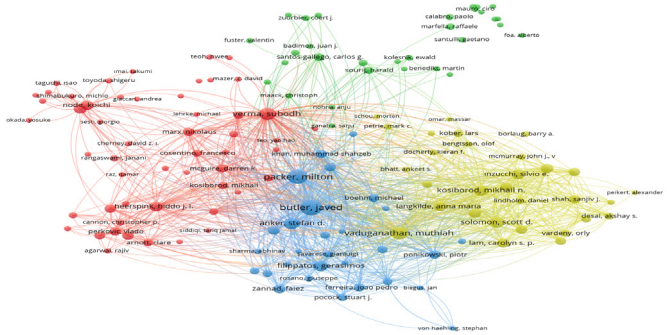

Figure 4. Academic collaboration network analysis
(Large circles represent the most influential researchers, while lines represent scientific collaborations.)

Figure 4 spell out the scores obtained with respect to the academic collaborations and bibliographic connections of those who published at least five articles about SGLT2 inhibitors within the chronicles of the cardiac cardiovascular system region. A total of 6,180 researchers were evaluated, but only 144 authors who met the specified threshold were included in the analysis. With the aim of emphasizing productive researchers, the threshold was defined to increase the value of the results.

The image above shows the collaborative networks and relationships of researchers in the scientific publications of SGLT2 inhibitors. Each author is represented as a node, where the size of the node indicates the impact of the researcher's contribution to the literature. The interconnections between the nodes show the level of interactions and partnerships made within the field; closer the nodes are, the stronger the partnerships are. Different colors indicate clusters of researchers who work on similar topics or methodologies.

The red cluster shows high interconnections with other authors. A web of authors has formed strong connections among themselves. Writers of this cluster include but are not limited to Verma Subodh and Heerspink Hiddo[11] who are emerging leaders in this group, which allows ample subordination.

The green cluster has less degree of interconnections than the other clusters. Santos Gallego and Sourij Harald are central figures in this cluster. Others have observed that there is a lower assortment of scattered connections within these two names making it a more regional or central themed collaboration.

The blue cluster has very high interaction between authors with an extensive collaboration network. The interconnections with other authors are not limited. Therefore, Butler Javed and

Packer Milton have their role in the center of this group. The figures have no restriction to these boundaries and so are free to make connections to the rest of the authors.

The Yellow Cluster is multi-centered as the first few clusters, portraying clear levels between authors. Solomon Scott D and Inzucchi Silvio E are crucial participants that are noticed of power within this cluster which paves way for them to make cross section connections with others.

The scholars in specific interaction fields are represented as a colorized network of authors which depicts their academic relationships. This type of analysis focuses on the individual, collaborative networks as well as the strengths of interconnections.

Analysis of Citation Distribution Among Countries

Citations of publications on "SGLT2 inhibitors" under the specialty "cardiac cardiovascular system" were examined in terms of their coverage by a particular country through Web of Science (WoS). The results of this analysis, which attempts to show on the map the geographical distribution, regional concentrations, and international scientific collaboration of citations, are presented in Figure 5. This research demonstrates how the literature on SGLT2 inhibitors is constructed globally and helps in the analysis of academic contribution flows per country.

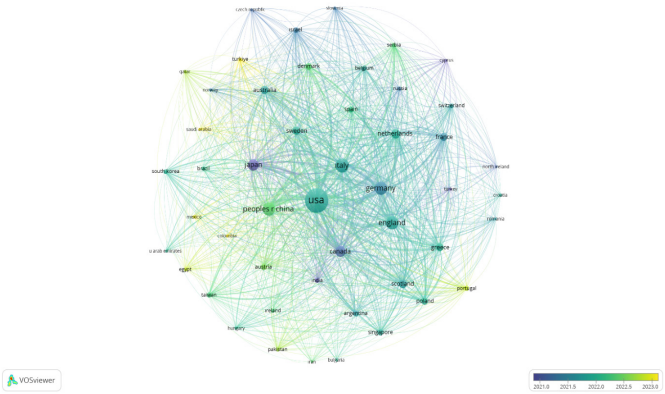

Figure 5. Country-based citation density

This figure determines the collaborations and citation distribution of member countries as regards to the SGLT2 inhibitors guidelined by the scholarly publications databased in WoS. Only countries with at least five published articles were included in the evaluation, which ultimately narrowed the participants for comparison down to 49 out of the total 86. The analysis revealed five major clusters of countries which represent the primary collaboration focus areas for SGLT2 inhibitors research. These results explain the flow of science and innovations between countries and allow for evaluating global SGLT2 inhibitors research activities.

The map shows where the SGLT2 inhibitors have defined the global network of citations, as well as the geographical distributions of collaborations. In the figure, the lines represent collaborative effort intensity between nations, whereas the circles represent literature contribution quantiles per country.

If circles define the nodes in the system of the International Scientific Citations Index, the United States (USA) stands out clearly as the major node. The USA also works closely with China, the United Kingdom, Canada, Germany, Italy, and Japan which shows its persistency in other nations' scientific endeavors as well as in dominating SGLT2 inhibitors research.

Together, European nations have formed an almost complete network, which little extension is needed for Germany, United Kingdom, France, Italy and the Netherlands already have sufficiently high citation rates and strong professional relations.

Japan and China are the clear leaders in Asia. China has a very active collaboration network with the USA, while Japan has solid ties with Europe and the USA. Far behind are India, South Korea, and Taiwan, which are more prominently known for having substantial international and intra-regional associations for research.

It is noted that the USA had primary ties with Canada and Australia, who are regarded as one of the leading research hubs in their respective areas.

Sweden, Switzerland, Spain, Israel, and Portugal have few connections, which allows them to contribute at a local level deepening the diversity of the literature in this particular field.

This figure offers a summary of the spatial distribution of the scientific activity of the "cardiac cardiovascular system" area of study and their international cooperation. The graph epitomizes the leading countries regarding scientific output and the international structure of the academic cooperation system within this field.

DISCUSSION

Justification of findings the latest bibliometric analysis undertakes a comprehensive assessment of the research output on SGLT2 inhibitors in cardiovascular science during the last ten years. Overall, the results suggest that there is an increasing scientific productivity, citation impact, and international collaboration engagement in this area. In juxtaposing our findings with other bibliometric studies, we note at least three prominent clinical markers which define the increased focus on SGLT2 inhibitors and their use for cardiovascular protection medicine–a marked increase in research activity at the global level. The temporal analysis of research activity from 2014 to 2024 indicates a sharp increase in the number of published articles on SGLT2 inhibitors, which is noticeable from the year 2020. This rise is consistent with Pan et al.[7] who noted an increased focus on SGLT2 inhibitors in cardiology. The rise in publications follows the period of key clinical trials, like the EMPA-REG OUTCOME study, demonstrating on the significant cardiovascular related advantages of these drugs, resulting on increased interest and funding.[4]

Our research supports the work of Chen et al.,[3] who noted a rise in citations for studies with major impacts toward SGLT2 inhibitors. The citation distribution indicates that the key cardiovascular and renal studies have the greatest impact on SGLT2 inhibitors thus solidifying their importance in the management of heart failure and chronic kidney disease.[5,6]

On the institutional contributions, this analysis shows that well-known research institutions like Harvard Medical School, the University of Toronto, or the University of Groningen have been primary contributors in developing this field. This is consistent with Wang et al.,[2] who documented similar institutional structures for researchers focusing on the comorbidity of diabetes and cardiovascular disease. The high level inter-institutional cooperation noted in our study suggest that SGLT2 inhibitors are the focus of multi-center and global studies.

The co-occurrence analysis illustrated that alongside "heart failure" and "diabetes mellitus," the terms "empagliflozin" and "dapagliflozin" are also quite popular. This is the same trend as Cardoso et al.,[8] who pointed out the focus heart failure received in conjunction with SGLT2 inhibitors. At the same time, our findings are in-sync with Chen et al.[1] who have noted a developing fusion of chronic kidney disease and heart diseases in focus of research.

The emergence of research clusters related to cardioprotective mechanisms suggests a changing paradigm beyond glucose control. This is also supported by the review of Cardoso et al.[8] who presented the nonglycemic effects of SGLT2 inhibitors such as inhibition of inflammation, oxidative stress, and arterial stiffness.

According to the research contribution map, the foremost countries contributing to SGLT2 inhibitor research are the United States, Europe, and China. The US comes out on top for citations and productivity, just as Chen et al.[1] pointed out for chronic kidney disease and cardiology. European countries, especially Germany, the UK, and the Netherlands, have strong regional cooperation, as noted by Zou et al.[6] On the other hand, there has been a shift in China's position as a major research contributor that highlights the increasing focus on SGLT2 inhibitors in Asia, as discussed by Pan et al.[7] This growth of involvement suggests that these Asian economies are becoming more favorable to the clinical use and even regulatory approval of SGLT2 inhibitors.

Multiple meta-analysis have supported the assertion of the cardiovascular advantages of SGLT2 inhibitors. McGuire et al.[5] and Toyama et al.[9] showed a pronounced decline in major adverse cardiovascular events (MACE) and hospital stays due to heart failures. Our bibliometric analysis confirms them by reporting significant citation impact for those meta-analyses, meaning that they have influenced research that followed these meta-analyses.

The results of this investigation reveal the increasing importance of SGLT2 inhibitors in Cardiology. The growing activity in research and partnerships around the globe indicate that these medications will remain in the forefront of global management of cardiovascular issues, especially in people suffering from diabetes and chronic kidney disease. Further studies need to be directed toward the totality of the cardiovascular and renal implications of these inhibitors as emphasized by Barbarawi et al.[15] Other non-glucose dependent effects like anti-inflammatory and metabolic effects should be studied in greater depth as well.[16] Studies in effectiveness of SGLT2 inhibitors versus other cardioprotective drugs described by Lo et.al.,[17] will add even more clinical knowledge. As discussed, this bibliometric review helps understand the increasing interest in the utilization of SGLT2 inhibitors in cardiovascular medicine and will serve as a basis for further research, policy, and clinical action for physicians and policymakers.

Limitations

This paper sheds light on the scope of scholarly activities regarding SGLT2 inhibitors through a bibliometric lens. However, in doing so, it overlooks some other critical aspects which are as equally valuable to better understand the scholarly activity surrounding SGLT2 inhibitors. The study is primarily focused on PubMed or Scopus due to its publication focus. The analysis is also restricted to the Web of Science database which leave out important studies that exist in other sources. More inclusive work can enhance the understanding of SGLT2 inhibitors in cardiovascular science.

CONCLUSION

The analysis demonstrates that there has been an increasing tendency to publish and cite works related to SGLT2 inhibitors and their impacts in cardiovascular science in the last 10 years,. The interdisciplinary cooperation increases, the number of publications and their citations grows, and suggests a clinical relevance that exceeds glucose metabolism. Major institutions and researchers have altered the development of the field, sited keyword co-occurrence networks, and citation networks, which show focus area in heart failures, diabetes, and renal protection. There is a strong international research network that illustrates the importance of the SGLT2 inhibitors to the international community. Research should also trailer to the long-term impact on renal and cardiovascular, the biology of their cardioprotective actions and comparative effectiveness research with other agents.

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.

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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Determination of obesity prejudice levels of health professionals working in Gaziantep province

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ABSTRACT

Aims: The aim of this study was to measure the obesity prejudice and empathic tendency of health personnel working in public hospitals in Gaziantep.

Methods: 458 healthcare professionals working in Gaziantep province participated in the study. Data were collected using "GAMS-27 Obesity Bias Scale (OBS)" and "Empathic Tendency Scale (ETS)".

Results: It was determined that 17.5% of the healthcare professionals were unprejudiced, 53.9% were prone to prejudice and 28.6% were prejudiced. However, 9.8% of them stated that their attitudes towards obese individuals were prejudiced and 90.2% were not prejudiced. Single people were found to be more prejudiced against obesity than married people. It was found that emergency department were more prejudiced against obese individuals and had lower empathic tendencies compared to other units. Obesity prejudice scores and empathic tendency scores of those who were satisfied with their physical appearance were significantly higher than those who were not satisfied. There was a weak positive relationship between obesity prejudice score and empathic tendency score, and a weak negative relationship between age and number of children. There was a weak positive correlation between empathic tendency score and obesity prejudice score, and a weak positive correlation between age and number of children and empathic tendency score. The mean score of the Empathic Tendency Scale (ETS) of the healthcare professionals was 69.42.

Conclusion: It was determined that healthcare professionals, especially those who considered themselves as thin, young and single, were prejudiced against obesity.

Keywords: Obesity, prejudice, healthcare professionals, hospital

INTRODUCTION

Obesity prejudice is a concept that includes negative attitudes, stereotypes and prejudices towards overweight and obese individuals and is defined as "obesophobia".[1] Research shows that obese individuals often encounter this prejudice in education, business life, health services and even family environment.[2]

Since healthcare professionals are in contact with patients at every stage from their admission to the hospital to their treatment processes, prejudiced attitudes among this group are particularly striking.[3] Prejudices against obese individuals create a worrying situation for various reasons. For example, factors such as the difficulty in caring for obese individuals, high risk of complications, difficulties in positioning and moving them, and inadequate materials to be used in treatment and care can negatively affect the attitudes of health professionals.[4]

This situation can lead to prejudice on the part of health professionals, causing obese people to avoid treatment, to cancel appointments and to delay the use of preventive health services.[5] In healthcare services, the patient-doctor relationship starts with the individual's application to the hospital and continues during treatment planning and follow-up. Therefore, prejudiced attitudes of healthcare professionals can negatively affect not only the health status of individuals but also the effectiveness of healthcare services.[2]

Empathy is defined by Rogers as "the process by which an individual puts himself/herself in the other person's shoes, accurately understands his/her feelings, thoughts, perceptions and emotions and communicates them to him/her".[6] Health professionals' establishing helping (therapeutic) relationships is considered a fundamental part of their profession.[7] The literature emphasizes that there is a strong positive

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relationship between helping behavior and empathy and shows that empathy is one of the most essential measurements of the therapeutic relationship.[8] Moreover, it is stated that effective use of empathy positively affects patient satisfaction and general health status.[9,10] It is stated that individuals who are met with empathy feel that they are understood and cared for, which contributes to their feeling better.[11,12]

Empathy is considered as a two-dimensional concept, namely empathic tendency (ET) and empathic skill (ES). Empathic tendency refers to an individual's potential to empathize and is defined as the willingness to understand the feelings of others, to be affected emotionally and to help.[13] Studies reveal that individuals with high empathic tendency exhibit helping behaviors more.[6,13]

There are various findings in the literature that health professionals may exhibit prejudiced attitudes towards obese individuals. It is thought that there is a relationship between empathic skills and prejudices. Therefore, with this study, it is thought that determining the factors associated with obesity prejudice and empathic skill status in health workers will be guiding in conducting intervention studies to reduce obesity prejudice.

METHODS

Ethics of Research

Ethics committee approval was obtained from Gaziantep University Non-interventional Clinical Researches Ethics Committee (Date: 26.01.2023, Decision No: 182.22.07). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Written permission was obtained from Gaziantep Provincial Directorate of Health to reach the participants. After the permissions were completed, the questionnaire form was sent to the healthcare professionals through the researchers. Voluntary consent was obtained for the participants to participate in the study before the questionnaire. Data was collected via Google form.

Type of Research

The model of this research is a relational screening model that aims to examine whether two or more variables vary together. At the same time, the research is a cross-sectional and quantitative study.

Sample

The population of the study consists of all health professionals and auxiliary staff working in public hospitals in Gaziantep province. The sample size of the study was determined as 319 people with a 95% confidence interval, 5% error margin, medium effect size and 80% power using the G power program version 3.1.9. 458 health workers working in Dr. Ersin Arslan Hospital, Abdulkadir Yüksel State Hospital, Oğuzeli District State Hospital, 25 December State Hospital and Şehitkamil State Hospital located in the central districts of Gaziantep participated in the study. Inclusion criteria were determined as working in the hospital and volunteering to participate in the study, exclusion criteria were determined as not wanting to participate in the study.

Data Collection Tools

Sociodemographic characteristics: In this study, the questionnaire form was developed by the researchers in line with the literature and consisted of 19 questions in total. In the questionnaire form, socio-demographic characteristics of the participants such as age, gender, marital status, and educational status were questioned. In addition, there were questions about the individuals' satisfaction with their physical appearance, whether there were obese individuals in their immediate environment, whether they felt obese in the past, and whether they had dieting experience. BMI <18.5: underweight. BMI 18.5-24.9: normal weight. BMI ≥25.0: overweight. BMI ≥30.0: obesity.

GAMS-27 Obesity Prejudice Scale (OPS): The GAMS-27 Obesity Prejudice Scale (OPS), developed by Ercan et al.[14] in 2015, is a scale consisting of 27 items using a 5-point Likert scale designed to assess obesity prejudice. In the reliability analysis of the scale, Cronbach-alpha reliability coefficient was found to be 0.847. In this study, Cronbach alpha was found to be 0.883. The items are divided into two groups as positive and negative statements and scored differently:

Positive Items (2, 4, 7, 10, 11, 11, 14, 15, 17, 20, 22, 25, 27): Scored from 5 to 1 starting from "Strongly agree". Negative Items (1, 3, 5, 6, 8, 9, 9, 12, 13, 16, 18, 19, 21, 23, 24, 26): Scored from 1 to 5 starting from "strongly agree". The scores that can be obtained from the Obesity Prejudice Scale (OPS) vary between 27 and 135. Scale scores are categorized as 68 points and below without prejudice; 68.01-84.99 points are prone to prejudice and 85 points and above are prejudiced. These categories were determined to increase the discriminative power of the scale and to evaluate prejudice levels more clearly.[14]

Empathic Tendency Scale (ETS): The Empathic Tendency Scale, developed by Üstün Dökmen,[15] is a 20-item scale designed to assess the potential of individuals to empathize in their daily lives. The scale uses a 5-point Likert-type rating. It was stated that approximately half of the items of the scale were written negatively in order to balance the participants' tendency to say "yes". Cronbach alpha coefficient of the scale was found as 0.82.[15] In this study, Cronbach alpha was found to be 0.744.

Statistical Analysis

SPSS 24.0 package program was used for statistical analysis of the research data. Descriptive statistics for continuous variables (mean, standard deviation (SD), minimum, maximum) and frequency distributions for categorical variables were determined. Data were evaluated using chi-square, dependent groups t test and correlation analysis.

RESULTS

A total of 458 health personnel working in Gaziantep province participated in the study. The general characteristics of the participants are shown in **Table 1**. The ages of the participants were 30.75±7.74 (18-59); 57% were female and 43% were male. 53.5% were married and 46.5% were single. 54.1% of the participants had no children. The proportion of participants with one, two, three and more children is 14.2%, 17.5% and

14.2%, respectively. The average working year of the healthcare professionals was 6.49±7.52 years. Of the participants, 3.9% were primary and secondary school graduates, 16.6% were high school graduates, 67.2% were university graduates, and 12.2% were postgraduate/doctoral graduates. 10.9% of the participants were doctors, 52.4% were nurses-midwives, 13.3% were health technicians, 2.4% were technical services, 2.2% were security-cleaning personnel, 2.4% were medical secretaries, and 1.7% were in other jobs. 20.7% worked in emergency rooms; 79.3% worked in other units. 37.8% worked 40 hours or less; 56.8% worked 41-60 hours; 5.5% worked 61 hours or more.

Table 1. General characteristics of healthcare professionals

	n	%	Obesity prejudice scores X±SD	p	Empathic tendency total score X±SD	p
Gender*						
Female	261	57.0	78.19±10.80	0.197	69.18±7.37	0.528
Male	197	43.0	79.84±12.26		69.74±.8.11	
Marital status*						
Married	245	53.5	77.61±11.37	0.003	70.37±7.48	0.003
Single	213	46.5	80.38±11.41		68.33±7.80	
Number of children						
No	248	54.1	79.92±11.39	0.825	68.38±7.74	0.125
One	65	14.2	78.20±13.38		67.35±7.42	
Two	80	17.5	76.18±10.54		72.21±6.64	
Three and above	65	14.2	79.09±10.38		72.05±7.49	
Education status						
Primary school-secondary school graduate	18	3.9	81.33±11.51	0.004	71.67±8.51	0.175
High school	76	16.6	82.34±12.11		70.61±8.58	
University	308	67.2	78.55±11.39		69.22±7.41	
Graduate/PhD	56	12.2	75.38±9.75		68.20±7.57	
Profession						
Doctor	46	10.9	75.17±10.25	0.004	68.48±1.22	0.228
Nurse-midwife	240	52.4	78.48±.71		69.15±.46	
Health technician	60	13.3	79.52±1.40		68.17±.97	
Patient services	11	2.4	81.73±4.49		70.73±2.68	
Technical services	10	2.2	78.90±2.76		69.80±2.43	
Security cleaning	72	15.7	82.92±1.41		71.38±.98	
Medical secretary	11	2.4	73.09±2.76		69.27±2.26	
Other	8	1.7	76.25±6.69		72.75±3.35	
Unit of assignment						
Emergency	95	20.7	80.89±9.71	0.018	68.01±7.43	0.050
Other	363	79.3	78.38±11.84		69.79±7.73	
Working hours per week						
<40	173	37.8	79.67±12.12	0.632	69.39±8.14	0.013
41-60	260	56.8	78.39±10.99		69.85±7.33	
>61	25	5.5	78.88±11.85		65.20±7.2	
Satisfaction with the working environment						
Yes	253	55.2	80.58±11.83	0.000	70.40±7.79	0.001
Partially	172	37.6	76.09±10.47		68.59±7.37	
No	33	7.2	80.73±11.0		66.24±8.00	
BMI						
Underweight	16	3.5	84.00±11.04	0.005	68.56±8.95	0.330
Normal	246	53.7	70.08±10.76		68.90±7.58	
Overweight	149	32.5	76.96±11.91		70.04±8.16	
Obese	47	10.3	82.38±12.62		70.49±6.10	
Tenure as health personnel			6.49±7.52			
BMI			24.80±4.16			

*Mann-Whitney U test, SD: Standard deviation, BMI: Body-mass index

According to body-mass index (BMI) classification, 3.5% were underweight, 53.7% were normal, 32.5% were overweight, and 10.3% were obese.

Gender and weekly working hours did not change obesity prejudice scores. Those who were single had higher obesity prejudice scores than those who were married.

The obesity prejudice scores of those working in the emergency department were found to be high and the total scores of empathic tendency were found to be significantly lower than those working in other units ($p<0.05$).

Individuals' perceptions and experiences regarding obesity and physical appearance according to their obesity prejudice scores and empathic tendencies are presented in Table 2. 90.2% of the healthcare professionals state that they are not prejudiced against obese individuals. The obesity prejudice score of those who stated that they were not prejudiced was higher than those who stated that they were prejudiced. The total score of empathic tendency of those who stated that they were not prejudiced was higher than those who stated that they were prejudiced ($p<0.05$). 10.9% defined themselves as underweight, 74.2% as normal weight, 14.8% as obese. 50.9% did not have a period in their lives when they found themselves as obese. Obesity prejudice scores and empathic tendency scores were not found to be different in the case of finding oneself overweight in a period of life ($p>0.05$).

76.6% of the healthcare professionals were satisfied with their physical appearance. Obesity prejudice scores and empathic tendency scores of those who were satisfied with their physical appearance were significantly higher than those who were not satisfied ($p<0.05$).

Table 3 shows the presence of obese individuals around the participants. 95.5% of the participants had obese individuals in their environment. Of those who had obese people around them, 23.3% had obesity in their friends, 15.4% had obesity in their neighbors, 15.0% had obesity in their aunts/aunties, and 12.2% had obesity in their mothers.

The mean score of obesity prejudice scale was 78.90±11.46 and the mean score of empathic tendency was 69.42±7.69.

According to the obesity prejudice scale, 17.5% were found to be unprejudiced, 52.9% were found to be prejudiced, and 28.6% were found to be prejudiced (Table 4).

Table 3. The participants' percentage of overweight individuals in their surroundings

Having an obese person close to them*	n	%
No	49	5.0
Yes	409	95.5
Obese individual in their surrounding		
Mother	121	12.2
Father	55	5.6
Brother/sister	76	7.7
Grandmother/grandfather	53	5.4
Auntie	148	15.0
Uncle	81	8.2
Friend	230	23.3
Neighbor	152	15.4
Other relatives	23	2.3

*Multiple response analysis was applied to questions permitting multiple selections. The table presents the frequency and percentage of each selected response

Table 4. Obesity prejudice status and empathic tendency scores of healthcare professionals

Obesity prejudice scale classification	n	%
Without prejudice	80	17.5
Prone to prejudice	247	53.9
Biased	131	28.6
	Scale score (mean±SD)	
Obesity prejudice scale score	78.90±11.46	
Empathic tendency total score	69.42±7.69	

The factors associated with obesity prejudice and empathic tendency scores are presented in Table 5. There is a weak positive correlation between obesity prejudice score and empathic tendency score and a weak negative correlation

Table 2. Perceptions and experiences of individuals regarding obesity and physical appearance

	n	%	Obesity prejudice scores X±SD	p	Empathic tendency total score X±SD	p
How would you describe your attitude towards obese people						
I am biased	45	9.8	71.87±9.848	0.000	66.58±7.127	0.008
I am unprejudiced	413	90.2	79.67±11.381		69.73±7.700	
Satisfaction with physical appearance						
I am satisfied	351	76.6	79.61±11.833	0.013	70.09±7.780	0.001
Not satisfied	107	23.4	76.57±9.874		67.21±7.005	
How to define yourself						
Weak	50	10.9	80.08±11.462	0.840	68.16±7.713	0.329
Normal/average weight	340	74.2	78.74±11.227		69.76±7.822	
Fat	68	14.8	78.82±12.727		68.68±6.974	
Was there a time in your life when you found yourself fat?						
Yes	233	50.9	78.11±12.142	0.064	68.91±7.384	0.268
No	225	49.1	79.72±10.691		69.95±7.989	

SD: Standard deviation

between age and number of children (p<0.05). There is a weak positive correlation between empathic tendency score and obesity prejudice score, and a weak positive correlation between age and number of children and empathic tendency score (p<0.05).

Table 5. Pearson correlation coefficients between scale scores and demographic variables

		Obesity prejudice score	Empathic tendency score
Age	r	-.122	.165
	p	.009	.000
Number of children	r	-.097	.207
	p	.038	.000
Years of employment	r	-.079	.088
	p	.090	.061
BMI	r	.	.085
	p	.904	.071
Obesity prejudice score	r	1.000	.141
	p	.006	.002
Empathic tendency score	r	.141**	1.000
	p	.002	

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

DISCUSSION

In studies conducted with healthcare professionals, it is revealed that the majority of healthcare professionals have prejudice attitudes towards obese individuals. When obese patients want to receive services from healthcare professionals in this field, it causes delays in the correct, effective and timely treatment of their existing diseases due to their reluctance to receive healthcare services due to prejudiced approach. This leads to the progression of the diseases of the obese patient group and the increase in health expenses spent on this group.[16-19] The limited research on prejudice against obesity in many professions, including health care, has shown that this prejudice exists to a significant extent. Among healthcare professionals, the idea that patients with obesity are non-compliant with treatment, weak-willed, unsuccessful, lazy, unintelligent and dishonest is quite high.[20-22]

In the studies examined using the Obesity Prejudice Scale (OPS); Sert et al.[23] found the total OPS score average of 78.55 in health college students, Öztürk Altınkaynak and his team[24] found the total OPS scale score average of 74.51 in their study on midwifery students, Okumuşoğlu's[25] OPS score average was 82.42 in the study conducted with 4th year students studying in different departments of the university, and Ünal's[26] OPS average was 80.61 in the study. In our study, the OPS score was determined as 78.90. In all these studies, it was determined that there was a tendency to prejudice according to the OPS score; the reason for these similarities is thought to be because the participants were students or health professionals related to health. In the study conducted by Ünal,[26] 29 (11.7%) were found to be unprejudiced, 138 (55.6%) were prone to prejudice, and 81 (32.7%) were found to be prejudiced when classifying the OPS score among healthcare professionals. In this study, similarly, 80 (17.5%) were found to be unprejudiced, 247 (53.9%) were prone to prejudice, and 131 (28.6%) were found to be prejudiced. The reason for the similar results in both studies may be due to the fact that they included all healthcare professionals. In the study conducted by Ünal,[26] it was determined that the average OPS score of healthcare professionals was 80.61, but the numerical difference between healthcare professionals was not statistically significant. In our study, it was observed that the OPS scores among healthcare professionals were 78.90; however, when grouping was made, the OPS scores of physicians were found to be lower, and this difference was statistically significant. The reason for the low OPS score average of physicians is thought to be that they have more face-to-face contact with obese individuals compared to other professional groups, starting from their internship experiences throughout their education process and in their work lives, and physicians are the first to deal with the problems they experience.

In the study conducted by Koyu et al.[27] at the faculty of health sciences, the OPS average score was determined as 85.28 and the average age as 20.07, and the OPS score was evaluated as biased according to the categorization, while in our study, the OPS score was determined as 78.90 and the average age as 30.75 (18-59), and it was determined as prone to bias in its evaluation. In our study, a statistically significant and weak negative relationship was found between the obesity prejudice scale and age (p: 0.009, r: 0.122). It was observed that the obesity prejudice scale scores decreased as age progressed. This situation reveals results consistent with other studies. Therefore, it is thought that the prejudice scale scores may have been found lower compared to other studies. In our study, it can be suggested that the similar results to the OPS average scores obtained especially in studies conducted with students may be due to the fact that the average age of our participants (30.75) was not very high.

In the study conducted by Okumuşoğlu,[25] it was determined that there was no difference in terms of prejudice between genders. In Ünal's study[26] the OPS scores were similar according to genders and the difference was not found to be statistically significant. In our study, similar to these, the OPS scores were similar according to genders and no statistically significant difference was found (p>0.05). In the study of Yavuz et al.,[28] when marital status was examined, it was found that the OPS scores were higher in married individuals, but this difference was not found to be statistically significant. In contrast, in our study, the OPS scores were found to be higher in singles and this difference was found to be statistically significant. It is thought that the observation of higher prejudice scores in single healthcare professionals is related to the fact that single individuals are generally thinner and that prejudice rates are higher in young people. In general, it can be concluded that obesity prejudice is higher in young and single individuals.

In a multinational study conducted by Puhl and King[20] examining weight prejudice, those with lower BMI were found to have higher prejudices towards obesity. In a study conducted by Welborn[2] with a similar group, examining obesity phobia and anti-fat attitude, it was similarly observed

that obesity prejudice decreased as BMI increased. In our study, those with the highest OPS scores were found in the underweight group according to BMI, similar to other studies, and were found to be statistically significant. However, in our study, as BMI increased, the ETS score increased, but it was not found to be statistically significant. The reason why obesity prejudice is high among healthcare professionals with low BMI, both in our study and in other studies, may be due to insufficient empathy.[16,22]

In the study conducted by Koç[29] in which he examined the empathic tendency level according to demographic data, he examined the empathic tendency level according to different professional groups, and no statistically significant difference was found between age and empathic tendency level. On the contrary, in our study, a statistically significant difference was found between empathic tendency level and age. Here, in the study conducted by Koç, the participants were taken from 5 types of professional groups, namely teacher, doctor, lawyer, religious official and freelance, so it can be thought that all of them could be health professions. Even though there are different professional groups in our study, they are all health-related branches.

In the study conducted by Özcan[30] with nurses working in a state hospital, ETS mean score was determined as 65.95. In the study conducted by Akgöz et al.[31] with physicians, this mean was determined as 69.26, and in the study conducted by Ünal,[26] it was determined as 72.44. In the study conducted by Dizer and İyigün[32] with intensive care nurses, the ETS mean score was found as 70.50, in the study conducted by Yiğitbaş et al.[33] with a group of students receiving health education, it was found as 66.07, and in the study conducted by Tutuk et al.[7] with 1st and 4th year students of the nursing department, it was found as 66.55. In our study, the ETS mean score of healthcare professionals was determined as 69.42, and it was seen that this value showed an empathy level close to the average of the studies conducted with other healthcare professionals and students.

In Ünal's study,[26] when the attitudes of healthcare professionals were evaluated according to their own prejudice statements, it was seen that the majority of the groups that stated that they were unprejudiced, prejudiced and had no opinion were prone to prejudice. It was determined that the highest OPS score average was in the group that described themselves as unprejudiced. Similarly, in our study, the OPS scores of those who described themselves as unprejudiced were found to be higher and this difference was found to be statistically significant. Both studies show that although the individual expressed himself without prejudice, the level of prejudice was high in the scale assessment. While there was no significant difference between the ETS scores of individuals according to their own prejudice statements in Ünal's study[26] in our study, it was determined that the ETS scores of those who described themselves as unprejudiced were higher and this difference was found to be statistically significant.

According to the study by Öztürk Altınkaynak et al.[24] the highest OPS score average was found in those who defined themselves as thin in terms of body perception and the lowest in those who defined themselves as fat; in the study conducted by Ünal,[26] the OPS scores were highest in the group that defined themselves as thin according to similar body perception groups, and the difference between the groups was statistically significant. In our study, when individuals evaluated themselves in terms of weight status, the OPS score was found to be the highest in the group that defined themselves as thin, but it was not found to be statistically significant. This is again an expected picture, as a result similar to the objectively evaluated BMI and OPS classification was found. When we look at the relationship between the individual's body perception and ETS; in the study conducted by Ünal, the difference between the ETS scores according to body perception groups was not found to be significant and, in our study, no statistical significance was found in terms of ETS scores.

CONCLUSION

The majority of the participants who participated in the study were found to be prone to prejudice according to the OPS score as in previous studies. The majority of them were young and single participants who saw themselves as weak. Again, it was determined that the majority of the participants had an obese person close to them. The reason for this attitude towards overweight patients is the difficulties experienced in the diagnosis, treatment and follow-up process, and these processes may increase prejudice and decrease the level of empathy in healthcare professionals. In order to reduce prejudice against obese patients and increase empathy levels, the curriculum content can be enriched in this respect during the training process related to the department of the relevant personnel. Thanks to this, their approaches may be more positive, having received the necessary training before starting the profession.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission the Gaziantep University Non-interventional Clinical Researches Ethics Committee (Date: 26.01.2023, Decision No: 182.22.07).

Informed Consent

Written informed consent forms were obtained from participants in the study.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Declaration

The authors report there are no competing interests 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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Metabolic syndrome as a risk factor in contrast-induced acute kidney injury*

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ABSTRACT

Aims: The expanding use of contrast media has made contrast-induced acute kidney injury (CI-AKI) a cause of acute renal failure. This study investigated the relationship between metabolic syndrome (MS), insulin resistance, and contrast-induced acute kidney injury.

Methods: This study encompassed 94 hospitalized patients (73 male) with creatinine levels of 1.0 and above who underwent contrast-enhanced computed tomography for various reasons in the internal medicine clinics of Dicle University Faculty of Medicine. Patients whose creatinine levels were routinely measured before and 48 hours after tomography and whose anamnesis information was sufficient for the International Diabetes Federation metabolic syndrome criteria were retrospectively included in the study. HOMA-IR values were calculated.

Results: CI-AKI developed in 10 (10.6%) patients out of 94. MS was identified in 60% of the group that developed CI-AKI and 38.1% that did not. Insulin resistance was observed in 30% of the group that developed CI-AKI and 17.9% that did not. Despite the observed difference, it did not achieve statistical significance. Considerable differences were found between the two groups regarding albumin, urea, creatinine, uric acid, C-reactive protein, and hemoglobin levels. CI-AKI was significantly more common in individuals with low creatinine clearance and in those with creatinine ≥1.3 mg/dl.

Conclusion: Our study showed that a higher rate of patients with MS was detected in the group with CI-AKI. MS has been accused of being a risk factor for CI-AKI. Therefore, caution should be exercised when administering contrast to patients with MS.

Keywords: Contrast-induced acute kidney injury, insulin resistance, metabolic syndrome

*Our research's data was presented as an Oral Presentation abstract in Clinical Kidney Journal, Oxford Academy, 2009;2(Supp 2):ii178.

INTRODUCTION

Contrast-induced acute kidney injury (CI-AKI) was considered the third most common cause of acute renal failure (ARF), following hypotension and postoperative complications, according to hospital settings.[1] Nonetheless, modern findings suggest that the reported prevalence rates were biased and inflated.[2]

In 2020, the American College of Radiology and the National Kidney Foundation Consensus revealed that the prevalence of CI-AKI is significantly lower than previously reported. The guideline concluded that most cases of CI-AKI following intravenous contrast administration are not directly caused by the contrast medium itself, but rather by coincident nephrotoxic exposures.[2,3] In light of this, the term CA-AKI was recommended over CI-AKI to describe instances of AKI occurring after contrast exposure when the exact cause remains uncertain.[3]

Acute kidney injury (AKI) continued to be defined based on the established kidney disease; improving global outcomes (KDIGO) criteria, which include: an increase in serum creatinine by ≥0.3 mg/dl within 48 hours, a ≥50% rise in serum creatinine within 48 hours, a ≥1.5-fold increase within 7 days, or urine output less than 0.5 ml/kg/hour for at least 6 hours.[4]

The 2018 guidelines published by the ESUR Contrast Medium Safety Committee recommended 'post-contrast acute kidney injury' (PC-AKI) as the preferred term for renal function deterioration following contrast medium administration. It was emphasized that CI-AKI can have multiple potential causes. Key patient-related risk factors for PC-AKI include chronic kidney disease (CKD) and dehydration.[5]

Across two meta-analyses of 19,000 patients who received IV contrast medium, the incidence of PC-AKI was reported as

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6.4% (95% CI, 5.0-8.1) and 5.0% (95% CI, 3.8-6.5).[5,6] Although 1% of patients experienced sustained renal dysfunction over two months, the need for renal replacement therapy (RRT) was rare, with a weighted incidence of just 0.06%.[6]

Preexisting renal failure, diabetes mellitus, advanced age, use of nephrotoxic drugs, use of high amounts of contrast media, or use of ionic, hyperosmolar contrast media, congestive heart failure, anemia, and dehydration are the most important risk factors for the development of CI-AKI. Metabolic syndrome (MS) is one of the suggested risk factors for CI-AKI.[7]

Metabolic syndrome is a metabolic disease that is formed by the accumulation of a group of diseases that lead to cardiovascular diseases, the main culprit being insulin resistance.[8] Abdominal obesity, impaired glucose tolerance associated with insulin resistance and hyperinsulinemia, dyslipidemia, and hypertension are the main components of this syndrome.[9]

The exact mechanism of CI-AKI is not known in detail. Many mechanisms have been proposed for etiological factors. Iodine contrast can induce cytotoxicity in nephrons, tubular epithelial cells, and endothelial cells, leading to mitochondrial dysfunction, apoptosis, pyroptosis, necrosis, and interstitial inflammation. It may also alter renal hemodynamics, resulting in intramedullary ischemia and hypoxia.[10] In addition to renal medullary hypoxia and direct tubular toxicity caused by contrast, reactive oxygen radicals, oxidative stress, renin-angiotensin-aldosterone system activation, and increased endothelin I, which are among the etiological factors of MS, are also among these proposed mechanisms.[11-14] This study aims to examine the relationship between MS, which is considered a possible new risk factor for CI-AKI, and insulin resistance and CI-AKI.

METHODS

Ethics

Since this study was conducted before 2020, there was no ethics committee requirement at that time, and the study was retrospective, so ethics committee approval was not obtained. Prior the study, institutional approval was obtained. All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design and Participants

This is a single-center retrospective study. Patients hospitalized in Internal Medicine Clinics at Dicle University who were going to have contrast tomography for any reason and whose creatinine values were 1.0 mg/dl and above were enrolled in this study.

Patients with serum creatinine values <1.0 mg/dl, diabetic patients receiving insulin treatment, patients undergoing hemodialysis, those unable to calculate fasting insulin, and critically ill patients requiring intensive care were excluded from the study.

Procedure

Before the tomography, serum creatinine, urea, lipid profile (cholesterol, HDL, LDL, triglyceride), albumin, uric acid, CRP, fasting insulin, fasting glucose, and hemoglobin were obtained. Serum creatinine levels were checked 48 hours after tomography. The patients' age, gender, body weight, height, waist circumference, and body-mass index (BMI) were noted.

Risk factors were evaluated by investigation of diabetes, hypertension, coronary artery disease, hyperlipidemia, stroke, heart failure, and smoking history.

The drugs used by the patients, especially in the last 48 hours before tomography [Angiotensin-converting-enzyme inhibitors (ACEI), Angiotensin receptor blockers (ARB's), acetylsalicylic acid (ASA), N-acetylcysteine, statin, diuretic, non-steroidal anti-inflammatory drugs (NSAID)], were recorded from the patient files.

Using the 2005 International Diabetes Federation (IDF) criteria, patients were categorized into those with and without MS. HOMA-IR values were calculated to measure insulin resistance (HOMA-IR=glucose (mg/dl)xinsulin (μU/dl)/405). HOMA-IR values above 2.5 suggest insulin resistance.

The patients' creatinine clearance was determined with the modification of diet in renal disease (MDRD) formula [GFR=186x(Scr) 1.154x(age) 0.203x(0.742 if female)].[7]

CKD is defined as abnormalities in kidney structure or function that persist for at least three months and have implications for health. These abnormalities may include a reduced glomerular filtration rate (eGFR & lt; 60 ml/min/1.73 m^2) or evidence of kidney damage, such as albuminuria, structural changes seen on imaging, or abnormalities in urine or blood tests. To make a diagnosis of CKD, one or more of the following criteria must be present for ≥3 months:[4]

- eGFR less than 60 ml/min/1.73 m^2
- Albumin-to-creatinine ratio (ACR) ≥30 mg/g
- Urinary abnormalities (e.g., hematuria, casts)
- Structural abnormalities of the kidney (e.g., seen on ultrasound)
- History of kidney transplantation

CKD is classified into five stages based on eGFR, as shown below:

- **Stage G1:** eGFR ≥90 ml/min/1.73 m^2 (normal or high kidney function, but with evidence of kidney damage)
- **Stage G2:** eGFR 60-89 ml/min/1.73 m^2 (mild decrease in function, with evidence of kidney damage)
- **Stage G3a:** eGFR 45-59 ml/min/1.73 m^2 (mild to moderate decrease in kidney function)
- **Stage G3b:** eGFR 30-44 ml/min/1.73 m^2 (moderate to severe decrease in kidney function)
- **Stage G4:** eGFR 15-29 ml/min/1.73 m^2 (severe decrease in kidney function)
- **Stage G5:** eGFR & lt;15 ml/min/1.73 m^2 (kidney failure, also known as end-stage renal disease-ESRD)

Echocardiography recorded the left ventricular ejection fraction (EF). The patients' blood pressure values for systole and diastole during the tomography scan were measured and recorded, and their hydration status was determined.

All patients were routinely given 100 ml of low-osmolar nonionic monomer iohexol (Omnipaque vial, 300 mg-100 ml vial, Opakim Medical Products Limited Company, İstanbul) intravenously during the tomography scan.

Acute kidney injury (AKI) is defined based on the established kidney disease; improving global outcomes (KDIGO) criteria.[4]

Statistical Analysis

Data analysis was performed using the SPSS 16.0 software after the study. Continuous variables were presented as mean±standard deviation, while frequencies were reported as percentages (%). The student T test was employed to compare group means, and the Chi-square test was used to assess differences in frequency distributions. For comparing means with non-homogeneous distributions, the Mann-Whitney U test was applied. The analysis of receiver operating characteristic (ROC) curves determined the cut-off value, sensitivity, and specificity. A p-value of <0.05 was considered statistically significant.

RESULTS

73 male (77.7%) and 21 female (22.3%) patients were enrolled in the study. MS was detected in 39 patients (41.4%). 17 of these patients were female (43.6%) and 22 were male (56.4%). CI-AKI developed in 10 patients out of 94 patients. Of the 10 patients who developed nephropathy, 9 were male and 1 was female (M/F 90/10%). This difference observed between genders did not reach the level of statistical significance (p=0.322). Patients were divided into two groups; those who developed CI-AKI and those who did not.

MS was 60% in the group that developed CI-AKI and 38.1% in the group that did not (p=0.182). Insulin resistance was detected in 30% of the group that developed nephropathy and 17.9% in the group that did not (p=0.356). The mean baseline creatinine values of patients with MS were 1.29, and the mean baseline creatinine values of patients without MS were 1.26. No significant difference was found in baseline creatinine levels between those with and without MS.

The mean age was 69.7±8.9 in the CI-AKI (+) group and 60±17.4 in the CI-AKI (-) group (p>0.05). Advanced age is considered a risk factor for CI-AKI, but in our study, no statistically significant difference was found between the groups that developed nephropathy and those that did not.

A significant difference was found between the groups that developed nephropathy and those that did not (p=0.022) in terms of baseline creatinine clearance levels (As shown in **Figure 1**). The creatinine clearances calculated with MDRD were lower in the group that developed nephropathy. Those with creatinine ≥1.3 were 60% in the group that developed nephropathy and 22.6% in the group that did not (p=0.011). The renal dysfunction is related to the nephropathy that develops after contrast application (**Figure 1, 2**).

A considerable difference was found between the two groups in the evaluated albumin, urea, creatinine, uric acid, CRP, and hemoglobin values of the patients (**Table**).

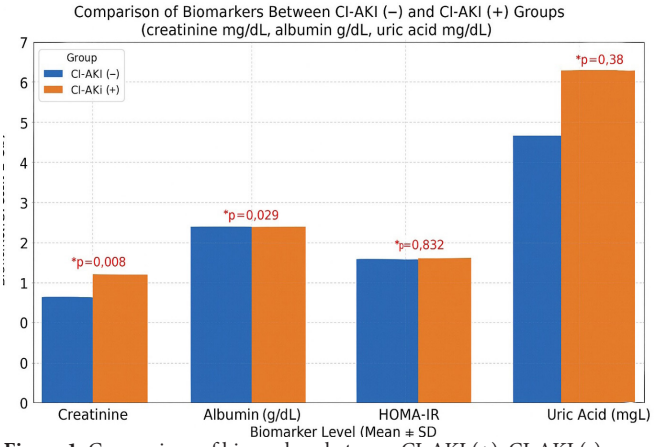

Figure 1. Comparison of biomarkers between CI-AKI (+), CI-AKI (-) groups (creatinine mg/dl, albumin g/dl, uric acid mg/dl)

CI-AKI: Contrast-induced acute kidney injury

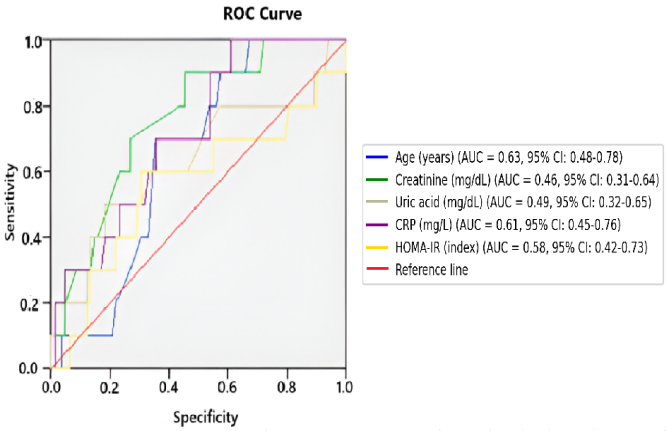

Figure 2. Receiver operating characteristic curves for individual predictors of contrast-induced acute kidney injury, including age (years), creatinine (mg/dl), uric acid (mg/dl), C-reactive protein (mg/L), and HOMA-IR (index)

HOMA-IR: Homeostatic model assessment of insulin resistance

There was no significant difference between the two groups in the evaluated parameters of fasting blood sugar, insulin, cholesterol, triglyceride, LDL, HDL, HOMA-IR, systolic blood pressure, diastolic blood pressure, waist circumference, weight, and BMI.

In our study, the number of diabetic patients was 5 (6%). None of the diabetic patients developed contrast nephropathy.

Congestive heart failure (CHF) is one of the previously determined risk factors for CI-AKI. CHF was detected in 30% of the group that developed CI-AKI and 8.3% of the group that did not. This difference was statistically significant (p=0.036).

No significant difference was observed between the two groups in the evaluation of hypertension, smoking, coronary artery disease, and stroke history of the patients (As shown in **Table**).

Among the evaluated patients, ASA use was 30% in the group that developed nephropathy and 13.1% in the group that did not develop nephropathy; Statin use was 10%, 6%, ACEI use was 40%, 25%, and Diuretic use was 40%, 21%, correspondingly. No significant difference was detected between all these groups.

Table. Demographic and laboratory characteristics of patients with and without contrast-induced acute kidney injury

Parameter	CI-AKI (+) (n=10)	CI-AKI (–) (n=84)	p-value
Age (years)	69.7±8.9	60.0±17.4	0.116
Systolic blood pressure (mmHg)	119±18.5	118±15.0	0.935
Diastolic blood pressure (mmHg)	76±12.6	75±12.0	0.839
Waist circumference (cm)	96±13	94±13	0.634
Weight (kg)	62±11.7	71±15.0	0.063
Body-mass index (kg/m^2)	22.4±3.4	25.0±5.5	0.064
Urea (mg/dl)	84±34	49±25	<0.001*
Creatinine (mg/dl)	1.66±1.08	1.20±0.30	0.008*
Albumin (g/dl)	2.4±0.6	3.0±0.7	0.029*
Fasting blood glucose (mg/dl)	88.6±22.0	89.0±23.0	0.921
Insulin (µIU/ml)	10.3±11.9	7.16±8.6	0.291
Hemoglobin (g/dl)	10.4±1.7	12.1±2.3	0.021*
Total cholesterol (mg/dl)	139±37	156±40	0.230
Triglyceride (mg/dl)	138±48	137±75	0.994
HDL-C (mg/dl)	31±15	32±13	0.788
LDL-C (mg/dl)	95±55	95±31	0.991
Uric acid (mg/dl)	7.13±3.3	5.58±2.0	0.038*
CRP (mg/L)	102±96	49±65	0.025*
eGFR (MDRD, ml/min/1.73 m^2)	52±16.8	65±17.2	0.022*
HOMA-IR (index)	1.8±1.5	1.6±2.2	0.832
Congestive heart failure (%)	30%	8.3%	0.036*
Metabolic syndrome (%)	60%	38.1%	0.182
Sex (male/female, %)	90%/10%	76%/23%	0.322
Diabetes mellitus (%)	0%	6%	0.428
Stroke (%)	0%	1.2%	0.729
Hypertension (%)	40%	28.6%	0.455
Smoking (%)	60%	47%	0.437
Coronary artery disease (%)	30%	11.9%	0.117
Aspirin use (%)	30%	13.1%	0.156
Statin use (%)	10%	6%	0.621
ACEI use (%)	40%	25%	0.310
Diuretic use (%)	40%	21%	0.190
Hydration status (%)	40%	66.7%	0.097
Insulin resistance (%)	30%	17.9%	0.356
Chronic kidney disease (%)	60%	34.5%	0.115
Creatinine ≥1.3 mg/dl (%)	60%	22.6%	0.011
Hypoalbuminemia (%)	90%	66.7%	0.131

CI-AKI: Contrast-induced acute kidney injury, HDL-C: High-density lipoprotein cholesterol, LDL-C: Low-density lipoprotein cholesterol, CRP: C-reactive protein, MDRD: Modification of diet in renal disease formula, HOMA-IR: Homeostatic model assessment of insulin resistance, ACEI: Angiotensin-converting enzyme inhibitor, eGFR: Estimated glomerular filtration rate

DISCUSSION

With the advancement of imaging techniques, CI-AKI has emerged as a prevalent issue in clinical practice in recent years.[1] CI-AKI prolongs hospital stays, contributing to higher morbidity and mortality rates and escalating treatment costs. As a result, it is crucial to identify the risk factors for CI-AKI early and implement the currently recommended preventive measures.

The risk of developing CI-AKI can be predicted by preexisting renal failure, diabetes, hypovolemia, anemia, advanced age, CHF, excessive use of contrast medium, use of non-ionic hyperosmolar contrast medium, and concurrent use of other nephrotoxic agents. MS has been evaluated as a risk factor for the development of CI-AKI. MS is a group of diseases that are based on insulin resistance, abdominal obesity, diabetes or impaired glucose tolerance, hypertension, high triglyceride levels, and decreased HDL, leading to increased cardiovascular risk.[8,9]

In this study, patients with plasma creatinine values >1.0 mg/dl and those who underwent tomography with contrast media for any reason were evaluated. Patients were grouped using IDF criteria in terms of MS, and HOMA-IR was calculated to determine insulin resistance. Patients ' creatinine levels were assessed before contrast administration and 48 hours following imaging, and creatinine clearance was calculated based on the MDRD formula.

Various mechanisms contribute to the pathophysiology of CI-AKI. These are renal medullary hypoxia and direct tubular toxicity. These mechanisms are also further increased by increased RAS activity, reactive oxygen species, oxidative stress, and increased endothelin 1 activity, which are etiological factors of MS.[15]

Renin and angiotensin 2 are potential mediators leading to intrarenal vasoconstriction in experimental CI-AKI studies. Abdominal obesity additionally increases the amount of RAS components.[16] Increased endothelin 1 and decreased nitric oxide (NO) result in vasoconstriction by decreased renal medullary blood flow.[17,18] Decreased NO activity and increased endothelin I are distinct features of MS. However, HT, dyslipidemia, glucose intolerance, and hyperuricemia are components of MS, which increase the risk of developing CI-AKI. Toprak and colleagues identified metabolic syndrome as a risk factor for the development of CI-AKI in their study. In this research, patients who underwent coronary angiography were categorized into two groups; MS and non-MS. It was observed that CI-AKI development significantly differed between the two groups, with a higher incidence in the MS group. MS increased the risk of nephropathy by 4.26, impaired glucose tolerance by 4.72, high triglyceride by 4.06, and multiple vessel involvement by 3.14 times. These were evaluated as predictors of CI-AKI in MS patients.[7]

In our study, the prevalence of MS was 60% in the group that developed CI-AKI and 38.1% in the group that did not develop CI-AKI. Despite the higher MS rate, this difference did not achieve statistical significance (p=0.182). The lack of significance could be attributed to the relatively small sample size. Out of the 10 patients who developed CI-AKI, 6 (60%) had MS.

We calculated HOMA-IR values to evaluate insulin resistance. Insulin resistance was found to be 30% in the group that developed CI-AKI and 17.9% in the group that did not develop CI-AKI (p=0.356). Although a higher rate of insulin resistance was observed in the group that developed CI-AKI, statistical significance was not observed. This may be due to the small number of patients.

Preexisting renal failure is considered one of the most significant risk factors for CI-AKI. A GFR <60 ml/min is a key risk factor for the development of CI-AKI.[19] In a study by Davidson et al.[20] involving 1144 patients who underwent percutaneous coronary angiography (PCAG), preexisting renal failure was identified as the primary risk factor for triggering CI-AKI. Another study found that CI-AKI developed in 2% of 378 patients undergoing PCAG, but in 30% of those with a baseline creatinine level greater than 1.5 mg/dl.[21] Additionally, in a cohort of 2034 patients, a pre-procedure serum creatinine level of 2 mg/dl or higher was found to be the strongest risk factor for CI-AKI.[22] In our study, a significant correlation was found between creatine clearance and CI-AKI. Again, CI-AKI development reached a significant level in the group with a creatinine level of 1.3 and above. In our study, the development of CI-AKI was found to be more frequent in patients with poor hydration status, with a trend toward statistical significance (p: 0.097). If contrast agent use is necessary in patients with impaired renal function, optimal hydration should be provided, and agents with the lowest dose and low osmolarity should be used.

DM plays a role in the development of CI-AKI. In a study conducted by Lautin et al.,[23] the incidence of CI-AKI was determined as 2% in patients without diabetes and azotemia. The incidence was determined as 16% in diabetics with preserved renal function and 38% in diabetics with impaired renal function. Although the risk of CI-AKI is lower in diabetic patients with preserved renal function and without proteinuria or microalbuminuria, those with impaired renal function constitute the highest risk group for CI-AKI due to the synergistic effect. The number of diabetic patients in this study was limited to 5 patients, and CI-AKI was not detected in any of them. This number was limited because most of the diabetic patients admitted to our hospital were on insulin treatment, and we excluded patients taking insulin from the study.

HT is stated as a minor risk factor for the development of CI-AKI in some articles.[17,18,24] In one study, HT was reported as an independent risk factor for CI-AKI in 8628 patients who underwent percutaneous catheterization. HT is also a component of MS Toprak et al.[7] found no correlation between HT and CI-AKI in their study. No significant difference was found in our study either.

The relationship between hypercholesterolemia and CI-AKI has been investigated in the literature.[25,26] According to these studies, hypercholesterolemia causes the development of CI-AKI by reducing NO synthesis. In our study, we could not find a relationship between hypercholesterolemia and CI-AKI. Toprak et al.[7] found a strong relationship between high triglycerides and CI-AKI in their study. In our study, no significance was found between triglyceride, HDL, LDL levels, and CI-AKI.

EF is a measure used to indicate left ventricular function. It is 67±9% in normal individuals. In patients with stage IV heart failure, especially if the EF value is below 50%, the cardiac performance of the patients is impaired as well as their renal perfusion, and when these patients are exposed to contrast media, the development of CI-AKI is higher than in normal individuals.[27-29] In our study, CHF was found to be higher in the group that developed CI-AKI (p=0.036).

Hyperuricemia is among the minor risk factors for the development of CI-AK.[30] It is also a minor component of metabolic syndrome. High uric acid level plays a role in the pathogenesis of CI-AKI by activating RAS, reactive oxygen species, and inhibiting NO production.[31,32] In a cohort study of 1,440 patients, serum uric acid levels of ≥8.0 mg/dl were found to be significantly associated with an elevated risk of contrast-induced acute kidney injury (CI-AKI).[33]

In our study, a statistically significant difference was found between high uric acid and CI-AKI, as shown in Figure 1 (p=0.038).

Although the relationship between age and CI-AKI is still debated, the 2019 ACR guidelines advise renal function assessment in individuals over 60 years prior to ICM administration. By contrast, the 2018 ESUR guidelines[10] did not recognize age itself as a risk factor for CI-AKI. The apparent association may rather reflect the increased prevalence of renal dysfunction and other age-related comorbidities.[34]

In our study, the mean age in the group that developed CI-AKI was 69.7±8.9, and the mean age in the group that did not develop CI-AKI was 60±17.4. There was no significant relationship between age and contrast nephropathy (p=0.116).

Limitations

The study had several limitations. It had all the limitations of a retrospective design and a single-center study. Additionally, a small sample size likely contributes to non-significant results, such as the relation between MS and insulin resistance, which did not reach significance. Moreover, we acknowledge the increased risk of type I errors due to multiple comparisons. Diabetic patients who were hospitalized and receiving insulin therapy were excluded. Therefore, a limited number of diabetic patients treated with oral antidiabetic agents could be included. Additionally, since hemodialysis may alter insulin levels, patients with end-stage CKD undergoing hemodialysis were also excluded from the study. Critical patients who were full and required to follow up in intensive care conditions were excluded from the study. These exclusions might lead to selection bias and impact our results. Despite these limitations, this pilot study provides preliminary evidence of a relationship between CI-AKI, MS, and insulin resistance.

CONCLUSION

Consequently, although CI-AKI is rare in the general population, it can be serious in high-risk patients. Being aware of risk factors helps identify these patients before the procedure. Given the absence of a specific treatment for CI-AKI, prevention through early risk recognition remains essential. Metabolic syndrome has recently been blamed for the development of CI-AKI. Similar pathophysiological events are present in both metabolic syndrome and CI-AKI development, supporting the idea that an interaction between the two events may be involved. In our study, metabolic syndrome was present in 6 out of 10 patients who developed CI-AKI (60%). However, due to the small sample

size, no statistically significant result could be reached. In conclusion, our study showed that a higher rate of patients with MS was detected in the group with CI-AKI. However, the results provide preliminary evidence of a non-significant trend linking MS and insulin resistance to CI-AKI, alongside reaffirming established risk factors, including renal impairment and congestive heart failure. Therefore, caution should be exercised when administering contrast to patients with MS. Our results have to be confirmed by larger-scale, prospective longitudinal studies.

ETHICAL DECLARATIONS

Ethics Committee Approval

Since this study was conducted before 2020, ethics committee approval was not obtained.

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 antibiofilm effect of vancomycin, melatonin, and boric acid combination on caries due to microleakage under prosthetic restoration

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ABSTRACT

Aims: Drug-resistant oral bacteria causing dental caries under prosthetic restorations have become a significant clinical challenge that needs to be addressed. This study aims to demonstrate the antibiofilm effect of vancomycin (VAN) combined with melatonin (MEL) and boric acid (BOR) against biofilm formation caused by *Escherichia coli (E. coli)* and *Lactobacillus acidophilus (L. acidophilus)* on dentin of tooth surfaces under restorations due to microleakage.

Methods: Extracted human teeth, free from caries, resorption, or fractures, were collected by slicing 2 mm dentin discs. A total of 64 dentin discs were inoculated with *E. coli* and *L. acidophilus* and randomly assigned to five experimental groups: MEL, BOR, MEL+VAN, BOR+VAN, and MEL+BOR+VAN, along with a control group. Antibiofilm activity and combination indices were analyzed using the MTT viability test and the Chou-Talalay method, respectively. The biofilm structure was examined using scanning electron microscopy.

Results: MEL and VAN demonstrated antimicrobial effects against *E. coli* and *L. acidophilus* bacteria in unary combinations, while BOR showed ineffectiveness. However, a notable synergistic interaction was observed in the binary combinations of VAN. Interestingly, a significant synergistic effect (CI<1) was noted in the triple combination against both bacterial species ($p<0.05$). Upon examining this effect within the triple combination, it became apparent that VAN exhibited a Favorable Dose Reduction Index (DRI>1) ($p<0.05$). When evaluating these synergistic and dose reduction results alongside scanning electron microscopy image analysis, it can be concluded that the triple combination of MEL+BOR+VAN likely induces the most optimal antibiofilm effect on dental caries bacteria.

Conclusion: The tendency of cements used in the luting of prosthetic restorations to microbial colonization and their tendency to dissolve in oral fluids increases the formation of caries under crowns and bridges due to microleakage, which may lead to tooth loss. Combining melatonin and boric acid with vancomycin may offer a potential treatment option for preventing this problem, as it exhibits strong antimicrobial properties. Thanks to this combination, the microbial load in the areas under prosthetic restorations can be reduced, and both the development of caries and the progression of existing active caries can be stopped. Thus, oral infections resulting from microleakage and their associated systemic complications can be reduced, and the longevity of restorations, as well as patient comfort, can be increased.

Keywords: Melatonin, boric acid, vancomycin, dentin, caries

INTRODUCTION

The oral cavity is a complex ecosystem where a dynamic balance exists between microbial communities and the host's defense mechanisms. Disruption of this balance can lead to various oral diseases, including dental caries and root decay. Among these, biofilm formation on dentin surfaces is a critical factor in the progression of these conditions. *Escherichia coli (E. coli)* and *Lactobacillus acidophilus (L. acidophilus)* are known to play pivotal roles in biofilm development, contributing to microbial colonization and persistence.[1,2] These biofilms pose a significant challenge in prosthetic dental treatments, where microleakage around crowns and bridges can serve as a nidus for bacterial infiltration, leading to secondary caries and root decay.[3,4]

To address this issue, antimicrobial agents such as melatonin (MEL), boric acid (BOR), and vancomycin (VAN) have garnered attention for their potential efficacy in oral healthcare. These compounds have shown promising antibacterial and anti-inflammatory properties in various contexts.[5,6] Melatonin,

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a known antioxidant and antimicrobial hormone, has been shown to inhibit bacterial growth and biofilm formation in the oral cavity.[7] Boric acid, a compound with well-established antibacterial activity, has been reported to disrupt bacterial membranes and biofilm integrity, making it a valuable adjunct in caries prevention.[8] Vancomycin, a glycopeptide antibiotic, remains a gold standard for treating gram-positive bacterial infections, including *E. coli* and *L. acidophilus*, which can contribute to caries and root decay in compromised dental environments.[9] However, the application of these agents in managing biofilms on dentin surfaces, particularly within the scope of prosthetic dentistry, remains underexplored. By targeting bacterial populations responsible for microleakage-related complications, these agents could significantly enhance the longevity and success of prosthetic restorations. When these three agents are combined, the bactericidal effect of vancomycin, the cell permeability-increasing structure of boric acid, and the biofilm-inhibiting property of melatonin may create a synergistic effect. This combination offers a potential strategy to prevent the colonization of microorganisms such as *E. coli* and *L. acidophilus*, which play a role in the development of secondary caries under prosthetic restorations, especially due to microleakage.[10-12]

The current study investigates the antimicrobial effects of MEL, BOR, and VAN on biofilms formed by *E. coli* and *L. acidophilus* on dentin surfaces. Using established methodologies such as the MTT assay and scanning electron microscopy (SEM), we evaluated the viability and structural integrity of biofilms following treatment. This research aims to elucidate the potential of these agents for integration into oral care products, such as mouthwashes, toothpaste, or dissolvable tablets, to prevent biofilm-related complications in prosthetic dentistry. By reducing the bacterial load associated with microleakage, these interventions could mitigate the risk of secondary caries and root decay, thereby improving patient outcomes and prosthesis durability. The null hypothesis of the study was that the combination of vancomycin, melatonin, and boric acid would not have a significantly greater antibiofilm effect compared to single or dual agent applications against caries-associated biofilms caused by *E. coli* and *L. acidophilus* on dentin surfaces affected by microleakage under prosthetic restorations.

METHODS

Ethics

This study received approval from the ethics committee of the Yozgat Bozok University Rectorate Non-interventional Clinical Researches Ethics Committee (Date: 09.04.2025, Decision No: 2025-GOKAEK-257_2025.04.09_443), and all experiments were conducted in accordance with the ethical guidelines of the Helsinki Declaration.

Preparation of Dentin Discs

This study utilized 64 permanent molars extracted for periodontal or orthodontic purposes, all of which maintained intact crowns. To avoid external contamination, the teeth underwent mechanical cleaning using a curette, ensuring no organic or inorganic residues remained on their surfaces. To maintain their biological integrity, the cleaned teeth were stored at room temperature in a 0.01% thymol solution. They were then embedded in 3 cm high and 2 cm wide polyvinyl chloride (PVC) cylinder molds with auto polymerized acrylic resin (Ortho-Jet Resin Acrylic; Lang Dental Manufacturing Co, Illinois, USA). Before completing the polymerization of acrylic resin, the teeth were positioned in molds, set 1 mm above the cementoenamel junction. During sample preparation, a large, water-cooled, low-speed diamond cutting saw (Metkon Microcut 201, HTP High Tech Products, İstanbul, Turkiye) was used to expose the dentin layer. Dentin discs, each 2 mm thick, were created by cutting 3 mm and 5 mm below the occlusal surface. The surfaces of these dentin discs were then polished using a circular medium-grained rotary abrasive tool (Model 902; Brasseler USA). Dentin discs were marked with an acetate pen, utilizing a metal mold that features a 6 mm diameter circular cavity at its center. After marking, a skilled dentist produced standard samples, measuring 6 mm in diameter and 2 mm in thickness, with a water-cooled aerator (Bien-Air Tornado; Bien-Air Dental, Bienne, Switzerland). A digital caliper (Mitutoyo 500-196-30; Mitutoyo Corp., Kawasaki, Japan) was used to verify the accuracy of the measurements. Finally, all prepared samples were rinsed with distilled water and then treated with isopropyl alcohol for 3 minutes to remove any organic and inorganic residues from the surface. To minimize inter-group bias in the study, the samples were randomly assigned to the experimental groups.

Minimum Inhibitor Concentration (MIC) Determination

MIC values of the compounds against bacterial strains were determined using a micro-well dilution method. To determine the MIC values, *E. coli* (ATCC 11229) and *L. acidophilus* (ATCC 11975) in a 12-h Luria-Bertani (LB) broth and DE MAN, ROGOSA and SHARPE (MRS) broth culture, respectively, were adjusted to 0.5 McFarland. Each substance was dissolved in dimethyl sulfoxide (DMSO), and serial twofold dilutions were made in a concentration range of 4 to 512 µg/ml in microplate wells containing nutrient broth. The growth of microorganisms was visually determined after incubation for 24 hours at 35°C. The lowest concentration at which no visible growth (turbidity) was taken as the MIC. Unary, binary, and ternary combinations of MEL, BOR, and VAN were added to the wells in increasing doses and incubated for 24 hours. The well with no turbidity at the end of the period was selected as the MIC value.

Minimal Biofilm Inhibitory Concentration (MBIC)

Firstly, dental discs were transferred into wells to form biofilm on them. Dental discs in a 24-well plate were treated with 500 µl of a 0.5 McFarland bacterial sample and then incubated overnight for 16 hours. At the end of the period, the dental disc samples were incubated for 72 hours to promote biofilm formation, with the medium changed every 24 hours. After the dental disc surface is covered with a bacterial biofilm layer, bacteria that could not adhere were gently washed with DPBS and removed from the medium. Samples were thoroughly vortexed with 500 µl of DPBS and then plated in a new 24-

well plate. Unary, binary, and ternary combinations of MEL, BOR, and VAN were added to the wells in increasing doses and incubated for 24 hours. An MTT assay gives an accurate estimate of the number of viable cells. Thus, we performed an MTT assay according to AFST-EUCAST guidelines. During the experiment, one-part MTT is mixed with nine parts medium (LB Broth for *E. coli* and MRS broth for *L. acidophilus*) and used. The MTT solution, prepared with fresh medium, was added and incubated in the dark for at least 4 hours in the incubator. Then, the MTT solution was withdrawn, and DMSO and 100 µl Sorenson's glycine buffer (glycine 0.1M, NaCl 0.1M, pH 10.5) were added to the medium and left on the mixer in the dark for 15-20 minutes. Samples were loaded onto a 96-well plate without a lid and read at 570-630 nm on a microplate reader. Unary, binary, and triple combinations were evaluated using the obtained absorbance values with the Calcusyn synergy analysis program.

Synergy Model

Synergy measurement by microplate synergy analysis was used to determine the effect of unary, binary, and triple combinations of MEL, BOR, and VAN on potency compared to their activities (Table 2). The antibiofilm effects of MEL, BOR, and VAN were studied for the first time on *E. coli* and *L. acidophilus* dentin biofilm. The MTT cell proliferation assay was used to evaluate the results of the in vitro pharmacodynamic drug interaction analysis of the selected drugs, employing different unary, binary, and ternary drug combinations.[13] Absorbance data (CLARIOstar microplate reader) were loaded for automated calculation of the slope of the median-effect plot (m), the dose that produces 50% effect such as IC50 (Dm), and the linear correlation coefficient of the median-effect plot (r) parameters, as well as the Combination Index (CI) and Dose Reduction Index (DRI) using CalcuSyn software, version 2.11, commonly used to study drug interactions described by Chou[14] and Chou and Talalay.[15]

Scanning Electron Microscopy

Scanning electron microscopy (SEM) was conducted using *E. coli* and *L. acidophilus* biofilms formed on the surface of dentin discs. The samples were washed twice with DPBS and then fixed in 2.5% glutaraldehyde in phosphate buffer for 16 hours. Shortly after, they were refixed in 2% osmium tetroxide for an additional two hours. Then, they were dehydrated through ethanol rinses (30%, 50%, 90%, 95%, and 100%) and mounted and sputter-coated with gold. Sample surfaces were examined using a scanning electron microscope (SEM) (Zeiss LEO 440, Cambridge, UK).

Statistical Analysis

The statistical significance of differences was determined by the one-way analysis of variance (one-way ANOVA) followed by Tukey's test. The SPSS for Windows computer program was used for statistical analyses. The results of test values were reported as mean values ±SD of three independent assays, and differences among groups were considered to be significant at $p<0.05$.

RESULTS

Susceptibility Testing and Synergy Analysis

For the antibacterial activity studies of the test substances, the selected pathogenic gram (-) *E. coli* (ATCC 11229) and *L. acidophilus* (ATCC 11975) bacterial species were used. The plate-well technique was used to calculate the MIC values of single molecules and combinations. Accordingly, the MIC values of the BOR molecule could not be calculated since they were >512 µg/ml ($p<0.05$). MEL MIC values were measured as 16-64 µg/ml ($p<0.05$). VAN MIC value was measured as 16-128 µg/ml ($p<0.05$). When we examined the binary combinations, we found that the concentrations were 16-64 µg/ml for BOR+VAN and 8 µg/ml for MEL+VAN ($p<0.05$). When we examined the triple combinations, the concentration was measured as 4 µg/ml (Table 1).

MTT test was performed to measure the minimal biofilm inhibitory concentration (MBIC) effects of single molecules and combinations. The ratios and effect values used for combinations are explained in Table 2-4. The activity values of the combinations were determined by the Chou-Talalay CI (mass-action law) method. After performing the MTT cell proliferation test for each substance alone against bacteria, CompuSyn software was used to calculate the mass-action law parameters (Dm), (m), and (r). Accordingly, the Dm values (IC50) of the tested substances in *L. acidophilus* were found to be between 78.00, 127.00, and 15.00µg/ml for MEL, BOR, and VAN, respectively. In *E. coli*, the Dm values (IC50) of the tested substances were between 35.00, 172.00, and 112.00µg/ml for MEL, BOR, and VAN, respectively. The % inhibition of the tested substances in *L. acidophilus* ranged from 77.35%, 70.21%, and 6.42% for MEL, BOR, and VAN, respectively. In *E. coli*, the % inhibition of the tested substances ranged from 54.54%, 148.49%, and 13.58% for MEL, BOR, and VAN, respectively (Table 5, 6). The Dose Reduction Index (Fa-DRI) for MEL, BOR, and VAN combinations are presented in Table 7, 8 respectively. The Chou-Talalay method for drug combination is based on the median effect equation, which provides the theoretical basis for the CI, which allows the quantitative determination of drug interactions where CI <1, =1, and >1 indicate synergy, additive effect, and antagonism (Table 4). Accordingly, in *L. acidophilus*, the Dm values (IC50) of the tested binary and triple combinations were between 9.41-13.56 and 6.25 µg/ml, respectively. In *E. coli*, the Dm values (IC50) of the tested binary and triple combinations were between 14.86-59.78 and 5.68 µg/ml, respectively.

Table 1. MIC value of unary, binary, and triple combinations of the agents

							One-way ANOVA	
MIC (µg/ml)	**BOR**	**MEL**	**VAN**	**BOR VAN**	**MEL VAN**	**MEL BOR VAN**	**F**	**Sig.**
E. coli	ND	16^{a*}	128^{c}	64^{b}	8^{a}	4^{a}	344.41	.000
L. acidophilus	ND	64^{c}	16^{b}	16^{b}	8^{a}	4^{a}	339.69	.000

*Values followed by the same letter in the row are not significantly different, MIC: Minimum inhibitor concentration, ANOVA: Analysis of variance, BOR: Boric acid, MEL: Melatonin, VAN: Vancomycin, Sig.: Significance, *E. coli: Escherichia coli, L. acidophilus: Lactobacillus acidophilus,* ND: Not detected

Table 2. Concentrations of substances used (µg/ml)		
MEL	BOR	VAN
25	37.5	12.5
50	75	25
100	150	50
200	300	100
400	600	200

MEL: Melatonin, BOR: Boric acid, VAN: Vancomycin

Table 3. Combination ratios used in the study		
MEL 2	MEL+VAN 2/1	MEL+BOR+VAN 2/3/1
BOR 3	BOR+VAN 3/1	
VAN 1		

MEL: Melatonin, BOR: Boric acid, VAN: Vancomycin

This study evaluated the synergistic-antagonistic effects of MEL, BOR, and VAN combinations with CI values for fa=0.5. Accordingly, when the binary and triple combinations tested in *L. acidophilus* were examined at fa=0.5, MEL+VAN (0.83) and MEL+BOR+VAN (0.77) showed a moderate synergistic effect, and BOR+VAN (0.94) displayed an additive impact (Table 5). When the binary and triple combinations tested in *E. coli* were examined at fa=0.5, MEL+VAN (0.78) and MEL+BOR+VAN (0.56) showed synergistic effects, and BOR+VAN (0.64) exhibited a moderate synergistic impact (Table 6).

Table 4. CI method			
Range of CI	Description	Range of CI	Description
<0.1	Very strong synergy	1.10-1.20	Mild antagonism
0.1-0.3	Strong synergy	1.20-1.45	Moderate antagonism
0.3-0.7	Synergy	1.45-3.3	Antagonism
0.7-0.85	Moderate synergy	3.3-10	Strong antagonism
0.85-0.90	Light synergy	10>	Very strong antagonism
0.90-1.10	Additive		

CI: Combination Index

Table 5. Parameters were calculated from the median effect equation and median effect plot. 'm' is the slope, and m=1, >1 and <1 indicate hyperbolic, sigmoidal, and flat sigmoidal shape, respectively; 'Dm' denotes power; and 'r' is the linear correlation coefficient					
	CI values at				
L. acidophilus	ED50	Dm	m	r	% inhibition
MEL	N/A	78.00	0.83	0.95	77.35
BOR	N/A	127.00	0.68	0.94	70.21
VAN	N/A	15.00	0.75	0.99	6.42
MEL+VAN	0.83	9.41	1.06	0.96	
BOR+VAN	0.94	13.56	1.27	0.97	
MEL+BOR+VAN	0.77	6.25	1.15	0.98	

L. acidophilus: Lactobacillus acidophilus, CI: Combination Index, MEL: Melatonin, BOR: Boric acid, VAN: Vancomycin

Table 6. Parameters were calculated from the median effect equation and median effect plot. 'm' is the slope, and m=1, >1 and <1 indicate hyperbolic, sigmoidal, and flat sigmoidal shape, respectively; 'Dm' denotes power; and 'r' is the linear correlation coefficient					
	CI values at				
E. coli	ED50	Dm	m	r	% inhibition
MEL	N/A	35.00	1.05	0.95	54.54
BOR	N/A	172.00	1.04	0.96	148.49
VAN	N/A	112.00	1.11	0.95	13.58
MEL+VAN	0.78	14.86	1.15	0.95	
BOR+VAN	0.64	59.78	1.09	0.94	
MEL+BOR+VAN	0.56	5.68	0.90	0.98	

E. coli: Escherichia coli, CI: Combination Index

This study also focused on determining the appropriate Dose Reduction Index (DRI) for the dual and triple drug combinations based on actual experimental data points. The Fa-DRI table shows the results. DRI, DRI=1, >1 and <1 indicate no dose reduction, appropriate dose reduction, and inappropriate dose reduction for each drug in the combination, respectively. Typically, the primary objective of combination therapy is to achieve synergistic effects (CI<1) by reducing the dose of specific toxic drugs (DRI>1) and, consequently, to minimize the likelihood of drug resistance. Accordingly, when the Fa-DRI table was examined in detail at fa=0.5 (Table 7, 8), at 50% inhibition (fa=0.5) in *L. acidophilus*, the binary combinations (1.41-3.15) showed an appropriate dose reduction (DRI>1). The triple combinations MEL/BOR/VAN (3.25/3.14/1.46) showed an appropriate dose reduction (DRI>1). At 50% inhibition (fa=0.5) in *E. coli*, the binary combinations (1.44-4.82) showed an appropriate dose reduction (DRI>1), while the triple combination MEL/BOR/VAN (4.59/9.11/1.51) showed an appropriate dose reduction (DRI>1). These results suggest that the combined use of MEL/BOR has the potential to significantly enhance the effectiveness of dental caries treatment.

Table 7. DRI, DRI=1, >1, and <1 indicate no dose reduction, appropriate dose reduction, and inappropriate dose reduction for each drug in the combination, respectively						
L. acidophilus	Drug alone			DRI		
Fa	MEL	VAN		MEL	VAN	
0.5	78.00	15.00		3.15	1.44	
Fa	BOR	VAN		BOR	VAN	
0.5	127.00	15.00		2.77	1.41	
Fa	MEL	BOR	VAN	MEL	BOR	VAN
0.5	78.00	127.00	15.00	3.25	3.14	1.46

DRI: Dose Reduction Index, *L. acidophilus,* MEL: Melatonin, VAN: Vancomycin, BOR: Boric acid

SEM Analysis

When the SEM images in Figure are evaluated using ImageJ software, it becomes clear that BOR does not exhibit antibiofilm properties on its own. In the control dentin disc surface images for both *E. coli* and *L. acidophilus*, it is evident that the area is covered with a greater number of bacteria.

Table 8. DRI, DRI=1, >1, and <1 indicate no dose reduction, appropriate dose reduction, and inappropriate dose reduction for each drug in the combination, respectively

E. coli	Drug alone		DRI			
Fa	**MEL**	**VAN**	**MEL**	**VAN**		
0.5	35.00	112.00	1.55	1.44		
Fa	**BOR**	**VAN**	**BOR**	**VAN**		
0.5	172.00	112.00	4.82	2.26		
Fa	**MEL**	**BOR**	**VAN**	**MEL**	**BOR**	**VAN**
0.5	35.00	172.00	112.00	4.59	9.11	1.51

DRI: Dose Reduction Index, *E. coli: Escherichia coli,* **MEL: Melatonin, VAN: Vancomycin, BOR: Boric acid**

When the SEM images of BOR and MEL are compared with BOR+VAN and MEL+VAN for *E. coli* and *L. acidophilus*, it is seen that the single combinations are less effective.

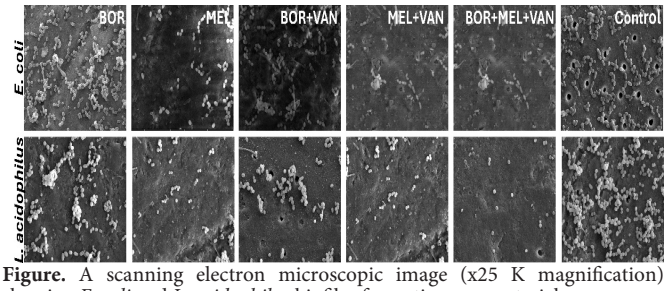

Figure. A scanning electron microscopic image (x25 K magnification) showing *E. coli* and *L. acidophilus* biofilm formations on materials

E. coli: Escherichia coli, L. acidophilus: Lactobacillus acidophilus

When both bacterial biofilms are evaluated for BOR+MEL+VAN, it is determined that the highest antibiofilm effect occurs. In accordance with the MIC and Synergy tests, when the SEM images are examined, the potency order of BOR+MEL+VAN > MEL+VAN > BOR+VAN > MEL > BOR is revealed. When SEM analysis images for E. coli were examined in five different areas, biofilm removal was 50%, 10%, 15%, 5%, and 3% on the disk surfaces applied with BOR, MEL, BOR+VAN, MEL+VAN, and BOR+MEL+VAN, respectively (Figure). Similarly, when SEM analysis images for L. acidophilus were examined in five different areas, biofilm removal was 40%, 7%, 10%, 5%, and 2% on the disk surfaces applied with BOR, MEL, BOR+VAN, MEL+VAN, and BOR+MEL+VAN, respectively (**Figure**).

DISCUSSION

This study aims to investigate the antimicrobial activity of melatonin and boric acid against *L. acidophilus* and *E. coli* bacteria that cause dental caries in human dentin tissue. Based on the findings of our study, our null hypothesis was rejected. Vancomycin was determined as the active ingredient in combination studies and used as the reference antimicrobial agent.[16] The findings revealed that the triple combination showed the highest antimicrobial activity, while single molecules showed lower inhibition. Previous studies have demonstrated that *L. acidophilus* plays a crucial role in the progression of dental caries, producing acidic metabolites that demineralize the dentin matrix.[17] *E. coli*, on the other hand, is not a dominant microorganism in the normal oral flora, has been associated with dental infections and periodontal diseases, and has been reported to trigger tissue damage by secreting bioactive molecules.[18] The antimicrobial activity of melatonin can be attributed to its effects on oxidative stress and bacterial metabolism. In addition to its antioxidant and immunomodulatory properties, melatonin is reported to have antibacterial effects by affecting bacterial virulence factors of oxidative stress.[19,20] It is well established that oxidative stress plays a significant role in the pathogenesis of periodontal diseases, and that melatonin promotes healing in gingival tissues.[21] Boric acid is defined as an element that disrupts bacterial membrane stability and inhibits metabolic activity.[22,23] Additionally, it has been reported that boric acid promotes remineralization in dental tissues and contributes to stabilizing the hydroxyapatite crystal structure.[24] Considering the clinical and academic importance of this study, the potential effects of combining melatonin and boric acid applications should be evaluated in the future.

The SEM analysis of the dentin disc surfaces revealed significant differences in the antibiofilm efficacy of the various treatment combinations. BOR alone showed minimal antibiofilm activity, with SEM images indicating a high bacterial density for both *E. coli* and *L. acidophilus* on the treated surfaces. This was further confirmed by the low biofilm removal percentages, which were recorded as 3% for *E. coli* and 2% for *L. acidophilus*. In contrast, the combination of BOR with MEL+VAN demonstrated a stronger antibiofilm effect, though still inferior to the triple combination. The highest biofilm removal efficacy was observed with the triple combination of BOR+MEL+VAN, with biofilm removal rates of 50% for *E. coli* and 40% for *L. acidophilus*, indicating a significant synergistic effect. These findings align with the MIC and synergy tests, which revealed that the efficacy of the combinations followed the order: BOR+MEL+VAN > MEL+VAN > BOR+VAN > MEL > BOR. In particular, further research is required on the pharmacokinetic profile, dosage, and administration methods to optimize the antibacterial activity of MEL+VAN and BOR+MEL+VAN combinations.

The substantial reduction in biofilm formation observed with the triple combination emphasizes its potential as an effective therapeutic option for preventing caries associated with microleakage under prosthetic restorations. Future in vivo and clinical studies will more clearly demonstrate the usability of these bioactive compounds in the prevention and treatment of dental caries.

Limitations

This study was conducted in vitro, which may limit the generalizability of the results obtained to clinical practice. The oral cavity is a complex environment where numerous variables, including saliva, pH fluctuations, enzymatic activity, mechanical stress, and microbial diversity, interact. Therefore, it is not guaranteed that the antimicrobial effects obtained under laboratory conditions will be observed at the same level in vivo. In addition, although an expert dentist performed the preparation of dentin discs according to standard protocols, it is essential to consider that patient-derived biological samples may exhibit individual variations.

Confirmation of these findings with future animal models or clinical studies will further strengthen the scientific validity of the study.

CONCLUSION

Today, the robust antimicrobial agents investigated in this study are crucial in dentistry because of their beneficial properties. They are particularly significant in clinical settings. Maintaining tooth integrity is critical for oral health. Therefore, it is crucial to minimize the microbial load from pathogens such as *L. acidophilus* and *E. coli* on dentin discs. The findings from this study will aid in the development of effective antimicrobial agents for oral hygiene and their implementation in clinical practice.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Yozgat Bozok University Rectorate Non-interventional Clinical Researches Ethics Committee (Date: 09.04.2025, Decision No: 2025-GOKAEK-257_2025.04.09_443).

Informed Consent

Since extracted human teeth without caries, resorption or fractures are used, informed consent is not required.

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.

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request. All data analyzed during this study are included in this published article as tables and figures.

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Are fat free mass, fat mass and meal frequency associated with malnutrition in institutionalized elderly: a cross-sectional study

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ABSTRACT

Aims: Malnutrition is a major concern that increases morbidity and mortality in older adults living in nursing homes. This study aimed to evaluate the nutritional status, body composition, and dietary intake of older adults in nursing homes while identifying the risk factors contributing to malnutrition.

Methods: This is a descriptive and cross-sectional study conducted with 150 older adults from two nursing homes. Malnutrition was assessed using the full version of mini nutritional assessment (MNA). Data were collected by face to face interview and anthropometric measurements and body composition analysis were performed. Statistical analyses included the Mann-Whitney U test, independent sample T test, Chi-square test, Spearman correlation coefficient and logistic regression.

Results: Among participants 81.80% were male. Mean age was 75.13±7.35 years. The prevalence of malnutrition/malnutrition risk was 14.7%. While energy, macronutrient intake, and nutrient adequacy ratio (NAR) were similar between participants with good nutritional status and malnutrition/malnutrition risk, vitamin E intake was significantly higher in older adults with good nutritional status (p=0.009). A higher number of chronic diseases significantly increased the risk of malnutrition (OR=2.083, p=0.038, OR:2.065, p=0.027). However, consuming more meals per day (OR=0.086 p<0.001, OR:0.130, p=0.001), higher fat mass (OR=0.911, p=0.030) and a greater Fat Free Mass Index (OR 0.697, p=0.009) were found to be protective.

Conclusion: Assessing nutritional status, determining food consumption and identifying the factors contributing to malnutrition are crucial for the early prevention and management of malnutrition in older adults. Longitudinal studies with larger sample sizes are needed to develop effective strategies for improving the nutritional well-being of nursing home residents.

Keywords: Malnutrition, nursing homes, elderly, meal frequency, Fat Free Mass Index, FFMI, fat mass

INTRODUCTION

Aging is defined as accumulation of damage as a result of impaired repair mechanisms, and progressive loss of function which finally results to increase in risk of morbidity and mortality.[1] World's population is aging which is evidenced with people aged over 65 years or over worldwide outnumbered the children under five years old.[2] Moreover projections indicate number of people over 60 years old will become 1.4 billion by 2030 and 2.1 billion by 2050. Aging increases the need for primary health care and long term care and better trained workforce in society.[3]

One of the major problems in elderly is malnutrition, which causes worsening of health and life quality and increasing risk of infection, pressure ulcers and decreasing wound healing.[4,5] Malnutrition is a state of lack of nutritional intake as a result of starvation, disease or ageing which leads to alteration in body composition and body cell mass leading to a decrease in physical and mental function and impaired disease outcome.[6]

Prevalence of malnutrition/malnutrition risk is lower in community dwelling older adults,[7,8] while it increases in long term care facilities or in nursing homes.[5,7-9] There are many reasons contributing to malnutrition in older adults including physiological, socioeconomic and neuropsychological factors which causes inadequate dietary intake leading to undernutrition.[4] Biological changes related to aging such as decreased gastric emptying time, oral changes leading to difficulty in chewing, swallowing and loss of sense of taste and smell may cause decreased energy and nutrient intake.[4,10] In addition to this, chronic diseases increase metabolic demands and impairs nutrient absorption and also cause polypharmacy which can also lead to decrease in food intake.[10,11] To optimize nutritional status and reduce malnutrition/malnutrition risk in nursing homes, optimal dietary intake with adequate energy and protein is needed however data regarding about food and nutrient intake in nursing homes is rare.[9,12] Therefore it is essential to detect early malnutrition risk with systematic

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tools such as Mini Nutritional Assessment (MNA) and monitor food intake in nursing homes[5]. Futhermore both aging and malnutrition leads to alteration in body composition which results in a significant decrease especially in fat free mass that may cause a decline in functional capacity.[9,13]

The aim of this study was to assess the nutritional status, body composition and energy and nutrient intake of older adults living in nursing homes and find the potential risks associated with malnutrition.

METHODS

Study Design and Participants

This is a descriptive and cross-sectional study which was conducted in 2 nursing homes affiliated with municipalities located in Bursa province of Turkiye, between March-May 2017. Study was designed according to the guidelines in Declaration of Helsinki and approved by the Doğu Akdeniz University Scientific Researches and Publication Ethics Committee (Date: 06.03.2017, Decision No: 2017/39-05). Study was conducted with older adults 60 years and over who do not have any obstacles for anthropometric measurements, who can communicate, and who were willing to give an informed consent. Older adults who were bed ridden (n: 11), had dementia (n: 12) and who had psychiatric problems (n: 2) were excluded from the study. The study was completed with 150 older adults (40 women, 110 men). In 2017, there were only two nursing homes affiliated with municipalities in Bursa province. Both institutions agreed to participate in the research. Therefore, instead of performing a priori sample size calculation, we adopted a total population sampling method by including all eligible and consenting residents from these two nursing homes. The sample size (n: 150) reflects the entire accessible and consenting population within the study setting during the data collection period.

Primary outcomes of the study were defined as assessment of nutritional status, assessment of body composition and its relation with nutritional status and finding the association between malnutrition/malnutrition risk and chronic diseases, polypharmacy, eating habits and energy and nutrient intake.

Data Collection

All participants were interviewed face to face via a survey. The survey consists of 4 sections. First section was developed by the authors and aimed to determine the general background, eating habits and health status of the participants. The second section included a 24 hour dietary recall in order to analyze energy and nutrient intake of the older adults. For the assessment of nutritional status MNA full form was used in the third section and 4th section included anthropometric measurements and body composition data which were measured by the researcher dietitian.

General Background, Eating Habits and Health Status

Data relating to socio-demographic and personal features, educational status, duration of stay in a nursing home, number and type of chronic diseases and medications used, meal frequency, appetite, edibility of meals served in nursing homes were collected in this section.

24 Hour Dietary Recall

Food consumption was assessed with a 24-hour dietary recall. Energy and nutrient intake were analyzed with Nutrition Information Systems Package Program (Beslenme Bilgi Sistemleri Paket Programı 7.0 (BEBİS 7.0).[14] Standard recipes of the food served in nursing homes were applied to the program and the energy and nutrient intake of the older adults were calculated. For the assessment of the adequacy of participant's nutritional intake, nutrient adequacy ratio (NAR) was calculated according to the formula below.[15] Turkish Dietary Guidelines 2022 was taken as reference intake of specific nutrients according to age and gender.[16]

$$NAR = \frac{\text{Daily Specific nutrient intake}}{\text{Reference intake of a secific nutrient}}$$

Mini Nutritional Assessment Full Form (MNA-FF)

The MNA FF has been developed and validated as a tool to assess nutritional status in older adults, commonly used in nursing homes, community, hospitals, and home care. According to the full MNA®, a total score greater than 24 indicates satisfactory nutritional status, a score between 17 and 23.5 indicates risk of malnutrition, and a score <17 indicates malnutrition.[17] Although the full MNA® categorizes individuals into three nutritional status groups, the number of older adults identified as malnourished in this study was very small (0.7%). Therefore, those classified as malnourished and those at risk of malnutrition were combined into a single group for analysis, and all statistical evaluations were conducted based on two groups.

Anthropometric Measurements

For assessment of body composition [total body fat (kg), body fat percentage (%), fat free mass (FFM) (kg)], bioelectric impedance analysis (BIA) was used which is a fast, inexpensive, noninvasive, and a portable method.[18] TANITA BC 418, a segmental body composition analyzer (Tokyo, Japan) with single-frequency constant electrical currents of 500 µA at 50 kHz was used for measurements with an empty bladder, fasting for 8 hours, and wearing light clothing without shoes to the nearest 0.1 kg.[19]

A stadiometer was used to measure height standing still, in an upright position and the head in the Frankfurt plane without shoes. A flexible non stretch tape was used to measure middle upper arm, calf circumference (MUAC) to the nearest 0.1 cm. For measurement of MUAC the arm was first bent to 90 degree angle and the midpoint between olecranon and acromion processes was identified and marked. The arm was then allowed to hang straight down and a measuring tape was wrapped around marked midpoint. Calf circumference (CC) was measured by wrapping the tape around the widest part of the calf. Body-mass index (BMI) (kg/m^2) was calculated by dividing body weight (kg) into the square meters of height[20] and Fat Free Mass Index (FFMI) was calculated by dividing FFM into the square meters of height by the researcher.[21]

Statistical Analysis

Collected data was analyzed with Statistical Package for Social Science 24.0 software (SPSS). Arithmetic mean±standard deviation, median and minimum maximum values were

used for presenting quantitative variables. Shapiro Wilk test was used for testing normality. For independent variables with 2 categories, Mann-Whitney U test was used. Fisher's and Pearson's chi-square was used for comparing qualitative variables. Correlation between variables was evaluated with the Spearman's Correlation Coefficient. Logistic regression was used to relate malnutrition/malnutrition risk with age, gender, marital status, meal frequency, number of chronic diseases, polypharmacy, FFMI and fat mass in 2 different models. For defining malnutrition/malnutrition risk cut of point of MNA was used. Since BMI, CC and MUAC are the variables used to calculate MNA score they are not included into the regression models. A p-value of <0.05 was deemed as statistically significant.

RESULTS

The study consisted of 110 (73.3%) male and 40 (26.70%) female total 150 participants who were 60 years and older. According to the MNA, 85.30% of the participants had good nutritional status. While 16.40% of males had malnutrition/malnutrition risk, only 10% of female had malnutrition/malnutrition risk. There was no difference in MNA scores between males and females (p>0.05) (Table 1).

Comparison of general characteristics, health status and eating habits of the participants were shown in Table 2. No difference was found in between the groups according to age, sex, educational status, length of stay in the nursing home, loss of appetite and ability to eat meals served in the nursing

Table 1. Distribution of nutritional status of the older adults according to gender

MNA score		X±SD		Minimum		Maximum		p*
Male (n=110)		24.8±2.70		15.00		29.00		0.139
Female (n=40)		25.32±2.77		17.50		29.00		
		Male (n=110)		Female (n=40)		Total (n=150)		
		n	%	SD	%	n	%	p**
MNA classification	Good nutritional status	92	83.60	36	90.00	128	85.30	0.438
	Malnutrition risk & malnutrition	18	16.40	4	10.00	22	14.70	

p<0.05, *Mann-Whitney U test, **Fisher's Chi-square, MNA: Mini Nutritional assessment, SD: Standard deviation

Table 2. Distribution of socio-demographic characteristics, health status and eating habits of participants according to nutritional status

	Good nutritional status		Malnourished/malnutrition risk		Total		p
Gender*	**n**	**%**	**n**	**%**	**n**	**%**	
Male	92	71.90	18	81.80	110	73.30	0.330
Female	36	28.10	4	18.20	40	26.70	
Age (years)§	**X±SD**	**Min-max**	**Median**	**X±SD**	**Min-max**	**Median**	
Mean age§	75.13±7.35	62-102	74.00	72.91±7.75	65-96	71.00	0.109
Age (years)*	**n**	**%**	**n**	**%**	**n**	**%**	
65-75	66	51.60	15	68.20	81	54.00	
76-85	54	42.20	6	27.30	60	40.00	0.351
85+	8	6.30	1	4.50	9	6.00	
Marital status*	**n**	**%**	**n**	**%**	**n**	**%**	
Married	77	60.20	6	27.30	83	55.30	0.004
Single/divorced/widow	51	39.80	16	72.70	67	44.70	
Educational status*	**n**	**%**	**n**	**%**	**n**	**%**	
Illiterate	16	12.50	2	9.10	18	12.00	
Primary/secondary school	70	54.70	15	68.20	85	56.70	0.498
High school/university	42	32.80	5	22.70	47	31.30	
Duration of stay in nursing home*	**n**	**%**	**n**	**%**	**n**	**%**	
<12 months	69	53.90	11	50.00	80	53.40	
1-5 years	34	26.60	4	18.20	38	25.30	0.386
>6 years	25	19.50	7	31.80	32	21.30	
Loss of appetite‡	**n**	**%**	**n**	**%**			
Yes	24	18.80	5	22.7	29	19.30	0.426
No	104	81.30	17	77.3	121	80.70	
Able to eat meals served in nursing home‡	**n**	**%**	**n**	**%**	**n**	**%**	
Yes	105	82.00	17	77.3	122	81.30	0.392
No	23	18.00	5	22.7	28	18.70	
Medication use	**X±SD**	**Min-max**	**Median**	**X±SD**	**Min-max**	**Median**	
Medication use per day§	2.88±1.72	0-8	3.00	4.36±1.94	1-8	4.00	0.002
Chronic diseases	**X±SD**	**Min-max**	**Median**	**X±SD**	**Min-max**	**Median**	
Number of chronic diseases§	3.14±1.82	0-8	3.00	4.54±1.59	2-8	4.00	0.001
Total number of meals consumed§	**X±SD**	**Min-max**	**Median**	**X±SD**	**Min-max**	**Median**	
Meals consumed/day	4.17±0.89	3-6	4.00	2.95±0.78	1-4	3.00	<0.001

‡Fisher's Chi-square, *Pearson's Chi-square, §Mann-Whitney U test, n: Number of participants, X±SD: Mean±standard deviation, Min: Minimum, Max: Maximum

home (p>0.05). On the contrary it was found that the older adults with good nutritional status had fewer chronic diseases, used less medication, consumed more meals per day and had a significantly higher rate of being married when compared to those with malnutrition/malnutrition risk (p<0.05).

Table 3 shows the comparison of anthropometric measurements according to nutritional status and gender. No difference was found between the female participants. However male participants with good nutritional status had significantly higher weight, total body fat (kg), body fat percentage (%), FFM (kg) and FFMI (kg/m^2) than the participants with malnutrition/malnutrition risk (p<0.05).

Comparison of energy and macronutrient intake and NAR according to nutritional status was shown on Table 4. No significant difference was found between the participants with good nutritional status and malnutrition/malnutrition risk except the vitamin E. Nutrient adequacy ratio of vitamin E was significantly higher in participants with good nutritional status (p=0.009).

Table 5 shows the correlation between MNA score and number of chronic diseases, number of medications used, meals consumed and age. A moderate strong negative correlation was found between number of chronic diseases, and number of medications used per day while a moderate strong positive correlation was found between total number of meals consumed per day (p<0.001). According to these results as number of chronic diseases and medication used increases MNA score decreases, on the contrary as meal frequency increases MNA score increases.

Many factors may influence nutritional status. According to the models in Table 6, age, gender, marital status and number of medications used were not associated with nutritional status. Meal frequency, fat mass and FFMI were found to be protective against malnutrition/malnutrition risk while having chronic diseases was found to be a risk factor for malnutrition/malnutrition risk. One unit increase in daily meal count was found 11.62 fold (OR: 0.086) (p<0.001) protective in the first model and 7.69 fold (OR:0.130) (p<0.001) in the second model and one unit increase in FFMI (kg/m^2) (p=0.009) has a 1.43 fold (OR:0.697) (Model 1), one unit increase in fat mass (kg) (p=0.030) has a 1.09 fold (OR=0.911) protective from malnutrition/malnutrition risk (Model 2). On the contrary for each additional chronic disease malnutrition risk increases by 2.083 times (p=0.038) in the first model and 2.065 times (p=0.027) in the second model.

DISCUSSION

Malnutrition is a growing problem in older adults, especially for those over 65 years of age which leads to muscle weakness, decreased functionality, increased risk of infection and mortality. Therefore, early diagnosis of malnutrition is very important to prevent malnutrition or slow the progression of its consequences.[22] This study was conducted in order to assess malnutrition prevalence in nursing homes, to determine the body composition of older adults and find the factors contributing to malnutrition. Based on full MNA 14.70% of the older adults found to have malnutrition risk/malnutrition (Table 1) which was lower when compared to other studies. Various studies showed different malnutrition/

Table 3. Comparison of anthropometric measurements of participants according to gender and nutritional status

	MNA										
Anthropometric easurements	**Good nutritional status**					**Malnutrition risk & malnutrition**					
Male (SD=110)	**n**	**X±SD**	**Median**	**Min**	**Max**	**n**	**X±SD**	**Median**	**Min**	**Max**	**p***
Height (cm)	92	164.32±9.00	165.00	140.00	183.00	18	166.11±6.29	166.50	155.00	180.00	0.588
Weight (kg)	92	76.11±13.74	75.50	50.00	108.90	18	64.46±13.23	59.40	49.30	94.20	0.002
BMI (kg/m^2)	92	28.34±5.19	27.05	19.10	41.10	18	23.38±4.82	22.40	16.70	34.60	<0.001
MUAC (cm)	92	27.51±3.12	28.00	20.00	34.00	18	24.58±2.93	25.00	20.00	31.00	0.001
Calf circumference (cm)	92	32.03±2.19	32.00	27.00	38.00	18	28.33±2.32	28.00	26.00	36.00	<0.001
Total body fat (kg)	92	21.15±8.49	20.00	8.90	50.60	18	15.02±7.80	12.50	4.90	31.30	0.005
Body fat percentage (%)	92	26.74±7.28	26.10	12.70	49.90	18	21.07±7.37	20.65	9.70	38.20	0.005
Fat free mass (kg)	92	54.74±8.49	54.50	28.40	77.8v	18	50.48±6.46	50.90	41.60	65.80	0.027
Fat Free Mass Index (kg/m^2)	92	20.27±2.77	19.90	10.50	28.50	18	18.28±2.06	17.70	15.00	24.10	0.001
Female (SD=40)	**n**	**X±SD**	**Median**	**Min**	**Max**	**n**	**X±SD**	**Median**	**Min**	**Max**	**p***
Height (cm)	36	149.99±9.15	148.50	132.00	176.00	4	156.25±7.89	156.50	147.00	165.00	0.175
Weight (kg)	36	71.50±17.59	67.90	47.80	141.00	4	68.57±13.36	73.00	49.20	79.10	0.892
BMI (kg/m^2)	36	31.43±5.37	31.05	23.30	42.30	4	28.62±7.92	29.90	18.10	36.60	0.513
MUAC (cm)	36	27.61±3.58	27.00	20.00	36.00	4	25.25±3.77	25.00	21.00	30.00	0.239
Calf circumference (cm)	36	30.92±1.81	31.00	27.00	34.00	4	27.75±1.26	29.00	27.00	30.00	0.022
Total body fat (kg)	36	26.35±9.65	24.90	11.10	45.90	4	23.47±10.72	25.60	9.40	33.20	0.718
Body fat percentage (%)	36	37.50±8.54	39.30	16.50	50.70	4	32.82±10.56	35.10	19.10	42.00	0.344
Fat free mass (kg)	36	42.29±7.46	41.90	24.60	63.30	4	49.32±13.35	45.40	37.80	68.60	0.176
Fat Free Mass Index (kg/m^2)	36	18.87±3.10	19.20	9.30	24.30	4	20.28±5.33	20.20	13.80	26.80	0.528

*Mann-Whitney U test, X±SD: Mean±standard deviation, Min: Minimum, Max: Maximum, MNA: Mini nutritional assessment, BMI: Body-mass index, MUAC: Middle upper arm, calf circumference

Table 4. Comparison of the daily energy and macronutrient intake (a) and NAR (b) of elderly individuals according to nutritional status									
	Good nutritional status (n=128)				Malnutrition risk & malnutrition (n=22)				
Energy and macronutrients (a)	**X±SD**	**Median**	**Min**	**Max**	**X±SD**	**Median**	**Min**	**Max**	**p***
Energy (kcal)†	1860.27±358.33	1841.91	937.00	2688.91	1734.83±485.30	1715.58	701.89	2484.74	0.154
Protein (gr)§	80.83±20.65	77.73	39.37	155.19	75.77±23.77	74.02	26.82	121.37	0.543
Protein (%)§	17.78±3.12	17.00	12.00	30.00	17.95±4.71	18.00	12.00	37.00	0.991
Carbohydrate (gr)†	155.86±41.03	155.84	58.01	248.72	138.82±51.83	141.04	48.03	228.97	0.086
Carbohydrate (%)§	33.50±6.39	33.00	18.00	60.00	31.59±6.36	32.00	22.00	42.00	0.274
Fat (gr)†	100.75±23.37	100.77	27.07	161.05	96.72±30.19	103.58	32.31	151.85	0.476
Fat (%)§	48.72±7.22	49.00	23.00	69.00	50.41±8.83	51.00	22.00	61.00	0.201
NAR of nutrients (b)	**X±SD**	**Median**	**Min**	**Max**	**X±SD**	**Median**	**Min**	**Max**	**p***
Protein (gr)§	1.07±0.31	1.04	0.44	1.87	1.15±0.44	1.09	0.47	1.95	0.570
Carbohydrate (gr)§	1.19±0.31	1.19	0.45	1.91	1.06±0.39	1.08	0.37	1.76	0.154
Fiber (gr)§	0.86±0.30	0.84	0.22	2.66	0.87±0.28	0.97	0.24	1.38	0.293
Vitamin A (mcg)§	1.78±0.94	1.56	0.30	5.63	1.61±0.80	1.36	0.40	3.72	0.235
Vitamin E (mg)§	1.22±0.40	1.19	0.15	2.44	0.94±0.46	1.05	0.19	1.91	0.009
Vitamin K (mcg)§	3.34±1.52	2.99	0.27	8.21	2.78±1.39	2.66	0.54	6.09	0.141
Vitamin B12 (µg)§	1.41±0.59	1.25	0.50	3.13	1.33±0.63	1.19	0.23	2.68	0.690
Vitamin B1 (mg)§	0.64±0.16	0.65	0.28	1.41	0.62±0.15	0.62	0.19	0.90	1.000
Vitamin B2 (mg)§	1.17±0.27	1.17	0.55	1.76	1.09±0.28	1.13	0.32	1.39	0.410
Vitamin B6 (mg)§	0.76±0.18	0.77	0.38	1.21	0.68±0.24	0.69	0.18	1.15	0.151
Folate (µg)§§	0.96±0.27	0.95	0.44	2.64	0.90±0.22	0.90	0.35	1.33	0.547
Calcium (mg)§	0.95±0.23	0.97	0.30	1.44	0.93±0.28	0.99	0.28	1.38	0.784
Potassium (mg)§	0.47±0.12	0.46	0.19	0.98	0.46±0.13	0.52	0.16	0.63	0.728
Magnesium (mg)§	0.73±0.18	0.72	0.32	1.27	0.72±0.19	0.72	0.25	0.99	0.892
Phosphorus (mg)§	2.12±0.42	2.09	1.15	3.18	2.06±0.51	2.13	0.71	2.67	0.842
Iron (mg)§	1.05±0.27	1.05	0.42	2.07	0.97±0.28	1.01	0.20	1.37	0.459

§Mann-Whitney U test, †Independent sample T test, X±SD: Mean±standard deviation, Min: Minimum, Max: Maximum, NAR: Nutrient adequacy ratio

Table 5. Correlation of age, number of medications used, number of chronic diseases and meal frequency with MNA score		
Variable		**MNA score**
Age	r	-0.097
	p	0.239
Number of medications used daily	r	-0.453
	p	<0.001
Number of chronic diseases	r	-0.372
	p	<0.001
Total number of meals consumed daily	r	0.493
	p	<0.001

r: Spearman correlation coefficient, MNA: Mini nutritional assessment

malnutrition risk prevalence altering between 16-63%.[5,7-9] The low prevalence can be explained with the selection criteria of this study which excluded the patients who were bed ridden, had dementia and psychiatric problems and moreover the variation between all these studies might be related with different screening methods used for detecting malnutrition. Even though malnutrition is an important problem in nursing homes or residential care centers still there is no universal malnutrition screening method.[22]

When anthropometric measurements and body composition data were analyzed, it was found that male participants who were malnourished/at risk of malnutrition had significantly lower weight (kg), BMI (kg/m^2), MUAC (cm), CC (cm), total body fat (kg), body fat percentage (%), FFM (kg) and FFMI (kg) than the ones who had good nutritional status ($p<0.05$). For the female participants the only significant difference was with CC. Calf circumference of participants who were malnourished/at risk of malnutrition was lower ($p=0.022$). A study conducted with 154 community dwelling older adults which analyzed BMI, MUAC, CC, FMI, FFM and FFMI reported no significant difference between the well-nourished participants and participants at risk of malnutrition about BMI, MUAC, CC, FMI and FFMI. The only difference found between the groups was FFM.[11] On the contrary, a study which was conducted with 100 instiutionalized older women found that the ones who were malnourished had significantly lower weight, BMI, body fat (%), MUAC and CC than the ones who were well nourished.[23] Another study which was conducted with 296 geriatric obese outpatients, it was found that patients who were undernourished had significantly lower MUAC, CC, skeletal muscle mass, FFM, however no difference was found about BMI.[24] Most of the screening methods assessing malnutrition use anthropometric measurements as a

Table 6. Association of malnutrition/malnutrition risk with respect to age, gender, meal frequency, number of chronic diseases, daily medication used and FFMI

		Model 1		
Malnutrition/malnutrition risk*	**B**	**SE**	**p**	**OR (95% CI)**
Constant	10.007	5.165	0.053	22181.152
Age (years)	-0.008	0.058	0.895	0.992 (0.887-1.111)
Gender (Ref: female)	-0.590	0.884	0.505	0.554 (0.098-3.135)
Marital status (Ref: married)	0.691	0.732	0.346	1.995 (0.475-8.380)
Total number of meals consumed daily	-2.448	0.656	<0.001	0.086 (0.024-0.312)
Number of chronic diseases	0.734	0.354	0.038	2.083 (1.041-4.168)
Number of medications used daily	0.252	0.324	0.437	1.286 (0.682-2.426)
FFMI (kg/m^2)	-0.362	0.139	0.009	0.697 (0.530-0.915)
Nagelkerke R^2		58.8%		
		Model 2		
Malnutrition/malnutrition risk*	**B**	**SE**	**p**	**OR (95% CI)**
Constant	3.124	4.439	0.482	22.735
Age (years)	-0.003	0.055	0.963	0.997 (0.896-1.110)
Gender (Ref: female)	0.045	0.868	0.959	1.046 (0191-5.731)
Marital status (Ref: married)	0.686	0.731	0.348	1.985 (0.474-8.319)
Total number of meals consumed daily	-2.038	0.609	0.001	0.130 (0.040-0.430)
Number of chronic diseases	0.725	0.328	0.027	2.065 (1.086-3.926)
Number of medications used daily	0.237	0.296	0.424	1.267 (0.709-2.264)
Fat mass (kg)	-0.094	0.043	0.030	0.911 (0.837-0.991)
Nagelkerke R^2		56.7%		

*Malnutrition/malnutrition risk is defined according to the MNA score, MNA: Mini nutritional assessment, FFMI: Fat Free Mass Index, SE: Standard error, OR: Odds ratio, CI: Confidence interval, B: Beta coefficient

determinant of malnutrition, moreover low muscle mass has also recently been used as a part of malnutrition definition[25] so it is expected to see lower anthropometric measurements in malnourished patients. In this current study it was found similar results with other studies about anthropometric measurements in males, the reason that there was no difference in anthropometric measurements of females is thought to be related with lower number of females in whole sample and low malnutrition/malnutrition risk percentage which caused an imbalance between the groups. When further analyses were done about body composition parameters, it was found that each unit increase in fat mass (kg) (OR: 0.911) and FFMI (kg/m^2) (OR: 0.697) were protective against malnutrition/malnutrition risk ($p<0.05$). Parallel to this study, a study done in China with 386 older adults in nursing homes also found that body fat mass, muscle strength and Skeletal Muscle Index are valid predictors for assessing nutritional risk.[26] A prospective cohort study done with 378 older hospital patients also found that high risk of malnutrition was significantly associated with low muscle mass.[27] Another longitudinal study conducted in Mexico with 241 older adults found that excess fat mass was protective against risk of malnutrition.[28]

Although one of the main determinants of nutritional assessment is the assessment of food intake which was strengthened by the Global Leadership Initiative on Malnutrition (GLIM) consensus,[13] there are few studies analyzing energy and nutrient intake in nursing home residents according to their nutritional status.[9,29] In this study a single 24-hour food recall was used to assess dietary intake. Analysis of the data showed that, energy and macronutrient intakes were similar between the groups ($p>0.05$). Nutrient adequacy ratio of nutrients were also evaluated according to the Turkish Dietary Guidelines, which also showed that there were no difference between the groups except for vitamin E. Older adults with good nutritional status had a significantly higher adequate intake of vitamin E than those with malnutrition/malnutrition risk ($p=0.009$). Although no difference was found between the groups it was seen that both of the groups had inadequate intakes of fiber, vitamin B1, vitamin B6, folate, calcium, potassium and magnesium (**Table 4**) which shows that even though nutritional status was assessed as well nourished, micronutrient intake may be inadequate. A study conducted in Belgium with 74 nursing home residents, which assessed nutritional intake by weighed food records over a 5-day period found that older adults with good nutritional status consumed significantly more energy but similar carbohydrate (g), protein (g) and fat (g) than malnourished ones.[29] Another study done with both institutionalized and community-dwelling elderly, that assessed nutritional status with 2 non-consecutive 24 hour recalls, 8-15 days apart, it was found that inadequate nutrient intake was generally higher for those at risk of malnutrition or malnourished (except for carbohydrates and protein) than for those who were well nourished.[9] Another study done in Portugal with 563 nursing home residents and 837 community dwelling older adults,

assessed dietary intake with 24 hour dietary recalls that repeated every 8-15 day apart across a whole year. Among both in nursing home residents and community dwellers energy intake was inversely associated with malnutrition risk. For macronutrients among nursing home residents, they found higher intake of carbohydrate, fat, monounsaturated fat, polyunsaturated fat and fiber, was protective against being at risk of malnutrition or malnourished. However, when macronutrient intake was adjusted according to the total energy intake the significance for macronutrients were lost. Regarding micronutrients vitamin C, sodium, potassium and magnesium are found associated with malnutrition risk. However, when model was adjusted according to energy intake significance was lost again. In community dwellers similar to nursing home residents, protein, total fat, monounsaturated fat, sodium, potassium and magnesium were inversely associated with malnutrition risk, but after adjusted to energy intake only sodium, and magnesium intake remain significantly associated.[30] When all these studies were examined, it was seen that studies evaluating energy and nutrient intakes have variations in their assessment methods, which may be the reason for the different outcomes.

Various demographic factors and factors related with health status may affect nutritional status such as age, education, marital status, chronic diseases and polypharmacy.[10,11] In this current study, it was found that older adults with good nutritional status had higher rates of being married, had significantly fewer chronic diseases and used fewer medications/day than those with malnutrition/malnutrition risk ($p<0.05$). On the other hand age, gender, educational status and duration of stay in nursing home did not differ between the groups ($p>0.05$) (Table 1). Moreover as the number of medications and chronic diseases increases MNA score decreases, on the contrary when the number of meals consumed increases MNA score increases ($p<0.05$) (Table 5). When further analysis was done for the significant variables, with multiple logistic regression analysis, number of chronic diseases were found to be significantly associated with malnutrition/malnutrition risk ($p<0.05$) while number of medications used and marital status were not ($p<0.05$). An additional chronic disease significantly increases malnutrition/malnutrition risk (OR: 2.083 model 1, OR: 2.065 model 2) ($p<0.05$). Different form our study, a study conducted with 28,004 elderly in India found that aging, being male, being widowed/divorced/separated and having fewer years of education were associated with being underweight in rural areas of India.[31] A study conducted with community dwelling elderly in Turkiye also found that increase in chronic diseases increases the risk of malnutrition, while gender and educational status did not pose a risk. However different from our study, they also found that aging and not being married were also significant risk factors.[32] Bayrak et al conducted a study with 238 community dwelling elderly also found no difference between the groups according to gender, educational status and marital status, however also no relationship with number of medications per day and number of chronic diseases were shown.[33] Another study done in Turkiye with 356 geriatric outpatients who admitted to a hospital. It was found that as number of chronic diseases and number of medications increases MNA score decreases.[34]

Several factors related with eating may affect nutritional status in elderly such as decreased appetite, long overnight fast and eating fewer number of meals.[35,36] In this current study it was found that older adults with good nutritional status eat more meals than those with malnutrition/malnutrition risk and when logistic regression analysis was done it was seen that each one unit increase in number of meals is protective (OR: 0.086 model 1, OR: 0.130 model 2) against malnutrition/malnutrition risk ($p<0.05$). Parallel to our findings, a cross-sectional study conducted 1771 older hospital patient also found that eating fewer than four meals per day increases malnutrition risk 1.878, and malnutrition 3.099 times.[35] Different from our study Bayrak et al.[33] conducted a study with 238 community dwelling elderly and found no difference about meal frequency between the older adults with good nutritional status and malnutrition/malnutrition risk. Another study done in Ethiopia with 594 community dwelling older adults reported that, eating less than 3 meals per day significantly increases undernutrition (OR: 2.01) ($p<0.05$).[37] Moreover, a study with 115 older adults in Turkiye, also found that those eating 1-2 meals/per day had significantly lower MNA scores than those eating 3-4 and 4-6 meals.[38] Evaluating the meal concept from different perspectives is very important since it is complex[36] and in order to make further assumptions longitudinal studies, with more precise definitions related to meals or eating occasions are needed.

Limitations

One of the limitations of this study was the self-reported dietary assessment which may have resulted in under or over reporting of the energy and nutrients consumed by the patients due to various reasons such as social norms and personal beliefs. Moreover a single 24 hour dietary recall may not reflect day to day variability in the diet. Weighed food records for more than one day may provide more accurate results. Another limitation of this study is, nursing homes were not randomly selected since this study was only possible in cooperating institutions. Therefore, these institutions may not be represent all nursing homes.

CONCLUSION

As a conclusion, in district of Bursa, among the nursing home residents malnutrition/malnutrition risk was determined as 14.70%. According to our findings increase in number of chronic diseases, increased risk of malnutrition while increase in fat mass, FFMI and number of meals eaten per day were found to be protective. Understanding these factors when caring for the elderly can help healthcare professionals for prevention of malnutrition. Longitudinal studies with larger sample sizes are needed to support these results and to assess energy and nutrient intake.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Doğu Akdeniz University Scientific Researches and Publication Ethics Committee (Date: 06.03.2017, Decision No: 2017/39-05).

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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Immature granulocytes are a potential biomarker in the early diagnosis of lower extremity subacute arterial thrombosis

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ABSTRACT

Aims: Acute arterial embolism in peripheral arteries is generally diagnosed quickly. In contrast, subacute arterial thrombosis (SAT), which arises as an acute exacerbation of chronic peripheral artery disease (PAD), is often more challenging to diagnose rapidly, primarily due to the development of collateral circulation. This study aims to investigate the role of immature granulocytes (IG) in the early diagnosis of SAT in patients with chronic PAD.

Methods: This retrospective study was conducted at a single center between 2019 and 2021. A total of 99 patients with chronic lower extremity PAD were included in the study. Of these, 27 patients (27.2%) who developed exacerbations in the form of SAT were assigned to the SAT group. The remaining 72 patients (72.8%) with chronic PAD were included in the control group. Blood samples from patients in both groups were collected at their first admission before receiving any treatment. Complete blood count parameters were analyzed using an automatic hematological analyzer and compared between the two groups.

Results: Comparison between the control and SAT groups revealed significant differences in hemogram parameters. These parameters included white blood cell count (WBC, p<0.001), neutrophil count (NEUT#, p<0.001), lymphocyte count (LYMPH#, p=0.004), eosinophil count (EO#, p=0.035), neutrophil percentage (NEUT%, p<0.001), lymphocyte percentage (LYMPH%, p<0.001), monocyte percentage (MONO%, p=0.013), eosinophil percentage (EO%, p=0.008), immature granulocyte count (IG#, p<0.001), immature granulocyte percentage (IG%, p=0.002), neutrophil-to-lymphocyte ratio (NLR, p<0.001). These parameters were statistically significantly different in patients with SAT compared to patients with chronic atherosclerotic lower extremity peripheral artery.

Conclusion: Our study demonstrates that immature granulocytes show 81% sensitivity and %59 specificity for the early diagnosis of SAT. These findings suggest that immature granulocytes may serve as a reliable biomarker for the early detection of SAT.

Keywords: Peripheral arterial disease, diagnosis, immature granulocytes

INTRODUCTION

Acute arterial occlusion (AAO) is generally considered a vascular emergency. If acute arterial occlusion is not diagnosed and treated quickly, it may progress in a short time and lead to loss of limb and even life. There are six known P findings in AAO. These include the "six Ps" of pain, pallor, paralysis, paresthesia, pulselessness, and poikilothermia.[1,2] Patients with acute embolic occlusion tend to have a sudden onset with more severe symptoms, as collateralization in the vascular structure does not occur at this point. Treatment is possible with the ease of early diagnosis in AAO.[3,4]

Arterial occlusions can sometimes be detected in the subacute or chronic phase. SAT develops based on chronic PAD.[5-6] Diagnosis and treatment may be delayed due to collateral circulation. If a delay occurs, it may result in increased morbidity and mortality. The main goal of the treatment is to perform any intervention at the best time and save limb vitality in the best way possible. In such a delay, mortality and morbidity rates increase.

Percentage of immature granulocytes (IG%) is a newly discovered inflammatory serum marker. Usually, there is no IG in the systemic blood of healthy people. Therefore, most physicians do not know these immature granulocytes' number IG (IG#) and % IG. IGs are the precursors of neutrophil cells, and they ınclude myelocytes, promyelocytes, and metamyelocytes. IG% values can accurately reflect inflammation in the body. Some studies have shown that the IG% in the blood increases earlier than parameters such as C-reactive protein (CRP) and leukocytes.[7-9] IG% can be rapidly determined by routine blood serum examination. IG# and IG% can be measured quickly and inexpensively in automatic hematological analyzers in almost every laboratory.[10-12]

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IG% has been measured in numerous ıllness. A study reported the IG count as a prognostic biomarker in patients with severe acute pancreatitis.[9] In this study, we aimed to investigate the role of IG in the early diagnosis of SAT.

METHODS

Before starting this study, approval was obtained from the Kastamonu University Clinical Researches Ethics Committee (Date: 12.01.2022, Decision No: 2020-KAEK-143-138). The Declaration of Helsinki's ethical rules and principles were carried out in all procedures.

This study was conducted retrospectively in our cardiovascular surgery clinic between 2019 and 2021. A total of 99 patients with chronic PAD in the lower extremity were included in the study. The diagnosis of chronic PAD was established based on clinical findings such as claudication, smoking history, previous PAD-related surgeries, and imaging evidence of arterial disease. Patients without hemogram data, those under 18, pregnant women, trauma patients, and those with active infections were excluded from the study.

The onset of new symptoms, including coldness, pallor, and cyanosis, in patients with chronic PAD raised suspicion of subacute arterial thrombosis (SAT). The diagnosis was confirmed through Doppler ultrasonography and contrast-enhanced computed tomography (CT). The detection of thrombosis in combination with collateral circulation on Doppler ultrasonography or contrast-enhanced CT was indicative of subacute arterial thrombosis.

A total of 99 patients with chronic PAD were included in the study. Of these, 27 patients (27.2%) diagnosed with SAT were assigned to the SAT group, while the remaining 72 patients (72.8%) were included in the control group. Hemogram parameters were compared between the SAT and control groups. The diagnostic values of IG count and percentage, white blood cell (WBC) count, neutrophil count and neutrophil-leukocyte ratio (NLR) were determined and the sensitivity and specificity rates of these markers were compared.

The patients' data were retrospectively achieved from the hospital database. Blood sample data from the patient's initial visit were used for analysis before receiving any treatment. Complete blood count (CBC) parameters, calculated using an automated hematology analyzer (XN-1000 Hematology Analyzer, Sysmex Corporation, Japan), were examined.

Statistical Analysis

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 18.0 for Windows (SPSS Inc., Chicago, USA). Descriptive statistics for the data were presented as frequencies and percentages for categorical variables and as median (25^{th} percentile, 75^{th} percentile) for continuous variables. The Mann-Whitney U test was used to compare the data between the control and SAT groups, as the data did not follow a normal distribution. The chi-square test was employed to analyze categorical variables. Receiver operating characteristic (ROC) analysis and Youden's index were used to determine the area under the curve (AUC), cut-off values, sensitivity, and specificity. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 99 patients who met the inclusion criteria were included in the study. Of these, 27 patients (27.2%) were assigned to the SAT group. The mean age in the SAT group was 66 years (range: 45-87), with 20 male patients (74%) and seven female patients (26%). In the control group, consisting of 72 patients (72.8%), the mean age was 69 years (range: 50-88), with 53 male patients (73%) and 19 female patients (27%). There were no statistically significant differences between the two groups regarding age (p=0.603) and gender (p=0.962).

Revascularization was performed in patients in the SAT group with total occlusion and ischemia. Patients without total occlusion were managed medically. All surgical interventions were open procedures, and no patients underwent endovascular interventions.

Comparing the SAT and control groups, significant differences were observed in several hemogram parameters (Table 1). These included WBC (p<0.001), NEUT# (p<0.001), LYMPH# (p=0.004), EO# (p=0.035), NEUT% (p<0.001), LYMPH% (p<0.001), MONO% (p=0.013), EO% (p=0.008), IG# (p<0.001), IG% (p=0.002), NLR (p<0.001). These parameters were significantly different in patients with SAT compared to those with chronic atherosclerotic lower extremity PAD.

Table 1. Comparison of hemogram data of the groups

	Control (n=72)	SAT (n=27)	p-value
	Median (IQR)		
WBC	7.46 (5.95; 9.23)	11.71 (9.27; 14.01)	<0.001
NEUT#	4.27 (3.48; 6.48)	8.78 (6.96; 11.22)	<0.001
LYMPH#	1.87 (1.42; 2.54)	1.26 (0.95; 1.87)	0.004
EO#	0.12 (0.07; 0.18)	0.06 (0.01; 0.15)	0.035
NEUT%	60.4 (51.9; 71.1)	79.1 (65.9; 86.7)	<0.001
LYMP%	26.4 (19.2; 34.0)	12.5 (7.2; 23.8)	<0.001
MONO%	8.15 (6.80; 10.05)	7.10 (4.8; 8.4)	0.013
EO%	1.55 (0.80; 2.75)	0.6 (0.10; 1.50)	0.008
IG#	0.03 (0.02; 0.05)	0.08 (0.04; 0.13)	<0.001
IG%	0.4 (0.22; 0.60)	0.7 (0.4; 1.2)	0.002
NLR	2.14 (1.49; 3.74)	6.25 (2.6; 12.1)	<0.001

SAT: Subacute arterial thrombosis, IQR: Interquartile range, WBC: White blood cell, NEUT#: Neutrophil count, LYMPH#: Lymphocyte count, EO#: Eosinophil count, NEUT%: Neutrophil percent, LYMPH%: Lymphocyte percent, MONO%: Monocyte percent, EO%: Eosinophil percent, IG#: Immature granulocyte count, IG%: Immature granulocyte percent, NLR: Neutrophil leucocyte ratio; The data has been presented as median, interquartile range. p<0.05 is considered significant

In the ROC analysis (Table 2 and Figure 1), moderate to high predictive values were observed for the following tests: WBC (cut-off: 9.25, AUC: 0.783), NEUT# (cut-off: 6.74, AUC: 0.820), NEUT% (cut-off: 73.9, AUC: 0.801), IG# (cut-off: 0.35, AUC: 0.759), IG% (cut-off: 0.65, AUC: 0.699), NLR (cut-off: 4.76, AUC: 0.793). When immature granulocyte parameters (IG#, IG%, were added to the routine hemogram parameters in SAT patients, immature granulocytes showed 81% sensitivity and 59% specificity for the early diagnosis of SAT (Table 2).

Table 2. ROC analysis values of hemogram data in SAT group

	Cut-off	AUC	95% CI	p-value	Sensitivity %	Specificity %
WBC	9.25	0.783	0.68-0.89	0.000	77	76
NEUT#	6.74	0.820	0.72-0.91	0.000	77	77
NEUT%	73.9	0.801	0.69-0.90	0.000	70	84
IG#	0.35	0.759	0.65-0.86	0.000	81	59
IG%	0.65	0.699	0.58-0.81	0.002	55	80
NLR	4.76	0.793	0.68-0.89	0.000	70	86

SAT: Subacute arterial thrombosis, AUC: Area under the curve, CI: Confidence interval, WBC: White blood cell, NEUT#: Neutrophil count, NEUT%: Neutrophil percent, IG#: Immature granulocyte count, IG%: Immature granulocyte percent, NLR: Neutrophil leucocyte ratio, p<0.05 is considered significant

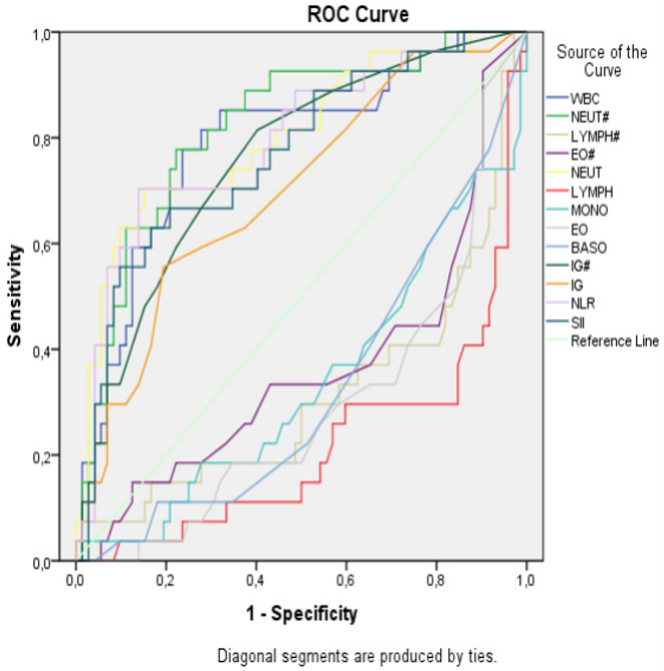

Figure. In the ROC analysis

Moderate-high predictive properties were detected in the following tests; WBC (cut off: 9.25, AUC: 0.783), NEUT# (cut off: 6.74, AUC: 0.820), NEUT% (cut off: 73.9, AUC: 0.801), IG# (cut off: 0.35, AUC: 0.759), IG% (cut off: 0.65, AUC: 0.699), NLR (cut off: 4.76, AUC: 0.793)

ROC: Receiver operating characteristic, WBC: White blood cell, AUC: Area under the curve, NEUT#: Neutrophil count, NEUT%: Neutrophil percent, IG#: Immature granulocyte count, NLR: Neutrophil-leukocyte ratio

DISCUSSION

AAO is a well-recognized vascular emergency that, if diagnosed and treated promptly, can minimize morbidity and mortality. However, diagnosing SAT can present significant challenges. SAT often develops based on chronic PAD, and its diagnosis may be delayed due to the presence of collateral circulation, which can mask the typical symptoms of acute ischemia. This delay in diagnosis and treatment leads to a higher risk of limb loss and increased mortality, underscoring the need for timely identification of SAT. Early diagnosis can improve outcomes and reduce postoperative complications and associated medical costs.[5]

Immature granulocytes (IGs) are generally absent in the peripheral blood of healthy individuals. However, under conditions such as severe inflammation, infection, or acute tissue injury, IGs can be detected in the blood as an early marker for these pathologies. The presence of IGs has been well-documented in the literature as a prognostic marker in a variety of diseases, including sepsis, acute pancreatitis, and myocardial infarction.[7-9] In inflammatory conditions, IGs are typically detected earlier than conventional markers, such as CRP or white blood cell count, making them valuable for early diagnosis.[10-12] Neutrophils, the most abundant type of granulocytes, play a central role in the body's immune response. Neutrophils are produced from hematopoietic stem cells and undergo various stages of maturation, with immature forms (promyelocytes, myelocytes, and metamyelocytes) typically confined to the bone marrow. However, immature forms are released into the peripheral blood during conditions such as infection or acute inflammation. These IGs contribute significantly to the immune response, and studies have shown that they are involved in the pathophysiology of vascular diseases, including atherosclerosis and thrombosis.[13,14] Their role in inflammation and tissue repair has been linked to both the onset and progression of thrombotic events, making them essential candidates for early diagnostic markers in arterial thrombosis.[15,16]

In our study, we found that IGs, specifically IG count (IG#) and percentage (IG%), along with routine hemogram parameters such as WBC, neutrophils, and the NLR, were significantly elevated in patients with SAT compared to those with chronic PAD alone. The ROC analysis showed that IGs and these inflammatory markers had moderate to high predictive values for diagnosing SAT. Specifically, WBC, NEUT#, NEUT%, IG#, and NLR demonstrated good diagnostic performance with AUC values ranging from 0.699 to 0.820. These findings indicate that immature granulocytes show 81% sensitivity and 59% specificity for the early diagnosis of SAT. This suggests that immature granulocytes could serve as a valuable biomarker for the early detection of SAT, thereby improving diagnostic precision and treatment outcomes. Studies in other cardiovascular contexts further support the importance of IGs in vascular diseases. For instance, Korkut et al.[17] demonstrated that IG levels could predict mortality in patients with ST-elevation myocardial infarction (STEMI), with sensitivity and specificity rates of 72% and 77%, respectively. Similarly, studies on critical COVID-19 patients revealed that IGs were positively correlated with thrombotic complications, reinforcing their role in thrombotic processes.[18] Additionally, Karahan et al.[19] found IGs to be valuable in assessing the severity of vaso-occlusive crises in sickle cell anemia. These findings align with our results, suggesting that IGs could be an essential biomarker for arterial thrombosis, including in PAD-related complications such as SAT.

Acute arterial embolism (AAE) can usually be diagnosed quickly, but SAT, particularly in patients with chronic PAD, may have a more insidious onset. This delay in diagnosis is often associated with poorer outcomes, including increased amputation rates and prolonged hospital stays.[20] Given that both SAT and AAE may present with similar clinical symptoms, a reliable early biomarker such as IGs could significantly enhance the ability to differentiate between these conditions, ensuring timely and appropriate intervention. In clinical practice, angiography remains the gold standard for

diagnosing arterial occlusions, but this invasive procedure is not always readily available in all clinical settings. Therefore, a non-invasive biomarker, like IGs, that can help predict SAT and guide decision-making could be highly beneficial.

Limitations

While our study highlights the potential role of IGs as an early diagnostic tool for SAT, it is essential to note that the study's retrospective nature is a limitation. Future prospective studies with larger sample sizes and multicenter designs are needed to validate these findings further and clarify the pathophysiology of IGs in vascular thrombosis. Additionally, while IGs show promise as a diagnostic marker, their role in guiding treatment decisions and improving long-term outcomes remains to be fully explored.

CONCLUSION

Our study suggests that immature granulocytes, exceptionally IG# and IG%, may be valuable biomarkers with high sensitivity (81%) and specificity (59%) for the early diagnosis of SAT. These tests are both simple and cost-effective. Future prospective studies are required to further elucidate the role of immature granulocytes as biomarkers in vascular thrombosis.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Kastamonu University Clinical Researches Ethics Committee (Date: 12.01.2022, Decision No: 2020-KAEK-143-138).

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.

Availability of Data and Materials

The datasets generated and/or analysed during the current study are available in the "ZENODO" repository, https://doi.org/10.5281/zenodo.7805604.

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The Prognostic Nutritional Index as a predictor of in-hospital mortality in geriatric intensive care patients

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ABSTRACT

Aims: This study aimed to evaluate the prognostic value of the Prognostic Nutritional Index (PNI) in predicting in-hospital mortality among geriatric patients admitted to the intensive care unit (ICU).

Methods: This single-center, retrospective cohort study included 337 patients aged ≥65 years who were admitted to the ICU between June and December 2024. Patients were divided into two groups based on clinical outcomes: survivors and non-survivors. Demographic data, comorbidities, clinical outcomes, and laboratory values including serum albumin and lymphocyte count were analyzed. PNI was calculated as: PNI=[10×serum albumin (g/dl)]+[0.005×total lymphocyte count (/mm^3)]. Statistical analyses included univariate and multivariate logistic regression and receiver operating characteristic (ROC) curve analysis.

Results: Among 337 patients, 195 (57.9%) died during ICU stay. PNI scores were significantly lower in non-survivors (p=0.001), with an optimal cut-off value of ≤29.8 (sensitivity: 43.1%, specificity: 90.1%). The area under the ROC curve for PNI was 0.661, indicating limited discriminatory power. Multivariate analysis identified prolonged ICU stay (OR=1.052), elevated WBC (OR=1.044), hypoalbuminemia (OR=2.283), increased urea (OR=1.006), lactate (OR=1.144), sepsis (OR=2.362), and stroke (OR=2.746) as independent predictors of mortality (p<0.05).

Conclusion: Low PNI scores are associated with in-hospital mortality in geriatric ICU patients. However, given its low sensitivity and moderate AUC, PNI should not be used as a standalone predictor. Instead, as a simple and cost-effective biomarker, it may serve as a supportive tool alongside other clinical parameters for early risk stratification in geriatric intensive care settings.

Keywords: Prognostic Nutritional Index, malnutrition, geriatric patients, intensive care unit, mortality, albumin, lymphocyte count

INTRODUCTION

With people around the world living longer than ever before, the global population is aging rapidly. Geriatric individuals are at high risk for nutritional deficiencies and malnutrition due to factors such as reduced functional capacity, multiple comorbidities, and polypharmacy.[1] Malnutrition has been associated with increased risk of complications, prolonged hospital stays, greater need for intensive care, and higher rates of infection, ultimately leading to both in-hospital and post-discharge mortality.[2,3] While adequate nutritional status can accelerate recovery, reduce the risk of infection, and improve the prognosis of critically ill patients, malnutrition adversely affects this process by increasing the rate of complications and delaying recovery.[4]

The Prognostic Nutritional Index (PNI) is a scoring system that reflects an individual's immunological, inflammatory, and nutritional status based on serum albumin levels and total lymphocyte count.[5] Both parameters are key indicators of overall health and have been recognized as prognostic factors in various clinical conditions. Total lymphocyte count serves as a valuable marker of immune function, and low levels may indicate immunodeficiency. Previous studies have demonstrated that low lymphocyte counts and hypoalbuminemia are associated with increased mortality in many chronic diseases.[6,7] In critically ill patients, hypoalbuminemia may arise due to inadequate nutritional intake, liver dysfunction, protein loss, and systemic inflammatory responses.[8] PNI has been shown to be an important prognostic indicator for predicting outcomes and mortality in various clinical settings, including malignancies, infections, and cardiovascular diseases.[9-11]

However, although the PNI is a practical, easily calculable, and low-cost assessment tool, its adequacy in predicting in-hospital mortality as a standalone marker in geriatric ICU patients remains debatable. A recent study among geriatric ICU patients demonstrated that lower PNI scores were significantly associated with increased mortality, yet emphasized that despite its clinical practicality, the prognostic power of PNI may be limited.[12] In contrast, another study

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involving patients with acute respiratory failure reported that the modified nutrition risk in critically ill (mNUTRIC) score provided greater sensitivity and stronger prognostic accuracy compared to both PNI and NRS-2002.[13] Nevertheless, the ability of PNI to be calculated using routinely available biochemical parameters, along with its speed and ease of use, continues to offer a considerable advantage, particularly in healthcare settings with limited resources.

Therefore, the aim of this study was to evaluate the prognostic value of PNI in predicting in-hospital mortality among geriatric ICU patients. We hypothesized that lower PNI scores would be associated with increased mortality, reflecting the combined impact of inflammation and malnutrition in this vulnerable patient population.

METHODS

Study Design

This study was designed as a single-center, retrospective cohort analysis. The study protocol was approved by the Kartal Koşuyolu High Specialization Training and Research Hospital Clinical Researches Ethics Committee (Date: 07.01.2025, Decision No: 2025/01/999). The study was conducted in accordance with the principles outlined in the Declaration of Helsinki.

Study Population

The medical records of patients aged 65 years and older who were admitted to the ICU of Tuzla State Hospital between June 2024 and December 2024 were retrospectively reviewed.

Inclusion criteria: Age ≥65 years, admission to the ICU, and availability of serum albumin and total lymphocyte count measurements taken within the first 24 hours of ICU admission.

Exclusion criteria: Absence of albumin or lymphocyte values at ICU admission, missing data in medical records, admission due to trauma or postoperative reasons, and patients with hematological disorders or receiving immunosuppressive therapy.

Study Protocol

Patients were categorized into two groups: those who were discharged and those who died in the ICU (exitus). All data were compared and analyzed between these two groups. The included patients were evaluated based on the following parameters:

- **Baseline demographic data:** Age, sex, and comorbidities
- **Clinical data:** Length of ICU stay, sepsis, and mortality
- **Laboratory parameters at ICU admission:** White blood cell, hemoglobin, neutrophil, lymphocyte, monocyte, eosinophil, platelet, mean platelet volume, red cell distribution width, C-reactive protein, albumin, calcium, sodium, chloride, magnesium, potassium, urea, creatinine, and lactate

The PNI was calculated using serum albumin levels and total lymphocyte counts.

The formula for PNI calculation was as follows;

PNI=[10×serum albumin (g/dl)]+[0.005×total lymphocyte count (/mm^3)]

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics version 22. The Kolmogorov-Smirnov test was used to assess the normality of distribution for continuous variables. Descriptive statistical methods were applied to summarize the data, including minimum, maximum, mean, standard deviation, median, interquartile range (IQR), and frequency.

For the comparison of quantitative variables, the student's T test was used when the data followed a normal distribution, while the Mann-Whitney U test was applied for non-normally distributed variables. For the analysis of categorical variables, the Chi-square test, Fisher's exact Chi-square test, and continuity correction (Yates' correction) were utilized as appropriate.

To identify independent predictors, a multivariate logistic regression analysis was performed. The optimal cut-off point was determined based on receiver operating characteristic (ROC) curve analysis. A p-value <0.05 was considered statistically significant.

RESULTS

A total of 337 geriatric patients (aged 65-98) were included. Of these, 195 (57.9%) died during ICU stay (exitus), and 142 (42.1%) were discharged.

No significant differences were observed between groups in age or gender (p>0.05). However, ICU stay duration, and the incidence of sepsis (76.4%), pneumonia (45.6%), and stroke (27.2%) were significantly higher among exitus group (p<0.05). No significant association was found between mortality and other comorbidities (p>0.05) (**Table 1**).

Laboratory parameters including white blood cell count, neutrophils, mean platelet volume, red cell distribution width, C-reactive protein, procalcitonin, urea, creatinine, and lactate were significantly higher in the exitus group compared to the discharged (p<0.05). Conversely, levels of hemoglobin, lymphocyte, eosinophil, albumin, and calcium were significantly lower in the exitus group (p<0.05) (**Table 2**).

PNI scores were significantly lower in the exitus group (p=0.001) (**Figure 1**).

ROC analysis for PNI revealed an AUC of 0.661 (SE: 0.029; 95% CI: 0.608-0.711; p=0.001). The optimal PNI cut-off was ≤29.8, yielding 43.1% sensitivity and 90.1% specificity (**Figure 2**).

In the regression model (Nagelkerke R^2=0.347; accuracy=76.9%), significant predictors of mortality included ICU stay (OR=1.052), elevated white blood cell (OR=1.044), low albumin (OR=2.283), high urea (OR=1.006), elevated lactate (OR=1.144), sepsis (OR=2.362), and stroke (OR=2.746) (p<0.05) (**Table 3**).

Table 1. Comparative analysis based on mortality outcomes			
	Discharged (n=142)	Exitus (n=195)	p
Age (year)	79.99±8.67	81.49±7.91	[1]0.106
Duration of ICU (days)	5.5 (3-11.25)	12 (5-25)	[2]0.001*
Gender, n (%)			
Male	61 (43%)	93 (47.7%)	[3]0.389
Female	81 (57%)	102 (52.3%)	
Sepsis	72 (50.7%)	149 (76.4%)	[3]0.001*
Mechanical ventilation	62 (43.6%)	101(51.8%)	[3]0.172
Comorbidity, n (%)			
Pneumonia	49 (34.5%)	89 (45.6%)	[3]0.040*
Hypertension	56 (39.4%)	76 (39%)	[3]0.932
Stroke	21 (14.8%)	53 (27.2%)	[3]0.007*
Alzheimer	27 (19%)	43 (22.1%)	[3]0.497
Diabetes mellitus	26 (18.3%)	39 (20%)	[3]0.698
COPD	34 (23.9%)	28 (14.4%)	[3]0.025*
Congestive heart failure	20 (14.1%)	36 (18.5%)	[3]0.286
Coronary artery disease	14 (9.9%)	12 (6.2%)	[4]0.293
Chronic renal failure	7 (4.9%)	10 (5.1%)	[4]1.000
Malignancy	6 (4.2%)	7 (3.6%)	[4]0.990
Acute renal failure	4 (2.8%)	7 (3.6%)	[5]0.766
Parkinson	4 (2.8%)	6 (3.1%)	[5]1.000
Epilepsy	4 (2.8%)	5 (2.6%)	[5]1.000
Atrial fibrillation	4 (2.8%)	5 (2.6%)	[5]1.000
Pulmonery odema	6 (4.2%)	3 (1.5%)	[5]0.175
Pulmonary embolism	1 (0.7%)	3 (1.5%)	[5]0.641

Normally distributed variables are presented as mean±standard deviation (SD), while non-normally distributed variables are expressed as median (interquartile range), [1]Student T test, [2]Mann-Whitney U test, [3]Chi-square test, [4]Continuity (yates) correction, [5]Fisher's exact test, *p<0.05, ICU: Intensive care unit, COPD: Chronic obstructive pulmonary disease

Table 2. Comparison of biochemical parameters between groups			
	Discharged median (IQR)	Exitus median (IQR)	p
White blood cell (10^3/mm^3)	10.76 (7.9-14)	13.03 (9.7-18)	0.001*
Hemoglobin (g/dl)	10.9 (8.9-12.3)	9.9 (8.6-11.5)	0.008*
Neutrophil (10^3/mm^3)	8.96 (6-11.7)	11.14 (7.6-15.7)	0.001*
Lymphocyte (10^3/mm^3)	975 (587.5-1425)	810 (510-1210)	0.024*
Monocyte (10^3/mm^3)	0.5 (0.3-0.7)	0.5 (0.3-0.7)	0.836
Eosinophil (10^3/mm^3)	0.04 (0-0.1)	0.01 (0-0.1)	0.001*
Platelet (10^3/mm^3)	225.5 (153.3-287)	210 (136-299)	0.432
Mean platelet volume (fL)	11 (10-12)	11.5 (10.4-12.4)	0.010*
RDW (%)	50 (46.8-54.5)	51.9 (48-58.3)	0.007*
CRP (mg/L)	86.3 (23.4-138)	138.44 (66.2-211)	0.001*
Procalcitonin (ng/ml)	0.38 (0.1-1.3)	1.36 (0.3-7.7)	0.001*
Albumin (g/dl)	3 (2.7-3.3)	2.6 (2.2-3)	0.001*
Calcium (mg/dl)	8.26 (7.8-8.6)	7.91 (7.4-8.5)	0.001*
Sodium (mmol/L)	140 (137-144)	141 (137-146)	0.543
Chloride (mmol/L)	102 (98-108)	104 (98-109)	0.288
Magnesium (mg/dl)	1.94 (1.7-2.2)	1.97 (1.8-2.2)	0.070
Potassium (mmol/L)	4.05 (3.6-4.5)	3.98 (3.5-4.7)	0.870
Urea (mg/dl)	60 (38-92.3)	85.2 (56.6-127.6)	0.001*
Creatinine (mg/dl)	0.98 (0.7-1.4)	1.28 (0.8-2)	0.002*
Lactate (mmol/L)	1.9 (1.3-2.9)	2.5 (1.7-4.2)	0.001*
PNI	34.9 (31.8-38.5)	31.9 (26-37)	0.001*

Mann-Whitney U test, *p<0.05, IQR: Interquartile range, RDW: Red cell distribution width, CRP: C-reactive protein, PNI: Prognostic Nutritional Index

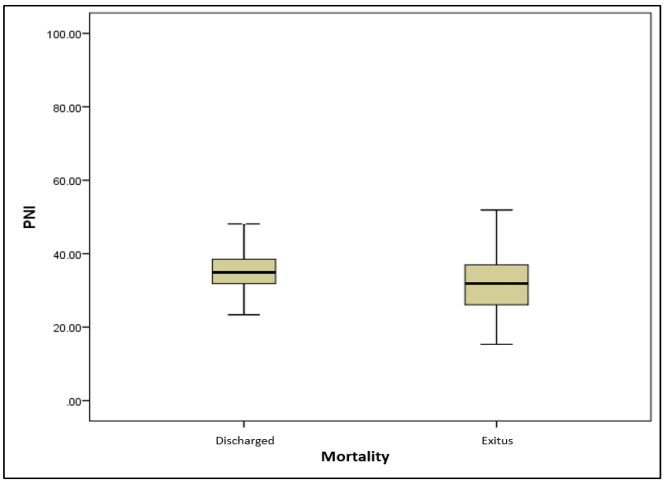

Figure 1. Box plot of PNI values according to mortality status
PNI: Prognostic Nutritional Index

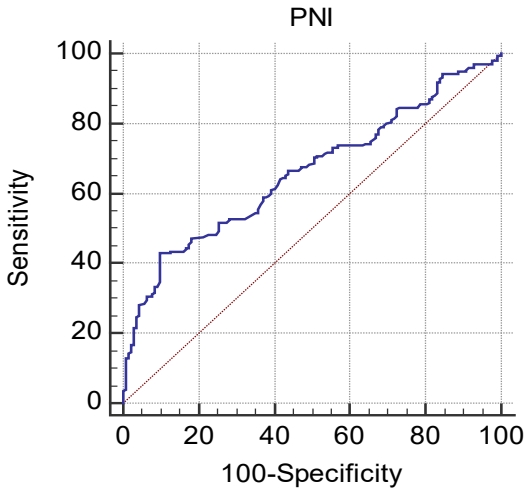

Figure 2. ROC curve of PNI for predicting in-hospital mortality
ROC: Receiver operating characteristic, PNI: Prognostic Nutritional Index

Table 3. Logistic regression analysis of independent predictors of in-hospital mortality				
		95% CI		
Step 13	**OR**	**Lower**	**Upper**	**p**
Duration of ICU	1.052	1.031	1.074	0.001*
White blood cell	1.044	1.000	1.090	0.048*
Albumin	2.283	1.385	3.774	0.001*
Urea	1.006	1.001	1.011	0.018*
Lactate	1.144	1.004	1.303	0.044*
Sepsis	2.362	1.337	4.173	0.003*
Stroke	2.746	1.41	5.349	0.003*

CI: Confidence interval, OR: Odds ratio, ICU: Intensive care unit

DISCUSSION

In this study, we investigated the prognostic value of the PNI in predicting in-hospital mortality among geriatric patients admitted to the ICU. Our findings demonstrated that patients who died had significantly lower PNI scores, with a determined cut-off value of 29.8. These results suggest that PNI may serve as a valuable prognostic biomarker in critically ill elderly patients. However, the relatively low sensitivity (43.1%)

and moderate AUC value (0.661) indicate that PNI may have limited discriminatory power when used alone and should be interpreted in conjunction with other clinical indicators.

Geriatric patients in the ICU experience high mortality rates due to multiple comorbidities, reduced physiological reserves, and increased vulnerability. Although commonly used scoring systems such as SOFA and APACHE II are comprehensive and reliable in mortality prediction, their complexity and reliance on numerous variables may limit their routine application in clinical practice.[14,15] In contrast, PNI relies solely on two laboratory parameters (serum albumin and total lymphocyte count) making it a simple and practical tool. Malnutrition and immunosuppression, which are prevalent in the elderly population, further enhance the clinical relevance of PNI.

PNI was initially developed to assess surgical risk and perioperative immunonutritional status in patients undergoing gastrointestinal surgery.[16] Since then, it has been shown to be associated with prognosis in a wide range of clinical conditions, including cardiovascular diseases, various cancers, and infections.[5,17] The literature contains similar findings in different patient populations. Keskin et al.[18] reported that PNI was an independent predictor of mortality in patients undergoing coronary artery bypass surgery. Hayashi et al.[17] found that higher PNI scores were associated with shorter durations of mechanical ventilation, shorter ICU stays, and lower rates of infection. In oncology, Ofluoglu et al.[19] demonstrated that PNI was a valuable biomarker for predicting surgical complications in patients with locally advanced rectal cancer and that preoperative nutritional optimization could improve treatment outcomes. In our study, the association between low PNI values and mortality can be interpreted as a reflection of both malnutrition and immunosuppression. Particularly, hypoalbuminemia is a strong indicator of nutritional deficiency and systemic inflammation,[20,21] while a reduced lymphocyte count suggests compromised immune function and a suppressed inflammatory response.[22] Consistent with these findings, our regression analysis revealed that low albumin levels increased the risk of mortality by 2.28 times.

The prognostic value of PNI has also been highlighted in geriatric orthopedic surgery patients. Taşkın et al.[23] reported significantly lower preoperative PNI scores in patients with femoral fractures who died postoperatively, with a cut-off value of 29 and a six-month mortality rate of 22.4%. Arslan et al.[24] also found lower PNI levels in the mortality group, although it was not identified as an independent predictor. These findings underscore the relationship between PNI, nutritional status, and immune function in elderly patients. Similarly, our study found that PNI scores were significantly lower in the exitus group.

Recent literature supports the role of PNI as a robust nutritional indicator in elderly ICU patients. Akgün et al.[12] reported that among elderly individuals with acute decompensated heart failure in the coronary ICU, low PNI scores were associated with increased mortality, longer ICU stay, and higher 12-month rehospitalization rates. Moreover, in a 2025 study by Küçük et al.,[13] mNUTRIC and NRS-2002 were compared in ICU patients admitted for respiratory failure. The mNUTRIC score, which incorporates disease severity and length of prior hospitalization, showed stronger predictive capacity for both short- and long-term mortality compared to traditional tools like NRS-2002. The authors emphasized that combining mNUTRIC with clinical markers could enhance risk stratification. Although our study did not compare mNUTRIC and PNI directly, our findings underscore the importance of multimodal nutritional risk assessment in ICU patients. Given the relatively low sensitivity and AUC of PNI, it is advisable to use it as a supportive measure alongside more comprehensive tools such as mNUTRIC.

The cut-off value for PNI identified in our study (29.8) was lower than those reported in some previous studies. This difference may be attributed to the characteristics of our patient population, which consisted of very elderly individuals with multiple comorbidities and more severe clinical conditions requiring intensive care. These findings suggest that PNI thresholds may vary depending on the clinical setting and patient demographics.

Additionally, among other key findings, rates of sepsis (56.1%), pneumonia (50.3%), and stroke (45.9%) were markedly higher in patients who died. Logistic regression analysis identified sepsis and stroke as independent risk factors for mortality, increasing the risk by 2.36 and 2.74 times, respectively. These results highlight the significant impact of infectious and neurological complications on mortality, particularly in the geriatric population.

Limitations

This study has several limitations. First, the retrospective and single-center design may limit generalizability. Second, we evaluated only in-hospital mortality; long-term outcomes such as functional recovery or quality of life were not assessed. Third, we did not conduct a direct comparison between PNI and other tools such as mNUTRIC in this dataset. Nevertheless, our findings contribute to the growing body of evidence supporting the role of nutritional indices in ICU prognostication and emphasize the clinical utility of PNI as part of a comprehensive, multimodal assessment strategy for elderly critically ill patients.

CONCLUSION

In conclusion, this study demonstrated that low PNI values are significantly associated with in-hospital mortality in geriatric intensive care patients. As a simple and cost-effective parameter, PNI may be utilized to support early risk stratification in elderly patients admitted to the ICU. However, given its high specificity but limited sensitivity, PNI should not be used as a standalone prognostic tool. Instead, it may serve as a useful adjunct to clinical assessment or more comprehensive scoring systems to improve the accuracy of mortality prediction and to guide timely and individualized treatment strategies.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Kartal Koşuyolu High Specialization Training and Research Hospital Clinical Researches Ethics Committee (Date: 07.01.2025, Decision No: 2025/01/999).

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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Stress levels and influencing factors in pediatric nursing

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ABSTRACT

Aims: Nurses are in frontline interaction with patients/healthy individuals and their relatives and other healthcare team members due to their professional roles. The impact of the pediatric patient has been emphasized as the most stressful factor among nurses, and critical events have been shown to increase stress significantly. In our study, we aimed to determine the stress factors, coping styles, and burnout levels of pediatric nurses working in different departments in Balıkesir Atatürk City Hospital, which is a tertiary hospital located in Balıkesir province and where referral acceptance and patient density are high.

Methods: Between November 2024 and December 2024, the questionnaire was distributed face-to-face to volunteer participants after informing them about the survey. No sample selection was made in the study. The questionnaire was distributed to 110 people due to employees who were on leave on the dates of the study and who stated that they did not want to participate in the study. The statistics were realized with the data obtained from 96 people who completed the questionnaire properly. An introductory form including demographic data, the Maslach Burnout Inventory (MBI), and the Perceived Stress Scale (PSS) questionnaire was applied.

Results: 90.6% of the participants were female. The mean age was 33.2±8.7 years. 56% declared that they were married as their marital status. Of the volunteers included in the study, 47.9% had no children. The mean MB-emotional, MB-desensitization and MB-personal failure subgroups of the MBI were 21.7±7.4, 11.6±6.25 and 25.9±6.9, respectively. PSS was evaluated as 44.3±3.6. When the sub-dimensions of the MBI were examined, no significant results were found according to age and gender, and the results shown lead to the conclusion that there is burnout in nurses. While there was no difference between the number of children and burnout in the MB-Emotional Scale, MB-desensitization was found to be significantly higher in those who did not have children ($p<0.05$). MB-personal failure was not found to be significant between having children. Again, there was no statistical difference between the subgroups of the scales and marital status ($p>0.05$).

Conclusion: When the department where the nurses worked and the scales were compared, it was found that the nurses working in the neonatal intensive care unit were statistically significant in terms of emotional burnout, while the desensitization subscale did not differ between the departments, and the nurses working in the pediatric emergency department were statistically significant in terms of personal failure. No significant difference was found between the departments in terms of the PSS. Nurses working in pediatric departments, especially in neonatal intensive care and pediatric emergency departments, are more at risk for emotional burnout and personal failure. It is thought that taking necessary precautions in the early period of burnout may contribute positively to individuals.

Keywords: Stress level, nurse, pediatric

INTRODUCTION

Emergency departments are units established to meet the needs of patients, especially in life-threatening situations, and where necessary services are provided. The main aim of the emergency department team is to provide safe, adequate, and rapid care services. Critical patient care, and rapid and effective assessment lead to increased stress levels in nurses working in the emergency department. Stress factor is considered to be one of the main causes of turnover, especially in the field of nursing, and plays a very important role in 50% of turnover, as well as causing decreased performance, absenteeism, and unrest in the work environment.[1]

The patient's health status and proximity to death are patient-centered factors that affect the stress level in nurses the most. In this sense, cardiovascular, gynecologic, and pediatric emergencies are the most challenging situations, and musculoskeletal trauma, respiratory distress, and cardiac problems stand out among the events involving children.[2] Stress level is also associated with a decrease in the number of patients. Identification with the patient, lack of experience, reactions from family members, and the knowledge that the situation may worsen at any time increase the risk. In the literature, the impact of the pediatric patient was emphasized

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as the most stressful factor among nurses, and it was revealed that critical events increased stress significantly.[3-7]

Burnout rates of the repair conducted among healthcare professionals in intensive care units were found to be between 40-70%.[8] In one study, the working ward with the highest stress load was the emergency department. The nature and working environment of different departments may affect the pressure and organizational support of nursing staff.[9] In terms of sudden public health emergencies, emergency medical personnel working at the frontline of hospitals face higher occupational exposure risks, excessive workloads and severe psychological effects.

Pediatric nurses are more susceptible to workplace stress and mental health problems than nurses working in other services due to reasons such as working style and environment, family expectations, and social concerns related to the treatment of pediatric patients.[10] Studies have shown that the stress experienced by nurses is related to their length of service.[11] However, very few articles have investigated stress factors among pediatric nurses with different lengths of service. In our study, we aimed to determine the stress factors, coping styles, and burnout levels of pediatric nurses working in different departments at Balıkesir Atatürk City Hospital, a tertiary hospital located in Balıkesir province with high referral acceptance and patient density. We aimed to investigate the stress level and problems encountered by asking the Perceived Stress Scale (PSS) and Maslak Burnout Scale (MBS) questions to pediatric nurses working in different units.

METHODS

The study was carried out with the permission of Balıkesir Atatürk City Hospital Scientific Researches Ethics Committee (Date: 28.11.2024, Decision No: 2024/11/63). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

The population of the study consisted of nurses working in various units of the Department of Pediatrics at Balıkesir Atatürk City Hospital. A total of 172 nurses work in the Department of Pediatrics at Balıkesir Atatürk City Hospital, of which 74 nurses work in Neonatal Intensive Care, 30 nurses work in Pediatric Intensive Care, 10 nurses work in Pediatrics Service, 39 nurses work in Pediatric Emergency Service, 14 nurses work in the baby room, and 5 nurses work in outpatient clinics. In this hospital, the management and supervision of nursing services are carried out by the hospital chief nurse. Nurses work in two shifts, 08:00-16:00 and 16:00-08:00. In the emergency department, the working system is 16:00-08:00 hours on weekdays and 24 hours on weekends. Approximately 3 nurses are working in all wards during the day shift and 1 or 2 nurses are working on shifts, depending on the ward. The criteria for participation in the study were 1) being a nurse working in any of the pediatric health and diseases units, 2) Agree to participate in the study 3) Working in the same unit for at least 1 month.

The data collection tool was distributed face-to-face between November 2024 and December 2024 after informing the volunteer participants about the questionnaire. The questionnaires were distributed to participants individually, with instructions to complete them on their own and submit them personally within a few days. No sample selection was made in the study. The questionnaire was distributed to 110 people due to employees who were on leave on the dates of the study and who stated that they did not want to participate in the study. Statistics were realized with the data obtained from 96 respondents who completed the questionnaire properly.

The participants were asked a questionnaire consisting of an introductory form and scales including age, gender, marital status, race, number of children, educational status, unit of employment, and how long they have been working in the same unit.

Maslach Burnout Inventory (MBI): It was developed by Maslach and Jackson,[12] and its validity and reliability study in Turkiye was conducted by Olcay[13] and Ergin.[14] This scale consists of 22 Likert-type questions. For each item, one of five options (never, very rarely, sometimes, most of the time, or always) should be selected and answered. In addition, the scale has three dimensions; emotional burnout (EB, 9 items), desensitization (D, 5 items) and personal failure (PF, 8 items). For each sub-dimension, the scores of emotional burnouts (1, 2, 3, 6, 8, 13, 14, 16, 20), desensitization (5, 10, 11, 15, 22) and personal failure (4, 7, 9, 12, 17, 18, 19) items are summed.

When evaluating the MBI, the minimum score that can be obtained from the emotional burnout dimension is 8, and the maximum score is 40. While the minimum score in the desensitization dimension is 6, the maximum score is 30. In the dimension of decreased sense of personal accomplishment, the minimum score is 8, and the maximum score is 40. High scores in emotional burnout and desensitization and low scores in decreased sense of personal accomplishment are accepted as indicators of burnout.

Emotional burnout is used to express the excessive stress and emotional overload of individuals in business life. Desensitization deals with the relationship of burnout with other people. Employees who experience desensitization experience a number of physical and mental problems, such as extreme fatigue, restlessness, irritability, and depression. After a while, the person in this situation passes to the last stage and experiences a decrease in personal success.

The PSS was developed by Cohen et al.[15] consisting of a total of 14 items, the PSS was developed to measure how stressful the events in an individual's life are perceived to be. Participants rate each question between 0 and 4 points. It is evaluated on a 5-point Likert-Type Scale ranging from "never (0)," almost never (1), occasionally (2), often (3), and very often (4)." The 7 items with positive statements are reverse scored. The scores of the PSS-14 vary between 0 and 56, with an increase in score indicating an increase in stress. Reliability and validity analyses were performed, and it was found that the scale was positively correlated with individual life events and depression and negatively correlated with personal satisfaction and perceived social support scores.[16]

The Turkish adaptation of the PSS was carried out by Eskin et al.[16] The results of the adaptation study confirmed that the scale maintains its validity and reliability in Turkish samples,

with acceptable internal consistency coefficients (Cronbach's alpha values) and factor structures similar to the original version.

In the evaluation of these inventory scores; emotional burnout; 10-16 points range (low burnout), 17-26 points range (normal burnout), 27 points and above (high burnout). Desensitization was determined as the 0-6-point range (low burnout), the 7-12-point range (normal burnout), and 13 points and above (high burnout). Personal failure was determined as 39 points and above (low burnout), 32-38 points (normal burnout), and 0-31 points (high burnout).[17]

Statistical Analysis

Data analysis of the data was performed with the SPSS Statistics 22 Program in a computer environment. Frequency (n), percentage (%), mean, and standard deviation were used as descriptive statistics. "Independent T test" was used for comparisons between two groups, and 'one-way analysis of variance' was used for comparisons of three or more groups.

RESULTS

90.6% of the participants were female. The mean age was 33.2 ± 8.7 years. 56% declared that they were married as their marital status. Of the volunteers included in the study, 47.9% had no children. The educational status was 40 high school graduates and 56 had bachelor's and master's degrees (Table 1).

Among the volunteers, 31 were working in neonatal intensive care, 15 in pediatric intensive care, 26 in pediatric emergency department, 4 in pediatric polyclinic and 9 in pediatric ward. The duration of employment in the same department was mostly between 1-3 years (42%). The questions "Would you prefer the health sector again?" and "Are you satisfied with your job?" were answered "no" with a high rate (Table 1).

The mean MB-emotional, MB-desensitization and MB-personal failure subgroups of MBI were 21.7±7.4, 11.6±6.25 and 25.9±6.9, respectively. The PSS was evaluated as 44.3±3.6 (Table 2).

When the sub-dimensions of the MBI were examined, no significant results were found according to age and gender, and the results shown lead to the conclusion that there is burnout in nurses. While there was no difference between the number of children and MB-emotional burnout, MB-desensitization was found to be significantly higher in those who did not have children ($p<0.05$). MB-personal failure was not found to be significant between having children. There was no statistical difference between the subgroups of the scales and marital status ($p>0.05$) (Table 3-6).

When the department where the nurses worked and the scales were compared, it was found that the nurses working in the neonatal intensive care unit were statistically significant in terms of emotional burnout, while the desensitization subscale did not differ between the departments, and the nurses working in the pediatric emergency department were statistically significant in terms of personal failure. No significant difference was found between the departments in terms of the PSS.

Table 1. Demographic characteristics of the participants

Variables		n (%)
Gender	Female	87 (90.6)
	Male	9 (9.4)
Age	18-25 years	20 (20.8)
	25-35 years	41 (42.7)
	Over 35 years	35 (36.5)
Nationality	Turkish	92 (95.8)
	Other	4 (4.2)
Marital status	Single	40 (41.7)
	Married	56 (58.3)
Number of children	No	46 (47.9)
	1 child	40 (42.7)
	≥2 children	10 (10.4)
Education status	High school	40 (41.7)
	Bachelor's degree	41 (42.7)
	Master's degree	15 (15.6)
Working duration in the same department	<6 months	13 (13.5)
	6-12 months	19 (19.8)
	1-3 years	42 (43.8)
	3-5 years	13 (13.5)
	More than 5 years	8 (8.3)
Working unit	Pediatric inpatient service	9 (9.4)
	Pediatric intensive care	15 (15.4)
	Neonatal intensive care	31 (32.3)
	Pediatric emergency service	26 (27.1)
	Child polyclinic	4 (4.2)
	Nursery	11 (11.5)
Would you prefer the healthcare sector again?	Yes	23 (23.9)
	No	62 (64.5)
	Undecided	9 (9.3)
Are you satisfied with your job?	Yes	14 (14.5)
	No	71 (73.9)
	Undecided	11 (11.4)

Table 2. Mean scores of the scales according to the answers given by the participants

Maslach burnout inventory subscales	
MB-emotional	21.7±7.4
MB-desensitization	11.6±6.25
MB-personal failure	25.9±6.9
Perceived Stress Scale	44.3±3.6

Table 3. Comparison of the subgroups of the scales and gender ($p<0.05$)

	Female	Male	p
MB-emotional	21.7±7.3	21.9±9.3	0.1
MB-desensitization	11.4±6.2	13.7±6.3	0.8
MB-personal failure	25.8±7	26.4±6.6	0.9
Perceived Stress Scale	44.3±3.6	44.2±4.4	0.4

MB: Maslach burnout

Table 4. Comparison of the subgroups of the scales and age groups (p<0.05)

	Age 18-25	Age 25-35	Over 35	p
MB-emotional	19.5±7.9	21.3±7.4	23.4±7	0.15
MB-desensitization	9±5	12.4±6.2	12.2±6.09	0.1
MB-personal failure	24.7±6.9	26.5±7.13	25.9±6.8	0.6
Perceived Stress Scale	42.3±3.4	43.1±2.8	41.2±3.9	0.2

MB: Maslach burnout

Table 5. Comparison of the subgroups of the scales with the number of children (p<0.05)

	No children	1 child	2 or more children	p
MB-emotional	20.8±8.65	22.8±6.3	21.2±5.5	0.4
MB-desensitization	9.6±6.8	13.5±5.3	13.3±4	0.01*
MB-personal failure	26.5±8	25.9±6	23±4.1	0.6
Perceived Stress Scale	41.6±4.2	42.1±3.8	41.5±3.8	0,2

MB: Maslach burnout

There is a linear relationship between MB-emotional and MB-depersonalization burnout levels of the participants, while an inverse linear relationship was found between MB-emotional and MB-personal failure. It shows that nurses who start to burn out emotionally will also cause burnout in terms of desensitization (Figure).

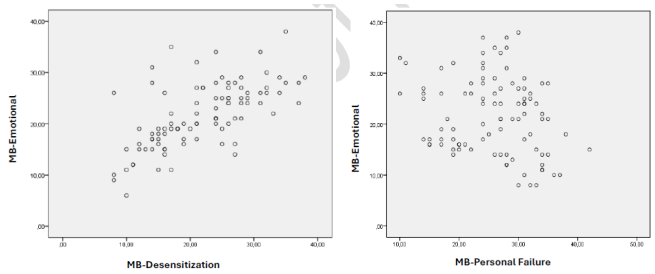

Figure. The relationship between emotional involvement of MB-depersonalization and MB-personal failure

MB: Maslach burnout

DISCUSSION

Healthcare workers experience stress and burnout due to various factors in their workplaces. Being in constant contact with people and being exposed to life-threatening situations increases this risk. The fact that nurses are in contact with highly risky pediatric patients and their parents increases this risk.

Social life and character traits of the individual are very important among the causes of burnout. Individual factors have positive and negative effects on burnout. These factors can be listed as gender, education, marital status, age, personal stress, occupational satisfaction, personal expectation, performance, motivation status, personality and personal resilience, experience, limitations, and stress. In addition, living conditions at the workplace and the relationship with coworkers are also effective.[18]

In our study, no difference was found between male and female genders in terms of burnout, whereas Balcı et al.[19] conducted a study on nurses and discovered that male gender showed more burnout. In another article, similar to our study, no difference was found between genders.[20]

Although there was no difference in terms of marital status, Maslach and Jackson[12] stated that married people can solve problems better and show better resistance to problems than single people. This may reduce the burnout level of the person. However, from another perspective, the increase in stress factors due to the increase in family responsibilities of married individuals may increase intolerance in the workplace.

Young age is one of the accepted risk factors for burnout. In our study, there was no relationship between age and sub-dimensions of burnout level (p>0.05). In a similar study conducted on intensive care nurses, no statistical difference was shown in relation to age, but a statistical difference was demonstrated in terms of the desensitization subscale in the single group.[21] In the study conducted by Karlıdağ et al.[22] with physicians, similar to our study, no significant difference was shown with marital status.

In a study conducted with nurses working in a state hospital in Denizli province, a relationship was shown between burnout level and years of experience, and an inverse relationship was shown between years of experience and burnout.[23] In our study, no statistical difference was found between years of work and experience and scale sub-dimensions. However, in a different study, it was found that working for more than 10 years was a higher risk factor among physicians.[24] This was attributed to the inability to realize their ideals with advancing years of life and being in social and economic depression.

In a study, it was found that the physical activity levels of nurses working, especially in the ward, were low. In addition, it was concluded that the quality-of-life levels of nurses were low and burnout levels were high.[25] Reduced physical activity leads to shift work, and snacking behavior leads to obesity.[26]

In studies on burnout, it is emphasized that negative conditions in the workplace are a greater factor rather than family characteristics.[27] In a burnout study conducted with nurses in a tertiary hospital in China, it was revealed that working the night shift was a bigger problem in terms of

Table 6. The relationship between the subgroups of the scales and the departments in which the nurses work

	Polyclinic	Neonatal intensive care unit	Pediatric intensive care unit	Pediatric service	Pediatric emergency service	Nursery	p
MB-emotional	23.5±4.1	24.1±6.8	24.6±7.1	21.7±6.8	17.8±8.18	19.2±5.7	0.01*
MB-desensitization	14±7.3	12.6±5.3	15.5±6.3	11.7±4.1	18.46±7	10.09±4.1	0.1
MB-personal failure	24±9.9	23.8±6.7	25.2±5.2	20±6.1	29.9±6.6	28.9±3.8	<0.01*
Perceived Stress Scale	44.5±2.08	44.3±3.7	44±3.3	45.7±4.8	44.2±3.7	43.9±3.7	0.9

MB: Maslach burnout

occupational burnout.[28] In this study, it was also stated that being younger than 30 years of age was also risky.

Night shifts and long working hours are among the main factors that negatively affect both the physical and psychological health of nurses, thereby increasing their levels of burnout.[29] Numerous studies in the literature report that nurses experience higher burnout levels due to problems associated with shift work systems. In a study conducted by Sagherian et al.,[30] it was found that nurses who constantly work night shifts have significantly higher levels of emotional exhaustion and depersonalization compared to their colleagues who work only during the day. This situation is explained by factors such as disrupted sleep patterns, chronic fatigue, changes in biological rhythm, and social isolation. Similarly, Geurts et al.[31] emphasized that long working hours and consecutive shifts in nurses restrict resting time, which undermines psychological well-being and paves the way for burnout. Additionally, Karhula et al.[32] stated that nurses working in irregular shift systems experience lower job satisfaction, which directly contributes to the development of burnout syndrome.

Nurses' difficulties in maintaining work-life balance, distancing themselves from social life, and insufficient rest lead to decreased professional motivation and negatively affect the quality of patient care. Therefore, improving working conditions is of great importance in protecting nurses from burnout.[33]

When the burnout scores of nurses based on their current clinical departments are examined, it is observed that those working in neonatal intensive care units are at higher risk in terms of emotional exhaustion, while those working in pediatric emergency units have higher scores related to personal accomplishment failure. Similar to our findings, another study reported that nurses working in intensive care units exhibited significantly higher levels of emotional exhaustion and depersonalization compared to those in other departments.[34] This can be attributed to the higher levels of responsibility and workload in intensive care and emergency units relative to other settings.

In our study, a significant and positive correlation was found between participants' emotional exhaustion (EE) and depersonalization (DP) levels. This finding supports the widely accepted model of burnout in the literature, which suggests that individuals who are emotionally exhausted tend to become indifferent and detached from the people they serve over time.[12,34,35]

However, a negative correlation was found between emotional exhaustion and personal accomplishment (PA) in our study, which contradicts the frequently reported expectation of a positive correlation in the literature.[29] This unexpected finding can be interpreted in several ways: (1) Burned-out individuals may evaluate success based on internal rather than traditional criteria; (2) the feeling of failure may be suppressed due to psychological defense mechanisms; (3) experienced individuals may maintain their sense of competence due to stronger coping skills; (4) institutional support and team solidarity may enhance the feeling of personal success.

Although there are few studies supporting this finding in the literature, some research has reported weak or non-significant relationships between emotional exhaustion and perceived personal failure.[36,37] Therefore, this unique finding in our study highlights the importance of evaluating the dimensions of burnout independently. We argue that addressing these dimensions separately can lead to more meaningful and clear conclusions.

For instance, the weak correlation between emotional exhaustion and personal accomplishment may stem from the fact that these two constructs reflect different psychological states. Emotional exhaustion is mainly related to the depletion of one's emotional energy, while the perception of personal failure is associated with an individual's inability to realize their potential and achieve personal goals. This indicates that each burnout dimension has its own specific effects that may not directly overlap with the perception of personal failure.

These unique findings suggest that independently evaluating the dimensions of burnout may help us better understand the relationship between burnout and perceived personal failure. This approach provides a broader perspective both theoretically and practically, enabling a clearer analysis of these two constructs. Due to their professional roles, nurses are in constant communication and interaction with patients, healthy individuals, their families, and other members of the healthcare team. Therefore, taking necessary measures in the early stages of burnout may provide positive contributions to individuals. Recommended solutions include improving working conditions, enhancing communication, and increasing social activities to address these contributing factors.

Limitations

The strengths of the article are as follows: Stress and burnout among pediatric nurses, especially those working in intensive care and emergency services, is a highly relevant topic. The comparison of nurses working in different pediatric units (e.g., neonatal ICU, pediatric emergency, outpatient clinic) allows for the identification of specific sources of stress. The use of validated and reliable Turkish versions of the MBI and PSS enhances the scientific validity of the measurements. Detailed analyses of participants' demographic characteristics such as age, gender, marital status, educational level, and parental status were conducted. The sample size was appropriate for the study. However, the limitations include the fact that the study was conducted in a single hospital in Balıkesir, limiting generalizability. No comparisons were made with other cities or institutions. Furthermore, due to the small number of nurses in certain groups (e.g., nursery), statistically reliable comparisons may be challenging.

CONCLUSION

As a result, burnout is prevalent in pediatric departments, which are among the most stressful areas in the healthcare sector. Nurses working in neonatal intensive care and pediatric emergency departments are at higher risk in terms of emotional exhaustion and personal failure. This study

revealed that nurses experience moderate to high levels of stress and burnout, particularly due to long working hours and night shifts. These findings underscore the need for institutional measures to regulate shift patterns and reduce workload. Providing psychological support and improving team communication can help mitigate burnout symptoms. Additionally, promoting professional development and social activities may enhance well-being. Overall, a supportive and balanced work environment is essential for sustaining nurses' mental health and quality of care.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Balıkesir Atatürk City Hospital Scientific Researches Ethics Committee (Date: 19.09.2024, Decision No: 2024/09/51).

Informed Consent

Signed and informed consent forms were obtained from the nurses who participated in the study.

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 the relationship between health literacy and mindful eating in obesity patients*

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ABSTRACT

Aims: Obesity is a multifactorial chronic disease and is a significant cause of morbidity and mortality when left untreated. Preventive health services play a substantial role in the fight against diseases that can cause a global crisis such as obesity. The primary goal of preventive health services in obesity is to ensure that people acquire healthy eating habits. It has been shown that factors such as maladaptive social attitudes, emotional eating have a significant effect on mindful eating. Health literacy and mindful eating are essential concepts in developing healthy eating habits. In this study, we aim to measure the health literacy levels of obese individuals, evaluate their mindful eating, and reveal whether there is any relationship between them.

Methods: The study consists of obese patients who were eligible and applied to Ankara Etlik City Hospital Obesity Center between August-December 2024. The individuals who gave their consent were given a form that evaluated their socio-demographic information, the Turkish Health Literacy Survey-32 (THLS-32) and the Mindful Eating Questionnaire (MEQ) and mental status examinations were conducted through face-to-face interviews by two psychiatrists in accordance with DSM-5 diagnostic criteria. Individuals under the age of 18 and those with conditions that could impair judgment were excluded from the study. With regard to eating disorders, participants were likewise evaluated by the interviewers based on DSM-5 diagnostic criteria.

Results: A total of 232 obese individuals were included in the study (191 female, 41 male). When the health literacy scores were examined, 3.0% (n=7) were inadequate (0-25), 23.7% (n=55) were problematic-limited (26-33), 47.8% (n=111) were sufficient (34-42), 24.6% (n=57) were excellent (43-50), and the general mindful eating scores were 2.90±0.541. When the relationship between health literacy and mindful eating is examined, it is seen that there is a positive (r=0.157) significant relationship at general score (r=0.146), treatment and service score (r=0.137), disease prevention and health promotion - access to health related-information (r=0.167), disease prevention and health promotion - understanding health related information (r=0.141), access to health-related information (r=0.154) and understanding health related-information (r=0.157).

Conclusion: Obesity treatment requires a multidimensional approach. For this process to be practical, many factors, such as healthy diet, physical activity, psychological support, and increasing health literacy, should be considered together. Healthy diet is an integral part of this multidimensional approach. Determining the psychological and individual factors associated with obesity, determining these factors, and increasing health literacy with dietary education and awareness-based practices can contribute to a more efficient, permanent, and sustainable weight loss process for obese patients.

Keywords: Obesity, health literacy, mindfulness, disordered eating behavior

*This study has been accepted to be presented in the poster session at the 3rd International 27th National Clinical Education Symposium to be held on 27-30 April 2025.

INTRODUCTION

Obesity is a chronic disease characterized by an increase in body fat mass, arising from the complex interaction of metabolic, genetic, socio-cultural, and behavioral factors. If left untreated, it can lead to significant morbidity and mortality. According to the World Health Organization (WHO) and the global burden of disease (GBD) studies, obesity constitutes a major risk factor for life-threatening conditions such as ischemic heart disease, type 2 diabetes, and cerebrovascular diseases. The disease burden attributable to high body-mass index (BMI) has increased approximately 2.5-fold between 1990 and 2021, ranking among the leading causes of disability-adjusted life years (DALYs) globally.[1]

The treatment of obesity requires a targeted multidimensional approach. Weight loss programs should be carefully planned according to individual characteristics and maladaptive thoughts and attıtudes.[2] In addition to many metabolic and endocrine causes in obesity, impaired eating behavior, loss of emotional management, emotional eating, difficulties in healthy diet and physical activity are important obstacles to weight loss and therefore obesity. The importance of targeted

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health programs and special interventions focusing on the relevant obstacles for a healthy lifestyle and habits in obesity treatment is better understood over time.[3]

Diseases whose prevalence is increasing day by day in our country and in the world and can cause a global crisis also require more importance to be given to preventive health services. Preventive health services aim to help individuals gain healthy living habits. Health literacy plays a major role in acquiring healthy lifestyle habits.[4]

First defined by Simonds in 1974, 'health literacy' is defined by the World Health Organization as the use and understanding of health-improving information and cognitive, motivational and social skills that affect individuals' access to health services.[5]

Health literacy also includes the ability to correctly understand and interpret the health system, the ability to communicate correctly with health professionals, and the ability to use health information received correctly and effectively. It increases individuals' participation in preventive health services by ensuring that they adopt health-improving behaviors.[6,7]

Studies show that individuals with high or sufficient health literacy are more careful about healthy nutrition, prefer foods with less sugar, and adopt health-improving behaviors such as healthy eating habits, awareness of emotional eating, learning emotional triggers and how to deal with them. Increasing awareness and differentiation between physical and emotional hunger and regular physical activity; while those with low levels have less information about health problems caused by obesity and make less effort to maintain ideal weight.[8]

The sustainability of healthy eating habits is not solely dependent on health literacy. Individual awareness-based constructs, such as mindful eating and self-efficacy, also play a critical role in this process. While health literacy facilitates access to and understanding of health-related information, mindful eating behavior enhances the likelihood of translating this knowledge into actionable behavior. In this sense, these two concepts are complementary in nature. According to Bandura's self-efficacy theory, individuals who believe in their ability to control eating behavior despite emotional or environmental triggers are more likely to engage in mindful eating practices.[9] Therefore, when considered together, health literacy, self-efficacy, and mindfulness play a pivotal role in the adoption and maintenance of healthy lifestyle behaviors.[10]

Mindfulness is the process of focusing one's attention on the present moment. Mindful eating also includes awareness of internal and external cues that affect food desire, food choices, the amount eaten, and the way food is eaten, as well as learning to make conscious choices and be more aware of cues indicating satiety. Paying attention to these factors has been shown to lead to healthier eating.[11]

Obesity is not a phenomenon in itself; it is a complex condition where individual characteristics, along with endocrine and genetic factors, have important effects. When evaluating individual characteristics, it is necessary to keep in mind how the person perceives the disease, how much they adopt health-enhancing behaviors, as well as the level of consciousness with which they seek treatment, and important factors such as mindful eating, which are thought to be important determinants of healthy eating. Multidimensional treatment approaches and personalized treatment plans will have a chance to be more effective with the understanding of these factors.[3,11]

Accordingly, this study aims to evaluate awareness-based individual factors, specifically health literacy and mindful eating, in an integrated manner. In the existing literature, these two constructs are often addressed independently, and their interrelationship has not been sufficiently explored.[12] From this perspective, the study seeks to make an original contribution to the field.

The first hypothesis of this study posits that higher levels of health literacy in individuals with obesity will be positively associated with increased mindful eating behavior. The second hypothesis suggests that higher levels of both health literacy and mindful eating will be negatively associated with dysfunctional eating behaviors, specifically emotional eating and disinhibition. We believe that health literacy and mindful eating may be important in terms of obesity awareness, treatment and healthy diet. Our aim in this study is to measure the health literacy levels of obese individuals, to evaluate their mindful eating and to reveal whether there is any relationship between them.

METHODS

Before the study, approval was obtained from the Ankara Etlik City Hospital Scientific Researches Evaluation and Ethics Committee (Date: 14.08.2024, Decision No: AEŞH-BADEK-2024-659). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study is a descriptive and cross-sectional study conducted with individuals over the age of 18, with a BMI ≥30 kg/m^2, who applied to the Ankara Etlik City Hospital Obesity Center between August 2024 and December 2024, were informed about this study, agreed to participate, and gave informed consent. Those with a neurological/mental disorder such as epilepsy, dementia, delirium, those diagnosed with a severe mental illness during an exacerbation period, and those with a cognitive or physical disability that would prevent them from participating in the study were excluded from the study.

Data Collection Tools

The individuals who gave their consent to participate in the study underwent mental status examinations and were given a form that assessed their sociodemographic information (such as age, education level, occupational status), and the Turkiye Health Literacy Survey-32 (THLS-32) and MEQ were applied.

Sociodemographic Data Collection Form: This is a form that includes patients' sociodemographic data such as age, education, and employment status, as well as information about the disease.

Turkiye Health Literacy Survey-32 (THLS-32): It is a scale consisting of 32 questions developed based on the Health Literacy in Eight Europe (HLS-EU) Study Conceptual Framework.[13] The conceptual framework includes "two health-related dimensions (treatment and service, disease

prevention and health promotion)" and "four information-acquiring processes (access, understanding, assessment, and use/application) concerning health-related decision-making and practices." The validity and reliability study in our country was conducted by Okyay et al.[14] The items are expressed as 0: very easy, 1: easy, 2: difficult, 3: very difficult, 4: I have no idea on a 5-point Likert-type scale. It is scored between 0-50. 50 - gives the highest literacy score.

Mindful Eating Questionnaire (MEQ): Developed by Framson et al.[15] in 2009. It aims to examine the relationship between eating behavior, awareness and emotional state. The scale consists of a total of 30 questions. The 5-point Likert Scale (1: never, 2: rarely, 3: sometimes, 4: often, 5: always) was used as adapted by Köse et al.[16] The subscales; disinhibition, emotional eating, control of eating, focusing, eating discipline, mindfulness, and interference were examined under 7 headings. While a high score obtained for each sub-dimension of the scale shows that the participant has the characteristic in which the relevant sub-dimension is evaluated, the scale also measures the total mindful eating score. Questions 1, 7, 9, 11, 13, 15, 18, 24, 25 and 27 are scored directly. The remaining questions are scored in reverse (1=5, 2=4, 3=3, 4=2, 5=1).

Statistical Analysis

The analysis of the research data was conducted using the SPSS 26 program. The descriptive findings in the study were given with numbers, percentages, minimum/maximum values, mean, standard deviation and median values. T test was used to compare two independent groups showing normal distribution. Mann-Whitney U test was used to compare two independent groups not showing normal distribution. Spearman correlation test was used to evaluate the relationships between variables not showing normal distribution. As stated in pages 23, 46, 77 and 79 of the Reliability and Validity Study of Turkiye Health Literacy Scales, index score calculation for matrix components was made for cases where at least 80% of the relevant questions were answered. According to this guideline, a score for the entire sample could not be obtained for each matrix.

RESULTS

Descriptive findings regarding the characteristics of the participants included in the study are presented in Table 1, 2. According to these findings, the average age of the participants was determined as 39.47±10.644, the average age of obesity onset was 22.84±9.430, the average duration of obesity was 16.62±8.880, the average BMI was 43.43±8.915, average height was 163.61±9.630, and average weight was 115±19.697 as seen in Table 1. In Table 2, 82.3% (n=191) of the participants were female and 38.8% (n=90) were high school graduates. 49.1% (n=114) were housewives, 68.5% (n=159) were married, and 60.3% (n=140) earned less than 10 thousand TL per month. 92.7% (n=215) were living with their families, 61.2% (n=142) had known additional medical comorbidities, and 69.8% (n=162) were in the BMI >40 group. 53.9% (n=125) had no history of psychiatric follow-up treatment, and 77.2% (n=179) did not currently have any mental health complaints. 78.4% (n=182) of the participants had a history of eating disorders, with 46.1% (n=107) having night eating, 68.5% (n=159) emotional eating, 14.7% (n=34) binge eating, 24.1% (n=56) grazing, and 19.0% (n=44) having other eating disorders. Among the weight loss methods, the most preferred one is dieting (41.6%; n=229).

Table 1. Participants' information on obesity

	Minimum	Maximum	Mean	SD	Median
Age	18.00	62.00	39.47	10.644	40.00
Obesity onset age	9.00	57.00	22.84	9.430	20.00
Obesity duration	2.00	44.00	16.62	8.880	15.50
Height	108.00	191.00	163.61	9.630	163.00
Weight	77.00	168.00	115.83	19.697	112.00
BMI	30.84	138.89	43.43	8.915	41.96

SD: Standard deviation, BMI: Body-mass index

Table 2. Descriptive findings regarding participant characteristics

		n	%
Sex	Female	191	82.3
	Male	41	17.7
Education	Literate	2	0.9
	Primary	44	19.0
	Middle school	25	10.8
	High school	90	38.8
	University/college	71	30.6
Occupation	Unemployed	18	7.8
	Student	11	4.7
	Housewife	114	49.1
	Worker/civil servant	47	20.3
	Retired	10	4.3
	Freelance/other	32	13.8
Marital status	Single	45	19.4
	Married	159	68.5
	Widow	6	2.6
	Divorced/living separately	22	9.5
Economic income	Under minimum wage	140	60.3
	Above minimum wage	92	39.7
Household	Alone	13	5.6
	Family	215	92.7
	Other	4	1.7
Comorbidity	Yes	142	61.2
	No	90	38.8
BMI	30-34.9	13	5.6
	35-39.9	57	24.6
	>40	162	69.8
Previous psychiatric follow-up treatment	Yes	107	46.1
	No	125	53.9
Current psychological complaint	Yes	53	22.8
	No	179	77.2
Eating disorder history	Yes	182	78.4
	No	50	21.6
Weight loss methods*	Diet	229/232	
	Herbal methods	88/232	
	Sports/exercise	120/232	
	Medication	54/232	
	Acupuncture	48/232	
	Surgery	11/232	

*Due to multiple response options, the number of responses given is greater than the number of samples. BMI: Body-mass index

The distribution of THLS-32 scale categories is given in Table 3. According to these findings; In the general score, 3.0% (n=7) of the participants had insufficient (0-25), 23.7% (n=55) problematic-limited (26-33), 47.8% (n=111) sufficient (34-42), 24.6% (n=57) excellent (43-50) level. In the treatment and service score, 2.2% (n=5) of the participants had insufficient (0-25), 12.9% (n=30) problematic-limited (26-33), 57.3% (n=133) sufficient (34-42), 26.3% (n=61) excellent (43-50) level. In the disease prevention and health promotion score, 6.9% (n=16) of the participants had insufficient (0-25), 9.1% (n=21) had problematic-limited (26-33), 43.5% (n=101) had sufficient (34-42), and 29.3% (n=68) had excellent (43-50) levels.

The statistical findings regarding the MEQ are given in Table 4. According to these findings, it was seen that the total mindful eating score of the participants was 2.90±0.541. The disinhibition score was 2.81±0.994, the emotional eating score was 2.72±1.164, the control of eating score was 2.89±1.004, the focusing score was 3.32±0.476, the eating discipline score was 2.63±0.785, the mindfulness score was 2.77±0.580 and the interference score was 3.40±0.981.

Table 4. Statistical findings regarding the MEQ

Variable	n	Maximum	Mean	SD	Median
Total mindful eating	232	4.07	2.90	0.541	2.90
Disinhibition	232	5.00	2.81	0.994	3.00
Emotional eating	232	5.00	2.72	1.164	2.60
Control of eating	232	5.00	2.89	1.004	2.75
Focusing	232	5.00	3.32	0.476	3.33
Eating discipline	232	4.75	2.63	0.785	2.50
Mindfulness	232	4.20	2.77	0.580	2.80
Interference	232	5.00	3.40	0.981	3.50

MEQ: Mindful Eating Questionnaire, SD: Standard deviation

The characteristics of the participants included in the study and the Spearman correlation analysis findings regarding the THLS-32 and MEQ are given in Table 5. According to these findings, it was found that there was a positive significant relationship between the participants' ages and total mindful eating (r=0.196), disinhibition (r=0.178), eating discipline (r=0.162) and interference (r=0.194); there was a negative significant relationship between the participants' ages and total mindful eating score (r=-0.272), treatment and service score (r=-0.304) and disease prevention and health promotion score (r=-0.214); there was a positive significant relationship between the participants' obesity duration and total Mindful Eating (r=0.257), disinhibition (r=0.179), emotional eating (r=0.235), control of eating (r=0.145) and interference (r=0.159). It was determined that there was a positive significant relationship between the participants' BMI values and emotional eating (r=0.176).

Table 5. Correlation findings between demographic variables and the THLS-32[1] Sub-Scales and MEQ[2] Sub-Scales

		Age	Obesity duration	BMI
General[1]	r	-0.272	-0.110	0.002
	p	0.000	0.095	0.980
	n	230	230	230
Treatment and service[1]	r	-0.304	-0.115	-0.044
	p	0.000	0.083	0.504
	n	229	229	229
Disease prevention and health promotion[1]	r	-0.214	-0.100	0.039
	p	0.001	0.134	0.555
	n	226	226	226
Total mindful eating[2]	r	0.196	0.257	0.073
	p	0.003	0.000	0.266
	n	232	232	232
Disinhibition[2]	r	0.125	0.179	0.071
	p	0.057	0.006	0.278
	n	232	232	232
Emotional eating[2]	r	0.178	0.235	0.176
	p	0.007	0.000	0.007
	n	232	232	232
Control of eating[2]	r	0.036	0.145	0.039
	p	0.588	0.027	0.551
	n	232	232	232
Focusing[2]	r	0.062	0.047	-0.008
	p	0.347	0.473	0.904
	n	232	232	232
Eating discipline[2]	r	0.162	0.113	-0.058
	p	0.013	0.087	0.382
	n	232	232	232
Mindfulness[2]	r	0.045	0.075	-0.024
	p	0.498	0.258	0.720
	n	232	232	232
Interference[2]	r	0.194	0.159	0.068
	p	0.003	0.015	0.302
	n	232	232	232

THLS-32: Turkish Health Literacy Scale-32, MEQ: Mindful Eating Questionnaire, SD: Standard deviation

Table 3. Distribution of THLS-32 Scale categories

Category	General		Treatment and service		Disease prevention and health promotion	
	Number	%	Number	%	Number	%
Inadequate (0-25)	7	3.0	5	2.2	16	6.9
Problematic-limited (26-33)	55	23.7	30	12.9	21	9.1
Adequate (34-42)	111	47.8	133	57.3	101	43.5
Excellent (43-50)	57	24.6	61	26.3	68	29.3

THLS-32: Turkish Health Literacy Scale-32

As a result of the analyses conducted to determine whether there are differences in the THLS-32 and MEQ according to the gender of the participants included in the study, it was determined that there was a significant difference in the disinhibition and emotional eating scores according to the gender of the participants (p<0.05). When the findings were examined; It was determined that the average of men (3.12±1.065) was higher than the average of women (2.74±0.967) in the disinhibition score, and the average of men (3.19±1.160) was higher than the average of women (2.62±1.143) in the emotional eating score.

As a result of the analyses conducted to determine whether there are differences in the THLS-32 and MEQ according to the education levels of the participants included in the study, it was determined that there were significant differences in the general, treatment and service and emotional eating scores according to the education levels of the participants (p<0.05). As a result of the Bonferroni-corrected multiple comparison tests conducted to determine which groups the differences were between; It was determined that the average of university/college graduates in the general health literacy score (38.99±6.691) was higher than the average of those who were only literate (24.74±6.261), the average of university/college graduates in the Treatment and Service score (40.43±6.255) was higher than the average of primary school graduates (37.13±6.757), and the average of primary school graduates in the emotional eating score (3.23±1.188) was higher than the average of high school graduates (2.59±1.088) and university/college graduates (2.57±1.202).

As a result of the analyses carried out to determine whether there were differences according to the participants' BMI levels, it was determined that there was no significant difference in the THLS-32 and MEQ according to the participants' BMI levels (p>0.05).

The analysis findings conducted to determine whether there were any differences in the THLS-32 and MEQ according to the eating disorder history of the participants included in the study are given in Table 6. As a result of the analyses, it was determined that there was a significant difference in the participants' total mindful eating, disinhibition, emotional eating, control of eating and interference scores (p<0.05). When the findings were examined: In the total mindful eating score, the average of those without a history of eating disorders (3.26±0.542) was higher than the average of those with a history of eating disorders (2.80±0.500); In the disinhibition score, the average of those without a history of eating disorders (3.34±0.915) was higher than the average of those with a history of eating disorders (2.66±0.967); in the emotional eating score, the average of those without a history of eating disorders (3.76±0.943) was higher than the average of those with a history of eating disorders (2.44±1.052); In the control of eating score, the average of those without a history of eating disorders (3.19±1.077) was higher than the average of those with a history of eating disorders (2.81±0.970); it was determined that the mean interference score of those without an eating disorder history (3.66±0.966) was higher than the mean of those with an eating disorder history (3.33±0.975).

Table 6. Differences regarding eating disorder history and THLS-32[1] Sub-Scales and MEQ[2] Sub-Scales

Variable	Eating disorder	n	Mean±SD	Average rank	t/Z	p
General[1]	Yes	181	37.58±6.923	115.41	-0.041	0.967
	No	49	37.33±6.634	115.85		
Treatment and service[1]	Yes	180	39.05±6.667	116.45	-0.634	0.526
	No	49	38.22±6.770	109.68		
Disease prevention and health promotion[1]	Yes	178	36.12±8.262	112.96	-0.242	0.809
	No	48	36.38±7.825	115.52		
Total mindful eating[2]	Yes	182	2.80±0.500	104.82	-5.577*	0.000
	No	50	3.26±0.542	159.02		
Disinhibition[2]	Yes	182	2.66±0.967	106.32	-4.414	0.000
	No	50	3.34±0.915	153.54		
Emotional eating[2]	Yes	182	2.44±1.052	100.30	-7.029	0.000
	No	50	3.76±0.943	175.47		
Control of eating[2]	Yes	182	2.81±0.970	110.97	-2.399	0.016
	No	50	3.19±1.077	136.62		
Focusing[2]	Yes	182	3.29±0.484	112.57	-1.718	0.086
	No	50	3.41±0.434	130.82		
Eating discipline[2]	Yes	182	2.58±0.780	113.15	-1.457	0.145
	No	50	2.80±0.786	128.71		
Mindfulness[2]	Yes	182	2.77±0.573	116.23	-0.118	0.906
	No	50	2.79±0.610	117.49		
Interference[2]	Yes	181	3.33±0.975	110.48	-2.420	0.016
	No	50	3.66±0,966	135.98		

*T test, THLS-32: Turkish Health Literacy Scale-32, MEQ: Mindful Eating Questionnaire, SD: Standard deviation

The Spearman correlation analysis findings regarding the relationships between THLS-32 and MEQ are given in Table 7. According to these findings: There is a positive significant relationship (r=0.161) between Disinhibition and disease prevention and health promotion-using/applying information; There is a positive significant relationship (r=0.146) between

Table 7. Inter-Scale correlation findings of THLS-32[1] and MEQ[2]

		Total mindful eating[2]	Disinhibition[2]	Emotional eating[2]	Control of eating[2]	Focusing[2]	Eating discipline[2]	Mindfulness[2]	Interference[2]
General	r	-0.016	-0.002	-0.051	-0.027	0.146	0.036	-0.053	0.022
	p	0.811	0.980	0.441	0.679	0.027	0.589	0.426	0.741
	n	230	230	230	230	230	230	230	229
Treatment and service[1]	r	-0.072	-0.074	-0.110	-0.045	0.137	0.053	-0.070	-0.048
	p	0.278	0.264	0.096	0.502	0.039	0.426	0.290	0.469
	n	229	229	229	229	229	229	229	228
Treatment and service[1]- access to information[1]	r	-0.113	-0.113	-0.109	-0.031	0.116	0.000	-0.109	-0.106
	p	0.100	0.100	0.110	0.656	0.091	0.996	0.113	0.121
	n	215	215	215	215	215	215	215	214
Treatment and service[1] -understanding information[1]	r	-0.033	-0.006	-0.117	-0.045	0.128	0.108	-0.014	0.027
	p	0.633	0.934	0.094	0.521	0.066	0.122	0.838	0.702
	n	206	206	206	206	206	206	206	206
Treatment and service[1]- assessment of information[1]	r	0.011	0.000	-0.105	0.049	0.106	0.086	-0.007	0.078
	p	0.878	0.997	0.139	0.488	0.137	0.229	0.923	0.274
	n	199	199	199	199	199	199	199	198
Treatment and service[1]- use/application of information[1]	r	-0.112	-0.077	-0.120	-0.085	0.077	-0.010	-0.084	-0.106
	p	0.104	0.261	0.081	0.215	0.264	0.888	0.224	0.122
	n	213	213	213	213	213	213	213	212
Disease prevention and health promotion[1]	r	0.034	0.077	0.001	-0.019	0.120	-0.004	-0.021	0.101
	p	0.613	0.250	0.992	0.780	0.072	0.957	0.749	0.129
	n	226	226	226	226	226	226	226	225
Disease prevention and health promotion[1] - access to information[1]	r	-0.011	0.020	-0.051	-0.105	0.167	0.042	-0.028	0.073
	p	0.873	0.779	0.463	0.135	0.017	0.550	0.694	0.298
	n	206	206	206	206	206	206	206	205
Disease prevention and health promotion[1] - understanding information[1]	r	-0.008	0.009	-0.069	-0.036	0.141	0.077	-0.004	0.048
	p	0.908	0.894	0.328	0.607	0.046	0.279	0.954	0.496
	n	202	202	202	202	202	202	202	201
Disease prevention and health promotion[1] - assessment of information[1]	r	-0.057	-0.049	-0.065	-0.063	0.087	0.036	-0.094	-0.002
	p	0.437	0.503	0.375	0.389	0.230	0.621	0.197	0.978
	n	190	190	190	190	190	190	190	189
Disease prevention and health promotion[1] - use/application of information[1]	r	0.095	0.161	0.089	0.024	0.072	-0.023	-0.079	0.124
	p	0.182	0.023	0.212	0.739	0.313	0.743	0.267	0.083
	n	199	199	199	199	199	199	199	198
Access to health-related information[1]	r	-0.052	-0.047	-0.053	-0.076	0.154	0.041	-0.075	-0.023
	p	0.438	0.478	0.425	0.255	0.020	0.544	0.261	0.737
	n	226	226	226	226	226	226	226	225
Understanding health-related information[1]	r	-0.005	0.012	-0.094	-0.039	0.157	0.113	-0.008	0.037
	p	0.937	0.854	0.161	0.559	0.019	0.094	0.902	0.584
	n	222	222	222	222	222	222	222	221
Assesment of health-related information[1]	r	-0.042	-0.035	-0.107	-0.033	0.111	0.035	-0.071	0.040
	p	0.536	0.610	0.115	0.628	0.101	0.608	0.299	0.559
	n	218	218	218	218	218	218	218	217
Using/applying health-related information[1]	r	-0.004	0.047	0.007	-0.026	0.052	-0.067	-0.083	0.014
	p	0.954	0.484	0.914	0.694	0.432	0.318	0.214	0.836
	n	227	227	227	227	227	227	227	226

THLS-32: Turkish Health Literacy Scale-32, MEQ: Mindful Eating Questionnaire

focusing and general health literacy score; There is a positive significant relationship between focusing and treatment and service score (r=0.137), disease prevention and health promotion-access to information score (r=0.167), disease prevention and health promotion-understanding information score (r=0.141), access to health-related information score (r=0.154), and understanding health-related information score (r=0.157).

DISCUSSION

Obesity is one of the most important health problems in Turkiye as well as all over the world. This study aimed to investigate the relationship between health literacy and mindful eating in obese patients. 232 patients participated in the study and it was determined that the number of women (n=191) was higher than men (n=41). Although it is known that the prevalence of obesity is higher in women, in line with the literature, the female rate is also high in our study.[17]

It is predicted that obesity will continue to be a significant global health problem in the coming years, and it is important to determine the controllable individual factors that cause obesity.[18] Health literacy, which causes people to make healthier choices throughout their lives and to be more careful about healthy nutrition, is an important variable that can be improved. In previous studies, the health literacy level of adults in our country has been determined to vary between 6% and 72.9%, and many studies have stated that health literacy is at an inadequate level.[4]

Health literacy is not merely the acquisition of information; it is also recognized as a cognitive and social competency that guides individuals in making informed health-related decisions. Recent meta-analyses have demonstrated that low levels of health literacy may lead to adverse health outcomes, particularly in relation to obesity and other chronic diseases.[13]

Health literacy has been examined in community-based samples in chronic patients and various groups, but there are not many studies conducted on obese patients.[4] In our study, it was found that 3.0% (n=7) of the participants had inadequate (0-25), 23.7% (n=55) problematic-limited (26-33), 47.8% (n=111) sufficient (34-42), and 24.6% (n=57) excellent levels of health literacy in obese patients.

In a study evaluating health literacy and obesity-related behaviors in obese patients, it was determined that 71.4% of the individuals had inadequate health literacy levels and 28.6% had sufficient levels.[4] In another study conducted on obese patients, it was observed that 31% of them had "insufficient" health literacy, 37.7% had "problematic/limited" health literacy, 21.1% had "sufficient" health literacy, and 10.2% had "excellent" health literacy.[5] The results obtained from our study were found to be partially different from the literature. The fact that the health literacy of obese patients was 46.7% sufficient may be related to the fact that the patient group studied applied to a treatment center that has an important place in obesity treatment and that they were a patient group that sought treatment. To our knowledge, this study is the first study to examine the relationship between health literacy and mindful eating in obese patients.

Obesity is seen as a behavioral problem associated with uncontrolled eating. Mindful eating is a healthy weight control tool that comes to the forefront by trying to change unhealthy eating behaviors and is an alternative approach to weight loss methods.[19] Studies on obesity, eating behavior, and body weight management with mindful eating have shown that mindfulness practices provide improvement in eating behavior and are effective in losing body weight in obese individuals.[20,21]

In our study, when the mindful eating scores of the patients were examined, it was seen that the average MEQ score of the participants was 2.90±0.541 (Total score 87±16.23). The relationship between obesity and mindful eating has been studied mostly in student and young samples. In a study conducted with university students, the students' average MEQ total score was found to be high at 97.63±13.26. In another study, the average MEQ total score was found to be 98.11±13.81 in the general population.[22,23] In our study, it was observed that the MEQ total scores of the obese patients were lower than the mindful eating scores in the studies conducted with the general population and students. This situation suggests that eating behaviors among individuals with obesity tend to be more automatic and are maintained at a lower level of awareness.[24]

Mindful eating and health literacy are affected by variables such as individuals' individual characteristics and socioeconomic status. In a study conducted on healthcare professionals, it was found that as the participants' ages increased, the scores of "disinhibition", "discipline of eating", "interference" increased and the total score of "MEQ" decreased.[25] In our study, it was found that the total mindful eating, emotional eating, discipline of eating and interference scores increased as the participants' ages increased. It was found that there was a positive and significant relationship between the duration of obesity and total mindful eating, disinhibition, emotional eating, control of eating and interference. Although this situation contradicts the fact that the patients continued to be obese, it may indicate that the patients' attention to mindful eating may have increased along with their exposure to obesity and their search for treatment. Some studies have observed that as the duration of obesity increases, individuals may experience greater awareness of their eating behaviors; however, this heightened awareness does not always translate into actual behavioral change.[26]

In studies evaluating mindful eating, the relationship between mindful eating and BMI has been frequently emphasized[21]. The results of studies examining the relationship between BMI and mindful eating are quite different. In some studies, mindful eating scores decreased with increasing BMI,[22] while in some other studies, there was no relationship between these two or it has been stated that as the BMI value increases, the total scale score decreases, but this difference is not statistically significant.[16]

In our study, unlike other studies, it was found that mindful eating scores increase as BMI increases. This finding contradicts the general trend in the literature and represents an unexpected result. It suggests that while eating awareness may be increasing among individuals with obesity, this increase

has not yet fully translated into healthy eating behaviors. In line with the concept of the "awareness-performance gap", individuals may develop a cognitive awareness of the need to change unhealthy eating habits, yet the translation of this awareness into behavior may occur gradually and over time.[27] Systematic reviews indicate that mindful eating interventions may have limited long-term effectiveness in producing sustained behavioral changes in eating patterns.[28] Although individuals with higher BMI are generally thought to exhibit lower levels of mindful eating, studies have emphasized that BMI alone is not a sufficient determinant, and should be interpreted alongside individual and cognitive factors.[29]

When we look at the changes in mindful eating according to gender in our study, it was found that disinhibition and emotional eating scores were higher in men. There are different results in the literature regarding the relationship between gender and mindful eating. In some studies, it was determined that men have higher "emotional eating" scores than women and women have higher "discipline of eating" scores than men; there are also other studies showing that men have higher "emotional eating" scores than women and "control of eating", "focusing" and "discipline of eating" scores are lower than women.[25] When other studies with different samples and different numbers of participants are examined, it was seen that the MEQ scale scores did not show a significant difference according to gender.[16]

A very few studies have compared obesity-related factors with health literacy. Health literacy defines both cognitive and social skills that affect an individual's access to health services during the process of protecting, improving and treating their health in case of deterioration. Health literacy may vary depending on many personal and cultural variables.[4] In recent studies, a positive association has been identified between digital health literacy and nutritional awareness, which appears to positively influence individuals' ability to make healthy decisions.[30]

In our study, as the age of the participants increased, the health literacy general score, treatment and service score, and disease prevention and health promotion score decreased; when examined in terms of gender and BMI, it was understood that there was no significant difference, and higher scores were obtained in the more educated group in the general score and treatment service score. In most studies evaluating health literacy, it is reported that health literacy scores decrease with age.[31] Similarly, it can be said that health literacy increases as the level of education increases, and all studies on the determinants of health literacy agree that "level of education" is the key determinant.[32]

It can be said that individuals with a high level of education have high general literacy skills, the ability to access, understand and apply health-related information, and the ability to comment with an investigative and critical perspective by obtaining information from different sources. It can be generalized that as the level of education increases, individuals can better access and understand the information they are curious about about their health.[32]

Eating disorders are frequently seen together with disturbed eating behaviors in obesity. In our study, it was determined that 182 out of 232 patients had at least one eating disorder. Consistent with the literature and expected[33] it was determined that the total mindful eating, disinhibition, emotional eating, control of eating and interference scores of those with eating disorders were statistically significantly high, but no relationship was found between the presence of an eating disorder and the health literacy total score and its subscales. This finding suggests that health literacy alone may not be sufficient to positively influence eating behaviors. Although individuals may possess the necessary knowledge, they may still struggle to translate this knowledge into actual behavior. In eating disorders, emotional regulation difficulties, in addition to cognitive factors, are known to play a significant role. Therefore, information-based approaches alone may be inadequate, and comprehensive interventions supported by psychoeducation are required.[34]

Finally, when the relationship between health literacy and mindful eating was evaluated in our study, it was seen that there was a positive significant relationship between mindful eating and health literacy in the total scores, and between the sub-dimensions of health literacy such as preventing diseases and improving health and accessing and understanding information, accessing and understanding health-related information.

These findings indicate that health professionals should not solely focus on biomedical interventions, but also consider individuals' abilities to access health information and their levels of awareness.[35] Programs developed in this direction may contribute to sustainable behavioral changes in obesity treatment. The results suggest that the integration of individuals' competencies in accessing, understanding, and applying health information, along with their awareness of eating behaviors, is essential in the design of effective treatment processes.[36] This study, particularly conducted with treatment-seeking individuals in a clinical context, is believed to offer a valuable contribution to the literature.[37] In line with systematic approaches, a joint consideration of health literacy levels, access to treatment, and mindful eating behaviors can provide a framework for effective and sustainable interventions in the fight against obesity.[27]

This study examined the relationship between health literacy and mindful behavior and was not designed to make causal inferences. Therefore, the use of longitudinal designs in future studies will increase the validity and reliability of the findings. In particular, the use of structured observation protocols and objective measurement tools scored by independent raters will reduce the limitations of self-reported data. In addition, experimental designs, especially randomized controlled trials are needed to evaluate the effects of mindfulness-based interventions. Such studies will allow a more robust assessment of the causal relationships between variables such as cognitive mindfulness, emotional eating, and health literacy. Thus, the effects of psychoeducational interventions in obesity management can be more reliably demonstrated.

Limitations

This study has some methodological and sample-based limitations. First, the inclusion of individuals who only applied to an obesity center resulted in the sample consisting of individuals who were seeking treatment and had high health motivation, limiting the generalizability of the findings. This may have created a sample bias, especially in awareness-based variables such as health literacy and conscious eating. Second, however, the fact that the sample consisted of voluntary participants may have introduced a potential selection bias and could limit the generalizability of the findings. Third, the fact that the data were based on self-reporting may have been affected by sources such as social desirability, response bias, and recall errors. Fourth, since variables such as health literacy have multidimensional structures, cultural, digital, and cognitive components could not all be controlled in this study. Fifth, the cross-sectional design of the study does not allow for the evaluation of causal relationships between variables, allowing interpretation only at the level of the relationship. Finally, the high proportion of female participants in the sample may have limited the power of gender-based analyses.

CONCLUSION

The approach to obesity and disordered eating behaviors, as well as their treatment, constitutes a complex and multidimensional process. In recent years, innovative strategies focusing on mindfulness, mindful eating, and healthy nutrition have gained increasing importance in managing these conditions. A fundamental requirement in this context is that individuals know, learn, or receive education about what a healthy diet entails. One of the most effective tools in acquiring and maintaining such knowledge and behaviors is a high level of health literacy. In addition to identifying the psychological and individual factors associated with obesity, enhancing health literacy through nutrition education and mindfulness-based practices may contribute to a more effective, lasting, and sustainable weight management process in individuals with obesity. In this regard, understanding the relationship between health literacy and mindful eating can facilitate the development of personalized nutritional interventions, supporting the creation of more targeted and behaviorally oriented treatment plans in clinical practice. These findings underscore the importance of designing interventions that promote mindful eating behaviors while taking individuals' health literacy levels into account in the treatment of obesity.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Ankara Etlik City Hospital Scientific Researches Evaluation and Ethics Committee (Date: 14.08.2024, Decision No: AEŞH-BADEK-2024-659.

Informed Consent

All patients signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Original Article

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Evaluation of artificial intelligence in thoracic surgery internship education: accuracy and usability of AI-generated exam questions

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ABSTRACT

Aims: This study aims to evaluate the usefulness and reliability of artificial intelligence (AI) applications in thoracic surgery internship education and exam preparation.

Methods: Claude Sonnet 3.7 AI was provided with core topics covered in the 5th-year thoracic surgery internship and was instructed to generate a 20-question multiple-choice exam, including an answer key. Four thoracic surgery specialists assessed the AI-generated questions using the Delphi panel method, classifying them as correct, minor error, or major error. Major errors included the absence of the correct answer among choices, incorrect AI-marked answers, or contradictions with established medical knowledge. A second exam was manually created by a thoracic surgery specialist and evaluated using the same methodology. Seven volunteer 5th-year medical students completed both exams, and the correlation between their scores was statistically analyzed.

Results: Among AI-generated questions, 8 (40%) contained major errors, while 1 (5%) had a minor error. The expert-generated exam had a perfect accuracy rate, whereas the AI-generated exam had significantly lower accuracy (p=0.001). Median scores were 75 (67-100) for the AI exam and 85 (70-95) for the expert exam. No significant correlation was found between students' scores (r=0.042, p=0.929).

Conclusion: AI-generated questions had a high error rate (40% major, 5% minor), making them unreliable for unsupervised use in medical education. While AI may provide partial benefits under expert supervision, it currently lacks the accuracy required for independent implementation in thoracic surgery education.

Keywords: Artificial ıntelligence, thoracic surgery education, multiple choice tests, delphi technique

INTRODUCTION

Artificial intelligence (AI) applications have rapidly evolved, demonstrating significant potential in various domains of medical education, including clinical decision support, diagnostic accuracy improvement, and personalized learning experiences. Recent studies suggest that AI-generated content can be useful in medical training by automating question generation, simulating clinical cases, and enhancing student engagement.[1,2] However, concerns regarding the accuracy, reliability, and ethical implications of AI-generated educational materials remain.[3,4]

Thoracic surgery is a highly specialized field that requires a deep understanding of complex surgical procedures, anatomical structures, and perioperative management. The effectiveness of AI in generating thoracic surgery-related multiple-choice questions (MCQs) for medical students has not been extensively studied. Prior research has demonstrated that AI-generated MCQs can sometimes contain factual inaccuracies or misleading information, necessitating thorough expert review before implementation. While artificial intelligence holds significant potential in the future of medical education, the persistent reliance on traditional teaching methods presents challenges for integrating such innovative tools. Moreover, although the content of this study is not strictly limited to thoracic surgery knowledge, it was conducted within the context of thoracic surgery education and assessed by experts in the field. Therefore, the study aims to contribute not only to surgical education but also to the broader conversation on the role of AI in developing assessment tools for specialized medical domains.

The Delphi method has been widely used to assess the validity of educational content by utilizing expert consensus.[5] This approach ensures that medical assessments maintain high accuracy and educational value. Given the increasing reliance on AI in medical education, it is essential to evaluate its role in thoracic surgery training, particularly regarding its ability to generate reliable and high-quality exam questions.

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In this study, we assess the quality of AI-generated MCQs for thoracic surgery internships and compare them to expert-generated questions. We aim to determine whether AI can provide a valuable tool for medical education or if its current limitations make it unsuitable for unsupervised use. The results of this study could contribute to understanding the feasibility of AI-assisted education in thoracic surgery and inform best practices for AI integration into medical curricula.

METHODS

Ethical Considerations

The study was conducted following ethical guidelines for educational research and the principles of the Helsinki Declaration. Informed consent was obtained from all student participants. As the study did not involve patient data, ethics committee approval was not required under the Helsinki Declaration.

Study Design

This study was designed as a comparative analysis to evaluate the accuracy and usability of artificial intelligence (AI)-generated multiple-choice questions (MCQs) in thoracic surgery internship education. The study included an AI-generated exam and an expert-generated exam, both assessed for content accuracy by a panel of thoracic surgery specialists. The study also investigated the correlation between medical students' scores on both exams.

AI-Generated Exam

Claude Sonnet 3.7 AI was provided with the key topics covered in the 5th-year medical school thoracic surgery internship curriculum. The AI was instructed to generate a 20-question multiple-choice exam with five answer choices per question and an answer key. No additional instructions regarding difficulty level or question style were given.

Expert Evaluation and Classification of AI-Generated Questions

Three thoracic surgery specialists independently evaluated the AI-generated questions. The questions were classified into three categories:

Correct: No errors detected.

Minor error: Small mistakes that did not alter the meaning of the question or the correct answer.

Major Error: Errors that invalidated the question, including:

- Presence of multiple correct answers
- Incorrect AI-marked correct answer
- Contradictions with established medical knowledge
- Absence of the correct answer in the options

In addition to accuracy, the experts also classified each question by difficulty level (on a scale of 1 to 4) and topic (e.g., Pneumothorax, Pleural Effusion). Finally, a Delphi panel was conducted to reach a consensus on the classification of each question.

Expert-Generated Exam

A second 20-question MCQ exam was independently created by a thoracic surgery specialist, following the same curriculum and format as the AI-generated exam. This exam was also reviewed by the same three thoracic surgery experts using the Delphi method to ensure question validity.

Student Participation and Examination Process

Seven 5th-year medical students voluntarily participated in the study. Each student completed both the AI-generated and expert-generated exams under standardized testing conditions. A minimum 24-hour gap was maintained between the two exams to minimize recall bias.

Statistical Analysis

The median and interquartile range (IQR) of student scores were calculated for both exams. The correlation between students' scores on the AI-generated and expert-generated exams was assessed using Pearson's correlation coefficient. Fischer's exact test was used to compare the accuracy rates of the two exams. Statistical significance was set at $p<0.05$.

RESULTS

Evaluation of AI-Generated Questions

Out of the 20 multiple-choice questions (MCQs) generated by Claude Sonnet 3.7 AI, 8 questions (40%) contained major errors, while 1 question (5%) had a minor error. The breakdown of major errors is as follows:

- 3 questions (15%) contained two correct answers.
- 3 questions (15%) had a correct question, but the AI incorrectly marked the answer key.
- 2 questions (10%) presented medically inaccurate information, and the correct answer was missing from the answer choices.

The remaining 11 questions (55%) were classified as correct and free from any errors. The one minor error (5%) did not contradict general medical knowledge and did not change the correct answer. Therefore, it was included in the student assessment. In total, the student exam was conducted using 12 questions-11 correct and 1 with a minor error.

Evaluation of Expert-Generated Questions

The expert-generated exam underwent the same review process by the panel of three thoracic surgery specialists. No major or minor errors were identified in any of the 20 questions, indicating a perfect accuracy rate. As detailed in Table 4, the questions addressed a broad range of thoracic surgery topics, including pleural effusion, blunt trauma, pneumothorax, and esophageal cancer. The difficulty levels varied between 2 and 4, reflecting an appropriate range of complexity. These results underscore the reliability, clinical accuracy, and content diversity of expert-generated questions in medical education.

Student Performance Comparison

Seven 5th-year medical students participated in the study and completed both exams. The scores were analyzed as follows:

- The median score for the AI-generated exam was 75 (IQR: 67-100).
- The median score for the expert-generated exam was 85 (IQR: 70-95).

Although the AI-generated exam resulted in a slightly lower median score, there was variability among student performances.

Correlation Between AI and Expert-Generated Exam Scores

Statistical analysis using Pearson's correlation coefficient revealed no significant correlation between students' scores on the AI-generated and expert-generated exams (r=0.042, p=0.929) (Table 1). This suggests that the AI-generated exam did not consistently measure students' knowledge in a manner comparable to the expert-created exam.

Table 1. Comparison of AI-generated and expert-generated exam scores in thoracic surgery internship

	AI-generated exam score	Expert-generated exam score	p-value
Student 1	83	90	0.929
Student 2	67	95	
Student 3	92	90	
Student 4	100	85	
Student 5	67	85	
Student 6	75	70	
Student 7	67	85	

AI: Artificial intelligence

The expert-generated exam had a perfect accuracy rate, while the AI-generated exam showed significantly lower accuracy, with a statistically significant difference (p=0.001) (Table 2).

Table 2. Comparison of accuracy between expert-generated and AI-generated exams

	Correct questions (n)	Incorrect questions (n)	p-value
Expert-generated exam	20	0	0.001
AI-generated exam	11	9	

AI: Artificial intelligence

Out of 20 AI-generated questions, 11 were correct, 1 had a minor error, and 8 had major errors. Errors were more frequent in questions with higher difficulty levels (3-4), particularly in topics like lung cancer and pleural effusion. This indicates potential limitations of AI in complex or specialized medical domains (Table 3, 4).

DISCUSSION

AI has gained increasing attention in medical education, particularly in question generation, personalized learning, and decision support systems.[6-8] AI-driven educational tools, such as large language models (LLMs), have demonstrated potential in creating medical assessments, but their reliability remains a concern.[9,10] Our study evaluated the accuracy of

Table 3. Evaluation of AI-generated questions based on accuracy, difficulty, and topic

Question number	Accuracy	Difficulty level (1-4)	Topic
1	Major error	3	Blunt trauma
2	Correct	2	Blunt trauma
3	Major error	2	Penetrating trauma
4	Correct	2	Blunt trauma
5	Correct	2	Blunt trauma
6	Correct	3	Penetrating trauma
7	Correct	3	Pneumothorax
8	Correct	2	Pneumothorax
9	Correct	2	Pneumothorax
10	Minor error	2	Pneumothorax
11	Correct	3	Pneumothorax
12	Major error	2	Pneumothorax
13	Major error	2	Pleural effusion
14	Correct	3	Pleural effusion
15	Major error	3	Pleural effusion
16	Major error	3	Pleural effusion
17	Major error	4	Lung cancer
18	Major error	4	Lung cancer
19	Correct	2	Esophageal cancer
20	Correct	3	Esophageal cancer

AI: Artificial intelligence

Table 4. Evaluation of expert-generated questions based on accuracy, difficulty, and topic

Question number	Accuracy	Difficulty level (1-4)	Topic
1	Correct	2	Pleural effusion
2	Correct	3	Blunt trauma
3	Correct	2	Pneumothorax
4	Correct	2	Benign lung tumors
5	Correct	2	Esophageal cancer
6	Correct	2	Pneumothorax
7	Correct	3	Pleural effusion
8	Correct	2	Esophageal cancer
9	Correct	2	Pneumothorax
10	Correct	3	Blunt trauma
11	Correct	4	Blunt trauma
12	Correct	3	Pleural effusion
13	Correct	3	Foreign body aspiration
14	Correct	3	Lung abcess
15	Correct	3	Blunt trauma
16	Correct	3	Blunt trauma
17	Correct	4	Blunt trauma
18	Correct	3	Pneumothorax
19	Correct	3	Primary hyperhidrosis
20	Correct	2	Pleural effusion

AI-generated multiple-choice questions (MCQs) in thoracic surgery and compared student performance on AI-generated versus expert-generated exams. The results revealed a high major error rate (40%) in AI-generated questions, raising significant concerns about its unsupervised use in medical education.

Accuracy of AI-Generated Exam Questions

AI models have been praised for their ability to process vast amounts of medical knowledge quickly, yet their tendency to generate factually incorrect or misleading content limits their effectiveness.[11] Our findings align with previous studies that identified hallucinations (fabricated information presented as fact) in AI-generated medical content. The presence of multiple correct answers, incorrect answer keys, and medically inaccurate statements suggests that AI lacks contextual understanding and struggles with precise question formulation. The Delphi method, used in this study to assess question quality, confirmed that AI-generated exams contain errors that could mislead students and compromise medical training standards.

Another important finding of this study is the observed limitations of the AI model when generating questions related to real-life clinical reasoning and practical medical knowledge. The majority of major errors occurred in questions addressing applied clinical scenarios rather than purely theoretical content. This supports concerns that large language models, while effective in generating grammatically correct and seemingly plausible questions, may still fall short in domains requiring context-specific judgment or experiential understanding-especially in areas essential for junior medical assistants. Therefore, AI-generated content should be carefully reviewed before use in high-stakes educational settings, particularly when clinical decision-making is involved.

Comparison with Expert-Generated Questions

The expert-created exam had no major or minor errors, highlighting the superiority of human oversight in medical education. Expert validation ensures that questions align with evidence-based medicine, guidelines, and clinically relevant scenarios. The significantly lower error rate in expert-created exams reinforces the necessity of subject matter expertise in medical assessments.

Student Performance and Reliability of AI-Generated Exams

Despite the error-prone nature of AI-generated questions, student scores did not significantly correlate between the AI-generated and expert-generated exams ($r=0.042$, $p=0.929$). This suggests that AI-generated questions did not assess students' knowledge in the same manner as expert-designed exams. In contrast, studies have shown that expert-curated exams are better aligned with curriculum learning objectives and clinical competencies.[12,13] AI-based test generation tools must be refined to create consistent and standardized assessments.

Potential Role of AI in Medical Education

While AI-generated questions had a high error rate, AI could still be a valuable tool under expert supervision. AI may assist in generating a first draft of questions, which experts can refine for accuracy and clinical relevance. Previous research has demonstrated that AI can be useful for creating adaptive learning experiences and identifying knowledge gaps in students.[12,13] However, current AI technology is not yet reliable enough for unsupervised use in medical education.

Limitations

One limitation of this study is the small sample size of medical students (n=7), which may not fully represent the broader population. Additionally, only one AI model (Claude Sonnet 3.7 AI) was tested, and other LLMs, such as GPT-4 or Med-PaLM, might yield different results. In this context, it is important to note that the Claude Sonnet 3.7 model was not specifically trained by the authors using medical content or example questions; all generated questions were produced based solely on the model's pre-existing capabilities. This limits control over the content generation process and highlights the need for external validation mechanisms.

Future studies should explore larger student cohorts, test multiple AI models, and assess longitudinal performance improvements with AI-generated content. Furthermore, developing AI-guided question verification systems could mitigate the risk of erroneous content and enhance reliability in educational settings.

CONCLUSION

Our study demonstrates that AI-generated MCQs have a high error rate (40% major errors, 5% minor errors), making them unsuitable for standalone use in medical education. However, AI may have potential as a supplementary tool for question generation under expert supervision. Future advancements in AI technology, combined with rigorous human validation, could enhance the accuracy, reliability, and educational utility of AI-generated assessments. Until then, expert oversight remains essential to ensure high-quality medical education and patient safety.

ETHICAL DECLARATIONS

Ethics Committee Approval

As the study did not involve patient data, ethics committee approval was not required under the Helsinki Declaration.

Informed Consent

Informed consent was obtained from all student participants.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

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

Author Contributions

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

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Review

HEALTH SCIENCES
MEDICINE

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Cancer and foot health: special podologic approaches to oncology patients

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ABSTRACT

Cancer comprises a heterogeneous group of diseases associated with substantial global mortality and morbidity. Therapeutic modalities for these diseases frequently produce adverse effects-most notably skin and nail toxicities, hand-foot syndrome (HFS; palmar-plantar erythrodysesthesia), and peripheral neuropathy-that can markedly diminish patients' quality of life. Podiatric care is therefore critical for preventing and mitigating these sequelae. In this review, we systematically examine the foot-related complications of cancer therapy, describe their underlying pathophysiology, and delineate multidisciplinary podiatric interventions. We also highlight the benefits of close collaboration between podiatrists and oncology specialists in maintaining foot health during treatment. Finally, we summarise the specific effects of chemotherapy, radiotherapy, and immunotherapy on the feet and provide evidence-based recommendations for their management.

Keywords: Cancer, foot deformities, nail toxicities, podological care

INTRODUCTION

Cancer is a complex, multifactorial group of diseases associated with high global mortality and morbidity rates.[1] Despite substantial advances in diagnostic and therapeutic techniques, preserving patients' quality of life and minimising treatment-related adverse effects remain core objectives of contemporary oncology care.[2-4] Achieving these goals is challenging because anticancer therapies can compromise not only physical health but also psychosocial well-being.

Foot-related complications occupy a prominent place among treatment sequelae. Chemotherapy, in particular, may cause skin and nail toxicities-onycholysis, onychomadesis, melanonychia, leukonychia, paronychia, nail thickening, brittle nails, and fungal infections-together with oedema, xerosis, hand–foot syndrome (HFS), and peripheral neuropathy, all of which markedly diminish quality of life.[3-5] Nevertheless, awareness of foot health remains limited and this domain is frequently neglected, jeopardising treatment success and patient comfort.[5,6]

Podiatry is a multidisciplinary discipline devoted to preserving and enhancing foot health by addressing cutaneous, nail, anatomical, and functional concerns.[7] Chemotherapy, radiotherapy, and immunotherapy are known to induce immunological, circulatory, neuropathic, and metabolic alterations that adversely affect the feet.[8] Resultant problems-including nail toxicities, HFS, oedema, xerosis, hyperkeratosis, and neuropathy-can directly impair quality of life and, in severe cases, necessitate dose modification or discontinuation of cancer therapy.[5]

Effective management of these adverse effects is therefore critical for sustaining both quality of life and adherence to oncological treatment. A holistic strategy-engaging patients, podiatrists, and oncology teams-is required for prevention, early detection, and treatment of foot-related conditions. Through tailored preventive and therapeutic interventions, podiatry not only alleviates symptoms but also supports the overall success of cancer treatment.

Accordingly, this review systematically evaluates the significance of foot health during cancer therapy, delineates common foot-related complications in oncology patients, and summarises evidence-based podiatric approaches for their prevention and management.

THE EFFECTS OF THERAPIES ON FOOT HEALTH: PATHOPHYSIOLOGY AND CLINICAL APPROACHES

Cutaneous Effects

Cancer chemotherapy, particularly with the introduction of newer agents, has been associated with an expanding spectrum of cutaneous adverse effects. The most frequent reactions include alopecia, mucositis, hand-foot syndrome (HFS), dermatitis, xerosis, nail abnormalities, and paronychia. From a podiatric perspective, xerosis, nail pathology, and paronychia are especially significant. Nail disorders may manifest as structural deformation, brittleness, or discolouration, whereas paronychia is characterised by periungual inflammation, pain,

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and swelling, all of which can markedly diminish patients' quality of life. These complications limit daily activities and may necessitate treatment interruption because of secondary infection. Consequently, early identification and management of chemotherapy-induced cutaneous toxicity are essential to preserve quality of life and reduce morbidity.[9,10-12]

Podiatric Approach

Podiatric management of chemotherapy-induced cutaneous toxicities requires comprehensive care that preserves skin and nail integrity, prevents complications, and maintains quality of life. Preventive measures for conditions such as nail disorders and paronychia include regular nail care, strict hygiene, and consistent use of barrier-enhancing topical agents. Appropriate footwear and orthotic supports reduce mechanical pressure, whereas antiseptic treatment or prompt referral for medical intervention is warranted when infection is suspected, as in paronychia. Barrier-repair emollients should be prescribed to minimise xerosis and desquamation. Working as part of a multidisciplinary oncology team, podiatrists can enhance patient comfort and support treatment adherence through early recognition and targeted management of cutaneous symptoms. These strategies are essential for mitigating chemotherapy-related adverse effects.[10-12]

Nail Toxicities

Chemotherapy-induced nail toxicities result from direct injury to the nail matrix, nail bed and periungual tissues. Common manifestations include Beau's lines, onychomadesis, melanonychia, onycholysis, paronychia, periungual pyogenic granulomas and secondary fungal infections.[13,14] These conditions compromise both appearance and function, restrict daily activities and predispose patients to serious sequelae such as bacterial or fungal infection. Prompt recognition and treatment, supported by targeted podiatric interventions, are essential to limit morbidity, preserve quality of life and prevent interruptions in chemotherapy.[9,13,14]

Beau's Lines and Onychomadesis

Beau's lines are transverse grooves that form when the nail matrix is damaged by toxic agents and are frequently observed in drug-induced nail abnormalities, where they can compromise fine motor function. By contrast, onychomadesis is a more severe manifestation, characterised by complete separation of the nail plate from the matrix, and is a recognised indicator of chemotherapy-related toxicity.[13,14]

Melanonychia and Pigmentation Changes

Melanonychia is a pigmentation change produced by melanin deposition in the nail bed and is most often associated with cytotoxic agents or epidermal growth factor receptor (EGFR) inhibitors. Nail pigmentation should therefore be monitored regularly, particularly for features that might indicate malignant melanoma, which can present in a similar manner.[13,14] Although longitudinal melanonychia is usually drug-induced, it can, albeit rarely, be an early sign of malignant melanoma-especially when the band is asymmetrical, dark, or progressively changing.[15,18]

Onycholysis and Severe Reactions

Onycholysis is characterised by separation of the nail plate from the nail bed and is frequently associated with chemotherapeutic agents, including EGFR inhibitors, taxanes and 5-fluorouracil.[6,18]

Paronychia and Periungual Abscesses

Paronychia is characterised by periungual inflammation, pain and swelling, and is frequently linked to treatment with EGFR inhibitors. Periungual abscesses, which result from infection of the surrounding tissues, are most often observed during the second month of therapy.[13,18]

Periungual Pyogenic Granulomas

Periungual pyogenic granulomas present as painful granulation tissue around the nail and have been linked to certain chemotherapeutic agents.[14]

Disruptions in Skin Barrier and Hyperkeratotic Areas

Skin rashes, xerosis, hyperpigmentation and hyperkeratosis are skin-barrier disturbances reported with agents such as cyclophosphamide, chlorambucil and related drugs.[12]

Ingrown Toenail

Ingrown toenails, resulting from altered nail growth, are frequently observed in patients receiving chemotherapy.[19]

Nail Fungus (Onychomycosis)

Onychomycosis, which often develops in the context of immunosuppression, typically presents with nail thickening, discolouration and structural deformity.[20]

Podiatric Approach

Effective management of chemotherapy-induced nail and skin alterations begins with early patient education and structured preventive strategies. Patients should receive detailed information before treatment about potential adverse effects and the measures required to mitigate them. Key preventive elements include the early use of emollients and the avoidance of mechanical trauma such as friction, pressure, irritants and adhesives. Careful footwear selection and strict foot-hygiene protocols further reduce infection risk, enhance quality of life and help maintain treatment continuity.[6]

Preventive and supportive measures must be integrated with the targeted management of specific nail and skin conditions. For Beau's lines or onychomadesis, regular nail trimming and nail-strengthening preparations are advisable. Pigmentation changes such as melanonychia require close surveillance for early signs of malignancy. In onycholysis, cleansing the affected area with antiseptics and offloading pressure with soft insoles are essential. Severe or refractory reactions warrant prompt referral to a dermatologist or oncology specialist.[13,14]

Paronychia and periungual abscesses require prompt, effective intervention to minimise the risk of secondary infection. Topical antiseptics should be applied to curtail microbial proliferation, and excessive moisture must be avoided to preserve periungual tissue integrity. Initial management of

periungual pyogenic granulomas includes meticulous hygiene and the application of protective dressings; more advanced lesions may necessitate surgical excision or cryotherapy in collaboration with dermatology specialists.[13-17]

Management of skin-barrier disruption and hyperkeratotic lesions should include barrier-restoring, hydrating formulations to promote epidermal regeneration. Pressure-relieving soft insoles can further reduce friction and alleviate symptoms. Ingrown toenails are best addressed with regular, appropriate trimming and, when necessary, podiatric corrective techniques. Onychomycosis requires topical or systemic antifungal therapy supplemented by mechanical debridement of the affected nail. Finally, maintaining nail hygiene and avoiding persistently moist environments are essential to limit pathogen proliferation and prevent reinfection.[18,20]

All of these strategies should be implemented within a multidisciplinary care model that fosters effective collaboration among podiatrists, dermatologists and oncology specialists. Early diagnosis, regular follow-up and timely application of evidence-based treatment protocols are essential for mitigating chemotherapy-induced nail and skin toxicities and for improving patients' quality of life. A holistic, team-based approach not only addresses current symptoms but also minimises the risk of future complications.

Hand-Foot Syndrome

HFS is a common skin reaction associated with chemotherapy, typically starting with numbness, tingling, and burning sensations on the palms and soles. These symptoms can progress to include edema, cracking, desquamation, or sharply demarcated erythema and may lead to blistering and ulceration in advanced stages. HFS is particularly linked to drugs such as PLD (pegylated liposomal doxorubicin), docetaxel, 5-FU (5-fluorouracil), capecitabine, and S-1 (a combination oral fluoropyrimidine chemotherapy composed of tegafur, gimeracil, and oteracil), with the risk heightened by continuous infusion or medications maintaining high serum levels. Although not life-threatening, HFS is painful and significantly impairs quality of life by restricting daily activities.[20] HFS is commonly classified into grades 1 to 3 based on clinical severity. Grade 1 is characterized by minimal skin changes such as mild erythema, edema, or hyperkeratosis; symptoms are typically painless and can be managed with moisturizers and protective measures to avoid irritation. Grade 2 involves blistering, desquamation, and painful hyperkeratosis that may limit instrumental activities of daily living; treatment includes topical corticosteroids, emollients, and, when necessary, chemotherapy dose adjustments. Grade 3 is marked by ulceration, severe pain, and significant restriction in self-care activities, often requiring treatment interruption, wound care, and infection prevention strategies. This grading system provides a valuable framework for guiding therapeutic decision-making.[21]

HFS is a frequent cutaneous reaction to chemotherapy that usually begins with numbness, tingling and burning of the palms and soles. These initial sensations may progress to oedema, fissuring, desquamation or sharply demarcated erythema and, in advanced stages, to blistering or ulceration. The condition is particularly associated with pegylated liposomal doxorubicin (PLD), docetaxel, 5-fluorouracil (5-FU), capecitabine and S-1 (a combination oral fluoropyrimidine that contains tegafur, gimeracil and oteracil). Continuous infusions or agents that sustain high serum drug levels further increase risk. Although not life-threatening, HFS is painful and significantly restricts daily activities, thereby impairing quality of life.[20]

Clinically, HFS is graded from 1 to 3 according to severity. Grade 1 involves minimal skin changes-mild erythema, oedema or hyperkeratosis-that are usually painless and managed with emollients and simple protective measures. Grade 2 is characterised by blistering, desquamation or painful hyperkeratosis that limits instrumental activities of daily living; treatment comprises topical corticosteroids, emollients and, when necessary, chemotherapy dose modification. Grade 3 presents with ulceration, severe pain and pronounced limitation of self-care activities, often necessitating treatment interruption, comprehensive wound care and stringent infection-control measures. This grading system provides a practical framework for therapeutic decision-making.[21]

Podiatric Approach

A comprehensive podiatric strategy is essential for mitigating HFS-related morbidity and improving patients' quality of life. Key measures include rigorous hand and foot hygiene, preservation of the skin barrier and routine use of hydrating products to minimize irritation. Proper footwear, soft insoles and toe protectors help to off-load pressure on vulnerable areas. In advanced cases characterized by desquamation, blistering or ulceration, scheduled follow-up is required for wound care and infection control. Patient education is equally important, fostering early recognition of cutaneous changes and timely preventive action. Collectively, podiatric interventions lessen HFS-related pain, support daily functioning and reinforce adherence to anticancer therapy.[7]

Early assessment of foot health can prevent minor issues from progressing into more severe complications. Regular maintenance of appropriate footwear and strict hygiene practices lower the risk of infection, thereby enhancing both quality of life and adherence to treatment. Supportive measures-particularly the use of urea-based emollients-help to mitigate cutaneous toxicities, reduce the incidence of hand-foot skin reaction (HFSR) and delay symptom onset. This strategy alleviates discomfort while effectively addressing scaling, erythema and fissuring.[6,21]

Beyond standard skincare and pressure-relief measures, recent studies emphasize the prophylactic value of localized cold applications-particularly cryotherapy-administered during chemotherapy infusion. By lowering drug perfusion to the distal extremities, cryotherapy significantly reduces both the incidence and severity of hand–foot syndrome, especially in patients treated with capecitabine or liposomal doxorubicin. Integrating this technique into podiatric preventive protocols

can enhance patient comfort and promote adherence to anticancer therapy.[20,22,23]

Peripheral Neuropathy

Peripheral neuropathy is a serious complication that causes sensory loss, impaired neuromuscular control of the lower extremities and balance disturbances, thereby increasing the risk of falls. Chemotherapy-induced peripheral neuropathy (CIPN) develops in response to agents such as taxanes, platinum compounds and proteasome inhibitors. It typically presents as numbness, tingling and neuropathic pain in the hands and feet. Symptoms persist long after the completion of chemotherapy in roughly 30% of patients and, in those treated with oxaliplatin, may endure for several years. CIPN therefore not only diminishes quality of life but can also necessitate dose modification or even discontinuation of anticancer therapy.[24,25]

Podiatric Approach

CIPN management benefits from a podiatric approach delivered within a multidisciplinary team to reduce symptoms, preserve mobility and enhance quality of life. Regular foot examinations are essential for early detection of neuropathic changes and for maintaining skin integrity. Footwear should be optimized to minimize pressure points, and cushioning insoles can provide further support. Barrier-restoring emollients are recommended for daily skin care, and strict hygiene protocols must be upheld.

Foot-protection measures are essential to prevent injury in the context of sensory loss, and any trauma or infection should trigger prompt intervention. Patients with balance impairment may benefit from assistive devices and targeted exercise programmers. Although novel treatments for neuropathic pain are under investigation, patient education remains crucial to foster active engagement in self-care.

When symptoms are severe, referral to the appropriate specialist should be made within the multidisciplinary team. Together, these measures help limit the quality-of-life reduction associated with CIPN, promote adherence to anticancer therapy and support overall well-being.[24,26]

Radiotherapy and immunotherapy can also produce cutaneous adverse effects that compromise foot health.[27] Radiotherapy may induce erythema, dryness, desquamation, fibrosis or oedema within the irradiated field, and these reactions can involve the lower extremities when treatment sites are located distally. Resultant skin changes weaken the dermal barrier and increase susceptibility to infection and ulceration. Immune-checkpoint inhibitors have been linked to inflammatory dermatoses, including rash and lichenoid eruptions, which may likewise affect the feet. Although less prevalent than chemotherapy-related toxicities, these reactions can cause discomfort, restrict mobility and diminish quality of life.[27,28]

Podiatric management should include regular skin assessment, liberal use of emollients, and protective dressings when indicated. Severe or persistent lesions warrant early referral to dermatology or wound-care specialists.[28]

THE ROLE OF PODIATRY IN ONCOLOGY PATIENTS

Podiatric Approaches in Maintaining Foot Health

Podiatry is essential to preventing and managing the skin and nail complications that arise during cancer therapy. By prioritizing early diagnosis and preventive care, podiatric interventions reduce adverse events and promote adherence to oncological treatment. Pre-chemotherapy education should therefore teach patients how to maintain skin integrity through regular moisturization and how to select footwear that minimizes friction and pressure.[6,17]

Podiatric Assessment and Intervention in Cancer Treatments

Podiatry forms an essential part of multidisciplinary care for patients receiving chemotherapy. Podiatrists should follow the assessment and intervention sequence detailed in **Table**. Nail toxicities such as Beau's lines, onycholysis, melanonychia and paronychia heighten infection risk and limit daily activities, thereby reducing quality of life. Effective management includes regular nail care, antiseptic treatment and referral to specialist services when necessary. Where structural deformities affect the nail matrix or surrounding tissues, protective devices are recommended and additional precautions taken to prevent infection.[6,14]

Podiatric care focuses on the early detection and management of HFS by prescribing pressure-reducing insoles and specialized footwear to maintain mobility and by applying barrier-enhancing products and wound-care protocols to halt the progression of cracking, blistering and desquamation.[17]

For CIPN, podiatrists perform regular foot examinations to identify neuropathic changes promptly and prevent sensory-related injuries. They improve balance by optimizing footwear and cushioning insoles, recommend emollients and strict hygiene to preserve skin integrity and incorporate targeted exercise programmers and assistive devices for patients with postural instability.[24]

Enhancing Patient Comfort Through Multidisciplinary Management

Podiatrists collaborate with dermatologists, oncologists and other healthcare professionals to deliver a multidisciplinary strategy for managing chemotherapy-induced adverse effects. This coordinated care pathway facilitates timely referral of patients with severe manifestations to the appropriate specialist. Regular follow-up and prompt intervention help to avoid treatment interruptions, thereby safeguarding overall health and sustaining quality of life.[6,7]

Beyond symptom relief, podiatric interventions are designed to prevent long-term complications. By improving physical comfort, they enhance adherence to therapy and contribute meaningfully to the overall success of cancer treatment. Consequently, podiatry plays a critical role in improving quality of life and reducing treatment-related challenges in oncology patients.[4-6]

Table. Podological assessment and intervention in cancer treatments

Cancer treatment phase	Common foot-related issues	Assessment focus & tools	Recommended interventions	Potential benefits/rationale
Pre-treatment (diagnostic/baseline evaluation)	- Pre-existing foot pathologies (e.g., calluses, corns, fungal infections) - Structural deformities (e.g., hammertoes, bunions) - Diabetic foot risk (if comorbidity exists)	- Thorough clinical examination (inspection, palpation) - Biomechanical assessment (gait analysis, foot structure) - Neurovascular assessment (monofilament, Doppler if needed)	- Treat pre-existing conditions (callus debridement, antifungal therapy) - Patient education on foot hygiene, footwear choices - Referral for custom orthotics if needed	- Reduces risk of complications during treatment (e.g., infection) - Ensures a baseline for monitoring changes - Improves patient comfort and mobility
During chemotherapy	- Chemotherapy-induced peripheral neuropathy: numbness, tingling, neuropathic pain - Nail changes (onycholysis, discoloration) - Increased risk of infection (immunosuppression)	- Sensory testing (tuning fork, monofilament) to track neuropathy progression – Regular nail inspection for discoloration, lifting - Skin integrity checks (fissures, ulcerations)	- Protective offloading or cushioning insoles to reduce pressure in neuropathic areas - Gentle nail care to prevent ingrown nails; sterile technique to avoid infection - Emollients to reduce skin dryness and cracking - Patient education on temperature checks (avoid burns/cold injury)	- Decreases pain and functional impairment - Early detection and management of potential infections - Maintains foot health despite immune compromise
During radiotherapy	- Radiation dermatitis on feet (if the treatment field includes lower extremities) - Skin dryness, desquamation, erythema - Risk of ulcerations on weight-bearing areas	- Detailed skin assessment (visual scoring scales like RTOG*) - Palpation for tenderness, edema, or fluid retention - Footwear assessment (ensure minimal friction)	- Use of non-adherent dressings and topical agents (hydrogels, silicones) for radiation dermatitis - Pressure offloading with cushioned footwear or insoles - Regular foot inspections to detect early skin breakdown	- Minimizes pain and risk of secondary infections - Promotes healing of irritated or damaged skin - Improves patient adherence to radiotherapy by reducing discomfort
During immunotherapy	Inflammatory skin reactions (rash, lichenoid eruptions), erythema, dryness involving the feet	Regular visual inspection for rash, desquamation, and irritation; assessment for discomfort and walking difficulty	Emollients for dryness, non-irritating skin cleansers, dermatology referral if widespread or persistent; cushioning insoles if mobility is affected	Reduces symptom burden, enhances mobility, supports treatment adherence through improved comfort
Post-surgery/post-transplant	- Edema or lymphedema in lower extremities - Surgical wound healing issues around incisions (especially if reconstructive surgery on/near foot) - Limited mobility / activity intolerance	- Edema/lymphedema measurement (tape measure, volumetric assessment) - Wound inspection (signs of infection, dehiscence) - Mobility assessment (gait stability, use of assistive devices)	- Compression therapy or garments for lymphedema - Gentle range-of-motion exercises, rehabilitation plan - Pressure-relieving insoles or specialized footwear for wound sites - Collaboration with physical therapy for gait retraining	- Facilitates faster recovery post-surgery - Reduces complications such as infection or prolonged edema - Enhances overall functional outcomes (improved walking ability, independence)
Palliative/end-of-life care	- Painful neuropathy, chronic wounds, or ulcers - Nail and skin pathologies often neglected - Reduced ability to self-care (mobility constraints)	- Pain assessment scales (e.g., VAS, numeric rating) specific to foot discomfort - Inspection for pressure ulcers, fungal infections - Family/caregiver involvement in foot care evaluation	- Comfort-focused foot care (nail trimming, callus reduction, gentle massage) - Appropriate offloading devices to prevent pressure ulcers - Coordination with hospice or home-care nurses for ongoing foot monitoring - Patient/caregiver education on daily foot checks	- Alleviates foot pain and discomfort, improving quality of life - Prevents secondary infections and complications in fragile patients - Provides dignity and comfort in palliative settings

Notes and References:
***RTOG (Radiation Therapy Oncology Group) scoring system is commonly used for grading radiation dermatitis severity.**
Common sources in scientific literature include:
- **Supportive Care in Cancer (Springer)**
- **Journal of the American Podiatric Medical Association**
- **Cancer Nursing (Lippincott Williams & Wilkins)**
- **European Journal of Oncology Nursing**

This table offers a broad overview; actual clinical practices may vary based on institutional protocols, patient comorbidities, and specific oncology team recommendations.

CONCLUSION

Cancer therapy can markedly diminish quality of life through skin and nail toxicities, hand-foot syndrome and peripheral neuropathy. These adverse effects cause physical discomfort and disrupt psychosocial well-being, sometimes even necessitating treatment interruption. In this context, podiatry is critical for preserving and restoring foot health in oncology patients. Podiatric care must be delivered within a multidisciplinary framework to facilitate early symptom detection and complication prevention. Core measures include patient education, regular foot examinations and evidence-based interventions tailored to the individual. Individualized care plans for nail toxicities and hand-foot syndrome, together with strict infection control, judicious footwear selection and pressure-relieving strategies, are indispensable for safeguarding skin and nail integrity. Embedding podiatrists in oncology teams promotes a holistic model of care. Such collaboration not only controls side effects but also improves treatment adherence and optimizes therapeutic

outcomes. Early podiatric intervention is particularly valuable for chemotherapy-induced peripheral neuropathy, helping to preserve mobility and reduce fall risk. Overall, the management of foot and nail complications underscores the pivotal role of podiatry in oncology. Prioritizing foot health can substantially enhance patient outcomes and quality of life. Raising awareness, deepening the integration of podiatrists into cancer-care teams, expanding clinical practice and fostering research are essential steps toward more comprehensive and effective supportive care.

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Referee Evaluation Process

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Author Contributions

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

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Letter to the Editor

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Advanced cervical cancer: how to interpret the new standard of care

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Dear Editor,

As pivotal practice-changing studies, the KEYNOTE-826 (KN-826) and BEATcc trials provided the opportunity to add immune checkpoint inhibitors (ICPIs) to the combination of platinum-taxane doublet chemotherapy and bevacizumab, which has been the standard of care for advanced cervical cancer for many years.[1-3] Based on subgroup analysis of KN-826, adding pembrolizumab to chemotherapy provided clinically meaningful progression-free survival (PFS) and overall survival (OS) benefit in programmed death-ligand 1 (PD-L1) combined positive score (CPS) ≥1 tumors and independent of concomitant bevacizumab use. The BEATcc study was initiated at approximately the same time as KN-826 and its results were announced very recently. The addition of atezolizumab to platinum-based doublet chemotherapy plus bevacizumab significantly improved PFS and OS in a cohort of patients included independently of PD-L1. Combination with ICPI represents the current benchmark for the first-line treatment of advanced cervical cancer. However, there are still issues that need to be questioned in terms of precision medicine.

In the KN-826 study, the proportion of PD-L1 negative patients was only 11.4%, whereas the patients with a PD-L1 CPS ≥10 represented more than half (51.3%). On the other side, the PD-L1 rate was not stated in the BEATcc study. Advanced cervical cancer has been reported to have lower PD-L1 positivity rates in real life.[4] Therefore, PD-L1 negative patients who are more likely to be encountered in real life, appear to be relatively underrepresented in studies.

These two randomized trials suggest nuances of benefit in certain patient groups. According to the subgroup analysis, age of the women (cut off of 65), stage of the disease at diagnosis (denovo metastatic or recurrent disease), previous exposure to chemoradiotherapy may influence the extent of benefit. The proportion of patients aged ≥65 years was less than 20% in both studies. Women over the age of 65 are more likely to present with advanced disease at diagnosis and have higher rates of comorbidities compared with younger women.[5] The proportion of patients achieving a complet response (CR) was found to be approximately 30% in both studies. It may be considered to evaluate whether local treatment would be beneficial in these patients.

To summarize briefly, we believe that studies that are not limited by the selection criteria of randomized clinical trials, reflect real-life practices, and measure outcomes for larger patient groups with more balanced representation of different subgroups would be valuable.

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