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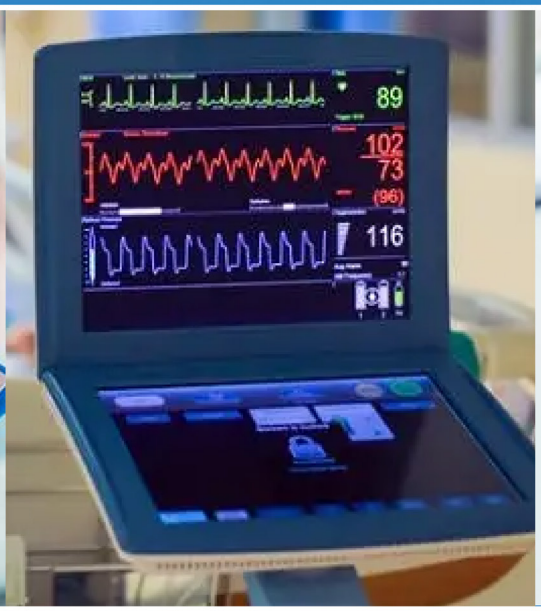

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Dear Colleagues,

We are pleased to share that the Intercontinental Journal of Internal Medicine continues to strengthen its contribution to the scientific community with high quality and up to date studies. Following a productive and successful year, we proudly continue our publication journey in 2026 with renewed enthusiasm and commitment to scientific excellence.

Our primary aim remains to enhance our journal's international visibility and reputation, representing our country in the global academic arena while ensuring that valuable research from around the world reaches our readers. We are committed to maintaining rigorous scientific standards and supporting the dissemination of innovative and impactful research in the field of internal medicine.

As we enter another year of publication, we are delighted to present original research articles, case reports, review articles, systematic reviews, meta-analyses, brief reports, and letters to the editor, all of which we believe will contribute meaningfully to the literature and clinical practice.

I would like to sincerely thank our readers for their continued interest and support, our authors for entrusting us with their valuable work, our reviewers for their meticulous and unbiased evaluations, and our editorial team for their dedication and hard work in sustaining the regular publication of ICJIM.
We look forward to another productive year together.

Sincerely yours,

Asst. Prof. Duygu FELEK

Editor-in-Chief

The Intercontinental Journal of
Internal Medicine

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LETTER TO THE EDITOR

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Original Article

Evaluation of inflammatory markers in the diagnosis, differential diagnosis, and prognosis of pulmonary sarcoidosis

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ABSTRACT

Aims: Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), systemic immune-inflammation index (SII), C-reactive protein-to-albumin ratio (CAR), and prognostic nutritional index (PNI) are practical and readily available laboratory markers that provide valuable information regarding the diagnosis, disease severity, and prognosis of various inflammatory conditions. This study aimed to evaluate the diagnostic and prognostic utility of these inflammatory indices (NLR, PLR, LMR, SII, CAR, and PNI) in patients with pulmonary sarcoidosis.

Methods: This retrospective study included 107 patients diagnosed with sarcoidosis and 103 healthy control subjects who were evaluated at Şişli Etfal Training and Research Hospital between November 15, 2019, and November 15, 2024. Demographic characteristics, radiological findings, disease stages, and baseline laboratory parameters-including neutrophil, lymphocyte, platelet counts, C-reactive protein, and albumin levels-were recorded. The inflammatory indices were calculated, and statistical and regression analyses were performed to assess their diagnostic and prognostic significance.

Results: The study population consisted of 107 patients with pulmonary sarcoidosis and 103 healthy controls. A statistically significant difference in PNI values was observed among different disease stages in the patient group ($F=7.099$, $p<0.01$). Pairwise comparisons revealed significant differences in PNI values between stage 1 and stage 2 ($p<0.05$), stage 2 and stage 3 ($p<0.01$), and stage 2 and stage 4 ($p<0.05$). CAR values also differed significantly across disease stages ($H=18.286$, $p<0.01$). Additionally, PNI values were significantly lower in patients with poor prognosis compared to those with good prognosis ($t=2.966$, $p<0.01$).

Conclusion: Inflammatory indices derived from routine laboratory parameters demonstrate diagnostic and stage-related associations in pulmonary sarcoidosis. Among these markers, PNI was the only inflammatory index independently associated with poor prognosis, suggesting that nutritional-inflammatory status may provide additional prognostic information in clinical practice.

Keywords: Pulmonary sarcoidosis, inflammation, prognosis, prognostic nutritional index, Neutrophil-to-lymphocyte ratio

INTRODUCTION

Sarcoidosis is a systemic granulomatous disease of unknown etiology, characterized by noncaseating granuloma formation resulting from an exaggerated immune response to unidentified antigens. The disease most commonly affects the lungs and intrathoracic lymph nodes, although extrapulmonary involvement is frequently observed and contributes significantly to disease heterogeneity and prognosis.[1,2] The clinical course ranges from spontaneous remission to chronic progressive disease with pulmonary fibrosis, underscoring the need for reliable biomarkers that reflect inflammatory burden and disease activity.[1]

The immunopathogenesis of sarcoidosis is driven by dysregulated interactions between activated macrophages, monocytes, and T lymphocytes, leading to persistent granulomatous inflammation. This process is accompanied by systemic inflammatory activation and increased production of proinflammatory cytokines and acute-phase reactants.[2,3] In granulomatous and chronic inflammatory diseases, such immune activation is known to influence circulating leukocyte subsets, platelet activation, and nutritional-inflammatory balance, which can be quantified using composite inflammatory indices derived from routine laboratory tests.[3-6]

In recent years, inflammation-based indices such as the neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), platelet-to-lymphocyte ratio (PLR), systemic immune inflammation index (SII), C-reactive protein-to-albumin ratio (CAR), and prognostic nutritional index (PNI) have gained increasing attention as accessible markers reflecting systemic inflammation and immune-nutritional status. These indices have demonstrated diagnostic and prognostic relevance in various chronic inflammatory and immune-mediated disorders, including granulomatous diseases.[3]

Several previous studies have investigated selected inflammatory markers in sarcoidosis. Elevated levels of

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classical biomarkers such as angiotensin-converting enzyme, soluble interleukin-2 receptor, interleukin-18, and C-reactive protein have been associated with disease activity and organ involvement.[3-5] However, these biomarkers are not always routinely available and may lack sufficient specificity for clinical decision-making. More recently, hematological indices such as NLR and PLR have been evaluated in sarcoidosis, with studies reporting associations with radiological stage, extrapulmonary involvement, and prognosis.[6-8] Nevertheless, the results remain inconsistent, and most studies have focused on a limited number of indices without comprehensive evaluation across disease stages and outcomes.[3,5-8]

Importantly, there is a paucity of data simultaneously assessing multiple inflammation-based indices-including SII, CAR, and PNI-in patients with newly diagnosed pulmonary sarcoidosis, particularly in relation to radiological staging and clinical prognosis.[6-8] The potential role of combined inflammatory and nutritional indices in reflecting disease severity and predicting outcomes in sarcoidosis therefore remains insufficiently defined.[3-6]

Accordingly, the primary aim of this study was to evaluate the diagnostic value of systemic inflammatory indices in distinguishing patients with newly diagnosed pulmonary sarcoidosis from healthy controls. The secondary aim was to investigate the associations of these indices with radiological disease stages and clinical prognosis, thereby addressing an important gap in the existing literature and exploring their potential utility as practical biomarkers in clinical assessment and risk stratification.[5,6-8]

METHODS

Ethics

The study was conducted with the permission of the Clinical Researches Ethics Committee of Şişli Hamidiye Eftal Training and Research Hospital (Date: 03.12.2024, Decision No: 2840). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design

This study was designed as a single-center, retrospective cohort study conducted at the Chest Diseases Outpatient Clinics of Şişli Hamidiye Eftal Training and Research Hospital. Medical records of patients evaluated between November 15, 2019, and November 15, 2024, were systematically reviewed. Adult patients with a definitive diagnosis of sarcoidosis were included based on compatible clinical manifestations, radiological findings, and histopathological confirmation, in accordance with established diagnostic criteria. A control group of individuals without sarcoidosis was included to assess the diagnostic value of systemic inflammatory indices. Due to the retrospective nature of the study, no additional diagnostic or therapeutic interventions were performed. All laboratory analyses, imaging studies, pulmonary function tests, and clinical assessments were conducted as part of routine clinical care at the time of diagnosis and during standard outpatient follow-up.

The primary objective of the study was to evaluate the diagnostic and prognostic significance of baseline systemic inflammatory indices measured at the time of diagnosis. Accordingly, inflammatory indices were compared between patients with and without sarcoidosis, and their associations with disease severity, radiological stage, and clinical outcomes were analyzed. Follow-up data were obtained from outpatient clinic visits and electronic medical records, allowing longitudinal assessment of disease course. This retrospective observational design enabled the evaluation of real-world clinical data without influencing patient management.

Clinical prognosis was predefined prior to analysis and categorized as poor or favorable based on objective criteria assessed during follow-up. Poor prognosis was defined by the presence of one or more of the following: need for systemic therapy (systemic corticosteroids and/or immunosuppressive agents) due to disease progression or persistent symptoms; radiological progression, including worsening radiological stage or development of new parenchymal or fibrotic changes; or a ≥10% relative decline in forced vital capacity (FVC) compared with baseline. Patients who did not meet these criteria and remained clinically stable or showed improvement during follow-up were classified as having a favorable prognosis. The predefined follow-up duration was 24 months after diagnosis.

Study Population

The study population consisted of patients with sarcoidosis and healthy control subjects.

Sarcoidosis Group

The sarcoidosis group included 107 patients with a definitive diagnosis of sarcoidosis established through compatible clinical findings, radiological features, and histopathological confirmation.

Control Group

The control group consisted of 103 healthy individuals with complete baseline laboratory data, selected from individuals attending outpatient clinics or health screening programs. Participants in the control group had no history of sarcoidosis or other inflammatory, autoimmune, malignant, or chronic systemic diseases that could affect systemic inflammatory parameters. None were receiving systemic corticosteroids, immunosuppressive agents, or anti-inflammatory treatments at the time of enrollment.

Inclusion and Exclusion Criteria

Participants aged ≥18 years with available baseline laboratory data and documented informed consent were eligible for inclusion. To minimize confounding related to systemic inflammation, pregnant women and individuals with malignancy, metabolic disorders, rheumatologic diseases, vasculitis, inflammatory bowel disease, hematological disorders, chronic kidney disease, autoimmune diseases, cardiovascular disease, chronic lung diseases, or other serious comorbid conditions were excluded.

Data Collection and Laboratory Measurements

Demographic and clinical data were retrospectively obtained from electronic medical records of the patients. Data regarding age, sex, posteroanterior (PA) chest X-ray and thoracic computed tomography (CT) findings, hemoglobin, serum albumin and CRP levels, neutrophil, lymphocyte, monocyte, and platelet counts, radiological stage of sarcoidosis, pulmonary function test parameters, extrapulmonary involvement, treatment requirements, and

clinical course during follow-up were recorded. Baseline systemic inflammatory indices-including NLR, LMR, PLR, SII, CAR, PNI-were calculated using standard formulas derived from laboratory parameters obtained at the time of diagnosis.

The inflammatory indices were calculated as follows: NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count; LMR was calculated as the absolute lymphocyte count divided by the absolute monocyte count; PLR was defined as the platelet count divided by the lymphocyte count; SII was calculated using the formula platelet count×neutrophil count/lymphocyte count; CAR was calculated as serum C-reactive protein level divided by serum albumin level; and PNI was calculated as serum albumin (g/L)+5× total lymphocyte count (10^9/L). These formulas are widely accepted and have been previously validated as reliable indicators of systemic inflammation and nutritional status in chronic inflammatory and granulomatous diseases. The inflammatory indices were calculated using standard and previously validated formulas as described in the literature.[6,7,9,10]

Radiological Staging

Patients with sarcoidosis were radiologically staged according to standard chest X-ray classification into five categories: stage 0, normal chest radiograph; stage 1, bilateral hilar lymphadenopathy; stage 2, bilateral hilar lymphadenopathy with pulmonary parenchymal involvement; stage 3, pulmonary parenchymal involvement without hilar lymphadenopathy; and stage 4, pulmonary fibrosis.

Statistical Analysis

Patient data collected within the scope of the study were analyzed using the IBM Statistical Package for the Social Sciences (SPSS) for Windows 29.0 (IBM Corp., Armonk, NY). Frequency and percentage values for categorical and mean and standard deviation for continuous data were given as descriptive values. For comparisons between two groups, the independent sample t-test was used, and the Pearson' chi-square test was used to compare categorical variables. The specificity and sensitivity of the study results were evaluated via ROC analysis. Univariable analyses were performed to evaluate the association between each clinical and laboratory variable and poor prognosis in patients with sarcoidosis.

Univariable logistic regression models were constructed for the statistical evaluation of demographic characteristics, smoking exposure, radiological stage, extrapulmonary involvement. Baseline CRP levels, and systemic inflammatory indices, including NLR, LMR, PLR, SII, CAR, and PNI. odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for each variable. Variables demonstrating clinical relevance and/or a p-value <0.10 in univariable analyses were considered candidates for inclusion in multivariable models. Multivariable logistic regression analysis was performed to identify independent predictors of poor prognosis in patients with sarcoidosis. A parsimonious multivariable model was constructed by including variables with clinical significance and those meeting the predefined statistical threshold in univariable analysis. Adjusted odds ratios with 95% CIs were reported. All statistical tests were two-sided, and a p-value <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics

The study population consisted of 210 participants, including 107 patients with pulmonary sarcoidosis and 103 healthy control subjects (**Figure**). Sarcoidosis group comprised 73 (68.2%) female and 34 (31.8%) male patients, while the control group consisted of 57 (55.3%) female and 46 (44.7%) male participants without any statistically significant intergroup difference in terms of gender distribution (p=0.055). The mean age was 51.87 years in the sarcoidosis group and 51.67 years in the control group, without any significant intergroup difference (p=0.925) (**Table 1**). Patients with sarcoidosis demonstrated significantly altered inflammation-based indices compared with controls, reflecting a higher systemic inflammatory burden at the time of diagnosis.

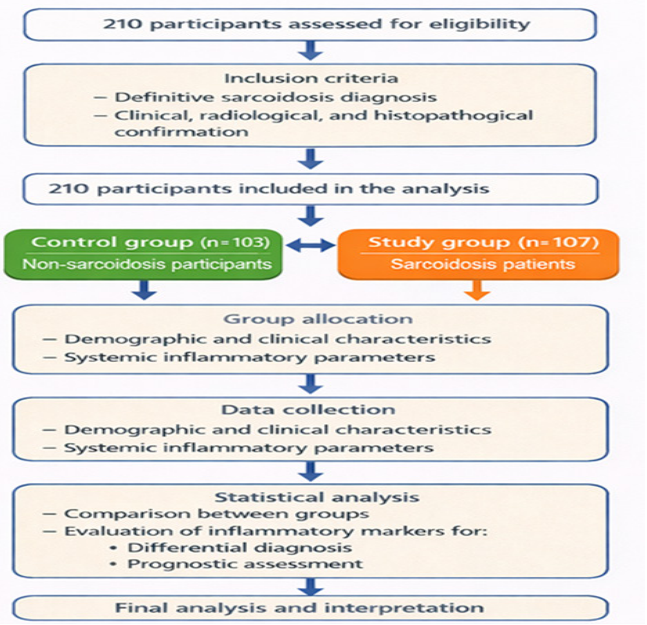

Figure. Flowchart of patient selection and study design

Compared with the control group, patients with sarcoidosis exhibited significantly lower hemoglobin (Hb) and hematocrit (HCT) levels (p=0.042 and p=0.038, respectively). Additionally, significant differences were identified between the two groups regarding alkaline phosphatase (ALP), albumin, CRP, and all evaluated inflammatory indices, including NLR, LMR, PLR, CAR, PNI, and SII (all p<0.01) (**Table 2**).

When inflammatory indices of the patients with sarcoidosis were analyzed according to radiological stages, a statistically significant difference was observed for PNI values (F=7.099, p<0.01). Post-hoc analysis with Tukey correction revealed significant differences between stages 1 and 2 (p=0.041), stages 2 and 3 (p<0.01), and stages 2 and 4 (p=0.015). Similarly, LMR values differed significantly across radiological stages (H=9.816, p=0.02), mainly driven by differences observed between stage 2 and stage 3 (p=0.007) and between stages 2 and 4 (p=0.026). CAR values also showed significant variation among stages (H=18.286, p<0.01), primarily due to differences between stage 1 and stage 2 (p<0.01) and between stage 2 and stage 3 (p=0.001). No statistically significant stage-related differences were observed for NLR, PLR, or SII (**Tables 2 and 3**). Regarding clinical prognosis, PNI values were significantly lower in patients with a poor prognosis than in those with a favorable prognosis (p=0.004). No significant correlations

were detected between prognosis and NLR, LMR, PLR, CAR, or SII values (Table 4).

Table 1. Comparison of study groups in terms of demographic characteristics, hematological parameters, and inflammatory markers

Variables	Study group (n=107)	Control group (n=103)	p-value
Gender n (%)			0.055[3]
Female	73 (68.2)	57 (55.3)	
Male	34 (31.8)	46 (44.7)	
Age	51.87±15 (23-87)	51.67±15.8 (19-81)	0.925[1]
Albumin (g/L)	41.9 (32.1-51)	43.2 (31.7-50.2)	0.0001**[2]
White blood cell ($x10^9$/L)	6.8 (3.41-12.91)	7.29 (4.52-10.9)	0.204[2]
Neutrophil ($x10^9$/L)	4.39 (1.89-11.15)	4.2 (0.39-9.29)	0.169[2]
Lymphocyte ($x10^9$/L)	1.64 (0.24-4.2)	2.22 (0.98-4.4)	0.0001**[2]
Platelet ($x10^9$/L)	265 (100-533)	252 (150-433)	0.289[2]
Monocyte ($x10^9$/L)	0.51 (0.12-1.2)	0.4 (0.2-2.3)	0.002**[2]
C-reactive protein (mg/L)	8.14 (0.3-198)	2.06 (0.1-8)	0.0001**[2]
NLR	1.89 (0.99-14.22)	1.39 (-9.38- 3.63)	0.0001**
LMR	3.39 (0.49-25.58)	5.23 (1-12.47)	0.0001**
PLR	152.9 (74.9-825)	116.84 (51.14-300)	0.0001**
CAR score	0.199 (0.007-6)	0.048 (0.002-0.178)	0.0001**
PNI	41.91 (32.11-51.01)	43.21 (31.71-50.21)	0.0001**
SII index	649.03 (268.46-8563.5)	500.63 (58.03-1716.8)	0.0001**

NLR: Neutrophil-to-lymphocyte ratio, LMR: Lymphocyte-to-monocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune-inflammation index, CAR: C-reactive protein-to-albumin ratio, PNI: Prognostic nutritional index. [1]: Analysis of Variance ANOVA; [2]: Kruskal- Wallis test; *: p<0.05; **: p<0.01; Parameters indicated with *, **, **2 are represented as median (min-max) values

ROC analyses demonstrated that all evaluated inflammatory indices had statistically significant discriminatory ability for sarcoidosis. The optimal cut-off values, sensitivities, and specificities were as follows: NLR, cut-off 1.54 (sensitivity 65.4%, specificity 65.0%); LMR, cut-off 4.47 (sensitivity 71.8%, specificity 72.0%); PLR, cut-off 133.82 (sensitivity 68.2%, specificity 68.0%); CAR, cut-off 0.0805 (sensitivity 72.9%, specificity 73.8%); PNI, cut-off 42.57 (sensitivity 64.1%, specificity 64.5%); and SII, cut-off 559.99 (sensitivity 62.6%, specificity 62.3%). All ROC analyses were statistically significant (p<0.01) (Table 5).

Table 4. Comparison of inflammatory markers according to prognosis in study groups

Inflammation markers	Poor prognosis (n=55)	Improvement (n=52)	p-value
	Mean±SD	Mean±SD	
PNI	42.16±3 (32.4-51.01)	40.37±3.3 (32.11-47.01)	0.004**[1]
	(Min-max)	(Min-max)	
NLR	1.93 (1.07-4.75)	1.795 (0.99-14.22)	0.62[2]
LMR	3.61 (1.09-25.58)	2.91 (0.49-9)	0.06[2]
PLR	147.95 (74.9-383.12)	169.175 (76.28-825)	0.243[2]
CAR score	0.141 (0.01-2.421)	0.23 (0.007-6)	0.331[2]
SII	633.46 (294.13-2120.7)	678.79 (268.46-8563.5)	0.184[2]

NLR: Neutrophil-to-lymphocyte ratio, LMR: Lymphocyte-to-monocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune-inflammation index, CAR: C-reactive protein-to-albumin ratio, PNI: Prognostic nutritional index, Min: Minimum, Max: Maximum. [1]: Independent samples t test; [2]: Mann- Whitney U test; **: p<0.01

Comparison of Inflammatory Indices Between Sarcoidosis and Control Groups and Prognostic Analyses

In univariable logistic regression analyses, several clinical and laboratory parameters-including age, smoking burden, radiological stage, extrapulmonary involvement, CRP, and all evaluated inflammation-based indices (NLR, LMR, PLR, SII, CAR, and PNI)-were significantly associated with poor prognosis in patients with sarcoidosis (Table 6). However, after adjustment for potential confounders (age, sex, radiological stage, extrapulmonary involvement, smoking status, and CRP) in multivariable analysis, only PNI remained independently

Table 2. Comparison of inflammatory markers according to stages of sarcoidosis in the study groups

Inflammatory markers	Stage 1 n=18	Stage 2 n=42	Stage 3 n=30	Stage 4 n=17	p-value
PNI mean±SD	41.92±2.3 (36.01-45.51)	39.66±3.5 (32.11-47.01)	42.64±2.8 (38.01-51.01)	42.28±2.5 (37.01-46.01)	0.0001**[1]
NLR (min-max)	1.735 (1.08-5.62)	2.04 (0.99-14.22)	1.805 (1.07-4.75)	1.93 (1.24-4.21)	0.676[2]
LMR (min-max)	4.06 (1.29-7.57)	2.785 (0.49-9)	4.285 (1.78-11.09)	3.61 (1.57-25.58)	0.02*[2]
PLR (min-max)	157.925 (76.28-331.58)	173.995 (77.14-825)	140.8 (74.9-274.74)	134.41 (75.56-305.38)	0.124[2]
CAR score (min-max)	0.131 (0.007-0.466)	0.307 (0.01-6)	0.102 (0.01-2.063)	0.209 (0.016-0.946)	0.0004**[2]
SII (min-max)	678.79 (307.7-2811.73)	826.16 (268.46-8563.5)	631.32 (316.4-1994.63)	540.37 (294.13-1947.97)	0.154[2]

NLR: Neutrophil-to-lymphocyte ratio, LMR: Lymphocyte-to-monocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune-inflammation index, CAR: C-reactive protein-to-albumin ratio, PNI: Prognostic nutritional index, Min: Minimum, Max: Maximum. [1]: Analysis of Variance ANOVA; [2]: Kruskal-Wallis test; *: p<0.05; **: p<0.01; Parameters PNI, and PLR are indicated as median (min-max) values, while the other parameters are srepresented as mean ±SD (min-max) values

Table 3. Investigation of the effect of inflammatory markers on sarcoidosis by logistic regression analysis

Sarcoidosis		B	SE	Wald	SD	p-value	Exp (B)
Inflammatory markers (NLR, LMR, PLR, CAR score, PNI, SII)	NLR	-0.946	0.489	3.734	1	0.053	0.388
	LMR	0.077	0.074	1.081	1	0.298	1.080
	PLR	-0.014	0.007	4.497	1	0.034*	0.986
	CAR score	-18.950	3.626	27.310	1	0.0001**	0.000
	PNI	-0.015	0.070	0.048	1	0.827	0.985
	SII	0.002	0.001	1.853	1	0.173	1.002
	Constant	4.584	3.277	1.957	1	0.162	97.935

NLR: Neutrophil-to-lymphocyte ratio, LMR: Lymphocyte-to-monocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune-inflammation index, CAR: C-reactive protein-to-albumin ratio, PNI: Prognostic nutritional index. NLR, LMR, PLR, CAR Score, PNI, and SII simultaneously significantly affect Sarcoidosis. (Logistic Regression Analysis; p<0.001)

Table 5. Results of ROC analysis for inflammatory markers according to prognosis in study groups

Cut-off value for NLR					
Risk factor sarcoidosis	AUC (%)	Cut off	p-value	Sensitivity (%)	Specificity (%)
NLR	0,709 (0,639;0,778)	1,54	0,0001**	65,40%	65,00%
Cut-off value for LMR					
Risk factor sarcoidosis	AUC (%)	Cut off	p-value	Sensitivity (%)	Specificity (%)
LMR	0.75 (0.684; 0.816)	4.47	0.0001**	71.80%	72.00%
Cut-off value for PLR					
Risk factor sarcoidosis	AUC (%)	Cut off	p-value	Sensitivity (%)	Specificity (%)
PLR	0.724 (0.656; 0.791)	133.815	0.0001**	68.20%	68.00%
Cut-off value for CAR score					
Risk faktörü sarcoidosis	AUC (%)	Cut off	p-value	Sensitivity (%)	Specificity (%)
CAR score	0.827 (0.77; 0.884)	0.0805	0.0001**	72.90%	73.80%
Cut-off value for PNI					
Risk factor sarcoidosis	AUC (%)	Cut off	p-value	Sensitivity (%)	Specificity (%)
PNI	0.677 (0.605; 0.749)	42.565	0.0001**	64.10%	64.50%
Cut-off value for SII					
Risk factor sarcoidosis	AUC (%)	Cut off	p-value	Sensitivity (%)	Specificity (%)
SII	0.705 (0.636; 0.774)	559.985	0.0001**	62.60%	62.10%

NLR: Neutrophil-to-lymphocyte ratio, LMR: Lymphocyte-to-monocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune-inflammation index, CAR: C-reactive protein-to-albumin ratio, PNI: Prognostic nutritional index, AUC: Area under the curve

Table 6. Univariable logistic regression analysis for predictors of poor prognosis in sarcoidosis

Variables	OR (95% CI)	p value
Age (years)	1.03 (1.01–1.06)	0.012
Female sex	0.78 (0.41–1.49)	0.458
Smoking (pack-years)	1.02 (1.00–1.04)	0.036
Radiological stage	1.41 (1.08–1.86)	0.011
Extrapulmonary involvement	2.18 (1.16–4.10)	0.016
C-reactive protein (mg/L)	1.06 (1.02–1.10)	0.002
NLR	1.74 (1.28–2.36)	<0.001
LMR	0.71 (0.58–0.86)	<0.001
PLR	1.01 (1.00–1.02)	<0.001
SII	1.001 (1.000–1.002)	<0.001
CAR	2.63 (1.74–3.96)	<0.001
PNI	0.88 (0.82–0.94)	<0.001

CI: Confidence interval, OR: Odds Ratio, NLR: Neutrophil-to-lymphocyte ratio, LMR: Lymphocyte-to-monocyte ratio, PLR: Platelet-to-lymphocyte ratio, SII: Systemic immune-inflammation index, CAR: C-reactive protein-to-albumin ratio, PNI: prognostic nutritional index

Table 7. Multivariable logistic regression analysis for poor prognosis

Variables	Adjusted OR (95% CI) median (95% CI)	p value
Age	1.02 (0.99-1.05)	0.15
Female sex	0.91 (0.45-1.86)	0.80
Radiological stage	1.29 (0.96-1.74)	0.09
Extrapulmonary involvement	1.94 (1.01-3.71)	0.047
C-reactive protein (mg/L)	1.04 (1.00-1.08)	0.041
Smoking (≤20 pack-years)	1.21 (0.62-2.35)	0.58
Smoking (>20 pack-years)	1.89 (1.01-3.56)	0.044
PNI	0.91 (0.84-0.98)	0.014

CI: Confidence interval, PNI: Prognostic nutritional index

associated with poor prognosis (adjusted OR 0.91, 95% CI 0.84-0.98; p=0.014), while extrapulmonary involvement, CRP levels, and heavy smoking (>20 pack-years) also retained prognostic significance (Table 7). Other inflammation-based indices lost statistical significance, suggesting that their apparent prognostic effects may be mediated by confounding clinical and inflammatory factors.

Regarding diagnostic discrimination, univariable analyses demonstrated that higher NLR, LMR, PLR, SII, and CAR values, along with lower PNI values, were significantly associated with the presence of sarcoidosis compared with controls (all p<0.05). In multivariable analysis, only CAR and LMR remained independently associated with sarcoidosis, whereas the other indices did not retain significance, indicating substantial overlap and possible collinearity among inflammation-based parameters derived from shared hematological components.

Association Between Inflammatory Indices and Radiological Disease Stages

Stage-based subgroup analyses demonstrated significant differences in selected inflammatory indices across radiological stages of sarcoidosis. PNI values differed significantly according to disease stage (one-way ANOVA, F=7.099; p=0.0001). Pairwise comparisons revealed that PNI values were significantly lower in stage 2 compared with stage 1 (p=0.041), stage 3 (p=0.0001), and stage 4 (p=0.015), indicating progressive impairment of nutritional-inflammatory status with advancing radiological involvement. Similarly, CAR values showed a significant variation across radiological stages (Kruskal-Wallis test, H=18.286; p=0.0004). Patients with more advanced stages exhibited higher CAR levels, reflecting increased systemic inflammation relative to albumin levels. These findings support a close association between inflammatory burden and radiological disease extent.

Prognostic Analyses and Clinical Outcomes

In univariable logistic regression analyses evaluating predictors of poor prognosis among patients with sarcoidosis (Table 6), increasing age, cumulative smoking exposure, higher radiological stage, extrapulmonary involvement, and elevated

CRP levels were significantly associated with adverse outcomes. Among inflammation-based indices, higher derived NLR, PLR, SII, and CAR were associated with an increased risk of poor prognosis, whereas higher LMR and PNI were associated with a reduced risk. Notably, NLR (OR 1.74, 95% CI 1.28-2.36), CAR (OR 2.63, 95% CI 1.74-3.96), and PNI (OR 0.88, 95% CI 0.82-0.94) demonstrated the strongest univariable associations with prognosis (all p<0.001). In multivariable logistic regression analysis (**Table 7**), extrapulmonary involvement (adjusted OR 1.94, p=0.047), CRP levels (adjusted OR 1.04, p=0.041), smoking exposure greater than 20 pack-years (adjusted OR 1.89, p=0.044), and PNI (adjusted OR 0.91, p=0.014) remained independently associated with poor prognosis. PNI consistently emerged as an independent protective factor, underscoring the prognostic relevance of nutritional-inflammatory status in sarcoidosis.

Subgroup and Pairwise Analyses

When patients were stratified according to radiological stage, significant differences were observed in systemic inflammatory indices. PNI values progressively decreased with advancing radiological stage (p<0.01), with post-hoc analyses revealing significant differences between stage 1 and stage 2 (p=0.041), stage 2 and stage 3 (p<0.001), and stage 2 and stage 4 (p=0.015). Similarly, CAR and SII values increased significantly across higher radiological stages (p<0.01), indicating a stronger systemic inflammatory burden in advanced disease. In prognosis-based subgroup analyses, patients with poor prognosis exhibited significantly lower PNI values and higher CAR levels compared with those with good prognosis (p<0.01 for both), suggesting that combined inflammatory-nutritional indices may reflect disease severity and clinical outcomes.

DISCUSSION

In this study, systemic inflammatory indices derived from routine laboratory parameters were comprehensively evaluated in patients with newly diagnosed pulmonary sarcoidosis. The main findings demonstrate that several inflammation-based indices differ significantly between sarcoidosis patients and healthy controls and that selected indices are associated with radiological disease stage and clinical prognosis. These results support the concept that sarcoidosis is characterized by persistent systemic immune activation extending beyond localized granulomatous inflammation.[3,11] These observations indicate that sarcoidosis is not merely a localized granulomatous disorder confined to affected organs, but rather a condition characterized by sustained systemic immune activation and dysregulated inflammatory responses.[3,11,12]

Granuloma formation in sarcoidosis is driven by complex interactions between activated macrophages, T lymphocytes, and pro-inflammatory cytokines, processes that are known to influence circulating leukocyte subsets, platelet activation, and acute-phase reactants.[13-15]

Consequently, composite inflammatory indices such as NLR, LMR, CAR, SII, and PNI may reflect the global inflammatory burden and immune–nutritional imbalance associated with disease activity and progression. Previous studies have reported alterations in hematological and inflammatory profiles in patients with sarcoidosis; however, the majority of these investigations have primarily focused on single inflammatory markers or a limited number of indices. Moreover, these studies have often evaluated diagnostic associations in isolation, without comprehensively examining the simultaneous relationships between multiple inflammation-based indices, radiological disease staging, and longitudinal clinical outcomes. As a result, the integrated prognostic value of routinely available composite inflammatory indices in sarcoidosis remains insufficiently characterized.[16,17]

Neutrophil- and platelet-based indices, including NLR, LMR, and PLR, were significantly altered in the sarcoidosis group compared with controls, indicating an underlying systemic inflammatory response. Similar alterations in leukocyte-derived ratios have been reported in previous studies on sarcoidosis and other granulomatous lung diseases, reflecting enhanced innate immune activity and relative lymphocyte suppression.[6,18] However, consistent with more recent reports, these indices did not reliably distinguish radiological stages or prognostic subgroups in our cohort.[19] This suggests that while NLR, LMR, and PLR may be useful markers of systemic inflammation, their ability to reflect disease severity or long-term outcome in sarcoidosis is limited.

The CAR score demonstrated a strong association with both radiological stage and sarcoidosis diagnosis in multivariable analysis. CAR integrates CRP, a marker of acute-phase inflammatory response, with serum albumin, which reflects chronic inflammation and nutritional status. Recent studies have highlighted the prognostic value of CAR in chronic inflammatory and interstitial lung diseases, emphasizing its ability to capture both inflammatory burden and systemic catabolic state.[20,21] Our findings extend these observations to pulmonary sarcoidosis, suggesting that CAR may represent a sensitive and practical biomarker for disease activity and severity assessment at diagnosis. In contrast to leukocyte-based ratios, CAR remained independently associated with both radiological stage and disease diagnosis after multivariable adjustment, suggesting a closer relationship with the underlying inflammatory activity of sarcoidosis. Given that sarcoidosis is characterized by persistent granulomatous inflammation and systemic acute-phase responses, CAR may better capture disease-related inflammatory burden than indices derived solely from circulating blood cell counts.[22-24]

PNI was another index that showed significant differences across radiological stages and prognosis subgroups, with lower PNI values observed in patients with poorer outcomes. PNI reflects the interaction between immune competence and nutritional status, both of which are increasingly recognized as determinants of disease progression in chronic inflammatory conditions. Previous studies have demonstrated the prognostic relevance of PNI in chronic lung diseases and systemic inflammatory disorders, and our results suggest a similar role in sarcoidosis, where chronic inflammation and immune dysregulation may contribute to nutritional impairment and adverse clinical outcomes.[23,25]

Although SII values were significantly higher in sarcoidosis patients compared with healthy controls, no significant association with radiological stage or clinical prognosis was observed. This finding is consistent with recent evidence suggesting that SII primarily reflects acute systemic inflammatory responses driven by neutrophilia and thrombocytosis, rather than chronic immune dysregulation

or fibrotic disease processes.[26] Given the heterogeneous, often indolent, and sometimes self-limiting course of sarcoidosis, SII alone may therefore be insufficient to capture disease severity or predict long-term outcomes.

An important methodological consideration is that inflammation-based indices such as NLR, PLR, SII, CAR, and PNI are mathematical constructs derived from overlapping hematological and biochemical parameters. Consequently, observed correlations among these indices may partially result from numerical interdependence rather than representing independent biological pathways. This limitation has been highlighted in recent methodological and immunopathological studies, emphasizing the need for cautious interpretation of correlated composite inflammatory indices and for multivariable analyses to identify truly independent prognostic markers.[27,28]

Overall, the present study demonstrates that not all systemic inflammatory indices provide equal clinical information in pulmonary sarcoidosis. While leukocyte-derived ratios may indicate the presence of systemic inflammation, combined indices incorporating inflammatory and nutritional components-particularly CAR and PNI-appear to offer greater clinical relevance for evaluating disease severity and prognosis. These markers are inexpensive, widely available, and easily applicable in routine clinical practice, supporting their potential role as adjunctive tools in the assessment and follow-up of patients with pulmonary sarcoidosis.[23,28]

In the present study, a statistically significant variation in PNI values was observed across radiological stages of pulmonary sarcoidosis, with pairwise differences particularly evident between stage 1 and stage 2, stage 2 and stage 3, and stage 2 and stage 4. These findings suggest that nutritional and immunological status, as reflected by PNI, may deteriorate in parallel with disease progression. This observation is biologically plausible, as advanced sarcoidosis is characterized by persistent systemic inflammation, chronic immune activation, and increased metabolic demand, all of which may negatively affect serum albumin levels and lymphocyte counts.[22] Similar associations between lower PNI values and increased disease severity or worse clinical outcomes have been reported in chronic inflammatory and granulomatous diseases, supporting the role of PNI as an integrated marker of immune competence and nutritional reserve.[29]

Our findings indicate that not all inflammation-based indices provide equivalent clinical information in pulmonary sarcoidosis. Neutrophil-and platelet-derived ratios such as NLR, LMR, and PLR were significantly altered in patients compared with controls, reflecting systemic inflammatory activation; however, these indices did not reliably distinguish radiological stages or prognostic subgroups. This is consistent with previous studies reporting that leukocyte-derived ratios primarily reflect inflammatory burden rather than disease severity or long-term outcome. Differences among studies may be explained by heterogeneity in disease phenotype, extent of extrapulmonary involvement, and methodological approaches.[29,30-32]

In contrast, indices integrating inflammatory and nutritional components demonstrated greater clinical relevance. CAR varied significantly across radiological stages, supporting its role as a marker of systemic inflammatory activity, although it did not retain independent prognostic significance. Notably, PNI was the only index independently associated with prognosis, suggesting that immune-nutritional status plays a central role in long-term outcomes in sarcoidosis. This finding may reflect the impact of chronic inflammation on nutritional reserve and immune competence. Finally, given that these indices are mathematically derived from overlapping hematological parameters, observed correlations should be interpreted cautiously, as numerical interdependence may contribute to apparent associations. Overall, PNI appears to be the most robust and clinically meaningful marker for prognostic stratification in pulmonary sarcoidosis.[31,32]

Limitations

Several limitations of this study should be acknowledged. First, the retrospective and single-center design may limit the generalizability of the findings and carries an inherent risk of selection bias. Second, although inflammatory indices demonstrated statistically significant diagnostic performance, however the area under the ROC curves demonstrated mostly a modest diagnostic performance (approximately 0.65-0.75), indicating its limited discriminative ability. Therefore, these indices should not be considered definitive diagnostic or prognostic tools but rather as adjunctive markers that may complement clinical, radiological, and histopathological assessment.

Third, radiological staging in sarcoidosis does not always directly reflect inflammatory activity, as fibrotic or chronic changes may persist despite alleviated systemic inflammation. Accordingly, the associations observed between inflammatory indices and radiological stages should be interpreted with caution. Fourth, although multivariable analyses were adjusted for major confounders, residual confounding factors cannot be completely excluded. Finally, prognostic outcomes were based on clinical and radiological follow-up parameters, and longer prospective studies incorporating functional and biomarker-based endpoints are needed to validate our findings.

CONCLUSION

Sarcoidosis is a heterogeneous granulomatous disease with variable clinical outcomes ranging from spontaneous remission to chronic progression. In this study, several inflammation-based indices derived from routine laboratory parameters showed significant diagnostic and stage-related differences in patients with pulmonary sarcoidosis. However, after multivariable adjustment, the PNI was the only inflammatory marker independently associated with poor prognosis.

These findings indicate that while multiple inflammatory ratios reflect systemic inflammatory burden and disease stage, PNI may offer additional prognostic value beyond conventional clinical and radiological assessment. Therefore, PNI may serve as a practical and noninvasive adjunctive marker for risk stratification in routine clinical practice.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of the Clinical Researches Ethics Committee of Şişli Hamidiye Eftal Training and Research Hospital (Date: 03.12.2024, Decision No: 2840).

Informed Consent

As this was a retrospective study, formal written informed consent was not required and was therefore not obtained.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

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Author Contributions

The author is solely responsible for the conception, data collection, analysis, and writing of this manuscript.

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Original Article

Staphylococcus aureus nasal carriage rates, and risk factors in hemodialysis patients

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ABSTRACT

Aims: The aim of this study is to determine the rates of *Staphylococcus aureus (S. aureus)* nasal carriage, considered one of the most important sources of infection in patients undergoing haemodialysis treatment due to chronic kidney disease, and the susceptibility of *S. aureus* to mupirocin and fusidic acid.

Methods: The study included a total of 165 patients, comprising 55 women (33.3%) and 109 men (66.03%), who had been receiving treatment at the same dialysis centre for at least one year and underwent haemodialysis three times a week. Nasal swab samples were inoculated onto mannitol-salt agar (Beslab, Turkiye). The media were incubated at 37 °C for 72 hours. Methicillin resistance was determined on Mueller-Hinton agar medium using cefoxitin discs (Bioanalyse, Turkiye), and mupirocin and fusidic acid sensitivities were determined using the disc diffusion method with discs of these antibiotics (Bioanalyse, Turkiye).

Results: A total of 165 patients were tested, and *S. aureus* was detected in 14 (8.48%); 9 (5.45%) were meticillin-sensitive; of the sensitive strains, 2 were resistant to mupirocin and 2 were resistant to fusidic acid. In 5 (3.03%) of the 165 patients, methicillin-resistant *S. aureus* was detected; 1 was resistant to mupirocin and 1 was resistant to fusidic acid.

Conclusion: It has been found that the rate of *S. aureus* nasal carriage is low in haemodialysis patients. The resistance rates of methicillin-sensitive strains to mupirocin and fusidic acid were higher than the resistance rates of susceptible strains. Eliminating nasal carriage is an important approach to protecting dialysis patients from infection.

Keywords: Hemodialysis patients, nasal carriage, *Staphylococcus aureus*, mupirocin, fusidic acid

INTRODUCTION

Infections in hemodialysis patients and end-stage renal failure patients are an important cause of mortality and morbidity. In patients with end-stage chronic kidney disease, *Staphylococcus aureus (S. aureus)* causes serious infections, numerous complications and prolonged hospital stays, which generally result in high costs.[1-4] *S. aureus* is the most common bacterium in vascular access-related infections in dialysis patients and has a high mortality rate.[2,5] Methicillin-resistant *Staphylococcus aureus* (MRSA) and coagulase-negative staphylococci are frequently isolated as causative agents of catheter-related bacteremia in hemodialysis patients and peritoneal dialysis catheter infection and peritonitis in peritoneal dialysis patients. The high rate of resistance to mupirocin, one of the topical antimicrobials used in the eradication of *S. aureus* nasal carriage in these patients, is also an important problem.[3,6] The most frequently colonized body site of *S. aureus* is the nose. It has been reported that nasal carriage of *S.aureus* plays an important role in the pathogenesis of infections due to this agent.[2-5]

The relationship between *S. aureus* nasal carriage in hemodialysis patients and infections developing due to this agent has been shown in many studies. It has been reported that the rates of bacteremia and catheter-related infections are higher in *S. aureus* nasal carriers than in non-carriers. MRSA have an important place in staphylococcal infections. Many studies have reported the relationship between nasal MRSA carriage and MRSA infections. The main risk factors for MRSA nasal carriage are hospitalization, broad-spectrum antibiotic use, surgical intervention, residence in a nursing home, presence of hospital personnel in the family, etc.[1,3,6-8]

The aim of this study was to determine the rates of nasal carriage of *S.aureus* in hemodialysis patients, the risk factors associated with carriage, and the susceptibilities to mupirocin and fusidic acid in patients with nasal carriage of *S. aureus*.

METHODS

The mean age of the patients was 52±12.08. Informed consent forms were obtained from hemodialysis patients for the study, and ethical committee approval was obtained from the Ankara Bilkent City Hospital Medical Researches Scientific and Ethical Evaluation Board (Date: 04.12.2024, Decision No: TABED 1-24-384). The results are presented in tabular form.

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All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

A total of 165 hemodialysis patients, including 55 (33.3%) females and 109 (66.03%) males, who were dialyzed at the Private Ankara Balgat Dialysis Center were included in the study. Written informed consent was obtained from all individual participants prior to their inclusion in the study. Nasal swab samples obtained from the patients were sown on Mannitol-salt agar (Beslab, Turkiye) medium. The media were incubated in an oven at 37°C for 24-.48 hours. Colonies that grew on Mannitol salt agar medium with yellow color reflex were evaluated as *S. aureus*, and the strains with positive catalase and coagulase tests were evaluated as *S. aureus*. MRSA1 strains was determined on Mueller Hinton agar medium with cefoxitin disk (Bioanalyse, Turkiye) and mupirocin and fusidic acid susceptibilities were determined by disk diffusion method with the discs of these antibiotics (Bioanalyse, Turkiye).

RESULTS

Of the 165 hemodialysis *S.aureus* nasal carriage was detected in 14 (8.48%) patients, 9 (5.45%) of whom had methicillin-sensitive *S. aureus* (MSSA) nasal carriage and 5 (3.03%) had methicillin-resistant *S. aureus* (MRSA) nasal carriage.

Of a total of 5 MRSA strains, 1 was resistant to mupirocin and 1 was resistant to fusidic acid. Of a total of 9 MSSA strains, 2 were resistant to mupirocin and 2 were resistant to fusidic acid. It was determined that mupirocin and fusidic acid resistance was higher in MSSA strains (**Table 1**).

Table 1. Mupirocin and fusidic acid resistance MSSA, and MRSA strains

Agent	Mupirosin resistant (n)	Fusidic acid resistant (n)
MSSA (n:9)	2	2
MRSA (n:5)	1	1
Total (n:14)	3	3

MSSA: Methicillin-sensitive *Staphylococcus aureus*

All patients who grew MRSA and MSSA in nasal cultures had a history of antibiotic use in the last 6 months and hospital or outpatient clinic admission in the last year as risk factors. Congestive heart failure was present in 3 patients with MRSA and 7 patients with MSSA nasal cultures. Diabetes mellitus was present in one patient with MRSA growth and in two patients with MSSA growth. Two patients who grew MSSA in nasal culture had a history of surgical intervention and one patient had a family history of healthcare personnel. None of the patients who grew MRSA and MSSA in nasal cultures had a history of nursing home stay, hospitalization in the last 1 year, immunosuppressive treatment or malignancy. The risk factors in patients with MRSA and MSSA growth in nasal cultures are shown in **Table 2**.

DISCUSSION

S. aureus nasal carriage plays a key role in the pathogenesis and epidemiology of *S. aureus* infections.[3,4,8-10] *S. aureus* nasal carriage rates in hemodialysis patients and patients receiving continuous outpatient peritoneal dialysis treatment have been reported to be higher than those in the general population.[3,6-10] *S. aureus* infections are common in hemodialysis patients due to hospitalization, immunosuppression, invasive interventions (hemodialysis catheter, subclavian catheter, etc.), frequent antibiotic use and high staphylococcal colonization on the skin and nose.[2,8,9]

Nasal carriage of *S.aureus* is one of the most important risk factors in the pathogenesis of catheter infections, bacteremia and sepsis in hemodialysis patients.[2,3,8-11]

Compared to the general population, hemodialysis patients have been reported to be more colonized with *S. aureus*. Scheuch et al.[9] found *S. aureus* carriage in an average of 40% of hemodialysis patients in their cross-sectional study, while the carriage rate in the general population was reported as 27%.

Ferrara et al.[12] *S. aureus* colonisation was detected in 25 (53.19%) of all analysed patients, with intermittent colonisation observed in 21 of these. Additionally, 38% tested positive for *S. aureus* only in samples taken during the 6th or 7th week. Of the 58 isolates, 17.2% (n=10) showed resistance to methicillin (oxacillin), while 25.86% (n=15) exhibited high vancomycin MIC values (2 µg/ml).

S. aureus is one of the most common causative agents of catheter-related bacteremia and sepsis in hemodialysis patients.[13] Eradication of *S. aureus* nasal carriage with topical antibiotics in patients receiving hemodialysis and peritoneal dialysis treatment has been reported to cause a significant decrease in infection rates due to this agent.[1,3-9]

Çelik et al.[13] investigated the rate of *S. aureus* nasal carriage and risk factors in 127 patients on hemodialysis. In this study, *S. aureus* nasal carriage was found in 41 (32.3%) patients, while MRSA nasal carriage was found in five (3.9%) patients. When risk factors were evaluated, a statistically significant relationship was found between *S. aureus* carriage and concomitant gastrointestinal disease and history of antibiotic use in the last year. In the present study, all of the patients with *S. aureus* nasal carriage had a history of antibiotic use within 6 months and a history of admission to hospital or outpatient clinic within the last year as risk factors. In addition, it was noteworthy that 10 (71.4%) patients with *S. aureus* nasal carriage had congestive heart failure.

Table 2. Risk factors in patients with MRSA and MSSA growth in nasal cultures

R AAccompanying ffeatures R Nasal culture reresults	DM (n*)	Antibiotic use in the last 6 months	History of admission to hospital or outpatient clinic in the last year	CHF	History of surgical intervention	Presence of health personnel in the family	Staying in a care home	Hospitalization in the last 1 year	History of immunosuppressive therapy or malignancy
MRSA (n:5)	1/5	5/5	5/5	3/5	0/5	0/5	0/5	0/5	0/5
MSAA (n:9)	2/9	9/9	9/9	7/9	2/9	1/9	0/9	0/9	0/9
Total	3/14	14/14	14/14	10/14	2/14	1/14	0/14	0/14	0/14

MRSA: Methicillin-resistant *Staphylococcus aureus,* MSSA: Methicillin-sensitive, DM: Diabetes mellitus, CHF: Congestive heart failure, Staphylococcus aureus, n*: Patient number

Risk factors for MRSA nasal carriage in hemodialysis patients have been reported as advanced age (≥75 years), prolonged hospitalization, history of repeated antibiotic use, and proximity to another MRSA colonized area. In the present study, the rates of *S. aureus* and MRSA nasal carriage in hemodialysis patients were lower than the rates reported in the literature. The reasons for this situation may include the implementation of infection control measures in patients and the application of nasal fusidic acid cream to patients who are nasal carriers. The main risk factors for MRSA and MSSA nasal carriage in hemodialysis patients were antibiotic use in the last 6 months, history of hospital or outpatient clinic admission in the last year and congestive heart failure.[1,5-8]

MRSA nasal carriage has been reported to be associated with poor clinical outcomes in outpatients on hemodialysis. Early identification of colonized patients, isolation and elimination of carriage with decolonization regimen is an appropriate approach to minimize MRSA transmission rates.[4,6,9,11] In studies conducted in hemodialysis patients in our country, *S. aureus* nasal carriage rates were reported by Cesur et al.[8] 22.1%, Kurutepe et al.[10] 33%, Çelik et al.[13] 32.3%. The rates of MRSA nasal carriage in hemodialysis patients were reported as 11% by Kurutepe et al.;[10] 1.8% by Mutlu et al.,[11] and 3.9% by Çelik et al.[13] Out of Turkiye; Lu et al.[14] reported *S. aureus* carriage rate as 22% and MRSA carriage rate as 2.4%, Lederer et al.[15] reported *S. aureus* carriage rate as 53% and MRSA carriage rate as 12% in hemodialysis patients.

In our study, the resistance rates of MSSA strains to mupirocin and fusidic acid, which are topical antibiotics that can be used in the eradication of *S. aureus* nasal carriage, were higher than the resistance rates of MRSA strains to mupirocin and fusidic acid.

Limitations

The limitation of our study is that we could not determine whether *S.aureus* carriage was permanent or transient carriage because the patients were not followed up for a long period of time. In our study, the rate of *S.aureus* nasal carriage was found to be low in hemodialysis patients. Possible reasons for this may be that hemodialysis patients apply to dialysis centers on a daily basis, attention is paid to infection control measures in the dialysis center, and mupirocin pomade is applied to patients with nasal carriage. In another limitation is molecular confirmation test (mec A gene via PCR) was not performed.

CONCLUSION

As a result, infection is a significant cause of morbidity and mortality in haemodialysis patients. Due to immunosuppression in patients, infection symptoms and findings may often be absent, leading to delays in diagnosis. Therefore, preventive approaches are important. Based on mupirocin and fusidic acid susceptibility results in haemodialysis patients, we believe that eliminating nasal carriage will reduce the frequency of infections, which are a major cause of morbidity and mortality in these patients.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was initiated with the approval of the Ankara Bilkent City Hospital Medical Researches Scientific and Ethics Committee (Date: 04.12.2024, Decision No: TABED 1-24-384).

Informed Consent

Written informed consent was obtained from all individual participants prior to their inclusion in the study. Participants were fully informed about the study's aims, procedures, potential risks and benefits, and their rights-including the right to withdraw at any time without consequence. All participants voluntarily signed a written informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

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Original Article

U-shaped relationship between BMI and cardiometabolic risk: a six-group cross-sectional study

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ABSTRACT

Aims: Body-mass index (BMI) is a major determinant of cardiometabolic risk, yet the risk patterns in both low and high BMI categories remain incompletely characterized. This study aimed to investigate cardiometabolic risk markers across six BMI-based groups and to identify independent predictors of risk.

Methods: A total of 120 participants were stratified into six BMI groups. Anthropometric measurements, blood pressure, and laboratory parameters, including hsCRP, lipid profile, fasting glucose, insulin, HOMA-IR, and complete blood count, were collected. Comparisons among groups were performed using one-way ANOVA or Kruskal-Wallis tests as appropriate. Pearson or Spearman correlation analyses assessed associations between hsCRP and other laboratory markers. Multinomial logistic regression was used to identify independent predictors of group status, with BMI groups collapsed into three categories for model stability.

Results: Age and height did not differ significantly among BMI groups, while body weight and waist circumference differed as expected ($p<0.001$). hsCRP demonstrated a U-shaped association across BMI groups, with the lowest levels in the moderate BMI range and elevated levels observed in both the lowest and highest BMI groups. Correlation analyses revealed significant positive associations of hsCRP with triglycerides, TG/HDL ratio, fasting insulin, HOMA-IR, and MPV (all $p<0.001$). Multinomial logistic regression confirmed hsCRP as an independent predictor of BMI group status ($p=0.001$)..

Conclusion: Cardiometabolic risk markers exhibit a non-linear, U-shaped relationship with BMI. Importantly, elevated risk was detected not only in the high BMI groups but also in participants with low BMI, which emphasizes the need to consider underweight individuals in cardiometabolic risk assessment. hsCRP emerged as a robust independent predictor of BMI-associated risk, reinforcing its potential role in early detection strategies.

Keywords: Body-mass index, cardiometabolic risk, high-sensitivity C-reactive protein (hsCRP), underweight, obesity

INTRODUCTION

Body-mass index (BMI) is a simple and practical anthropometric measurement commonly used in assessing nutritional status. Increased BMI has been well documented in the literature to increase the risk of hypertension, dyslipidemia, insulin resistance, and cardiovascular disease (CVD).[1,2] On the other hand, it is increasingly emphasized that not only an elevated BMI but also a low BMI may be associated with adverse health outcomes.[3,4] Recent large-scale studies have reported a U-shaped or J-shaped relationship between BMI and cardiovascular mortality, suggesting that individuals with low BMI may have metabolic or inflammatory vulnerabilities that cannot be explained by traditional risk factors.[3,5,6]

Inflammation plays a central role in the development of cardiometabolic diseases, and high-sensitivity C-reactive protein (hsCRP) is one of the most commonly used biomarkers of low-grade systemic inflammation.[7] Elevated hsCRP levels are associated with endothelial dysfunction, atherogenesis, plaque instability, and future cardiovascular events.[8,9] Although it is known that hsCRP levels are elevated in obese individuals, how hsCRP behaves across the entire BMI spectrum-particularly in lean individuals-has not been sufficiently elucidated.[10] Understanding the inflammatory profile at extreme BMI values may shed light on the biological basis of the U-shaped risk pattern observed in epidemiological studies.

In addition to inflammation, insulin resistance, dyslipidemia, and changes in platelet activity are also important components of cardiometabolic risk.[11,12] The triglyceride/HDL ratio (TG/HDL), along with indicators such as the HOMA-IR scoring system and mean platelet volume (MPV), are considered early biochemical markers of atherogenic and proinflammatory conditions.[11-13] These markers may provide additional information about subclinical cardiometabolic disorders that occur in individuals with low or high weight. However, the number of studies that evaluate inflammatory and metabolic

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parameters together, divide BMI into multiple categories, and specifically evaluate the low BMI group is limited.[14,15]

The limited evidence on how inflammatory and metabolic cardiometabolic markers change across the broad spectrum of BMI highlights the need to clarify the risk profile of lean individuals in particular. This study aims to compare inflammatory and cardiometabolic risk indicators across six different BMI categories and to assess whether lean individuals exhibit adverse biomarker patterns similar to those seen in obese individuals. The combined consideration of hsCRP and basic metabolic parameters will contribute to a more comprehensive understanding of subclinical cardiometabolic risk across BMI groups.

METHODS

Ethics

Prior to the initiation of the study, all participants were informed about the study procedures and signed an informed consent form. Ethical approval was obtained from the Etlik City Hospital Clinical Researches Ethics Committee (Date: 06.08.2025, Decision No: 2025-243). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Patient Selection and Inclusion/Exclusion Criteria

This study was designed as a cross-sectional study at the Internal Medicine Department of Kırıkkale University Faculty of Medicine, between September 2025 and November 2025. The sample size was calculated using the G*Power 3.1.9.7 software. For a one-way analysis of variance (ANOVA), assuming a significance level (α) of 0.05, a statistical power (1-β) of 0.95, and an effect size (Cohen's f) of 0.498, the required minimum sample size was determined to be 90 participants across six groups. In the present study, a total of 120 participants were included, thereby increasing the statistical power beyond the initially targeted level.

The study was designed to include 6 groups and a total of 120 patients. Individuals aged 18 to 80 who had no acute or chronic illnesses, were not taking any medication, and were visiting the hospital for routine check-ups were included in the study. The individuals included in the study were divided into 6 groups of 20 people each according to their BMI (kg/m2). Individuals with a BMI below 18.5 (Underweight) were assigned to group 1, individuals between 18.5 and 25 to group 2, individuals between 25 and 30 (Overweight) to group 3, individuals between 30 and 35 (Obese Class I) to group 4, individuals between 35 and 40 (Obese Class II) group 5, and individuals with a BMI over 40 are classified as group 6 (Obese Class III). The exclusion criteria for all groups were defined as the presence of any acute or chronic disease determined by detailed medical history, physical examination, blood pressure measurement, and comprehensive laboratory evaluation; fasting plasma glucose ≥126 mg/dl; blood pressure ≥140/90 mmHg; clinically significant hyperlipidemia (including markedly elevated LDL-cholesterol requiring medical treatment); abnormal hepatic or renal function tests; hsCRP levels >10 mg/L; use of any medication; pregnancy or breastfeeding; and current or past smoking. Participants were assigned to six BMI-based groups, with an equal number of males and females (10/10) in each group to ensure balanced sex distribution across all groups.

Study Design

Venous blood samples were collected from the individuals included in the study at the time of admission, following an 8-hour fasting period. Blood samples obtained for serum-based tests were drawn into serum separation tubes, allowed to clot at room temperature for 1 hour, and then centrifuged at 1000×g for 20 minutes. After serum separation, biochemical and hormonal parameters were analyzed immediately using an automated analyzer. For complete blood count (CBC) analyses, samples were collected into EDTA tubes. All blood samples were analyzed in the Biochemistry Laboratory of Kırıkkale University.

In our study, serum levels of 25-hydroxyvitamin D, ferritin, fasting insulin, thyroid-stimulating hormone (TSH), and free thyroxine (free T4) were measured using the electrochemiluminescence immunoassay (ECLIA) method on the Cobas 8000 e801 analyzer (Roche Diagnostics, Japan, 2019). C-reactive protein (CRP), hs-CRP, fasting plasma glucose (FPG), blood urea nitrogen (BUN), creatinine, sodium, potassium, calcium, phosphorus, albumin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), triglycerides, total cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) levels were measured photometrically using the Cobas 8000 c702 analyzer (Roche Diagnostics, Japan, 2018). The triglyceride-to–high-density lipoprotein cholesterol (TG/HDL-C) ratio was calculated and included in the analysis as an additional cardiometabolic risk marker. The CBC was performed using the BC-6800 Auto Hematology Analyzer (Mindray, Hong Kong, 2018) based on the SF Cube method for white blood cells and subtypes, DC impedance for platelet count, and the colorimetric method for hemoglobin. HbA1c was measured using the high-performance liquid chromatography (HPLC) method on the Premier Hb9210 device (Trinity Biotech, USA, 2020). The HOMA-IR index (homeostatic model assessment for insulin resistance) for each participant was calculated by multiplying the FPG level by the fasting insulin level and dividing the result by 405.[16]

The erythrocyte sedimentation rate (ESR) was determined using the Sistat ESR-40 analyzer (Sistat Diagnostics, Turkiye, 2018), which operates based on an automated photometric reading principle. Measurements were conducted in accordance with a procedure compliant with the Westergren method.

In the study, the patients' age (years), height (cm), and body weight (kg) were measured. Based on these data, the BMI (kg/m^2) was calculated. BMI was calculated by dividing the participants' body weight in kilograms by the square of their height in meters. Additionally, the participants' waist circumference (cm) was recorded. Waist circumference measurement was taken while standing upright on a flat surface by measuring the circumference at the level of the midline, just above both anterior superior iliac spines and aligned with the umbilicus. Systolic (SBP) and diastolic blood pressure (DBP) measurements were obtained in the seated position using a validated automatic device. Mean arterial pressure (MAP) was calculated for each patient using the standard formula: MAP=DBP+(SBP-DBP)/3.[17] The data were recorded on patient forms.

Statistical Analysis

All data collected in the study were analyzed using SPSS version 27.0. For numerical variables, mean and standard deviation were calculated. Normality analysis was performed to determine the appropriate statistical method. Comparisons among the BMI groups were performed using ANOVA when the data were normally distributed and the homogeneity of variances assumption was satisfied; otherwise, the non-parametric Kruskal-Wallis test was applied. Post hoc analyses were conducted following significant ANOVA or Kruskal-Wallis results to identify pairwise group differences, using Tukey's test or Dunn's test with Bonferroni correction, respectively. Categorical variables between groups were compared using the chi-square test. Pearson and Spearman correlation tests were used for correlation analyses depending on data distribution and were performed separately within groups as appropriate. Fisher's z transformation was applied to compare correlation coefficients between two groups.

To identify independent predictors of BMI group status, multinomial logistic regression was performed, initially including hsCRP, HOMA-IR, TRIG/HDL ratio, MPV, and other relevant laboratory and anthropometric parameters as predictors. Stepwise selection was applied to retain only statistically significant variables in the final model. Trend analysis was conducted to assess the presence of linear and non-linear (U-shaped) relationships between BMI categories and hsCRP levels. A p-value of <0.05 was considered statistically significant.

RESULTS

Groups consisted of individuals without chronic comorbidities and not on any long-term medication for any reason. In addition, all participants in all groups were non-smokers with no history of smoking,

Groups were compared in terms of age, height, waist circumference, and body weight. No significant differences were observed between the groups in terms of age and height. Each study group included an equal number of males and females (10/10). As expected, body weight and waist circumference differed significantly among the groups (both p<0.001), given that the groups were defined based on BMI ranges. The distribution of participants by sex, age, and anthropometric measurements is presented in **Table 1**.

The systemic blood pressure parameters systolic blood pressure (SBP), diastolic blood pressure (DBP), and MAP were calculated for each patient according to BMI categories and compared between groups. The mean±standard deviation values for the groups are presented in **Table 2**.

Table 2. Comparison of systolic, diastolic, and mean arterial pressure values between groups

BMI group (kg/m²)	SBP (mmHg)	DBP (mmHg)	MAP (mmHg)
Group 1: underweight (<18.5) (n=20)	96.00±4.91	60.15 ± 3.50	72.10 ± 3.48
Group 2: normal (18.5-24.9) (n=20)	99.50±7.70	61.40±5.12	74.10±5.72
Group 3: overweight (25-29.9) (n=20)	114.30±7.47	77.35±4.28	89.67±5.29
Group 4: obese class I (30-34.9) (n=20)	119.70±5.38	79.35±3.13	92.80±3.78
Group 5: obese class II (35-39.9) (n=20)	119.75±4.47	83.75±3.34	95.75±3.57
Group 6: obese class III (≥40) (n=20)	124.25±2.94	93.65±3.01	103.85±2.89
p value	<0.001	<0.001	<0.001

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, MAP: Mean arterial pressure

Blood pressure and MAP differed significantly among BMI groups (one-way ANOVA, p<0.001 for all parameters). Post-hoc analyses revealed a consistent trend across all variables: groups 1 and 2 exhibited significantly lower systolic blood pressure, diastolic blood pressure, and MAP values compared with the other groups. groups 3 and 4 generally showed intermediate values with no significant differences between them for diastolic blood pressure and MAP, while group 5 displayed slightly higher values than groups 3 and 4 for diastolic blood pressure and MAP. group 6 demonstrated the highest systolic and diastolic blood pressure, as well as MAP values, and was significantly different from all other groups (p<0.05).

Groups were compared in terms of hematological parameters (white blood cell count, hemoglobin, platelet count, neutrophil count, and MPV), biochemical parameters (urea, creatinine, eGFR, sodium, potassium, calcium, phosphorus, albumin, FPG, ALT, and AST), lipid profiles (total cholesterol, LDL, HDL, triglycerides, and TG/HDL ratio), hormonal and vitamin levels (fasting insulin, TSH, free T4, and 25-OH Vitamin D), as well as inflammatory and tumor markers (CRP, hsCRP, ESR, and HOMA-IR). Statistically significant differences between the groups were observed in CRP, FPG, HbA1c, HOMA-IR, fasting insulin, total cholesterol, LDL, HDL, triglycerides, TG/HDL ratio, MPV, 25-OH Vitamin D, and ESR (p<0.05 for all). These results are summarized in **Table 3**.

Parameters found to be statistically significant in the table were evaluated using post-hoc analysis.

Post-hoc Tukey HSD analysis for CRP levels indicated that group 6 had significantly higher CRP compared with groups 2 and 3 (p<0.05). No other group comparisons reached

Table 1. Distribution of groups in terms of age, sex, height, body weight and waist circumference

BMI group (kg/m²)	Age (years)	Sex (M/F), n	Height (cm)	Body weight (kg)	Waist circumference (cm)
Group 1: underweight (<18.5) (n=20)	28.0±2.6	10/10	165.5±10.2	48.9±7.0	63.7±2.0
Group 2: normal (18.5–24.9) (n=20)	28.1±2.6	10/10	169.0±7.9	65.3±7.6	65.5±1.7
Group 3: overweight (25–29.9) (n=20)	27.8±3.6	10/10	168.3±9.1	79.0±10.6	69.3±1.5
Group 4: obese class I (30–34.9) (n=20)	27.5±3.3	10/10	162.3±6.4	85.0±6.6	71.0±1.1
Group 5: obese class II (35–39.9) (n=20)	28.2±3.5	10/10	162.8±11.3	97.7±15.1	73.1±4.0
Group 6: obese class III (≥40) (n=20)	27.4±3.3	10/10	162.5±8.9	118.2±18.7	76.5±5.1
p value	0.956	-	0.089	<0.001	<0.001

All groups were matched for sex (10 males and 10 females per group), and p values were not calculated due to equal distribution by study design

Table 3. Distribution of groups in terms of hemogram and biochemical parameters

Parameter	Group 1 underweight (n=20)	Group 2 normal (n=20)	Group 3 overweight (n=20)	Group 4 obese class I (n=20)	Group 5 obese class II (n=20)	Group 6 obese class III (n=20)	p value
Urea (mg/dl)	24.85±8.57	27.05±6.75	25.30±7.23	21.55±6.48	26.00±6.74	23.25±5.50	0.158
Creatinine (mg/dl)	0.70±0.11	0.70±0.08	0.66±0.12	0.66±0.10	0.71±0.11	0.64±0.07	0.166
eGFR	99.6±11.2	101.3±8.1	104.9±12.7	109.1±12.4	103.9±11.7	105.5±11.1	0.132
Sodium (mEq/L)	141.0±2.6	140.8±1.4	140.6±2.2	140.1±1.4	140.3±1.7	140.9±1.5	0.571
Potassium (mEq/L)	4.45±0.40	4.66±0.34	4.68±0.45	4.62±0.38	4.65±0.41	4.61±0.40	0.476
Calcium (mg/dl)	9.37±0.45	9.67±0.39	9.56±0.40	9.56±0.33	9.56±0.55	9.55±0.31	0.349
Phosphorus (mg/dl)	3.74±0.60	3.66±0.42	3.63±0.53	3.66±0.41	3.95±0.45	3.89±0.41	0.179
Albumin (g/dl)	4.44±0.26	4.56±0.21	4.55±0.26	4.50±0.34	4.51±0.39	4.58±0.27	0.714
Fasting plasma glucose (mg/dl)	92.80±10.48	95.40±11.32	91.70±13.62	89.25±3.85	97.55±10.50	99.95±12.48	0.026
CRP (mg/dl)	3.75±0.73	3.17±0.94	3.34±0.82	3.65±0.68	3.79±0.67	4.15±0.66	<0.001
ALT (U/L)	16.40±6.29	24.15±11.88	22.70±8.78	19.95±7.42	21.85±10.57	20.40±8.49	0.130
AST (U/L)	17.30±3.59	18.65±6.12	18.15±6.29	15.60±3.15	18.10±5.40	20.60±6.48	0.102
Hemoglobin A1c (%)	5.47±0.24	5.54±0.28	5.58±0.25	5.57±0.19	5.56±0.24	5.72±0.13	0.027
Total cholesterol (mg/dl)	175.9±8.0	171.6±9.2	193.0±12.8	215.1±9.4	237.9±10.7	250.3±10.6	<0.001
LDL (mg/dl)	121.8±10.7	98.3±11.5	121.3±14.5	146.3±11.9	169.8±13.9	189.2±14.2	<0.001
HDL (mg/dl)	38.5±4.68	56.5±3.44	48.5±3.59	44.8±3.48	40.3±3.65	32.5±3.63	<0.001
Triglycerides (mg/dl)	77.9±9.6	84.2±5.8	115.6±9.8	119.4±9.4	138.7±12.9	142.3±21.2	<0.001
TG/HDL ratio	2.04±0.26	1.49±0.10	2.39±0.24	2.67±0.22	3.45±0.30	4.39±0.61	<0.001
25-OH vitamin D (ng/ml)	11.4±2.0	13.1±1.8	13.1±1.9	11.6±1.9	10.5±2.5	11.8±2.6	<0.001
Ferritin (ng/ml)	35.85±17.28	39.06±11.63	32.20±8.25	36.52±7.64	38.02±8.04	39.99±6.84	0.235
Fasting insulin (µU/ml)	7.31±1.52	6.43±1.05	7.38±1.67	13.13±1.75	20.15±3.69	26.43±4.73	<0.001
TSH (mIU/L)	1.98±0.90	2.17±1.03	1.92±0.90	2.06±1.04	2.30±0.97	2.42±1.00	0.574
Free T4 (ng/dl)	1.20±0.16	1.24±0.32	1.16±0.17	1.21±0.13	1.21±0.15	1.29±0.17	0.489
White blood Cells (x10^3/µL)	7.05±1.53	6.93±1.04	7.16±1.16	7.33±1.00	7.53±0.97	7.81±0.94	0.140
MPV (fL)	10.65±0.18	9.91±0.14	10.30±0.13	10.53±0.11	10.63±0.11	10.94±0.11	<0.001
Hemoglobin (g/dl)	13.33±1.11	13.71±1.05	13.68±1.15	13.50±0.64	13.34±0.81	13.38±0.68	0.643
Platelet (10^3/µL)	238.80±50.74	241.45±39.77	227.67±47.25	239.00±42.37	211.98±21.83	225.45±27.94	0.160
Neutrophil (10^3/µL)	4.16±1.43	4.45±1.76	3.97±1.18	4.38±1.48	4.35±1.78	4.20±1.46	0.930
ESR (mm/h)	19.15±3.91	17.35±8.29	18.70±6.30	19.15±4.73	19.45±4.81	24.00±3.67	<0.001
HOMA IR	1.65±0.25	1.50±0.24	1.63±0.25	2.89±0.38	4.78±0.52	6.46±1.16	<0.001

Egfr: Estimated glomerular filtration rate, CRP: C-reactive protein, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, TG/HDL ratio: Triglyceride to high-density lipoprotein cholesterol ratio, 25-OH vitamin D, 25-hydroxyvitamin D, TSH: Thyroid-stimulating hormone, Free T4: Free thyroxine, MPV: Mean platelet volume, ESR: Erythrocyte sedimentation rate, HOMA-IR: Homeostasis model assessment of insulin resistance

statistical significance (p≥0.05), suggesting that systemic inflammation, as reflected by CRP, was particularly elevated in group 6 relative to some of the earlier groups.

Post-hoc Games–Howell analysis for ESR revealed that group 6 had significantly higher ESR values compared with groups 1, 2, 3, 4, and 5 (p<0.05). No significant differences were observed between groups 1, 2, 3, 4, and 5 (p≥0.05).

ANOVA revealed a weakly significant difference in FPG levels among the groups (p=0.026). Post-hoc Tukey HSD analysis indicated that group 6 had significantly higher FPG levels compared with group 1 (p=0.009). No other significant differences were observed between the remaining groups (p≥0.05).

One-way ANOVA analysis showed a marginally significant difference in HbA1c levels among the groups (p=0.027). Post-hoc Tukey HSD analysis revealed that group 6 had significantly higher HbA1c levels compared with group 1 (p=0.009). No significant differences were observed between the other groups (p≥0.05).

Post-hoc Games–Howell analysis revealed that insulin levels in groups 4, 5, and 6 were significantly higher compared with groups 1, 2, and 3 (p<0.05). Additionally, insulin levels in group 5 were significantly higher than in group 4 (p<0.05), and insulin levels in group 6 were significantly higher than in groups 4 and 5 (p≤0.001). No other significant differences were observed between the remaining groups (p≥0.05).

Post-hoc Games–Howell analysis revealed that HOMA-IR values in groups 4, 5, and 6 were significantly higher compared with groups 1, 2, and 3 (p<0.05). Additionally, HOMA-IR values in groups 5 and 6 were also significantly higher than in group 4 (p<0.05). No significant differences were observed in all other group comparisons (p≥0.05).

Post-hoc Games-Howell analysis demonstrated that triglyceride levels were significantly higher in groups 3-6 compared with groups 1 and 2 (p<0.05). No statistically significant differences were observed between groups 3 and 4 or between groups 5 and 6 (p≥0.05).

Post-hoc Tukey HSD analysis for HDL cholesterol levels showed that Group 1 had significantly lower HDL levels

compared with groups 2, 3, 4, and 6 (p<0.05), while no significant difference was observed with groups 5 (p≥0.05). Group 2 exhibited significantly higher HDL levels than all other groups (p<0.05). Group 3 had significantly higher HDL levels than groups 1, 5, and 6, but significantly lower levels than group 2 and higher levels than group 4 (p<0.05). Group 4 showed significantly higher HDL levels than groups 1, 5, and 6, but lower levels than groups 2 and 3 (p<0.05). Group 5 had significantly lower HDL levels than groups 2, 3, and 4, but higher levels than group 6, with no significant difference compared with groups 1 (p<0.05).

Post-hoc Tukey HSD analysis for total cholesterol levels indicated that group 1 had significantly lower total cholesterol compared with groups 3, 4, 5, and 6 (p < 0.05), while the difference with group 2 was not significant (p≥0.05). Group 2 also showed significantly lower total cholesterol levels than groups 3-6 (p<0.05). Group 3 had significantly higher total cholesterol compared with groups 1 and 2, but lower levels than groups 4, 5, and 6 (p<0.05). group 4 showed significantly higher total cholesterol than groups 1-3, but lower levels than groups 5 and 6 (p<0.05). Group 5 had significantly higher total cholesterol compared with groups 1-4, but lower levels than group 6 (p<0.05).

Post-hoc Tukey HSD analysis revealed significant differences in total cholesterol levels among most groups. Group 1 had significantly higher levels than group 2 (p<0.05), but did not differ from group 3 (p≥0.05); however, it had significantly lower levels compared with groups 4, 5, and 6 (p<0.05). Group 2 had significantly lower levels than all other groups (p<0.05). Group 3 did not differ from group 1 but showed significantly lower levels than groups 4, 5, and 6 (p<0.05). Group 4 had significantly higher levels than groups 1, 2, and 3, but lower levels than groups 5 and 6 (p<0.05). Group 5 showed significantly higher levels than groups 1-4, but lower levels than group 6 (p<0.05). Finally, group 6 had the highest total cholesterol levels compared with all other groups (p<0.05).

Post-hoc analysis using the Games-Howell test revealed significant differences in the TG/HDL ratio among the six groups. Group 1 had a significantly higher TG/HDL ratio than group 2 (p<0.05), but significantly lower ratios compared with groups 3-6 (p<0.05). Group 2 exhibited significantly lower TG/HDL ratios than groups 3-6 (p<0.05). Group 3 differed significantly from groups 4-6, while group 4 showed significantly lower values than groups 5 and 6 (p<0.05). Group 5 also differed significantly from group 6 (p<0.05). Overall, the TG/HDL ratio demonstrated an increasing trend across the groups, indicating progressively higher cardiometabolic risk in the later groups.

Post-hoc Tukey HSD analysis for MPV demonstrated that group 1 had significantly higher MPV values compared with groups 2 and 3, but significantly lower values than group 6 (p<0.05). No significant differences were observed between group 1 and groups 4 or 5 (p≥0.05). Group 2 exhibited significantly lower MPV values than all other groups (p<0.05). Group 3 had significantly lower MPV values than groups 4, 5, and 6 (p<0.05). No significant difference was observed between groups 4 and 5, whereas groups 6 showed significantly higher MPV values compared with all other groups (p<0.05).

Post-hoc Tukey HSD analysis for 25-OH Vitamin D levels revealed that group 2 and group 3 had significantly higher 25-OH Vitamin D levels compared with group 5 (p=0.004). No other pairwise comparisons between groups reached statistical significance (p≥0.05).

Evaluation of hsCRP Results

The mean hsCRP levels of the groups were 1.82±0.06, 1.65±0.16, 1.66±0.23, 1.71±0.15, 1.88±0.19, and 2.00±0.22 mg/L, respectively, from group 1 to group 6. The mean hsCRP levels of the groups are shown in **Figure**.

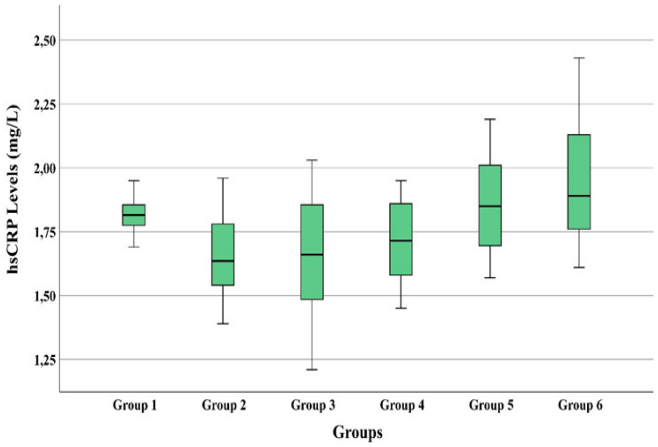

Figure. Distribution of hsCRP levels in the groups

HsCRP levels were evaluated among the six groups using one-way ANOVA, and statistically significant differences were found between the groups (p<0.001). The Games-Howell post hoc test was applied to determine which groups showed significant differences. The mean differences and p-values for statistically significant data, obtained by comparing all groups, are presented in **Table 4**.

Table 4. Games-howell post hoc results for differences in hsCRP levels between groups

Groups	Mean difference	p (games-howell)	Significance
1 vs 2	0.164	<0.001	Significant
1 vs 6	-0.187	0.015	Significant
2 vs 5	-0.229	0.003	Significant
2 vs 6	-0.350	<0.001	Significant
3 vs 5	-0.227	0.021	Significant
3 vs 6	-0.348	<0.001	Significant
4 vs 5	-0.173	0.038	Significant
4 vs 6	-0.294	<0.001	Significant

Only group comparisons with p<0.05 are shown

The relationships between hsCRP levels and other laboratory parameters were evaluated using Pearson or Spearman correlation analysis. When evaluated in all patients, hsCRP was positively correlated with CRP (r=0.31, p<0.001), total cholesterol (r=0.36, p<0.001), LDL (r=0.40, p<0.001), HDL (r=-0.41, p<0.001), triglycerides (r=0.24, p<0.001), TG/HDL ratio (r=0.37, p<0.001), fasting insulin (r=0.39, p<0.001), MPV (r=0.41, p<0.001), and HOMA-IR (r=0.40, p<0.001). No significant correlation was found between hsCRP and other parameters (p>0.05).

In different BMI groups, significant correlations between hsCRP and parameters were limited, and no strong relationship was observed, especially outside of lipid profile and insulin resistance parameters. All correlation results are presented in **Table 5**.

Table 5. Correlation between hsCRP levels and hemogram and biochemical parameters

Parameter	Group 1: underweight (n=20)	Group 2: normal (n=20)	Group 3: overweight (n=20)	Group 4: obese class I (n=20)	Group 5: obese class II (n=20)	Group 6: obese class III (n=20)	Total (n=120)
Urea (mg/dl)	-0.07 (0.756)	-0.31 (0.182)	0.07 (0.741)	0.00 (0.994)	-0.07 (0.766)	0.29 (0.213)	-0.03 (0.729)
Creatinine (mg/dl)	0.15 (0.513)	0.23 (0.312)	0.19 (0.421)	0.06 (0.781)	-0.12 (0.610)	0.21 (0.356)	0.06 (0.460)
eGFR	-0.29 (0.210)	0.29 (0.206)	0.07 (0.749)	0.03 (0.901)	0.07 (0.749)	0.04 (0.866)	0.04 (0.615)
Sodium (mEq/L)	0.05 (0.819)	0.16 (0.498)	-0.42 (0.065)	-0.34 (0.133)	0.10 (0.646)	0.12 (0.612)	-0.04 (0.662)
Potassium (mEq/L)	0.21 (0.357)	0.05 (0.813)	-0.24 (0.301)	-0.09 (0.690)	-0.14 (0.549)	0.13 (0.573)	-0.08 (0.379)
Calcium (mg/dl)	-0.00 (0.974)	-0.06 (0.778)	-0.09 (0.679)	-0.05 (0.814)	-0.10 (0.651)	0.38 (0.096)	-0.04 (0.606)
Phosphorus (mg/dl)	-0.26 (0.259)	-0.18 (0.432)	-0.23 (0.315)	0.13 (0.564)	-0.00 (0.972)	0.07 (0.758)	0.05 (0.537)
Albumin (g/dl)	0.02 (0.907)	-0.12 (0.591)	0.16 (0.494)	0.12 (0.588)	0.11 (0.634)	0.52 (0.017)*	0.14 (0.125)
Fasting plasma glucose (mg/dl)	-0.10 (0.674)	0.01 (0.957)	0.07 (0.754)	-0.15 (0.523)	0.24 (0.291)	-0.12 (0.592)	0.13 (0.136)
CRP (mg/dl)	0.04 (0.855)	0.32 (0.168)	-0.08 (0.708)	0.11 (0.646)	0.28 (0.223)	0.25 (0.287)	0.31 (<0.001)*
ALT (U/L)	-0.02 (0.927)	0.03 (0.879)	0.14 (0.530)	-0.05 (0.810)	0.07 (0.750)	0.00 (0.971)	-0.02 (0.775)
AST (U/L)	0.22 (0.340)	-0.13 (0.559)	-0.30 (0.191)	0.14 (0.553)	0.27 (0.236)	-0.18 (0.428)	0.00 (0.929)
Hemoglobin A1c (%)	-0.37 (0.105)	-0.40 (0.074)	-0.02 (0.904)	0.11 (0.631)	-0.09 (0.701)	0.20 (0.387)	0.01 (0.911)
Total cholesterol (mg/dl)	0.05 (0.810)	0.09 (0.679)	-0.10 (0.659)	0.02 (0.921)	0.34 (0.140)	-0.18 (0.425)	0.36 (<0.001)*
LDL (mg/dl)	0.01 (0.944)	0.03 (0.874)	-0.07 (0.762)	0.01 (0.937)	0.33 (0.145)	-0.25 (0.285)	0.40 (<0.001)*
HDL (mg/dl)	0.06 (0.783)	0.03 (0.894)	-0.10 (0.665)	-0.00 (0.989)	-0.17 (0.468)	0.44 (0.049)*	-0.41 (<0.001)*
Triglycerides (mg/dl)	-0.01 (0.956)	0.31 (0.181)	0.03 (0.877)	0.00 (0.983)	-0.16 (0.497)	-0.01 (0.961)	0.24 (<0.001)*
TG/HDL ratio	-0.07 (0.747)	0.32 (0.167)	0.11 (0.617)	0.00 (0.988)	0.00 (0.985)	-0.35 (0.126)	0.37 (<0.001)*
25-OH Vitamin D (ng/ml)	0.10 (0.658)	-0.16 (0.489)	-0.31 (0.175)	-0.07 (0.753)	0.01 (0.967)	0.34 (0.140)	-0.14 (0.099)
Ferritin (ng/ml)	-0.09 (0.705)	0.22 (0.350)	-0.27 (0.248)	0.30 (0.197)	0.00 (0.997)	0.04 (0.846)	0.08 (0.099)
Fasting insulin (µU/ml)	0.34 (0.141)	-0.00 (0.985)	0.18 (0.939)	0.03 (0.895)	-0.19 (0.402)	-0.06 (0.786)	0.39 (<0.001)*
TSH (mIU/L)	0.13 (0.565)	-0.19 (0.404)	-0.14 (0.539)	0.10 (0.652)	-0.03 (0.884)	0.08 (0.738)	0.04 (0.446)
Free T4 (ng/dl)	-0.27 (0.249)	0.15 (0.510)	0.17 (0.466)	0.21 (0.358)	-0.19 (0.420)	-0.27 (0.243)	0.06 (0.514)
White blood cells (x10³/µL)	0.04 (0.860)	0.01 (0.958)	0.50 (0.023)*	-0.28 (0.219)	0.19 (0.419)	-0.15 (0.518)	0.17 (0.053)
MPV (fL)	-0.17 (0.468)	-0.11 (0.644)	-0.25 (0.278)	0.03 (0.870)	0.31 (0.184)	-0.02 (0.908)	0.41 (<0.001)*
Hemoglobin (g/dl)	0.30 (0.197)	0.18 (0.448)	0.00 (0.975)	-0.17 (0.456)	0.35 (0.121)	0.24 (0.302)	0.03 (0.735)
Platelet (10³/µL)	0.18 (0.448)	-0.43 (0.058)	-0.02 (0.925)	0.09 (0.688)	0.05 (0.833)	-0.13 (0.559)	-0.11 (0.197)
Neutrophil (10³/µL)	-0.06 (0.794)	0.06 (0.787)	-0.54 (0.013)*	0.05 (0.821)	0.38 (0.098)	-0.22 (0.331)	0.11 (0.209)
ESR (mm/h)	-0.24 (0.298)	-0.17 (0.450)	-0.15 (0.509)	0.03 (0.885)	-0.12 (0.600)	0.31 (0.176)	0.10 (0.235)
HOMA IR	0.38 (0.098)	-0.00 (0.976)	0.10 (0.670)	-0.00 (0.985)	-0.06 (0.798)	-0.19 (0.419)	0.40 (<0.001)*

eGFR: Estimated glomerular filtration rate, CRP: C-reactive protein, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, TG/HDL ratio: Triglyceride to high-density lipoprotein cholesterol ratio, 25-OH vitamin D: 25-hydroxyvitamin D, TSH: Thyroid-stimulating hormone, Free T4: Free thyroxine, MPV: Mean platelet volume, ESR: Erythrocyte sedimentation rate, HOMA-IR: Homeostasis model assessment of insulin resistance. Correlation coefficients (r) and corresponding p-values are shown in parentheses; statistically significant correlations are denoted by an asterisk (*)

Results showed a significant quadratic association between BMI and hsCRP (cBMI²: B=0.000, p=0.030), indicating a U-shaped pattern, with higher hsCRP levels observed at both low and high BMI ranges, and lower levels at intermediate BMI. Linear cBMI was not significant (B=-0.006, p=0.114), and all covariates showed no statistically significant effects, confirming the minimal adjustment approach. This approach provides a stable and robust analysis, avoiding multicollinearity and outlier issues encountered in previous multinomial logistic regression models. These data are presented in **Table 6**.

These findings indicate that the relationship between BMI and inflammatory burden is not solely a linear increase but rather exhibits a non-linear (U-shaped) pattern that varies across different BMI levels. Trend analysis defines the shape of the relationship, and group-based comparisons were

Table 6. Association between BMI and hsCRP: linear quadratic regression

Variable	B	Std. error	Beta	t	p	95% CI	VIF
Constant	1.293	0.193	–	6.703	0.000	0.911-1.676	–
cBMI	-0.006	0.004	-0.263	-1.591	0.114	-0.013-0.001	4.038
cBMI²	0.000	0.000	0.194	2.202	0.030	0.000-0.001	1.141
FPG	0.001	0.002	0.049	0.566	0.573	-0.002-0.004	1.104
LDL	0.002	0.001	0.305	1.819	0.072	0.000-0.004	4.157
HOMA-IR	0.031	0.020	0.291	1.511	0.133	-0.010-0.071	5.449

B: Unstandardized regression coefficient, Beta: Standardized regression coefficient, SE: Standard error, CI: Confidence interval, VIF: Variance inflation factor, Cbmi: BMI centered by subtracting the mean, cBMI²: Quadratic term of centered BMI, HOMA-IR: Homeostatic Model Assessment of Insulin Resistance, LDL: Low-density lipoprotein cholesterol, FPG: Fasting plasma glucose. Dependent variable: natural logarithm of hsCRP (ln_hsCRP). The model includes minimal metabolic covariates (fasting glucose, LDL, HOMA-IR) to adjust for potential confounding. VIF values <5 indicate acceptable multicollinearity. cBMI² significance demonstrates a U-shaped association between BMI and hsCRP. Linear cBMI term represents deviation from mean BMI

used to assess which BMI group exhibited the minimum inflammatory burden. In previous analyses and post-hoc comparisons, the middle BMI group (group 2) was found to have the lowest significant values in terms of inflammatory burden, while the low BMI group (group 1) showed increased cardiometabolic risk indicators.

DISCUSSION

Our study found that hsCRP levels were 1.82±0.06, 1.65±0.16, 1.66±0.23, 1.71±0.15, 1.88±0.19, and 2.00±0.22 mg/L, respectively, from group 1 to group 6. In light of this data, the most important result of our study is that the relationship between BMI and hs-CRP, one of the inflammatory and cardiometabolic markers, exhibits a U-shaped distribution rather than a linear one, and that increased inflammatory and metabolic risk is revealed in the low BMI group. A review of the literature reveals that a study by Liqiang et al.[18] demonstrated that the relationship between inflammatory parameters such as hsCRP and BMI is non-linear and parallels the increase in obesity levels. Similarly, the study by Zhang et al.[19] emphasized the non-linear relationship between hsCRP and BMI and demonstrated a U-shaped or J-shaped distribution, revealing that hsCRP levels were high, particularly in the low BMI group. The study by Baek and Yoon emphasized that hsCRP levels increase as the degree of obesity increases and showed that hsCRP levels increase even more in patients who are both obese and have inflammatory findings.[20] In contrast, a study by Ghiasi Hafezi et al.[21] found a perfectly linear relationship between BMI and hsCRP levels. Similarly, in the study conducted by Tassone et al.,[22] the relationship between BMI and hsCRP was found to be linear. The possible difference between the results of our study and those of the two other studies can be attributed to sample selection. Furthermore, the small number of patients with extreme BMI values in both studies suggests that this is the fundamental reason for the emergence of a linear structure. However, in these studies, BMI data was used as a linear variable rather than a categorical variable, and we believe that the resulting analytical models directly revealing linear trends may be the probable cause of this outcome.

In our study, a quadratic linear regression model revealed a significant U-shaped association between BMI and hsCRP levels ($cBMI^2$: B=0.000, p=0.030), indicating that inflammatory burden is higher at both low and high BMI values and lower in the middle BMI range. This pattern was observed after adjusting for minimal metabolic covariates (fasting glucose, LDL, HOMA-IR), supporting the robustness of the U-shaped relationship between BMI and cardiometabolic risk. The study by Liu-Galvin et al.[23] reported that individuals within the normal BMI range may also carry a significant risk of inflammatory burden and metabolic impairment, emphasizing that BMI alone does not fully reflect cardiometabolic health. The study by Park et al.[24] emphasized that individuals with a normal BMI may be cardiometabolically unhealthy due to a high body fat percentage, and that BMI data alone is not sufficient to indicate cardiometabolic risk. In a meta-analysis conducted by Mohammadian Khonsar et al.,[25] it was demonstrated that cardiometabolic parameters were elevated in patients with normal BMI but high body fat percentage, emphasizing that BMI data alone is insufficient. Similar to the literature, our study also demonstrated that BMI should not be considered solely as an index reflecting body weight; when evaluated alongside inflammatory and metabolic risk markers, it can reveal different risk profiles. However, it also shows that a low BMI does not always offer a protective metabolic profile and that inflammatory and cardiometabolic risk is lower within the normal BMI range. This result shows that cardiometabolic risk is not limited to increases in obesity levels but can also be significant at low BMI levels, emphasizing that low BMI should not be considered a metabolically safe profile.

Our study revealed a significant relationship between increased BMI and cardiometabolic risk parameters. The study by Zhang et al.[26] showed that both inflammatory markers and cardiometabolic risk were higher, particularly in individuals with high BMI. The study by Ramos-Arellano et al.[27] specifically examined individuals with high BMI; it revealed that cardiometabolic indicators such as hsCRP, fasting insulin levels, lipid levels, and MAP were significantly elevated. The study by Fujii et al.[28] also found that as BMI increases, blood pressure rises and cardiometabolic parameters deteriorate. However, a study by Palatini et al.[29] showed that there was no deterioration in cardiometabolic risk parameters in young patients with high BMI. In a prospective cohort analysis conducted by Li et al.,[30] no significant deterioration in cardiometabolic risk parameters was observed in overweight and obese individuals compared to those of normal weight. It is anticipated that the inconsistent results between our study and the two other studies stem from the patient population. The fact that the individuals included in both studies were young or middle-aged may explain why there was no significant deterioration in cardiometabolic risk parameters.

Our study demonstrated a U-shaped association between BMI and hsCRP levels using a quadratic linear regression model, showing that inflammatory burden and cardiometabolic risk were relatively low in the middle BMI range, while risk increased at both low and high BMI values. These results are consistent with previously reported high BMI-related risks in the literature and additionally highlight an elevated risk in the low BMI group. Numerous clinical studies have been conducted on the possible biochemical mechanism underlying this finding. A study by Ellulu et al.[31] showed that increased adipokine production in the high BMI group increased hsCRP synthesis in the liver and that this effect was associated with risk factors such as insulin resistance, dyslipidemia, and blood pressure. In a study by Buchmann et al.[32] investigating inflammation, metabolic syndrome, and muscle mass loss, elevated hsCRP levels were shown to be associated with metabolic and muscle metabolism impairment. Although similar studies in the low BMI group are limited, a study by Nakajima et al.[33] observed impaired inflammatory parameters in elderly patients. Similarly, Li et al.[34] reported that inflammatory parameters worsened in elderly patients. Although the authors did not demonstrate the existence of a directly measured biological mechanism linking low body weight to inflammation, conceptual frameworks such as the malnutrition-inflammation complex provide an explanation for the elevation of inflammatory markers in low BMI. These findings suggest that the detection of increased inflammation in the low BMI group in our study has a reasonable basis in the literature.

The clinical significance of this study is that it emphasizes that BMI may be limited in assessing cardiometabolic risk and should be supported by additional biomarkers. The study

by Coral et al.[35] emphasized that BMI data alone may not be a sufficient indicator for assessing cardiometabolic risk. The study by Liu-Galvin et al.[36] also supports the current findings, emphasizing that individuals with low BMI do not always have a protective metabolic profile and may carry a risk in terms of inflammatory burden. Our findings suggest that BMI alone may not be a sufficient indicator for assessing cardiometabolic risk, consistent with the literature. However, it is thought that evaluations based solely on anthropometric measurements may be insufficient in the clinical follow-up of individuals with extreme BMI values and that a more comprehensive approach incorporating inflammatory/metabolic markers may be beneficial. In this context, our study highlights the potential importance of considering inflammatory parameters in addition to BMI in the assessment of cardiometabolic risk, as easily accessible inflammatory markers such as hsCRP show significant differences across BMI categories.

Overall, the findings indicate that BMI is not the sole determinant of cardiometabolic risk and that individuals with low BMI should also be carefully monitored for inflammatory burden and metabolic risk. These results emphasize the importance of considering inflammatory parameters in addition to BMI in clinical practice and shed light on the development of risk assessment strategies targeting the low BMI group.

Strengths of the Study

The analysis of BMI in multiple categories and the use of readily accessible inflammatory markers such as hsCRP have enabled a detailed examination of cardiometabolic risk in low and high BMI groups. Demonstrating that inflammatory parameters are significantly elevated, particularly in the low BMI group, constitutes the most important and original contribution of this study, as this is a topic rarely addressed in the literature. This finding emphasizes that individuals with low BMI do not always have a protective metabolic profile and may carry risk in terms of inflammatory burden.

Limitations

This study has some limitations. First, due to its cross-sectional design, causal inferences cannot be made regarding the relationships between BMI and inflammatory and cardiometabolic markers. Additionally, the relatively limited number of patients in the groups formed according to BMI categories may have restricted the detection of within-group variation and smaller effect sizes. Although BMI is a practical and widely used measure, it may not reflect body composition and fat distribution alone; waist circumference measurements, which we used in this study, may contribute to a more accurate assessment of cardiometabolic risk. Furthermore, hsCRP measurements were taken at a single time point, and temporal changes in inflammatory load could not be evaluated. The absence of other inflammatory cytokines, such as IL-6 and TNF-α, or detailed nutrition and physical activity data in the study, limits the in-depth investigation of possible mechanisms.

CONCLUSION

In this study, the relationship between BMI and cardiometabolic risk markers was not observed to be solely linear. Our analyses showed that even in the low BMI group, the inflammatory burden (hsCRP) increased and cardiometabolic risk rose. In the moderate BMI group, the risk was relatively low, while in the high BMI group, the risk increased again, thus revealing a U-shaped trend. The findings support that not only obesity but also low BMI may be an important determinant of cardiometabolic risk. These results emphasize the need to monitor individuals with low BMI for cardiometabolic risk in clinical evaluations.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of the Etlik City Hospital Clinical Researches Ethics Committee (Date: 05.07.2023, Decision No: 2023-25).

Informed Consent

Written informed consent was obtained from all individual participants prior to their inclusion in the study. Participants were fully informed about the study's aims, procedures, potential risks and benefits, and their rights-including the right to withdraw at any time without consequence. All participants voluntarily signed a written informed consent form.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

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Author Contributions

Concept: A.H., A.Ç.; Design: A.H., A.Ç.; Control: A.H., A.Ç.; Data Collection and/or Processing: A.H.; Analysis an/or Interpretation: A.H., A.Ç.; Literature Review: A.H.; Article Writing: A.H., A.Ç.; Critical Review: A.H., A.Ç.

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Review

Cachexia in oncology patients

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ABSTRACT

Cancer-related cachexia is a complex metabolic syndrome characterized by involuntary weight loss, systemic inflammation, and a significant disruption of protein-energy homeostasis. It serves as a primary determinant of mortality and negatively impacts the efficacy of oncological treatments such as chemotherapy. The prevalence of cachexia ranges between 40% and 70%, with the highest incidence observed in pancreatic and gastrointestinal cancers. The pathophysiology is driven by pro-inflammatory cytokines secreted by tumors (e.g., TNF-α, IL-1, IL-6), which cause systemic catabolism, such as faster proteolysis in skeletal muscles and more lipolysis in adipose tissue. Furthermore, the syndrome involves the impairment of the central nervous system's homeostatic control over energy balance, leading to anorexia and high resting energy expenditure. Diagnosis is mainly based on keeping an eye on unintentional weight loss and body mass index (BMI), with a weight loss of 5% being a key sign of a bad prognosis. Effective management requires a multisystemic and multidisciplinary approach. This includes early nutritional interventions (oral, enteral, or parenteral), the use of appetite stimulants (orexigens), and tailored exercise programs to mitigate muscle atrophy. Additionally, comprehensive symptom management-addressing pain, nausea, and psychological distress-is essential for holistic care. As cachexia gets worse, it may not respond to standard treatments, which will lead to a decline that cannot be stopped. Given the increasing global incidence of cancer, there is a critical need for specialized teams and further research to develop effective, targeted treatment strategies for this challenging condition.

Keywords: Cancer, cachexia, inflammation, weight loss, oncology

INTRODUCTION

Cachexia is characterized by involuntary weight loss and loss of homeostatic control of protein-energy balance. Although it usually develops in association with malignancies, it can also occur in association with certain neurological and rheumatological diseases such as heart failure, renal pathologies, chronic obstructive pulmonary disease, and multiple sclerosis.[1,2]

The disruption of protein-energy homeostasis in cachexia is very different from the easily reversible weight loss resulting from inadequate food intake. In cachexia, there is a combined picture of increased energy consumption, increased catabolism due to the underlying etiology, and the development of inflammation.[3]

Cachexia is considered one of the primary determinants of mortality in cancer patients. Studies have found that 80% of patients with stomach and pancreatic cancer, in particular, were cachectic at the time of death.[4] In addition, there are publications indicating that cachexia negatively affects the response rate to chemotherapy.[5] For this reason, cancer patients should be closely monitored for weight loss, and the development of cachexia should be prevented.

EPIDEMIOLOGY

Cancer incidence is increasing worldwide every day. Among the reasons for this are population growth and higher diagnosis rates driven by advances in blood tests and imaging methods. Research indicates that the United States will detect approximately 2 million new cancer cases in 2023. In addition, over 600.000 cancer-related deaths were reported.[6]

Different prevalence rates have been identified for cachexia in cancer patients, generally ranging from 40% to 70%.[7] This range is due to variations in the incidence of cachexia associated with different malignancies. In particular, the prevalence of cachexia is above 50% in gastrointestinal system, pancreatic, and head and neck cancers, while it is below 50% in prostate, lung, and hematological malignancies.[8]

PATHOPHYSIOLOGY

Advances in the pathophysiological mechanism of cachexia have mostly emerged in the recent past. The reason for this situation may be that cachexia often occurs in the final stages of malignant patients, and the use of invasive and metabolic tests in these patients is limited. Studies conducted recently have revealed that cachexia is a multi-organ syndrome; the brain, intestines, immune system, adipose tissue, muscle tissue, and numerous hormonal mechanisms are associated with cachexia, as summarized in **Figure 1**.[9]

One of the key points in cancer-related cachexia is the disruption of central homeostatic control over energy balance. Decreased food intake is often a leading cause of weight loss.

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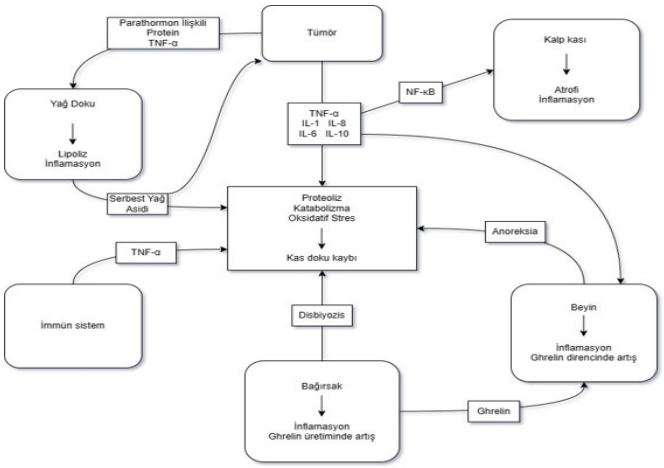

Figure 1. Molecular mechanism in cancer-related cachexia

However, the cause of weight loss is not solely due to an energy deficit resulting from reduced food intake. In these patients, high energy expenditure at rest creates an energy deficit, which can exceed 1200 kilocalories per day.[10] Tumor cells often compete with other tissues for energy, fuels, and substrates. As a result of insufficient substrates and fuels reaching the tissues, increased lipolysis, increased gluconeogenesis, and protein breakdown occur.[11]

Cytokines secreted by tumor cells are also considered an important cause of cancer-related cachexia. Tumor cells secrete various molecules that can cause catabolism in target tissues, such as proinflammatory cytokines, heat shock proteins, and eicosanoids, as summarized in **Table**. As a secondary response to these molecules, proteolysis, lipolysis, and even apoptosis may develop in target organs.[12]

Table. Cytokines secreted by tumor cells and the immune system in cancer cachexia

Tumor-related catabolic factors	Proinflammatory factors released as a result of tumor-immune system interactions
Activins	IL-1α IL-1β
Myostatin	IL-6 IL-11 IL-17
TGF-β	TNF-α
Serotonin	IFN-γ
Parathyroid hormone-related protein	GDF 15 (Growth Differentiation Factor 15)
Adrenomedullin	LIF (Leukemia Inhibitory Factor)
HSP 70-90	TWEAK (TNF-associated apoptosis trigger)
	TRAF 6 (TNF receptor-associated factor 6)
	Oncostatin M
	PGE2

TGF-β: Transforming growth factor beta, HSP: Henoch-Schönlein purpura, IL: Interleukin, TNF-α: Tumor necrosis factor-alpha, IFN: Interferon-gamma, PGE: Prostaglandin

In cancer-related cachexia, it has been established that the mediobasal hypothalamus is functionally impaired by peripheral inflammation, thereby impairing the activity of neurons regulating proteolysis, lipolysis, and appetite. This effect is thought to result specifically from IL-1B-dependent catabolism.[13]

Skeletal muscle atrophy observed in cancer cachexia occurs as a result of cytokines secreted by the tumor and surrounding stromal tissue and the pathways activated by the immune system in response. Generally, this activation leads to the destruction of myofibrillar proteins that provide contraction function to skeletal muscles. This results in muscle atrophy and muscle weakness. On the other hand, growth factors such as TGF-B cause sarcomere dysfunction as a result of their calcium-mediated effect.[14] The signaling pathways of cancer-mediated skeletal muscle atrophy are summarized in **Figure 2**.

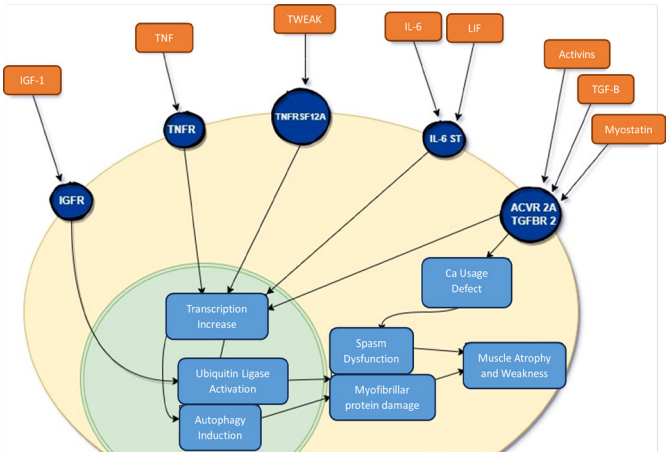

Figure 2. Signaling pathways of skeletal muscle atrophy in cancer cachexia

In addition to skeletal muscle loss, fat tissue loss is also a significant cause of cachexia in cancer patients. Studies have determined that fat tissue loss is due to lipolysis rather than apoptosis and that the rate of lipolysis in the body increases by approximately 50% in cachectic patients.[15] Furthermore, biopsy evaluations of cachectic patients revealed that the lipolytic effect of catecholamines and natriuretic peptides in white adipose tissue is 2-3 times higher in cancer-related cachexia patients.[16]

DIAGNOSIS

Weight loss is usually the first noticeable sign of cachexia. Weight loss may even be the first sign of cancer, allowing patients to be diagnosed. After intentional weight loss has been ruled out in these patients, other alternative etiologies should be investigated.[17]

Weight loss is typically the first sign of cachexia and varies in each patient. Weight loss can be slow, rapid, intense, continuous, or intermittent. It must be monitored over time and compared to the patient's pre-cancer weight. The severity of weight loss can provide insight into the prognosis. A 5% weight loss is considered the first threshold for poor prognosis, and the risk of poor prognosis increases with greater weight loss.[18]

To grade cachexia, studies conducted internationally on more than 10.000 patients have resulted in a system based on body mass index (BMI) and weight loss that predicts prognosis.[19] This classification is summarized in **Figure 3**.

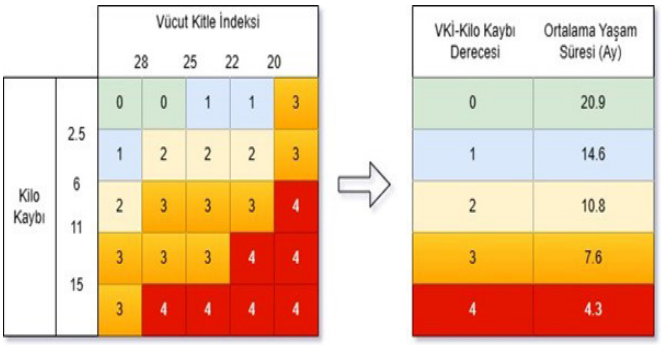

Figure 3. Prognosis grading based on weight loss in patients with advanced cancer

Various studies have been conducted recently for the diagnosis of cancer cachexia. Although there is still no consensus on skeletal muscle loss, decreased food intake, metabolic changes, and catabolism measurement, it is predicted that these will be among the diagnostic methods in the future[20] Management: Cancer-related cachexia develops over time. Cachexia will develop in most patients with advanced lung, esophageal, stomach, colon, and liver cancer. It is essential to be aware of this, take early, systematic precautions, and not wait until it is completely obvious to intervene. The approach to cachexia should not be limited to oral nutritional solutions but should be multisystemic.[21]

There is no clear consensus on the point at which treatment for cachexia should begin. Some studies have used the concept of pre-cachexia to objectively define the threshold for early intervention. Although the term "pre-cachexia" is defined as weight loss of 2% or more, it is not a widely used concept today.[22] Ensuring adequate nutrition is fundamental in cancer cachexia. First-line approaches recommend consulting a nutritionist to increase the quantity and quality of oral nutritional products. Providing adequate active nutritional support in patients experiencing rapid weight loss enhances their tolerance to the administered treatment, such as chemotherapy.[23] On the other hand, active nutritional support is often insufficient, especially in patients with advanced cancer. Compliance with oral nutritional solutions is generally low in these patients. In such cases, enteral or parenteral nutritional support should be administered without delay.[24] Appetite stimulants (orexigens) are available for patients with cachexia who have a poor appetite. Although the primary effect of these drugs is not to stimulate appetite, they have been shown to increase appetite in various settings and are considered appropriate for use in cachectic patients. Cannabinoids, corticosteroids, and progestogens generally have appetite-stimulating properties. However, these drugs also have side effects. Corticosteroids accelerate skeletal muscle atrophy, which is already present in cachectic patients. Progestogens also accelerate muscle atrophy and further increase the risk of thromboembolism, which is already high, especially in cancer patients.[25]

In recent years, new agents that increase food intake have been investigated. In particular, growth hormone-releasing receptor type 1 agonists and melanocortin receptor 4 agonists, which act on the hypothalamus in the central nervous system, have been shown to increase appetite and are available for use in appropriate patients.[26,27] In addition to nutritional recommendations, regular exercise is also recommended to prevent skeletal muscle loss in cachectic patients. Appropriate exercise programs should be planned for patients, taking into account the risk of falling, to the extent that it is safe for them.[28] In a study of patients undergoing chemotherapy, the group that performed aerobic exercise and resistance training showed improvements in muscle strength across the body.[29] Cachexia is not the only finding in cancer patients and always occurs alongside other findings. Accompanying symptoms vary depending on the patient's malignancy, the chemotherapy or other treatments they are receiving, and the toxicity of the treatment, and they can change rapidly, with new symptoms emerging. Studies have shown that clinicians fail to identify accompanying symptoms in approximately 50% of these patients.[30] It should be remembered that the management of accompanying symptoms is also part of cachexia management. Certain symptoms, in particular, increase the severity of cachexia more than others. These include pain, nausea, vomiting, dysphagia, early satiety, oral and dental problems, swallowing difficulties, constipation, diarrhea, anxiety, depression, and insomnia.[25] All these symptoms should not be ignored; they should be carefully examined at every visit, and comprehensive symptomatic treatments should be planned. One important element of supportive care is the formation of a multidisciplinary team. Clinical studies have found that patients benefit more and have a better disease course in clinics where palliative care and oncology physicians work together.[31]

In addition to cachexia treatment, another important consideration is dose adjustment in patients receiving active systemic chemotherapy. The required chemotherapy dose may decrease as a result of weight loss and skeletal muscle loss; failure to reduce the dose may lead to toxicity.[32] Studies have concluded that a multisystemic approach to cancer-related cachexia has a proportional distribution, as summarized in **Figure 4**.

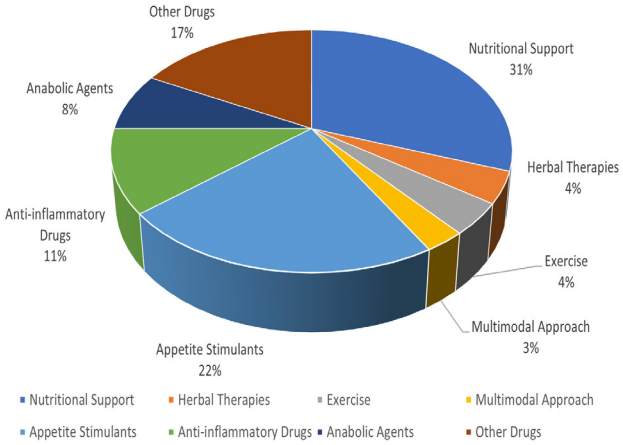

Figure 4. Proportional distribution of therapeutic approaches in cancer-related cachexia treatment

Cancer-related cachexia can become resistant to therapeutic treatments over time. This situation is usually caused by an underlying disease that does not respond to antineoplastic treatment. Patients experience increased weight loss and progressively worsening catabolism, and death becomes inevitable.[33]

CONCLUSION

In cancer-related cachexia, many pathophysiological mechanisms remain unclear, and there is no consensus on most issues. Therefore, it is evident that more research is needed from all angles. The increasing incidence of cancer each year highlights the need to establish experienced teams that will closely monitor patients in order to develop specialized, effective treatment approaches for cancer cachexia.

ETHICAL DECLARATIONS

Peer Review Process

This review was externally peer-reviewed.

Conflict of Interest

The authors declare no conflicts of interest.

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Letter to the Editor

Nivolumab incuded colitis in a cancer patient: therapeutic dilemmas and patient-related factors

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Dear Editor,

Nivolumab is a current type of monoclonal IgG4 antibody used to treat many types of cancer, including stomach cancer, lymphoma, malignant melanoma and non-small cell lung cancer.[1] Side effects associated with immune checkpoint inhibitors and tyrosine kinase inhibitors are increasingly recognized and presented as literature information.[1,2] One of the most commonly affected systems is the gastrointestinal system.[1,3] This case report presents a case of nivolumab-associated colitis in a patient with metastatic lung cancer, where treatment decisions were complicated by oncologic needs and patient compliance issues.

A 61-year-old male patient presented to our outpatient clinic with complaints of passing bloody, watery stools 8-10 times a day and fatigue. His medical history included hypertension and his treatment for metastatic lung cancer (liver metastases and lymph node metastases). He was receiving nivolumab therapy during his oncological treatment and reported that his symptoms began after five cycles of nivolumab. Blood tests revealed mild anemia (hemoglobin: 13.4 g/dl, hematocrit: 40%, WBC: 8.86 K/uL), elevated C-reactive protein level (39.38 mg/L), and elevated sedimentation rate (43 mm/h). Routine blood tests were within normal limits. Stool microscopy revealed abundant erythrocytes and leukocytes in all fields. Stool culture was negative for Salmonella, Shigella, and Aeromonas. Colonoscopy findings were consistent with pancolitis; there were widespread millimetric ulcers in the colon mucosa, submucosal vascular structures were obliterated (**Figure**), and multiple biopsies were taken. Biopsy findings were consistent with ulcerations, crypt abscesses, active severe inflammation, and inflammatory bowel disease. Immunohistochemical analysis of tissue samples taken for CMV colitis was negative. Because there was no history of inflammatory bowel disease or chronic colitis before nivolumab treatment, infectious causes of colitis had been excluded, and cases of nivolumab-induced colitis had been reported in the literature, a diagnosis of nivolumab-associated colitis was made based on our endoscopic and histopathological findings. Upon consultation with the patient's oncologist, discontinuation of nivolumab was not possible due to oncological necessity. Mesalazine was started as a first-line treatment, but the patient could not tolerate it. Systemic steroid therapy was considered, but the prednisolone-azathioprine combination was not approved by the oncology team. Budesonide, which has a more limited systemic effect and a lower risk of adverse outcomes, was started. The patient stated that he was feeling well on budesonide treatment and did not attend her outpatient clinic follow-ups despite phone calls. A few months later, our patient presented to our hospital's Emergency Department again with bloody diarrhea. He was informed that he had neglected his budesonide treatment because he was feeling well. A second colonoscopy revealed pancolitis, similar to the findings previously identified. No infectious or parasitic cause of pancolitis was identified, and the patient was started on methylprednisolone. However, the patient again failed to attend outpatient clinic follow-ups. A few months later, the patient underwent orthopedic surgery for a vertebral fracture and was subsequently admitted to intensive care. He was subsequently pronounced deceased due to complications from the surgery.

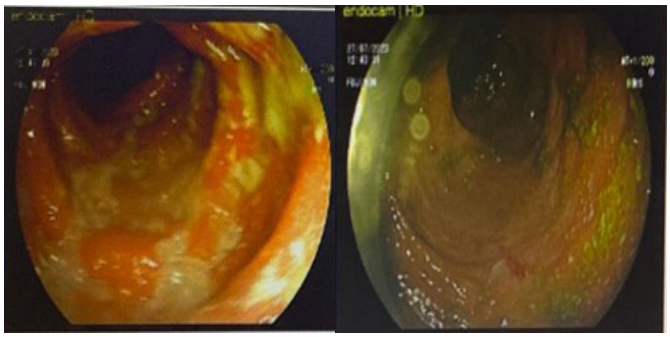

Figure. Endoscopic appearance of nivolumab induced colitis

Immune checkpoint inhibitors have become a crucial component of cancer treatment, but they carry the risk of developing serious immune-related side effects, including colitis.[4,5] Nivolumab-induced colitis can mimic ulcerative colitis or infectious colitis endoscopically and

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histopathologically, but the clinical course can also be quite variable.[3-5] In this case, treatment options were limited by both oncological limitations and the patient's failure to attend regular outpatient clinic visits. Lack of follow-up and intolerance to standard therapy complicated disease management and contributed to the adverse clinical course. This case report clearly highlights the importance of a multidisciplinary approach, close follow-up, and patient compliance in the successful management of immune checkpoint inhibitor-associated colitis.

ETHICAL DECLARATIONS

Informed Consent

Written informed consent was obtained from the patient for the publication of this correspondence and any related clinical details.

Peer Review Process

This letter was externally peer-reviewed.

Conflict of Interest

The authors declare no conflicts of interest.

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Author Contributions

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