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Assessing Cardiovascular Risk in Inflammatory Bowel Disease Using Novel Inflammatory and Dyslipidemia Markers: An Evaluation of PAI, MHO, and SII

Burcu Ağırbaş Çelen[1], Hasan Eruzun[2], Yasemin Gökden[3]

[1]Department of Internal Medicine, University of Health Sciences, Prof. Dr. Cemil Taşcıoğlu City Hospital, Istanbul, Türkiye
[2]Department of Gastroenterology, Samsun Training and Research Hospital, Samsun, Türkiye
[3]Department of Gastroenterology, University of Health Sciences, Prof. Dr. Cemil Taşcıoğlu City Hospital, Istanbul, Türkiye

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Corresponding author: Hasan Eruzunm, e-mail: hasaneruzun@gmail.com

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Abstract

Objective: Inflammatory Bowel Disease (IBD), encompassing Crohn's Disease (CD) and Ulcerative Colitis (UC), is a chronic immune-mediated condition associated with systemic inflammation that may increase the risk of cardiovascular disease (CVD). This study aimed to investigate the utility of novel, accessible inflammatory and atherogenic biomarkers-Plasma Atherogenic Index (PAI), Monocyte-to-HDL Ratio (MHO), and Systemic Immune-Inflammation Index (SII)-in assessing cardiovascular risk and disease activity in IBD patients compared to healthy controls. We also evaluated the association of these markers with Abdominal Aortic Calcification (AAC), a surrogate for subclinical atherosclerosis.

Methods: This retrospective, single-center study included 99 IBD patients (40 with CD, 59 with UC) and 70 healthy controls evaluated between January 2017 and April 2023. Demographic, clinical, and laboratory data were collected from patient files. PAI (log[Triglycerides/HDL-C]), MHO (Monocyte/HDL-C), and SII ([Platelet × Neutrophil]/Lymphocyte) were calculated. Disease activity was assessed using the Crohn's Disease Activity Index (CDAI) for CD and the Mayo score for UC. AAC was assessed in patients with available abdominal computed tomography (CT) scans. Statistical analyses included group comparisons and Receiver Operating Characteristic (ROC) curve analyses.

Results: IBD patients demonstrated significantly higher levels of PAI, MHO, SII, and Neutrophil-to-Lymphocyte Ratio (NLR) compared to the healthy control group ($p < 0.05$ for all). Within the IBD cohort, patients with active disease exhibited significantly higher SII and NLR values compared to those in remission. However, PAI levels did not differ significantly between active and inactive disease states. Of the 63 patients evaluated with CT, 40 (63.5%) had AAC. Patients with AAC had significantly higher levels of CRP, NLR, SII, MHO, and PAI compared to those without AAC ($p < 0.01$ for all). ROC analysis identified PAI and MHO as strong predictors of AAC presence.

Conclusion: The novel, easily calculable biomarkers PAI, MHO, and SII are significantly elevated in patients with IBD, suggesting a heightened pro-inflammatory and pro-atherogenic state. The strong association of these markers with AAC reinforces their potential utility in identifying subclinical atherosclerosis and increased cardiovascular risk in this patient population. These findings suggest that routine calculation of these indices could aid in cardiovascular risk stratification for IBD patients, although further validation through large-scale, prospective studies is warranted.

Keywords: Abdominal aortic calcification, cardiovascular risk, inflammatory bowel disease, monocyte-to-hdl ratio, neutrophil-to-lymphocyte ratio, plasma atherogenic index, systemic immune-inflammation index.

INTRODUCTION

Inflammatory Bowel Disease (IBD) is a term for a group of chronic, immune-mediated disorders characterized by relapsing and remitting inflammation of the gastrointestinal tract, often accompanied by extraintestinal manifestations.[1] Its two primary forms are Ulcerative Colitis (UC) and Crohn's Disease (CD). While the etiology is not fully understood, IBD is believed to result from a complex interaction among genetic predisposition, environmental factors, microbial dysbiosis, and a dysregulated immune response.

Cardiovascular disease (CVD) is a leading cause of mortality worldwide, with atherosclerosis as its main underlying pathology. Systemic inflammation plays a critical role in the development of CVD, and its contribution to atherogenesis is well-documented in chronic inflammatory conditions such as rheumatoid arthritis.[2] Key mechanisms-including endothelial dysfunction, increased arterial stiffness, and pro-inflammatory cytokine production-are common to both IBD and atherogenesis.[2-8] The prevailing hypothesis suggests that immune dysregulation and inflammatory burden in IBD promote the formation of atherosclerotic plaques.[9,10] Consequently, large-scale studies and meta-analyses have shown that IBD patients have a significantly increased risk of coronary artery disease (CAD), myocardial infarction, and stroke.[4,11-14] Furthermore, disease activity itself has been identified as an independent risk factor for these acute arterial events.[15]

- Patients with Inflammatory Bowel Disease have significantly higher levels of Plasma Atherogenic Index, Monocyte-to-HDL Ratio, and Systemic Immune-Inflammation Index compared to healthy controls, indicating a heightened pro-inflammatory and pro-atherogenic state in IBD.
- PAI, MHO, and SII are strongly associated with Abdominal Aortic Calcification, a surrogate marker of subclinical atherosclerosis, suggesting their potential role in cardiovascular risk assessment in IBD patients.
- Active IBD is linked to higher levels of inflammatory markers, including CRP, NLR, and SII. However, PAI did not significantly correlate with disease activity, suggesting it may reflect a more chronic cardiovascular risk rather than acute inflammation.
- PAI and MHO were identified as strong predictors for the presence of AAC, highlighting their potential as cost-effective biomarkers for identifying subclinical atherosclerosis and enhancing cardiovascular risk stratification in IBD patients.
- Routine integration of PAI, MHO, and SII into clinical practice could help identify high-risk IBD patients for targeted cardiovascular risk management, though further prospective studies are needed to validate these biomarkers and their role in improving long-term cardiovascular outcomes.

Given this heightened risk, there is a need for improved risk stratification tools. Abdominal Aortic Calcification (AAC), detectable on CT scans, has been identified as a marker of early atherosclerosis. Data from the Framingham Heart Study demonstrated that AAC is an independent risk factor for the progression of coronary artery calcification and is predictive of future cardiovascular events.16 Concurrently, several simple, blood-based biomarkers have emerged. The Plasma Atherogenic Index (PAI), calculated as the logarithm of the Triglyceride/HDL-C ratio, is a novel biomarker that integrates two independent CVD risk factors.[17,18] PAI has been associated with cardiovascular disease in a variety of other clinical settings.[19-24]

The primary aim of this study was to investigate these inflammatory and atherogenic markers (PAI, MHO, SII, NLR) in IBD patients and compare them to healthy controls to assess their role in determining increased CVD risk. A secondary aim was to evaluate the relationship between these markers and AAC, thereby testing their utility as predictors of subclinical atherosclerosis.

METHODS

Study Design and Population

This retrospective, cross-sectional study was conducted at the Gastroenterology Clinic of Cemil Taşçıoğlu City Hospital in İstanbul, Türkiye. We reviewed the records of patients evaluated between January 2017 and April 2023. The study included 99 adult patients (≥18 years) with a confirmed diagnosis of IBD (40 with CD, 59 with UC) and a control group of 70 healthy individuals without known chronic diseases or chronic medication use. Exclusion criteria included age under 18, other chronic inflammatory diseases, recent surgery, known CVD, severe liver or kidney disease, pregnancy, malignancy, recent systemic infection, and current use of statin medications.

Ethical Approval

The study protocol was approved by the Cemil Taşçıoğlu City Hospital Clinical Research Ethics Committee (Approval Number: 119, Date: 31.07.2023). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data Collection and Calculations

Demographic, clinical, and laboratory data were collected from patient files. The following indices were calculated from routine blood tests:

• NLR: Absolute Neutrophil Count / Absolute Lymphocyte Count
• SII: (Platelet Count × Absolute Neutrophil Count) / Absolute Lymphocyte Count
• MHO: Absolute Monocyte Count / HDL-C Level
• PAI: log (Triglyceride Level / HDL-C Level)

Assessment of Disease Activity and AAC

Disease activity was assessed using established scoring systems. For Ulcerative Colitis, the Mayo score was used, with a score >2 defining active disease. For Crohn's Disease, the Crohn's Disease Activity Index (CDAI) was used, with a score >150 indicating active disease.

For IBD patients who had undergone abdominal CT scans as part of their clinical care, the images were retrospectively analyzed by a single radiologist for the presence of visible AAC in the abdominal aorta.

Statistical Analysis

Analyses were performed using SPSS software (version 26.0, IBM Corp, Armonk, NY, USA). Group comparisons were made using Student's t-test, ANOVA, Mann-Whitney U test, or Kruskal-Wallis tests as appropriate. Kolmogorov-Smirnov analysis was used to assess normality. Categorical variables were compared using the Chi-square test. ROC curve analysis was used to evaluate the predictive capacity of the biomarkers. A p-value of <0.05 was considered statistically significant.

RESULTS

Baseline Cohort Characteristics

A total of 169 individuals were enrolled in the study, comprising 99 patients with IBD (40 with CD and 59 with UC) and 70 healthy controls. A comprehensive summary of the cohort's baseline demographic and clinical characteristics is provided in Table 1. The three groups were well-matched, with no statistically significant differences in age, sex distribution, or Body Mass Index (BMI). Among the IBD patients, the most common disease location for CD was ileocolonic (57.5%), while UC was most frequently characterized by distal colitis or pancolitis (37.3% for each). Active disease was present in 32.5% of CD patients and 27.1% of UC patients at the time of data collection. Medication usage varied: 5-ASA preparations were the most common treatment in UC patients (91.5%), while azathioprine was most frequently used in the CD cohort (45.0%).

Comparison of Laboratory Biomarkers Across Groups

A detailed comparison of laboratory biomarkers across the CD, UC, and control groups is presented in Table 2. In the analysis of lipid parameters, IBD patients exhibited a significantly more atherogenic profile, characterized by lower HDL-C levels ($p = 0.01$ for both CD and UC vs. control) and consequently higher PAI values ($p = 0.003$ for CD, $p = 0.017$ for UC). No significant differences were observed in LDL-C or triglyceride levels. The vast majority of inflammatory markers and indices were significantly elevated in IBD patients. Compared to controls, both CD and UC patients had significantly higher neutrophil counts, CRP, ESR, platelet counts, Neutrophil-to-Lymphocyte Ratio (NLR), Systemic Immune-Inflammation Index (SII), and

Table 1. Baseline Demographic and Clinical Characteristics of Study Participants

Characteristic	Crohn's Disease (n=40)	Ulcerative Colitis (n=59)	Control (n=70)	p-value
Demographics				
Age (years, mean ± SD)	41.8 ± 10.4	44.4 ± 13.7	39.9 ± 9.2	0.09
Sex (Male, n (%))	17 (42.5%)	31 (52.5%)	28 (40.0%)	0.491
BMI (kg/m², mean ± SD)	25.66 ± 5.33	25.84 ± 4.35	24.66 ± 3.91	>0.05
Crohn's Disease Clinical Features				
Location: Colonic / Ileocolonic / Ileal (%)	5.0 / 57.5 / 37.5	-	-	-
Behavior: Inflammatory / Stricturing / Fistulizing (%)	57.5 / 17.5 / 25.0	-	-	-
Active Disease (CDAI > 150) (%)	32.5%	-	-	-
Perianal Involvement (%)	15.0%	-	-	-
Extraintestinal Manifestations (Arthralgia/Arthritis) (%)	30.0%	-	-	-
Ulcerative Colitis Clinical Features				
Location: Proctitis / Distal Colitis / Pancolitis (%)	-	25.4 / 37.3 / 37.3	-	-
Active Disease (Mayo > 2) (%)	-	27.1%	-	-
Perianal Involvement (%)	-	5.1%	-	-
Extraintestinal Manifestations (Arthralgia/Arthritis) (%)	-	22.0%	-	-
Medication Usage (n,%)				
5-ASA	15 (37.5%)	54 (91.5%)	-	-
Azathioprine (AZT)	18 (45.0%)	11 (18.6%)	-	-
Corticosteroids (CS)	11 (27.5%)	2 (3.4%)	-	-
Anti-TNF	5 (12.5%)	2 (3.4%)	-	-

Table 2. Comparison of Laboratory Biomarkers Across Study Groups

Parameter (mean ± SD or median [IQR])	Crohn's Disease (n=40)	Ulcerative Colitis (n=59)	Control (n=70)	p-value (IBD vs Control)
Lipid Parameters				
HDL-C (mg/dL)	46.4 ± 14.2	45.5 ± 12.9	53.0 ± 14.1	CD: 0.01, UC: 0.01
LDL-C (mg/dL)	107.05 ± 40.43	103.3 ± 39.48	126.15 ± 17.77	>0.05
Triglycerides (mg/dL)	126.65 ± 60.34	111.95 ± 59.44	99.77 ± 59.8	>0.05
PAI	0.41 ± 0.25	0.36 ± 0.23	0.22 ± 0.09	CD: 0.003, UC: 0.017
Inflammatory Parameters				
Neutrophil Count (10^3/mm³)	5.69 ± 2.5	5.01 ± 2.27	2.54 ± 0.76	<0.001 for both
Lymphocyte Count (10^3/mm³)	1.93 ± 0.82	2.00 ± 0.65	1.88 ± 0.57	>0.05
CRP (mg/L)	24.67 [0.33-284]	13.94 [0.42-137]	2.0 ± 1.41	CD: 0.002, UC: 0.008
ESR (mm/h)	19.9 [2-90]	21.6 [2-113]	5.4 ± 3.6	<0.001 for both
Inflammatory Indices				
Platelet Count (10^3/mm³)	318.4 ± 93.9	317.3 ± 112.1	257.6 ± 55.3	CD: 0.003, UC: 0.001
NLR	3.88 [1.1-29.0]	2.78 [0.71-17.4]	1.54 ± 0.82	CD: <0.001, UC: 0.023
SII	1367.6 [327-10678]	948.6 [105-7126]	229.9 ± 81.2	CD: <0.001, UC: 0.025
MHO	13.5 [3.9-46]	11.7 [3.4-40]	9.9 [3.7-10]	CD: 0.019, UC: 0.029
LMO	3.81 ± 1.59	4.6 ± 1.94	2.0 ± 1.21	>0.05

Monocyte-to-HDL Ratio (MHO). However, lymphocyte counts and the Lymphocyte-to-Monocyte Ratio (LMO) were not significantly different between the groups.

Subgroup Analyses

Subgroup analyses were performed to assess the relationship between biomarkers and disease activity or the presence of subclinical atherosclerosis. The results are summarized in Table 3.

• **Disease Activity:** In both CD and UC, active disease was associated with a significantly heightened inflammatory state, marked by higher levels of CRP, NLR, and SII, and a lower LMO ($p < 0.05$ for all). There were notable differences in lipid profiles: active CD was associated with significantly lower HDL-C and triglycerides, while active UC was associated with lower LDL-C. However, PAI was not significantly associated with disease activity in either group.

• **Abdominal Aortic Calcification:** AAC was identified in 40 of the 62 IBD patients with available imaging (63.5%). The presence of AAC was strongly associated with a pro-inflammatory and pro-atherogenic profile. As shown in Table 3, patients with AAC had significantly higher levels of CRP, NLR, SII, MHO, and PAI compared to those without AAC.

Specific Analyses of PAI and ROC Findings

Further analyses specific to PAI are detailed in Table 4. PAI was found to be significantly higher in males than females within the UC and con-

Table 3. Subgroup Analyses Based on Disease Activity and Presence of Aortic Calcification

Parameter	Inactive CD (n=27)	Active CD (n=13)	p	Inactive UC (n=43)	Active UC (n=16)	p	AAC Negative (n=22)	AAC Positive (n=40)	p
BMI (kg/m²)	27.01±5.01	22.96±5.07	.016	25.99±4.3	25.45±4.62	.732	26.67±5.17	25.1±4.5	.3
HDL-C (mg/dL)	50.2±12.8	38.5±14.3	.023	46.7±10.6	42.3±17.6	.098	-	-	-
LDL-C (mg/dL)	118.15±48.35	84±32.98	.123	109.91±35.75	85.56±44.58	.021	-	-	-
Triglycerides (mg/dL)	142±61.87	94.77±43.7	.011	118.74±65.22	93.69±35.51	.159	-	-	-
CRP (mg/L)	4.7	66.03	<.001	4.5	39.26	<.001	4.77	35.2	.001
NLR	2.53±1.42	4.43±1.27	<.001	2.69	6.01	<.001	2.32±1.1	4.48±1.3	<.001
SII	771.5	2605.8	.012	725.2	2555.3	<.001	662.9	1613.2	.002
LMO	4.43	2.53	<.001	4.85	2.74	<.001	3.83	4.2	.444
MHO	19.49±12.55	10.32±3.66	<.001	10.05±4.4	16.64±9.98	.001	10.15±4.11	17.96±11.12	.001
PAI	0.42±0.02	0.38±0.03	.696	0.37±0.02	0.35±0.02	.878	0.23±0.02		

Table 4. Specific Analyses of the Plasma Atherogenic Index

Analysis Type	Group	Detail / Compared Variable	Value	p-value
PAI Comparison by Gender	Crohn's Disease	Male vs Female	0.40 vs 0.42	0.512
	Ulcerative Colitis	Male vs Female	0.43 vs 0.29	0.020
	Control	Male vs Female	0.43 vs 0.08	<0.001
PAI Correlations (Pearson r)	Crohn's Disease	With Age	0.261	0.134
		With BMI	0.256	0.115
	Ulcerative Colitis	With Age	0.203	0.122
	57.5 / 17.5 / 25.0	With BMI	0.010	0.992
	Control	With Age	0.553	<0.01
		With BMI	0.475	<0.01

Table 5. ROC analysis of Ulcerative Colitis and Crohn's diseases patients for SII and NLR

Ulcerative colitis	Sensitivity	Specifity	Cut-off	AUC	p
NLO	84.6	72.7	2.69	0.7	0.00
SII	69.2	63.6	786	0.72	0.02
Crohn's Disease	**Sensitivity**	**Specifity**	**Cut-off**	**AUC**	**p**
NLO	93	74.4	2.82	0.86	0.00
SII	93	74	876	0.9	0.00

trol groups, but this was not the case in the CD group. Additionally, PAI showed a significant positive correlation with age and BMI in the healthy control group; however, this association was not observed in either of the IBD cohorts.

Receiver Operating Characteristic (ROC) curve analysis was used to assess the predictive value of these indices. NLR and SII were significant predictors of active disease in both CD (AUC 0.772 and 0.726, respectively) and UC (AUC 0.865 and 0.904, respectively) (Table 5). In contrast, PAI and MHO emerged as the strongest predictors of the presence of AAC (AUC 0.790 and 0.785) (Figure 1).

DISCUSSION

This study elucidates the clinical utility of novel, accessible biomarkers-PAI, MHO, and SII-in the context of IBD. Our principal findings demonstrate that patients with IBD have significantly elevated levels of PAI, MHO, and SII compared to healthy controls, strongly supporting the growing paradigm of IBD as a systemic condition characterized by atherogenic dyslipidemia and chronic inflammation. The most compelling aspect of our research is the robust association between these simple blood markers and the presence of AAC, a surrogate for subclinical atherosclerosis. These findings underscore the critical importance of proactive cardiovascular risk screening in the comprehensive management of IBD.

The significantly elevated PAI and MHO levels observed in our IBD cohort reflect a pathophysiological state known as "inflammatory dyslipidemia." It is well-established that chronic inflammation directly alters hepatic lipid metabolism, increasing triglyceride (TG) synthesis while impairing both the quantity and function of anti-atherogenic HDL

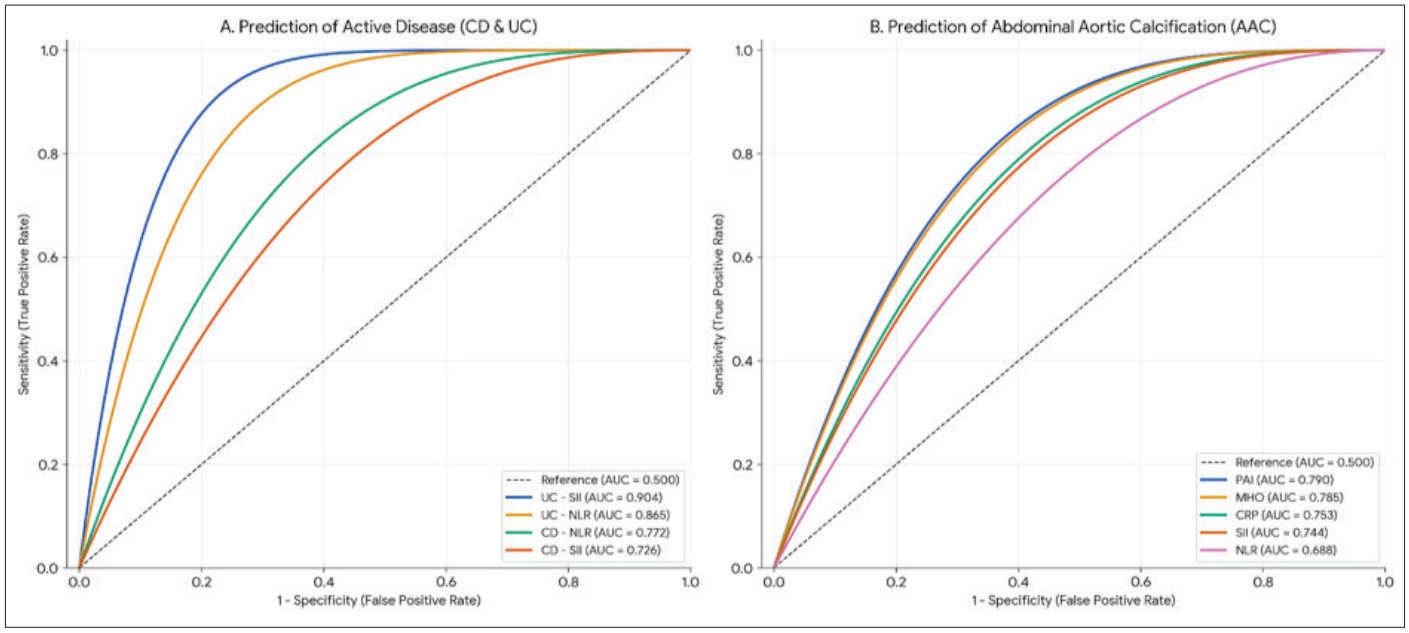

Figure 1. ROC analysis of parameters and prediction of active disease and AAC.

cholesterol (HDL-C). PAI, as the logarithmic ratio of TG to HDL-C, effectively captures this imbalance and serves as a strong proxy for the presence of small, dense LDL particles, which more readily penetrate the arterial wall to initiate atherosclerosis.[25] Concurrently, a high MHO reflects dual pathology: an increase in pro-inflammatory monocytes, the cellular precursors to foam cells in atheromatous plaques, and a decrease in protective HDL. Recent large-scale meta-analyses confirm that patients with IBD have a 20-30% higher risk of myocardial infarction and stroke-risks not fully explained by traditional factors but directly linked to the underlying inflammatory burden.[13,14]

In parallel, our study reaffirms the role of hematological inflammatory indices like the NLR and SII. The fact that both markers were elevated in IBD patients and correlated significantly with disease activity aligns with their known pathophysiology. Active inflammation stimulates the bone marrow to release neutrophils and platelets while promoting the migration of lymphocytes into inflamed gut tissue, resulting in the characteristic peripheral blood signature of elevated NLR and SII. Contemporary research suggests that these indices are not only useful for tracking disease activity but may also predict long-term complications and therapeutic response to biologics. This positions NLR and SII as valuable, cost-effective tools for both dynamic monitoring and prognostication in IBD care.

An intriguing finding from our study is the dissociation between markers of acute inflammation and PAI. While NLR and SII tracked well with disease activity, PAI levels did not differ significantly between active and remission states. This suggests that PAI may reflect a more chronic, established atherogenic state rather than fluctuating with acute inflammatory flares. This observation could be partially explained by the complex metabolic effects of active IBD, where malabsorption or the use of certain medications like corticosteroids might confound the lipid profile, masking the true relationship of PAI with an acute flare. This distinction highlights the complementary roles these biomarkers can play: NLR and SII can help answer, "How active is the disease right now?" while PAI can address, "What is the patient's long-term, cumulative cardiovascular risk?"

Perhaps the most clinically impactful contribution of our study is the powerful and consistent association demonstrated between all the investigated biomarkers and the presence of AAC. We found that patients with detectable aortic calcification had significantly higher levels of PAI, MHO, SII, NLR, and CRP. AAC is a well-established indicator of subclinical atherosclerosis and an independent predictor of future cardiovascular events. The high predictive performance of PAI (AUC = 0.790) and MHO (AUC = 0.785) for identifying patients with AAC provides tangible, anatomical evidence that these blood tests reflect a real-world atherosclerotic burden, not just a theoretical risk. Current literature confirms an increased prevalence of both AAC and coronary artery calcification (CAC) in IBD patients, findings directly linked to the cumulative inflammatory burden.[16] This strongly suggests that the incidental finding of AAC on CT scans performed for other indications should be diligently reported and integrated into the patient's cardiovascular risk profile.

These findings support modern mechanistic models linking IBD and atherosclerosis via the "gut-vascular axis." This concept moves beyond general systemic inflammation to include more specific pathways. Gut dysbiosis and increased intestinal permeability in IBD allow the translocation of microbial products (e.g., LPS) and pro-atherogenic metabolites (e.g., Trimethylamine N-oxide, or TMAO) into the systemic circulation. These molecules can directly promote endothelial dysfunction, monocyte activation, and foam cell formation, thereby accelerating atherosclerosis. From this perspective, the elevated biomarkers we observed, such as MHO and PAI, can be seen as downstream reflections of this complex interplay between gut-derived factors and systemic inflammation.

Finally, the limitations of this study must be acknowledged, including its retrospective, single-center design and relatively small cohort size, which may affect the generalizability of the results. Additionally, the potential confounding effects of IBD medications on these biomark-

ers were not fully analyzed, and AAC evaluation was not performed by multiple radiologists. Despite these limitations, our work provides strong evidence for the utility of simple biomarkers in IBD-related cardiovascular risk assessment. In clinical practice, the routine calculation of these indices, particularly PAI and MHO, could help identify high-risk patients for earlier, more aggressive management of modifiable cardiovascular risk factors. There is a pressing need for prospective, multi-center studies to validate these findings, incorporate these markers into new IBD-specific cardiovascular risk calculators, and investigate the impact of IBD therapies, especially biologics, on these markers and long-term cardiovascular outcomes.

CONCLUSION

This study confirms that the simple, cost-effective biomarkers PAI, MHO, and SII are significantly elevated in patients with Inflammatory Bowel Disease and are strongly predictive of subclinical atherosclerosis, as evidenced by their association with abdominal aortic calcification. These findings support the modern paradigm of IBD as a systemic disease that actively promotes atherogenesis through a complex interplay of systemic inflammation and gut-specific factors, such as microbial dysbiosis. Clinically, the routine integration of these indices into patient care could enhance cardiovascular risk stratification, enabling more targeted and timely preventive strategies. Future prospective, randomized controlled trials are warranted to validate the prognostic value of these markers and to elucidate how specific IBD therapies may modulate them to improve long-term cardiovascular outcomes.

Ethics Committee Approval: The study's protocol received approval from Prof. Dr. Cemil Taşcıoğlu City Hospital Clinical Research Ethics Committee (Approval Number: 119, Date: 31.07.2023).

Informed Consent: Written informed consent was obtained from the patients participating in this study.

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