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ORIGINAL RESEARCH

The Clinical Significance and Prognostic Value of Inflammatory Hematological Indices in Young Patients with Coronary Artery Disease

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Objective: This study primarily investigates the relationship between inflammatory hematological indices [neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), systemic immune inflammation index (SII), system inflammation response index (SIRI), and pan-immune inflammation value (PIV)] and acute coronary syndrome (ACS) in young patients, with secondary objectives to explore their association with coronary artery disease (CAD) severity and long-term prognosis.

Methods: This observational study enrolled 986 CAD patients (aged 18–35 years) undergoing coronary angiography at Beijing Anzhen Hospital between January 2013 and December 2021. Participants were divided into ACS and non-ACS groups and further stratified by Gensini score into mild, moderate, and severe lesion groups. Patients were followed for a median of 8 years for major adverse cardiovascular events (MACE). Statistical analyses included Spearman correlation, ROC curves, and logistic regression to evaluate the relationships between inflammatory indices and ACS, coronary severity, and long-term outcomes.

Results: The prevalence of ACS progressively increased with higher quartiles of NLR, PLR, MLR, SII, SIRI, and PIV (*P* for trend <0.05). All indices were independently associated with ACS risk ($P < 0.05$), with ROC analysis indicating that SIRI (AUC = 0.720) and PIV (AUC = 0.721) had better predictive performance for ACS compared to other indices. NLR, MLR, and SIRI showed significant positive correlations with Gensini score and were independent predictors of coronary lesion severity ($P<0.05$). For long-term prognosis, smoking, familial hypercholesterolemia, higher Gensini score, and lower PLR were independent predictors of MACE, whereas other indices showed limited prognostic value.

Conclusion: In young patients with CAD, SIRI and PIV are valuable for ACS prediction, and several indices correlate with lesion severity. However, their limited long-term prognostic utility suggests distinct pathological mechanisms may govern disease progression in this unique population.

Keywords: young patients, coronary artery disease, inflammatory hematological indices, major adverse cardiovascular events, coronary severity

Introduction

The incidence of coronary artery disease (CAD) is rapidly rising among young populations due to increasing rates of obesity, smoking, dyslipidemia, and unhealthy lifestyles.[1] CAD has become one of the leading causes of sudden cardiac death in adults under the age of 35.[2] Young patients with CAD are more prone to develop acute coronary syndromes (ACS) such as myocardial infarction.[3] According to the China Acute Myocardial Infarction (CAMI) Registry, approximately 8.5% of patients with myocardial infarction are under 45 years of age.[4] Myocardial infarction in young adults now represents a major global cause of mortality, exhibiting high recurrence and death rates that pose significant public health concerns.[5,6] Therefore, there is an urgent need to develop easily applicable strategies for predicting the risk of fatal events in high-risk patients.

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As a major contributor to CAD, atherosclerosis is marked by a chronic inflammatory state in the vascular system. This process stems from the interaction between immune responses and metabolic disturbances, which promotes the development and progression of coronary artery lesions.[7] Neutrophils, monocytes, platelets, and lymphocytes play key roles in driving inflammation, thereby directly linking their activity to the pathogenesis of atherosclerosis.[8] Accordingly, numerous studies have shown that the level of chronic inflammation can be gauged by the count and proportion of immune-related cells.[9] Widely used inflammatory hematological indices, such as neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), monocyte to lymphocyte ratio (MLR), systemic inflammatory immune index (SII), systemic inflammatory response index (SIRI) and pan immune-inflammation value (PIV), have been extensively applied in research on CAD and its risk factors.[7–18] These biomarkers offer the advantage of supporting multidimensional clinical assessment without adding to patients' financial burden. As the earliest applied inflammatory hematological indices, NLR and PLR are recognized as independent risk factors for no-reflow phenomenon, severe vascular lesions, and both short- and long-term major adverse cardiovascular events (MACE) in patients with CAD.[9–11] Elevated MLR has been associated with higher incidence of ACS and long-term MACE.[9,12] Moreover, composite inflammatory indices such as SII, SIRI, and PIV have also been correlated with coronary artery disease development, severity of vascular lesions, and adverse clinical outcomes.[13–16] However, current evidence on inflammatory hematological indices is primarily derived from middle-aged and elderly populations, whereas data in younger patients remain limited. Notably, studies have shown that young individuals with CAD demonstrate heightened inflammatory activity relative to older patients, including increased inflammatory cell infiltration within atherosclerotic plaques.[19] This observation implies that inflammatory hematological indices may have enhanced predictive value specifically in symptomatic young adults with CAD.

This study aims to primarily investigate the predictive value of various inflammatory hematological indices for ACS in young patients with CAD. Furthermore, as secondary objectives, we sought to explore their association with the severity of coronary artery lesions and their impact on long-term clinical prognosis.

Materials and Methods

Study Design and Subjects

In this single-center observational study, young patients with symptoms of chest tightness or chest pain who underwent coronary angiography at Beijing Anzhen Hospital between January 2013 and December 2021 were selected. 986 patients (95.4% male) who met all the inclusion criteria and did not meet any of the exclusion criteria were enrolled (Figure 1). Inclusion criteria: (1) coronary angiography was performed during hospitalization and CAD was diagnosed; (2) Between the ages of 18 and 35; (3) Had complete relevant clinical data and laboratory examination results. Exclusion criteria: (1) A history of CAD with previous percutaneous coronary intervention or coronary artery bypass grafting; (2) Underwent coronary artery bypass grafting this time; (3) Cardiomyopathy, congenital heart disease, valvular heart disease, myocarditis, infective endocarditis, rheumatic heart disease, Kawasaki disease; (4) Various acute and chronic infectious diseases; (5) Hematologic disorders or taking drugs that affect blood cells; (6) Autoimmune diseases or taking immunosuppressive agents; (7) Severe hepatic and renal dysfunction; (8) Active or previous malignant tumors; (9) Lack of follow-up data. According to the examination results, young patients were divided into the ACS group and the non-ACS group. Then, the Gensini score (GS) was derived from coronary angiography results and used to categorize the patients into mild group (GS < 25), moderate group (25≤ GS≤ 50), and severe group (GS>50). All the patients were followed up and divided into the major adverse cardiovascular events (MACE) group and the non-MACE group according to whether MACE occurred. This study was approved by the Institutional Ethics Committee at Beijing Anzhen Hospital (Ethics Approval No. 2025285x).

Data Collection

The clinical data used in the study, including age, sex, height, weight, hypertension, diabetes, smoking and family history were retrospectively obtained from electronic medical records. Baseline fasting venous blood samples were collected from all participants to evaluate neutrophil (NEU), lymphocyte (LYM), monocyte (MON), platelet counts (PLT), PDW,

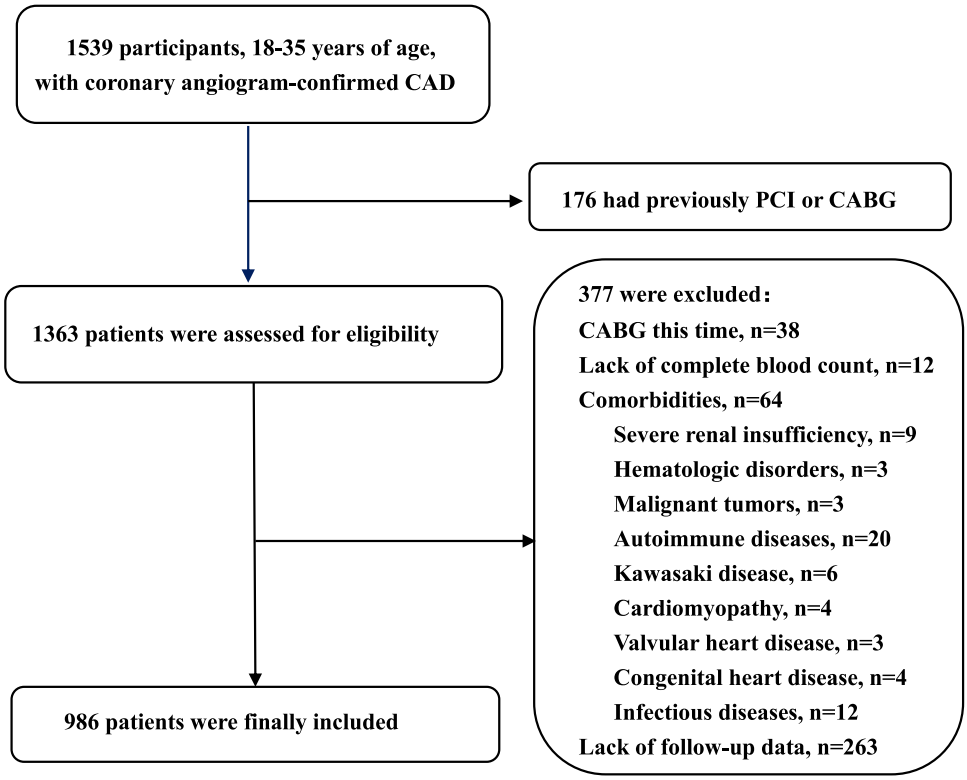

Figure 1 The flow chart of study population selection.
Abbreviations: CAD, coronary artery disease; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting.

hsCRP and creatinine (Cr), total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), uric acid (UA) and other variables. The neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), monocyte to lymphocyte ratio (MLR), systemic immune-inflammation index (SII), systemic inflammation response index (SIRI) and pan immune-inflammation value (PIV) were calculated. Color Doppler echocardiography was performed to collect left ventricular ejection fraction (LVEF).

Definitions

1. CAD is defined as lesion stenosis ≥50% in any epicardial coronary artery with a diameter ≥ 2 mm. ACS diagnosis relies on clinical presentation, ECG findings, and biochemical evidence of myocardial injury, which is determined by the European Society of Cardiology 2023 guidelines.[20]
2. Hypertriglyceridemia is defined as TG ≥ 1.7 mmol/L, hypercholesterolemia is defined as TC ≥ 5.2 mmol/L, high LDL-C level is defined as LDL-C ≥ 3.4 mmol/L, and low HDL-C level is defined as HDL-C < 1.0 mmol/L.
3. Familial hypercholesterolemia (FH) is defined by satisfying two or more of the following criteria: LDL-C ≥ 4.68 mmol/L, tendon/skin xanthomas, and FH history or family history of premature CAD.[21]
4. Inflammatory hematological ratios calculated as previously described: NLR = neutrophil count ($\times 10^9$/L)/lymphocyte count ($\times 10^9$/L); PLR = platelet count ($\times 10^9$/L)/lymphocyte count ($\times 10^9$/L); MLR= monocyte count ($\times 10^9$/L)/lymphocyte count ($\times 10^9$/L); SII = [neutrophil count ($\times 10^9$/L) × platelet count ($\times 10^9$/L)/lymphocyte count ($\times 10^9$/L)]; SIRI= [neutrophil count ($\times 10^9$/L) × monocyte count ($\times 10^9$/L)/lymphocyte count ($\times 10^9$/L)]; PIV= [neutrophil count ($\times 10^9$/L) ×platelet count ($\times 10^9$/L) × monocyte count ($\times 10^9$/L)/lymphocyte count ($\times 10^9$/L)].[9,22]
5. Gensini score (GS) was used to evaluate the severity of coronary artery stenosis, which was calculated as the sum of all the lesion points. The score of each lesion point = the score of the lesion site× the score of the degree of stenosis, as previously described.[23]

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Clinical Outcomes

For young patients with CAD who underwent CAG, MACEs that occurred after discharge, including all-cause death, myocardial infarction, ischemic and hemorrhagic strokes, interventional therapy for unstable angina, and hospitalization for heart failure were recorded. Post- discharge follow-up data were collected by reviewing the inpatient and outpatient electronic records. For patients lost to follow-up after discharge, endpoint events were ascertained through telephone interviews conducted with the patients or their immediate family members.

Statistical Analysis

Statistical analyses were performed using SPSS 26.0 software (IBM SPSS Inc., Chicago, USA) and GraphPad Prism 5. The normality of the data was examined using Kolmogorov–Smirnov test. Continuous variables were presented as mean ± standard deviation (SD) or median with interquartile range (IQR), as appropriate. For normally distributed data, differences between two groups were assessed using the independent samples *t*-test, while differences among three groups were analyzed using one-way ANOVA. For nonnormally distributed data, the Mann–Whitney *U*-test was used to compare two groups, and the Kruskal–Wallis *H*-test was applied for comparisons among the three groups. Categorical variables were summarized as numbers and percentages (%), and group differences were evaluated with the chi-square test. Correlations between the inflammatory indices and Gensini scores were assessed using Spearman correlation coefficient. Univariate and multivariate logistic regression analyses were performed to identify the predictive value of NLR, PLR, MLR, SII, SIRI and PIV for ACS. Due to the substantial multicollinearity observed among these composite inflammatory indices, each index was analyzed in a separate multivariate model to avoid unstable estimates. In the multivariate logistic regression analysis, we adjusted for potential confounders, primarily those with significant p-values in baseline characteristics. Three models were formulated: Model 1 was analyzed with no covariate adjusted. Model 2 adjusted for age and male. Model 3 was further adjusted for smoking, triglyceride, total cholesterol, HDL-C and LDL-C. Receiver-operating characteristic (ROC) curve analysis was used to determine the best cut off value of NLR, PLR, MLR, SII, SIRI and PIV in predicting ACS. Multivariable ordinal logistic regression was performed to identify the factors influencing Gensini scores. In addition, univariate and multivariate logistic regression analyses were also performed to identify the independent predictors of MACE. A two-sided p-value of less than 0.05 was considered statistically significant for all tests.

Results

Baseline Characteristics of ACS and Non-ACS Patients

A total of 986 young patients with CAD were included in this study, comprising 493 patients in the ACS group and another 493 patients in the non-ACS group. The differences between the two groups were analyzed, as shown in Table 1. The mean age of patients in the ACS group was 33 (30–34) years, while that in the non-ACS group was 33 (31–34) years. The ACS group had a slightly higher proportion of male patients (96.8%) compared to the non-ACS group (94.1%) (P=0.047). In addition, the prevalence of smoking and low HDL-C was higher in the ACS patients (all P<0.05). Compared with the non-ACS group, the ACS group had significantly lower levels of systolic blood pressure (SBP), diastolic blood pressure (DBP), blood urea nitrogen (BUN), and HDL-C, but higher levels of fasting blood glucose (FBG), TG, TC, LDL-C, and hs-CRP (all P<0.05). Additionally, hematological analysis revealed higher counts of NEU, MON, and PLT in the ACS group (all P<0.05); the Ginsini score was also slightly elevated (P=0.011). However, LVEF was significantly lower in ACS patients (P<0.05).

Relation of Inflammatory Hematological Indices and the Presence of ACS

Inflammatory hematological indices, including NLR, PLR, MLR, SII, SIRI and PIV, were categorized based on quartiles to investigate the association between elevated levels of these indices and the incidence of ACS in young patients. The results showed that NLR, MLR, SII, SIRI, and PIV were significantly elevated in the ACS group (all P<0.001), while no

Table 1 Baseline Clinical Characteristics of Study Participants

Characteristics	ACS (n=493)	Non-ACS (n=493)	*P*
Age (years)	33 (30–34)	33 (31–34)	0.073
Male, n (%)	477 (96.8)	464 (94.1)	0.047*
SBP (mmHg)	123 (113–135)	128 (120–136)	<0.001*
DBP (mmHg)	76 (70, 85)	80 (70, 87)	0.001*
Heart rate (bpm)	75 (68.5–84.5)	74.5 (70–81.5)	0.492
Drinker, n (%)	100 (20.3)	87 (17.7)	0.298
Medical history and coronary risk factors			
Smoking, n (%)	366 (74.2)	289 (58.7)	<0.001*
BMI (kg/m^2)	28.39 (25.88–31.41)	28.06 (25.45–30.90)	0.145
Hypertension, n (%)	219 (44.4)	239 (48.5)	0.202
Diabetes mellitus, n (%)	99 (20.1)	113 (22.9)	0.278
Hypertriglyceridemia, n (%)	291 (59.1)	269 (54.5)	0.147
Hypercholesterolemia, n (%)	172 (34.9)	158 (32.0)	0.345
High LDL-C, n (%)	169 (34.3)	147 (29.9)	0.145
Low HDL-C, n (%)	359 (72.8)	327 (66.3)	0.027*
Family history of CAD, n (%)	51 (10.3)	45 (9.1)	0.519
Familial hypercholesterolemia, n (%)	10 (2.0)	15 (3.0)	0.311
Laboratory results			
BUN (mmol/L)	4.50 (3.80–5.40)	4.70 (3.90–5.60)	0.023*
CR (μmol/L)	74.15 (67.28–83.95)	74.70 (66.00–83.40)	0.706
eGFR (mL/min/1.73 m^2)	116.24 (103.24–122.35)	116.45 (105.63–122.41)	0.647
FBG (mmol/L)	5.43 (4.93–6.66)	5.26 (4.83–6.11)	0.002*
HbA1c (%)	5.6 (5.4–6.4)	5.6 (5.3–6.5)	0.686
TG (mmol/L)	1.95 (1.39–3.06)	1.81 (1.22–2.62)	<0.001*
TC (mmol/L)	4.71 (3.74–5.48)	4.31 (3.44–5.43)	0.001*
HDL-C (mmol/L)	0.88 (0.76–1.02)	0.91 (0.79–1.03)	0.027*
LDL-C (mmol/L)	2.92 (2.19–3.64)	2.58 (1.93–3.48)	0.001*
UA (μmol/L)	410.05 (345.78–470.28)	409.10 (353.00–472.25)	0.665
NEU (×10^9/L)	6.50 (4.78–9.24)	4.62 (3.77–5.80)	<0.001*
MON (×10^9/L)	0.50 (0.37–0.67)	0.41 (0.32–0.49)	<0.001*
LYM (×10^9/L)	2.13 (1.69–2.65)	2.10 (1.71–2.57)	0.486
PLT (×10^9/L)	256.00 (219.50–296.50)	241.00 (205.50–287.00)	0.002*
PDW (%)	12.6 (11.3–14.65)	12.9 (11.4–15.3)	0.095
hs CRP (mg/L)	5.17 (1.80–18.57)	1.40 (0.72–4.07)	<0.001*
Cardiac function			
LVEF	58 (52–63)	64 (60–67)	<0.001*
Degree of coronary lesion			
Gensini score	38 (21.5–62)	32 (20–60)	0.011*

Notes: Data are expressed as medians with interquartile range for continuous variables with non-normal distribution and number (%) for categorical variables. * *P*<0.05.

Abbreviations: ACS, acute coronary syndrome; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; CAD, coronary artery disease; BUN, blood urea nitrogen; CR, creatinine; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; UA, uric acid; NEU, neutrophil; MON, monocyte; LYM, lymphocyte; PLT, platelet; PDW, platelet distribution width; hs CRP, high-sensitivity C-reactive protein; LVEF, left ventricular ejection fraction.

significant difference in PLR was observed between the ACS and non-ACS groups. In addition, the prevalence of ACS was gradually increased with rising quartile levels of all the inflammatory hematological indices. (NLR, MLR, SII, SIRI and PIV, $P_{\text{for trend}}$<0.001; PLR, $P_{\text{for trend}}$=0.043) (Table 2).

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Table 2 Relation of Inflammatory Hematological Indices and ACS

Characteristics	ACS (n=493)	Non-ACS (n=493)	*P*
NLR	2.955 (2.088–4.586)	2.173 (1.667–2.975)	<0.001*
NLR quartiles			
0.828–1.841	83 (16.84)	163 (33.06)	
1.843–2.483	110 (22.31)	137 (27.79)	
2.495–3.632	114 (23.12)	133 (26.98)	
3.638–29.133	186 (37.73)	60 (12.17)	
P for trend			<0.001*
PLR	118.627 (93.616–155.588)	114.762 (91.754–142.924)	0.089
PLR quartiles			
46.988–93.106	117 (23.73)	129 (26.17)	
93.117–117.363	118 (23.94)	129 (26.17)	
117.424–150.055	117 (23.73)	130 (26.37)	
150.220–632.667	141 (28.60)	105 (21.29)	
P for trend			0.043*
MLR	0.235 (0.173–0.322)	0.189 (0.145–0.248)	<0.001*
MLR quartiles			
0.005–0.157	94 (19.07)	159 (32.25)	
0.158–0.211	105 (21.30)	138 (27.99)	
0.212–0.278	126 (25.56)	118 (23.94)	
0.279–1.093	168 (34.07)	78 (15.82)	
P for trend			<0.001*
SII	773.119 (512.978–1228.702)	521.289 (384.614–763.832)	<0.001*
SII quartiles			
163.725–431.034	83 (16.84)	163 (33.06)	
431.221–627.910	98 (19.88)	149 (30.22)	
628.409–941.151	126 (25.56)	118 (23.94)	
942.849–14,042.267	186 (37.72)	63 (12.78)	
P for trend			<0.001*
SIRI	1.534 (0.885–2.735)	0.859 (0.566–1.325)	<0.001*
SIRI quartiles			
0.023–0.667	71 (14.40)	175 (35.50)	
0.668–1.109	100 (20.28)	147 (29.82)	
1.110–1.855	121 (24.54)	126 (25.56)	
1.857–23.889	201 (40.78)	45 (9.12)	
P for trend			<0.001*
PIV	397.162 (227.629–730.625)	204.390 (136.414–340.805)	<0.001*
PIV quartiles			
4.778–162.906	69 (14.00)	177 (35.90)	
162.956–276.592	107 (21.70)	140 (28.40)	
276.838–506.554	125 (25.35)	122 (24.75)	
506.653–11,514.659	192 (38.95)	54 (10.95)	
P for trend			<0.001*

Notes: Data are expressed as medians with interquartile range for continuous variables with non-normal distribution and number (%) for categorical variables. * *P*<0.05.

Abbreviations: ACS, acute coronary syndrome; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; PIV, pan-immune-inflammation value.

Univariate and Multivariate Logistic Regression Analysis for ACS

Collinearity diagnostics were performed for the inflammatory hematological indices (NLR, PLR, MLR, SII, SIRI and PIV). The results indicated that the variance inflation factor (VIF) for inflammatory hematological indices exceeded 10 (VIF of NLR 25.981, VIF of SII 57.194, VIF of SIRI 45.886, VIF of PIV 58.832), suggesting the presence of

Table 3 Univariate and Multivariate Logistic Regression Analysis for ACS

Variables		OR	95% CI	*P*
NLR	Model 1	1.627	1.470–1.800	<0.001*
	Model 2	1.635	1.476–1.812	<0.001*
	Model 3	1.654	1.488–1.838	<0.001*
PLR	Model 1	1.003	1.001–1.006	0.016*
	Model 2	1.003	1.001–1.006	0.009*
	Model 3	1.005	1.002–1.007	0.001*
MLR	Model 1	170.130	44.201–654.831	<0.001*
	Model 2	158.684	41.413–608.033	<0.001*
	Model 3	175.705	44.494–693.815	<0.001*
SII	Model 1	1.002	1.001–1.002	<0.001*
	Model 2	1.002	1.001–1.002	<0.001*
	Model 3	1.002	1.001–1.002	<0.001*
SIRI	Model 1	2.379	2.010–2.816	<0.001*
	Model 2	2.363	1.996–2.798	<0.001*
	Model 3	2.315	1.954–2.744	<0.001*
PIV	Model 1	1.003	1.002–1.004	<0.001*
	Model 2	1.003	1.002–1.004	<0.001*
	Model 3	1.003	1.002–1.004	<0.001*

Notes: Model 1 was unadjusted univariate analysis; Model 2 was adjusted for age, male; Model 3 was further adjusted for smoking, triglyceride, total cholesterol, HDL-C and LDL-C. * *P*<0.05.

Abbreviations: ACS, acute coronary syndrome; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; SII, systemic inflammatory immune index; SIRI, systemic inflammatory response index; PIV, pan immune-inflammation value; OR, odds ratio; CI, confidence interval.

multicollinearity. As shown in Table 3, in young patients with CAD, after adjustment for traditional cardiovascular risk factors in separate models, NLR, PLR, MLR, SII, SIRI and PIV each remained significantly associated with the risk of ACS in both univariate and multivariate analyses (NLR, MLR, SII, SIRI and PIV, P <0.001; PLR, P <0.05).

ROC Curve Analysis of Inflammatory Hematological Indices for ACS

ROC curve analysis was applied to assess the predictive value of inflammatory hematological indices for the occurrence of ACS. The results demonstrated that, with the exception of PLR, the other inflammatory hematological indices all possessed some predictive value for ACS (all P<0.001) (Table 4). The area under the curve (AUC) of SIRI (AUC: 0.720; 95% CI, 0.689–0.752) and PIV (AUC: 0.721; 95% CI, 0.689–0.752) for predicting ACS were greater than that of SII, MLR and NLR (all P<0.05) (Figure 2).

Baseline Characteristics and Inflammatory Hematological Indices of CAD Patients with Different Gensini Scores

986 young patients with CAD were divided into three groups according to the Gensini score. The mean age of patients in the mild, moderate, and severe groups was 33 (31–34), 33 (30–34), and 33 (31–34) years, respectively. The proportion of males in the three groups was 94.27%, 95.96% and 96.19%, respectively. There was no significant difference in the proportions of hypertension, diabetes, family history of CAD and familial hypercholesterolemia among the three groups (all P>0.05). Compared to the mild group, patients in the moderate and severe groups had a higher prevalence of smoking, hypercholesterolemia, and those with high LDL-C, as well as higher levels of TC, LDL-C, NEU, and hs-CRP (all P<0.05). Furthermore, the severe group demonstrated significantly higher MON level when compared with both the mild and moderate groups (P=0.001). Comparison of LVEF among the three groups showed statistically significant differences, and with increasing Gensini score, LVEF showed a decreasing trend (P<0.001) (Table 5).

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Table 4 Receiver Operating Characteristic (ROC) Curve Analysis for ACS

Variables	AUC	Sensitivity	Specificity	Best Cut-Off Point	95% CI	*P*
NLR	0.679	0.406	0.866	3.504	0.646–0.712	<0.001*
PLR	0.531	0.990	0.002	49.561	0.495–0.567	0.089
MLR	0.644	0.503	0.712	0.235	0.610–0.678	<0.001*
SII	0.687	0.452	0.830	845.866	0.654–0.720	<0.001*
SIRI	0.720	0.479	0.868	1.638	0.689–0.752	<0.001*
PIV	0.721	0.511	0.822	393.756	0.689–0.752	<0.001*

Notes: * *P*<0.05.
Abbreviations: ACS, acute coronary syndrome; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; SII, systemic inflammatory immune index; SIRI, systemic inflammatory response index; PIV, pan immune-inflammation value; AUC, under the curve; CI, confidence interval.

The inflammatory hematological indices of the three groups, including NLR, PLR, MLR, SII, SIRI and PIV were compared and the differences were statistically significant except for PLR. As shown in Figure 3, with the increase in Gensini score, the five hematological indices showed an upward trend (all $P<0.05$).

Correlation Analysis of Inflammatory Hematological Indices with Gensini Score

Spearman correlation analysis between inflammatory hematological indices and Gensini scores in patients with CAD revealed positive correlations for all indicators (all $P<0.001$), with the exception of PLR ($P=0.115$). The rank correlation coefficients of NLR, MLR, SII, SIRI and PIV with Gensini scores were 0.171, 0.127, 0.151, 0.166 and 0.150, respectively (Table 6). Furthermore, this correlation held true consistently in both ACS patients and non-ACS patients ($P<0.05$).

Ordinal Multivariable Logistic Regression Analysis for Degree of Coronary Lesions in CAD

This study constructed a multifactorial ordered logistic regression model by incorporating the degree of coronary artery lesions (categorized as mild, moderate, or severe) as the ordinal dependent variable and established influential factors of

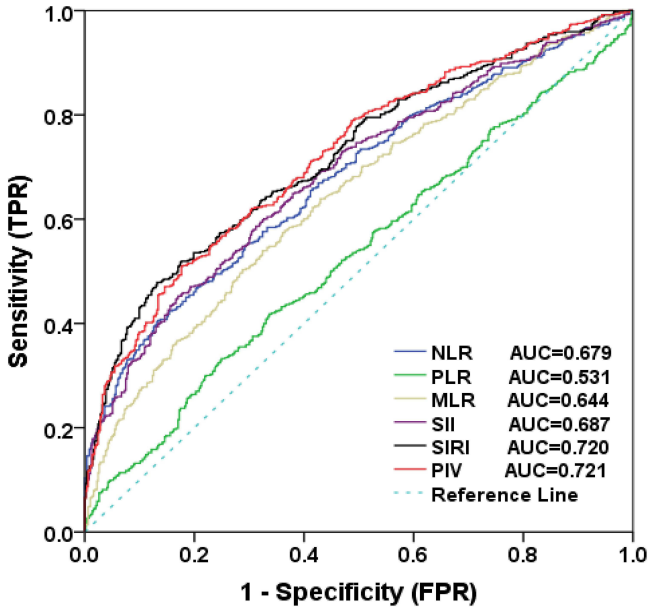

Figure 2 Receiver-operating characteristic (ROC) curve analysis for ACS.
Abbreviations: NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; SII, systemic inflammatory immune index; SIRI, systemic inflammatory response index; PIV, pan immune-inflammation value; AUC, under the curve; TPR, true positive rate; FPR, false positive rate.

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Table 5 Comparison of Clinical Features of CAD Patients with Different Gensini Scores

Characteristics	Mild Group (n=349)	Moderate Group (n=322)	Severe Group (n=315)	*P*
Age (years)	33 (31–34)	33 (30–34)	33 (31–34)	0.641
Male, n (%)	329 (94.27)	309 (95.96)	303 (96.19)	0.426
SBP (mmHg)	126 (120–135)	125 (117–139)	125 (115–135)	0.610
DBP (mmHg)	79 (70–87)	79 (70–88)	77 (70–85)	0.434
Heart rate (bpm)	74 (69–81)	75 (68–83)	75 (70–86)	0.147
Drinker, n (%)	76 (21.78)	64 (19.88)	47 (14.92)	0.067
Smoking, n (%)	212 (60.74)	221 (68.63) [a]	221 (70.16) [a]	0.022*
BMI (kg/m^2)	28.07 (25.35–31.06)	28.39 (25.94–31.40)	28.08 (25.68–30.82)	0.547
Hypertension, n (%)	153 (43.84)	164 (50.93)	141 (44.76)	0.141
Diabetes mellitus, n (%)	73 (20.92)	63 (19.57)	76 (24.13)	0.355
Hypertriglyceridemia, n (%)	181 (51.86)	191 (59.32)	183 (58.10)	0.167
Hypercholesterolemia, n (%)	93 (26.65)	118 (36.65) [a]	114 (36.19) [a]	0.011*
High LDL-C, n (%)	87 (24.93)	113 (35.09) [a]	112 (35.56) [a]	0.005*
Low HDL-C, n (%)	230 (65.90)	221 (68.63)	231 (73.33)	0.154
Family history of CAD, n (%)	35 (10.03)	34 (10.56)	27 (8.57)	0.681
Familial hypercholesterolemia, n (%)	4 (1.15)	11 (3.42)	10 (3.17)	0.09
BUN (mmol/L)	4.6 (3.8–5.5)	4.6 (3.8–5.6)	4.59 (3.82–5.44)	0.773
CR (μmol/L)	74.4 (65.6–83.0)	75.2 (67.9–83.8)	73.4 (66.6–84.4)	0.564
eGFR ($mL/min/1.73\ m^2$)	116.39 (106.12–122.32)	115.06 (103.86–122.08)	116.97 (104.56–122.42)	0.871
FBG (mmol/L)	5.31 (4.87–6.14)	5.32 (4.91–6.12)	5.41 (4.89–6.84)	0.379
HbA1c (%)	5.7 (5.3–6.35)	5.6 (5.3–6.1)	5.6 (5.4–6.88)	0.183
TG (mmol/L)	1.78 (1.24–2.67)	1.99 (1.34–2.97)	1.87 (1.39–2.88)	0.089
TC (mmol/L)	4.27 (3.44–5.28)	4.63 (3.69–5.64) [a]	4.69 (3.68–5.61) [a]	0.001*
HDL-C (mmol/L)	0.92 (0.80–1.03)	0.88 (0.77–1.02)	0.88 (0.75–1.02) [a]	0.033*
LDL-C (mmol/L)	2.59 (1.97–3.35)	2.77 (2.12–3.67) [a]	2.86 (2.07–3.78) [a]	0.005*
UA (μmol/L)	405.6 (340.63–459.45)	414.70 (354.80–485.85)	408.30 (348.78–471.38)	0.102
NEU ($\times 10^9/L$)	4.82 (3.86–6.69)	5.33 (4.15–7.41) [a]	5.74 (4.40–8.17) [a]	<0.001*
MON ($\times 10^9/L$)	0.42 (0.34–0.53)	0.45 (0.34–0.59)	0.47 (0.36–0.64) [ab]	0.001*
LYM ($\times 10^9/L$)	2.15 (1.81–2.64)	2.12 (1.70–2.56)	2.09 (1.61–2.59)	0.119
PLT ($\times 10^9/L$)	252.00 (210.00–292.00)	247.5 (213.25–291.00)	248.00 (211.00–291.00)	0.944
PDW (%)	12.8 (11.3–14.5)	12.65 (11.3–14.93)	12.9 (11.3–15.5)	0.334
hs CRP (mg/L)	1.78 (0.84–5.64)	3.30 (1.15–9.65) [a]	3.54 (0.98–12.96) [a]	<0.001*
Cardiac function				
LVEF	63 (58–67)	61 (55–65) [a]	60 (52–65) [ab]	<0.001*

Notes: Data are expressed as medians with interquartile range for continuous variables with non-normal distribution and number (%) for categorical variables. * $P<0.05$. [a] $P<0.05$ compared to the mild group, [b] $P<0.05$ compared to the moderate group.

Abbreviations: CAD, coronary artery disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; BUN, blood urea nitrogen; CR, creatinine; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; UA, uric acid; NEU, neutrophil; MON, monocyte; LYM, lymphocyte; PLT, platelet; PDW, platelet distribution width; hs CRP, high-sensitivity C- reactive protein; LVEF, left ventricular ejection fraction.

coronary lesion severity in CAD as independent variables. Collinearity diagnostics were performed for factors including TC, HDL-C, LDL-C, hs-CRP, NLR, MLR, SII, SIRI, PIV, and LVEF. The results indicated that the VIF for inflammatory hematological indices exceeded 10 (VIF of NLR 25.401, VIF of SII 41.642, VIF of SIRI 46.183, VIF of PIV 57.486), suggesting the presence of multicollinearity. If these factors are included in the unified model, the predictive effect would be compromised due to multicollinearity. Therefore, multifactorial ordered logistic models were constructed for NLR, MLR, SII, SIRI and PIV, respectively, to evaluate their prediction effect on the degree of coronary lesion. The test of parallel lines indicated that all models incorporating different inflammatory hematological indices yielded p-values exceeding 0.1, thus satisfying the prerequisite assumptions for ordinal logistic regression analysis. The results showed that LVEF, NLR, MLR and SIRI were independent risk factors for the degree of coronary lesion in young patients with CAD (Table 7).

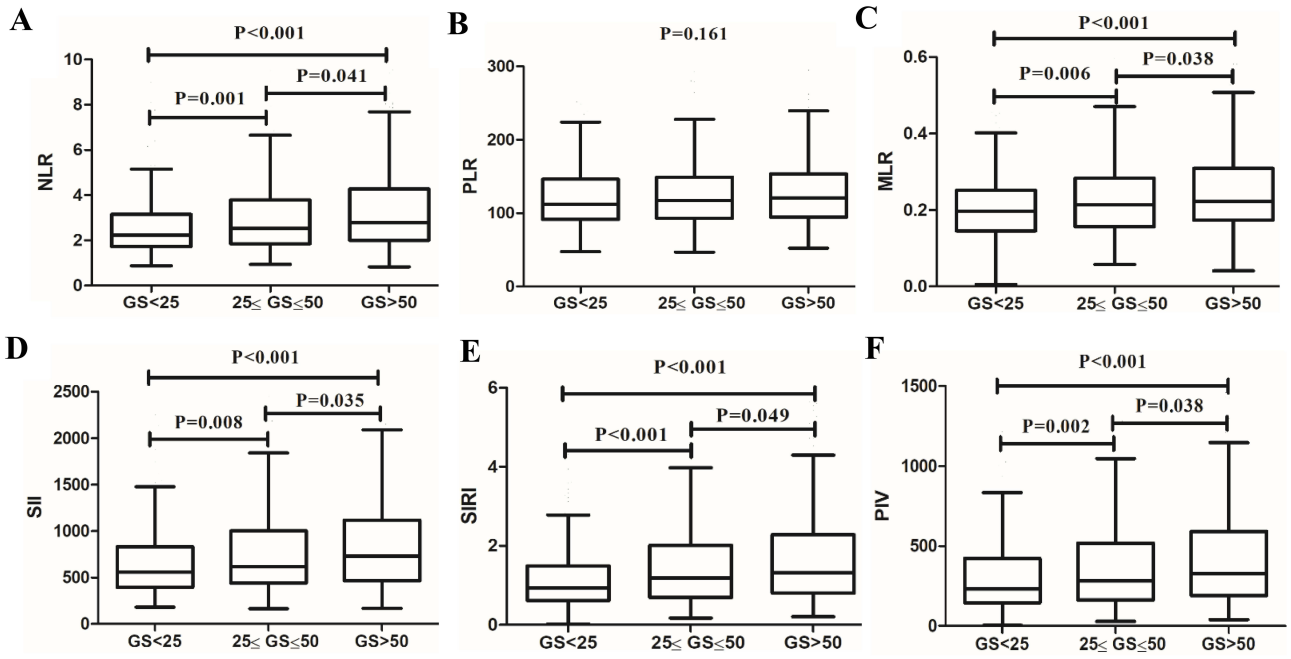

Figure 3 Comparison of inflammatory hematological indices among the GS >25, 25≤GS≤50 and GS<50 groups. (**A**) NLR; (**B**) PLR; (**C**) MLR; (**D**) SII; (**E**) SIRI; (**F**) PIV.
Abbreviations: NLR neutrophil to lymphocyte ratio, PLR platelet to lymphocyte ratio, MLR monocyte to lymphocyte ratio, SII systemic inflammatory immune index, SIRI systemic inflammatory response index, PIV pan immune-inflammation value, GS Gensini score.

Baseline Characteristics and Inflammatory Hematological Indices of CAD Patients in MACE and Non-MACE Groups

All enrolled patients were followed up for a median of 8 (5–10) years. The MACE group comprised 306 patients with an age of 33 (30–34) years, of whom 96.1% were male. The non-MACE group consisted of 680 patients with an age of 33 (31–34) years, with males accounting for 95.1%. Compared with the non-MACE group, patients in the MACE group had a significantly higher prevalence of smoking, hypercholesterolemia, elevated LDL-C levels, and familial hypercholesterolemia (all $P < 0.05$). Additionally, the MACE group showed significantly higher levels of TC, LDL-C, NEU, and hs-CRP, but lower PLT counts (all $P < 0.05$). Gensini scores were notably higher and LVEF was lower in the MACE group (both $P < 0.05$; Table 8). Regarding inflammatory hematological indices, NLR ($P = 0.050$) and SIRI ($P = 0.059$) were marginally elevated in the MACE group, though these differences did not reach statistical significance. In contrast, PLR was significantly lower in MACE patients ($P = 0.013$; Figure 4).

Table 6 Correlation of Inflammatory Hematological Indices with Gensini Score in Different Diagnosis

Indicators	CAD		ACS		Non-ACS	
	r	*P*	*r*	*P*	*r*	*P*
NLR	0.171	<0.001*	0.198	<0.001*	0.102	0.023*
PLR	0.050	0.115	0.026	0.561	0.067	0.139
MLR	0.127	<0.001*	0.106	0.018*	0.108	0.017*
SII	0.151	<0.001*	0.160	<0.001*	0.108	0.016*
SIRI	0.166	<0.001*	0.169	<0.001*	0.121	0.007*
PIV	0.150	<0.001*	0.143	0.001*	0.120	0.007*

Notes: * *P*<0.05.
Abbreviations: CAD, coronary artery disease; ACS, acute coronary syndrome; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; PIV, pan-immune-inflammation value.

Table 7 Ordinal Multivariable Logistic Regression Analysis for Degree of Coronary Lesions in CAD

Ordinal Multivariable Logistic Regression Analysis of NLR and GS					
Indicators	**β**	**Standard Error**	**Wald**	**OR (95% CI)**	***P***
TC	0.057	0.036	2.537	1.035 (0.992–1.080)	0.111
HDL-C	−0.377	0.255	2.187	0.791 (0.587–1.066)	0.139
LDL-C	0.001	0.011	0.015	1.001 (0.987–1.015)	0.902
hsCRP	0.011	0.007	2.578	1.007 (0.998–1.015)	0.108
LVEF	−0.037	0.008	21.514	0.978 (0.969–0.987)	<0.001*
NLR	0.076	0.030	6.343	1.048 (1.011–1.085)	0.012*
Smoking	0.215	0.128	2.833	1.134 (0.973–1.320)	0.092
Ordinal Multivariable Logistic Regression Analysis of MLR and GS					
Indicators	**β**	**Standard Error**	**Wald**	**OR (95% CI)**	***P***
TC	0.063	0.036	3.133	1.039 (0.996–1.084)	0.077
HDL-C	−0.373	0.256	2.119	0.798 (0.592–1.075)	0.146
LDL-C	0.001	0.011	0.003	1.000 (0.987–1.014)	0.959
hsCRP	0.008	0.007	1.432	1.005 (0.997–1.014)	0.231
LVEF	−0.038	0.008	23.112	0.978 (0.968–0.987)	<0.001*
MLR	1.511	0.543	7.744	2.392 (1.262–4.535)	0.005*
Smoking	0.209	0.128	2.652	1.130 (0.970–1.317)	0.103
Ordinal Multivariable Logistic Regression Analysis of SII and GS					
Indicators	**β**	**Standard Error**	**Wald**	**OR (95% CI)**	***P***
TC	0.058	0.036	2.660	1.036 (0.993–1.080)	0.103
HDL-C	−0.368	0.254	2.099	0.794 (0.590–1.069)	0.147
LDL-C	0.002	0.011	0.019	1.001 (0.987–1.015)	0.891
hsCRP	0.012	0.007	3.232	1.008 (0.999–1.016)	0.072
LVEF	−0.038	0.008	23.293	0.977 (0.968–0.986)	<0.001*
SII	0.000	0.000	2.692	1.000 (1.000–1.000)	0.101
Smoking	0.216	0.128	2.847	1.134 (0.974–1.321)	0.092
Ordinal Multivariable Logistic Regression Analysis of SIRI and GS					
Indicators	**β**	**Standard Error**	**Wald**	**OR (95% CI)**	***P***
TC	0.059	0.036	2.786	1.037 (0.994–1.082)	0.095
HDL-C	−0.375	0.255	2.163	0.794 (0.590–1.070)	0.141
LDL-C	0.001	0.011	0.011	1.001 (0.987–1.015)	0.917
hsCRP	0.009	0.007	1.688	1.006 (0.997–1.014)	0.194
LVEF	−0.037	0.008	22.148	0.978 (0.969–0.987)	<0.001*
SIRI	0.086	0.041	4.349	1.048 (1.000–1.099)	0.037*
Smoking	0.202	0.128	2.486	1.126 (0.966–1.312)	0.115
Ordinal Multivariable Logistic Regression Analysis of PIV and GS					
Indicators	**β**	**Standard Error**	**Wald**	**OR (95% CI)**	***P***
TC	0.059	0.036	2.721	1.036 (0.993–1.081)	0.099
HDL-C	−0.362	0.255	2.050	0.797 (0.593–1.073)	0.152
LDL-C	0.001	0.011	0.015	1.001 (0.987–1.015)	0.903
hsCRP	0.012	0.007	2.924	1.007 (0.999–1.016)	0.087
LVEF	−0.039	0.008	24.013	0.977 (0.968–0.986)	<0.001*

(*Continued*)

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Table 7 (Continued).

PIV	0.000	0.000	1.492	1.000 (1.000–1.000)	0.222
Smoking	0.208	0.128	2.652	1.130 (0.970–1.316)	0.103

Notes: * *P*<0.05.

Abbreviations: CAD, coronary artery disease; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; hs CRP, high-sensitivity C- reactive protein; LVEF, left ventricular ejection fraction; NLR, neutrophil to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; SII, systemic immune-inflammation index; SIRI, systemic inflammation response index; PIV, pan-immune-inflammation value; GS, Gensini score; OR, odds ratio.

Table 8 Basic Clinical Characteristics Between MACE Groups and Non-MACE Groups in Patients with CAD

Characteristics	**MACE (n=306)**	**Non-MACE (n=680)**	***P***
Age (years)	33 (30–34)	33 (31–34)	0.286
Male, n (%)	294 (96.1)	647 (95.1)	0.517
SBP (mmHg)	124 (116–135)	126 (118–136)	0.150
DBP (mmHg)	77.5 (70–85.25)	78 (70–86)	0.237
HR (bpm)	74 (68.5–82)	75 (69–83.25)	0.274
Drinker, n (%)	50 (16.3)	137 (20.1)	0.155
Medical history and coronary risk factors			
Smoking, n (%)	230 (75.2)	424 (62.4)	<0.001*
BMI (kg/m^2)	27.92 (25.56–31.40)	28.15 (25.66–30.87)	0.958
Hypertension, n (%)	151 (49.3)	307 (45.1)	0.221
Diabetes mellitus, n (%)	77 (25.2)	135 (19.9)	0.06
Hypertriglyceridemia, n (%)	182 (59.5)	373 (54.9)	0.223
Hypercholesterolemia, n (%)	118 (38.6)	207 (30.4)	0.015*
High LDL-C, n (%)	113 (36.9)	199 (29.3)	0.021*
Low HDL-C, n (%)	359 (72.8)	327 (66.3)	0.286
Family history of CAD, n (%)	29 (9.5)	67 (9.9)	0.854
Familial hypercholesterolemia, n (%)	14 (4.6)	11 (1.6)	0.006*
Laboratory results			
BUN (mmol/L)	4.68 (3.81–5.50)	4.54 (3.80–5.47)	0.320
CR (μmol/L)	73.25 (66.78–83.48)	74.80 (66.40–83.85)	0.696
eGFR (mL/min/1.73 m^2)	116.71 (105.78–124.09)	116.18 (104.70–121.85)	0.284
FBG (mmol/L)	5.35 (4.86–6.51)	5.33 (4.90–6.40)	0.916
HbA1c (%)	5.7 (5.3–6.7)	5.6 (5.3–6.2)	0.368
TG (mmol/L)	2.00 (1.36–3.19)	1.84 (1.32–2.69)	0.050
TC (mmol/L)	4.76 (3.69–5.83)	4.44 (3.54–5.36)	0.006*
HDL-C (mmol/L)	0.88 (0.76–1.01)	0.89 (0.78–1.03)	0.151
LDL-C (mmol/L)	2.85 (2.14–3.77)	2.69 (2.01–3.48)	0.016*
UA (μmol/L)	420.30 (354.23–481.60)	404.30 (346.70–467.50)	0.109
NEU (×10^9/L)	5.73 (4.38–7.69)	5.22 (4.00–7.20)	0.011*
MON (×10^9/L)	0.46 (0.35–0.62)	0.44 (0.34–0.57)	0.129
LYM (×10^9/L)	2.14 (1.71–2.58)	2.12 (1.70–2.61)	0.726
PLT (×10^9/L)	241.00 (201.00–280.00)	253.00 (215.00–297.00)	0.001*
hs CRP (mg/L)	3.65 (1.00–9.60)	2.54 (0.94–7.86)	0.049*

(*Continued*)

Table 8 (Continued).

Characteristics	MACE (n=306)	Non-MACE (n=680)	*P*
Cardiac function			
LVEF	60 (55–65)	62 (56–66)	0.025*
Degree of coronary lesion			
Ginsini score	45 (25.5–78.25)	32 (20–53.75)	<0.001*

Notes: Data are expressed as medians with interquartile range for continuous variables with non-normal distribution and number (%) for categorical variables. * *P*<0.05.

Abbreviations: MACE, major adverse cardiovascular events; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; BMI, body mass index; CAD, coronary artery disease; BUN, blood urea nitrogen; CR, creatinine; eGFR, estimated glomerular filtration rate; FBG, fasting blood glucose; HbA1c, glycosylated hemoglobin; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; UA, uric acid; NEU, neutrophil; MON, monocyte; LYM, lymphocyte; PLT, platelet; hs CRP, high-sensitivity C- reactive protein; LVEF, left ventricular ejection fraction.

Univariate and Multivariate Logistic Regression Analysis for MACE and Non-MACE Patients

Univariate logistic regression analysis showed that smoking, familial hypercholesterolemia, hypercholesterolemia, high LDL-C, LVEF, Ginsini score, NEU and PLR were associated with the occurrence of MACE in young patients with CAD (all *P*<0.05). Then, these variables were incorporated into the multivariate logistic regression analysis. The results showed that smoking, familial hypercholesterolemia, Ginsini score and a lower PLR continued to be independent risk factors for the MACE occurrence in young CAD patients (all *P*<0.05) (Table 9).

Discussion

This study revealed a gradual increase in the prevalence of ACS with ascending levels of systemic inflammatory indices, including NLR, PLR, MLR, SII, SIRI and PIV. Among these indices, SIRI and PIV demonstrated statistically better

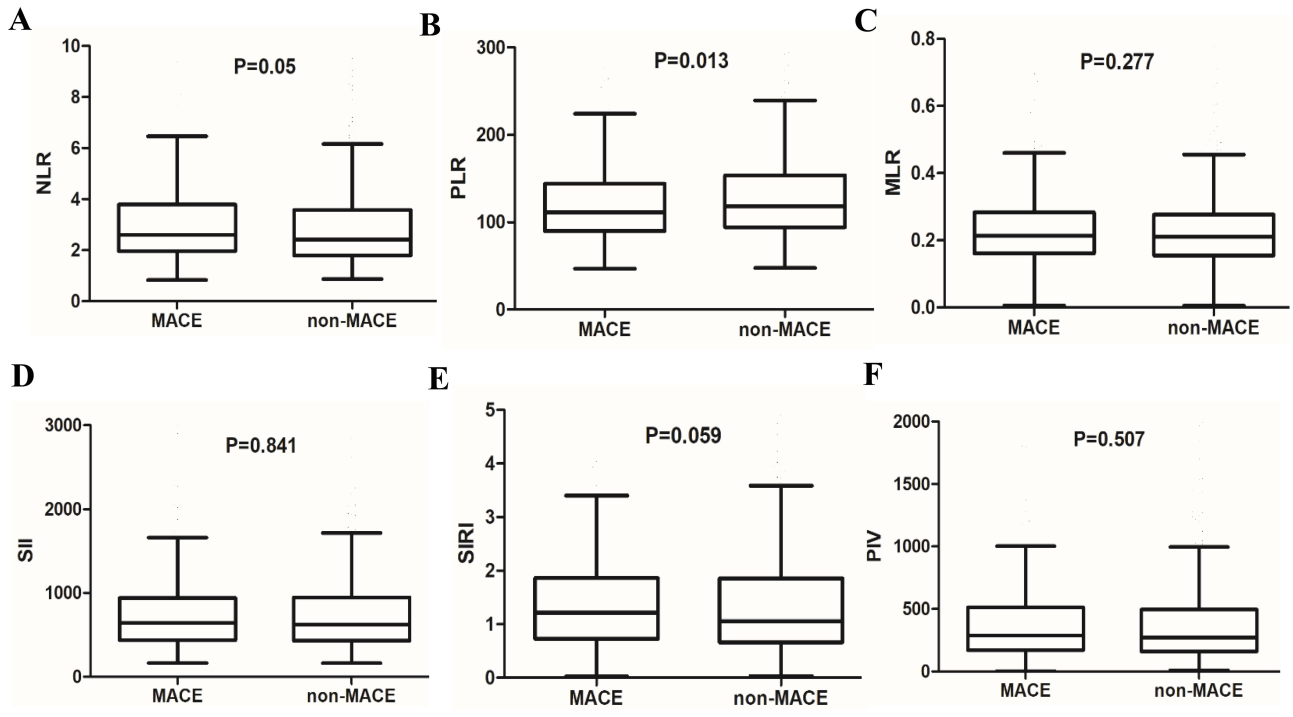

Figure 4 Comparison of inflammatory hematological indices between the MACE and non-MACE groups. (**A**) NLR; (**B**) PLR; (**C**) MLR; (**D**) SII; (**E**) SIRI; (**F**) PIV.

Abbreviations: NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; MLR, monocyte to lymphocyte ratio; SII, systemic inflammatory immune index; SIRI, systemic inflammatory response index; PIV, pan immune-inflammation value; MACE, major adverse cardiovascular events.

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Table 9 Univariate and Multivariate Logistic Regression Analysis for MACE and Non-MACE Patients

Variables	Univariate Analysis			Multivariable Analysis		
	OR	95% CI	*P*	OR	95% CI	*P*
Smoking	1.820	1.345–2.462	<0.001*	1.600	1.161–2.205	0.004*
Familial hypercholesterolemia	2.916	1.308–6.500	0.009*	2.710	1.089–6.748	0.032*
Diabetes mellitus	1.357	0.986–1.869	0.061			
Hypercholesterolemia	1.417	1.068–1.881	0.016*	1.126	0.729–1.740	0.591
High LDL-C	1.399	1.052–1.861	0.021*	1.052	0.677–1.634	0.821
hsCRP	1.011	0.996–1.025	0.162			
LVEF	0.979	0.964–0.996	0.014*	0.991	0.973–1.010	0.352
Ginsini score	1.014	1.009–1.018	<0.001*	1.011	1.007–1.016	<0.001*
NEU	1.049	1.003–1.097	0.035*	1.019	0.968–1.073	0.466
PLR	0.995	0.992–0.998	0.002*	0.995	0.992–0.998	0.004*

Notes: * *P*<0.05.

Abbreviations: MACE, major adverse cardiovascular events; LDL-C, low-density lipoprotein cholesterol; hs CRP, high-sensitivity C- reactive protein; LVEF, left ventricular ejection fraction; NEU, neutrophil; PLR, platelet to lymphocyte ratio; OR, odds ratio; CI, confidence interval.

predictive performance for ACS in young patients presenting with chest pain compared to the others. Furthermore, NLR, MLR, and SIRI exhibited a significant positive correlation with the Gensini score. These three indices, along with LVEF, were established as independent predictors of a higher Gensini score. Finally, smoking, familial hypercholesterolemia, a higher Gensini score, and a lower PLR were identified as independent risk factors for long-term MACE in young patients with CAD.

In various studies, the age standard for "young adults" is defined as 35 to 55 years, while those under 35 are classified as "very young".[3,24] Although very young patients (≤35 years) accounted for only ~1% of all ACS cases, they have a higher risk of cardiogenic shock and significantly increased 30-day mortality.[24] This calls for greater clinical attention. Traditional risk factors such as male gender, hypertension, smoking, obesity, hyperlipidemia, and family history of cardiovascular disease are commonly found in young adults with ACS.[25] Furthermore, clinical characteristics and risk factors vary across different age groups. Compared to ACS patients aged 36 to 44, those between 18 and 35 years exhibit a higher prevalence of smoking, obesity, and hyperlipidemia.[1] This study yielded similar findings, indicating a higher proportion of males and smoking among very young ACS patients, as well as more pronounced dyslipidemia, characterized by decreased HDL-C as well as elevated triglyceride and LDL-C levels. It suggests that smoking and hyperlipidemia are more likely to lead to plaque instability. Since both groups consisted of patients with CAD, no significant differences were observed in terms of obesity or family history of cardiovascular disease.

Myocardial ischemia and hypoxia resulting from ACS trigger a cascade of inflammatory responses, characterized by infiltration of numerous inflammatory cells and release of abundant inflammatory mediators, thereby exacerbating myocardial injury.[26] Elevated white blood cell counts and C-reactive protein levels have been observed in ACS patients, with these markers correlating with disease severity, atherosclerotic plaque stability, and patient mortality.[27] Moreover, white blood cells and their subtypes (including neutrophils, monocytes, and lymphocytes) serve as easily measurable clinical indicators for assessing inflammatory status in these patient.[28] Neutrophils, as a crucial subset of white blood cells, are the first immune cells to arrive at the culprit lesion site in ACS and are regarded as key initiators of the subsequent inflammatory cascade following myocardial infarction.[29] Neutrophils have been shown to induce smooth muscle cell disintegration and death, thereby amplifying inflammation and contributing to atherosclerotic plaque destabilization.[30] Through Toll-like receptor 2-mediated activation mechanisms, neutrophils enhance the secretion of inflammatory factors such as matrix metalloproteinase-9, promoting thrombosis initiated by endothelial cell detachment.[31] Furthermore, neutrophil extracellular traps exacerbate coronary thrombosis, directly damage vascular endothelial cells and cardiomyocytes, and sustain the local inflammatory response.[32] Monocytes actively participate in endogenous inflammation-related processes. In response to biological signals, they migrate from the bloodstream to

endothelial cells and differentiate into macrophages and foam cells. This process promotes the secretion of pro-inflammatory cytokines, production of matrix metalloproteinases, and generation of reactive oxidizing substances, leading to the accumulation and infiltration of inflammatory cells into ischemic areas. Consequently, monocyte-driven processes aggravate cardiomyocyte injury in the ischemic region, ultimately causing degradation of the cardiomyocyte membrane and fibrin cytoskeleton, and resulting in cell death.[33] Notably, neutrophils, monocytes, and their effector molecules predominantly accumulate at sites of spotty calcification, intensifying vascular wall inflammation and increasing plaque vulnerability.[34] Lymphocytes function as central regulators in atherosclerotic disease. During the chronic phase, the balance between pro-inflammatory and anti-inflammatory lymphocyte subsets dictates plaque progression and stability; in the acute phase of ACS, systemic lymphocytopenia combined with localized immune activation imbalance within plaques synergistically accelerates disease progression and influences long-term prognosis.[9,35] Platelets contribute significantly to vascular wall inflammation through multiple mechanisms: releasing granular contents, expressing specific surface molecules, and generating platelet microparticles. These coordinated actions promote leukocyte recruitment and induce endothelial cell injury, thereby driving both the initiation and progression of atherosclerotic lesions.[36] Moreover, activated platelets and their mutually amplifying interaction with the coagulation system represent a crucial mechanism underlying intracoronary thrombosis and subsequent ACS development. Thus, the integrated assessment of these hematologic parameters holds enhanced predictive value for ACS compared to individual marker evaluation.

Studies have established the NLR as an independent risk factor for premature coronary artery disease (PCAD), with demonstrated diagnostic utility for ACS in this patient population (AUC = 0.735).[37] In contrast, the present study found no significant difference in PLR between PCAD patients and controls.[37] Supporting this observation, Trakarnwijitr et al reported an age-dependent relationship between PLR and CAD, where elevated PLR (≥146.7) showed a negative association with PCAD in patients under 55 years.[38] Meanwhile, research by Han et al highlighted the significant diagnostic value of SII, SIRI, and PIV for premature myocardial infarction (PMI), with SIRI ≥1.495 emerging as an independent risk factor for PMI.[39] Both SII and SIRI maintained independent associations with CAD in individuals under 45 years of age.[40] The findings of this study are consistent with previous reports. Among young patients with CAD under 35 years of age, NLR, PLR, MLR, SII, SIRI, and PIV remain independent risk factors for ACS after adjustment for traditional risk factors (including age, gender, smoking, and dyslipidemia). Notably, SIRI and PIV showed a statistically higher diagnostic value for ACS compared to other inflammatory hematological indices, while PLR showed no significant diagnostic utility. However, the overall diagnostic performance of SIRI and PIV was moderate, underscoring the need for complementary assessment tools and further validation using decision-curve or reclassification analyses. The severity of CAD in young adults is primarily assessed through the extent of coronary atherosclerosis and the degree of luminal stenosis. The Gensini scoring system, which assigns differential weighting coefficients based on stenosis severity across coronary branches, offers a more objective and comprehensive evaluation of disease severity, serving as a reliable indicator for quantifying coronary artery lesions.[11,40] Previous investigations examining the relationship between inflammatory hematological indices and CAD severity in young adults have produced limited and inconsistent results, largely attributable to variations in study population characteristics (including age distribution), sample sizes, assessment criteria, and statistical methodologies. Caimi et al's study of 120 patients aged ≤45 years with recent acute myocardial infarction found no significant differences in NLR across subgroups stratified by the number of stenotic coronary vessels.[41] In contrast, Zhu et al's research involving 132 PCAD patients aged 25–73 years identified PLR as an independent risk factor for severe coronary artery disease (Gensini score >60), demonstrating good predictive value for severe lesions (AUC=0.777).[11] Another recent study of 194 CAD patients under 45 years revealed positive correlations between both SII and SIRI with Gensini scores.[40] In our current investigation, Spearman correlation analysis demonstrated significant positive correlations between NLR, MLR, SII, SIRI, PIV and Gensini scores in young CAD patients. These correlations remained consistent across both ACS and non-ACS subgroups, with stronger associations observed in the ACS population, suggesting that these inflammatory hematological indices may serve as indicators of the underlying inflammatory state associated with coronary lesion severity in this demographic. Furthermore, when patients were stratified into mild, moderate, and severe groups based on Gensini scores, multivariate ordinal logistic regression analysis identified LVEF, NLR, MLR, and SIRI as independent risk factors for coronary artery disease severity. However,

it is important to note that the correlation coefficients for these indices were weak ($r < 0.2$), indicating that while they reflect the inflammatory processes involved in atherosclerosis, they are not strong predictors of the anatomical extent of coronary lesions when considered alone. This highlights the complex, multifactorial nature of atherosclerosis progression in young adults.

The association between inflammatory hematological indices and clinical prognosis in young patients with CAD remains inadequately investigated, with most existing studies failing to establish significant associations. Caimi et al reported that in young patients (≤45 years), NLR levels decreased significantly at both 3 and 12 months following myocardial infarction.[41] Importantly, no significant difference in baseline NLR values was observed between patients with and without adverse events during 18-month follow-up.[41] Similarly, a retrospective analysis of 681 patients with a mean follow-up of 8.5 years demonstrated that the prognostic value of PLR for cardiovascular mortality was confined to elderly patients (≥65 years), with no significant association detected in younger cohorts (<65 years).[42] Our study, with a mean follow-up of 8 years in CAD patients under 35 years of age, yielded consistent results: no significant differences were observed in NLR, MLR, SII, SIRI, and PIV between patients with and without MACE, indicating limited prognostic utility of these inflammatory hematological indices in this specific population. Notably, while conventional risk factors including smoking, familial hypercholesterolemia, and Gensini score served as independent predictors of MACE in young patients, PLR demonstrated a negative correlation with MACE occurrence. This inverse relationship aligns with previous observations that patients with PCAD exhibit significantly lower PLR compared to elderly patients, suggesting fundamentally distinct inflammatory pathways driving the disease process in these age groups.[42,43] The paradoxical behavior of PLR—showing an independent association with ACS yet an inverse relationship with long-term MACE—merits further mechanistic consideration. One possible explanation lies in the dual role of platelets in acute versus chronic phases of coronary disease. In the acute setting, elevated PLR may reflect heightened platelet activation and consumption, contributing directly to thrombus formation and the manifestation of ACS.[38,39] Conversely, for long-term prognosis, lower PLR in young patients may indicate a distinct pathophysiological landscape. Unlike the quantitative platelet increases typically associated with chronic inflammation-induced megakaryocytic proliferation in older adults, atherosclerosis in young patients appears to be primarily driven by qualitative alterations in platelet function.[38] Supporting this concept, studies have demonstrated enhanced GPIb-mediated platelet adhesion in PCAD patients, suggesting excessive von Willebrand factor-platelet interactions may play a pathogenic role without necessarily elevating platelet counts.[44] Furthermore, the balance between pro- and anti-inflammatory forces may differ between age groups. Emerging evidence suggests that premature CAD involves an imbalance between pro- and anti-inflammatory cytokines coupled with impaired regulatory T-cell function, collectively accelerating atherosclerotic progression.[38] This dysregulation could decouple traditional inflammatory markers from long-term outcomes, as the chronic inflammatory milieu may be maintained by mechanisms not adequately captured by baseline PLR. These observations underscore that the prognostic utility of PLR, and inflammatory hematological indices more broadly, may be context-dependent and age-specific. In young CAD patients, PLR appears to reflect acute thrombotic propensity rather than serving as a marker of chronic inflammatory burden. This distinction is critical for correct interpretation of these indices in clinical practice and highlights the need for age-stratified approaches when using inflammatory biomarkers for risk prediction.

This study has several limitations that should be acknowledged. First, as a single-center retrospective investigation, incomplete documentation may have resulted in missing data. Furthermore, the observational nature of retrospective studies inherently limits the ability to rigorously control for potential confounding factors. Second, the study population was restricted to young patients under 35 years of age diagnosed with CAD through coronary angiography. The relatively low incidence of CAD in this age group resulted in a limited sample size. Additionally, patients who had no subsequent medical records at our institution and were lost to telephone follow-up were excluded due to lack of prognostic information, introducing potential selection bias. Finally, given the multicollinearity among inflammatory hematological indices, we conducted multivariate logistic regression analyses for these indicators separately from other variables. This approach allowed for a relatively accurate assessment of their individual impacts on disease progression.

Conclusions

This study provides the first systematic analysis of the association between inflammatory hematological indices—NLR, PLR, MLR, SII, SIRI, and PIV—and the occurrence of ACS, severity of coronary artery lesions, and long-term outcomes in patients under 35 years of age with CAD. The results showed that all the inflammatory markers investigated were independent risk factors for ACS in young CAD patients, with SIRI and PIV exhibiting the highest predictive value among the indices studied, although the overall predictive capacity remained modest. Moreover, NLR, MLR, and SIRI were identified as independent risk factors for the severity of coronary artery disease, although the strength of these associations was weak. These findings may be valuable for identifying young CAD patients at high risk of ACS and for understanding the inflammatory milieu associated with their condition. However, during long-term follow-up, most of these indices failed to predict MACE; instead, traditional risk factors—including smoking, familial hypercholesterolemia, and a higher Gensini score—emerged as the dominant predictors of adverse outcomes. The limited prognostic value of inflammatory hematological indices for long-term events suggests that distinct pathological mechanisms may govern disease progression in young CAD patients. Further multicenter, prospective studies are needed to validate these findings and to explore the underlying pathways.

Abbreviations

NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; MLR, monocyte-to-lymphocyte ratio; SII, systemic immune inflammation index; SIRI, system inflammation response index; PIV, pan-immune inflammation value; ACS, acute coronary syndrome; CAD, coronary artery disease; MACE, major adverse cardiovascular events; LVEF, left ventricular ejection fraction; GS, Gensini score; NEU, neutrophil; LYM, lymphocyte; MON, monocyte; PLT, platelet; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Data Sharing Statement

Data from this study are available from the corresponding author upon request.

Ethical Approval and Informed Consent

This study was conducted and reported in accordance with RECORD reporting guidelines. It adhered to the principles of the Declaration of Helsinki and approved by the Institutional Ethics Committee of Beijing Anzhen Hospital (The ethics approval number was 2025285x). Written informed consent was waived by the ethics committee because of the data retrospectively obtained from electronic medical records.

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Author Contributions

Dongmei Shi: Conceptualization, Methodology, Writing - review and editing. Jiayin Sun: Conceptualization, Methodology, Formal analysis, Writing - original draft. Shuchang Qi: Data curation, Investigation. Meihuizi Yu: Data curation, Investigation. Sitong Lei: Data curation, Investigation. Wei Han: Formal Analysis, Supervision, Project administration, Writing - review and editing, Conceptualization. Sijing Wu: Investigation, Validation, Writing - review and editing. Yujie Zhou: Formal Analysis, Resources, Supervision, Writing - review and editing, Conceptualization. All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that there are no conflicts of interest.

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