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Original Article

Systemic Inflammatory Indices as Biomarkers for Diagnosing and Predicting Coronary Artery Disease

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ABSTRACT

Coronary artery disease (CAD) is the main cause of mortality worldwide. Inflammation is linked to progression in CAD. The study aimed to estimate the values of main inflammatory indices: the systemic inflammation index (SII), the systemic inflammation response index (SIRI), and the aggregate index of systemic inflammation (AISI) for diagnosing and predicting CAD. This case-control study included (200) participants, (140) patients who were categorized into 80 acute coronary syndrome (ACS) and 60 chronic coronary syndrome patients (CCS) because of coronary angiograms, in addition to 60 health controls. For each participant, the main inflammatory indices SII, SIRI, and AISI were computed based on hematological parameters, as well as serum concentrations of fasting sugar, lipids, hs-CRP, and other biochemical profiles, which were estimated by an immune turbidimetric assay. Clinical and demographic information was documented by a specially designed questionnaire form. ROC and regression analysis were used to assess the predictive values for CAD. Among ACS patients, levels of inflammatory indices SII and AISI were markedly raised in comparison to CCS and controls ($p<0.001$) while SIRI increased non-significantly ($p=0.054$), WBC, NLR, PLR, and hs-CRP were also elevated ($p<0.001$). Logistic regression analyses exposed SII, AISI, hs-CRP, and NLR as strong significant predictors of ACS (OR: 1.901, 1.810, 1.760 and 1.336, all $p<0.001$), respectively, while SIRI showed slightly lower predictive value (OR:0.908, $p=0.020$). SII had the highest diagnostic accuracy with an area under the curve (AUC) of 0.934, with an excellent sensitivity and specificity of 88.6% and 83.3% ($p=0.020$). AISI followed with noteworthy diagnostic capacity AUC:0.921 with 84.8% sensitivity and 92.6% specificity ($p=0.005$). The SII and AISI have arisen as significant clinical prognostic biomarkers for ACS diagnosis; they could serve as novel predictors for CAD assessment. Combination with clinical assessments could help refine risk stratification and guide treatment intervention.

Keywords: CAD, SII, SIRI, AISI, Inflammatory markers.

1 Introduction

Coronary artery disease (CAD) persists as the primary contributor of mortality all over the world [1]. Despite advancements in medical research and therapeutic interventions, the burden of CAD continues to rise, necessitating the development of novel diagnostic and prognostic tools [2]. Among all risk factors, atherosclerosis has a major role. However, there was numerous evidence supporting that systemic inflammation is a key contributor in the development of atherosclerotic plaques. Inflammation is the main factor that makes one dispose of plaque formation, plaque rupture, and thrombosis [3,4].

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Among all inflammatory markers implicated in atherosclerosis development, white blood cells (WBC) and subtypes play a central role in CAD progression and markedly lead to an elevated risk of thrombus and an acute coronary syndrome (ACS) event. That's why more attention has returned to hematological-based blood markers, especially WBC subtypes for systemic inflammation in clinical practice [5,6].

Epidemiological studies declare that WBC subtypes are crucial immune system cells. It increased the risk of coronary atherosclerosis development and predicted the outcomes of an ACS event; recently it may act as an independent risk factor for future CAD [4,7]. Moreover, these inflammatory indices serve as indicators to predict recurrent onset and mortality rate among those patients with already existing CAD [8]. WBC cell-based calculated inflammatory indices like SII, SIRI, and AISI have emerged as some of the most important promising novel

inflammatory biomarkers for predicting and diagnosing ACS status [9,10]. These recent inflammatory markers are more reliable and stable than other blood parameters because they are based on calculating three independent WBC subtypes which show the degree of overall inflammatory condition in terms of the ratio of the WBC subtypes [11,12]. There were numerous studies reinforcing the usefulness of these markers to predict CAD outcomes. SII was identified as an independent indicator of CAD [13,14], increased SIRI led to worsening of CAD among patients initially diagnosed with CAD [15], and it was also related to the development of ACS among CCS patients [16]. Both SII and SIRI were recognized as new markers for evaluating CAD severity [17,18]. There were numerous studies comparing inflammatory indices like SII and SIRI in CAD, while there are only a few studies regarding AISI [19].

However, to date, no studies have simultaneously evaluated and compared all three indices, SII, SIRI, and AISI, in both ACS and CCS patients against healthy controls to determine their combined diagnostic and predictive accuracy for CAD. Furthermore, data from the Iraqi/regional population regarding these inflammatory indices remain scarce. Therefore, this study aimed to evaluate the potential role of SII, SIRI, and AISI as inflammatory biomarkers for diagnosing and predicting ACS, along with investigating their association with the occurrence and severity of CAD for more diagnostic accuracy.

2 Methods and Materials

2.1 Collection of Study Samples

The present case-control research study was performed at the specialized surgical Cardiac Center hospital in Erbil City, from December 2024 to June 2025. 140 patients (80 ACS and 60 CCS) met the exclusion and inclusion criteria for the present study. In addition, 60 participants were included as health controls. Exclusion criteria: Patients with heart failure, myocarditis, congenital heart illnesses, low platelet count, bleeding and clotting abnormalities, peripheral arterial occlusive diseases, cancer, undergoing hemodialysis, or systemic inflammatory diseases such as autoimmune, rheumatoid, and infectious diseases were excluded. Inclusion criteria: Included participants were more than 18 years old, and patients underwent coronary angiography (CAG) and were selected according to the CAD diagnostic guideline formulated by the American College of Cardiology (ACC)/the American Heart Association (AHA) [20]. As well, the number and degree of occluded coronary vessels were diagnosed according to the CAG result by a specialized cardiologist. The control participants were also selected based on age and sex, matched with the patient group and confirmed as healthy individuals and free from diabetes, hypertension, and obesity.

2.2 Clinical Definition

The ACS group included patients who had clear symptoms of CAD, like increased levels of cardiac enzymes, especially troponin, ECG changes, and CAG detected with coronary artery occlusion. ACS were categorized into myocardial infarction in which ST increased (STEMI), myocardial infarction in which ST did not increase (NSTEMI), and unstable angina (UA). Patients with a positive troponin test without arterial occlusion were excluded from the study. The CCS was defined as a patient having chronic chest pain or angina without myocardial destruction and having a minimum 50% stenosis in one of the main arteries identified by CAG. The clinical profile of study participants was collected by a specially designed questionnaire form through interviews and hospital medical records.

2.3 Laboratory Assessment

The fasting peripheral blood specimens (5 mL) were collected directly from each participant right after admission and prior to CAG using venipuncture techniques through standardized phlebotomy procedures to ensure consistency and accuracy. The EDTA whole blood was used for the evaluation of hematological parameters. Serum was directly separated by centrifuge at 2000 rpm for 20 minutes in the gel tube. Markers of SII, SIRI, and AISI were calculated from CBC, which was performed by Sysmex Europe GmbH, Norderstedt, Germany, using an automated hematology analyzer calibrated according to manufacturer specifications. The Roche Cobas systems, such as the Cobas e 411 (Roche Diagnostics GmbH) and Cobas 6000, were used for analyzing fasting blood sugar, HbA1C, hs-CRP, lipid profiles, total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), urea, creatinine, and troponin I.

2.4 Calculation of inflammatory indices

The hematological inflammatory indices have been assessed as follows: platelet to lymphocytes proportion (PLT/Lym); neutrophil to lymphocytes proportion (Neu/Lym); monocyte to lymphocyte proportion (Mon/Lym); systemic immune inflammation index (SII) by (Neu × PLT)/Lym; systemic immune response index (SIRI) by (Neu × Mon)/Lym , and aggregate index of systemic inflammation (AISI) by (Neu × Mon × PLT)/Lym [18,21,22].

2.5 Data Analysis

Statistical analyses were conducted using GraphPad Prism software 9.01, USA. The Shapiro–Wilk and the Kolmogorov–Smirnov tests were utilized to detect the normal distribution of the data. The ANOVA test was employed for normally dispersed data, expressed as mean ± SE, while the Kruskal-Wallis's test was performed for non-normal distributed data, expressed as median (range). A p-value of less than 0.05 was regarded as a statistical difference. Logistic regression and Spearman's correlation test were employed to find the strength of the relationship between study markers. MedCalc software version 23.3.7, Belgium, performed the receiver operating characteristic (ROC) analysis to diagnose the accuracy of SII, SIRI, and AISI for CAD.

2.6 Ethical Considerations

Approval for the study was received from the Medical Ethics Committee of Erbil Polytechnic University (EPU) in Erbil, Iraq (Approval No. 24/0039 HRE, dated 28/10/2024). The overall research followed the Helsinki Declaration's ethical principles. Informed printed consent was signed by each participant before inclusion.

3 Results

3.1 Study subjects and demographic profile

The study involved 200 participants, including 80 ACS (52 men and 28 women), 60 CCS (36 men and 24 women), and 60 controls (28 men and 32 women). The mean age among CAD patients is higher than that pf controls, with ACS (60.1 ± 1.32 years), CCS patients (55.5 ± 1.02 years), and controls (51.5 ± 1.87 years) with substantial differences (p = 0.005). Males are more prevalent in CAD patients, while the substantial differences were not recorded between the study groups (p = 0.37). The BMI showed a marked difference between the groups, with ACS patients having the highest BMI (p = 0.020). Both SBP and DBP are significantly higher among ACS and CCS patients compared to controls (p < 0.001, p < 0.002), which reflects the high prevalence of hypertension among both patient groups, especially among CCS (p = 0.07). While the prevalence of diabetes mellitus was similar between ACS and CCS (p = 0.90). As well as other risk factors, dyslipidemia, positive family history of CAD, and current smoking were markedly increased among the ACS and CCS groups in comparison to controls (p = 0.005, p = 0.001, and p < 0.002) sequentially. Regarding medication use, aspirin, ticagrelor, and beta blockers were significantly higher among ACS patients (p = < 0.001, p = 0.038, p = 0.032), Table 1.

Table 1: Demographic and clinical profile of the CAD and health controls.

Variables	ACS (n=80)	CCS (n=60)	Controls (n=60)	p value
Age, mean ± SE	60.1±1.32	55.5. ± 1.02	51.5 ± 1.87	0.005**
Male, n %	52 (60)	36 (60)	28 (46.6)	0.37
BMI, Kg/m^2	28.4 (26.9 - 30.1)	28.3 (26.5 - 32.3)	26.1 (24.0 - 28.4)	0.020*
SBP, mmHg	140 (130 -150)	140 (130 - 154)	125 (120 - 140)	<0.001**
DBP, mmHg	90 (80 - 95)	90 (80.5 - 90.0)	80 (76 - 88)	0.002**
HR, beats/min	90 (71 - 93)	78 (71.0 - 93.0)	79 (68 - 91)	0.001**
Diabetes mellitus, n%	44 (55)	33 (55)	0	0.90
Hypertension, n%	46 (57.5)	42 (70)	0	0.070
Dyslipidemia, n%	38 (47.5)	36 (60)	15 (25)	0.005**
Family history, n%	52 (65)	39 (65)	18 (30)	0.001**
Current smoking, n%	42 (52.5)	26 (43.3)	14 (23.3)	0.002**
Medications				
Aspirin, n%	52 (65.0)	18 (30.0)	5 (8.33)	<0.001**
Clopidogrel, n%	23 (28.8)	5 (8.33)	0	0.280
Ticagrelor, n%	27 (33.8)	10 (16.7)	0	0.032*
B blockers, n%	29 (36.3)	12 (20.0)	0	0.038*
Statins, n%	45 (56.3)	27 (45)	0	0.271
Antihypertensive, n%	19 (23.8)	22 (36.7)	0	0.133
Antidiabetic, n%	38 (47.5)	30 (50.0)	0	0.864
Data summarized as median – interquartile range or mean ± standard error (SEM) or n (%); * statistical significance.				

3.2 Comparison of laboratory findings and measured parameters between study groups

The main parameters in the ACS patient groups were markedly higher (SII 744.2 and AISI 548.7) compared to CCS patients (SII 541and AISI 465.7) and controls (all p < 0.001). While SIRI showed a non-significant elevation in ACS 2.04 compared to CCS 1,903 and controls 1.04 (p =0.054), see Figure 1. All hematological parameters were significantly raised among ACS patients compared to CCS and controls, which consist of WBC (11.9 vs 8.7 vs 6,75, p < 0.001), neutrophil (8.0 vs 6.15 vs 3.0, p < 0.001), and PLT (285 vs 260 vs 190, p = 0.040). On the contrary, lymphocyte counts were lower in ACS 2.0 compared to CCS 2.5 and controls 2.7 (p = 0.003). No substantial differences were seen concerning monocyte count (p = 0.81), hemoglobin (Hb) level (p = 0.23) and HCT count (p = 0.70). While the concentration of hs-CRP was notably elevated among ACS 4.3 compared to CCS 3.2 and controls 0.9, (p < 0.001). Although the ratio concerning NLR and PLR markedly increased among ACS patients to 2.8 (p = 0.02) and 108 (p < 0.003) no substantial differences were seen concerning the MLR ratio of 0.29 (p = 0.78). Additionally, biochemical parameters including HbA1c (p = 0.06), blood glucose (p = 0.001), urea (p = 0.05), creatine (p = 0.05), and lipid profiles were markedly higher in the ACS patients compared to the CCS and controls group contrary; on the contrary, there was markedly lower of HDL-C levels (p < 0.001). as shown in Table 2 below:

Table 2: Comparison of the hematological and biochemical parameters among study groups.

Variables	ACS (n=80)	CCS (n=60)	Controls (n=60)	p value
SII	744.2 (493-1200)	541 (356 - 948)	225 (167.3-364)	<0.001**
SIRI	2.04 (1.350-3.20)	1.903 (1.12 - 2.83)	1.04 (0.51-1.188)	0.054
AISI	548.7 (390-882.3)	465.7 (230 - 906)	138.8 (97.34-195)	<0.001**
NLR	2.8 (1.97-5.38)	2.1 (1.47-3.150)	1.36 (0.83-2.06)	0.020*
MLR	0.29 (0.180-0.400)	0.29 (0.186 - 0.40)	0.26 (0.22-0.36)	0.78

Variables	ACS (n=80)	CCS (n=60)	Controls (n=60)	p value
PLR	108 (70.3-120)	97 (69 -100.8)	92 (77.5-101.2)	0.003**
WBC (×10^9/L)	11.9 (9.6- 13.5)	8.7 (7.2-11.1)	6.75 (5.8-6.8)	<0.001**
Lymphocytes (×10^9/L)	2.0 (1.9-2.30)	2.5 (2.1-4.2)	2.7 (2.3-3.62)	0.003**
Monocytes (×10^9/L)	0.8 (0.56-1.0)	0.9 (0.60-1.0)	0.6 (0.5-0.8)	0.81
Neutrophiles (×10^9/L)	8.0 (5.62-10.9)	6.15 (4.7-7.67)	3.0 (1.9-4.5)	<0.001**
PLT (×10^9/L)	285 (224-328)	260 (186-302.1)	190 (162-210)	0.040*
HGB (g/L)	14.5 (13.1-15.7)	14.1 (13.3-14.8)	14.5 (13.6- 15.4)	0.23
HCT (%)	42 (38-46)	41 (38-44.5)	42.9 (37.4-45.0)	0.70
hs-CRP (mg/dL)	4.3 (2.0-5.0)	3.2 (1.52 - 4.0)	0.9 (0.7-1.5)	<0.001**
Sugar (mg/dL)	150 (120 - 225)	112 (93 -197)	100 (90-120)	0.001**
HbA1c %	6.89 (5.8-7.94)	6.2 (5.4-9.3)	4.9 (4.3-5.6)	0.060
Creatine (mg/dL)	1.08 (0.78-1.31)	0.92 (0.70- 1.01)	0.81 (0.8- 1.0)	0.056
Urea (mg/dL)	31 (25.0-44.0)	29 (23.0 - 37.0)	27 (22.0 -30.8)	0.060
TC (mg/dL)	230 (186-258)	192 (149-235)	153 (125-195)	0.090
TG (mg/dL)	270 (189- 350)	183 (126-326)	135 (100-179)	<0.001**
HDL (mg/dL)	35 (30-39)	36 (31-40)	39 (34-45)	0.001**
LDL (mg/dL)	139 (100.3-175)	120 (100-151)	95(67-120)	<0.001**
VLDL (mg/dL)	55 (45-65)	49 (38.0-56.0)	30 (22-33.6)	0.083
None- HDL (mg/dL)	190 (153- 165)	154 (111-201)	109 (85-150)	<0.001**
TG/HDL Ratio(mg/dL)	7.95 (4.86-11.53)	5.48 (3.41- 9.45)	3.55(2.1-5.3)	<0.001**
LDL/HDL Ratio(mg/dL)	3.95 (3.13-4.87)	3.42 (2.73-3.90)	2.5 (1.90-3.05)	0.360
Data summarized as Median - interquartile range or n (%); *Statistical significance.				

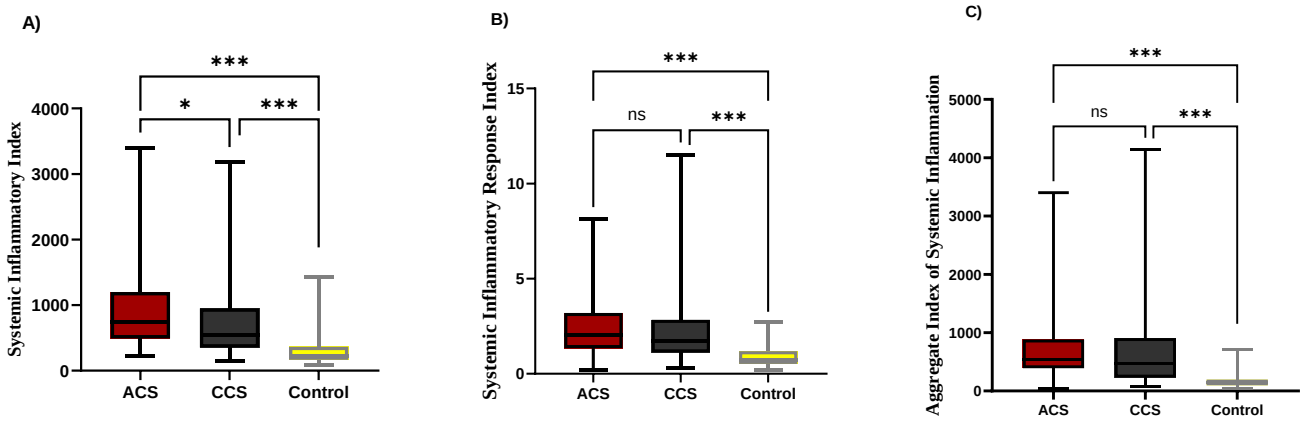

Figure 1: Difference in SII (A), SIRI (B) and AISI (C) between Acute Coronary Syndrome (ACS), Chronic Coronary Syndrome (CCS) and Control.

3.3 Logistic analysis of SII, SIRI, and AISI with CAD risks in ACS patients

Logistic regression univariate and multivariate analyses were done for traditional CAD risk factors (age, DM, HPT, family history of CAD, and smoking), as well as for lipid profiles, and inflammatory markers SII, SIRI, AISI, NLR, MLR, PLR, and hs-CRP to determine the independent risk factors for ACS development Table 3. Results of the univariate analysis showed that the predictive value for ACS was age (OR:1.03), male gender (OR:2.98), DM (OR:1.06), HPT (OR:1.47), smoking (OR:1.21), SII (OR:1.90), AISI (1.81), NLR (OR:1.33), CRP (OR:1.76), and LDL (OR:1.26). SIRI showed a significant but lower 0.90 odds ratio compared to SII and AISI. In the multivariate analysis, after adjusting for confounders, the strongest independent predictors of ACS were age (OR:1.46), male gender (OR:4.76), DM (OR:1.43), SII (OR:3.90), SIRI (OR:1.47), AISI (OR:2.80), and hs-CRP (5.13). The results emphasize the significant role of metabolic and inflammatory biomarkers in ACS advancement.

Table 3: Analysis of logistic regression among patients with ACS.

Variables	Univariate		Multivariate	
	OR (95 % CI)	p value	OR (95 % CI)	p value
Age	1.03 (0.456 - 1.76)	0.023*	1.460 (0.374-4.720)	0.070*

Variables	Univariate		Multivariate	
	OR (95 % CI)	p value	OR (95 % CI)	p value
Male	2.988 (1.688-3.292)	< 0.001**	4.762 (1.09-3.80)	0.002**
BMI	0.812 (0.676-0.900)	0.073		
Diabetes mellitus	1.064 (0.829-1.219)	0.031*	1.437 (0.984-1.765)	< 0.001**
Hypertension	1.471 (0.951-2.274)	0.060		
Family history CAD	0.736 (0.316-0.941)	0.890	0.985 (0.657-1.532)	0.632
Smoking	1.211 (0.788-1.860)	0.003**	0.765 (0.768-1.099)	0.056
SII	1.901 (0.938-2.325)	< 0.001**	3.90 (1.030-3.998)	0.013*
SIRI	0.908 (0.098-1.254)	0.020*	1.47 (0.580-2.566)	0.240
AISI	1.810 (0.973-1.976)	0.001**	2.802 (0.934-2.998)	0.027*
MLR	0.642 (0.078-1.064)	0.744		
NLR	1.336 (0.194-1.627)	0.001**	1.989 (0.765-1.980)	0.456
PLR	0.994 (0.842-1.295)	0.320		
WBC ($\times 10^9$/L)	0.924 (0.841-1.580)	0.056		
Lymphocytes ($\times 10^9$/L)	0.553 (0.741-0.899)	0.525		
Monocytes ($\times 10^9$/L)	0.406 (0.725-0.898)	0.721		
Neutrophiles ($\times 10^9$/L)	0.814 (0.331-0.799)	0.098		
PLT ($\times 10^9$/L)	0.998 (0.499-0.996)	0.002**	0.620 (0.466-0.952)	0.067
hs-CRP (mg/dL)	1.760 (0.891-1.860)	< 0.001**	5.314 (0.973-6.834)	< 0.001**
Sugar (mg/dL)	0.995 (0.893-0.998)	0.003**	0.893 (0.561-0.975)	0.047*
TC (mg/dL)	0.845 (0.149-0.903)	0.820		
TG (mg/dL)	0.187 (0.104-0.335)	0.062		
HDL-C (mg/dL)	2.267 (1.471-3.492)	0.427		
LDL (mg/dL)	1.263 (1.110-1.638)	0.854		
VLDL (mg/dL)	0.602 (0.180-0.126)	0.289		
OR: odd ratio; CI: confident intervals.				

3.4 The ROC curves demonstrate the capability of SII, SIRI, and AISI in predicting CAD

Both SII and AISI presented a powerful diagnostic performance among ACS patients. The AUC of SII was strong (0.93) with a 95% CI of 0.88-0.97 and showed significant differences (p = 0.020) with brilliant sensitivity and specificity of 88.6% and 83.3%, respectively, among ACS patients. Similarly, the AUC of AISI was 0.92 with a 95% CI of 0.87-0.97 with obviously significant differences (p = 0.005). If compared with SII, the specificity of AISI was higher (92.6%), while the sensitivity was slightly lower (84.8%). Regarding the SIRI, it showed slightly lower diagnostic performance compared to SII and AISI; the AUC was 0.87 with a 95% CI of 0.810-0.928 with high significant differences (p = 0.004), with medium sensitivity (77.2%) and very good specificity (87%). While in CCS patients, the AUC for SII was 0.84 with a 95% CI of 0.76-0.90 (p = 0.013), along with a sensitivity of 87.9% and a specificity of about 63%. Similarly, AISI achieved a very good AUC of about 0.85 and a 95% CI of 0.77-0.99 with highly significant differences (p < 0.001). While concerning SIRI, the AUC was about 0.79 with a 95% CI of 0.71-0.86 (p = 0.021) with low sensitivity of 62.1% and very good specificity of 87% Figure 2.

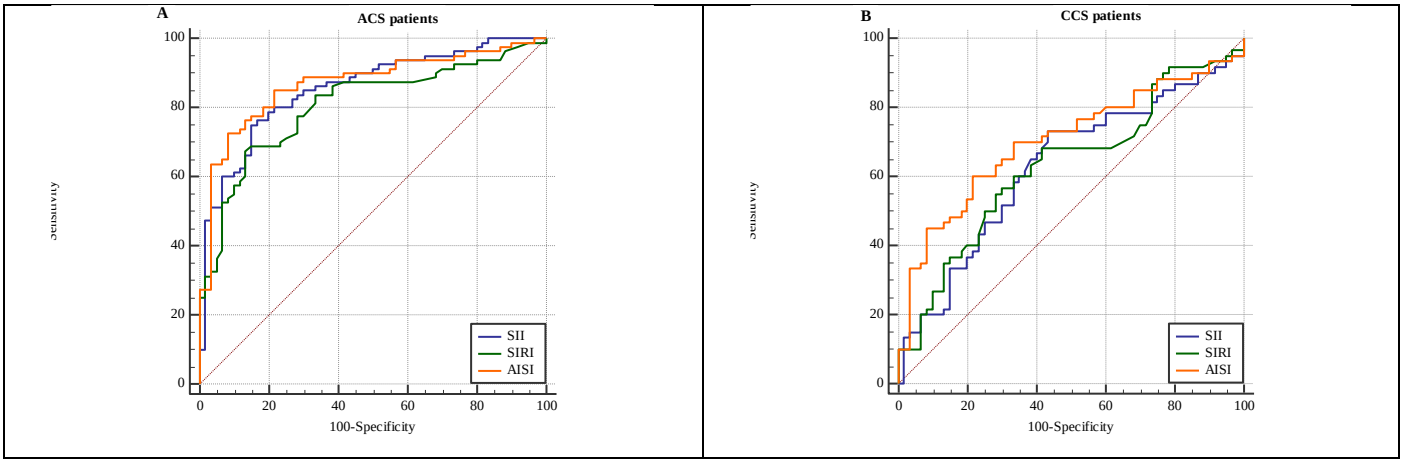

Figure 2: The ROC curve analysis: (A) in acute coronary syndrome (ACS) patients, (B) in chronic coronary syndrome (CCS) patients.

3.5 Comparison of the association between SII, SIRI, and AISI with other inflammatory and biochemical parameters among ACS and CCS patients

A correlation test was done between hematological indices, biochemical and other CAD risk factors among CAD patients, and in certain instances the correlations were positive Table 4. Age presented obviously strong positive correlation with ACS ($r = 0.9$, $p = 0.05$). Also, BMI showed a positive correlation with no substantial differences seen ($r = 0.28$, $p = 0.56$). The main parameters that related to our research sample, SII and AISI, had shown a strong positive correlation in ACS patients ($r = 0.79$, $p = 0.003$) and ($r = 710$, $p = 0.009$), subsequently. While SIRI showed a moderate positive correlation ($r = 0.557$, $p = 0.081$). In terms of WBC ratios, NLR showed a strong ($r = 702$, $p < 0.001$), PLR a moderate ($r = 0.550$, $p = 0.050$), while MLR showed a low non-significant ($r = 0.25$, $p = 0.49$) positive correlation. Other CBC-based parameters, WBC, neutrophil, PLT, and monocyte, are all positively correlated with ACS ($r = 0.620$, $p < 0.001$), ($r = 0.542$, $p < 0.001$), ($r = 0.687$, $p = 0.018$), and ($r = 0.246$, $p = 0.098$), respectively, whereas lymphocyte has negative correlations ($r = -0.430$, $p = 0.56$). Additionally, hs-CRP showed strong positive high significant correlation in ACS ($r = 0.76$, $p = 0.003$). Regarding other laboratory parameters such as sugar, HbA1c, TC, TG, LDL, and VLDL, all showed positive correlations in ACS with r values ranging from 0.04 to 0.59, and all $p > 0.05$, except HDL, which showed negative correlations ($r = -0.189$, $p = 0.007$). Although in CCS some positive correlations were identified, they were weaker than those observed among ACS.

Table 4: A Spearman's Correlation of inflammatory, hematological indices, and biochemical parameters with other CAD risk factors between ACS and CCS patients.

Variables	ACS		CCS	
	r	p value	R	p value
Age	0.990	0.050*	0.660	0.004*
BMI	0.289	0.564	0.372	0.075
SII	0.798	0.003**	0.555	0.054*
SIRI	0.557	0.081	0.476	0.041*
AISI	0.710	0.009*	0.545	0.061
WBC ($\times10^9$/L)	0.620	< 0.001**	0.512	<0.001**
Neutrophiles ($\times10^9$/L)	0.542	< 0.001**	0.514	0.019*
Lymphocytes ($\times10^9$/L)	-0.430	0.567	-0.576	0.342
Monocytes ($\times10^9$/L)	0.246	0.098	0.429	0.543
PLT ($\times10^9$/L)	0.687	0.018	0.478	0.007*
NLR	0.702	< 0.001**	0.577	0.005**
MLR	0.258	0.497	0.321	0.902
PLR	0.550	0.050	0.365	0.091
hs-CRP (mg/dL)	0.765	0.003**	0.578	<0.001**
Sugar (mg/dL)	0.591	0.283	0.105	0.432
HbA1C	0.427	0.321	0.323	0.453
TC (mg/dL)	0.318	0.560*	0.374	0.810
TG (mg/dL)	0.313	0.910	0.256	0.222
HDL-C (mg/dL)	-0.189	0.007**	-0.265	0.346
LDL (mg/dL)	0.040	0.760	0.125	0.328
VLDL (mg/dL)	0.071	0.542	0.460	0.098

4 Discussion

This research was conducted to evaluate the diagnostic ability of systemic inflammatory indices in predicting and detecting CAD, particularly focusing on their potential use as inflammatory biomarkers for ACS patients. The findings of this study explored that inflammation serves as a significant mediator in the pathogenesis of atherosclerosis and CAD development. Elevated systemic inflammatory indices and ACS may compromise the systemic inflammatory processes that participate in plaque instability, rupture, and eventually acute cardiovascular events. For us, we know this research tries to assess the combined relationship of SII, SIRI, and AISI together among patients with ACS, although previous research pointed only to the role of SII and SIRI in different CAD disorders.

In this research, SII and AISI were identified as strong predictor biomarkers that reflect the inflammatory events in ACS. Notably, patients with ACS had the highest levels of SII and AISI significantly compared to CCS and the control. Markedly elevated SII levels in ACS patients reinforce the concept that systemic inflammation contributes to the destabilization of the atherosclerotic plaque and resulting acute events [18]. A systematic review and meta-analysis study demonstrated that higher SII has prognostic value for adverse consequences in CAD patients [23].

In the present study After SII, AISI also elevated significantly among ACS patients; there are limited studies about the role of AISI in CAD. Firstly, Jiang and collaborators in 2024 [24] investigated the role of AISI in AMI, and they concluded that high AISI was associated with greater incidence of CAD and

CAD-related mortality and could be used as an early indicator for CAD progression. Another recent study showed that AISI was highly correlated with death among CAD patients [19]. Estimation of AISI among ACS patients is very important because high AISI indicates proinflammatory effects and abnormal platelet adhesion and aggregation that results in the formation of microthrombi and localized ischemia and oxygen depletion, which finally results in necrosis of the tissue [25]. More recently, AISI is not only used for a predictor but also useful as an independent prognostic marker, especially after the PCI procedure, and predicts post-PCI cardiac mortality causes [26]. That's why, to assess this relationship, further studies are required, as AISI is a multi-factorial index and able to be represented as an effective inflammation marker.

Even though the SIRI was elevated in the current study, the elevations were less obvious than those of SII and AISI. Since SIRI depends on the calculation of neutrophil and monocyte counts, and there were no substantial variations observed in monocyte count between groups, while SII depends on calculations of neutrophil and platelets counts, both markedly increased in ACS patients. According to the study, SIRI had a good diagnostic performance among young symptomatic CAD patients [27]. The high predictive value of SII and AISI in the present study highlights the significance of immune cell roles in triggering ACS events.

In the current study, NLR and PLR also showed excellent prognostic and diagnostic markers for ACS; both of them were significantly higher in ACS, results in line with previous studies [28-30]. While, regarding MLR, no differences have been seen between ACS and CCS patient groups, the present results are consistent with a previous study that demonstrates that MLR might not effectively reflect the all-inflammatory status in ACS [12].

Remarkably, CAD has a multifactorial nature; alongside systemic inflammation, several factors significantly contribute to the progression of atherosclerosis to ACS, such as age, gender, and conventional risk factors, including BMI, diabetes, hypertension, dyslipidemia, and smoking [31,32]. According to the study results of logistic analyses to explore independent risk factors for CAD progression among ACS patients, both the SII and AISI inflammatory indices showed high risk factors in both univariate and multivariate model analyses among ACS patients; they show a strong predictive power, and higher SII and AISI increase the odds of ACS occurrence. The result of the study is consistent with the work of Bayraktar and Coşgun, carried out in 2024 [17], which states that SII and SIRI were significant and independent predictors as far as the severity of CAD is concerned. Similar to the above findings, Liu et at., 2021, discovered that SII had a good correlation with the Gensini score and it was an independent predictor for the severity of CAD [33]. Thus, special attention to those patients who had SII and AISI at a high level highlights their potential as a powerful marker of ACS risk.

In addition to SII and AISI indices, conventional risk factors like age, gender, diabetes, hypertension, and smoking increased odds of ACS occurrences in the present study. Results are in line with previous studies [34,35] These factors participate in inflammatory processes to worsen endothelial dysfunction and hasten plaque progression and instability [36]. Moreover, other inflammatory markers, NLR, and hs-CPR showed an excellent predictive value significantly among ACS in both univariate and multivariate models, which highlighted the inflammatory activity related to ACS events, results consistent with previous studies [37,38]. There were several studies in the literature targeted to accurately calculate the SII or SIRI value associated with CAD diagnosis by ROC analysis [22,39]. Our research is a little different from the previous research in that we also calculate the value of the AISI, and the control group is a healthy person. So, we were more precise than previous work. Both SII and AISI showed a powerful diagnostic accuracy, and they emerged as strong indicators of ACS results in line with a previous study [34]. Based on the current study findings, SII was the most sensitive and AISI the most specific index. The high value of diagnostic accuracy indicates that SII is a potent and convenient biomarker in the predicting and diagnosing of ACS [17].

The current findings suggest that SII and AISI might be sensitive indicators that demonstrate acute inflammation in ACS. While the SIRI sensitivity and specificity are slightly lower than those the SII and AISI, the diagnostic performance is still clinically applicable. Such good properties of these indices, especially SII and AISI for the sensitivity and specificity, lend support to their promise for the early diagnosis of ACS, and due to their ready availability and cost-effectiveness, they are very appealing methods for risk stratification and early treatment in a clinical environment. It might be used instead of cardiac biomarkers and ECG to predict of ACS [40].

Additionally, the findings of the present study demonstrated that these systemic inflammatory indices have better sensitivity and specificity for ACS patients than for CCS patients. This is in good agreement with the scores of the previous study, in which it was stated that ACS patients have higher values of these novel inflammatory markers than those of stable CAD patients [18].

The correlation between the inflammatory indices and ACS was observed through the spearman correlation statistical test, suggesting their potential associations with systemic inflammation in CAD. Age showed a significant positive association with ACS, reflecting that older individuals are more prone to CAD development [41]. Among the inflammatory indices and inflammatory biomarkers, SII, AISI, NLR, and hs-CRP showed strong significant positive correlations with ACS; especially SII and hs-CRP showed the best correlations. These results are similar to the study of He and colleagues [42,43].

Moreover, both NLR and hs-CRP support the link between these indices and systemic inflammatory burden in ACS patients. A previous study declared that neutrophil-derived indicators strongly predict most of the mortality causes independent of CRP among CAD patients [44]. These inflammatory indices may be helpful in identifying patients with inflammation burdens that cannot be explained by hs-CRP alone. Interestingly, lymphocytes and HDL were shown to be negatively associated with ACS, as HDL itself is anti-inflammatory and cardioprotective. These associations indicate that systemic inflammation may be more common in those with lower HDL values, thereby further supporting the role of metabolic perturbation in ACS [22].

The main strength of the current study is that it is the first time SII, SIRI, and AISI together have been evaluated among ACS, CCS, and control groups. Simultaneous assessment of all three indices together provides a comprehensive view about systemic inflammation. The novelty of this research is that these inflammatory indices may offer better predictive value than traditional inflammatory markers because they are cost-effective and widely available biomarkers, especially for early diagnosis and risk assessment in patients supposed to have ACS. Nevertheless, their limitations still need to be clarified to address the challenges. First, several prospective researchers needed to validate the current findings. Second, the study was done in a single center, which limits the applicability of the results of these findings to a wider population. The inflammatory indices were assessed at one time, and time-dependent changes over time were not measured. Thus, prospective multicenter studies with prolonged follow up are needed to validate the prognosis usefulness of SII, SIRI, and AISI.

Conclusion

Collectively this study highlights the powerful association of SII and AISI with ACS incidence; they offer a significant prognostic value in coronary atherosclerosis, in comparative SIRI demonstrate lower diagnostic performance. As well as these indices provide a substantial advantage through reflecting underlying inflammatory processes that play a main role in the pathogenesis of ACS. Linking these markers in clinical practice could improve evaluating the prognosis and risk assessment and potentially treatment strategies for CAD patients, giving us a clue about the prognosis of CAD. Future studies ought to pay more attention to explaining the exact pathways between systemic inflammation and rupture of coronary plaques and try to discover therapeutic interventions directing these inflammatory pathways.

Conflict of interest

None

Financial Disclosure

None

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