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Original Article

Internal Medicine Section

Diagnostic Utility of the Systemic Immune-inflammation Index for Acute Coronary Syndrome in Young Adults: A Prospective Case-control Study

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ABSTRACT

Introduction: Acute Coronary Syndrome (ACS) in individuals under 40 years of age presents with distinct epidemiological characteristics, risk profiles and outcomes compared to older patients. Identifying cost-effective and reliable prognostic markers in this population is essential, particularly in resource-limited settings. Composite inflammatory indices, such as the Systemic Immune-inflammation Index (SII), derived from platelet, neutrophil, and lymphocyte counts, has emerged as a promising biomarker in cardiovascular disease risk stratification.

Aim: To evaluate the diagnostic utility of SII in differentiating young ACS patients from healthy controls, and to explore its prognostic value in predicting short-term Major Adverse Cardiac Events (MACE) within 30 days.

Materials and Methods: The present prospective case-control study was conducted including 30 ACS patients aged <40 years and 30 age and sex-matched healthy controls, demographic data, clinical history, and laboratory parameters were collected. SII was calculated ((Platelet count*neutrophil count) / lymphocyte count). Statistical analyses included ROC curve analysis for diagnostic performance and other respective statistics based on the variable and normality. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) (v24.0).

Results: The mean age of participants was 35.47±3.25 years, with 42 (70%) being male. The median SII was significantly higher in ACS patients compared to controls (p<0.001). ROC analysis demonstrated that SII (AUC 0.863, cutoff 613.875, sensitivity 96%, specificity 46%) for ACS diagnosis. Only two patients experienced MACE within 30 days, although the SII values were numerically higher, the difference was also statically significant (p=0.014).

Conclusion: The SII, derived from routine complete blood count parameters, demonstrated strong diagnostic performance in identifying acute coronary syndrome among young adults. Given its simplicity and low cost, SII may serve as an adjunct diagnostic biomarker in early ACS detection, particularly in resource-limited settings. However, its prognostic value for short-term adverse outcomes remains exploratory and requires validation through larger, multicentric, and homogenous cohort studies.

Keywords: Myocardial infarction, Neutrophil-to-lymphocyte ratio, Platelet-to-lymphocyte ratio, Premature coronary artery disease

INTRODUCTION

Acute Coronary Syndrome (ACS) in individuals younger than 40 years of age represents a distinct clinical entity with different epidemiological patterns, risk factors, and outcomes compared to older population [1]. Although less common, premature ACS carries significant morbidity and mortality, particularly in South Asian countries where cardiovascular risk factors manifest at an earlier age [2]. Additionally, ethnicity and geographical location are closely associated with the incidence of ACS in younger populations [3]. Globally, ACS in patients under 40 years accounts for approximately 0.4%-19 of all cases, and in India, nearly 25% of ACS events occur in this age group [2,4]. Premature ACS also imposes significant socioeconomic consequences. For example, in Canada, 1,894 individuals under 55 years died from Coronary Artery Disease (CAD) in 2012, underscoring its impact on healthcare systems and productivity [5].

Atherosclerosis, leads to thickening and hardening (arteriosclerosis), which can markedly reduce blood flow and increase the risk of Cardiovascular Disease (CVD), including CAD [6,7]. In this context, inflammatory biomarkers provide prognostic information beyond traditional necrosis markers, as they quantify the systemic immune response that contributes to both plaque vulnerability and thrombotic complications [6,7,8-11]. Thus, early identification of high-risk patients is critical for guiding timely interventions and improving outcomes. Conventional risk assessment tools and biomarkers, such as troponins and C-reactive Proteins (CRP), have limitations in sensitivity, specificity, and accessibility in resource-limited settings [12]. Consequently, there is growing interest in simple, cost-effective, and reliable haematological indices derived from routine laboratory tests as novel biomarkers [11,13,14].

The Systemic Immune-inflammation Index (SII), calculated as (platelets*neutrophil)/lymphocyte counts, integrates three readily available key haemotologic components into a single composite score, [13] and reflects the balance between host inflammatory and immune responses [15,16]. Originally validated in oncology for prognostication, SII has gained attention in cardiovascular research as a marker of systemic inflammation and a predictor of outcomes in CAD [17]. Studies suggest that SII may provide superior prognostic value compared to Neutrophil-to-Lymphocyte Ratio (NLR) or Platelet-to-Lymphocyte Ratio (PLR) [13-15,18]. However, data on the utility of SII in young ACS patients are sparse to the knowledge [13]. Given that premature ACS patients often present with fewer traditional risk factors and atypical clinical features, identifying reliable biomarkers in this population is clinically important.

The present study evaluated the role of SII in differentiating young ACS patients from healthy controls and explores its potential

prognostic association with Major Adverse Cardiac Events (MACE) at 30-days. The primary objective of this study was to evaluate the SII as a diagnostic marker for differentiating young ACS patients (<40 years) from healthy controls. The secondary objective was an exploratory evaluation of its prognostic association with short-term (30-day) MACE in young ACS patients.

MATERIALS AND METHODS

The present prospective case-control study conducted at the Department of General Medicine, Mahatma Gandhi Medical College Hospital and Research Institute (MGMCRI), Pondicherry, India, from March 2023 to March 2025.The study was approved by the Institutional Human Ethics Committee (IHEC) [MGMCRI/Res/01/2023/106/IHEC/100]. Written consent was obtained from all participants. The study adhered to the Declaration of Helsinki.

Sample size calculation: Sample size was estimated using data from Pinto AS et al. (2022), [19] where MACE incident in MI patients was 17.7%, with an Odds Ratio (OR) of 13.82 for high SII values. Based on these effect size estimates, with a two-sided significance level (α) of 0.05 and statistical power (1-β) of 80%, the minimum sample size was 30 participants per group (total 60) using OpenEpi Ver_3.0.

$$n=\frac{(Z_{\alpha/z}+Z_{\beta})^2\times((p_1(1-p_1)+p_2(1-p_2))}{(p_1-p_2)^2}=\frac{7.84\times0.217675}{0.05600}=30.46\sim30$$

(Deriving p1 from OR using the formula

$$OR=\frac{\frac{p_1}{1-p_1}}{\frac{p_2}{1-p_2}}\rightarrow0.2616$$

as for the conservative baseline risk for low SII (2.5%, then p2=0.025). This sample size was selected for feasibility in an exploratory analysis, but it is underpowered for definitive prognostic modelling.

Inclusion criteria: A total of 60 participants were enrolled, where 30 consecutive patients under 40-years of age with confirmed ACS (Unstable angina (UA), ST-Elevation Myocardial Infarction (STEMI) and Non-ST elevated myocardial infarction (NSTEMI) were recruited as cases and 30 age- and sex-matched healthy individuals without cardiovascular disease served as controls.

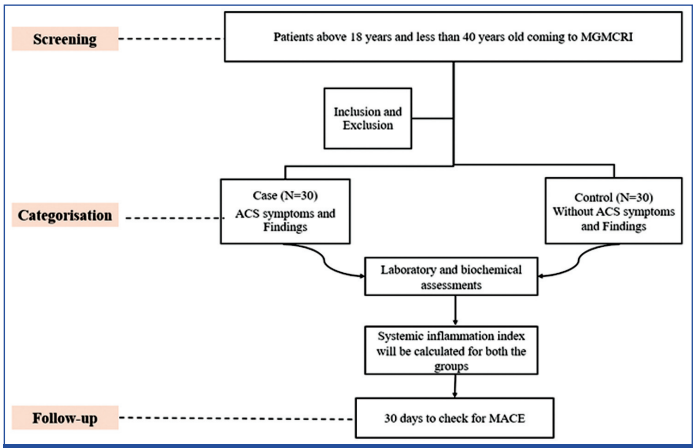
ACS group: Patients diagnosed with ACS using established American College of Cardiology (ACC) and European Society of Cardiology (ESC) criteria, [20,21] including STEMI (new ST-segment elevation at the J-point in two contiguous leads, with the cut-off point >0.1 mV in all the leads except V2 or V3; in V2-V3 the cut-off point was >0.2 mV in males older than 40-years or >0.25 mV in males younger than 40-year or >0.15 mV in females, accompanied by ischemic symptoms and elevated troponin-I above the 99th percentile Upper Reference Limit (URL)), NSTEMI (ischemic symptoms with elevated troponin-I above the 99th percentile of URL, without ST-segment elevation), and UA (ischemic symptoms without ST-segment or troponin-I elevation).

Control group: Controls were recruited from individuals undergoing routine health check-ups and aged >18 years and <40 years, with no history of CAD, Myocardial Infarction (MI), no prior inflammatory or haematological disorders, no coagulation or platelet disorders, chronic kidney disease, or malignancy.

Exclusion criteria: Patients with prior history of any cardiac disease or disorder, with active infection (fever), low platelet count (<150000 cells/mm^3), chronic inflammatory disease, patients with elevated Erythrocyte Sedimentation Rate (ESR) or CRP levels and with haematological malignancies, autoimmune disorders, or incomplete clinical or laboratory records were excluded.

Study Procedure

The sequence of study events is summarized in [Table/Fig-1]. Data collected using a standard proforma, included age, sex, co-morbidities, Electrocardiography (ECG) changes, Echocardiographic (ECHO) findings, coronary angiography results (Single, Double or Triple Vessel Disease (SVD, DVD, TVD)). Venous blood samples were obtained at admission for a Complete Blood Count (CBC), ESR, and high-sensitivity CRP (hs-CRP) testing. Also, troponin-I levels, and occurrence of MACE were also collected.



[Table/Fig-1]: Flow-chart to summarise the sequence of events.

SII was calculated for each subject. Heart Failure (HF) classification was assessed using the Killip scoring system [Table/Fig-2] [22,23].

Systemic Inflammation Response Index	(Neutrophil count × Monocyte count) ÷ Lymphocyte count
Systemic Immune-Inflammation Index	(Neutrophil count × Platelet count) ÷ Lymphocyte count
Aggregate Index of Systemic Inflammation	(Neutrophil count × Monocyte count × Platelet count) ÷ Lymphocyte count
Monocyte-to-Lymphocyte Ratio	Monocyte count ÷ Lymphocyte count
Platelet-to-Lymphocyte Ratio	Platelet count ÷ Lymphocyte count
Neutrophil-to-Lymphocyte Ratio	Neutrophil count ÷ Lymphocyte count

[Table/Fig-2]: Composite indices 22,23

For the purposes of the present study, MACE was defined as a composite outcome of reinfarction, non-fatal stroke, HF requiring hospitalisation, arrhythmias requiring intervention, and all-cause mortality [24].

Follow-up: ACS patients were followed for one month after discharge through outpatients visits or telephonic contact to record the occurrence of any MACE.

STATISTICAL ANALYSIS

SPSS version 24.0 (IBM Corp., Armonk, NY, USA) was used for all statistical analysis. Continuous variables were expressed Mean±Standard Deviation (SD) or median with Interquartile Range (IQR), and comparisons were made using the student's t-test or Mann-Whitney U test, depending on variable distribution. Categorical variables were expressed as frequencies and percentages and compared using the Chi-square test. Receiver Operating Characteristics (ROC) analysis was used to evaluates the diagnostic accuracy of the SII. Prognostic analysis was done using unadjusted Mann-Whitney U test. Statistically significant was set at p<0.05 (two-tailed).

RESULTS

A total of 60 patients were included, comprising 30 ACS patients and 30 age- and sex-matched healthy controls. The mean age of the participants was 35.47±3.25 years, with 70% of participants were male. Baseline demographic and clinical characteristics for both groups were summarised in [Table/Fig-3].

Parameters	Case (with ACS) n=30	Control (without ACS) n=30
Age (years)		
Mean±SD	35.46±3.26	35.52±3.25
30 to 40	23 (76.7)	23 (76.7)
19 to 29	7 (23.3)	7 (23.3)
Gender		
Male	21 (70.0)	21 (70.0)
Female	9 (30.0)	9 (30.0)

[Table/Fig-3]: Demographic and baseline clinical characteristics of the study participants.
SD: Standard deviation; Values given in brackets are percentages

Among the cases, 10 (33.3%) and 9 (30%) had one or two co-morbidities, while 11 (36.7%) of patients had >2 co-morbidity, while cases were healthy controls. Among the ACS patients, the subtypes and angiographic findings were presented in [Table/Fig-4].

Parameters	Case (with ACS) n=30 (n (%))
Electrocardiography (ECG) changes	
ST-elevated Myocardial Infarction (STEMI)	21 (70.0)
Non-ST-elevated Myocardial Infarction (NSTEMI)	5 (16.6)
Unstable angina	4 (13.3)
Coronary angiogram	
Single vessel disease	24 (80.0)
Double vessel disease	6 (20.0)

[Table/Fig-4]: ACS subtypes and angiographic findings among the ACS patients.

Haematological and inflammatory parameters: Haematological and inflammatory parameters were compared between cases and controls [Table/Fig-5]. All parameters were significantly higher in ACS cases (p<0.05), except platelet count and Absolute Leukocyte Count (ALC).

Parameters	Case (with ACS) n=30 Mean±SD	Control (without ACS) n=30 Mean±SD	p-value*
Haemoglobin (g/dL)	14.23±1.03	13.07±1.93	0.006
Total count (*10^9/L)	12533.33±2635.87	6671.67±1353.90	<0.001
hs-CRP (mg/L)	51.82±25.19	1.04±0.76	<0.001
Neutrophil (%)	78.57±5.11	65.67±9.44	<0.001
ANC (*10^9/L)	10331.79±1933.81	4419.70±1285.50	<0.001
Platelet count (*10^9/L)	331066.90±78863.12	304700.00±71828.89	0.181
Lymphocyte (%)	15.54±5.11	28.73±8.11	<0.001
ALC (*10^9/L)	2033.97±1879.33	760.55±228.22	0.375
ESR (mm/ hour)	25.83±9.65	11.57±2.94	<0.001
Troponin-I (ng/L)	20013.94±17.00	13510.73±7.02	<0.001

[Table/Fig-5]: Comparison between various laboratory and inflammatory parameters between patients with and without ACS.
*Student's t-test; p values<0.05 was significant and indicated in boldface. hs-CRP: high sensitivity C-reactive protein; ANC: Absolute neutrophil count; ALC: Absolute leukocyte count; ESR: Erythrocyte sedimentation rate; ACS: Acute coronary syndrome; SD: Standard deviation

The SII and NLR showed significant differences between cases and controls [Table/Fig-6]. SII was markedly elevated in ACS patients (1666.433±806.721) compared with controls (809.56±344.27, p<0.001), indicating a heightened inflammatory state and immune dysregulation. Similarly, the NLR was significantly higher in ACS patients (5.723±2.21) versus controls (2.584±1.209, p<0.001) [Table/Fig-6].

Parameters	Case (with ACS) n=30 Mean±SD	Control (without ACS) n=30 Mean±SD	p-value
SII	1666.433±806.721	809.56±344.27	<0.001
NLR	5.723±2.21	2.584±1.209	<0.001

[Table/Fig-6]: SII and NLR in ACS.
*Student t-test; p-values<0.05 were statistically significant and indicated in boldface; SII: Systemic immune inflammation index; NLR: Neutrophil-to-lymphocyte ratio; ACS: Acute coronary syndrome; SD: Standard deviation

Treatment and short-term outcomes: Among ACS patients, 28 patients (93.3%) underwent Percutaneous Coronary Intervention (PCI), and two patients (6.7%) received medical management with medications and rest. This reflects a predominant preference for revascularization through PCI, likely due to its well-established benefits in restoring coronary perfusion and reducing adverse cardiovascular outcomes. At 30-day follow-up, MACE occurred in two patients (6.7%). Clinical outcomes are shown in [Table/Fig-7].

Parameters	n (%)
Major Adverse Cardiac Events (MACE)	
Presence of MACE	2 (6.7%)
No MACE	28 (93.3)
Killip score – Heart Failure (HF) severity	
Class 1 (no signs of HF)	10 (33.3)
Class 2 (mild signs of HF)	9 (30.0)
Class 3 (moderate signs of HF)	9 (30.0)
Class 4 (cardiogenic shock)	2 (6.7)

[Table/Fig-7]: Clinical outcomes in patients with ACS, including defined MACE (n=30).

Prognostic association with MACE: Due to the very small number of MACE events (n=2), an unadjusted Mann-Whitney U test showed that SII values were higher in patients who experienced MACE compared with those who did not (p=0.014), where these findings should be interpreted as exploratory. Binary logistic regression showed that SII was an independent predictor of ACS (p=0.030; OR 1.000; 95% Confidence Interval (CI): 1.000 to 1.001), indicating a very small but statistically significant increase in the odds of ACS with rising SII values after adjusting age, gender, comorbidities and NLR [Table/Fig-8].

SII	p-value
ACS (vs controls)	<0.001
MACE (analysis not performed due to insufficient events, n=2)	0.014* (unadjusted Mann-Whitney U test)

[Table/Fig-8]: Association of SII as a predictor of ACS.
*p-value is unadjusted; ACS: Acute coronary syndrome; MACE: Major adverse cardiac events; SII: Systemic immune inflammatory index

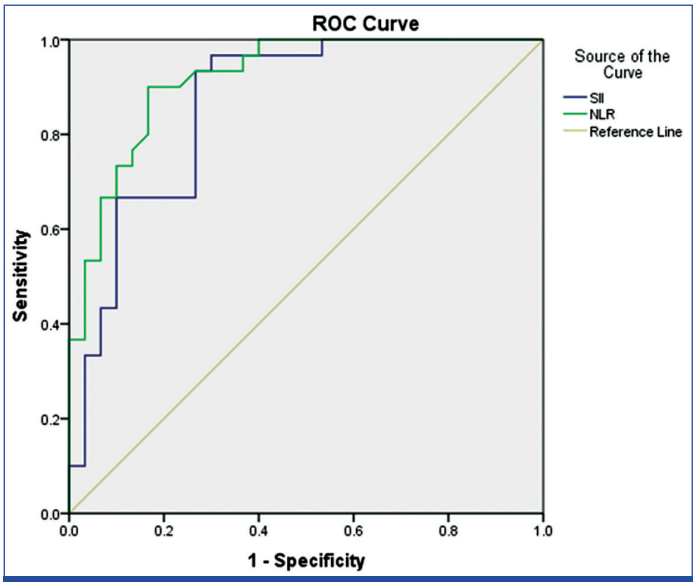
Diagnostic performance: ROC analysis revealed that SII had an Area Under Curve (AUC) of 0.863, with an optimal cutoff of 613.875, yielding a sensitivity of 96%, and 46% specificity. NLR showed an AUC is 0.919, with an optimal cutoff of 2.60, yielding 100% sensitivity and 40% specificity. Both SII and NLR are excellent diagnostic markers, with NLR showing slightly better overall performance. While SII offers a balance between sensitivity and specificity [Table/Fig-9,10].

DISCUSSION

In the present prospective case-control study, of 30 ACS patients under 40 years and 30 matched controls, SII was markedly elevated in cases (1666.433±806.721 vs 809.56±344.27; p<0.001) and emerged as an independent predictor of ACS (OR 1.000; 95% CI: 1.000-1.001; p 0.030). The AUC of 0.863 (sensitivity 96%, specificity

Variables	SII	NLR
AUC	0.863	0.919
Cut-off	613.875	2.60
Sensitivity (%)	96	100
Specificity (%)	46	40
PPV (%)	64	62.5
NPV (%)	92	100
LR+	1.78	1.67
LR-	0.087	0.00

[Table/Fig-9]: Sensitivity and specificity of SII and NLR in ACS prediction.
AUC: Area under curve; ACS: Acute coronary syndrome; NLR: Neutrophil-to-lymphocyte ratio; SII: Systemic immune inflammatory index; PPV: Positive predictive value; NPV: Negative predictive value; LR: Likelihood ratio



[Table/Fig-10]: ROC analysis of SII for ACS.

46%) showed a promising index in ACS. NLR also rose significant (AUC 0.919) and during one-month follow-up MACE occurred in 6.7% of patients, with SII predicting MACE (p=0.014). It should be noted that this cohort included STEMI, NSTEMI, and UA patients, which differ in baseline short-term MACE risk. The limited sample size precluded subtype-specific analyses, which could influence prognostic associations.

The SII integrates pro-inflammatory and immune-regulatory components by combining three pivotal hematologic parameters [13,14,25]. A 2022 systematic review found that SII outperformed standalone ratios in forecasting cardiovascular events, while in 2024 study in symptomatic youth confirmed its value as an early screening tool for CHD [13,15]. Wang S et al., reported that elevated SII associated with a 2.6-fold higher risk of short-term mortality and a 2.4-fold higher risk of long-term all-cause mortality, outperforming both NLR and PLR in prognostic discrimination [16]. Mechanistically, neutrophils promote plaque destabilization via proteolytic enzymes and reactive oxygen species; platelets amplify thrombo-inflammatory cascades through cytokine release; and lymphopenia reflects impaired immune regulation, all of which are captured by SII, offering a dynamic measure of systemic inflammation beyond single biomarkers such as CRP or troponin-I [26]. Additionally, in chronic HF cohorts, elevated SII independently predicted all-cause mortality (AUC 0.73), supporting its broader applicability in cardiovascular risk stratification [14].

The present study showed that ACS patients had markedly higher SII (1666.433±806.721) values, reflecting a pronounced inflammatory state. Ye Z et al., [15] observed that an SII threshold >88.8 independently predicted increased 30-day mortality in ACS cohort at real-time. Wang S et al. in a meta-analysis of 11 studies involving 16,596 patients, demonstrated that higher SII significantly predicted short-term mortality (HR 2.60; 95% CI 1.29-5.25) and long-term all-cause mortality (HR 2.40; 95% CI 1.25-4.59) [16]. Xie F et al. also reported that SII served as an independent predictor of treatment-related outcome in ACS patients post-PCI [27]. Furthermore, pooled analyses, [28] have linked a high NLR to increased risk of CAD (OR 1.62, 95% CI: 1.38-1.91), ACS (OR 1.64, 95% CI: 1.30-2.05), stroke (OR 2.36, 95% CI: 1.44-2.89), and composite cardiovascular events (OR 3.86, 95% CI: 1.73-8.64). Collectively, these findings reinforce the prognostic value of SII in ACS. Also, in this cohort included patients with STEMI, NSTEMI, and UA, these subtypes differ in their baseline risk for MACE, particularly in the acute and early post-event phases, with STEMI generally associated with the highest early event rates. The limited sample size precluded separate analyses for each ACS subtype, which could influence the observed association between SII and MACE. Therefore, the prognostic findings in this study should be interpreted cautiously and considered hypothesis-generating. Future studies evaluating SII in more homogeneous ACS subgroups, such as STEMI-only cohorts, are warranted to better assess its prognostic performance.

In the current study, MACE incidence was relatively low (6.7%) but still demonstrated significant association with elevated SII (OR: 1.000, p=0.014) and adverse outcomes. HF severity, as assessed by the Killip classification system, showed that most patients (60%) were in Classes 2 and 3, representing mild to moderate HF. Killip classification has been validated as a prognostic tool in STEMI [22]. An Indian epidemiological study found a male preponderance (58.7%) in ACS patients, with most patients in Killip Class IV (48.3%, p=0.0001) and higher mortality in those with Killip's class IV, elevated troponin-I, age >75 years, hypertension and dyslipidaemia [29]. The present study findings aligns with Pinto et al., [19] who reported significantly higher SII in STEMI versus NSTEMI/UA patients, and on OR 13.82 for MACE and OR 4.41 for mortality outperforming the Ejection Fraction (EF) and troponin-I as prognostic markers. While, SII was statistically associated with these events, the small number of events and lack of baseline risk adjustment in a healthy-control design limit the strength of prognostic inferences. These results should be interpreted as hypothesis-generating rather than confirmatory.

The present study also evaluated the diagnostic performance of SII and NLR in predicting ACS. SII demonstrated a balance between sensitivity (96%) and specificity (46%) and an AUC of 0.863, with an optimal cutoff value of 613.875, whereas NLR achieved AUC of 0.919, with an optimal cutoff value of 2.60 demonstrating a 100% sensitivity but lower specificity (46%). In contrast, studies in broader adult ACS population have reported different cut-off, for example Ji J et al., found that an SII threshold of 802.9*109/L had lower sensitivity (67.5%) but with higher specificity (79.6%) for ACS detection [30]. Huang J et al., reported an AUC of 0.64 for SII in predicting long-term outcomes in STEMI patients undergoing PCI, with 50% sensitivity and 74.1% specificity at a much higher cutoff of 1423.12*109/L [31]. The present study results were aligned to several studies on ACS patients [16,25,32,33]. These discrepancies highlight that optimal SII cut-offs and diagnostic accuracy can vary by patient age, ACS subtype, and whether the endpoint of interest is acute diagnosis or longer-term prognosis.

Limitation(s)

Despite its findings, this study has several limitations. This single-centre sample with 30 ACS patients and 30 controls limit statistical power and generalizability. A one-month follow-up restricts evaluation of longer-term outcomes and might miss late MACE events. Unmeasured confounders, including medication regimens, socio-economic factors, and lifestyle variables, may have influenced results. The absence of external validation in independent, multicentre cohorts necessitates further research before clinical adoption of SII for ACS screening and prognostication. Additionally, variability

in laboratory measurements across settings could influence SII reliability. The prognostic analysis was underpowered due to only two MACE events, preventing valid multivariable modelling. Small-event bias may produce artificially precise estimates and spurious statistical significance; therefore, prognostic results are exploratory only. Additionally, including all ACS subtypes without stratification introduces heterogeneity that may affect associations with MACE.

CONCLUSION(S)

The present study highlights the potential diagnostic value of the SII in young adults presenting with ACS. SII, derived from routine haematological parameters, demonstrated high sensitivity and acceptable diagnostic accuracy, suggesting its role as a simple, cost-effective biomarker for early ACS detection, especially in resource-limited settings. However, its prognostic value for short-term MACE remains inconclusive due to the limited sample size and very low event rate. The observed trends indicate that elevated SII levels may reflect heightened systemic inflammation associated with acute myocardial injury. Future large-scale, prospective studies focusing on homogeneous ACS subgroups, such as STEMI, are warranted to confirm these findings and clarify the prognostic significance of SII.

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