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Original Article

Internal Medicine Section

Systemic Immune-inflammation Index in Acute Coronary Syndrome and its Role in Predicting Disease Severity: A Cohort Study

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ABSTRACT

Introduction: Systemic Immune-inflammation Index (SII) is a novel marker of inflammation, used extensively in prognosticating various cancers. Recent studies have shown SII to be a predictor of adverse events and death in Acute Coronary Syndrome (ACS) patients who undergo intervention. The role of SII in medically managed SII patients has not been studied. There are no Indian studies available which study the prognosticative role of SII in ACS.

Aim: To study systemic immune-inflammation index in acute coronary syndrome and its role in predicting disease severity and mortality.

Materials and Methods: This prospective cohort study was conducted in Department of General Medicine at Father Muller Medical College Hospital, Mangaluru, India between February 2021 and July 2021. The study included 45 ST Elevation Myocardial Infarction (STEMI) and 45 Non ST Elevation Myocardial Infarction (NSTEMI)/Unstable Angina (UA) patients, aged 30 years or more. The SII, Neutrophil-to-Lymphocyte Ratio (NLR) and Total Leucocyte Count (TLC) were compared using independent sample t-test. Killip class, Thrombolysis In Myocardial Infarction (TIMI) and Global Registry of Acute Coronary Events (GRACE) 2.0 scores were used to determine disease severity. Pearson's and Spearman's correlation coefficient were used to determine correlation between parametric and non parametric parameters, respectively. Receiver Operator Curve (ROC) was used to see for predictability of outcomes. The role of SII to predict Major Adverse Cardiac Events (MACE) and death at one month follow-up period was assessed by Kaplan-Meier analysis and Cox regression analysis.

Results: The mean SII was significantly higher in the STEMI group (20.9 vs 9.79; t-value= 3.65, p-value <0.001). SII correlated significantly with Killip class (r=0.502), TIMI (r=0.417) and GRACE 2.0 scores (r=0.529), better than NLR or TLC. High SII were associated with a higher risk of MACE (Odds ratio=13.82, p-value <0.001) and death (OR=4.413, p-value=0.015). The SII had an Area Under the Curve of 0.67 for predicting MACE and had a negative predictive value of 96%. Kaplan-Meier analysis showed that patients with higher SII had a lower survival at one month (median: 24.5 days vs 29.32 days, Log-rank=6.44, p-value=0.011). The SII predicted MACE and death better than left ventricular Ejection Fraction (EF) and troponin I.

Conclusion: The SII is a cost-effective, novel marker of inflammation that can predict short term outcomes in ACS. This was the first cohort study which studied the role of SII in ACS in patients undergoing any type of intervention.

Keywords: Global registry of acute coronary events, Killip class, Neutrophil-to-lymphocyte ratio, Thrombolysis in myocardial infarction

INTRODUCTION

Cardiovascular diseases are the leading cause of mortality in India, accounting for nearly one-fourth of the total deaths[1]. Ischaemic heart disease-related events lead to around 3000 disability adjusted life years lost per 1,00,000 population every year [2]. The spectrum of Acute Coronary Syndrome (ACS) includes Unstable Angina (UA), Non ST Elevation Myocardial Infarction (NSTEMI) and ST Elevation Myocardial Infarction (STEMI). In the setting of an ACS, time is muscle. Early reperfusion by active intervention reduces myocardial damage, averting fatal complications and preventing mortality.

Acute coronary syndrome is a proinflammatory state leading to acute remodelling of the cardiac muscle. The inflammatory process is thought to have a favourable long-term effect, due to its angiogenesis and cellular healing abilities. However, in an acute setting, it can lead to dilation and rupture of the myocardium, further worsening the cardiac functionality. The ongoing ischaemia warrants an earlier reperfusion strategy.

In India, the problem with cardiovascular disease is two-fold. There has been a rapid epidemiological transition from infectious to non communicable diseases over the past few decades [3]. Due to the adaptation of sedentary lifestyle and insalubrious practices the incidence of diabetes, hypertension and dyslipidaemia, which are also risk factors for cardiovascular disease, has risen. Adding to this is the lacunae in the country's health infrastructure. An estimated 64.5% of the population reside in rural India where the resources are scarce. Even in urban areas, there is delay in referral of patients due to a heavy burden on the limited resources. The doctor-population ratio in India stands at just below 1 per 1000 population [4]. Out of this, the number of specialist doctors is fewer. Diagnosing a patient of ACS with the help of diagnostic criteria, assessing the severity of the disease and deciding on prioritising patients for intervention can hence be challenging. Since majority of the first medical contacts in India happen in the primary care setting, simple and reliable blood tests to assess the severity of the disease are essential.

The Neutrophil-to-Lymphocyte Ratio (NLR) has been used as a novel predictor of inflammation in various conditions. Systemic Immune-inflammation Index (SII), the product of NLR and platelet count, has been proposed as a new biomarker of mortality in various cancers [5-7]. The SII takes into account the proinflammatory and the prothrombotic changes in the vasculature. Lately, SII has been studied in stable coronary artery disease [8,9], chronic heart failure [10] and ACS. It has been shown that SII predicts mortality and morbidity in ACS patients receiving coronary intervention [11-13]. It has also been shown to predict the development of atrial fibrillation post STEMI [14]. The SII is also studied in STEMI patients who

develop no-reflow post primary Percutaneous Coronary Intervention (PCI) [15]. However, there are no Indian studies done which assess the role of SII in predicting outcomes in ACS. Also, a large number of patients in developing nations do not undergo any primary intervention and are only treated medically. There are no studies that include patients who receive medical line of management alone. The present study compared SII between the two types of ACS, correlated SII and NLR with ACS severity scores and determined the role of SII in predicting major cardiac events and mortality irrespective of the type of intervention.

MATERIALS AND METHODS

This prospective cohort study was conducted in the Department of General Medicine, Father Muller Medical College Hospital, Mangaluru, Karnataka, India from February 2021 to July 2021. The study included 90 patients (45 STEMI and 45 NSTEMI/UA) aged above 30 years with ACS. The study was approved by the Institutional Ethics Committee (IEC No:FMIEC/CCM/78/2021). The diagnosis of ACS was according to the criteria by the ESC/ACCF/AHA/WHF task force [16].

Inclusion criteria: The STEMI was diagnosed in patients with ST-segment elevation in the Electrocardiogram (ECG) meeting the criteria, (new ST-segment elevation at the J point in two contiguous leads with the cut-off point as greater than 0.1 mV in all leads other than V2 or V3 , in leads V2-V3 the cut-off point is greater than 0.2 mV in males older than 40-year-old and greater than 0.25 in males younger than 40-year-old, or greater than 0.15 mV in females) with symptoms of ischaemia or troponin elevated above the 99th percentile of the upper reference limit.

Exclusion criteria: Patients with evidence of infection (fever with localising symptoms), low platelet count (less than 150,000 cells/mm^3), haematological malignancies, and who underwent thrombolysis were excluded from the study.

Patients with a new onset Left Bundle Branch Block (LBBB) were considered to be in the STEMI group. Sgarbossa's criteria were used in patients with a known LBBB to be considered as STEMI [17]. The NSTEMI was diagnosed in patients with symptoms of ischaemia, with troponin elevated above the 99th percentile of the upper reference limit, but without ST-segment elevation. The UA was diagnosed in patients with symptoms of ischaemia without elevation in biomarkers or ST-elevation meeting the above criteria.

Patients who met the inclusion criteria were consecutively enrolled in the study. Detailed history, clinical examination was performed for all patients. All patients received the standard care of treatment with anticoagulants and antiplatelets (aspirin with clopidogrel or ticagrelor). Beta-blockers, angiotensin receptor blockers, diuretics and other medications were added when indicated. Patients subsequently underwent a PCI or received medical treatment.

Data Collection

The baseline demographic data like age, gender, history of substance abuse and co-morbidities (diabetes mellitus, hypertension, ischaemic heart disease, cerebrovascular disease) were collected. A thorough clinical examination was conducted and vitals (heart rate, blood pressure) were recorded. To assess the severity of the disease, Killip class [18], Thrombolysis In Myocardial Infarction (TIMI) score [19,20] and Global Registry of Acute Coronary Events (GRACE) 2.0 scores [21] were used at admission. Laboratory tests included estimation of total leucocyte counts, differential leucocyte counts, platelets, creatinine, troponin and erythrocyte sedimentation rate. The NLR was calculated as the ratio of neutrophil count to lymphocyte count. SII was calculated as the product of NLR and platelet count [6].

The ECG was taken at admission. A 2-dimensional echocardiography was done within six hours of admission by a cardiologist. Coronary angiogram was performed and the lesion was graded as single, double or triple vessel disease. Since the hospital was a referral centre, with patient population referred from distant areas, many patients were not eligible for primary PCI. All patients were followed up for one month. Outcomes were defined based on the occurrence of Major Adverse Cardiac Events (MACE) or death. The MACE was defined as worsening cardiac function, either as pulmonary oedema, cardiogenic shock, arrhythmias causing haemodynamic instability, recurrent myocardial infarction or death. Follow-up was done as an outpatient or via telephone.

STATISTICAL ANALYSIS

Statistical analysis was conducted using Statistical Package for the Social Sciences (SPSS) statistics, version 22.0 (Armonk, NY: IBM Corp). Kolmogorov-Smirnov test used to assess normality of distribution and parameters were expressed as mean and standard deviation. Independent sample t-test was used to compare parametric variables and Mann-Whitney U was used to compare non parametric variables among the two groups. Chi-square test was used for dichotomous data, and Odds Ratio (OR) and Relative Risk (RR) were calculated. Pearson's correlation coefficient and Spearman's rank correlation were used to correlate parametric and non parametric variables respectively. Receiver Operator Curve (ROC) was used to predict outcomes and the area under the curve was calculated. Survival analysis was conducted by Kaplan-Meier analysis and the log-rank test was used to determine significant difference in survival between the two groups. Cox regression analysis was used to determine predictors of survival. Tests were considered to be statistically significant if the p-value was <0.05.

RESULTS

The baseline characteristics of the population in both groups are given in [Table/Fig-1]. Both the groups were comparable in terms of age, gender and co-morbidities. History of ischaemic heart disease was significantly higher in the NSTEMI/UA group. The STEMI group had a lower mean arterial pressure and EF. The NLR and SII were higher in the STEMI group. In the overall study group, history of substance abuse was present in 40 (44.4%). The most common ECG abnormality was inferior STEMI 24 (26.7%) in the STEMI group and precordial t-wave inversions in the NSTEMI/UA group. About 10 (11.1%) had an apparently normal ECG [Table/Fig-2]. Echocardiographic findings commonly seen were in the anterolateral and inferior wall [Table/Fig-2]. Eight (8.9%) had a normal echocardiogram. A total of 81 patients underwent coronary angiogram, out of which triple vessel occlusion was the commonest finding. The death rate in the STEMI group [n=8 (17.8%)] was higher than in the NSTEMI/UA group [n=5 (11.1%)] (p-value=0.36).

Based on the cut-off values of 13.9 for SII and 4.62 for NLR, patients were divided into two groups. A high SII was associated with a higher risk of MACE {OR=13.82 (95% Confidence Interval-CI of 2.8-66.7), p-value=0.000} and with death {OR=4.413 (1.24-15.66), p-value=0.015}. High NLR was also associated with a higher risk of MACE {OR=5.94 (1.52-23.1), p-value=0.005}. However, high NLR was not associated with a risk of death (p-value=0.18).

To determine the predictive value of SII an NLR, ROC was used and the area under the curve was calculated. For MACE, SII had a better predictability when compared to NLR or TLC [Table/Fig-3].

An SII of 13.9 had a sensitivity of 75%, specificity of 69%, negative predictive value of 96%, and a positive predictive value of 34% for predicting MACE. The NLR had a lower sensitivity (68.7%), specificity (60.8%) and negative predictive value (90%) to predict MACE. The SII was better at predicting death when compared to NLR or TLC, but it was not statistically significant [Table/Fig-4].

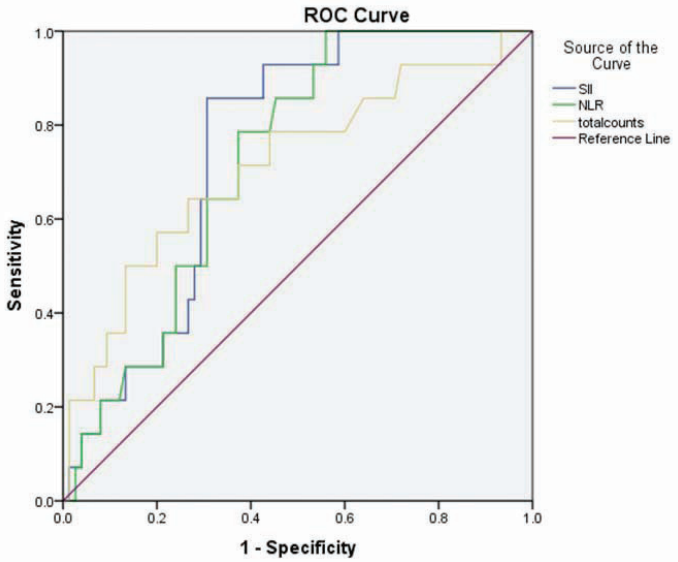
There was a significant correlation between SII and left ventricular EF (r=-0.28), Killip class (0.5), GRACE 2.0 score (0.529) and TIMI score (0.417). SII showed the strongest and most significant correlation with severity scores in comparison to other inflammatory markers. The TLC correlated better with troponin I and left ventricular EF.

Parameters	Total group Mean±SD (Min- Max)	STEMI Mean±SD (Min- Max)	NSTEMI/UA Mean±SD (Min- Max)	t-test/Chi-square test (p-value)
Age (years)	60.91±11.2 (30-87)	61.06±10.97 (38-87)	60.75±11.56 (30-86)	0.13 (0.89)*
Females [n (%)]	32 (35.6%)	14 (31.1%)	18 (40%)	0.77 (0.37)#
Co-morbidities				
Diabetes [n (%)]	41 (45.6%)	19 (42.2%)	22 (48.9%)	0.4 (0.52)#
Hypertension [n (%)]	54 (60%)	26 (57.7%)	28 (62.2%)	0.18 (0.66)#
Ischaemic heart disease [n (%)]	10 (11.1%)	2 (4.4%)	8 (17.8%)	4.05 (0.04)#
No co-morbidities [n (%)]	25 (27.7%)	16 (35.6%)	9 (20%)	2.71 (0.09)#
Vital				
Pulse rate (beats/min)	84.57±18.59 (35-147)	84.11±21.5 (35-147)	85.04±15.38 (55-130)	-0.23 (0.813)*
Mean arterial pressure (mmHg)	102.9±19.32 (65.3-153.3)	97.9±22 (65.3-153.3)	107.89±14.83 (81.67-146.67)	-2.5 **(0.013)***
Laboratory test				
Troponin I (ng/mL)	3.45±4.2 (n=89)	4.41±4.4 (0.06-10) (n=45)	2.47±3.7 (0-10) (n=44)	2.22 **(0.02)***
Ejection fraction (%)	45.80±10.30 (25-62) (n=88)	43.04±9.7 (27-61) (n=45)	48.69±10.1 (25-62) (n=43)	-2.6 **(0.009)***
Haemoglobin (gm%)	13.28±1.73 (7.4-16.5)	13.14±1.93 (7.4-16.5)	13.41±1.50 (9.8-16.1)	-0.74 (0.45)*
Erythrocyte sedimentation rate (mm in 1 hour)	24.70±24.78 (3-150) (n=65)	30.81±28.8 (3-150) (n=32)	18.78±18.74 (3-98) (n=33)	2.0 **(0.05)***
Total leucocyte count (cells/mm^3)	11359±3824 (4300-25000)	12838±3326 (6000-19700)	9873±3702 (4300-25000)	3.9 **(<0.001)***
Creatinine value	1.09±0.24 (0.61-1.32)	1.11±0.16 (0. 73-1.32)	1.02±0.13 (0.61-1.28)	0.16 (0.78)*
Differential count				
Neutrophil (%)	71.9±2.64 (42-96)	78.4±9.23 (48-96)	65.44±12.34 (42-92)	5.6 **(<0.001)***
Lymphocyte (%)	19.7±9.62 (4-44)	14.48±6.6 (4-31)	25.06±9.29 (5-44)	6.2 **(<0.001)***
Eosinophil (%)	2.34±3.04 (0-22)	1.66±1.93 (0-11)	3.02±3.75 (0-22)	-2.1 **(0.035)***
Monocyte (%)	5.9±2.27 (0-10)	5.44±2.51 (0-10)	6.35±1.93 (1-10)	-1.9 (0.06)*
Platelet (lakh cells/mm^3)	2.82±0.65 (1.51-5.10)	2.89±0.65 (1.77-4.84)	2.75±0.65 (1.51-5.10)	0.97 (0.33)*
Neutrophil-to-lymphocyte ratio	5.3±4.27 (1.05-24)	7.13±4.63 (1.55-24)	3.46±2.92 (1.05-18.4)	4.49 **(0.001)***
Systemic immune-inflammation index	15.35±15.39 (2.42-116.16)	20.9±18.13 (5.26-116.16)	9.79±9.35 (2.42-55.38)	3.65 **(<0.001)***
Random blood sugar (mg/dL)	197.9±93.7 (83-490)	199.8±90.16 (108-439)	196±98.2 (83-490)	0.19 (0.84)*
Glycated haemoglobin (gm%)	7.27±1.84 (5.1-13.2)	7.08±1.73 (5.2-12.3)	7.5±1.95 (5.1-13.2)	-1.1 (0.28)*
Major adverse cardiac event	16 (17.7%)	11 (24.4%)	5 (11.11%)	2.7 (0.09)*
Scores to assess severity of disease	**Median; IQR (min-max)**	**Median; IQR (min-max)**	**Median; IQR (min-max)**	**Mann-Whitney test**
Thrombolysis in Myocardial Infarction (TIMI) Score	3;3 (0-11)	5;4 (1-11)	3;3 (0-6)	-4.4 **(<0.001)***
Global Registry of Acute Coronary Events (GRACE) 2.0 score	108;42.25 (33-204)	122;33 (64-204)	91;38 (33-145)	-4.6 **(<0.001)***
Killip class	1;1 (1-4)	2:1.5 (1-4)	1;1 (1-3)	-2.8 **(0.005)***

[Table/Fig-1]: Baseline characteristics of the study population (45 in each group). *p-value calculated by independent test; #p-value calculated by Chi-square

Parameters	N (%)
History of substance use (n=40)	
Smoking only	15 (17%)
Alcohol only	6 (7%)
Both	19 (21%)
ECG changes (n=81)	
Inferior STEMI	18 (20%)
Anterolateral STEMI	17 (19%)
Precordial t-wave inversion	17 (19%)
Sinus rhythm	10 (11%)
Poor r-wave progression	5 (5.6%)
Inferolateral ST-depression	5 (5.6%)
Left bundle branch block	4 (4.4%)
Right bundle branch block	2 (2.2%)
Sinus bradycardia	2 (2.2%)
Sinus tachycardia	1 (1.1%)
Echocardiogram (n=87)	
Anterolateral wall hypokinesia	26 (26.8%)
Inferior wall hypokinesia	18 (20%)
Lateral wall hypokinesia	12 (13.3%)
Global hypokinesia	8 (8.9%)
Normal	8 (8.9%)
Left ventricular hypertrophy	5 (5.6%)
Inferolateral wall hypokinesia	5 (5.6%)
Anterior wall hypokinesia	5 (5.6%)
Type of intervention (n=90)	
Percutaneous intervention	51 (57%)
Medical management	39 (43.3%)
Coronary angiogram (n=81)	
Single vessel disease	25 (28%)
Double vessel disease	18 (20%)
Triple vessel disease	38 (42%)

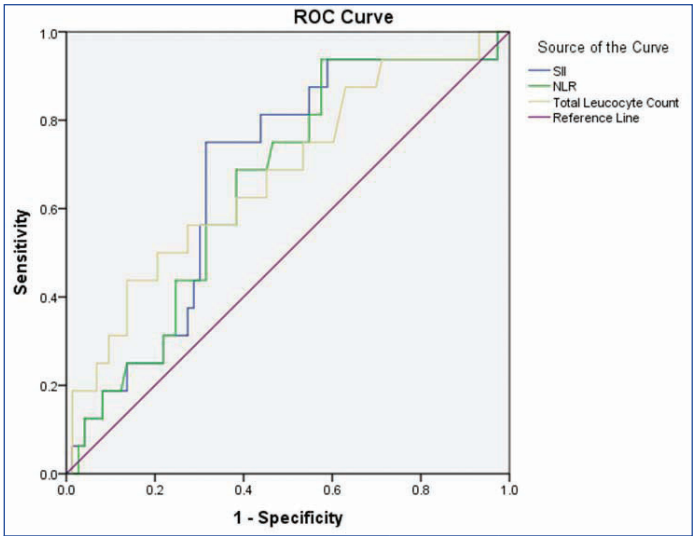
[Table/Fig-2]: Characteristics of the overall population.



Parameter	AUC	95% CI	Significance (p-value)
SII	0.678	0.54-0.81	**0.026**
NLR	0.65	0.50-0.79	0.053

[Table/Fig-3]: Receiver Operator Curve (ROC) for MACE.

All patients were followed-up for a duration of 30 days. Overall incidence in the time period was 17.7% for MACE, and 14.4% for death. Survival analysis showed that MACE and death were considerably higher in the high SII group than the low SII group. There were 52% MACE events in the high SII group compared to 8% in the low SII group, and 34% deaths in the high SII group compared to 8% in the low SII group [Table/Fig-5,6].



Parameter	AUC	95% CI	Significance (p-value)
Systemic immune-inflammation index	0.63	0.48-0.78	0.13
Neutrophil-to-lymphocyte ratio	0.62	0.46-0.77	0.17

[Table/Fig-4]: Receiver Operator Curve (ROC) for death.

Variables	Overall group	STEMI group	NSTEMI/UA group
Age ($)	0.11 (0.29)	0.03 (0.83)	0.28 (0.06)
Pulse rate ($)	0.11 (0.28)	0.15 (0.30)	0.07 (0.62)
Mean arterial pressure ($)	0.03 (0.77)	0.16 (0.29)	0.08 (0.58)
Haemoglobin ($)	-0.09 (0.39)	-0.05 (0.74)	-0.11 (0.45)
ESR ($)	0.26 **(0.03)**	0.22 (0.21)	0.11 (0.51)
Glycated Haemoglobin (HbA1c) ($)	-0.09 (0.45)	-0.14 (0.34)	0.13 (0.39)
Troponin I ($)	0.07 (0.48)	-0.05 (0.72)	0.09 (0.56)
Ejection fraction ($)	-0.28 **(0.01)**	-0.11 (0.48)	-0.38 **(0.01)**
Killip class (#)	0.502 **(<0.001)**	0.41 **(0.005)**	0.37 **(0.01)**
GRACE 2.0 score (#)	0.529 **(<0.001)**	0.15 (0.31)	0.37 **(0.012)**
TIMI score (#)	0.417 **(<0.001)**	0.17 (0.25)	0.22 (0.14)

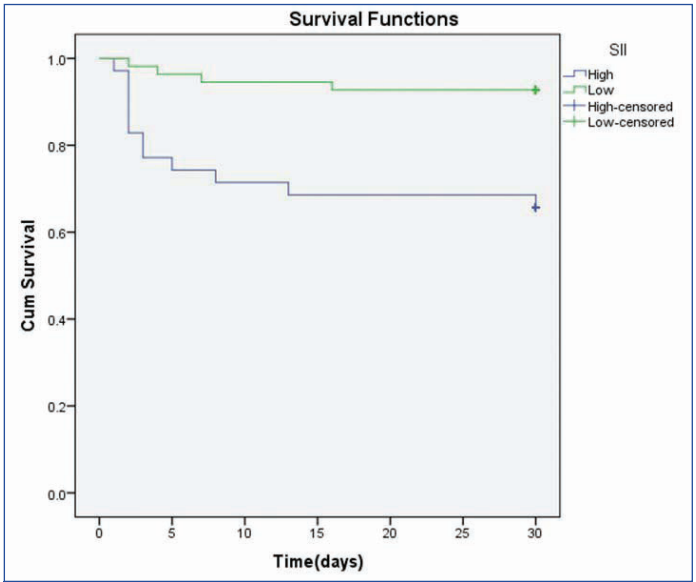
[Table/Fig-5]: Correlation between SII and other variables.
{Pearson's ($)/Spearman's (#) coefficient (p-value)}; ESR: Erythrocyte sedimentation rate; GRACE: Global registry of acute coronary events; TIMI: Thrombolysis in myocardial infarction

Parameters	TLC	NLR	SII
Killip score	0.43 (<0.001)	0.478 (<0.001)	0.502 **(<0.001)**
GRACE 2.0 score	0.289 (0.006)	0.502 (<0.001)	0.529 **(<0.001)**
TIMI score	0.316 (0.003)	0.421 (<0.001)	0.417 **(<0.001)**

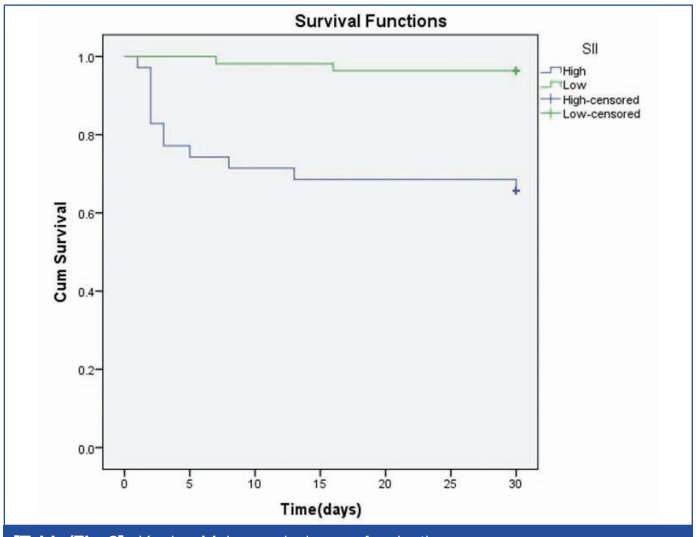
[Table/Fig-6]: Correlation between ACS severity scores and inflammatory markers {Spearman's coefficient (p-value)}
TLC: Total leucocyte count; NLR: Neutrophil-to-lymphocyte ratio; SII: Systemic immune-inflammation index; GRACE: Global registry of acute coronary events; TIMI: Thrombolysis in myocardial infarction

The mean duration for MACE was 21.8 days (95% CI of 17.55-26.04 days) in the high SII group compared to 28.34 days (95% CI of 26.73-29.95) in the low SII group which was significant (Log-rank=11.228, p-value=0.001). The survival curve for NLR was less significant in comparison to SII (Log-rank=4.65, p-value=0.031). However, there was no significance between the TLC groups (Log-rank=3.34, p-value=0.067). The mean survival duration was 24.5 (95% CI of 20.9-28.11) days in the high SII group compared to 29.32 (95% CI 28.23-30.41) days in the low SII group which was significant (Log-rank=6.441, p-value=0.011). There were no differences in the survival duration between the NLR (Log-rank=1.95, p-value=0.16) or the TLC groups (Log-rank=2.02, p-value=0.155).

Cox regression analysis showed that high SII was a predictor for MACE {Hazards Ratio (HR)=5.48; 95% CI of 1.76-17.04, p-value=0.001} and death (HR=4.05; 95% CI of 1.2-13.1, p-value=0.012). Univariate analysis showed that EF, TIMI score, Killip class, GRACE 2.0 score, NLR, SII, hypertension and the type of intervention were predictors of MACE. For predicting death TIMI, Killip class, GRACE 2.0 score, SII and the type of intervention had statistical significance but not NLR or EF. The SII was better than EF, TIMI score, Killip class, GRACE 2.0 score and NLR as a predictor of MACE. Only the type of intervention (medical or PCI) had a higher hazards ratio than SII. In multivariate analysis, after adjusting for haemoglobin, total counts and NLR, SII remained a predictor for MACE. SII predicted MACE, even after adjusting for the type of intervention. The association between SII and death did not remain after adjusting for the type of intervention. There was however a trend towards significance (HR=2.97, 95% CI 0.9-9.7, p-value=0.07) [Table/Fig-7-9].



[Table/Fig-7]: Kaplan-Meier survival curve for MACE.



[Table/Fig-8]: Kaplan-Meier survival curve for death.

DISCUSSION

The study was done to determine the usefulness of SII as a marker of inflammation in patients with ACS, and its role in prognosticating patients. SII was significantly higher in patients with STEMI than with NSTEMI or UA. SII correlated with Killip, TIMI and GRACE 2.0 scores better than other inflammatory markers. The SII had a better predictive value than NLR or total counts for MACE and death. Univariate analysis showed that SII was an independent and strong predictor of MACE and death. The SII was the only laboratory parameter that could predict survival at the one-month interval. SII can hence be considered as an independent and strong predictor of cardiovascular mortality and disease severity in ACS. Furthermore, SII in the present study was better at predicting MACE

Parameters	MACE (n=16)			Death (n=13)		
	Hazards ratio	95% Confidence interval	Significance	Hazards ratio	95% Glycated haemoglobin	Significance
Age	1.03	0.99-1.08	0.11	1.034	0.98-1.08	0.18
Pulse	1.01	0.98-1.03	0.37	0.999	0.96-1.003	0.93
MAP	0.97	0.94-1	0.091	0.97	0.95-1.01	0.17
Ejection fraction	0.94	0.90-0.99	0.027	0.96	0,91-1.01	0.17
TIMI score	1.29	1.1-1.5	0.002	1.28	1.07-1.52	**0.009**
Killip class	2.76	1.77-4.32	0.000	2.94	1.76-4.9	**<0.001**
GRACE 2.0 score	1.027	1.013-1.041	0.000	1.02	1.006-1.037	**0.009**
Haemoglobin	0.68	0.522-0.90	0.010	0.73	0.54-0.99	0.052
Total leucocyte count	2.41	0.9-6.49	0.079	2.15	0.72-6.62	0.168
NLR	2.98	1.03-8.68	0.034	2.175	0.71-6.65	0.165
SII	5.48	1.76-17.44	0.001	4.05	1.24-13.1	**0.014**
Hypertension	3.14	0.85-11.03	0.047	2.32	0.64-8.84	0.171
Diabetes mellitus	2.12	0.771-5.83	0.138	1.9	0.68-5.94	0.233
Type of intervention	7.57	2.17-33.3	0.001	9.90	2.22-50	**<0.001**

[Table/Fig-9]: Univariate analysis for predictors of MACE and death.
MACE: Major adverse cardiac events; MAP: Mean arterial pressure; NLR: Neutrophil-to-lymphocyte ratio; SII: Systemic immune-inflammation index

or death when compared to cardiac troponin or left ventricular ejection fraction.

The SII has been used as a marker of inflammation in various malignancies, as a predictor of mortality. The SII has been also studied lately in patients with cardiovascular disease. Higher SII has been shown to increase the risk of progression to complications in patients with stable coronary artery disease [8,9]. It has also shown to be a predictor of cardiac events and mortality in elderly patients post PCI in ACS [3]. The present study is the first study which analysed the role of SII in predicting outcomes in ACS patient irrespective of age and the type of intervention, and correlated it with various severity scores.

The findings of the present study are consistent with the study done by Huang J et al., [11]. Similar to the present study, they showed that subjects with higher SII had a lower survival rate. However, they only included elderly patients above the age of 65 years who underwent PCI in contrast to the present study, which included patients above 30 years irrespective of the intervention. Ocal L et al., showed that SII predicted in-hospital and long term events in STEMI patients [12]. A recent large retrospective study also showed SII to predict 30-day mortality in ACS, but the type of intervention received was not specified [13]. In patients with STEMI, SII has a similar predictive power as C-reactive protein, and better than NLR in predicting atrial fibrillation [14]. Esenboğa K et al. demonstrated that SII independently predicted no-reflow phenomenon post PCI in STEMI [15]. SII has also been used to study the effect of antiplatelets (ticagrelor and clopidogrel), as a marker of inflammation post ACS [22].

Several studies have shown that NLR is an independent predictor of all-cause mortality in ACS [23,24]. The present study showed that NLR was a predictor of outcomes in ACS, but when SII was added to the model, the predictability of NLR became insignificant. The SII also correlated better with severity scores in the present study.

The study has many advantages. It was a prospective cohort study with defined outcomes. The SII was compared with other haematological parameters and correlated with risk scores. An SII of 13.9 had a negative predictive value of 96% for major adverse cardiac events [Table/Fig-3]. This can have important practical implications in resource-scarce settings especially in rural India where the availability of treatment options is limited. The SII is a cost-effective laboratory parameter, calculated from the routine blood haemogram, which is a widely available test even in remote settings. The interpretation of SII does not require a specialist as there is no interobserver variability in interpreting the test. The high negative predictive value makes it a useful decision-making tool. Alongside clinical symptoms, it can be used as a parameter by which critical patients can be referred early especially in case of NSTEMI/UA where the ECG changes are not apparent, and when there is non availability of cardiac enzymes.

The study also validated the severity scores used in ACS, like the TIMI and the GRACE 2.0 scores. Both TIMI score and GRACE 2.0 scores have been validated to be prognosticators of ACS in various studies [19,25]. The GRACE 2.0 score and the Killip class were better predictors of mortality and adverse cardiac events than the TIMI score in our study.

Limitation(s)

It was a study done in a single centre, with a small sample size. The SII is a dynamic index, and its value can change depending on the presence of co-existing infections which can occur in patients admitted in critical care settings. Hence, the findings may not be generalisable in patients with co-existing sepsis. Also, this was a short-term follow-up study and the long-term outcomes were not established. The SII was measured at admission and was not serially monitored through the course of hospital stay. Despite all these limitations, this study shows a promising role of SII as a tool for decision making in patients with ACS. The role of inflammation as a driver of the disease process in ACS is also supported by the present study. Further multicentric studies, with a larger study population and a longer follow-up period are needed for a better understanding of the role of SII in ACS.

CONCLUSION(S)

The SII is an independent prognostic marker for MACE and short-term mortality ACS. The SII also correlates strongly with Killip class, TIMI and GRACE 2.0 scores. The SII was higher in the STEMI group compared to the NSTEMI/UA group. The SII is an inexpensive, readily available parameter which has a good predictive value in categorising high-risk patients, especially in resource-scarce settings. The SII is better than TLC and NLR in predicting short term outcomes.

REFERENCES

[1] World Health Organization. World health statistics 2021: monitoring health for the SDGs, sustainable development goals. Geneva: World Health Organization; 2021. [cited 2021 Nov 26].
[2] Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. Journal of the American College of Cardiology. 2020;76(25):2982-3021.
[3] Prabhakaran D, Jeemon P, Roy A. Cardiovascular diseases in India. Circulation. 2016;133(16):1605-20.

[4] Global Health Workforce statistics database [Internet]. [cited 2021 Nov 26]. Available from: https://www.who.int/data/gho/data/themes/topics/health-workforce.
[5] Huang H, Liu Q, Zhu L, Zhang Y, Lu X, Wu Y, et al. Prognostic value of preoperative systemic immune-inflammation index in patients with cervical cancer. Sci Rep. 2019;9(1):3284.
[6] Hu B, Yang XR, Xu Y, Sun YF, Sun C, Guo W, et al. Systemic Immune-inflammation index predicts prognosis of patients after curative resection for hepatocellular carcinoma. Clin Cancer Res. 2014;20(23):6212-22.
[7] Li C, Tian W, Zhao F, Li M, Ye Q, Wei Y, et al. Systemic immune-inflammation index, SII, for prognosis of elderly patients with newly diagnosed tumors. Oncotarget. 2018;9(82):35293-99.
[8] Yang YL, Wu CH, Hsu PF, Chen SC, Huang SS, Chan WL, et al. Systemic immune-inflammation index (SII) predicted clinical outcome in patients with coronary artery disease. Eur J Clin Invest. 2020;50(5):e13230.
[9] Candemir M, Kiziltunç E, Nurkoç S, Şahinarslan A. Relationship between Systemic Immune-Inflammation Index (SII) and the severity of stable coronary artery disease. Angiology. 2021;72(6):575-81.
[10] Seo M, Yamada T, Morita T, Furukawa Y, Tamaki S, Iwasaki Y, et al. P589Prognostic value of systemic immune-inflammation index in patients with chronic heart failure. Eur Heart J. 2018;39. Available from: https://doi.org/10.1093/eurheartj/ehy564.P589.
[11] Huang J, Zhang Q, Wang R, Ji H, Chen Y, Quan X, et al. Systemic Immune-Inflammatory Index Predicts Clinical Outcomes for Elderly Patients with Acute Myocardial Infarction Receiving Percutaneous Coronary Intervention. Med Sci Monit. 2019;25:9690-701.
[12] Ocal L, Keskin M, Cersit S, Eren H, Cakmak EO, Cakir H, et al. Systemic immune-inflammation index predicts in-hospital and long-term outcomes in patients with ST-segment elevation myocardial infarction. Eur Heart J. 2021;42.
[13] Su G, Zhang Y, Xiao R, Zhang T, Gong B. Systemic immune-inflammation index as a promising predictor of mortality in patients with acute coronary syndrome: A real-world study. J Int Med Res. 2021;49(5):03000605211016274.
[14] Bağcı A, Aksoy F. Systemic immune–inflammation index predicts new-onset atrial fibrillation after ST elevation myocardial infarction. Biomarkers in Medicine. 2021;15(10):731-39.
[15] Esenboğa K, Kurtul A, Yamantürk YY, Tan TS, Tutar DE. Systemic immune-inflammation index predicts no-reflow phenomenon after primary percutaneous coronary intervention. Acta Cardiologica. 2021;0(0):01-08.
[16] Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD et al. Third universal definition of myocardial infarction. European Heart Journal. 2012;33(20):2551-67.
[17] Das D, McGrath BM. Sgarbossa criteria for acute myocardial infarction. CMAJ. 2016;188(15):E395.
[18] Killip T, Kimball JT. Treatment of myocardial infarction in a coronary care unit: A Two year experience with 250 patients. Am J Cardiol. 1967;20(4):457-64.
[19] Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, et al. The TIMI risk score for unstable angina/non ST elevation MI: A method for prognostication and therapeutic decision making. JAMA. 2000;284(7):835-42.
[20] Morrow DA, Antman EM, Charlesworth A, Cairns R, Murphy SA, de Lemos JA, et al. TIMI risk score for st-elevation myocardial infarction: A convenient, bedside, clinical score for risk assessment at presentation. Circulation. 2000;102(17):2031-37.
[21] Fox KAA, FitzGerald G, Puymirat E, Huang W, Carruthers K, Simon T, et al. Should patients with acute coronary disease be stratified for management according to their risk? Derivation, external validation and outcomes using the updated GRACE risk score. BMJ Open. 2014;4(2):e004425.
[22] Adali MK, Buber I, Kilic O, Turkoz A, Yilmaz S. Ticagrelor improves systemic immune-inflammation index in acute coronary syndrome patients. Acta Cardiologica. 2021;01-07.
[23] Bajari R, Tak S. Predictive prognostic value of neutrophil–lymphocytes ratio in acute coronary syndrome. Indian Heart J. 2017;69(Suppl 1):S46-50.
[24] Angkananard T, Anothaisintawee T, McEvoy M, Attia J, Thakkinstian A. Neutrophil lymphocyte ratio and cardiovascular disease risk: A systematic review and meta-analysis. Biomed Res Int. 2018;2018:e2703518.
[25] Chen YH, Huang SS, Lin SJ. TIMI and GRACE risk scores predict both short-term and long-term outcomes in chinese patients with acute myocardial infarction. Acta Cardiol Sin. 2018;34(1):04-12.

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