Cardiovascular Topics

Systemic immune–inflammation index, and neutrophil-to-lymphocyte and platelet-to-lymphocyte ratios can predict clinical outcomes in patients with acute coronary syndrome

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Abstract

Objective: Inflammatory mechanisms play an important role in the pathogenesis of atherosclerosis and myocardial infarction. The clinical and prognostic importance of inflammatory parameters, such as neutrophil–lymphocyte (NLR) and platelet–lymphocyte ratios (PLR) in complete blood counts in acute myocardial infarction and other cardiovascular diseases has been demonstrated. However, systemic immune–inflammation index (SII) calculated from neutrophils, lymphocytes and platelets in the complete blood cell count has not been studied sufficiently and is thought to provide a better prediction. This study investigated whether haematological parameters such as SII, NLR and PLR were associated with clinical outcomes in acute coronary syndrome (ACS) patients.

Methods: We included 1 103 patients who underwent coronary angiography for ACS between January 2017 and December 2021. The association between major adverse cardiac events (MACE) that developed in hospital and at 50 months of follow up and SII, NLR and PLR was compared. Long-term MACE were defined as mortality, re-infarction and target-vessel revascularisation. SII was calculated using the formula: NLR × total platelet count in the peripheral blood (per mm^3).

Results: Of the 1 103 patients, 403 were diagnosed with ST-elevation myocardial infarction and 700 with non-ST-elevation myocardial infarction. The patients were divided into a MACE and a non-MACE group. In hospital and during the 50-month follow up, 195 MACE were observed. SII, PLR and NLR were found to be statistically significantly higher in the MACE group ($p < 0.001$). SII, C-reactive protein level, age and white blood cell count were independent predictors of MACE in ACS patients.

Conclusion: SII was found to be a strong independent predictor of poor outcomes in ACS patients. This predictive power was greater than that of PLR and NLR.

Keywords: acute coronary syndrome, neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, systemic immune–inflammation index

Submitted 8/3/22, accepted 27/2/23

Cardiovasc J Afr 2023; online publication www.cvja.co.za

DOI: 10.5830/CVJA-2023-011

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Cardiovascular diseases, mostly acute myocardial infarction, are still the most common cause of mortality and morbidity worldwide and lead to 17.9 million deaths, according to World Health Organisation data. Following acute myocardial infarction, rapid percutaneous coronary intervention (PCI) and revascularisation are the most effective treatments that affect the prognosis by limiting the infarct area and reducing the development of heart failure and other cardiovascular complications. Despite advances in PCI technology, increased experience and many risk-prediction models, major adverse cardiovascular events unfortunately still continue after acute myocardial infarction.

Inflammation is the key point of the atherosclerosis mechanism.[1] Many different factors play a role in the complex inflammatory response in acute myocardial infarction.[2] Neutrophil levels increase first in the inflammatory response following acute myocardial infarction and peak within one to three days.[3] Thereafter, monocyte and platelet levels increase due to increased adrenaline and glucocorticoid levels, and lymphocyte levels decrease. Many studies have shown the effect of increased inflammatory parameters such as neutrophil–lymphocyte ratio (NLR), platelet–lymphocyte ratio (PLR) and monocyte-to-lymphocyte ratio in blood counts in response to an excessive inflammatory response on the prognosis of acute myocardial infarction and other cardiovascular diseases in the short and long term.[4-6]

Systemic immune–inflammation index (SII), a novel inflammation-related index, is a comprehensive combination based on peripheral lymphocyte, neutrophil and platelet counts.

Although cardiovascular endpoints with NLR and PLR have been shown in some studies, their relationship with SII has not been shown sufficiently. It has however been shown that this index strongly predicts prognosis in malignancies,[7,8] and it has recently been studied in cardiovascular diseases.[9] In this study, we planned to compare the effect of a new inflammatory marker, the SII, and the more well-known parameters, NLR and PLR on mortality, re-infarction and target-vessel revascularisation in patients with acute coronary syndrome (ACS).

Methods

We included 1 103 patients with a diagnosis of acute myocardial infarction who underwent coronary angiography between January 2017 and December 2021. The inclusion criteria were as follows: 403 patients with ST-elevation myocardial infarction (STEMI) and 700 with non-ST-elevation myocardial infarction (NSTEMI) who were diagnosed based on the European Society of Cardiology guidelines on the fourth universal definition of myocardial infarction.[10] The hospital angiographic records were screened retrospectively.

We excluded patients with cardiogenic shock, severe infection, major surgery, bleeding, aortic dissection, myocarditis, endocarditis, hypertrophic cardiomyopathy, acute pulmonary embolism, stroke and tumour over the previous three months. We also excluded patients with no complete clinical data or on drug therapy potentially affecting coagulation, as well as those on whom coronary angiography was not performed and medically followed up.

All patients were followed up by a cardiovascular physician at an out-patient visit, and national medical records for all subjects were obtained. Long-term major adverse cardiac events (MACE) were defined as all-cause mortality, non-fatal re-infarction and repeat target-vessel revascularisation. The patients were divided into a MACE and a non-MACE group based on 50-month follow-up results. This study was approved by the local ethics committee (ethics committee date: 13.01.2022. number: 2022-265) and complied with the Declaration of Helsinki.

Current practice guidelines were followed for coronary interventions and the data were recorded in digital storage for quantitative analysis. The access site for coronary angiography was the femoral artery with the Judkins technique. Two experienced interventional cardiologists estimated the degree of coronary stenosis visually. Significant stenosis was defined as a luminal narrowing of > 50% in a major sub-epicardial vessel (left anterior descending, left circumflex or right coronary artery).

After stent placement, prasugrel, ticagrelor or clopidogrel were used for at least one year, and aspirin was used indefinitely.

Table 1. Baseline clinic and demographic characteristics of patients in the MACE and non-MACE groups

	Total	*MACE*		*Univariate regression*		
Variables	*(n = 1 103)*	*No (n = 908)*	*Yes (n = 195)*	*HR*	*95% CI*	p-*value*
Gender, *n* (%)						
Men	759 (68.8)	636 (70.0)	123 (63.1)	ref		
Women	344 (31.2)	272 (30.0)	72 (36.9)	1.30	0.97–1.74	0.081
Age, years, median (range)	68.2 ± 12.3	66.3 ± 11.8	77.3 ± 10.6	1.07	1.06–1.09	< 0.001*
Smoking, *n* (%)	212 (19.2)	189 (20.8)	23 (11.8)	0.53	0.34–0.82	0.004*
Hypertension, *n* (%)	592 (53.7)	495 (54.5)	97 (49.7)	0.79	0.60–1.05	0.104
Diabetes mellitus, *n* (%)	307 (27.8)	250 (27.5)	57 (29.2)	1.13	0.83–1.54	0.445
CHD, *n* (%)	178 (16.1)	143 (15.7)	35 (17.9)	1.17	0.81–1.68	0.413
Hyperlipidaemia, *n* (%)	625 (56.7)	539 (59.4)	86 (44.1)	0.61	0.46–0.81	< 0.001*
CHF, *n* (%)	8 (0.7)	3 (0.3)	5 (2.6)	4.42	1.82–10.76	< 0.001*
CRF, *n* (%)	18 (1.6)	10 (1.1)	8 (4.1)	2.11	1.01–4.42	0.048*
MI type, *n* (%)						
STEMI	403 (36.5)	327 (36.0)	76 (39.0)	ref		
NSTEMI	700 (63.5)	581 (64.0)	119 (61.0)	0.94	0.71–1.26	0.694
WBC (×10³ cells/µl)	9.5 (7.7-11.4)	9.1 (7.4–10.7)	12.5 (10.1–14.7)	1.24	1.21–1.28	< 0.001*
Haemoglobin (g/dl)	13.8 ± 1.8	14 ± 1.8	13.2 ± 1.8	0.79	0.73–0.86	< 0.001*
Neutrophil (×10³ cells/µl)	6.2 (4.6–7.8)	5.8 (4.4–7.1)	9.8 (7.6–12)	1.02	1.01–1.03	< 0.001*
Lymphocyte (×10³ cells/µl)	2.3 (1.6–3)	2.4 (1.8–3.1)	1.6 (1.1–2.3)	0.39	0.33–0.48	< 0.001*
Platelets (×10³ cells/µl)	218 (183–264)	217 (183–261)	233 (187–276)	1.03	1.01–1.06	0.007*
LDL-C (mg/dl)	114 (89–140)	116 (92–142)	103.5 (78.5–132)	0.98	0.97–0.99	< 0.001*
(mmol/l)	2.95 (2.31–3.63)	3.00 (2.38–3.68)	2.68 (2.03–3.42)			
Creatinin (mg/dl)	0.9 (0.8–1.1)	0.9 (0.8–1.1)	1.1 (0.9–1.4)	1.00	0.97–1.03	0.931
CRP (mg/dl)	5 (2.2–12)	4.3 (2.1–10)	10 (4.2–30.6)	1.01	1.01–1.01	< 0.001*
NLR	2.6 (1.8–4.2)	2.2 (1.7–3.3)	6.4 (4.2–9.1)	1.02	1.01–1.03	< 0.001*
PLR	98.5 (73–135.3)	91.8 (69.7–124.1)	148.6 (108.2–211.3)	1.02	1.01–1.03	< 0.001*
SII	564 (382.4–941.4)	501.8 (355.9–734.1)	1403.2 (1020–2195.5)	1.03	1.01–1.05	< 0.001*
Follow-up events (MACE)						
Mortality, *n* (%)	183 (16.6)	0 (0.0)	183 (93.8)	–	–	–
TVR, *n* (%)	13 (1.2)	0 (0.0)	13 (6.7)	–	–	–
RMI, *n* (%)	14 (1.3)	0 (0.0)	14 (7.2)	–	–	–

CHD: chronic heart disease, CHF: chronic heart failure, CRF: chronic renal failure, WBC: white blood cell, TVR: target-vessel revascularisation, RMI: re-myocardial infarction, LDL-C: low-density lipoprotein cholesterol, CRP: C-reactive protein, NLR: neutrophil–lymphocyte ratio, PLR: platelet–lymphocyte ratio, SII: serum immune–inflammation index, HR: hazard ratio, CI: confidence interval.
Numerical variables are shown as mean ± standard deviation or median (min–max) and categorical variables as numbers (%). Levels of SII are divided into 100.
*$p < 0.05$ indicates statistical significance.

All treatments were given following the European Society of Cardiology guidelines. The patient's adherence to medical therapy was standardised. According to coronary angiography results, PCI, coronary artery bypass surgery or medical treatment was performed.

The hospital electronic database was used for the results of laboratory parameters. All blood samples were collected within the first hour of admission and analysed in the central laboratory with an automatic blood counter, Beckman Coulter AU 2700 Plus (Beckman Coulter, Tokyo, Japan). Together with the complete blood cell count, creatinine, low-density lipoprotein cholesterol (LDL-C) and C-reactive protein (CRP) levels were measured.

The NLR was defined as the absolute number of neutrophils divided by the absolute number of lymphocytes, and the PLR as the absolute number of platelets by the absolute number of lymphocytes. SII was calculated using the following formula:

SII = NLR × total platelet count in the peripheral blood (per mm^3).

In hospital and 50-month follow-up events were compared with SII, NLR and PLR levels.

Statistical analysis

Statistical analyses of collected data were conducted using IBM SPSS Statistics for Windows 20.0 (IBM Corp, Armonk, NY, USA). Determination of the normally distributed data was conducted using the Kolmogorov–Smirnov test. Numerical variables that had normal distribution are expressed as mean ± standard deviation, while those with non-normal distribution are expressed as median (minimum–maximum). The categorical variables are expressed as numbers and percentages.

Multivariable Cox logistic regression analyses were conducted to establish any possible independent predictors of MACE. Age, gender, smoking, co-morbid conditions and laboratory parameters were included in the multivariable Cox regression model. The threshold value of SII in predicting MACE was determined by the Youden index method in receiver operating characteristic (ROC) curve analysis. Survival plots according to the threshold values of SII were done with Kaplan–Meier analysis. A p-value < 0.05 was taken as statistically significant.

Results

The study population consisted of 1 103 patients (mean age: 68.2 ± 12.3 years) with 759 male (68.8%) and 344 female (31.2%) patients. Of the patients, 700 (63.5%) were diagnosed with NSTEMI and 403 (36.5%) with STEMI. The patients were divided into a MACE and a non-MACE group based on the in-hospital and 50-month follow-up results.

MACE was observed in 195 patients (17.7%), including all-cause mortality in 183 patients (16.6%), myocardial re-infarction in 14 patients (1.3%) and target-vessel revascularisations in 13 patients (1.2%) during the 50-month follow-up period. The demographic and clinical characteristics of the patients are shown in Table 1.

Table 2. Demographic and clinical findings associated with MACE in the STEMI patients

	Total STEMI	*MACE*		*Univariate regression*		
Variables	*(n = 403)*	*No (n = 327)*	*Yes (n = 76)*	*HR*	*95% CI*	p-*value*
Gender, *n* (%)						
Men	304 (75.4)	257 (78.6)	47 (61.8)	ref		
Women	99 (24.6)	70 (21.4)	29 (38.2)	2.00	1.25–3.18	0.004*
Age, years	67.7 ± 12.6	65.9 ± 12.1	75.7 ± 11.5	1.06	1.04–1.08	< 0.001*
Smoker, *n* (%)	109 (27.0)	94 (28.7)	15 (19.7)	0.65	0.37–1.14	0.132
Hypertension, *n* (%)	192 (47.6)	160 (48.9)	32 (42.1)	0.74	0.46–1.17	0.192
Diabetes mellitus, *n* (%)	97 (24.1)	76 (23.2)	21 (27.6)	1.22	0.74–2.03	0.430
CHD, *n* (%)	36 (8.9)	29 (8.9)	7 (9.2)	1.10	0.51–2.40	0.809
Hyperlipidaemia, *n* (%)	239 (59.3)	210 (64.2)	29 (38.2)	0.42	0.26–0.66	< 0.001*
CHF, *n* (%)	2 (0.5)	1 (0.3)	1 (1.3)	2.84	0.39–20.41	0.301
CRF, *n* (%)	9 (2.2)	4 (1.2)	5 (6.6)	2.55	0.93–6.99	0.068
WBC (×10³ cells/µl)	10 (8.2–12.2)	9.6 (8–11.4)	13.2 (10.9–16)	1.24	1.18–1.3	< 0.001*
Haemoglobin (g/dl)	14 ± 1.8	14.1 ± 1.7	13.5 ± 1.9	0.87	0.76–0.98	0.025*
Neutrophils (×10³ cells/µl)	6.7 (5.2–8.5)	6.2 (4.9–7.5)	10.6 (9–13.4)	1.02	1.01–1.03	0.019*
Lymphocytes (×10³ cells/µl)	2.3 (1.6–3)	2.4 (1.7–3.2)	1.7 (1.3–2.3)	0.46	0.34–0.62	< 0.001*
Platelets (×10³ cells/µl)	217 (184–261)	212 (181–258)	240 (209–277)	1.03	1.01–1.05	0.002*
LDL-C (mg/dl)	115 (90–139)	116.5 (92–142)	106.5 (80–131)	0.97	0.95–0.99	0.013*
(mmol/l)	2.98 (2.38–3.60)	3.02 (2.38–3.68)	2.76 (2.07–3.39)			
Creatinine (mg/dl)	1 (0.8–1.2)	1 (0.8–1.2)	1.1 (0.9–1.4)	1.92	1.38–2.68	< 0.001*
CRP (mg/dl)	5.7 (2.4–13.8)	4.9 (2.2–11.7)	10.7 (4.5–43.9)	1.01	1.01–1.02	< 0.001*
NLR	2.9 (1.9–4.8)	2.5 (1.8–3.6)	6.4 (4.7–8.6)	1.23	1.18–1.28	< 0.001*
PLR	99.6 (71.2–137.5)	92.2 (67.4–127.7)	146.3 (106.1–210.8)	1.01	1.01–1.01	< 0.001*
SII	635.3 (407.3–1024)	556.7 (381–783.1)	1592.3 (1026.6–2333.8)	1.08	1.07–1.10	< 0.001*
Follow-up events (MACE)						
Mortality, *n* (%)	72 (17.9)	–	72 (94.7)	–	–	–
TVR, *n* (%)	6 (1.5)	–	6 (7.9)	–	–	–
RMI, *n* (%)	6 (1.5)	–	6 (7.9)	–	–	–

CHD: chronic heart disease, CHF: chronic heart failure, CRF: chronic renal failure, WBC: white blood cell, TVR: target-vessel revascularisation, RMI: re-myocardial infarction, LDL-C: low-density lipoprotein cholesterol, CRP: C-reactive protein, NLR: neutrophil–lymphocyte ratio, PLR: platelet–lymphocyte ratio, SII: serum immune–inflammation index, HR: hazard ratio, CI: confidence interval.
Numerical variables are shown as mean ± standard deviation or median (min–max) and categorical variables as numbers (%). Levels of SII are divided into 100.
*p < 0.05 indicates statistical significance.

Table 3. Demographic and clinical findings associated with MACE in the NSTEMI patients

	Total NSTEMI	*MACE*		*Univariate regression*		
Variables	*(n = 700)*	*No (n = 581)*	*Yes (n = 119)*	*HR*	*95% CI*	p-*value*
Gender, *n* (%)						
Men	455 (65.0)	379 (65.2)	76 (63.9)	ref		
Women	245 (35.0)	202 (34.8)	43 (36.1)	1.03	0.71–1.5	0.879
Age, years	68.5 ± 12.2	66.5 ± 11.6	78.4 ± 9.8	1.08	1.06–1.1	< 0.001*
Smoker, *n* (%)	103 (14.7)	95 (16.4)	8 (6.7)	0.39	0.19–0.79	0.009*
Hypertension, *n* (%)	400 (57.1)	335 (57.7)	65 (54.6)	0.83	0.58–1.19	0.312
Diabetes mellitus, *n* (%)	210 (30.0)	174 (29.9)	36 (30.3)	1.09	0.73–1.61	0.675
CHD, *n* (%)	142 (20.3)	114 (19.6)	28 (23.5)	1.20	0.78–1.83	0.409
Hyperlipidaemia, *n* (%)	386 (55.1)	329 (56.6)	57 (47.9)	0.77	0.54–1.11	0.156
CHF, *n* (%)	6 (0.9)	2 (0.3)	4 (3.4)	5.30	1.95–14.41	0.001*
CRF, *n* (%)	9 (1.3)	6 (1.0)	3 (2.5)	1.72	0.54–5.42	0.357
WBC (×10³ cells/µl)	9.1 (7.4–10.9)	8.8 (7.1–10.3)	11.8 (9.7–14.1)	1.26	1.21–1.31	< 0.001*
Haemoglobin (g/dl)	13.8 ± 1.8	13.9 ± 1.8	12.9 ± 1.8	0.75	0.67–0.83	< 0.001*
Neutrophils (×10³ cells/µl)	5.9 (4.4–7.4)	5.6 (4.2–6.8)	9.4 (7.3–11.3)	1.02	1.01–1.03	0.006*
Lymphocytes (×10³ cells/µl)	2.3 (1.6–3)	2.4 (1.8–3.1)	1.5 (1–2.1)	0.35	0.28–0.45	< 0.001*
Platelets (×10³ cells/µl)	220 (183–266)	219 (183–263)	224 (176–275)	1.00	0.98–1.02	0.400
LDL-C (mg/dl)	113 (89–141)	115 (92–143)	100.5 (78–134)	0.98	0.97–0.99	0.006*
(mmol/l)	2.93 (2.31–3.65)	2.98 (2.38–3.70)	2.60 (2.02–3.47)			
Creatinine (mg/dl)	0.9 (0.8–1.1)	0.9 (0.8–1.1)	1.1 (0.9–1.3)	1.00	0.96–1.03	0.886
CRP (mg/dl)	4.6 (2.2–11)	4.2 (2–9.4)	9.6 (3.8–26)	1.03	1.01–1.06	< 0.001*
NLR	2.4 (1.7–4)	2.1 (1.6–3.1)	6.3 (4.1–9.4)	1.02	1.01–1.04	< 0.001*
PLR	96.5 (74.1–135)	91.7 (70.9–122.5)	151.4 (116.9–215.7)	1.03	1.01–1.05	< 0.001*
SII	530.8 (370–884)	482.2 (341.4–702.5)	1325 (1005.1–2109.8)	1.02	1.01–1.02	< 0.001*
Follow-up events (MACE)						
Mortality, *n* (%)	111 (15.9)	–	111 (93.3)	–	–	–
TVR, *n* (%)	7 (1.0)	–	7 (5.9)	–	–	–
RMI, *n* (%)	8 (1.1)	–	8 (6.7)	–	–	–

CHD: chronic heart disease, CHF: chronic heart failure, CRF: chronic renal failure, WBC: white blood cell, TVR: target-vessel revascularisation, RMI: re-myocardial infarction, LDL-C: low-density lipoprotein cholesterol, CRP: C-reactive protein, NLR: neutrophil–lymphocyte ratio, PLR: platelet–lymphocyte ratio, SII: serum immune–inflammation index, HR: hazard ratio, CI: confidence interval.
Numerical variables are shown as mean ± standard deviation or median (min–max). and categorical variables as numbers (%). Levels of SII are divided into 100.
*$p < 0.05$ indicates statistical significance.

In both patients groups, age, white blood cell (WBC) count, haemoglobin, neutrophil, lymphocyte, platelet, LDL-C, CRP, NLR, PLR and SII levels were determined as potential risk factors for MACE (Table 1). The data were also evaluated separately in NSTEMI and STEMI patients. In STEMI patients, age, WBC, haemoglobin, neutrophil, lymphocyte, platelet, LDL-C, CRP, NLR, PLR and SII levels were found to be potential risk factors associated with MACE (Table 2). In NSTEMI patients, age, WBC, haemoglobin, neutrophil, lymphocyte, platelet, LDL-C, CRP, NLR, PLR and SII levels were found to be potential risk factors associated with MACE (Table 3).

Table 4. Independent predictors of MACE

	Univariate regression		
Variables	*HR*	*95% CI*	p-*value*
All patients			
Age	1.07	1.05–1.08	< 0.001*
WBC	1.19	1.15–1.23	< 0.001*
CRP	1.06	1.01–1.10	0.011*
SII	1.02	1.01–1.03	< 0.001*
	–2 log likelihood = 2211.0; $p < 0.001$		
STEMI patients			
Age	1.04	1.02–1.07	< 0.001*
Hyperlipidaemia	0.49	0.30–0.79	0.004*
WBC	1.12	1.05–1.20	0.001*
CRP	1.05	1.01–1.11	0.047*
SII	1.05	1.02–1.07	< 0.001*
	–2 log likelihood = 734.5; $p < 0.001$		
NSTEMI patients			
Age	1.07	1.06–1.10	< 0.001*
WBC	1.23	1.17–1.29	< 0.001*
CRP	1.07	1.01–1.13	0.011*
SII	1.02	1.01–1.03	< 0.001*
	–2 log likelihood = 1207.9; $p < 0.001$		

WBC: white blood cells, CRP: C-reactive protein, SII: serum immune–inflammation index, HR: hazard ratio, CI: confidence interval.
Levels of SII are divided into 100. *$p < 0.05$ indicates statistical significance.

The independent predictors of risk of MACE in the whole population and myocardial infarction subtypes in multivariate regression models, including potential risk factors, are shown in Table 4. Based on these data, age, WBC, CRP and SII were found to be co-independent predictors in both the whole population and in patients with STEMI and NSTEMI. While a 100-unit increase in SII level in STEMI patients increased the risk of MACE 1.05 times [hazard ratio (HR): 1.05; $p < 0.001$], this increase in risk was found to be 1.02 times in NSTEMI patients (HR: 1.02; $p < 0.001$) (Table 4).

The SII level showed superior diagnostic performance than WBC, CRP, NLR and PLR in predicting MACE in the whole population (Fig. 1A). The predictive value of SII level in predicting MACE in the whole population was found to be > 955.8 with 79.5% sensitivity and 87.9% specificity [area under the curve (AUC) ± standard error (SE): 0.876 ± 0.02; positive predictive value: 58.5%, negative predictive value: 95.2%; $p < 0.001$]. MACE risk was found to be 48.7 times higher in those with SII level > 955.8 compared to those with a level ≤ 955.8

[HR: 48.7; 95% confidence interval (CI) = 33.8–69.9; $p < 0.001$] (Fig. 1B).

The predictive value of SII level in predicting MACE in STEMI patients were found to be > 916.7, with 82.9% sensitivity and 83.2% specificity (AUC ± SE: 0.880 ± 0.02; positive predictive value: 53.4%, negative predictive value: 95.4%; $p < 0.001$). MACE risk was found to be 24.6 times higher in patients with SII level > 916.7 compared to those with a level ≤ 916.7 (HR: 24.6; 95% CI = 14.4–42.1; $p < 0.001$) (Fig. 1C).

The predictive value of SII level in predicting MACE in NSTEMI patients was found to be > 986 with 78.2% sensitivity and 90.7% specificity (AUC ± SE: 0.873 ± 0.02; positive predictive value: 63.3%, negative predictive value: 95.3%; $p < 0.001$). MACE risk was found to be 97.1 times higher in those with SII level > 986 compared to those with a level ≤ 986 (HR: 97.1; 95% CI = 59.2–159.1; $p < 0.001$) (Fig. 1D).

Discussion

The main finding of the study was that SII independently predicted in-hospital and long-term MACE in ACS patients. Although increased levels of NLR and PLR were associated with worse outcomes in ACS patients, they were not found to be independent predictors for MACE. These results show that SII was a much stronger predictor of MACE than NLR and PLR in these ACS patients.

To the best of our knowledge, there is no study that compares these three ratios in ACS patients. Many complicated risk scores with multiple parameters have been developed for early and late risk assessment after myocardial infarction. Instead of these challenging risk scores, easily accessible parameters obtained from complete blood counts can be used.[11]

SII is thought to be an excellent indicator of the immune response and systemic inflammation, consisting of neutrophils, platelets and lymphocytes. To date, there are few studies showing that SII is associated with a poor prognosis in cardiovascular diseases. The relationship between SII and short- and long-term mortality in patients with ACS was first reported by Su *et al*. They indicated that SII was a promising prognostic biomarker in patients with ACS.[12]

In their study, Fan *et al*. showed that NLR with SII was an independent predictor of MACE in ACS patients who underwent PCI.[13] In a study by Yang *et al*. in 5 602 patients with chronic coronary artery disease who underwent PCI, SII was a better predictor for major cardiovascular events than traditional risk factors.[14] In another study, SII was found to be associated with isolated coronary ectasia.[15] In a study of 510 patients,

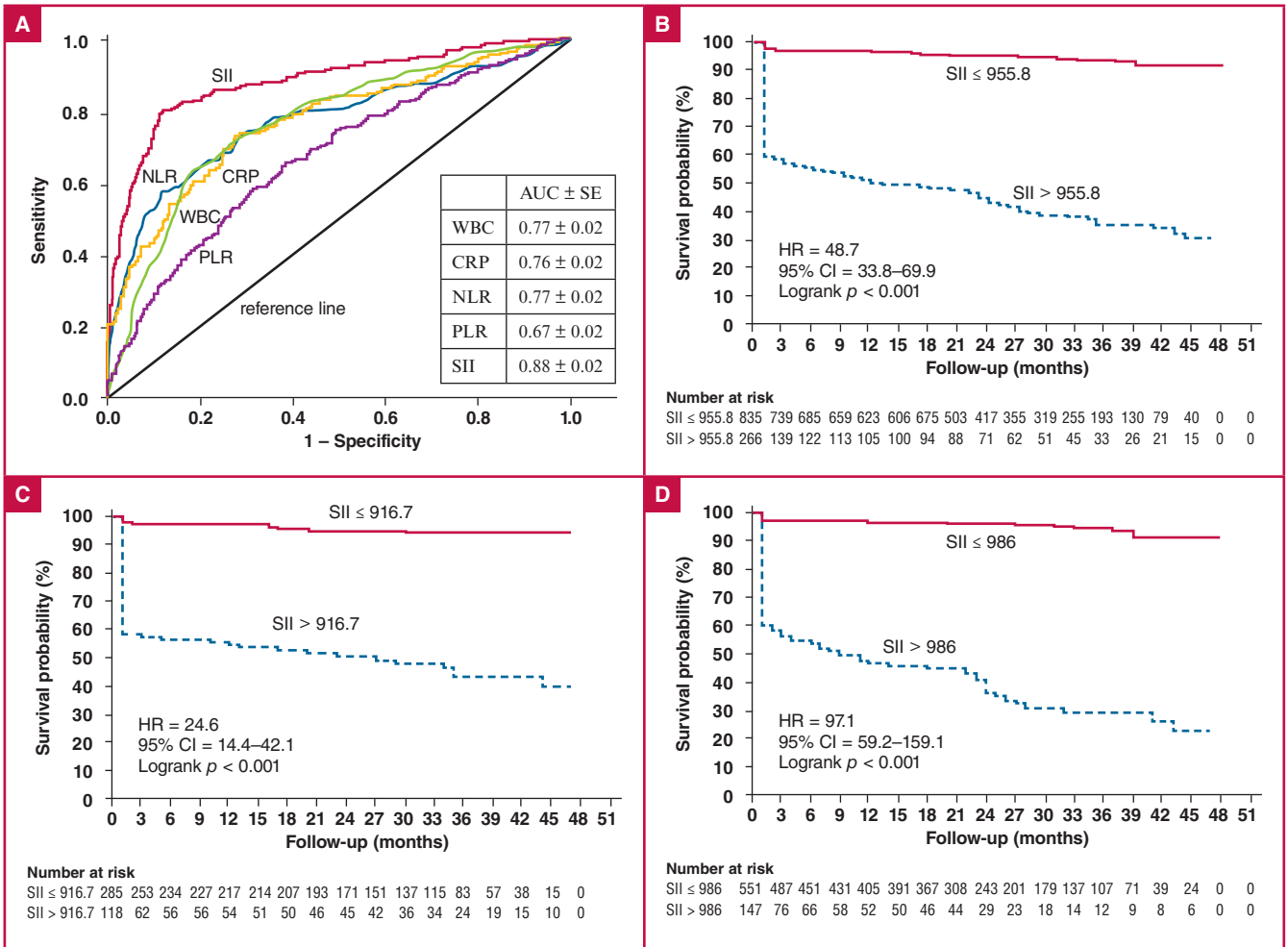

Fig. 1. (A) SII diagnostic performance assessment in predicting MACE, (B) Predictive value for MACE risk in all patients, (C) in STEMI patients, and (D) in NSTEMI patients.

it was shown that SII independently predicted the no-reflow phenomenon in STEMI patients.[16]

Except for coronary artery disease in 120 patients who underwent transcatheter aortic valve implantation (TAVI), the SII was shown to have predictive value for major adverse cardiac events and six-month short-term mortality.[17] In a study conducted with 4 606 patients with heart failure, the workers showed that increased SII predicted short-term mortality.[18] In addition, in patients with NSTEMI, increased SII level was shown to be an independent predictor of contrast-induced nephropathy.[19] All these studies indicate that increased SII levels are related to poor cardiovascular events in different cardiac pathologies.

The effect of SII level on prognosis rather than cardiovascular diseases has been shown foremost in malignancies. The inflammatory response plays an important role in malignancy development as well as in atherosclerosis. Based on this hypothesis, it has been shown in many studies and meta-analyses in patients with malignancy that SII can be used to predict a poor prognosis.[20-22] We found only one study in the field of malignancies in which SII was examined together with NLR and PLR. In this study by Liu *et al*., NLR and PLR with SII provided a prognosis prediction in metastatic non-small-cell lung cancer treated with nivolumab.[23]

In addition to SII, we studied the PLR together with NLR, which are two other indicators of inflammatory status in patients with acute myocardial infarction. In the study conducted with 2 518 patients diagnosed with STEMI, increased NLR and PLR were found to be associated with short- and long-term mortality.[5] In the meta-analysis including 10 245 patients, they revealed that the NLR is an indicator of hospitalisation and long-term prognosis in patients with STEMI undergoing PCI.[24] In a meta-analysis of 12 619 patients by Dong *et al*., the increased PLR was an indicator of in-hospital and long-term mortality in STEMI patients who underwent PCI.[25]

The reason why we used NLR and PLR together with SII in our study was to provide a more accurate estimation of three parameters compared to two parameters and to compare this index with these two more well-known ratios. In the present study, SII provided better prediction than PLR and NLR.

In our study results, apart from SII, CRP was also found to be an independent predictor for MACE. Many studies have already found that CRP is an independent predictor of mortality.[26] In the study conducted in 5 145 ACS patients, a significant correlation was found between high-sensitivity CRP, measured at the start of the study and 16 weeks later, and MACE.[27] WBC, another indicator of inflammation, was also discovered to be an independent predictor for MACE in our study. In a study conducted with 2 208 ACS patients, high baseline WBC levels were found to be associated with high six-month mortality rates.[28] Since SII, CRP and WBC all show level of inflammation, we found increased levels to be an independent predictor for MACE in our study, which supports the literature.

Our study found that SII, NLR and PLR could all be used to predict in-hospital and long-term MACE in ACS patients. Multivariate Cox regression models showed that all these markers were not independent predictors for MACE in ACS patients. Among these inflammatory markers, only SII was found to be an independent predictor for MACE. SII could therefore be an excellent clinical laboratory marker to identify high-risk ACS patients.

There were some limitations to this study. Our study differed from other studies in that NLR, PLR and SII were examined together and the study was performed on both STEMI and NSTEMI patients. It was conducted in a single centre and with a moderate number of patients, so there might be selection bias. Furthermore, it was a retrospective, cross-sectional study. For this reason, prospective studies with a larger number of patients are needed.

Conclusion

Although many laboratory markers are used to predict the prognosis of ACS patients, SII seems to be very strong compared to other indicators. It could enter routine clinical use in patients with ACS and other cardiovascular diseases.

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