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ORIGINAL RESEARCH

High Preoperative Systemic Immune-Inflammation Index Values Significantly Predicted Poor Outcomes After on-Pump Coronary Artery Bypass Surgery

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Purpose: On-pump coronary artery bypass grafting (CABG) is one of the most common revascularization surgical therapies for coronary artery disease (CAD). However, owing to the use of cardiopulmonary bypass ("on-pump"), the body develops systemic inflammatory response syndrome, which leads to the risk of morbidity and mortality. This study aimed to determine the perioperative outcomes of patients who underwent on-pump CABG surgery using the systemic immune-inflammation index (SII).

Patients and methods: This single-center retrospective study used secondary data from patients' electronic medical records and medical records archives at the National Cardiovascular Center Harapan Kita, who underwent on-pump CABG from January 2019 to December 2022. A total of 1056 on-pump CABG procedures were performed after exclusion. Lymphocyte, segmental neutrophil, and platelet counts from the preoperative data were used to calculate the SII values. An SII cutoff value of 528.715 × 10^3/mm^3 divided the patients into two groups.

Results: The SII value of 1056 patients were calculated, among which 490 (46%) patients had a preoperative SII value of ≥528.715 × 10^3/mm^3. Multivariate analysis showed that a high SII significantly prolonged the duration of surgery (OR 1.005, 95% CI 1.003–1.006) and cardiopulmonary bypass (CPB) time (OR 1.007, 95% CI 1.005–1.009). High SII values significantly predicted prolonged mechanical ventilation (OR 6.154, 95% CL 3.938–9.617), intensive care unit (ICU) stay (OR 6.332, 95% CL 4.232–9.474), and hospital stay (OR 3.517, 95% CL 2.711–4.562). Regarding other perioperative outcomes, a high SII significantly predicted the risk of postoperative atrial AF, cardiac arrest, acute myocardial infarction, and mortality.

Conclusion: A high preoperative SII value can predict morbidity and mortality in patients undergoing on-pump CABG surgery.

Keywords: systemic immune-inflammation index, on-pump coronary artery bypass graft, systemic inflammation, morbidity, mortality

Introduction

Reported that developing countries had an estimated 19 million deaths in 2010 by coronary artery disease (CAD), making it one of the leading causes of mortality.[1] CAD is often associated with atherosclerosis, a form of lipid accumulation and inflammation in the artery that reduces the blood flow in the lumen.[2] Once it forms, the lack of blood flow causes clinical complications such as myocardial infarction and stroke. CAD therapy involves lifestyle modifications, medications, and revascularization surgeries.

Coronary artery bypass grafting (CABG) is one of the most common revascularization surgeries for CAD patients. CABG is defined as a surgery in which autologous veins or arteries are used as grafts to bypass an obstructed coronary

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artery.[3] During its development, CABG can be performed using either cardiopulmonary bypass (on-pump) or without (off-pump). On-pump CABG uses cardiopulmonary bypass (CPB) to maintain blood flow, but it is often associated with complications in the form of systemic inflammation.

The mechanism of acute inflammation involves many cytokines that promote the synthesis of tumor necrosis factor (TNF), a major contributor to the activation of polymorphonuclear neutrophils (PMNs).[4] Due to blood exposure to artificial materials, the intrinsic coagulation factor initiates a cascade of factors that lead to a high platelet count in the blood.[5] This may lead to severe complications, such as thrombus formation in the blood flow.[6] During the use of CPB, using liquid to support the blood flow into the extracorporeal circuit causes a hemodilution effect that affects the lymphocyte count.[7] This leads to a higher count of neutrophils and platelets, but a lower lymphocyte count.

Several examples of scores for assessing the inflammatory process based on neutrophil and lymphocyte values include the Naples score (NS) and systemic immune-inflammation index (SII). The Naples score (NS) has emerged as a valuable prognostic tool in cancer patients and can be used to assess both the inflammatory and nutritional status of patients. NS is a composite of serum albumin levels, total cholesterol levels, neutrophil/lymphocyte ratio (NLR), and lymphocyte/monocyte ratio (LMR). NS can be used for risk stratification for long-term mortality in patients with ST-elevation myocardial infarction (STEMI) undergoing percutaneous coronary intervention (PCI).[8]

The systemic immune-inflammation index (SII) was introduced by Hu in 2014 as a predictor of the prognosis of cancer and inflammation-related diseases. The SII is formulated by multiplying the platelet count and neutrophil count and then divided by the lymphocyte count.[9] A previous study stated that high SII had a better prediction than traditional risk factors in determining the outcome of patients with CAD.[10] Another study suggested that SII $\geq 1119 \times 10^3/mm^3$ may be an independent predictive marker for both long-term mortality and appropriate intracardiac defibrillator (ICD) therapy in patients with heart failure with reduced ejection fraction (HFrEF).[11]

Longer use of ventilation machine and intensive care unit (ICU) stay were predicted by a high SII in patients after off-pump CABG.[12] Low SII was associated with consuming an anti-inflammatory diet after on-pump CABG surgery.[13] However, there is a lack of studies about the usage of SII in predicting morbidity and mortality in patients after on-pump CABG surgery. This study aimed to determine the role of SII in predicting the morbidity and mortality of patients after on-pump CABG surgery.

Methods

This single-center, retrospective study was conducted at the National Cardiovascular Center, Harapan Kita. The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the National Cardiovascular Center Harapan Kita (DP.04.03/KEP137/EC072/2023). Due to electronic medical records, written informed consent was not required, and all patient data were anonymized and de-identified. This study included all patients who underwent on-pump CABG surgery at the National Cardiovascular Center Harapan Kita from January 2019 to December 2022. Patients with the following criteria were excluded: incomplete preoperative data, renal failure requiring hemodialysis, emergency status, laboratory results older than one week, and patients who underwent valve surgery. 1574 on-pump CABG procedures were performed, and 518 patients were excluded based on the exclusion criteria (Figure 1). Patient characteristics, such as age, sex, body mass index (BMI), history of hypertension, diabetes mellitus, dyslipidemia, chronic obstructive pulmonary disorder, smoking, recent myocardial infarction (MI), family history of CAD, preoperative ejection fraction, left main (LM) disease, and EuroSCORE II, were recorded.

Intraoperative data included the duration of surgery, cardiopulmonary bypass (CPB) time, aortic cross-clamp time, and the number of grafts. The recorded perioperative outcome data includes the vasoactive-inotropic score (VIS), intra-aortic balloon pump (IABP), perioperative atrial fibrillation (PoAF), stroke, heart failure, cardiac arrest, acute myocardial infarction (AMI), septic shock, cardiogenic shock, and mortality. The VIS was determined by adding dopamine (μg/kg/min), dobutamine (μg/kg/min), 10 × milrinone (μg/kg/min), 100 × epinephrine (μg/kg/min), 100 × norepinephrine (μg/kg/min), and 10000 × vasopressin (μg/kg/min).

The patients were observed and evaluated during their stay in the ICU. Patients were extubated after they were hemodynamically stable. The prolonged duration of mechanical ventilation was defined as >24 hours since all

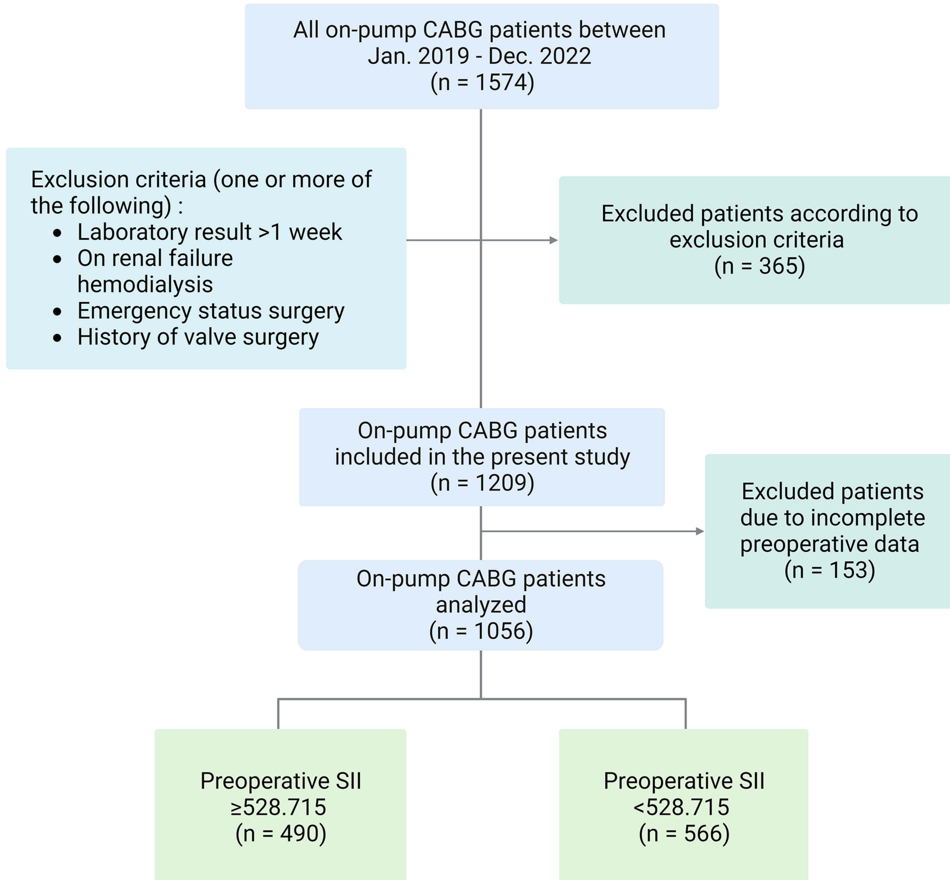

Figure 1 Flow chart of study population selection.

operations were performed (DO-MV > 24 h) by avoiding unnecessary use of anesthetic agents. Prolonged ICU stay was defined as >48 hours of ICU stay (LOS-ICU > 48 h). After the patients stabilized, they were transported to the surgery ward with a length of stay >7 days, defined as a prolonged hospital stay (LOS-H > 7 days). The poor outcomes comprise DO-MV > 24 h, LOS-ICU > 48 h, and LOS-H > 7 days. The mortality rate was evaluated 30 days after the postoperative day.

Statistical Analysis

All data were collected and analyzed using SPSS version 23.0 (SPSS Inc., Chicago, IL, USA). The normality test was performed using the Kolmogorov–Smirnov test. Normally distributed continuous variables are expressed as mean and standard deviation (SD) and analyzed using an unpaired *t*-test. In contrast, non-normally distributed data are expressed as medians and analyzed using the Mann–Whitney *U*-test. Categorical variables are expressed as numbers and analyzed using the chi-square test. Statistical significance was set at p <0.05. All significant variables were tested using Pearson's and Spearman correlations with a significance level of p <0.05.

Results

The identified cut-off value of preoperative SII in patients with poor outcomes in this study, obtained from the largest Youden index and achieving an AUC of 0.669, was 528.715 × 10^3/mm^3. This value demonstrated a sensitivity of 65% and a specificity of 67%. In the study, out of the 1056 patients present in the study, 490 (46%) had a preoperative SII of ≥528.715 × 10^3/mm^3. Table 1 presents the demographic characteristics of patients

Table 1 Patients Characteristics

Variables	Total Patients (n=1056)	SII <528.715 (n =566)	SII ≥528.715 (n = 490)	p-value
Age, years (Median [IQR])	59 (53–64)	60 (54–64)	58 (52–64)	0.203
Sex (%)				
• Male	916 (86.7%)	501 (88.5%)	415 (84.7%)	0.070
• Female	140 (13.3%)	65 (11.5%)	75 (15.3%)	
Body Mass Index, kg/m^2 (Median [min-max])	26.07 (11.90–76.89)	26.04 (11.90–43.26)	26.14 (13.84–76.89)	0.450
Hypertension (%)	644 (61.0%)	332 (58.7%)	312 (63.7%)	0.100
Diabetes Mellitus (%)	435 (41.2%)	226 (39.9%)	209 (42.7%)	0.381
Dyslipidemia (%)	293 (27.7%)	156 (27.6%)	137 (28.0%)	0.891
Chronic Obstructive Pulmonary Disorder (%)	9 (0.9%)	5 (0.9%)	4 (0.8%)	1.000
Smoking History (%)	588 (55.7%)	318 (56.2%)	270 (55.1%)	0.756
• Active Smoker	27 (2.6%)	19 (3.4%)	8 (1.6%)	0.082
Recent MI (%)	364 (34.5%)	192 (33.9%)	172 (35.1%)	0.697
Family History of CAD (%)	204 (19.3%)	103 (18.2%)	101 (20.6%)	0.348
Preoperative Ejection Fraction, % (Median [min-max])	57.00 (24–83)	57.00 (17–83)	56.00 (15–83)	0.143
LM Disease (%)	340 (32.2%)	166 (29.3%)	174 (35.5%)	0.035*
EuroSCORE II (Median [min-max])	1.02 (1.00–2.00)	1.02 (1.00–1.87)	1.02 (1.00–2.00)	0.034*

Note: Statistical significance ($p < 0.05$) is marked with *.
Abbreviations: IQR, interquartile range; SII, systemic immune-inflammation index; MI, myocardial infarction; CAD, coronary artery disease; LM, left main coronary artery.

Table 2 Intraoperative Data

Variables	Total Patients (n=1056)	SII <528.715 (n =566)	SII ≥ 528.715 (n = 490)	p-value
Duration of surgery, minutes (Median [min-max])	254 (90–880)	245 (97–630)	260 (90–880)	0.003*
CPB Time, minutes (Median [min-max])	90 (27–448)	88 (27.00–375.00)	92.3 (31.00–448.00)	0.002*
Aortic Cross-clamp time, minutes (Median [min-max])	48 (15–374)	47 (15.00–435.00)	49.4 (19.00–374.00)	0.006*
Number of grafts (%)				
• 1	22 (2.1%)	10 (1.8%)	12 (2.4%)	0.067
• 2	186 (17.6%)	113 (20.0%)	73 (14.9%)	
• 3	647 (61.3%)	345 (61.0%)	302 (61.6%)	
• 4	174 (16.5%)	85 (15.0%)	89 (18.2%)	
• 5	25 (2.4%)	13 (2.3%)	12 (2.4%)	

Note: Statistical significance ($p < 0.05$) is marked with *.
Abbreviations: SII, systemic immune-inflammation index; CPB, cardiopulmonary bypass.

with high SII values significantly correlated with LM disease and higher EuroSCORE scores, whereas Table 2 presents intraoperative data. Table 3 presents the univariate analysis, which showed that the presence of LM disease, longer duration of surgery, CPB time, aortic cross-clamp time, and the cutoff SII were significant predictors of poor perioperative outcomes. The multivariate analysis of preoperative variables in Table 4 shows that the duration of surgery (p=0.08) was insignificant and included as a confounding factor. The cut-off SII (p<0.001) was more significant than CPB time (p=0.020), although both were found to be independent factors in predicting poor perioperative outcomes. Table 5 shows that a high SII significantly prolonged the duration of mechanical ventilation, ICU stay, and hospital stay (p <0.05).

As shown in Table 6, a high SII value predicted other perioperative outcomes. Significant results were observed in higher-count VIS, use of IABP, PoAF, cardiac arrest, and acute myocardial infarct incidents.

Table 3 Univariate Analysis on Preoperative Variables That Were Significant with Poor Perioperative Outcomes

Variables	Univariate Analysis			
	OR	95% CL		p-Value
		Lower	Upper	
LM Disease	1.327	1.024	1.719	0.035*
EuroSCORE II	2.948	0.660	13.176	0.157
Aortic Cross-clamp time	1.007	1.005	1.008	<0.001*
Duration of surgery	1.005	1.003	1.006	<0.001*
CPB Time	1.007	1.005	1.009	<0.001*
Cutoff SII	3.773	2.920	4.874	<0.001*

Note: Statistical significance (p < 0.05) is marked with *.
Abbreviations: LM, left main; CPB, cardiopulmonary bypass.

Table 4 Multivariate Analysis on Preoperative Variables That Were Significant with Poor Perioperative Outcomes

Variables	Multivariate Analysis			
	OR	95% CL		p-value
		Lower	Upper	
Duration of surgery	1.002	1.000	1.008	0.080
CPB Time	1.004	1.001	1.008	0.020*
Cutoff SII	3.645	2.801	4.743	<0.001*

Note: Statistical significance (p < 0.05) is marked with *.
Abbreviations: CPB, cardiopulmonary bypass; SII, systemic immune-inflammation index.

Table 5 Analysis of High SII Values in Predicting Poor Perioperative Outcomes

Variables	OR	95% CL		p-value
		Lower	Upper	
Prolonged Mechanical Ventilation (>24 hours)	6.154	3.938	9.617	<0.001*
Prolonged ICU Stay (>48 hours)	6.332	4.232	9.474	<0.001*
Prolonged Hospital Stay (>7 days)	3.517	2.711	4.562	<0.001*

Statistical significance (p < 0.05) is marked with*.

Table 6 Analysis of High SII Values in Predicting Poor Perioperative Outcomes

Variables	OR	95% CL		p-value
		Lower	Upper	
VIS	1.003	1.001	1.006	<0.001*
IABP	8.309	4.072	16.957	<0.001*
PoAF	1.721	1.115	2.656	0.016*

(*Continued*)

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Table 6 (Continued).

Variables	OR	95% CL		p-value
		Lower	Upper	
Stroke	1.325	0.477	3.682	0.612
Heart Failure	0.769	0.128	4.622	1.000
Cardiac Arrest	4.475	1.925	10.403	<0.001*
AMI (%)	5.277	1.135	24.539	0.029*
Septic Shock (%)	4.650	0.518	41.745	0.189
Cardiogenic Shock (%)	1.156	0.162	8.235	1.000
Mortality (%)	3.505	1.883	6.523	<0.001*

Note: Statistical significance (p < 0.05) is marked with *.
Abbreviations: VIS, vasoactive-inotropic score; IABP, intra-aortic balloon pump; PoAF, perioperative atrial fibrillation; AMI, acute myocardial infarction.

A strongly significant result was shown in the higher SII, predicting the mortality rate (95% CI 1.883–6.523, $p \leq 0.001$).

Discussion

In this study, a high SII predicted poor perioperative outcomes after on-pump CABG. These outcomes included longer use of mechanical ventilation, intensive care unit stay, and stay in the surgical ward. The long-term use of mechanical ventilation is one of the most common complications in patients post-CABG surgery. It is related to the longer duration of CPB, which affects the hemodynamic status and the need for an inotropic agent.[14,15] Rapid weaning of the ventilator is related to factors such as metabolic derangement in arterial bicarbonate levels and hemodynamic stability.[16] The prolonged use of mechanical ventilation may lead to a longer stay in the ICU, due to a higher risk of complications.[17] The length of ICU stay is correlated with patient characteristics such as diabetes mellitus, hyperlipidemia, and a history of hypertension.[17] Another factor that causes the prolonged stay in the ICU is a possible sign of inflammation caused by exposure during open heart surgery, longer duration of surgery, and the use of cardiopulmonary bypass.[18]

During open heart surgery, the trauma to the body during the incision of the sternum, extraction of the internal mammary artery, and aortic manipulation leads to systemic inflammatory response syndrome (SIRS).[6] IL-6 and C-reactive protein (CRP) are the main markers in determining the SIRS. The magnitude of the CRP level is associated with the level of tissue injury during surgery.[19] Cardiopulmonary bypass initiates SIRS due to blood contact with the artificial surface that activates the inflammatory cascade at the humoral (coagulation system, pro-inflammatory cytokines) and cellular (leukocytes, platelets, vascular endothelial cells) levels.[6] This cascade includes different and complex pathways that intersect with each other, which would later cause injury due to ischemia-reperfusion, leading to an increase in the inflammatory response.[7]

Although it remains unclear, there is a relationship between the inflammatory response and the occurrence of PoAF.[20] The inflammation that persists post-open heart surgery could lead to a high level of CRP, which could predict PoAF.[20,21] Since a higher SII reflects a higher level of inflammation, this study showed that SII also predicts a higher likelihood of PoAF (p=0.016). Although PoAF is related to the incidence of stroke (p=0.612) and heart failure (p=1.000), it is not statistically significant.[21] However, regarding the same effect of systemic inflammation conditions, PoAF is interrelated to mortality due to heart failure and stroke.[22]

Over the past decade, artificial intelligence (AI) has demonstrated its efficacy, particularly in managing cardiovascular diseases, specifically AF and CAD. The potential and versatility of future AI applications in AF and CAD are promising, with the capability to revolutionize the diagnosis, risk classification, and optimization of therapies for these conditions. AI algorithms can integrate data from various sources, including wearable devices, imaging data, and electronic health records, providing a comprehensive overview of a patient's health to improve risk categorization and diagnostic precision. Physicians should equip themselves for AI by acquiring the necessary skills to utilize AI models and adeptly interpret their findings.[23]

The SII can be integrated with other scores, such as the electrocardiography (ECG) score. Various ECG scores have been proposed to predict outcomes related to ECG, one of which is the morphology-voltage-p wave duration (MVP) ECG risk score. The MVP ECG risk score has been demonstrated to have predictive value for both in-hospital and long-term atrial fibrillation (AF) diagnosis in a substantial population of patients with acute ischemic stroke (AIS).[24] Other scores, such as the electrocardiographic diastolic index (EDI), can also be employed. EDI plays a significant role in predicting diastolic dysfunction in adult patients undergoing transthoracic echocardiography.[25]

A higher VIS also corresponds to prolonged use of ventilation and ICU stays due to longer recovery time affected by inotropic support.[26] In this study, high SII levels predicted a higher use of VIS ($p < 0.001$), in accordance with a higher risk of mortality after on-pump CABG. The VIS is the numerical count of vasoactive and inotropic support after cardiac surgery. A previous study showed that VIS predicts morbidity and mortality after pediatric cardiac surgery.[27] Yamazaki et al showed that VIS was a better model for predicting morbidity and mortality in adult cardiac surgery than EuroSCORE and Parsonnet scores.[28]

IABP has been acknowledged as one of the most effective ways to deal with low cardiac output after post-CABG.[29] The analysis showed that the use of IABP in postoperative cardiac surgery is more common in the higher SII group ($p<0.001$). Although the findings suggest no significant difference in outcome when using IABP before and after surgery, the clinical use of IABP reduces the mortality rate.[30]

Since the introduction of SII, its use for assessing the prognosis of cancer and other inflammatory diseases has been rapidly updating.[9] A higher SII, according to its formulation, is accepted as a marker for a higher state of inflammation, including chronic inflammation. Cardiovascular disease (CVD) is an important condition affected by chronic inflammation.

In several studies, MI has shown a connection between its initiation and progression with inflammation. Platelets, leukocytes, and neutrophils are also involved in disease development. Saylik et al reported that the SII was noted for predicting cardiac death in patients with ST-elevation myocardial infarction.[31] This study acknowledges this report since the SII is statistically significant in predicting AMI ($p=0.029$).

Yang et al in their study proved that a higher SII is associated with a higher risk of death by cardiovascular means such as cardiac arrest and heart failure.[10] As stated by the result of this study, a high SII can predict the occurrence of cardiac arrest ($p<0,001$). Although insignificant in predicting heart failure ($p=1.000$), heart failure is considered a prevalent cause of cardiac arrest.[32]

A high SII value can predict a higher probability of mortality based on patient characteristics. Table 1 shows that patient characteristics, including LM disease and EuroSCORE II, were significantly associated with high SII values. Both of these criteria are related to an increased risk of mortality in patients after on-pump CABG.[33] The presence of LM disease is correlated with a higher risk of cardiac failure that leads to death in patients, as stated by a previous study.[34] A higher EuroSCORE II also leads to a higher mortality risk.

Receiver operating characteristic (ROC) analysis for the SII resulted in a cutoff value of $528.715 \times m^3/mm^3$ with 65% sensitivity and 67% specificity (Figure 2). This result was consistent with a study by Candemir et al which produced an SII cutoff value at $750 \times 10^3/mm^3$ (sensitivity 60% and specificity 70.11%) in patients with CAD.[35] Another study by Zengin showed that an SII cutoff value of $651,7 \times 10^3/mm^3$ (sensitivity 65% and specificity 64.9%), also predicted acute kidney injury (AKI) as a complication after patients undergo CABG.[36] The difference in the cutoff values of SII may be due to the different sample sizes and population characteristics.

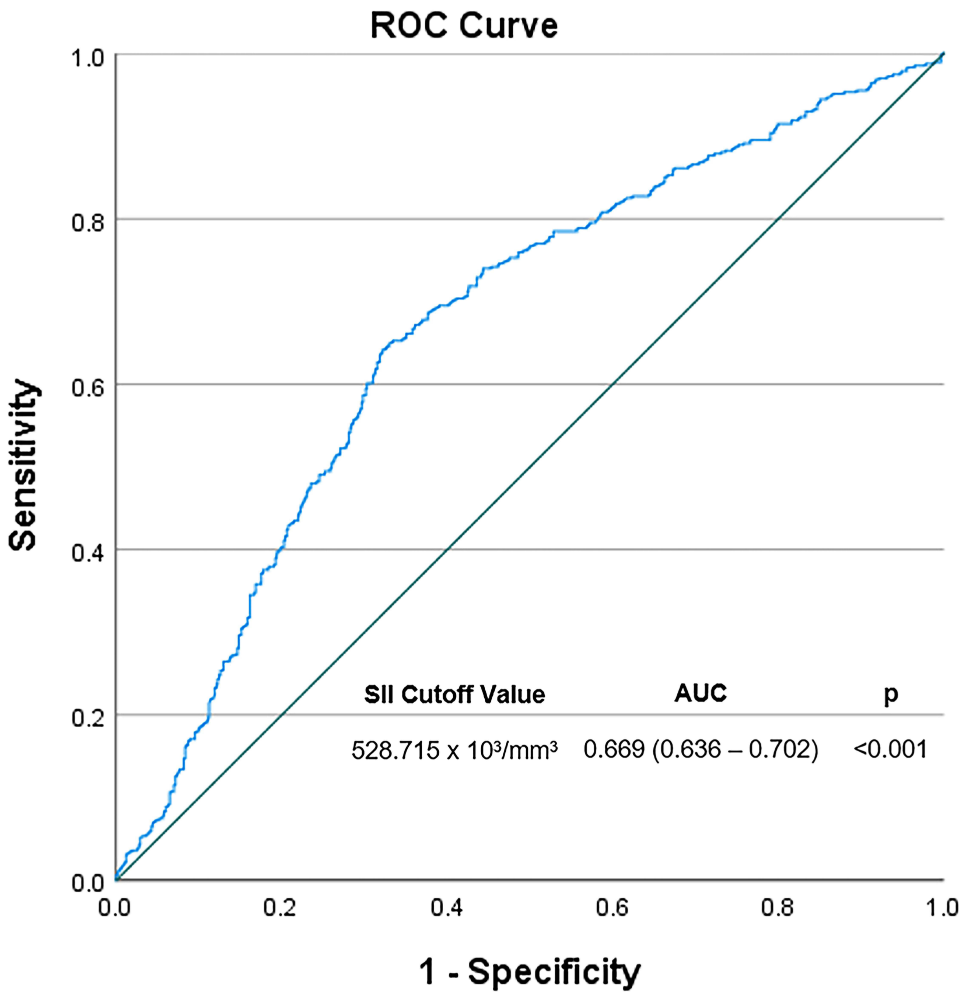

Figure 2 Receiver Operating Characteristic (ROC) curve for prediction of poor outcome based on SII. The highest area under the curve of 0.669 (p = <0.001*) for SII, with its respective cutoff value of 528.715×10^3 /mm^3. Poor outcomes were defined as ≥ 1: duration of mechanical ventilation >24 hours (DO-MV > 24 h), length of intensive care unit stay >48 hours (LOS-ICU > 48 h), and length of hospital stay >7 days (LOS-H > 7 days).
Abbreviations: AUC, area under the curve; SII, systemic immune-inflammation index.

Limitations and Implications

The limitations of this study include the exclusion of patient counts owing to the exclusion criteria. This was because of the incomplete medical records available. The high number of excluded patients makes the data not attributable to the Indonesian population. Since this study was conducted in a single center at the National Cardiovascular Center Harapan Kita, another study involving multiple centers and numerous populations could be considered as studies on the SII are still limited.

Conclusion

In patients undergoing on-pump CABG surgery, high SII values significantly predict a higher morbidity rate in the form of longer ventilation duration, ICU stay, and hospital stay. This may lead to poor outcomes and complications such as higher VIS, the need to use IABP, PoAF, cardiac arrest, AMI, and even mortality. Since SII is more recognized and is defined as more reliable than traditional risk factors, it could be used to provide information regarding perioperative prognosis.

Data Sharing Statement

Individual de-identified participant data from this study will be made available upon request after publication and will be available for 36 months following article publication. Researchers must state the aims of their analysis and provide a methodologically sound proposal directed toward the corresponding author.

Disclosure

The authors declare no conflicts of interest in this work.

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