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Association between Systemic Inflammatory Immunity Index and Intracoronary Thrombus Burden in Acute Myocardial Infarction with ST Segment Elevation (IMA EST) Patients Undergoing Primary Percutaneous Coronary Intervention at Haji Adam Malik Hospital

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ABSTRACT

Introduction: Acute coronary syndrome (ACS) account for 30% of deaths worldwide. High peri-procedural intracoronary thrombus burden is a strong predictor of poor outcome. Inflammation plays an important role in the pathogenesis of intracoronary thrombus formation. The systemic inflammatory immunity index represents the immune responses to inflammation, which consist of neutrophilia, thrombosis and decreased lymphocytes. The previous study showed that systemic inflammatory immunity index predicted high intracoronary thrombus burden in STEMI patients. This study aimed to evaluate systemic inflammatory immunity index in predicting the incidence of high intracoronary thrombus burden in STEMI patients.

Method: This research is a retrospective analytical observational study on 95 patients diagnosed with ACS in the period 1 January 2022-31 March 2023 at H. Adam Malik General Hospital, Medan. All patients involved had undergone primary percutaneous coronary intervention. Patient characteristics, risk factors, laboratory results and coronary angiography were recorded from the patient's medical record.

Results: There was a significant relationship between the systemic inflammatory immunity index value and the incidence of high intracoronary thrombus burden in STEMI patients ($P < 0.001$). The systemic inflammatory immunity index cut off point value > 1108 has a sensitivity of 89.4% and a specificity of 89.7% which has a better accuracy in predicting high intracoronary thrombus burden in STEMI patients.

Conclusion: Systemic inflammatory immunity index has a good accuracy to predict high intracoronary thrombus burden in STEMI patients.

Keywords

Acute Coronary Syndrome, High Thrombus Burden, Systemic Inflammatory Immunity Index

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INTRODUCTION

Coronary heart disease (CHD) is the leading cause of death worldwide. Based on physician diagnosis, the prevalence of coronary heart disease in Indonesia in 2018 was 1.5% or an estimated 1,017,290 people. North Sumatra Province estimated coronary heart disease based on doctor's diagnosis was around 1.3% or around 55,351 people.[1]

Acute coronary syndrome (ACS) is the leading cause of cardiac hospital admissions.[2] ACS accounts for 30% of all deaths worldwide. An estimated three million people experience myocardial infarction with ST segment elevation (IMA-EST) per year globally, and the average incidence of myocardial infarction without ST segment elevation (IMA-NEST) is estimated to be four million per year.[3]

Percutaneous coronary intervention (CCI) is the standard treatment for acute myocardial infarction. However, no-reflow phenomenon occurs in 2.3%-29% of patients after attempted occlusion.[4] In cases of high thrombus burden in the infarct-related artery, stent placement may cause distal thrombus shift in the microvascular bed.

Massive intracoronary thrombus burden has been reported in 16.4% of patients with ACS. Clinical studies show that high peri- procedural intracoronary thrombus burden is a strong predictor of poor patient outcomes, including no reflow phenomenon, stent thrombosis, myocardial infarction, and mortality. In ACS, after coronary plaque rupture, the endothelial cell barrier is disrupted resulting in interactions between extracellular matrix components and blood elements that trigger thrombus formation.[5]

Inflammation plays an important role in the pathogenesis of intracoronary thrombus formation. It has been reported that thrombosis in many coronary vessels is triggered by a severe inflammatory response in Covid-19 patients.[6] Inflammatory components are significant targets in preventing cardiovascular disease and various studies have focused on testing the efficacy of anti-inflammatory treatments in cases of acute myocardial infarction.[7]

Although invasive and pharmacological management strategies have been developed, thrombus management remains complex and inadequate. Therefore, identifying inflammatory predictors of intracoronary thrombus burden can contribute to pharmacological management research in acute myocardial infarction.[7] There is a need for biomarkers that can indicate intracoronary thrombus burden that has the potential to destabilise the lesion. This could guide early invasive intervention or pharmacological management to limit thrombus formation.[5]

Systemic inflammatory immunity index represents three immune responses to inflammation: neutrophilia, thrombosis and lymphocyte depletion. Systemic inflammatory immunity index is the multiplication of platelet count by neutrophil count and then divided by lymphocyte count. This parameter has been associated with cardiovascular disease. A cohort study showed a systemic inflammatory immunity index value >812 had a sensitivity of 82% and specificity of 73% in predicting high intracoronary thrombus burden ($p<0.001$). Other studies have shown that patients with high intracoronary thrombus burden have high neutrophil, leucocyte, platelet and systemic inflammatory immunity index values.[5-7]

METHOD

Study Design

This type of research is an observational analytic study with a retrospective cross-sectional study design, where sampling is done by consecutive sampling to assess the relationship between intracoronary thrombus burden and systemic inflammatory immunity index in patients with IMA- EST at H Adam Malik Hospital Medan.

Place and Time

This study was conducted on IMA-EST patients who underwent percutaneous coronary intervention at HAM Medan Hospital with secondary data collection from medical records conducted from the period 01 January 2022 to 31 March 2023.

Population and Sample

The target population is all IMA-EST patients. The target population was all IMA-EST patients who underwent percutaneous coronary intervention at H. Adam Malik Hospital. The sample is the affordable population that meets the inclusion and exclusion criteria, taken consecutively until the sample size is met.

Inclusion and Exclusion Criteria

The inclusion criteria in this study were patients with favourable clinical and examination findings as IMA-EST and undergoing primary percutaneous coronary intervention. Incomplete medical record data, under the treatment of anti-inflammatory, immunosuppressive and fibrinolytics, evidence of systemic inflammatory

disease, acute and chronic infection, chronic kidney disease, liver failure, haematological disorders, malignancy, and evidence of slow coronary flow, large artery morphology > 4 mm, ectasia or aneurysm.

Procedure

Before the study began, the researcher requested ethical clearance from the Standing Committee for Research Ethics Assessment of the Faculty of Medicine, University of North Sumatra. Each subject who was included as a research sample was explained and asked for approval using informed consent signed by the participant and researcher. All samples of this study were patients with diagnosed IMA-EST who underwent percutaneous coronary intervention who were admitted to the PJT of Haji Adam Malik Hospital Medan. The diagnosis of IMA-EST was based on ESC and PERKI guidelines.

The researcher examined the patient's medical record to see the history, physical examination, electrocardiography (ECG), blood laboratory, and angiography, then recorded the systemic inflammatory immunity index data. Blood tests were conducted at the Clinical Pathology Laboratory of the Hajj Adam Malik Hospital in Medan using Architech C4000 and C8000 equipment. ECG assessment using Bionet Cardiotouch 3000 with a speed of 25 mm/s and an amplitude of 10 mV, while angiography examination was performed in the cathlab room by a heart and vascular specialist in interventional cardiology.

Patients who met the inclusion and exclusion criteria were divided into 2 groups, the first group was IMA-EST patients who had intracoronary thrombus. While the second group is IMA-EST patients who do not experience intracoronary thrombus. After all the data obtained, data processing, analysis, and hypothesis testing will be carried out using SPSS ver.24. So that it will be known whether there is a significant difference in the value of the parameters tested in the two groups.

Data Management and Analysis

Statistical data processing and analysis used the SPSS programme. Categorical variables were presented with number or frequency (n) and percentage (%). Numerical variables were presented with a measure of mean and standard deviation for normally distributed data. Whereas data that are not normally distributed are presented in the form of medians. The Kolmogorov-Smirnov normality test was conducted to determine whether the data was normally distributed or not.

Data were compared by independent T-test or Mann Whitney U-test, while categorical data were compared by Chi-square test. Variables with a p value <0.05 were included for multivariate analysis. Receiving operating characteristic (ROC) curve analysis was used to assess the new cut off. The statistical significance threshold used was $p < 0.05$.

Research Ethics

This study has received ethical approval from the Health Research Ethics Committee of the Faculty of Medicine, University of North Sumatra and a research permit from Litbang Haji Adam Malik Medan.

RESULT

The proportion of patients with older age, male gender, history of smoking, dyslipidemia, type 2 DM, smoking and multivessel disease was higher in the high thrombus burden group compared with the low thrombus burden group, but not statistically significant. In the high thrombus burden group, most patients presented with disease onset > 12 hours (60.6%), while in the low thrombus burden group most patients presented with disease onset < 12 hours (69%). This was statistically significant with a P value <0.008.

Furthermore, the high thrombus load group had a median creatinine value of 1.14 (0.6 - 2.51) higher than the low thrombus load group with a median creatinine value of 0.84 (0.54 - 2.46). This was statistically significant with a P value of <0.024. However, ureum values were not significantly different between groups. In the high thrombus burden group, higher total cholesterol, higher LDL cholesterol, lower HDL cholesterol and higher triglyceride values were found compared to the low thrombus burden group, but not statistically

significant Based on the location of the blood vessels, high thrombus burden was mostly found in the RCA. This was statistically significant with a P value <0.036 (Table 1 and Table 2).

Table 1 Characteristics of Research Samples

Parameter	Value
Demographic Parameters	
Age, years*	57.25 ± 9.1
Gender, n (%)	
Man	82 (86.3%)
Woman	13 (13.7%)
Clinical Parameters	
Onset, n (%)	
≤ 12 hours	46 (48.4%)
> 12 hours	49 (51.6%)
Killip, n (%)	
Killip 1	72 (75.8%)
Killip 2	14 (14.7%)
Killip 3	4 (4.2%)
Killip 4	5 (5.3%)
Risk Factors	
Hypertension, n (%)	
DM type 2, n (%)	
Dyslipidemia, n (%)	
Smoking, n (%)	
Laboratory Parameters	
Leukocytes, x103/uL	11.52 (6.3 – 13.93)
Neutrophils, %*	74.94 ± 6.5
Lymphocytes, %*	14.87 ± 4.34
Platelets, x 103/uL	246 (130 – 371)
When blood sugar	149 (71 – 490)
Ureum, mg/dL	36 (11 – 91)
Creatinine, mg/dL	1.01 (0.54 – 2.51)
LDL, mg/dL*	114.89 ± 39.19
HDL, mg/dL	34 (20 – 52)
Triglycerides, mg/dL	125 (39 – 489)
Cholesterol total, mg/dL	168 (68 – 351)
Characteristics of Coronary Angiography	
Severita *s* , n (%)	
1VD	35 (36.8%)
2VD	22 (23.2%)
3VD	38 (40 %)
Thrombus location, n (%)	
LAD	39 (41.1%)
LCx	13 (13.7%)
L.M	3 (3.2%)
RCA	40 (42.1%)

Table 2. Characteristics of Study Samples Based on Thrombus Load Classification

Parameter	Value
Demographic Parameters	
Age, years*	57.25 ± 9.1
Gender, n (%)	
Man	82 (86.3%)
Woman	13 (13.7%)
Clinical Parameters	
Onset, n (%)	
≤ 12 hours	46 (48.4%)
> 12 hours	49 (51.6%)
Killip, n (%)	
Killip 1	72 (75.8%)
Killip 2	14 (14.7%)
Killip 3	4 (4.2%)
Killip 4	5 (5.3%)
Risk Factors	
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Dyslipidemia, n (%)	
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RCA	40 (42.1%)

The proportion of patients with older age, male gender, history of smoking, dyslipidemia, type 2 DM, smoking and multivessel disease was higher in the high thrombus burden group compared with the low thrombus burden group, but not statistically significant. In the high thrombus burden group, most patients presented with disease onset > 12 hours (60.6%), while in the low thrombus burden group most patients presented with disease onset < 12 hours (69%). This was statistically significant with a P value <0.008.

On laboratory examination, patients with high thrombus burden had a median leucocyte value of 11,940 (7,600 - 13,930) and a mean neutrophil value of 77.75 + 4.9% which was higher than the low thrombus burden

group with a median leucocyte value of 10,400 (6,310 - 13,540) and a mean neutrophil value of 68.56 + 5.06%. This was statistically significant with P < 0.047 and P < 0.001, respectively. Then the high thrombus load group had a mean lymphocyte value of 12.35 + 1.42% lower than the low thrombus load group with a mean lymphocyte value of 20.65 + 2.97%. This is statistically significant with a value of P < 0.001.

Furthermore, the high thrombus load group had a median creatinine value of 1.14 (0.6 - 2.51) higher than the low thrombus load group with a median creatinine value of 0.84 (0.54 - 2.46). This was statistically significant with a P value of <0.024. However, ureum values were not significantly different between groups. In the high thrombus burden group, higher total cholesterol, higher LDL cholesterol, lower HDL cholesterol and higher triglyceride values were found compared to the low thrombus burden group, but not statistically significant Based on the location of the blood vessels, high thrombus burden was mostly found in the RCA. This was statistically significant with a P value <0.036. This is shown in Table 2.

Relationship between Systemic Inflammatory Immunity Index and Thrombus Load

The high thrombus burden group had a higher median systemic inflammatory immunity index value of 1550 (780 - 3106) than the low thrombus burden group with a median systemic inflammatory immunity index value of 757 (549 - 2193). This was statistically significant with a P value of <0.001. On correlation analysis using the Spearman test, it appeared that the systemic inflammatory immunity index had a moderate positive correlation characterised by an r value above 0.6. This was sharpened by the box-plot diagram showing higher systemic inflammatory immunity index values in the high thrombus burden group compared to the low thrombus burden group. This is shown in table 3 and figure 1.

Table 3 Relationship between systemic inflammatory immunity index and thrombus burden in IMA-EST patients

Parameters	Low Thrombus Burden	High Thrombus Burden	*p- value*	*r- value*
	(n = 29)	(n = 66)		
Index Immunity Inflammation Systemic	757 (549-2193)	1550 (780-3106)	<0.001 [a]	0.774 [b]

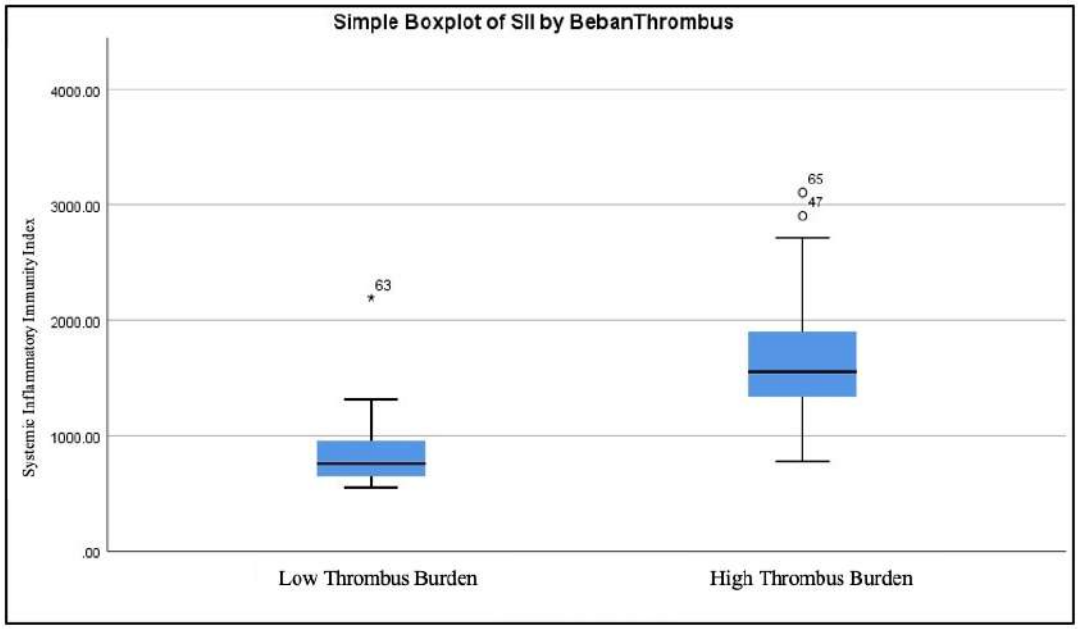

Figure 1. Box-Plot Diagram of Thrombus Burden and Systemic Inflammatory Immunity Index

In further analysis, statistically significant variables with a p-value below 0.05 were separated. Then all variables were subjected to multivariate test with logistic regression. Multivariate analysis showed the significance of systemic inflammatory immunity index, disease onset >12 hours and neutrophils on high

thrombus burden where systemic inflammatory immunity index had a p-value of 0.01 with an OR of 2.12 while neutrophils had a p-value of 0.002 with an OR of 1.31 and onset >12 hours had a p-value of 0.027 with an OR of 1.45. This is shown in Table 4.

Table 4. Logistic Regression Analysis of Research Variables on Thrombus Burden

Parameter	*p- value*	OR	LL CI 95%	UL CI 95%
SII	< 0.001	2.12	1.10	2.12
Onset > 12 O'clock	0.027	1.45	1.35	1.45
Neutrophils	0.002	1.31	1.25	1.31

In the receiver operating characteristic (ROC) curve analysis, the predictive ability of systemic inflammatory immunity index in predicting thrombus burden was analysed. There was a cut-off point value of 1108 with an area under the curve (AUC) of 0.936, sensitivity of 89.4% and specificity of 89.7%. This is shown in Figure 2 and Figure 3.

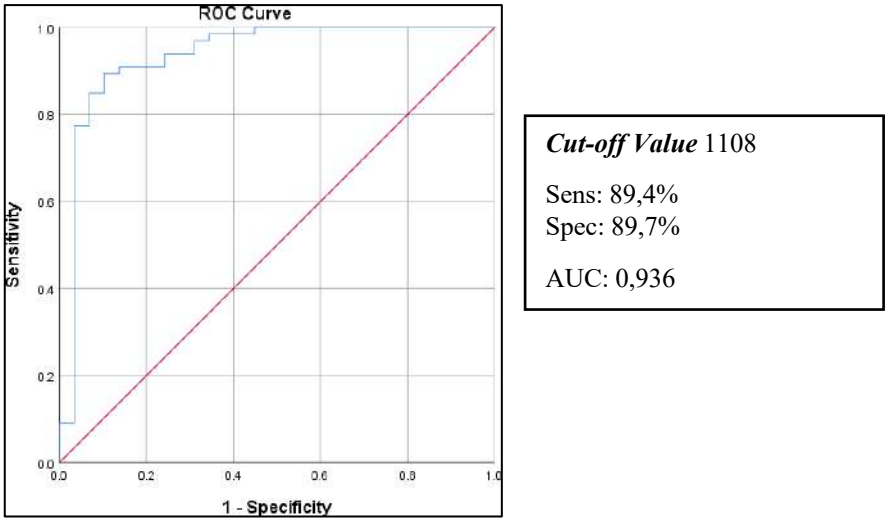

Figure 2. Receiving Operating Curve of Systemic Inflammatory Immunity Index against Thrombus Burden

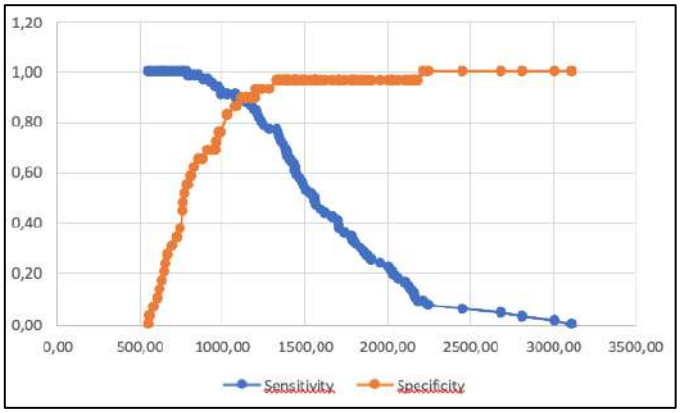

Figure 3. Graph of Sensitivity and Specificity against Cut-Off Value Systemic Inflammatory Immunity Index to Predict Thrombus Burden

DISCUSSION

High peri-procedural intracoronary thrombus burden is a strong predictor of poor patient outcomes.[7,8] In our study, two-thirds of the population showed high intracoronary thrombus burden based on TIMI criteria at IKPP. This study is consistent with previous studies where there is no statistical difference between age and thrombus burden.[5,7,9] Although there is no statistical difference, this study is consistent with the study of

Kumar et al where the proportion of patients with high thrombus burden was found in male gender, smoking history and hypercholesterolemia.[9] The study conducted by Manzi et al also showed the prevalence of high thrombus burden at IKPP in men rather than women.[10]

Smoking causes endothelial dysfunction, vasoconstriction, increases proinflammatory cytokines and increases platelet aggregation, which can lead to coronary thrombosis.[11] Dyslipidaemia causes LDL lipoproteins to enter the intima of blood vessels and undergo chemical modification, contributing to inflammatory mechanisms, followed by leukocyte infiltration and foam cell formation.[12] Ren et al revealed that foam cells release inflammatory factors, tissue factors, growth factors and matrix metalloproteinases that can increase thrombus formation.[11] Soltan et al's study showed that the ratio of monocytes to HDL was an independent factor of high thrombus burden in patients with SCA who underwent IKPP.[13]

Although there was no statistical difference, this study is consistent with Ge et al's study where the prevalence of hypertension was higher in the high thrombus burden group.[14] Hypertension can damage the vascular endothelium and can increase the permeability of the vascular wall to lipoproteins. Angiotensin II, a mediator of hypertension also acts as a stimulator of oxidative stress and proinflammatory cytokines.[12]

Immunothrombosis is a natural immune response induced by thrombus formation in blood vessels.26 The systemic inflammatory immunity index describes three main immune response pathways: inflammation by neutrophilia, thrombosis by platelets, and the body's stress response, by low lymphocytes. Systemic inflammatory immunity index is a biomarker that is easily and inexpensively calculated by simple routine blood count analysis for the evaluation of inflammation.[5,7] This study showed that the mean value of systemic inflammatory immunity index in the high thrombus burden group was higher, 1550 (780 - 3106), compared to the low thrombus burden group, 757 (549 - 2193) which was statistically significant with a P value <0.001. This study is consistent with the study of Dolu et al who showed a systemic inflammatory immunity index cut-off point value of >812 predicted high thrombus burden.[7] In this study the systemic inflammatory immunity index cut-off point value of 1108 had a sensitivity of 89.4% and specificity of 89.7% with an AUC value of 0.936 indicating a high level of accuracy in predicting high thrombus burden in IMA-EST patients.

This study was a retrospective observational analysis at one institution and the sample size in this study was relatively small. This study did not show the follow-up and outcomes of the patients. Confounding factors and other causes of increased systemic inflammatory immunity index were also not thoroughly recorded, such as other specific inflammatory factors.

CONCLUSION

Systemic inflammatory immunity index has a good accuracy to predict high intracoronary thrombus burden in STEMI patients.

DECLARATIONS

The research has received approval from Universitas Sumatera Utara and Adam Malik Hospital Health Research and Ethics Committee. All participants were informed about subject of the study.

CONSENT FOR PUBLICATION

The Authors agree to publication in Journal of Society Medicine.

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COMPETING INTERESTS

The authors declare that there is no conflict of interest in this research.

AUTHORS' CONTRIBUTIONS

All authors are responsible for conceptualization, manuscript preparation, manuscript editing, and manuscript assurance.

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