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Fibrinogen and Intracoronary Thrombus as Predictors of Major Adverse Cardiovascular Events In-Hospital in St-Elevation Myocardial Infarction (STEMI) Patients Undergoing Primary Percutaneous Coronary Intervention

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ABSTRACT

Background: Fibrinogen is an acute phase reactant involved in inflammation and coagulation in STEMI. Rupture of atherosclerotic plaque can cause the formation of intracoronary thrombus. Despite undergoing primary percutaneous coronary intervention (PCI), patients are at risk of experiencing major adverse cardiovascular events (MACE). ***Method:*** The research design used a prospective cohort. The independent variables are fibrinogen and intracoronary thrombus. Fibrinogen levels are examined when the patient arrives at the cardiac emergency unit. Intracoronary thrombus examination is carried out when the patient undergoes primary PCI. The outcomes studied were MACE during treatment in the form of cardiovascular death, cardiogenic shock, acute heart failure, malignant arrhythmias and persistent chest pain. ***Results:*** A total of 62 samples were involved in this research. There were 29 patients (46.7%) with high fibrinogen and 38 patients (61.3%) with large intracoronary thrombus. During follow-up during treatment, 26 patients (41.9%) experienced MACE. The cut-off fibrinogen value was 341.6 mg dl (AUC 0.809; 95% CI 0.696-0.923; p<0.001). Cox regression analysis using the backward log rank method showed that high fibrinogen (adjusted HR 3.45; 95% CI 1.29-9.23; p=0.13) and large intracoronary thrombus (adjusted HR 4.30; 95% CI 1.24-14.90; p=0.021) were independent predictors of MACE during hospitalization. Combined analysis of high fibrinogen and large intracoronary thrombus showed that 81.0% of patients experienced MACE during hospitalization (adjusted RR 2.87; 95% CI 1.12-7.35; Cohran and Mantel-Haenzel p=0.002). ***Conclusion:*** High fibrinogen and large intracoronary thrombus are independent predictors of MACE during hospitalization and can be applied as additional data for risk stratification in STEMI patients undergoing primary PCI.

Keywords: fibrinogen; intracoronary thrombus; STEMI; MACE

INTRODUCTION

Major Cardiovascular Events (MACE) are one of the complications of STEMI. Events that are classified as MACE are cardiovascular death, cardiogenic shock, heart failure, malignant arrhythmia, recurrent MI, persistent chest pain. Research conducted by Nasution et al found that MACE during treatment in STEMI patients was 43.3% [1]. In another study conducted by Wilar et al, the MACE value in STEMI patients during 6 months of observation was 41.4% [2].

Inflammation and coagulation play important roles in STEMI. Growing evidence supports the bidirectional role of inflammation and coagulation where inflammation can lead to activation of the coagulation system and vice versa [3]. Although seen as distinct mechanisms, inflammation and coagulation are an integrated system in response to injury. Dysregulation of either component can affect the balance and can lead to various disease manifestations due to excessive inflammation and coagulation [4].

The inflammatory response in STEMI is a defense mechanism aimed at preventing infection of the injured tissue. Inflammation also plays an important role in necrotic tissue repair. Hypoxia-reperfusion conditions can cause the formation of Reactive Oxygen Species (ROS) that trigger complex and diverse responses such as activation of adhesion molecules, chemokines and cytokines [5]. The coagulation system is a series of cascades to form a blood clot. The purpose of coagulation is for hemostasis, which is to stop bleeding from injured blood vessels [6].

Research on biomarkers has grown tremendously in the last few decades. These biomarkers provide an understanding of disease pathophysiology. One of the inflammatory markers and also known to have an effect on the coagulation system is fibrinogen. Fibrinogen is one of the first identified clotting factors. Fibrinogen has various effects such as platelet aggregation, endothelial lesions, plasma viscosity and fibrinolytic system. Thus, fibrinogen has direct implications on thrombin generation. In addition, the degradation products of fibrin can cause coronary artery restenosis [7] and are associated with the severity of coronary atherosclerosis [8].

Several studies have tried to look at the role of fibrinogen in Acute Coronary Syndrome (ACS). Sargowo et al and Setiawan et al conducted research on fibrinogen and Hs-CRP as biomarkers in ACS. In both studies, significant fibrinogen and Hs-CRP values were found in ACS patients compared to the control group [9,10]. Some studies found that high plasma fibrinogen correlated with post PCI events. Kavitha et al found that high basal fibrinogen values were associated with recurrent angina and post-stenting myocardial infarction [11]. In a long-term study by Jiang et al, it was found that high fibrinogen values at the time of Percutaneous Coronary Intervention (PCI) were associated with 2-year all-cause mortality [12]. Another study conducted by Ang et al also found that increased baseline fibrinogen values were associated with MACE within 2 years after PCI [13].

Although several studies have been conducted looking at fibrinogen levels as a marker of inflammation and coagulation in ACS patients as well as looking at major cardiovascular events post PCI, studies looking at the relationship between fibrinogen levels and intracoronary thrombus with MACE in STEMI patients undergoing invasive strategies are limited. Through this study, researchers can try to identify whether there is a correlation between fibrinogen levels and the degree of intracoronary thrombus with MACE. The results of this study may provide new insights in the management of STEMI patients undergoing invasive strategies, assist physicians in understanding patient prognosis and risk, and improve better treatment strategies.

METHOD

This study was conducted with a prospective cohort design. This study will assess the relationship between fibrinogen and the degree of intracoronary thrombus with MACE in STEMI patients undergoing primary PCI. In addition, the relationship between fibrinogen and the degree of intracoronary thrombus will be assessed. The study has obtained a research ethics permit from Udayana University / Prof. IGNG Ngoerah Denpasar.

Inclusion criteria in this study are: 1) STEMI patients who underwent invasive strategy; 2) STEMI patients who are willing to participate by signing the consent form after informed consent. Exclusion criteria in this study are: 1) Patients with chronic inflammatory diseases (e.g. ulcerative cholitis, Crohn's disease); 2) Patients with severe infection/sepsis; 3) Patients with autoimmune diseases (e.g. systemic lupus erythematosus, rheumatoid arthritis); 4) Patients with hypercoagulopathy; 5) Pregnant patients; 6) Cancer patients; 7) Acute stroke patients or history of stroke; 8) Patients with a history of previous long-term anticoagulant use (>4 weeks). The sampling technique used in this study was non-probability sampling, namely using consecutive sampling.

A total of 62 samples of STEMI patients who underwent primary PCI at Prof. dr. I.G.N.G. Ngoerah Hospital were taken venous blood samples at the emergency department of the integrated cardiac service of Prof. dr. I.G.N.G. Ngoerah Hospital. Blood samples were then sent to the Clinical Pathology Laboratory of Prof. Dr. I.G.N.G. Ngoerah Hospital. Fibrinogen levels were examined using the enzyme-linked immunosorbent assay (ELISA) method.

Examination of the degree of intracoronary thrombus was performed at the time the patient underwent primary PCI. Intracoronary thrombus was defined as a filling defect surrounded by contrast media. The degree of intracoronary thrombus was divided into grades 0-5. Evaluation of the degree of intracoronary thrombus was performed by at least two interventional consultant cardiologists. Kappa test was performed to avoid interpretation bias between interventional consultants.

MACE outcome assessment was performed after primary PCI until the occurrence of outcomes or during the treatment period. Mortality assessment was done by death certificate, ECG for identification of malignant arrhythmia, hemodynamic examination for cardiogenic shock, echocardiography and thoracic X-ray for acute heart failure, visual analog scale for persistent chest pain.

The data collected then in each group was then analyzed. Data analysis included descriptive analysis, reliability test, proportion comparison test, survival analysis, Cox regression test, Mantel-Haenszel test. Conclusions were drawn based on 95% confidence interval and p value <0.05. The entire data analysis was performed with the help of SPSS 29 software.

RESULTS

The results of the descriptive analysis of the study population are shown in Table 1 and Table 2.

Patients were categorized based on fibrinogen values, intracoronary thrombus and the presence or absence of MACE. Cut-off points used to declare high and low fibrinogen were obtained through Receiver Operating Characteristic (ROC) curves.

TABLE 1: Characteristics of research subjects.

Variables	Fibrinogen		P-value	Intracoronary thrombus		P-value
	High	Low		Great	Small	
Sociodemographics						
Age (years)	55.4± 7.5	54.3± 10.0	0,639*	57.1± 9.3	51.1± 6.9	0,009*
Gender						
Male	21 (42,9%)	28 57,1%)	0,349¶	27 (55,1%)	22 (44,9%)	0,062#
Female	8 (61,5%)	5 (61,5%)		11 (84,6%)	2 (15,4%)	
BMI						
Normal	11(40,7%)	16 (59,3%)		15 (55,6%)	12 (44,4%)	
Overweight	12 (52,2%)	11 (47,8%)	0,870#	16 (69,6%)	7 (30,4%)	0,618#
Obesity grade I	4 (50,0%)	4 (50,0%)		4 (50,0%)	4 (50,0%)	
Obesity grade II	2 (50,0%)	2 (50,0%)		3 (75,0%)	1 (25,0%)	
Smoking	20 (47,6%)	22 (52,4%)	1,000¶	23 (54,8%)	19 (45,2%)	0,167¶
Hypertension	23 (57,5%)	17 (42,5%)	0,033¶	24 (60,0%)	16 (40,0%)	1,000¶
Diabetes mellitus	12 (60,0%)	8 (40,0%)	0,181¶	11(55,0%)	9 (45,0%)	0,580¶
History of CHD	4 (57,1%)	3 (42,9%)	0,696#	5 (71,4%)	2 (28,6%)	0,696#
Dyslipidemia	18 (43,9%)	23 (56,1%)	0,596¶	21 (51,2%)	20 (48,8%)	0,029¶
STEMI						
Killip Class						
Killip I	13 (36,1%)	23 (63,9%)		18 (50,0%)	18 (50,0%)	
Killip II	8 (66,7%)	4 (33,3%)	0,122#	8 (66,7%)	4 (33,3%)	0,127#
Killip III	4 (80,0%)	1 (20,0%)		4 (80,0%)	1 (20,0%)	
Killip IV	4 (44,4%)	5 (55,6%)		8 (88,9%)	1 (11,1%)	
Onset (hour)	9.9± 8.7	7.7± 5.5	0,230^	9.9± 8.6	6.8± 3.5	0,051^
Echocardiography						
EF (%)	45.6± 8.4	44.3± 10.8	0,617*	44.0± 10.3	46.2± 8.7	0,396*
TAPSE (cm)	2.1± 0.3	2.1± 0.3	0,448^	2.1± 0.3	2.1± 0.3	0,742^
Angiography						
CAD 1 VD	5 (23,8%)	16 (76,2%)		12 (57,1%)	9 (42,9%)	
CAD 2 VD	9 (50,0%)	9 (50,0%)	0,22¶	8 (44,4%)	10 52,6%)	0,078¶
CAD 3 VD	15 (65,2%)	8 34,8%)		18 (78,3%)	5 21,7%)	
Intervention						
LAD	19 (50,0%)	19 (50,0%)		22 (57,9%)	16 (42,1%)	
LCx	3 (60,0%)	2 (40,0%)		1 (20,0%)	4 (80,0%)	
RCA	5 (38,5%)	8 (61,5%)	0,486#	11 (84,6%)	2 (15,4%)	0,116#
LM	1 (100,0%)	0 (0,0%)		1 (100,0%)	0 (0,00%)	
Conservative	1 (20,0%)	4 (80,0%)		3 (60,0%)	2 (40,0%)	

¶Normality test based on Chi-square.
#Fisher's Exact test for normality.
*Normality test based on Independent Sample t-test.
^Normality test based on Mann-Whitney U test.

TABLE 2: Characteristics of research subjects based on MACE.

	MACE	Non-MACE	P-value
Sociodemographics			
Age	58.8 (± 7.4)	51.9 (± 8.8)	<0,002*
Gender			
Male	16 (32,7%)	33 (67,3%)	0,009#
Female	10 (76,9%)	3 (23,1%)	
BMI			
Normal	9 (33,3%)	18 (66,7%)	0,476¶
Overweight	12 (52,1%)	11 (47,9%)	
Obesity Grade I	4 (50,0%)	4 (50,0%)	
Obesity Grade II	1 (25,0%)	3 (75,0%)	
Smoking	17 (40,5%)	25 (59,5%)	0,736¶
Hypertension	18 (45,0%)	22 (55,0%)	0,510¶
Diabetes mellitus	12 (60,0%)	8 (40,0%)	0,047¶
History of CHD	4 (57,1%)	3 (42,9%)	0,439#
Dyslipidemia	12 (29,3%)	29 (70,7%)	0,005¶
STEMI			
Killip Class			
Killip I	4 (11,1%)	32 (88,9%)	
Killip II	8 (66,7%)	4 (33,3%)	<0,001¶
Killip III	5 (100%)	0 (0%)	
Killip IV	9 (100%)	0 (0%)	
Onset (Hour)	11.67 (± 9.9)	6.6 (± 3.1)	0,019^
Echocardiography			
EF (%)	40.3% (± 10.9)	48.2% (± 7.2)	0,001*
TAPSE	2.0 (± 0.3)	2.1 (± 0.3)	0,326*
Angiography			
CAD 1VD	2 (9,5%)	19 (90,5%)	
CAD 2 VD	10 (55,5%)	8 (44,4%)	<0,001¶
CAD 3 VD	14 (60,9%)	9 (39,1%)	
Intervention			
LAD	13 (34,2%)	25 (65,8%)	
LCx	2 (40,0%)	3 (60,0%)	
RCA	6 (46,2%)	7 (53,8%)	0,249¶
LM	1 (100%)	0 (0%)	
Conservative/CABG	4 (80,0%)	1 (20,0%)	
Fibrinogen			
High	19 (65,5%)	10 (34,5%)	<0,001¶
Low	7 (21,2%)	26 (78,8%)	
Intracoronary thrombus			
Large thrombus	22 (57,9%)	16 (42,1%)	0,002#
Small thrombus	4 (16,7%)	20 (83,3%)	

¶Normality test based on Chi-square.
#Fisher's Exact test for normality.
*Normality test based on Independent Sample t-test.
^Normality test based on Mann-Whitney U test.

Major cardiovascular events observed in this study were cardiovascular death, cardiogenic shock, heart failure, malignant arrhythmia and persistent angina. The distribution of MACE can be seen in Table 3.

TABLE 3: Distribution of MACE during hospitalization.

MACE Type	Total	Percentage (%)
None	36	58,1
There is		
Death	4	6,5
Cardiogenic shock	6	9,7
Heart failure	9	14,5
Malignant arrhythmia	3	4,8
Persistent angina	4	6,5
Total	62	100

This study evaluated intracoronary thrombus and in STEMI patients undergoing primary PCI. Evaluation of intracoronary thrombus and was performed by two cardiac intervention consultant observers using criteria developed by the TIMI group classification through coronary angiography during PCI. The inter-observer reliability test used was the Cohen Kappa test.

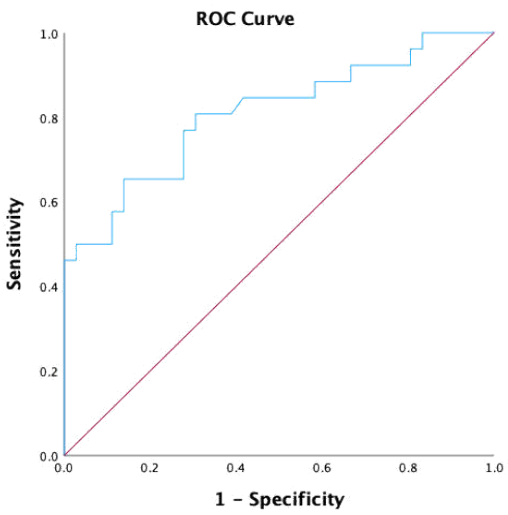
Based on the Cohen Kappa test, the results are said to have good reliability if the limit of agreement is between 0 and 1, where the result of 0 shows no agreement, increasing to 1 shows perfect agreement, >0.80 excellent agreement, 0.61-0.80 good agreement, 0.40-0.60 moderate agreement, and <0.41 poor agreement. The inter-observer reliability analysis is shown in Table 4. In this test, the percent of agreement between the two observers was 95.16. In the assessment of the degree of intracoronary thrombus, the Kappa agreement value was 0.897 and the asymptomatic standard error was 0.058 ($p < 0.001$). These results indicate a good reliability test on intracoronary thrombus between the two observers.

TABLE 4: Inter-observer intracoronary thrombus reliability test.

Variables	N of Vali Case	Percent of Agreement	Kappa Value	Asymptomatic Standard Error[a]	Approximate T[b]	Approximate Significance
Intracoronary thrombus	62	95,16	0,897	0,058	7,069	<0,001

[a]Not assuming the null hypothesis.
[b]Using the asymptomatic standard error assuming the null hypothesis.

Based on ROC curve analysis, the optimal cut-off point value of fibrinogen to predict outcomes is 341.6 mg/dl with a sensitivity of 73.1% and specificity of 72.2% (Figure 1). Area Under Curve (AUC) is 0.809. Using a cut-off point of 341.6 mg/dl, the study subjects were then grouped into two categories: high fibrinogen and low fibrinogen. After grouping, 29 patients with high fibrinogen and 33 patients with low fibrinogen were obtained.



Fibrinogen (mg/dl)	341,6
AUC	0,809
Sensitivity (%)	73,1
Specificity (%)	72,2
95% IC lower limit	0,696
95% IC upper limit	0,923

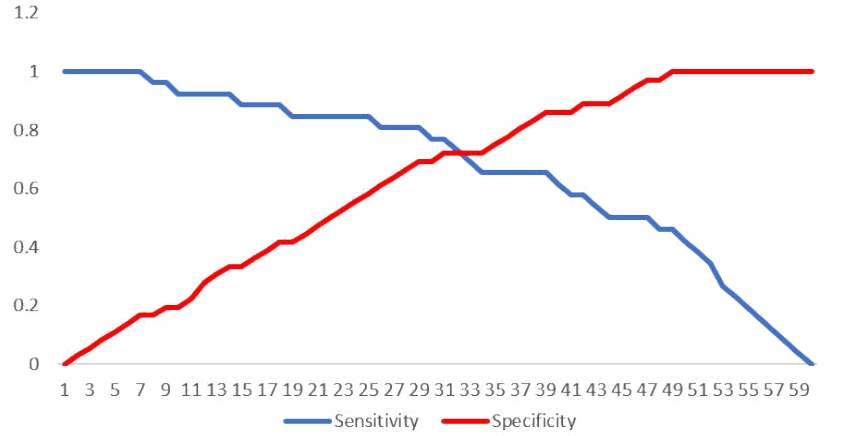


FIGURE 1: ROC curve in determining fibrinogen cut-off values.

Of the 62 STEMI patients who underwent primary PCI, there were 29 patients with high fibrinogen levels and 19 of them experienced SMI.

The Kaplan-Meier survival estimation picture of the occurrence of MCI based on the category of high and low fibrinogen levels is shown in Figure 2A.

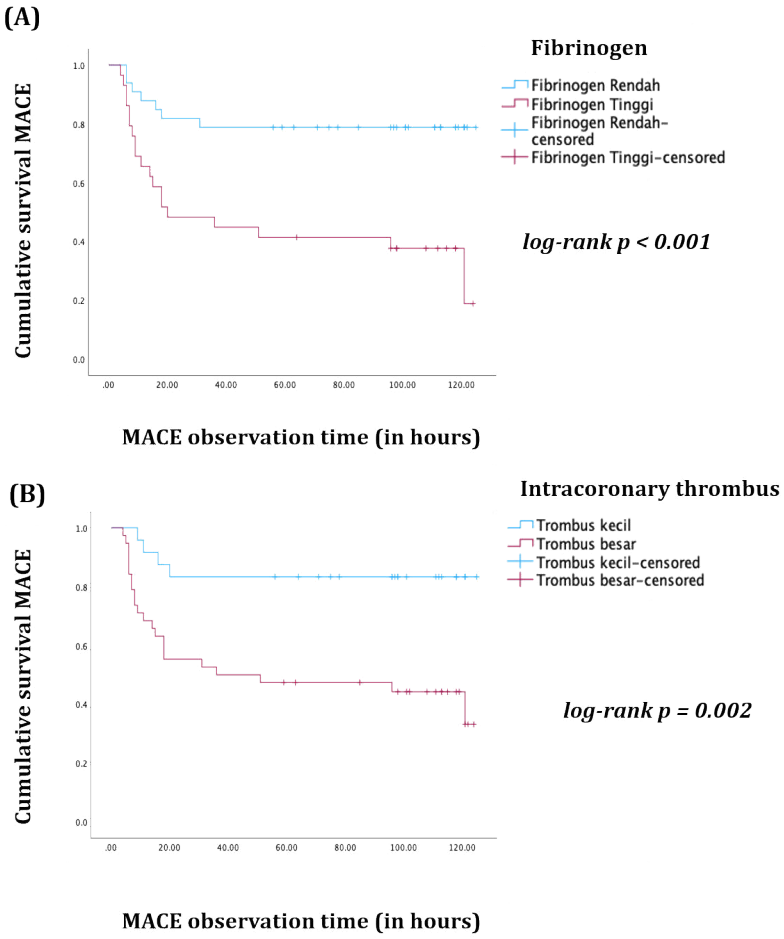


FIGURE 2: Kaplan-Meier survival estimation curves of the occurrence of FMD based on fibrinogen values (A), intracoronary thrombus (B).

Based on Table 5, the 5-day survival rate of patients with high fibrinogen was 34.5% and the mean survival time of patients was 58.1 hours (IK95% 38.7-77.4), while the 5-day survival rate in low fibrinogen was 78.8% and the mean survival time was 101.4 hours (IK 95% 85.8-116.9). After the log-rank test, there was a significant difference in the survival rate of patients with high and low fibrinogen with a p value <0.001.

In the intracoronary thrombus variable, there were 38 patients with large thrombus with 22 of them experiencing SMI. The Kaplan-Meier survival estimation of the occurrence of FMD based on the intracoronary thrombus category is shown in Figure 2B.

TABLE 5: Mean survival time based on fibrinogen value category, intracoronary thrombus.

Variables	Mean Survival Time (hour)	95% IK	5 Days Survival Rate	P-value
High fibrinogen	58,1	38,7-77,4	34,5%	<0,001*
Low fibrinogen	101,4	85,8-116,9	78,8%	
Large thrombus	65,0	47,7-82,3	42,1%	0,002*
Small thrombus	106,5	89,9-123,0	83,3%	

*Statistically significant.

Based on Table 5, the 5-day survival rate of patients with large thrombus was 42.1% and the mean survival time was 65.0 hours (IK 95% 47.7-82.3), while in small thrombus, the 5-day survival rate was 83.3% with a mean survival time of 106.5 hours (IK 95% 89.9-123.0). After the log-rank test, there was a significant difference in survival rate in patients with large and small thrombus with a p value = 0.002.

In this study fibrinogen, intracoronary thrombus and were used as independent variables and other factors such as age, gender, DM, dyslipidemia, Killip class, STEMI onset, EF, coronary angiography as control variables. In control variables with numerical data scale, namely age, EF and STEMI onset, data normality test was performed with Kolmogorov Smirnoff test and significance test with independent sample t-test. Control variables with categorical data scale (gender, DM, dyslipidemia, Killip class, coronary angiography) were subjected to Chi Square test.

TABLE 6: Multivariate analysis of Cox regression of fibrinogen and intracoronary thrombus on MFI using the backward method.

Variables	Unadjusted HR	95% IK	P-value	Adjusted HR	95% IK	P-value
Fibrinogen	4,10	1,72-9,78	<0,001*	3,45	1,29-9,23	0,013*
Intracoronary thrombus	4,53	1,56-13,16	0,001*	4,30	1,24-14,90	0,021*
Age	1,07	1,02-1,11	0,002*	1,01	0,94-1,09	0,764
Gender	2,95	1,32-6,56	0,012*	1,69	0,56-5,07	0,348
DM	0,47	0,21-1,01	0,061	0,55	0,19-1,58	0,264
Dyslipidemia	3,09	1,43-6,72	0,005*	1,84	0,57-5,94	0,308
Onset of STEMI	1,032	0,99-1,07	0,067	1,00	0,96-1,06	0,793
Killip Class						
Killip I			<0,001*			0,014*
Killip II	10,03	2,98-33,73	<0,001*	5,87	1,71-20,12	0,005*
Killip III	23,32	5,88-92,43	<0,001*	8,69	1,99-38,12	0,004*
Killip IV	16,45	4,92-54,94	<0,001*	6,20	1,51-25,43	0,011*
EF (%)	0,93	0,89-0,97	<0,001*	0,93	0,91-1,01	0,093
Angiography						
CAD 1VD			0,015*			0,017*
CAD 2VD	8,15	1,78-37,29	0,007*	5,69	1,17-27,57	0,031*
CAD 3VD	8,65	1,96-38,18	0,004*	1,54	0,29-8,26	0,615

*Statistically significant

Multivariate analysis (Table 6) used to determine the effect of fibrinogen and intracoronary thrombus on MFI independently was Cox regression. The variables included in the multivariate analysis were control variables that showed a p value <0.05. Multivariate analysis showed that high fibrinogen was an independent predictor of MACE during hospitalization in STEMI patients undergoing IKP (adjusted HR 3.45; 95% CI 1.29-9.23; p=0.013). This indicates that in STEMI patients who underwent IKP, after controlling for confounding variables, MFI during hospitalization was 3.45 times higher in patients with high fibrinogen compared to those with low fibrinogen.

Similarly, this study showed that large intracoronary thrombus was an independent predictor of FMD during hospitalization in STEMI patients who underwent IKP (adjusted HR 4.3; 95% CI 1.24-14.90; p=0.021).

This means that the risk of MFI in STEMI patients with large intracoronary thrombus after controlling for confounding factors is 4.3 times that of small intracoronary thrombus.

Analysis of the risk of developing MCI if the variables of fibrinogen and intracoronary thrombus are combined was performed with Structural Equation Modeling (SEM). SEM is a statistical method used to test and measure complex cause-and-effect relationships among variables in a model. In SEM, multivariate analysis is carried out by combining factor analysis, structural model and pathway analysis approaches. The approaches used are Cochran's and Mantel Haenszel.

In this study, a combined analysis of fibrinogen and intracoronary thrombus as predictors of MFI was performed. The results of SEM analysis are shown in the table below Table 7.

TABLE 7: Results of Structural Equation Modeling (SEM) analysis of fibrinogen and intracoronary thrombus on MCH.

Fibrinogen			MACE		Specific RR	Breslow-Day Homogeneity	Cochran's and Mantel-Haenszel
			Yes	No			
High	Thrombus	great	17 (81,0%)	4 (19,0%)	3,24	0,268	0,002*
		small	2 (25,0%)	6 (75,0%)			
Low	Thrombus	great	5 (29,4%)	12 (70,6%)	2,35		
		small	2 (12,5%)	14 (87,5%)			
Adjusted RR 95% IK						2,87 1,12-7,35	

*Statistically significant.

DISCUSSION

The development of science, especially in the cardiovascular field, has progressed rapidly, especially in the aspects of diagnostics and management. However, the high complication rate in STEMI remains a serious challenge.

One of the major complications that arise in STEMI is MACE which has a significant impact on patient outcomes. MACE involves a number of conditions such as cardiovascular death, cardiogenic shock, heart failure, malignant arrhythmias and persistent angina. The high mortality and morbidity caused by MACE prompts the need for early prediction and prevention efforts.

In this endeavor, prognostic biomarkers have become an important research focus in STEMI and one of the prominent biomarkers is inflammatory biomarkers. Understanding inflammatory and coagulation biomarkers in STEMI is expected to open new opportunities in risk assessment and patient management. The existence of these biomarkers not only provides insights into inflammation and coagulation at the cellular level, but also provides a basis for more effective prevention strategies.

Integration of information from various relevant biomarkers may improve the accuracy in assessing the risk of complications and lead to a personalized approach in STEMI management. Therefore, inflammatory and coagulation biomarkers are important alternatives in risk assessment for MACE as a potential complication in STEMI patients.

Research on fibrinogen in STEMI is a highly relevant area in an effort to better understand the pathophysiological mechanisms, prognosis and management of this condition. Fibrinogen is a protein involved in the coagulation process and has a key role in the body's response to inflammation and blood clot formation. This study evaluated fibrinogen and intracoronary thrombus on MACE in STEMI patients undergoing primary PCI.

In this study, 62 research subjects were taken by consecutive sampling from the research population. The average age of this research sample was 54.8 years. This is in accordance with research conducted by Dharma et al 2016 who found that the average age of STEMI patients was 55 years old. [14]. Other research conducted by Hendrickson et al. also obtained the age of STEMI patients 55 years [15]. In gender, the majority of STEMI patients are male. This is in accordance with the research conducted by Dharma et al., n.d.; Fraticelli et al., 2020; Li et al., 2023; Petrosyan et al., 2023 who found that men suffer more from STEMI [14,16-18]. In BMI, it was found that BMI in STEMI patients was 26.6. This is in accordance with research conducted by Fraticelli et al with BMI ≥ 25 [16]. Risk factors such as smoking, hypertension, DM and dyslipidemia were also identified as causes of STEMI in line with previous findings by Hendrickson 2022 and Fraticelli 2020 [15,16].

Killip III and IV classes are more likely to experience MACE. This is in accordance with the study of Li et al.which showed a higher rate of MACE in patients with Killip III and IV [17]. STEMI onset also affects MACE, where patients who experience MACE have a longer STEMI onset than those who do not experience MACE (11.7 ± 9.9 hours vs 6.6 ± 3.1 hours). These results are similar to those obtained in the study of Li et al. that STEMI patients who experienced MACE had a higher onset of 8 (4.00-17.00) hours vs 6 (3.00-12.00) hours [17].

In left ventricular function, STEMI patients who experienced MACE had lower EF compared to those who did not (MACE vs Non-MACE: 40.3% vs 48.2%). Similar results were also obtained by Li et al. who obtained the EF value of MACE vs non-MACE: 44.6% vs 52.3%. In the TAPSE examination, there was no significant difference between patients who experienced MACE or not. Similar results are in accordance with the study of Li et al. 2023 [17].

The number of affected vessels showed that patients with 3VD CAD were more likely to experience MACE. This finding is slightly different from Li's study which showed that 1VD CAD was more frequently associated with MACE events. Nonetheless, the results of the analysis were not significantly different from the findings in the study of Li et al. 2023 [17].

From the results of the data analysis that has been conducted, it appears that the overall characteristics of the subjects of this study do not show significant differences when compared to previous studies. This finding indicates that there is sufficient similarity between the two groups of subjects, both in terms of their demographic and clinical characteristics.

The AUC curve illustrates the extent to which the classification model is able to distinguish between positive and negative groups. If the AUC value is close to 1.0; the model is considered very good at discriminating. Conversely, if the AUC value is close to 0.5, it indicates that the model's performance is no better than chance. AUC curves above 0.5 signify increasingly better performance, while values below 0.5 indicate a model that predicts inversely. In addition to the AUC value, the shape of the ROC curve also provides visual information about the performance of the model with the curve getting closer to the upper left corner indicating better results. Determination of cut-off points using ROC curves involves analyzing sensitivity and specificity at various cut-off point values. The ROC curve visualizes this relationship. The point where the curve intersects provides the best balance between sensitivity and specificity. The cut-off point is the optimal threshold value to separate two categories on the analyzed variable.

In this study, the AUC value of fibrinogen on MACE was 0.809 with a sensitivity of 73.1% and specificity of 72.2%. Research conducted by Binti et al. obtained an AUC fibrinogen value of 0.670 with a sensitivity of 58.0% and specificity of 71.10%. [19].

Another study from Çetin et al., 2020 obtained an AUC value of MACE of 0.632 with a sensitivity of 56.7% and specificity of 70.7% [20]. Another study from Makkar et al., 2023 found that the AUC value of fibrinogen against TIMI≤ 1 which is a predictor of MACE is 0.805 with a sensitivity of 74.4% and specificity of 74.2% [21].

In this study, the cut-off point value was 341.6 mg/dl. Research conducted by Ang et al., 2017 obtained a cut-off point for the value of fibrinogen for the occurrence of MACE, which is 280 mg/dl [13]. Another study by Ang et al., 2013 found that the cut-off point of fibrinogen for the occurrence of MACE was 345 mg/dl [22]. Zhao et al. obtained a fibrinogen cut-off point for the occurrence of MACE with a value of 291.1 mg/dl [23]. Another study conducted by Shi et al., 2010 found that a fibrinogen value of 350 mg/dl was an independent predictor of MACE [24]. Another study from Hsieh et al. obtained a cut-off point of 333.5 mg/dl for fibrinogen values [25]. Research by Çetin et al., 2020 found that a fibrinogen value of ≥352.8 mg/dl had a significant MACE compared to lower fibrinogen values [20].

Thus, it can be concluded that the results of this study support the concept that fibrinogen has potential as a predictor of MACE. The uniformity of the cut-off point findings of fibrinogen values with previous studies adds validity and generality to the results of this study. The implication is that this study positively contributes to the understanding of the role of fibrinogen as a risk factor for MACE with the high AUC value strengthening the argument for the success of the classification model in predicting such risk.

From the cut-off point values above, high fibrinogen is an independent predictor of MACE. Survival analysis in this study showed that high fibrinogen was a predictor of MACE in STEMI patients (log-rank $p < 0.001$).

Research Ang et al. 2017 found that high fibrinogen was associated with MACE in ACS patients undergoing PCI (62.7% vs 36.0%, log-rank $p = 0.023$) [13]. This study also found that high fibrinogen was associated with hospitalization due to ACS, revascularization, MI, definitive stent thrombosis, stroke and death 24 hours post PCI. Landmark analysis found that there was an increase in total MACE and individual MACE that occurred at 24 hours to 2 years follow-up in the group with high fibrinogen levels. Another study conducted by Shi et al., 2010 also found that fibrinogen levels in patients with ACS were higher and associated with 30-day to 2-year MACE.

This study also found that in ACS patients, high fibrinogen was associated with clinically significant events compared to the group with low fibrinogen ($p < 0.05$) and this difference was particularly evident in patients who experienced MACE in the first 30 days compared to those who did not experience MACE.

This study also found that high fibrinogen was associated with worse short-term prognosis (OR 9.99; 95% CI 2.75-36.33; $p = 0.0005$). Survival analysis showed that the group with low fibrinogen levels had a higher MACE survival rate ($p = 0.001$).

The study Hsieh et al. who looked at the association of fibrinogen with the risk of cardiovascular disease and mortality in Taiwan found that on survival analysis, patients with high fibrinogen levels had a high incidence of CAD, stroke and all-cause mortality (log rank test $p < 0.001$ for CAD; $p = 0.042$ for stroke and $p < 0.001$ all-cause mortality) [25]. This study also found that patients with high fibrinogen had a greater risk of CAD than those with low fibrinogen even in individuals with low CRP levels. Zhao et al. showed that fibrinogen combined with Age, Creatinine and Ejection Fraction (ACEF) score can predict MACE after PCI in ACS patients. The integration of fibrinogen significantly helped the ability to discriminate the reclassification of ACEF score. In the survival analysis, it was found that the group with a low ACEF score had a greater event free survival compared to the group with a higher ACEF score ($p < 0.001$). Research Jiang et al., 2019 found that fibrinogen was an independent predictor of MACE (adjusted HR 1.0; IK 95% 0.95-1.12; $p = 0.005$) [26]. At 2 years follow up, the analysis of survival also showed that patients with high fibrinogen had higher all-cause mortality (log rank $p = 0.022$).

Thus, the overall study results emphasize that fibrinogen is an important indicator in evaluating the risk of MACE in ACS patients undergoing PCI. These findings support the importance of fibrinogen measurement as a potential predictive tool to aid in the identification and management of cardiovascular risk in such patient groups.

Large intracoronary thrombus is a phenomenon that indicates the formation of a significant sized blood clot within the coronary blood vessels, has a serious impact and is a risk factor for MACE. Recent studies have shown that the presence of large intracoronary thrombus is consistently identified as a predictor of MACE in STEMI patients undergoing primary PCI. This study found that large intracoronary thrombus was an independent predictor of MACE, with a 4-fold greater risk compared with low intracoronary thrombus (adjusted HR 4.30; 95% CI 1.24-14.90; $p<0.021$).

This finding is reinforced by previous studies, such as the study of Kumar et al. which showed an association between thrombus grade and MACE ($p<0.001$) [27]. Multivariate analysis showed that large intracoronary thrombus as an independent predictor of MACE (adjusted HR 2.2; 95% CI 1.51-3.24; $p<0.001$). Another study conducted by Scarparo et al. found that large intracoronary thrombus was a predictor of MACE [28]. Multivariate analysis found that large intracoronary thrombus was an independent predictor of MACE in anterior STEMI (adjusted HR 2.72; IK 95% 1.45-5.08; $p = 0.002$).

Research Tian et al., 2017 found that large intracoronary thrombus was a predictor of MACE [29]. Multivariate analysis showed that large intracoronary thrombus was an independent predictor of MACE (adjusted HR 2.62; IK 95% 1.24-4.54; p = 0.001). The study Sianos et al., 2007 found that large intracoronary thrombus was a predictor of MACE [30]. Multivariate analysis at 2-year follow-up showed that large intracoronary thrombus was an independent predictor of MACE (adjusted HR 1.88; 95% CI 1.30-2.72; p = 0.001).

Conclusions from these studies indicate that large intracoronary thrombus is a significant independent predictor of MACE in STEMI patients undergoing primary PCI. These findings provide a strong basis for improved prevention, diagnosis and patient management strategies with a focus on the identification and management of large burden thrombus.

Structural equation model (SEM) is a statistical method used to analyze complex relationships between variables in a model. SEM can be used to test and model causal relationships among these variables. The structural equation describes the causal relationship between the variables.

In this study, the risk of MACE in patients with high fibrinogen with large intracoronary thrombus was 81%. When compared to the low fibrinogen group with small intracoronary thrombus, the risk of MACE was 12.5%. Analysis showed the risk of MACE when both variables were combined (adjusted RR 2.87; 95% CI 1.12-7.36; Cochran's and Mantel-Haenszel p = 0.002).

Several studies have shown that high concentrations of γ′ fibrinogen in plasma can trigger the formation of blood clots that are highly resistant to fibrinolysis. [31-33]. Research Tabakcl et al., 2017 found that fibrinogen was not only an independent risk factor for patients with high SYNTAX scores, but also a determinant of coronary lesion complexity (OR 1.01; 95% CI 1.01-1.02; p < 0.001) [34]. Charach et al. provided new insights by using the Gensini score to estimate severity in patients with STEMI, NSTEMI, UAP, and angina syndrome [35]. Intracoronary thrombus, defined as a contrast media filling defect without calcification and dissection, is one of the scoring elements in the Gensini score. Gao et al. showed that fibrinogen was an independent risk factor for high Gensini score (AUC 0.656; 95% CI 0.59-0.76; p < 0.001) [33]. Another study from Duan (2021) showed that the ROC curve of fibrinogen was a predictor of high Gensini score in ACS patients (AUC 0.663; IK 95% 0.605-0.720; p<0.001 [36]. This value becomes even better especially when combined with the ratio to albumin (AUC 0.706; 95% CI 0.660-0.742).

Although no direct studies have explored the direct correlation between fibrinogen as a coagulation and inflammatory factor and intracoronary thrombus, the overall information above suggests that there is a complex interaction between fibrinogen and intracoronary thrombus. Fibrinogen, in addition to playing a vital role in platelet aggregation, plasma viscosity, and fibrin formation, is also closely associated with inflammation which has a key role in plaque rupture and thrombosis [26]. These findings not only open the door for further understanding of this relationship but also highlight the potential of fibrinogen as a target for the prevention and management of cardiovascular disease.

There were several weaknesses in this study. Some confounding factors that may affect the outcome, such as lifestyle, social aspects and the presence of comorbidities were not clearly evaluated in the study subjects.

Another limitation is that MACE monitoring is only during hospitalization. The lack of information regarding long-term prognosis makes it difficult to understand the overall picture. Thus, further research with a longer follow-up period is needed so that the results of the study are more representative and can be applied more broadly to the general population.

CONCLUSSION

The conclusions of this study are: 1) High fibrinogen is an independent predictor of MACE during hospitalization in STEMI patients undergoing primary PCI; 2) Large intracoronary thrombus is an independent predictor of MACE during hospitalization in STEMI patients undergoing primary PCI; 3) There is an interaction between fibrinogen and intracoronary thrombus on MACE during hospitalization in STEMI patients undergoing primary PCI. This study provides insight into how different biological factors may interact and influence prognosis in STEMI patients undergoing primary PCI. This allows for a more targeted approach in the clinical management of these patients, by holistically considering the factors involved.

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