IJSCIA

International Journal of Scientific Advances
ISSN: 2708-7972
Volume: 4 | Issue: 6 | Nov – Dec 2023 Available Online: www.ijscia.com
DOI: 10.51542/ijscia.v4i6.17

D-Dimer to Creatinine Ratio (DCR) and Intracoronary Thrombus Burden as Risk Factors for Hospitalized Major Cardiovascular Events (MACE) in Patients with ST Elevation Myocardial Infarction (STEMI)

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ABSTRACT

Background: STEMI pathophysiology is based on increased activity of coagulation, thrombosis, and inflammation. The role of STEMI biomarkers is essential for prognostic and risk stratification. Dimer-Creatinine Ratio (DCR) is a novel biomarker that could be combined with intracoronary thrombus burden according to TIMI Thrombus Grade to evaluate in hospital MACE in STEMI patients. ***Methods:*** A cohort prospective design was implemented in this study, with subjects of STEMI patients undergoing primary PCI. Low and high DCR values were determined by the ROC curve. Survival analysis with the Kaplan-Meier curve was used to evaluate MACE outcome according to DCR and intracoronary thrombus burden. Multivariate analysis Cox regression and stratification analysis were used to evaluate independent risk factors, the relationship of each variable, and in hospital MACE. ***Results:*** A total of 60 samples were included, 40 patients (66.7%) with high DCR and 36 patients (60%) with high intracoronary thrombus burden. 36 (59.8%) patients were known to have in hospital MACE. Cut-off point was used to determine high DCR was 1.51 (AUC 0.905; 95%CI: 0.825-0.989; p<0.001). Cox regression model backward log rank showed high DCR (adjusted HR 20.81; 95%CI: 2.18-98.16; p=0.007) and high intracoronary thrombus burden (adjusted HR 31.38; 95%CI: 4.51-89.15; p=0.017), smoking (adjusted HR 2.70; 95% CI 0.88-3.29; p=0.012), and diabetes mellitus (adjusted HR 7.55; 95% CI 1.13-11.58; p=0.035) played a role as independent risk factors of in-hospital MACE in STEMI patients. A combination of both high DCR and high intracoronary thrombus burden had a higher incidence of 91.2% of in hospital MACE according to stratification analysis (Mantel-Haenzel Common Estimate 14.33; Breslow-Day Homogeneity p=0.803; Cochran's and Mantel-Haenszel p=<0.013). ***Conclusion:*** High DCR and high intracoronary thrombus burden can be used as additional information for risk stratification of in hospital MACE in STEMI patients, especially when both parameters are combined.

Keywords: STEMI; D Dimer-Creatinine Ratio (DCR); intracoronary thrombus burden; Major Adverse Cardiovascular Events (MACE); cardiovascular death; cardiogenic shock; acute heart failure; malignant arrhythmia

INTRODUCTION

Cardiovascular disease is the number one cause of death worldwide. Approximately 17 million people died from cardiovascular disease in 2015, representing 31% of all global deaths. The cardiovascular disease that has the highest mortality and disability rate is coronary heart disease (CHD). Each year it is estimated that around 620,000 people have a coronary heart attack defined as the first hospitalization resulting from an Acute Myocardial Infarction or death from coronary heart disease and around 295,000 people have a recurrent attack.

Globally, the World Health Organization (WHO) estimates that non-communicable diseases cause about 60% of deaths and 43% of morbidity worldwide [1].

Acute Myocardial Infarction (AMI) especially ST-Elevation Myocardial Infarction (STEMI) is still the cause of cardiovascular morbidity and mortality in the general population. Acute to chronic inflammation can be involved in all stages of coronary atherosclerosis, from endothelial dysfunction, and plaque accumulation to clinical manifestations of acute disease [2].

Activation of the coagulation and fibrinolysis systems plays an important role in the pathogenesis and prognosis of ACS [3]. STEMI is a cardiac emergency in which myocardial cell death occurs as a result of total coronary artery occlusion [1].

The high morbidity and mortality of STEMI patients are caused by complications. Some of the complications include ischemic complications, mechanical complications, heart rhythm disturbances, embolism, and death. MACE are complications of STEMI that are directly related to patient survival. Heart failure with decreased left or right ventricular contractility is an important mechanical complication of STEMI. In right heart failure, left ventricular filling will be impaired leading to a sudden decrease in cardiac output. Mortality of heart failure after STEMI reaches 57% [1]. This decrease in contractility can lead to cardiogenic shock. Cardiogenic shock is a major predictor of in-hospital mortality, and there is a similar prevalence of cardiogenic shock in Non-ST Elevation Myocardial Infarction (NSTEMI) and ST Elevation Myocardial Infarction (STEMI) patient groups. Complications of STEMI that are also associated with survival rates are various malignant arrhythmias that can cause hemodynamic disturbances in patients, such as supraventricular tachyarrhythmias and persistent ventricular tachyarrhythmias, as well as high-grade atrioventricular block [4]. Ischemic complications that are included in major cardiovascular events are post-infarction angina, which describes an expansion of the infarct, recurrent infarction in another coronary artery territory, or reocclusion in the coronary artery associated with the infarct [1].

As a fibrinoid degradation product, D-dimer increases upon thrombosis and/or dissolution in the circulatory system and can be used clinically as a clinical biomarker of thrombosis [5]. Elevated D-dimer levels were also found to be associated with the severity of coronary artery disease in patients with ACS [6]. Recently, fibrin D-dimer has been increasingly evaluated in the incidence of atherosclerosis. One of the reasons is because it can be considered as a global marker of fibrin cross-linking turnover and activation of the hemostatic system [7]. In contrast to some other hemostasis markers, the D-dimer assay is more stable and more practical to measure, making it more suitable in clinical testing. In some literature, D-dimer concentrations can increase up to several months after STEMI, indicating that patients with STEMI have an increased state of coagulability [6]. Thus, D-dimer as a coagulation indicator may be a good biomarker in predicting cardiovascular ischemic events. Previous studies have assessed a positive correlation of D-dimer with ACS and stroke risk [6].

While other studies have also shown that plasma D-dimer is a good predictor of Major Adverse Cardiac Events (MACE) in cardiovascular disease [8]. However, most previous studies did not indicate whether anticoagulant drugs such as heparin were included in the study assessment. In a meta-analysis study by Biccirè et al.stated that in patients with ACS, D-dimer was associated with higher in-hospital and short/long-term complications. D-dimer was also higher in patients with the no-reflow phenomenon. The use of D-dimer may help identify patients with residual thrombotic risk after ACS [9]. Previous studies suggest that heparin may affect D-dimer levels which could affect the predictive value of D-dimer in patients with Coronary Heart Disease (CHD) [6]. So additional research is needed that can provide data on the role of D-dimer in CHD patients without prior anticoagulant use.

At the same time, serum creatinine levels, as one of the indicators reflecting renal function, are associated with systemic atherosclerosis. In addition, studies have found that creatinine levels correlate with the incidence, severity, and prognosis of coronary heart disease [10]. Previous studies have combined serum creatinine with other clinical indicators to assess risk and prognosis in cardiovascular disease patients. For example, the urea to creatinine ratio (UCR) was shown to be one of the predictors of long-term mortality in chronic heart failure with good ejection fraction patients. In addition, UCR was also found to have predictive value for the prognosis of patients with acute myocardial infarction complicated by acute heart failure [11].

The American College of Cardiology/American Heart Association (ACC/AHA) recommends the use of cardiovascular biomarkers for rapid diagnosis and prognostic assessment in patients with chest pain. Increased glomerular filtration rate and urinary creatinine albumin ratio significantly improve adverse cardiovascular outcomes (cardiovascular mortality, heart failure, coronary disease and stroke) [12]. In the study conducted by Cerne et al, a slight increase in serum creatinine concentration was evaluated as an independent predictor of all-cause and cardiovascular disease mortality in hypertensive patients, elderly and general population. In addition, serum creatinine concentration independently predicted mortality of CAD and post-myocardial infarction patients with normotensive, nonobese, and normoglycemic patients. Serum creatinine concentration independently predicts survival of post-stroke patients. There is a positive correlation of increased serum creatinine concentration as a marker for atherosclerotic vascular disease in general [10].

Intracoronary thrombus burden is a risk factor for long-term major cardiovascular events, including stent thrombosis, no reflow, and distal embolization. Intracoronary thrombus is a well-studied predictor, also associated with associated clinical and angiographic conditions [13]. In STEMI there is total obstruction due to intracoronary thrombosis. Increased blood viscosity is one of the mechanisms responsible for the etiopathogenesis of thrombus formation, has been discussed in many previous studies and it has been shown that many parameters are associated with increased viscosity [1]. The literature has classified the degree of coronary thrombus burden with the Thrombolysis in Myocardial Infarction (TIMI) classification.

The thrombus grading scale is an important modality used in the qualification and quantification of thrombus burden. The classification provides clinical assessment data and can influence management decisions before and during intervention [14].

The widely used TIMI thrombus grading scale was originally created by the TIMI study group investigators. The introduction of this universal classification reflects the severity of the thrombus assessed by its size and intracoronary thrombus burden. Overall, the TIMI classification relies on angiographic assessment of thrombus presence, size and estimation of clinical events experienced by the patient. This classification uses simple scoring ranging from grade 0 (no thrombus), to grade 5 where a very large thrombus completely blocks coronary blood vessel flow [15].

Many studies have focused on D-dimer and creatinine studies, respectively. It has been proven that both can provide additional information for diagnosis and risk assessment in patients with cardiovascular disease. However, there has been no study combining the ratio of these two indicators in the STEMI patient population especially in relation to the degree of coronary thrombus based on TIMI classification. Therefore, this study was conducted to combine D-dimer and creatinine ratio (DCR) as a new clinical biomarker, and test it as a risk factor for major cardiovascular events (MACE). It is hoped that this biomarker can help link data related to the degree of coronary thrombus with predictors of MACE in hospitalized patients.

SUBJECTS AND METHODS

This research constitutes a single-center, prospective observational cohort study collaboration to see the interaction of DCR values and intracoronary thrombus on MACE during hospitalization in STEMI patients. The sampling technique used in this study was non-probability sampling, namely by using consecutive sampling. The research took place at Prof. Dr. I G. N. G. Ngoerah Hospital, Denpasar, Bali. Blood samples in the form of D-Dimer and Creatinine were taken in the cardiac emergency room. Blood samples were then sent and examined at the clinical pathology laboratory of Prof. dr. I G. N. G. Ngoerah Hospital. Assessment of the degree of intracoronary thrombus was performed in STEMI patients undergoing primary percutaneous coronary intervention (PCI). Samples of patients with STEMI who underwent percutaneous coronary intervention and were hospitalized at Prof. dr. I G. N. G. Ngoerah Hospital.

Inclusion criteria: 1) STEMI patients who underwent primary percutaneous coronary intervention and were hospitalized at Prof. Dr. I.G.N.G. Ngoerah Hospital; 2) STEMI patients who are willing to participate by signing the consent form after explanation. Exclusion Criteria: 1). Patients with comorbid severe chronic kidney disease (stage IV and V); 2). Patients with acute stroke or history of stroke; 3). Patients with Deep Vein Thrombosis (DVT) or pulmonary embolism; 4). Patients with DIC (Disseminated Intravascular Coagulation); 5) Patients with severe infection or sepsis; 6) Patients with chronic hepatitis or hepatic cirrhosis; 7) Patients with a history of malignancy; 8) Patients with a previous history of long-term antiplatelet use (>4 weeks); 9) Patients with a previous history of long-term anticoagulant use (>4 weeks); 10) Patients with a previous diagnosis of chronic coronary syndrome/chronic coronary heart disease.

DCR Examination Procedure

All research samples were taken venous blood to be used as samples for DCR examination using reagents available at the Clinical Pathology Laboratory of Prof. dr. I G. N. G. Ngoerah Hospital using the enzyme-linked immunosorbent assay (ELISA) method. DCR examination was taken when the patient was in the cardiac emergency department or the first day of admission to Prof. Dr. I G. N. G. Ngoerah Hospital. The results of the examination of D-dimer levels are quantitatively expressed in mg/L. The cut off value of D-dimer expressed within normal limits is less than 0.5 mg/mL.

Procedure for Examining the Degree of Intracoronary Thrombus

Examination of the degree of intracoronary thrombus was performed in patients undergoing percutaneous coronary angiography intervention. Intracoronary thrombus is defined as a filling defect surrounded by contrast media. Thrombus evaluation was reviewed by a minimum of two interventional consultant cardiologists. Interpretation was generated through thrombus classification based on TIMI Classification. Low intracoronary thrombus grade is grade 0-2 and high is grade 3-5.

MACE Assessment Procedure

Outcome assessment of MACE is performed when the patient is admitted until the outcome occurs, including death certificate for cardiovascular death, ECG for malignant arrhythmia, hemodynamic examination for cardiogenic shock and echocardiography and thoracic X-Ray for acute heart failure.

All data collected in each group were then analyzed with the SPSS version 24.0 program. Data analysis performed included descriptive analysis, reliability test, comparison test, Homogeneity test, Receiver Operating Characteristic (ROC) curve analysis, Survival analysis, Multivariate analysis, Stratification analysis, with a confidence level in this study of 95% and $p<0.05$.

RESULTS

The results of the descriptive analysis of the study population are shown in Table 1-4. Patients were categorized into two groups based on presence of DCR and absence of DCR. The cut-off point in declaring high DCR and low DCR was obtained by creating a Reciever Operating Characteristics (ROC) curve.

TABLE 1: Sociodemographic Characteristics of Research Subjects by Category DCR Value and Degree of Intracoronary Thrombus.

Variables	DCR		P-value	Degree of Intracoronary Thrombus		P-value
	High	Low		High	Low	
	40 (66,7%)	(33,3%)		36 (60,0%)	24 (40,0%)	
Age (mean ± SD (years))	59,8±11,20	57,64±9,51	0,612μ	59,31±11,80	58,77±9,16	0,656μ
Gender (n (%))						
Male	34 (85,0)	17 (85,0)	0,658¶	31 (86,1)	20 (83,3)	0,522¶
Female	6 (15,0)	3 (15,0)		5 (13,9)	3 (16,7)	
Smoking (n (%))						
Yes	24 (60,0)	5 (25,0)	0,001¶*	23 (63,9)	6 (25,0)	0,005¶*
No	16	15 (75,0)		13 (36,1)	18 (75,0)	
Dyslipidemia (n (%))						
Yes	17 (42,5)	10 (50,0)	0,395¶	14 (38,9)	13 (54,2)	0,184¶
No	23 (56,5)	10 (50,0)		22 (61,1)	11 (45,8)	
Diabetes Mellitus (n (%))						
Yes	7 (17,5)	8 (40,0)	0,139¶	8 (22,2)	7 (29,2)	0,377¶
No	33 (82,5)	12 (60,0)		28 (77,8)	17 (70,8)	
Hypertension (n (%))						
Yes	13 (32,5)	7 (35,0)	0,534¶	14 (33,3)	8 (33,3)	1,000¶
No	27 (67,5)	13 (65,0)		24 (66,7)	16 (66,7)	
Obese (n (%))						
Yes	0 (0,0)	0 (0,0)	0,352¶	0 (0,0)	1 (4,3)	0,184¶
No	40 (100,0)	20 (100,0)		36 (100,0)	36 (100,0)	
Family history of coronary heart disease (n (%))						
Yes	3 (7,5)	1 (5,0)	0,593¶	3 (7,5)	1 (5,0)	0,593¶
No	37 (92,5)	19 (95,0)		37 (92,5)	19 (95,0)	

μ Normality test based on Independent Sample t-test,
¶ Normality test based on Chi-Square test,
# Normality test based on Mann-Witney U test,
* Statistically significant.

TABLE 2: Clinical Characteristics and Comorbidities of Study Subjects Based on DCR Value Category and Intracoronary Thrombus Degree.

Variables	DCR		P-value	Degree of Intracoronary Thrombus		P-value
	High	Low		High	Low	
	40 (66,7%)	20 (33,3%)		36 (60,0%)	24 (40,0%)	
Killip (n (%))						
I	27 (67,5)	11 (55,0)	0,728¶	25 (69,4)	13 (54,2)	0,082¶
II	6 (15,0)	5 (25,0)		3 (8,3)	8 (33,3)	
III	1 (2,5)	1 (5,0)		1 (2,8)	1 (4,2)	
IV	6 (15,0)	3 (15,0)		7 (19,4)	2 (8,3)	
Coroangiography result (n (%))						
CAD 1VD	7 (17,5)	9 (45,0)	0,002¶*	6 (16,7)	10 (41,7)	0,720¶*
CAD 2VD	13 (32,5)	8 (40,0)		13 (36,1)	8 (33,3)	
CAD 3VD	20 (50,0)	3 (15,0)		17 (47,2)	5 (25,0)	

Variables	DCR		P-value	Degree of Intracoronary Thrombus		P-value
	High	Low		High	Low	
	40 (66,7%)	20 (33,3%)		36 (60,0%)	24 (40,0%)	
Atrial Fibrillation (n (%))						
Yes	2 (5,0)	1 (5,0)	0,518¶	2 (5,6)	1 (4,2)	0,651¶
No	38 (95,0)	19 (95,0)		34 (94,4)	23 (95,8)	
Chronic Heart Failure (n (%))						
Yes	0 (0,0)	0 (0,0)	0,650¶	0 (0,0)	0 (0,0)	1,000¶
No	40 (100,0)	20 (100,0)		36 (100,0)	24 (100,0)	
LVEF (mean ± SD (%))	44,5±5,6	43,9±6,1	0,570#	44,3±6,1	43,8±7,6	0,915#
LV Diastolic (n (%))						
normal	24 (52,5)	14 (75,0)	0,396¶	20 (55,6)	15 (62,5)	0,857¶
decreased grade I	14 (35,0)	5 (25,0)		12 (33,3)	7 (29,2)	
decreased grade II	5 (12,5)	1 (5,0)		4 (10,4)	2 (8,3)	
TAPSE (mean ± SD (cm))	1,9±0,13	1,9±0,14	0,914#	1,9±0,13	1,9±0,14	0,257#
RWMA (n (%))						
Yes	40 (100,0)	20 (100,0)	0,940¶	36 (100,0)	36 (100,0)	1,000¶
No	0 (0,0)	0 (0,0)		0 (0,0)	0 (0,0)	
Intracoronary Thrombus (n (%))						
High	34 (85,0)	2 (10,0)	0,000¶			
Low	6 (15,0)	18 (90,0)				
DCR (n (%))						
High				34 (94,4)	6 (25,0)	0,000¶
Low				2 (5,6)	18 (75,0)	
Acetosal (n (%))						
Yes	38 (95,0)	20 (100,0)	0,547¶	34 (96,7)	24 (100,0)	0,513¶
No	2 (5,0)	0 (0,0)		2 (3,3)	0 (0,0)	
Clopidogrel (n (%))						
Yes	38 (95,0)	20(100,0)	0,547¶	34 (96,7)	23 (100,0)	0,646¶
No	2 (5,0)	0 (0,0)		2 (3,3)	0 (0,0)	
Enoxaparin (n (%))						
Yes	40 (100,0)	20 (100,0)	1,000¶	36 (100,0)	24 (100,0)	1,000¶
No	0 (0,0)	0 (0,0)		0 (0,0)	0 (0,0)	
Duration of medication (mean ± SD (hours))	1,52±1,47	1,31±0,52	0,492#	1,45±1,63	1,13±0,34	0,347#

μ Normality test based on Independent Sample t-test,
¶ Normality test based on Chi-Square test,
# Normality test based on Mann-Witney U test,
* Statistically significant.

TABLE 3: Characteristics of MACE Subjects Based on DCR Value Category and Degree of Intracoronary Thrombus.

Variables	DCR		P-value	Degree of Intracoronary Thrombus		P-value
	High	Low		High	Low	
	40 (66,7%)	20 (33,3%)		36 (60,0%)	24 (40,0%)	
Overall MACE (n (%))						
Yes	34 (85,0)	2 (10,0)	0,000*	32 (88,9)	4 (16,7)	0,000*
No	6 (15,0)	18 (90,0)		4 (11,1)	20 (83,3)	
Cardiovascular Death (n (%))						
Yes	3 (7,5)	1 (5,0)	0,593¶	4 (11,1)	0 (0,0)	0,124¶
No	37 (92,5)	19 (95,0)		32 (88,9)	24 (100,0)	
Cardiogenic Shock (n (%))						
Yes	23 (57,5)	1 (4,0)	0,000*	22 (61,1)	2 (8,3)	0,000*
No	17 (42,5)	19 (95,0)		14 (38,9)	22 (91,7)	
Acute Heart Failure (n (%))						
Yes	33 (82,5)	2 (10,0)	0,000*	40 (83,3)	4 (16,7)	0,000*
No	7 (12,5)	18 (90,0)		8 (16,7)	20 (83,3)	
Malignant Arrhythmia (n (%))						
Yes	12 (30,0)	0 (0,0)	0,004*	15 (31,3)	1 (4,2)	0,002*
No	28 (70,0)	20 (100,0)		33 (68,8)	23 (95,8)	

µ Normality test based on Independent Sample t-test,
¶ Normality test based on Chi-Square test,
# Normality test based on Mann-Witney U test,
* Statistically significant.

TABLE 4: Characteristics of Research Subjects Based on MACE Category.

Variables	MACE		P-value
	There is	None	
	36 (59,8%)	24 (40,8%)	
Demographic Characteristics			
Age (mean ± SD (years))	58,55±11,50	57,10±8,30	0,261*
Gender, n (%)			
Male	28 (46,6)	9 (15,0)	0,488ß
Female	15 (25,0)	8 (13,3)	
Smoking, n (%)			
Yes	25 (86,2)	4 (13,8)	0,000 ß
No	11 (35,5)	20 (64,5)	
Dyslipidemia, n (%)			
Yes	14 (51,9)	13 (48,1)	0,101ß
No	22 (66,7)	11 (33,3)	
Diabetes Mellitus, n (%)			
Yes	28 (62,2)	17 (37,8)	0,037ß
No	8 (53,3)	7 (46,7)	
Hypertension, n (%)			
Yes	14 (70,0)	6 (30,0)	0,202ß
No	22 (55,0)	18 (45,0)	

Variables	MACE		P-value
	There is	None	
	36 (59,8%)	24 (40,8%)	
Obese, n (%)			
Yes	0,0 (0)	0,00 (0)	0,000ß
No	36 (60,0)	24 (40,0)	
Family history of coronary heart disease, n (%)			
Yes	4 (100)	0,0 (0)	0,143ß
No	32 (57,1)	24 (42,9)	
Clinical Characteristics and Comorbidities			
Killip, n (%)			
I	24 (63,2)	14 (32,8)	0,263ß
II	4 (36,4)	7 (63,6)	
III	1 (50,0)	1 (50,0)	
IV	7 (77,8)	2 (22,2)	
Coroangiography result n (%)			
CAD 1VD	6 (37,5)	10 (62,5)	0,016ß
CAD 2VD	12 (57,1)	19 (42,9)	
CAD 3VD	18 (78,5)	5 (21,7)	
Atrial Fibrillation, n (%)			
Yes	2 (66,7)	1 (33,3)	0,650ß
No	34 (59,6)	23 (40,4)	
Chronic Heart Failure n (%)			
Yes	0,0 (0)	0,0 (0)	0,000ß
No	36 (60,0)	24 (40,0)	
Echocardiographic Characteristics			
LVEF (mean ± SD (%))	42,3±7,3	42,2±7,4	0,949ß
LV Diastolic, n (%)			
normal	20 (57,1)	15 (42,9)	0,000ß
decreased grade I	12 (63,2)	7 (36,8)	
decreased grade II	4 (66,7)	2 (33,3)	
TAPSE (mean ± SD (cm))	1,9±0,13	1,9±0,14	0,674ß
RWMA, n (%)			
Yes	36 (60,0)	24 (40,0)	0,000ß
No	0 (0)	0 (0)	
History of taking medication			
Acetosal, n (%)			
Yes	34 (58,6)	24 (41,4)	0,512ß
No	3 (100,0)	0,0 (0)	
Clopidogrel, n (%)			
Yes	34 (58,6)	24 (41,4)	0,356ß
No	2 (100,0)	0 (0)	
Enoxaparin, n (%)			
Yes	36 (60,0)	24 (40,0)	0,000ß
No	0,0 (0)	0,0 (0)	
Duration of medication (mean ± SD (hours))	1,45±1,74	1,45±1,74	0,460ß
MACE			
Cardiovascular Death, n (%)			
Yes	4 (100,0)	0,0 (0)	0,000ß
No	32 (57,1)	24 (42,9)	
Cardiogenic shock, n (%)			
Yes	24 (100,0)	0,0 (0)	0,000ß
No	12 (33,3)	24 (66,7)	

Acute Heart Failure, n (%)			
Yes	35 (100,0)	0,0 (0)	0,000ß
No	1 (4)	24 (96,0)	
Malignant arrhythmia, n (%)			
Yes	12 (100,0)	0,0 (0)	0,000ß
No	24 (50,0)	24 (50,0)	

ßNormality test based on Chi-Square,
*Normality test based on Independent Sample t-test,
Normality test based on Mann-Witney U.

The inter-observer reliability test used to assess the degree of intracoronary thrombus is the Cohen Kappa test by calculating the mean of examinations by both observers (two cardiac interventionists). This test evaluates the degree of intracoronary thrombus based on the TIMI classification using coronary angiography images assessed by the observers.

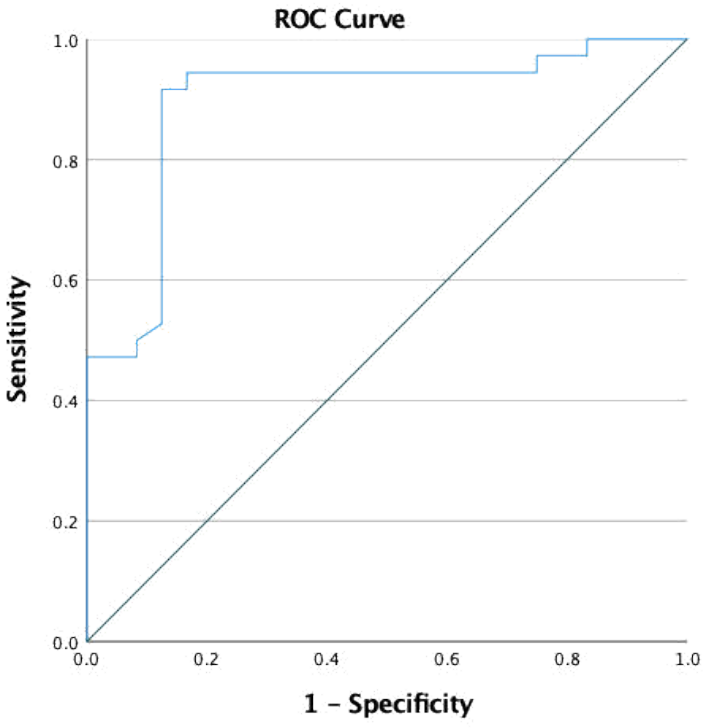
Based on the Cohen Kappa test, the results are said to have good reliability when the limit of agreement is between 0 and 1, where the result of 0 shows no agreement, increasing to 1 shows perfect agreement, >0.80 excellent agreement, 0.61 - 0.80 good agreement, 0.40 - 0.60 moderate agreement, and <0.41 poor agreement. The results of the inter-observer reliability analysis are shown in Table 5. Based on the table, we can see the high level of agreement from observer 1 and 2, namely the Agreement Kappa value of 0.839 and Asymptotic Standard Error of 0.060 ($p < 0.05$). These results indicate excellent agreement between the two observers.

TABLE 5: Measurement of Interobserver Reliability of Intracoronary Thrombus Degree.

	Value	Asymptotic Standard Error[a]	Approximate T[b]	Approximate Significance
Measure of Agreement Kappa	0.839	0.060	9.505	0.000
N of Valid Cases	60			

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

The cut-off value to determine the abnormally high DCR category using the data collected from this study by creating a ROC curve (Figure 1).



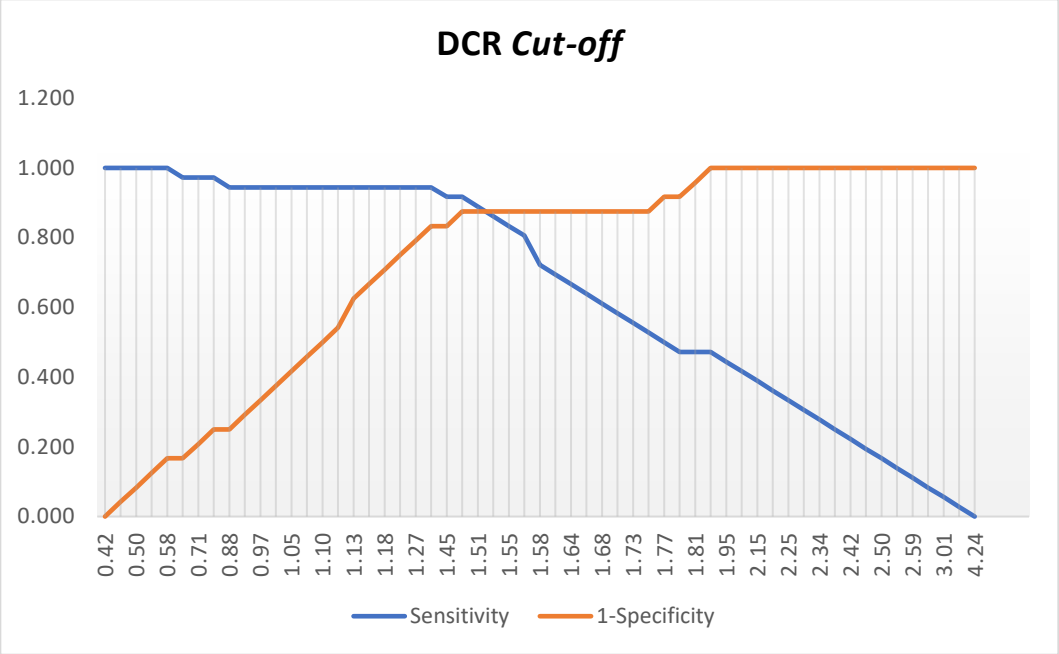


FIGURE 1: ROC Curve in Determining a High DCR Cut-off Point.

TABLE 6: AUC Value, Sensitivity and Specificity of MFI Predictors.

Variables	AUC	95% CI	Sensitivity (%)	Specificity (%)	P-value
D-Dimer	0,890	0,773-0,995	91,5	80,7	<0.001*
Creatinine	0,901	0,821-0,990	90,3	89,7	<0.001*
High DCR	0,905	0,825-0,989	94,8	85,9	<0.001*

*Statistically significant.

Based on ROC curve analysis, the optimal cut-off point value was obtained in stating a high DCR to predict outcomes by obtaining an optimal relationship between sensitivity and specificity of 1.51. Area Under Curve (AUC) is 0.905. Using a cut-off point of 1.51, 40 patients with high DCR and 20 patients with low DCR were obtained. DCR, which is a numerical scale, was converted into a nominal scale with two categories: high DCR and low DCR.

Of the 60 STEMI cases who underwent primary percutaneous coronary intervention during hospitalization observed during the study, it was found that 40 patients had high DCR and 36 patients had MACE. An overview of Kaplan Meier survival estimates of the occurrence of major cardiovascular events based on the High DCR and Low DCR categories is shown in Figure 2 and Table 7 below.

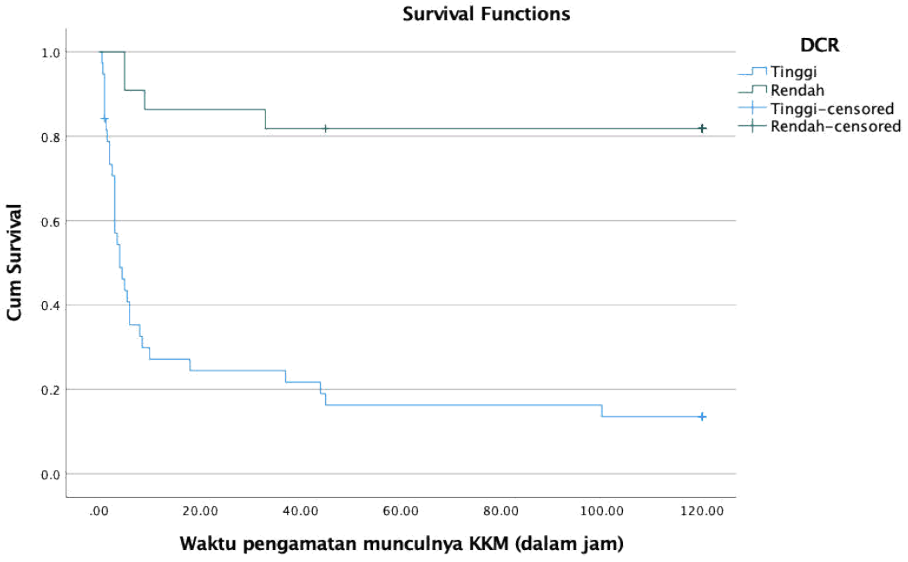


FIGURE 2: Kaplan-Meier Survival Estimation Curve of the Occurrence of Major Cardiovascular Events in STEMI Based on DCR.

TABLE 7: Mean Survival Time and 5 Days Survival Rate Based on DCR Value Category.

Variables	Mean Time Survival (hour)	95% CI	5 Days Survival Rate (%)	P-value
High DCR	25,48	12,09-38,96	13,8	<0.001*
Low DCR	100,54	83,17-117,19	91,8	<0.001*

*Statistically significant.

Based on Table 7, the 5-day survival rate of patients with high DCR was 13.8% and the mean time survival was 25.48 hours (95% CI = 12.09-38.96), while the 5-day survival rate of patients with low DCR was 91.8% and the mean time survival was 100.54 hours (95% CI = 83.17-117.19), After performing the Log Rank Test, it was found that there was a significant difference in the survival rate of patients with high and low DCR with a p value <0.001.

The effect of high DCR values on major cardiovascular events was significant compared to those with low DCR (p < 0.001). The Hazard Ratio (HR) was 15.98 (95% CI 3.80-67.20) as shown in Table 9. This means that the risk of major cardiovascular events in STEMI patients who underwent primary percutaneous coronary intervention during hospitalization was found to be 15-fold in patients with high DCR compared to patients with low DCR. The risk difference was statistically significant with p < 0.001. This HR value is still crude and has not controlled for other variables that are considered as confounders.

Of the 60 STEMI cases who underwent primary percutaneous coronary intervention during hospitalization observed during the study, 36 patients had high intracoronary thrombus burden and 24 patients had low intracoronary thrombus. Among those with MACE, there were 32 patients with high intracoronary thrombus and 4 patients with low intracoronary thrombus. The picture of Kaplan Meier survival estimation of major cardiovascular events based on DCR value category is shown in Figure 3 below.

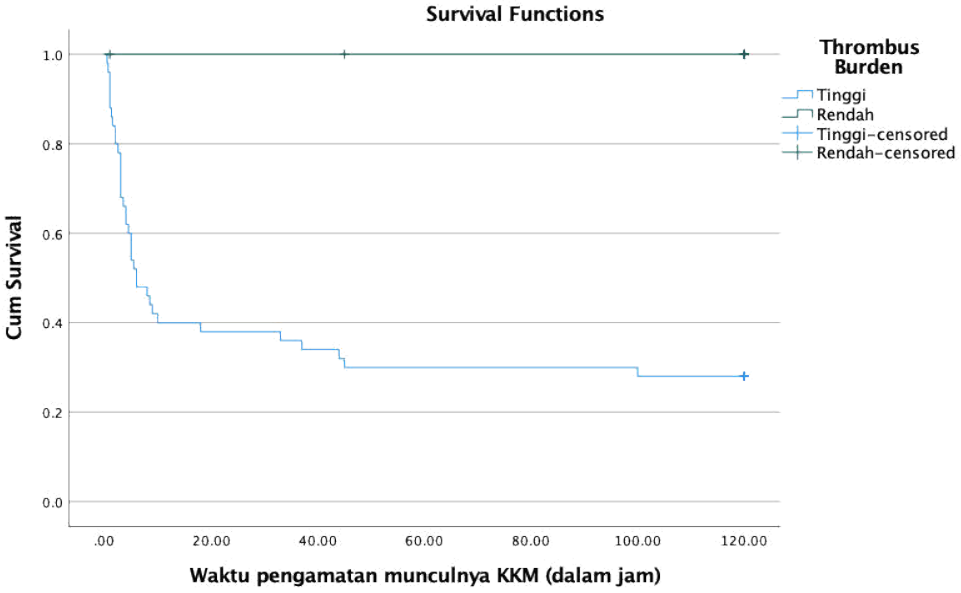


FIGURE 3: Kaplan-Meier Survival Estimation Curve of the Occurrence of FMD by the Degree of Intracoronary Thrombus.

TABLE 8: Mean Survival Time and 5 Days Survival Rate Based on Intracoronary Thrombus.

Variables	Mean Time Survival (hour)	95% CI	5 Days Survival Rate (%)	P-value
High Intracoronary Thrombus	24,82	13,39-36,25	9,6	<0.001*
Low Intracoronary Thrombus	114,38	103,63-125,13	94,4	<0.001*

*Statistically significant.

Based on Table 8, the 5-day survival rate of patients in the high intracoronary thrombus group was 9.6% and the mean time survival was 24.82 hours (95% CI = 13.39-36.25), while the 5-day survival rate of patients with low intracoronary thrombus was 94.4% and the mean time survival was 114.38 hours (95% CI = 103.63-125.13). The survival rate of high and low intracoronary thrombus patients was significant with a p value of <0.001.

The effect of high intracoronary thrombus on major cardiovascular events was significant compared to those with low intracoronary thrombus (p < 0.001). The Hazard Ratio (HR) was 29.45 (95% CI 5.32-86.14) as shown in Table 9. This means that the risk of major cardiovascular events in STEMI patients who underwent primary percutaneous coronary intervention during hospitalization was found to be 29-fold in patients with high intracoronary thrombus compared to patients with low intracoronary thrombus the difference in risk was statistically significant with p < 0.001.

This study used DCR and intracoronary thrombus as independent variables and other factors as control variables such as age, gender, dyslipidemia, hypertension, diabetes mellitus, smoking, obesity, family history of coronary heart disease, coronary angiography results, STEMI region, STEMI onset, Killip Class, drugs that affect coagulation and duration of medication. The effect of control variables on independent variables with numerical scale data (age variable) was tested for normality with the Kolmogorov-Smirnoff test and significance test with independent sample t-test.

The effect of control variables with categorical scale data (gender, dyslipidemia, hypertension, diabetes mellitus, smoking, obesity, coronary angiography results, Killip Class, STEMI region and drugs that affect platelets) was tested with Chi Square test.

The multivariate analysis used to determine the effect of DCR and high intracoronary thrombus on major cardiovascular events independently was Cox Regression. The variables included in the multivariate test were control variables that showed a p value <0.05. Multivariate analysis showed that high DCR was proven to be an independent predictor of major cardiovascular events in STEMI patients during hospitalization with an adjusted HR of 20.81 with 95% CI (2.18-130.16) and a p value of 0.007 (Table 9). This means that the MACE in STEMI patients during hospitalization with high DCR after controlling for confounding factors is almost 16 times that of patients with low DCR.

Similarly, this study showed that high intracoronary thrombus was shown to be an independent predictor of major cardiovascular events in STEMI patients with an adjusted HR of 31.38 with 95% CI (4.51-89.15) and a p value of 0.017 (Table 9). This means that the risk of MACE in patients with high intracoronary thrombus STEMI patients after controlling for confounding factors is 31-fold. In addition, other factors such as diabetes mellitus (adjusted HR 7.55; 95%CI: 1.13-11.58; p=0.035) and smoking (adjusted HR 2.70; 95% CI: 0.88-3.29; p=0.012) were also found to play an independent role as predictors of poor outcomes during hospitalization in the patient population.

TABLE 9: Multivariate analysis of Cox regression of DCR and intracoronary thrombus on MFI using the backward method.

Variables	Unadjusted HR	95%CI	P-value	Adjusted HR	95% CI	P-value
High DCR	15,98	3,80-67,20	<0.001*	20,81	2,18-98,16	0,007*
High Intracoronary Thrombus	29,45	7,72-81,12	<0.001*	31,38	4,51-89,15	0,017*
Coronary Angiography Results						
CAD 1VD			0,113			0,135
CAD 2VD	0,42	0,18-0,95	0,037*	1,26	0,55-2,88	0,590
CAD 3VD	0,76	0,38-1,52	0,041*	2,12	1,01-4,45	0,154
Smoking	3,63	1,89-6,95	<0.001*	2,70	0,88-3,29	0,012*
Diabetes Mellitus	4,22	1,77-8,41	<0.001*	7,55	1,13-11,58	0.035*
Killip Class						
I			0,547			0,932
II	0,74	0,34-1,63	0,461	0,91	0,39-2,13	0,826
III	0,41	0,12-1,37	0,147	0,78	0,19-3,06	0,718
IV	0,65	0,081-5,19	0,683	1,59	0,17-15,17	0,689

*Statistically significant.

Structural equation modeling (SEM) was used to analyze the interaction of DCR value with the degree of intracoronary thrombus. SEM is a good multivariate statistical analysis method that combines factor analysis, structural model and path analysis approaches, in this case using Cochran's and Mantel-Haenszel approaches.

In this study, the interaction of DCR and intracoronary thrombus as predictors of MFI from the results of Structural Equation Modeling analysis is shown in Table 10.

TABLE 10: Results of Structural Equation Modeling (SEM) Analysis Assessing the Interaction of DCR and Intracoronary Thrombus on MACE.

DCR			MACE		Breslow-Day Homogeneity Test (p)	Cochran's and Mantel-Haenszel (p)
			There is	None		
High	Intracoronary Thrombus	High	31 (91,2)	3 (8,8)	0,803	0,013*
		Low	1 (50,0)	1 (50,0)		
Low	Intracoronary Thrombus	High	3 (50,0)	3 (50,0)		
		Low	1 (5,6)	17 (94,4)		
Mantel-Haenzel Common Estimate			14,333			
95% CI			2,032 - 91,125			

*Statistically significant.

DISCUSSION

Along with the development of science, especially in the cardiovascular field, the understanding of pathophysiology, management and prevention of STEMI is also growing. However, STEMI is still a worldwide disease burden, which has become a major cause of death. Complications of STEMI are a cause of morbidity and mortality.

Major cardiovascular events are a form of STEMI complications associated with patient survival and quality of life consisting of cardiovascular death, cardiogenic shock, heart failure, and malignant arrhythmias. The high mortality and morbidity due to STEMI complications has prompted efforts to develop a risk stratification system for STEMI patients. Several STEMI stratification systems have been applied in daily practice, such as the TIMI score and GRACE score. However, the examination of troponin values or angiography as part of the two scores is a specialized examination, so a simple examination is needed that can be used as an effort to risk stratify STEMI patients. The coagulation process is one of the bases for STEMI, so coagulation biomarkers can also be used as an alternative method in STEMI risk stratification, especially as a predictor of STEMI complications, namely MACE.

It has been explained in the previous section that the basis of increased coagulation, platelet activation and inflammation has been associated with thrombotic potential and a high risk of complications. Coagulation activation can be measured by looking at DCR results by combining D-dimer and creatinine examinations. Various studies have linked D-dimer and creatinine as independent predictors of MACE in STEMI patients. This study evaluated each component and the interaction between them as predictors of MFI during hospitalization in STEMI patients undergoing percutaneous primary coronary intervention.

During the period of June to August 2023, a prospective cohort study was conducted at Prof. Dr. I.G.N.G. Ngoerah Hospital, Denpasar, Bali. An important finding of this study was a high DCR value as a predictor of MACE during hospitalization in STEMI patients undergoing percutaneous coronary intervention.

During the study, 60 STEMI patients who met the inclusion criteria were taken by consecutive sampling from the study population. There were 40 patients with high DCR and 20 patients with low DCR. In the intracoronary thrombus degree group, there were 36 patients with high results and 24 patients with low results. In this study, the sociodemographic characteristics and clinical comorbidities showed smoking, DM, more complex angiographic results were found to be higher in the high DCR group than the group of patients with low DCR in STEMI patients included in the sample. Dyslipidemia, obesity, AF, hypertension and patients who had received previous antiplatelet therapy were more common in the low DCR group compared to the high DCR group.

This basic characteristic is also described in previous studies where DCR increases in patients with high coagulation risk such as diabetes mellitus. Increases also occur in patients with cancer, inflammation/severe infection extensive trauma, postoperative, new bleeding, stroke, myocardial infarction, heart failure, liver disease, renal failure, pregnancy, old age (Gong et al, 2016). The study of DCR as a predictor of reperfusion disorders and long-term mortality in STEMI patients was also described by Yang et al, 2022. In this study, it was found that the use of antiplatelet drugs such as acetosal, clopidogrel, and anticoagulants such as enoxaparin was the first time, with an average duration of drug use of 1.45 hours from blood collection for complete blood examination in the emergency room.

In previous studies, it has also been explained that DCR values are associated with mortality rates in old age, diabetes and AF groups [12]. In this study it was also found that diabetes mellitus variables were significantly more in the group of patients with high DCR compared to the low DCR group. The same thing was found in the study of Sathananthan (2018). However, until now there has been no previous study that evaluates the interaction of DCR on intracoronary thrombus with MFI outcomes [16].

The clinical and comorbid characteristics of the subjects in this study showed that 5% of STEMI patients with high DCR had comorbid atrial fibrillation and no comorbid CHF, CKD and stroke, with similar characteristics found among the high coronary thrombus degree group. The mean LVEF and TAPSE of patients were 42% and 1.9 cm, respectively, and all patients had RWMA (regional wall motion abnormality) from echocardiographic examination.

Based on the characteristics of MACE from a total of 60 samples in this study, 40 patients (60%) with MACE were found, 20 patients (40%) did not experience MACE. Of all types of MACE, AHF was dominant in 35 patients (58%), followed by cardiogenic shock in 24 patients (25%), then malignant arrhythmia in 12 patients (20%) and finally cardiovascular death in 4 patients (6.6%) who experienced cardiovascular death during treatment.

In this study, the characteristics were also grouped based on the presence of MACE and no MACE in addition to grouping based on high and low DCR values as in the studies of Gong et al., 2016 and Miyosi 2020, in their study grouped patients based on mean age, LVEF, TAPSE, LV diastolic function and duration of DAPT or anticoagulant medication equally between patients with and without MACE. Male gender, smoking, dyslipidemia, hypertension, Killip class I, more complex coronary angiography results (CAD 2VD and 3VD) and LV diastolic grade I and II, diabetes mellitus were higher in the group of patients with MACE than the group of patients without MACE. While obesity, family history of coronary heart disease on the contrary was more dominant in the group of patients without MACE.[6,17].

Bivariate analysis of all variables stratified by groups with and without MACE was also conducted, and it was found that smoking, diabetes mellitus, coronary angiography results in addition to the independent variables studied, namely DCR and intracoronary thrombus, had a significant effect on MACE. Meanwhile, the variables that did not statistically significantly affect MFI were patient age, gender, dyslipidemia, hypertension, obesity, family history of coronary heart disease, killip class, STEMI region, atrial fibrillation, CHF, LVEF, LV diastolic, TAPSE, RWMA, TIMI post-action flow, history of taking acetosal, clopidogrel, enoxaparin and duration of medication. It was found that the patient's age had no significant effect on this study, which can be explained because the age range of the study sample was short and homogeneous, making the results insignificant in both the MACE and no MACE groups. All patients from echocardiography showed RWMA, all took acetosal and clopidogrel, and enoxaparin injection was the first time with the average duration of drug administration similar between the MACE group and without MACE making the effect also statistically insignificant. Meanwhile, the mean LVEF and TAPSE of patients in this study were also not significant, which may be due to the homogeneity of subject characteristics.

Based on the data obtained in this study, it can be compared with previous studies that the results obtained are not much different. A significant difference is the high homogeneity of the subjects which can make the results insignificant, this can be caused by the limited number of subjects. However, this data is sufficient to determine the outcomes of the MACE studied, which will be explained further in the next section.

A ROC curve analysis has been conducted by assessing the Area Under Curve (AUC), where an AUC result of 1.0 is interpreted as a highly accurate examination, with sensitivity and specificity reaching 100%, while a ROC curve with an AUC value of 0.0 describes a completely inaccurate examination. Thus, an AUC value that is closer to 1.0 represents a more accurate diagnostic test [18]. Whether or not the AUC value is satisfactory can be determined clinically or statistically. In addition, the DCR cut off point assessment was also determined in this study for the purpose of predicting outcomes to obtain an optimal relationship between sensitivity and specificity. So, it can be said if the DCR value with a high category has a good accuracy value as a predictor of MACE.

In this study, the AUC values of each parameter D-dimer and Creatinine, as well as the combination in the form of DCR were obtained. The AUC values for D-Dimer and Creatinine were 0.890 and 0.901, respectively. It was also seen that the sensitivity of D-dimer was 91.5% and the specificity was 80.7%. In accordance with the previous theory that D-dimer has high sensitivity with lower specificity, so D-Dimer is better in the exclusion modality. However, when combined with creatinine examination into DCR, the AUC number increased to 0.905 with a Standard Error of 0.044; (95%CI: 0.825-0.989; p value <0.001) with an increase in sensitivity of 94.8% and specificity of 85.9%. These results show that DCR as a combination of D-dimer and Creatinine has good diagnostic accuracy, compared to D-dimer alone, where these results are in accordance with the theory in previous studies that by combining the two examinations it is expected to increase the sensitivity and specificity of the examination.

The cut-off value for DCR in this study was 1.51, which means it can be categorized as high DCR≥ 1.51 and low DCR <1.51. The cut-off value linking DCR and STEMI incidence still varies, but is still at 1.40 to 1.55. A study conducted by Yang et al. in 2022 found a value of 1.41 as a cut-off value in categorizing high and low DCR groups in STEMI patients. The study conducted by Gong et al. in 2016 found a value of 1.45 to distinguish high and low DCR in STEMI patients. And another study conducted by Sibilitz et al. in 2022 found a value of 1.52 to distinguish high and low DCR in STEMI patients, all of these values were determined by assessment or ROC curves [12]

Various studies in determining the DCR cut-off did not have significantly different results. This could be due to the presence of coagulation factor D-dimer in the blood of patients with coagualtive conditions.

D-dimer is associated with systemic coagulation factor parameters including the presence of coagulation in STEMI patients. With various factors known to affect D dimer, this can be anticipated by excluding these subjects so that the results are more accurate. These factors include malignancy, DIC, sepsis, aplastic anemia, ITP and thrombocytosis.

Due to the involvement of various variables that can affect the DCR value, it is advisable for each laboratory to create its own cut-off point value [19]. The difference between this study compared to previous studies, in this study using independent variables in the form of D dimer, Creatinine and DCR combination. From the study of a total of 60 patients, 40 patients (66.7%) with high DCR and 20 patients (33.3%) with low DCR were obtained. DCR provides more objective data in correlation with atherosclerosis. Data will be more objective when in coronary heart disease D dimer increases with normal or low creatinine. So DCR can minimize bias when associated with coronary heart disease. In a study by Yang et al, DCR correlated with coronary stenosis severity scoring (Gensini Score) in STEMI patients, and DCR can be an independent predictor of higher Gensini scores. The Gensini score has been widely used as an indicator of the severity of coronary artery stenosis, so increased DCR predicts more severe coronary artery stenosis. In addition, measuring and calculating DCR in STEMI patients can be a reference value for rapid assessment of patients presenting to referral hospitals. It can also help provide additional data to optimize management [20].

This study showed that high DCR was proven to be an independent predictor of major cardiovascular events during hospitalization in STEMI patients after primary percutaneous coronary intervention (unadjusted HR of 15.98 (95% CI 3.80-67.20; p value = 0.007). This means that STEMI patients after primary percutaneous coronary intervention with high DCR had an almost 16-fold greater risk of experiencing major cardiovascular events during hospitalization than the group of patients with low DCR.

High intracoronary thrombus was also shown to be an independent predictor of major cardiovascular events during hospitalization in STEMI patients after primary percutaneous coronary intervention (unadjusted hazard ratio of 29.45 (95% CI 7.72-81.12; p value = 0.001). This means that STEMI patients after primary percutaneous coronary intervention with high intracoronary thrombus have a risk of experiencing major cardiovascular events during hospitalization that is almost 30 times greater than the group of patients with low intracoronary thrombus.

Furthermore, multivariate analysis using Cox Regression was performed to determine whether DCR and intracoronary thrombus were independent predictors for the occurrence of MACE. Variables included in the multivariate test were control variables that showed a p value of <0.25 and variables that were theoretically important [21]. In addition to DCR and intracoronary thrombus, the variables of coronary angiography results, smoking, diabetes mellitus and killip class had p values <0.25 and were included in the multivariate analysis.

After controlling for confounding variables on multivariate analysis, the high DCR group was shown to be an independent predictor of MACE (adjusted hazard ratio of 20.81 (95% CI 2.18-98.16; p value = 0.007). This means that a high DCR value is an independent predictor of major cardiovascular events with an almost 20-fold greater risk than a low DCR. Also, high intracoronary thrombus was shown to be an independent predictor of MACE (adjusted hazard ratio of 31.38 (95% CI 4.51-89.15; p value = 0.017). This means that high intracoronary thrombus is an independent predictor of major cardiovascular events with a 31-fold greater risk than low intracoronary thrombus. To strengthen the relationship between parameters with MFI during hospitalization.

Coronary thrombosis and occlusion are the pathological basis for STEMI. Rupture or erosion of the lipid-rich necrotic core activates unstable platelet aggregation, which is accelerated by fibrin formation, to form a thrombus. (Yang et al., 2022) In previous studies, D-dimer and creatinine are both associated with the occurrence of coronary heart disease, especially the severity of coronary artery disease. Pathomechanisms that may explain such outcomes include high D-dimer levels reflecting a systemic prothrombotic state and focal vessel wall-associated fibrinogenesis with unstable atherosclerotic plaque. Creatinine level can reflect renal function and is used to calculate eGFR and decreased eGFR leads to hypertensive state, oxidative stress, abnormal calcium and phosphorus metabolism, anemia and other factors, which further aggravates vascular endothelial damage, thereby accelerating the formation and progression of coronary atherosclerotic plaques [10].

To evaluate the interaction between DCR and the degree of intracoronary thrombus on MACE during hospitalization in STEMI patients, structural equation modeling analysis was performed according to Table 7. Based on the equation, there was an interaction between the predictors of high DCR and high intracoronary thrombus on the incidence of MACE during hospitalization in STEMI patients (91.2%, Cochran's and Mantel-Haenszel p = 0.013). This result was lower when compared to the high DCR and low intracoronary thrombus group on MFI during hospitalization in STEMI patients (50%, Cochran's and Mantel-Haenszel p = 0.013).

Further explained in the equation, the interaction of low DCR and low intracoronary thrombus in STEMI patients revealed a higher result of no MACE (94.4%, Cochran's and Mantel-Haenszel p = 0.013). The tendency of STEMI patients with high DCR to experience MACE during treatment was 14-fold in the condition of high degree of intracoronary thrombus expressed in Mantel-Haenzel Common

Estimate 14.333 (95%CI: 2.032 - 91.125; Cochran's and Mantel-Haenszel p value <0.001).

In contrast to previous studies, this study has novelty or specificity that assesses the predictors of MACE with DCR values and the degree of intracoronary thrombus both in combination and individually. And from the results of the SEM interaction test, DCR and intracoronary thrombus have an interaction on MFI during hospitalization in STEMI patients, where the interaction of high DCR and high intracoronary thrombus degree shows a better predictor of MFI.

This study provides data that is in accordance with research conducted by Yang, et al. The study assessed the interaction between DCR and Gensini Score as lesion complexity in IMA patients. It was concluded in the study that DCR has an association on lesion complexity based on Gensini Score and MFI during hospitalization in IMA patients. So, with supporting data, this study can provide additional data related to the usefulness of DCR as a risk stratification of STEMI patients, as an effort to better management.

This study was also able to prove the various factors that play a role as predictors of MACE. As in other studies where several factors play a role such as age, smoking, dyslipidemia, obesity, hypertension and others. There are also many studies on the relationship between these factors that play a role in predictors of MFI in STEMI patients [22].

Based on the results of multivariate analysis, in addition to high DCR and intracoronary thrombus. Other factors that contribute to MACE during hospitalization in STEMI patients are coronary complexity from coronary angiography results, smoking and DM. Of course, the results of this analysis have been adjusted using the Hazzard Ratio with the backward method.

As previously known, the process of STEMI is a complex process that occurs due to plaque rupture, coagulation, platelet activation, and inflammation. So that these factors play a lot of roles to produce coronary lesions. The more ballast factors, the higher the likelihood of MACE in STEMI patients. The study conducted by Wada et al in 2013 had similar results with this study, where it was mentioned that lesion complexity, smoking and DM were the ballast factors for the occurrence of MACE in STEMI patients. The effect of smoking on the body is in the form of a systemic inflammatory response through stimulation of the hematopoietic system which mainly occurs in the bone marrow, in the form of increased production of erythrocytes and leukocytes and a decrease in MCV and platelets [23]. The effect of smoking on platelets is an increase in atherosclerosis and a risk factor for atherosclerotic disease caused by an increased risk of thrombosis. This has an impact on the outcome of STEMI patients who are getting worse, until death occurs. Therefore, these factors can be considered as predictors of MACE in addition to DCR and intracoronary thrombus in STEMI patients.

In this study, there was a weakness in the small number of subjects and inadequate to be considered representative of the general population. The number of subjects included in this study was 60 patients, with less diverse risk factors and comorbidities. The results obtained from this study are based on a single center with a relatively small sample size, making it difficult to represent all STEMI patients. Some confounding factors were not clearly evaluated in the subjects, such as lifestyle, social life, and other comorbidities.

Because this study focuses on MACE during hospitalization, this study does not describe the patient's prognosis after completion of hospital treatment, nor does it follow up on these patients so that the patient's prognosis is not clearly known. Therefore, research development can be carried out with a larger number of subjects, diverse and longer follow-up periods, so that the research can be more representative of the general population.

CONCLUSSION

Based on the results of the research analysis, the following conclusions can be obtained:

1. High DCR is an independent predictor of MACE during hospitalization in STEMI patients post-primary percutaneous coronary intervention
2. High intracoronary thrombus is an independent predictor of MACE during hospitalization in STEMI patients post primary percutaneous coronary intervention
3. There is an interaction between DCR and high degree of intracoronary thrombus as a risk of MACE during hospitalization of STEMI patients undergoing primary percutaneous intervention, which results in a strong predictor of MACE in the combination group of DCR value categories and high intracoronary thrombus, compared to separate analysis. Therefore, DCR can provide additional information in the risk stratification of MFI during hospitalization in STEMI patients.

ACKNOWLEDGMENTS

All patients, all authors, and all support in the paper.

DECLARATIONS

Funding: No funding sources.
Conflict of interest: None declared
Ethical approval: The study was approved by Udayana University with the number 1033/UN14.2.2VII.14/LT/2023.

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