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Platelet Indices and Intracoronary Thrombus Grade as Predictors of In-Hospital Major Cardiovascular Events in Patients with ST Elevation Myocardial Infarction Post Primary Percutaneous Coronary Intervention

I Wayan Gunawan*, I Made Junior Rina Artha, I Kadek Susila Surya Darma

Department of Cardiology and Vascular Medicine, Faculty of Medicine Udayana University
Prof. dr. I.G.N.G. Ngoerah Hospital, Denpasar, Bali, Indonesia

E-mail: gunawan_roban91@yahoo.com; juniorinartha@gmail.com;
kadeksusila138@gmail.com

*Corresponding author details: I Wayan Gunawan, MD; gunawan_roban91@yahoo.com

ABSTRACT

Background: The high mortality rate of ST Elevation Myocardial Infarction (STEMI) is caused by its complications, especially in-hospital major cardiovascular events (MACE). This study aims to determine the relationship between platelet indices and intracoronary thrombus grade as predictors of in-hospital MACE and the interaction of the combination of both predictors in patients with STEMI post-primary percutaneous coronary intervention (PCI). ***Methods:*** This prospective cohort study was conducted with STEMI patients who underwent primary PCI. Data was analyzed by SPSS 24.0.0.0 version. ***Results:*** There were 71 samples: 46 patients (64.8%) with a high platelet index and 48 patients (67.6%) with a high intracoronary thrombus grade. During in-hospital follow-up, there were found that 42 patients (59.2%) experienced MACE. The cut-off value used classifies high platelet index for PDW 11.25 fl (AUC 0.892; CI 95% 0.786-0.999; p<0.001) and MPV 10.15 (AUC 0.901; CI 95% 0.812-0.990; p<0.001). The Cox regression backward log-rank model showed both high platelet indices (adjusted HR 38.13; CI 95% 5.16-282.03; p<0.001) and high Intracoronary Thrombus Grade (adjusted HR 31.67; CI 95% 4.28-234.54; p=0.001) played an independent role as predictors of MACE during hospitalization, regardless of the influence of coronary angiography results, Killip class, smoking and consumption of acetosal and clopidogrel. The combination of two predictors of high platelet indices and high Intracoronary Thrombus Grade based on SEM analysis showed that 95.2% experienced in-hospital MACE (Mantel-Haenzel Common Estimate 17.48; Breslow-Day Homogeneity p=0.772; Cochran's and Mantel-Haenszel p=<0.001), had better predictive ability as seen from the comparison of the respective AUC values, namely the combination, high platelet indices and high Intracoronary Thrombus Grade (0.942; 0.902; 0.873; p<0.001). ***Conclusion:*** High platelet indices and high intracoronary thrombus grade can be used as additional information for risk stratification of in-hospital MACE of STEMI patients post-primary PCI, especially when both variables were combined.

Keywords: platelet indices; platelet index; PDW; MPV; Intracoronary Thrombus Grade; major adverse cardiac event; MACE; cardiovascular disease mortality; cardiogenic shock; acute heart failure; malignant arrhythmia; STEMI.

INTRODUCTION

Progress in understanding the pathophysiology of the disease, supported by the development of evidence-based guidelines, has led to improvements in the diagnosis, management, and prevention of coronary heart disease. However, coronary heart disease, especially acute coronary syndrome (ACS), is still a significant burden of mortality and morbidity in developing countries [1–3]. Cardiovascular disease is the leading cause of death throughout the world; an estimated 17.9 million people died from cardiovascular disease in 2019, representing 32% of all global mortality. Of these mortality, 85% were caused by heart attacks and strokes.

Meanwhile, in Indonesia, 2018 Basic Health Research data shows that 15 out of 1,000 Indonesians suffer from coronary heart disease [4]. The UN Sustainable Development Goals (the UN Sustainable Development Goals) by 2030 is to reduce by a third premature deaths due to non-communicable diseases, especially cardiovascular diseases [5]. To reduce this global burden, WHO, supported by cardiovascular medical associations worldwide, has committed to expanding efforts to prevent and control cardiovascular disease, including developing tools, guides, and risk predictor markers [6].

ST-elevation myocardial infarction (STEMI), which is part of acute myocardial infarction (AMI), is the death of myocardial cells due to total blockage of the coronary artery. AMI cannot be separated from the hemostasis process, a physiological process of maintaining the balance of interactions that trigger thrombosis or bleeding[7]. IMA is a mutually reinforcing interaction between the physiological characteristics of circulating platelets, which easily cause thrombosis, and local processes related to atheroma plaque rupture in coronary artery, which trigger platelet activation through the involvement of inflammatory processes to cause thrombosis [8,9]. Activation of circulating platelets is described by platelet indices obtained from high PDW and/or MPV values, which are part of a complete blood examination. PDW is a part of the platelet indices that describes the relative distribution width of platelets in a volume index and indicates variations in platelet size, which can be a sign of active platelet release [10]. While MPV reflects changes in either the level of platelet stimulation or the rate of platelet production, other markers of increased platelet activity include increased platelet aggregation, increased thromboxane synthesis, and β-thromboglobulin release [11]. The Intracoronary Thrombus Grade is described by angiography results based on the established TIMI thrombus grade from the AHA. High platelet activation will have a high thrombotic potential, causing severe MI and the risk of MI complications, as MACE is also higher [12–15]. MACE from STEMI patients causes high morbidity and mortality, that is, cardiovascular death, acute heart failure, cardiogenic shock, non-cardiovascular death, stroke, recurrent myocardial infarction, repeated primary percutaneous coronary intervention revascularization, rehospitalization and malignant arrhythmias [16,17].

Various studies have shown the relationship between PDW or MPV and MACE in intra-hospital and post-hospitalization. PDW was found to independently predict poor long-term and in-hospital outcomes in patients with ACS [18]. Increased PDW is associated with increased severity of Coronary Artery Disease (CAD) in patients with ACS [20]. High MPV reflects high platelet activation in AMI patients and predicts MACE in AMI patients [10,19]. However, none of the previous studies have combined PDW and MPV parameters as platelet indices, and there are still very few studies showing the relationship between intracoronary thrombus burden and platelet indices on MACE. This study aims to determine the relationship between platelet indices and intracoronary thrombus grade as MACE during hospitalization and to determine the interaction of the combination of the two predictors on MACE during hospitalization in STEMI patients after primary percutaneous coronary intervention.

SUBJECTS AND METHODS

Study design

This research constitutes a single-center, prospective observational cohort study that investigates the association between platelet indices and intracoronary thrombus grade and its prognostic value in hospitalized STEMI patients with regards to the MACE, defined as a composite endpoint of cardiovascular-related mortality or cardiogenic shock or acute heart failure or malignant arrhythmias within the hospitalization period. This study obtained Ethical Clearance from the Research Ethics Commission of the Faculty of Medicine, Udayana University, aligning with the principles of the Declaration of Helsinki for clinical studies.

Population

Consecutively included in this study were individuals aged ≥18 years, admitted at Prof. Dr. IGNG Ngoerah Hospital for STEMI and undergoing primary percutaneous coronary interventions (PCI), who demonstrated a willingness to participate by providing informed consent. Exclusions included patients with STEMI with fibrinolytics, patients who had been previously diagnosed with Chronic coronary syndrome (CCS), patients with DIC (Disseminated Intravascular Coagulation), ITP (Idiopathic Thrombocytopenic Purpura), aplastic anemia, thrombocytosis, history of malignancy, history of previous long-term antiplatelet use (>4 weeks) and previous long-term anticoagulant use (>4 weeks). Sociodemographic data, clinical characteristics, comorbidities, usage of antiplatelet and anticoagulant therapy, and duration of use were collected from medical records.

Platelet indices (PDW and MPV) evaluation

The platelet indices and the intracoronary thrombus grade were evaluated at hospital admission. Platelet Distribution Width (PDW) and Mean Platelet Volume (MPV) examinations are part of a complete blood examination, which is a standard procedure in laboratory examinations of STEMI patients, carried out using whole blood reagents and using the Abbott Cell-dyn Ruby equipment available in the Pathology laboratory of Prof. Dr. IGNG. The examination was taken when the patient was in the cardiac emergency department or on the first day of hospitalization. The examination is taken when the patient is in the cardiac emergency department or on the first day the patient is admitted to the hospital. Research samples resulting from the examination of PDW and MVP levels were obtained from medical records. The MPV value is in SIMARS, and the PDW value from the tool printout is expressed in femtoliter (fL) units.

Intracoronary thrombus grade evaluation

Examination of the Intracoronary Thrombus Grade is carried out when the patient undergoes percutaneous coronary angiography intervention during primary percutaneous coronary intervention. Intracoronary thrombus is defined as a filling defect surrounded by a contrast medium. Thrombus evaluation was reviewed by a minimum of two interventional consultant cardiologists. Interpretation was generated through thrombus classification based on the TIMI Thrombus Grade Classification. The Intracoronary Thrombus Grade is low, namely grades 0-2, and high, namely grades 3-5.

Follow-up of MACE

The outcome was in-hospital MACE in the form of a composite of cardiovascular death, cardiogenic shock, acute heart failure, and/or malignant arrhythmia. The admitted patient carries out the MACE examination until the outcome occurs. Examinations in the MACE assessment include death certificates for cardiovascular deaths, ECG for malignant arrhythmias, hemodynamic examination for cardiogenic shock and echocardiography, and chest X-ray for acute heart failure.

Statistical analysis

Data are presented as means±SD (normally distributed continuous data), median (interquartile range) (skewed continuous data), or counts (percentage) for categorical data. Patients were initially categorized into two cohorts depending on platelet indices, intracoronary thrombus grade, and MACE occurrence. Comparative statistical analyses initially encompassed the Kolmogorov Smirnov, then continued with independent t-test for continuous variables (Mann-Whitney U test for variables with non-normal distribution), as well as Chi-squared tests for categorical variables. Receiver operating characteristic (ROC) analysis aided in determining optimal threshold values for predicting the combined outcome using both platelet indices (PDW and MPV) as well as intracoronary thrombus grade. Kaplan-Meier curves were employed to gauge event-free survival differences between these cohorts. Forward log-rank Cox regression was applied to identify independently associated risk factors as predictors of MACE, which, of course, has analyzed the collinearity assumptions of each independent variable. Lastly, structural equation modeling with Cochran's and Mantel-Haenszel was used to determine the interaction combination of platelet indices with the intracoronary thrombus grade on in-hospital MACE of STEMI patients who were undergoing primary percutaneous coronary intervention. Analysis was performed using the Statistical Package for Social Science software 24.0.0 (SPSS, Chicago). P-values <0.05 were considered significant.

RESULTS

The study enrolled 71 samples: 46 patients (64.8%) with a high platelet index and 48 (67.6%) with a high intracoronary thrombus grade. During hospital follow-up, there were found that 42 patients (59.2%) experienced MACE. The results of the descriptive analysis of the research population are shown in Table 1-4.

TABLE 1: Sociodemographic Characteristics of Research Subjects Based on Platelet Indices and Intracoronary Thrombus Grade Categories.

Variables	Platelet indices		p-value	Intracoronary Thrombus Grade		p-value
	High	Not High		High	Not High	
	46 (64.8%)	25 (35.2%)		48 (67.6%)	23 (32.4%)	
Age (mean ± SD (years))	59.2±11.60	57.24±9.74	0.476µ	58.35±11.80	58.83±9.16	0.866µ
Gender (n (%))						
Male	38 (82.6)	22 (88.0)	0.736¶	40 (83.3)	20 (87.0)	0.494¶
Female	8 (17.4)	3 (12.0)		8 (16.7)	3 (13.0)	
Smoking (n (%))						
Yes	28 (60.9)	5 (20.0)	0.001¶*	28 (58.3)	5 (21.7)	0.005¶*
No	18 (39.1)	20 (80.0)		20 (41.7)	18 (78.3)	
Dyslipidemia (n (%))						
Yes	20 (43.5)	12 (48.0)	0.805¶	18 (37.5)	14 (60.9)	0.078¶
No	26 (56.5)	13 (52.0)		30 (62.5)	9 (39.1)	
Diabetes Mellitus (n (%))						
Yes	11 (23.9)	8 (32.0)	0.576¶	12 (25.0)	7 (30.4)	0.775¶
No	35 (76.1)	17 (68.0)		36 (75.0)	16 (69.6)	
Hypertension (n (%))						
Yes	19 (41.3)	7 (28.0)	0.311¶	18 (37.5)	8 (34.8)	1.000¶
No	27 (58.7)	18 (72.0)		30 (62.5)	15 (65.2)	
Obese (n (%))						
Yes	0 (0.0)	1 (4.0)	0.352¶	0 (0.0)	1 (4.3)	0.352¶
No	46 (100.0)	24 (96.0)		48 (100.0)	22 (98.6)	
Family history of coronary heart disease (n (%))						
Yes	4 (8.7)	1 (4.0)	0.650¶	5 (10.4)	0 (0.0)	0.167¶
No	42 (91.3)	24 (96.0)		43 (89.6)	23 (100.0)	

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 Research Subjects Based on Platelet Indices and Intracoronary Thrombus Grade Categories.

Variables	Platelet indices		p-value	Intracoronary Thrombus Grade		p-value
	High	Not High		High	Not High	
	46 (64.8%)	25 (35.2%)		48 (67.6%)	23 (32.4%)	
Killip (n (%))						
I	34 (69.6)	14 (64.0)	0.828¶	34 (70.8)	14 (60.9)	0.053¶
II	4 (13.0)	7 (20.0)		4 (8.3)	7 (30.4)	
III	1 (2.2)	1 (4.0)		1 (2.1)	1 (4.3)	
IV	9 (15.2)	1 (12.0)		9 (18.8)	1 (4.3)	
Onset STEMI (n (%))						
<6 hours	18 (39.1)	6 (24.0)		18 (37.5)	6 (26.1)	
6-12 hours	18 (39.1)	18 (39.1)		18 (37.5)	14 (60.9)	0.171¶
>12 hours	10 (21.7)	10 (21.7)		12 (25.0)	3 (13.0)	
Coronary angiography result (n (%))						
CAD 1VD	9 (19.6)	13 (52.0)		12 (25.0)	10 (43.5)	
CAD 2VD	13 (28.3)	9 (36.0)	0.002¶*	14 (29.2)	8 (31.0)	0.120¶*
CAD 3VD	24 (52.2)	3 (12.0)		22 (45.8)	5 (38.0)	
Atrial Fibrillation (n (%))						
Yes	2 (4.3)	1 (4.0)	0.718¶	2 (4.2)	1 (4.2)	1.000¶
No	44 (95.7)	24 (96.0)		46 (95.8)	22 (95.8)	
Chronic Heart Failure (n (%))						
Yes	0 (0.0)	0 (0.0)	1.000¶	0 (0.0)	0 (0.0)	1.000¶
No	46 (100.0)	25 (100.0)		48 (100.0)	23 (100.0)	
LVEF (mean ± SD (%))	42.5±7.2	41.9±7.6	0.770#	42.2±7.3	42.6±7.6	0.815#
LV Diastolic (n (%))						
Normal	24 (57.1)	18 (42.9)		27 (56.3)	15 (65.2)	
Decreased grade I	14 (63.6)	8 (36.4)	0.876¶	16 (33.3)	6 (31.0)	0.770¶
Decreased grade II	4 (57.1)	3 (42.9)		5 (10.4)	2 (8.7)	
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	46 (100.0)	25 (100.0)	1.000¶	48 (100.0)	23 (100.0)	1.000¶
No	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Intracoronary Thrombus (n (%))						
High	42 (91.3)	6 (24.0)	0.000¶			
Not high	4 (8.7)	19 (76.0)				

Variables	Platelet indices		p-value	Intracoronary Thrombus Grade		p-value
	High	Not High		High	Not High	
	46 (64.8%)	25 (35.2%)		48 (67.6%)	23 (32.4%)	
Platelet indices (n (%))						
High				42 (87.5)	4 (17.4)	0.000¶
Not high				6 (12.5)	19 (82.6)	
Acetosal (n (%))						
Yes	43 (93.5)	25 (100.0)	0.547¶	45 (93.8)	23 (100.0)	0.546¶
No	3 (6.5)	0 (0.0)		3 (6.3)	0 (0.0)	
Clopidogrel (n (%))						
Yes	43 (93.5)	25(100.0)	0.547¶	45 (93.8)	23 (100.0)	0.546¶
No	3 (6.5)	0 (0.0)		3 (6.3)	0 (0.0)	
Enoxaparin (n (%))						
Yes	46 (100.0)	25 (100.0)	1.000¶	48 (100.0)	23 (100.0)	1.000¶
No	0 (0.0)	0 (0.0)		0 (0.0)	0 (0.0)	
Duration of drug consumption (n (%))						
<2 hours	34 (73.9)	20 (80.0)	0.395¶	34 (70.8)	20 (87.0)	0.115¶
≥2 hours	12 (26.1)	5 (20.0)		14 (29.2)	3 (13.0)	
Duration of drug consumption with onset of STEMI (n (%))						
<6 hours	25 (54.3)	9 (36.0)		24 (50.0)	10 (43.5)	
6-12 hours	11 (23.9)	11 (44.0)	0.195¶	12 (25.0)	10 (43.5)	0.234¶
>12 hours	10 (21.7)	5 (20.0)		12 (25.0)	3 (13.0)	
Duration of drug consumption (mean ± SD (hours))	1.43±1.67	1.20±0.41	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: MACE Characteristics of Research Subjects Based on Platelet Index Categories and Intracoronary Thrombus Grade.

Variables	Platelet indices		*p-value*	Intracoronary Thrombus Grade		*p-value*
	High	Not High		High	Not High	
	46 (64.8%)	25 (35.2%)		48 (67.6%)	23 (32.4%)	
Overall MACE (n (%))						
Yes	41 (89.1)	1 (4.0)	0.000*	41 (85.4)	1 (4.3)	0.000*
No	5 (10.9)	24 (96.0)		7 (14.6)	22 (95.7)	
Cardiovascular mortality (n (%))						
Yes	4 (8.7)	1 (4.0)	0.419¶	5 (10.4)	0 (0.0)	0.132¶
No	42 (91.3)	24 (96.0)		43 (89.6)	23 (100.0)	
Cardiogenic shock (n (%))						
Yes	27 (58.7)	1 (4.0)	0.000*	28 (58.3)	0 (0.0)	0.000*
No	19 (41.3)	24 (96.0)		20 (41.7)	23 (100.0)	

Variables	Platelet indices		p-value	Intracoronary Thrombus Grade		p-value
	High	High		High	Not High	
	46 (64.8%)	46 (64.8%)		48 (67.6%)	23 (32.4%)	
Acute Heart Failure (n (%))						
Yes	40 (87.0)	1 (4.0)	0.000*	40 (83.3)	1 (4.3)	0.000*
No	6 (13.0)	24 (96.0)		8 (16.7)	22 (95.7)	
Malignant Arrhythmia (n (%))						
Yes	15 (32.6)	0 (0.0)	0.001*	15 (31.3)	0 (0.0)	0.002*
No	31 (67.4)	25 (100.0)		33 (68.8)	23 (100.0)	

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 4: Characteristics of Research Subjects Based on MACE Category.

Variables	MACE		p-value
	With MACE	No MACE	
	42 (59.2%)	29 (40.8%)	
Sociodemographic Characteristics			
Age (mean ± SD (tahun))	58.79±12.11	58.10±9.20	0.798μ
Gender (n (%))			
Male	35 (58.3)	25 (41.7)	1.000¶
Female	7 (63.6)	4 (36.4)	
Smoking (n (%))			
Yes	28 (84.8)	5 (15.2)	0.000¶*
No	14 (36.8)	24 (63.2)	
Dyslipidemia (n (%))			
Yes	17 (53.1)	15 (46.9)	0.467¶
No	25 (64.1)	14 (35.9)	
Diabetes Mellitus (n (%))			
Yes	10 (52.6)	9 (47.4)	0.589¶
No	32 (61.5)	20 (38.5)	
Hypertension (n (%))			
Yes	17 (65.4)	9 (34.6)	0.462¶
No	25 (55.6)	20 (44.4)	
Obese (n (%))			
Yes	0 (0.0)	1 (100.0)	0.408¶
No	42 (60.0)	28 (40.0)	
Family history of coronary heart disease (n (%))			
Yes	5 (100.0)	0 (0.0)	0.774¶
No	42 (60.0)	28 (40.0)	
Clinical Characteristics and Comorbidities			
Killip (n (%))			
I	29 (60.4)	19 (39.6)	0.234¶
II	4 (36.4)	7 (63.6)	
III	1 (50.0)	1 (50.0)	
IV	8 (80.0)	2 (20.0)	

Variables	MACE		*p-value*
	With MACE	No MACE	
	42 (59.2%)	29 (40.8%)	
Coronary angiography result (n (%))			
CAD 1VD	8 (36.4)	14 (63.6)	
CAD 2VD	13 (59.1)	9 (40.9)	0.014¶*
CAD 3VD	21 (77.8)	6 (22.2)	
Atrial Fibrillation (n (%))			
Yes	2 (66.7)	1 (33.3)	1.000¶
No	40 (58.8)	28 (41.2)	
Chronic Heart Failure (n (%))			
Yes	0 (0.0)	0 (0.0)	1.000¶
No	42 (59.2)	40,8 29 (40.8)	
Onset STEMI (n (%))			
<6 hours	16 (66.7)	8 (33.3)	
6-12 hours	15 (46.9)	17 (53.1)	0.149¶
>12 hours	11 (73.3)	4 (26.7)	
Echocardiographic Characteristics			
LVEF (mean ± SD (%))	42.3±7.3	42.2±7.4	0.949#
LV Diastolic (n (%))			
Normal	24 (57.1)	18 (42.9)	
Decreased grade I	14 (63.6)	8 (36.4)	0.876¶
Decreased grade II	4 (57.1)	3 (42.9)	
TAPSE (mean ± SD (cm))	1.9±0.13	1.9±0.14	0.674#
RWMA			
Yes	42 (59.2)	29 (40.8)	1.000¶
No	0 (0.0)	0 (0.0)	
History of Taking Medication			
Acetosal (n (%))			
Yes	39 (57.4)	29 (42.6)	0.265¶
No	3 (100.0)	0 (0.0)	
Clopidogrel (n (%))			
Yes	39 (57.4)	1 (100.0)	0.265¶
No	42 (60.0)	28 (40.0)	
Enoxaparin (n (%))			
Yes	42 (59.2)	29 (40.8)	1.000¶
No	0 (0.0)	0 (0.0)	
Duration of drug consumption (n (%))			
<2 jam	31 (57.4)	23 (42.6)	0.778¶
≥2 jam	11 (64.7)	6 (35.3)	
Lama konsumsi obat (rerata ± SD (jam))	1.45±1.74	1.20±0.41	0.460#
Durasi konsumsi obat dengan onset STEMI (n (%))			
<6 hours	22 (64.7)	12 (35.3)	
6-12 hours	9 (40.9)	13 (59.1)	0.095¶
>12 hours	11 (73.3)	4 (26.7)	

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.

The inter-observer reliability test for assessing the intracoronary thrombus grade was performed with the Cohen Kappa test by calculating the mean of the examinations by both observers (cardiac interventionist physicians). This test mainly evaluates the intracoronary thrombus grade based on the TIMI classification using coronary angiography images assessed by observers. 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 inter-observer variability of the intracoronary thrombus degree values calculated by both observers is shown in Table 5. Based on the table, there is a high level of agreement between observers 1 and 2, namely, Agreement Kappa value of 0.819 and Asymptotic Standard Error of 0.057 ($p < 0.05$).

TABLE 5: Measurement of Inter-observer Reliability of Intracoronary Thrombus Grade.

	Value	Asymptotic Standard Error	Approximate T[b]	Approximate Significance
Measure of Agreement Kappa	0.872	0.050	11.008	0.000*
N of Valid Cases	71			

not assuming the null hypothesis.
Using the asymptotic standard error, assuming the null hypothesis.
* Statistically significant.

The cut-off values for determining abnormally high PDW categories using the data collected from this study were created using ROC curves (Figure 1 and Table 6).

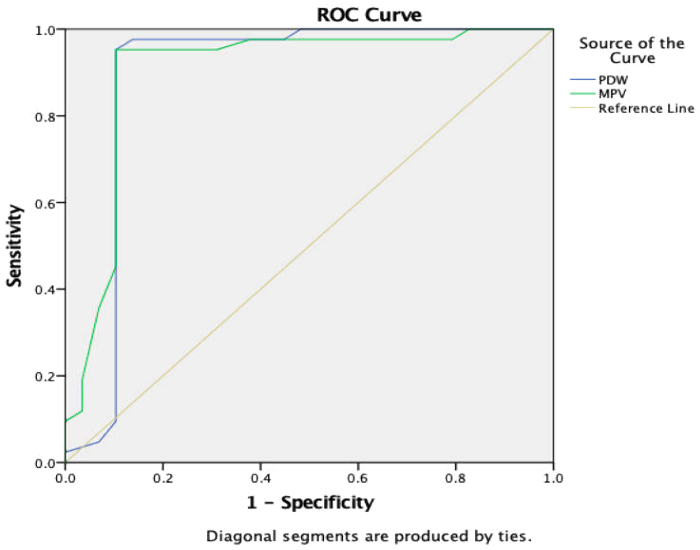

FIGURE 1: ROC Curve in Determining the Cut-off Point of PDW and High MPV.

TABLE 6: AUC, Sensitivity and Specificity of MACE Predictor.

Variables	AUC	95% IC	Sensitivity (%)	Specificity (%)	*Cut-off (fl)*	*p-value*
PDW	0.892	0.786-0.999	90.5	89.7	11.25	<0.001*
MPV	0.901	0.812-0.990	90.5	89.7	10.15	<0.001*

*Statistically significant

Based on ROC curve analysis, Youden Index obtained the optimal cut-off point value in stating high PDW and MPV to predict outcomes by obtaining the optimal relationship between sensitivity and specificity for PDW is 11.25 fl and for MPV is 10.15 fl. Area Under Curve (AUC) for PDW is 0.892 and for MPV is 0.901. PDW and MPV, which are numerical scales, were converted into nominal scales with two categories: high PDW and non-high PDW.

By using a cut-off point of PDW 11.25 fl and MPV 10.15 fl, we obtained high (abnormal) platelet indices data, namely values expressed by high PDW and/or high MPV, resulting in 46 (64.8%) patients with high platelet indices and 25 (35.2%) patients with non-high platelet indices ($p<0.001$ Chi-square test).

From a total of 71 STEMI patients who underwent primary percutaneous coronary intervention during hospitalization observed during the study, 42 patients experienced major cardiovascular events. A total of 41 patients had a high platelet indices, while 1 patient had a non-high platelet indices value. An overview of Kaplan Meier survival estimation of major cardiovascular events based on platelet indices category is shown in Figure 2 and Table 7 below.

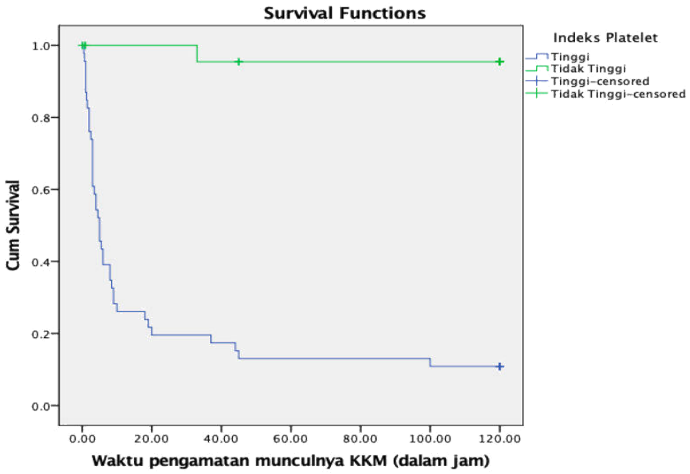

FIGURE 2: Kaplan-Meier Survival Estimation Curve of the Occurrence of Major Cardiovascular Events Based on High platelet indices.

TABLE 7: Mean survival value based on platelet indices.

Variables	Mean Time Survival (hour)	95% CI	Median Time Survival (hour)	95% CI	5 Days Survival Rate (%)	p-value
High Platelet Indices	22.14	11.14-33.14	5.00	11.14-33.14	12.4	<0.001*
No High Platelet Indices	116.05	108.47-123.62			95.5	

*Statistically significant

From this study, the mean length of survival of patients with a high platelet indices were 22.14 hours (95% CI = 11.14-33.14), while the mean length of survival of patients with a non-high platelet indices was 116.05 hours (95% CI = 108.47-123.62). The five-day survival rate of patients with a high platelet index was found to be 12.4%, while the five-day survival rate of patients with a non-high platelet index was 95.5%. After performing the Log Rank Test, it was found that the survival rate between patients with a high platelet indices and a non-high platelet indices was significantly different with a p value of <0.001.

The effect of high platelet indices on major cardiovascular events was significant, 46.24 times higher than those with non-high platelet indices values (p < 0.001). The Hazard Ratio (HR) was 46.24 (95% CI 6.30-339.28) as shown in Table 5.

This means that the risk of major cardiovascular events in STEMI patients who underwent primary percutaneous coronary intervention during hospitalization was 46.24 times higher in patients with a high platelet indices than in patients with a non-high platelet indices. 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. From a total of 71 STEMI patients who underwent primary percutaneous coronary intervention during hospitalization observed during the study, 48 patients had high intracoronary thrombus grade and 23 patients had non-high intracoronary thrombus grade. Among those with MACE, there were 41 patients with high intracoronary thrombus grade and 1 patient with low intracoronary thrombus grade. The Kaplan Meier survival estimation of major cardiovascular events by platelet indices category is shown in Figure 3 and Table 8 below.

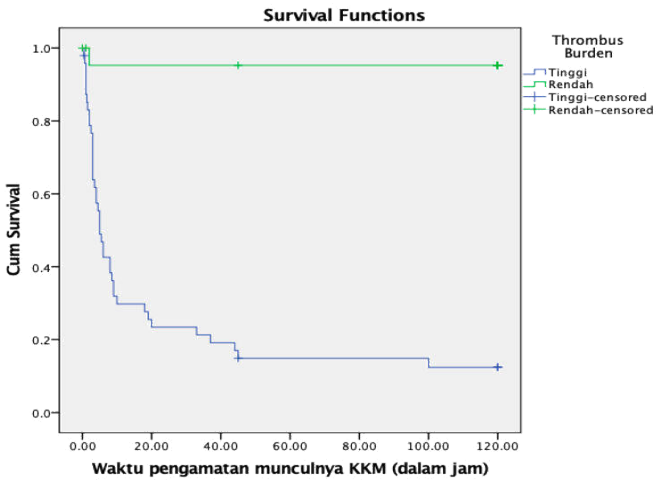

FIGURE 3: Kaplan-Meier Survival Estimation Curve of Major Cardiovascular Events by High Intracoronary Thrombus Grade.

TABLE 8: Mean survival based on intracoronary thrombus grade.

Variables	Mean Time Survival (hour)	95% CI	Median Time Survival (hour)	95% CI	5 Days Survival Rate (%)	p-value
High Intracoronary Thrombus Grade	24.82	13.39-36.25	5.00	3.32-6.68	10.9	<0.001*
Not High Intracoronary Thrombus Grade	114.38	103.63-125.13			95.2	

*Statistically significant

From this study, the mean length of survival of patients with high intacoronary thrombus was 24.82 hours (95% CI = 11.39-36.25), while the mean length of survival of patients with non-high intacoronary thrombus was 114.38 hours (95% CI = 103.63-125.13). Five days survival rate of patients with high intacoronary thrombus was found to be 10.9% while the five days survival rate of patients with non-high intacoronary thrombus was 95.2%. After performing the Log Rank Test, it was found that the survival rate between patients with high intracoronary thrombus and non-high intracoronary thrombus was significantly different, with a p-value of <0.001.

The effect of high intacoronary thrombus on major cardiovascular events was significant at 39 times higher than those with low intacoronary thrombus ($p < 0.001$). The Hazard Ratio (HR) was 39.00 (95% CI 5.32-286.146) 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 39 times higher in patients with high intracoronary thrombus than in patients with low intracoronary thrombus. The risk difference was statistically significant with $p < 0.001$. This HR value is also crude and has not controlled for other variables that are considered as confounders.

TABLE 9: Cox Regression Unadjusted and Adjusted Hazard Ratio Analysis of High Platelet Indices and High Intracoronary Thrombus Grade on MACE.

Variables	Unadjusted HR	95% CI	p-value	Adjusted HR[a]	95% CI	p-value	Adjusted HR[b]	95% CI	p-value
High platelet indices	**46.24**	6.30-339.28	**<0.001***	**38.13**	5.16-282.03	**0.000***			
High Intracoronary Thrombus Grade	**39.00**	5.32-286.15	**<0.001***				**31.67**	4.28-234.54	**0.001***
Coronary Angiography Results									
CAD 1VD			0.113			0.129			0.332
CAD 2VD	**0.42**	0.18-0.95	**0.037***	1.38	0.60-3.13	0.448	0.86	0.35-2.14	0.228
CAD 3VD	0.76	0.38-1.52	0.441	**2.13**	1.02-4.44	**0.43***	**1.58**	0.75-3.31	**0.009***

Variables	Unadjusted HR	95% CI	p-value	Adjusted HR[a]	95% CI	p-value	Adjusted HR[b]	95% CI	p-value
Smoking	**3.63**	1.89-6.95	**<0.001***	**2.29**	1.19-4.39	**0.013***	**2.32**	1.21-4.45	**0.011***
Killip Class									
I			0.547			0.461			0.848
II	0.74	0.34-1.63	0.461	0.63	0.23-1.72	0.367	1.03	0.42-2.53	0.947
III	0.41	0.12-1.37	0.147	0.39	0.09-1.72	0.219	1.67	0.41-6.85	0.479
IV	0.65	0.081-5.19	0.683	0.80	0.08-8.43	0.855	1.79	0.18-17.51	0.617
Acetosal	0,431	0.132-1.40	0.163	1.24	0.33-4.60	0.748	1.63	0.44-5.97	0.464
Clopidogrel	2.321	0.71-7.57	0.163						
Duration of drug consumption with onset of STEMI									
<6 hours			0.158			0.307			0.259
6-12 hours	0.937	0.454-1.935	0.861	1.22	0.57-2.63	0.613	1.74	0.82-3.69	0.151
>12 hours	0.466	0.193-1.125	0.089	0.61	0.22-1.69	0.341	1.06	0.431-2.63	0.893

*Statistically significant
[a]Adjusted HR based on high platelet indices
[b]Adjusted HR based on high degree of intracoronary thrombus

TABLE 10: Collinearity Test Between Independent Variables.

Variables	Intracoronary Thrombus Grade		OR	95% CI	p-value
	High	Not High			
Platelet indices (n (%))					
High	42 (91.3)	4 (8.7)	33.250	8.396-131.680	0.000*
Not High	6 (24.0)	19 (76.0)			

*Statistically significant

The variables in this study include platelet indices and intracoronary thrombus as independent variables and 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 platelets and thrombosis and duration of taking antiplatelet and anticoagulant drugs as control variables. The effect of control variables on independent variables with numerical data scale (age variable) was tested for normality with Kolmogorov-Smirnov 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 carried out Chi Square test.

The multivariate analysis used to determine the effect of high platelet indices and 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 of <0.25 and were considered important according to clinical theory, which of course had been analyzed for the assumption of collinearity of each independent variable to be covaried. In this study, a high platelet indices in circulation had a high association with the degree of intracoronary thrombus, where 91.3% of the high platelet indices group in circulation had a high intracoronary thrombus grade which was statistically significant ($p < 0.001$) (Table 10), so that almost always the group with a high platelet indices had high intracoronary thrombus. Therefore, multivariate Cox regression analysis was performed twice by separating the variables of platelet indices and the intracoronary thrombus grade so as not to mask the effects of other factors on MACE. Multivariate analysis showed that a high platelet indices proved to be an independent predictor of major cardiovascular events in STEMI patients after primary percutaneous coronary intervention during hospitalization with an adjusted HR value of 38.13 with 95% CI (5.16-282.03) and p value <0.001 (Table.9). This means that the risk of major cardiovascular events in STEMI patients after primary percutaneous coronary intervention during hospitalization with a high platelet indices after controlling for confounding factors is 38 times that of patients with a non-high platelet indices.

Similarly, this study showed that high intracoronary thrombus grade proved to be an independent predictor of major cardiovascular events in STEMI patients after primary percutaneous coronary intervention during hospitalization with an adjusted HR value of 31.67 with 95% CI (4.28-234.54 and p value of 0.001 (Table 9). This means that the risk of major cardiovascular events in STEMI patients after primary percutaneous coronary intervention during hospitalization with high intracoronary thrombus grade after controlling for confounding factors is 31

times that of patients with non-high intracoronary thrombus grade. To determine the interaction of platelet indices with the intracoronary thrombus grade on MACE during hospitalization in STEMI patients undergoing primary percutaneous coronary intervention using structural equation modeling analysis (Structural Equation Modeling), which is a 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 high platelet indices and high intracoronary thrombus grade as predictors of MACE from the results of Structural Equation Modeling analysis according to Table 11 and the comparison of AUC, sensitivity and specificity of each MACE predictor looks like Table 12.

TABLE 11: Results of Structural Equation Modeling Analysis.

Platelet indices			MACE		Breslow-Day Homogeneity Test (p)	Cochran's and Mantel-Haenszel (p)
			With MACE	No MACE		
High	Intracoronary Thrombus	High	40 (95.2)	2 (4.8)	0.772	<0.001*
		Not High	1 (25.0)	3 (75.0)		
Not High	Intracoronary Thrombus	High	1 (16.7)	5 (83.3)		
		Not High	0 (0.0)	19 (100.0)		
Mantel-Haenzel Common Estimate		17, 480				
95% KI		4,457 - 1346,906				

*Statistically significant

TABLE 12: AUC, Sensitivity and Specificity of MACE Predictor.

Variables	AUC	95% CI	Sensitivity (%)	Specificity (%)	Cut-off (fl)	P-value
PDW	0.892	0.786-0.999	90.5	89.7	11.25	<0.001*
MPV	0.901	0.812-0.990	90.5	89.7	10.15	<0.001*
High Platelet indices	0.902	0.815-0.989	97.6	82.8		<0.001*
High Intracoronary Thrombus Grade	0.873	0.776-0.970	92.9	82.8		<0.001*
Combination of High Platelet indices and High Intracoronary Thrombus Grade	0.942	0.876-1.000	95.2	93.1		<0.001*

*Statistically significant

DISCUSSION

Along with the development of science and technology in the field of health, there have been many advances in understanding the pathophysiological and biomolecular mechanisms of IMA diseases, including STEMI, which are the basis for improving the management and prevention of these diseases, but it turns out that STEMI is still a major cause of morbidity and mortality in developing countries. Morbidity and mortality in patients with STEMI are strongly associated with various complications that can be caused by STEMI.

Among the frequent and most feared complications of STEMI are major cardiovascular events, which are STEMI complications associated with patient survival consisting of cardiovascular death, cardiogenic shock, acute 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. The risk stratification system for IMA and STEMI that is often used and recognized today is the scoring system with the TIMI score and GRACE score. However, the components of these scores, including troponin values or angiography, are specialized examinations, so a simple examination is needed that can be used as an effort to risk stratify STEMI patients. The basis of patient risk stratification. STEMI certainly cannot be separated from an understanding of the pathophysiology of STEMI. One of the important ones is platelet activation and intracoronary thrombus.

High platelet activation has been associated with thrombotic potential and a high risk of complications. Activation can be simply and indirectly measured by platelet indices, in this case by using platelet distribution width (PDW) and mean platelet volume (MPV) values as part of a simple complete blood test (DL). Various studies have linked both PDW and MPV to the incidence of acute myocardial infarction.

During the period of July to September 2023, a prospective cohort study was conducted at Prof dr. I.G.N.G. Ngoerah Hospital, Denpasar. The important findings of this study are the first high platelet indices (MPV and/or PDW) as a predictor of MACE during hospitalization in STEMI patients undergoing primary percutaneous coronary intervention. Secondly, high intracoronary thrombus grade as a predictor of MACE during hospitalization in STEMI patients undergoing primary percutaneous coronary intervention. If the conditions of high intracoronary thrombus grade and high platelet indices appear together in one STEMI patient undergoing primary percutaneous coronary intervention, the predictor value of MACE during hospitalization is stronger.

During the study, 71 STEMI patients undergoing primary percutaneous coronary intervention who met the inclusion criteria were taken by consecutive sampling from the study population. In this study, the mean age, male gender, smoking, dyslipidemia, diabetes mellitus, hypertension, higher Killip class, more complex coronary angiography results (CAD 2VD and 3VD), were higher in the STEMI patient group with a high platelet indices compared to the patient group with a non-high platelet indices, as well as in STEMI with a high intracoronary thrombus grade compared to a non-high degree of intracoronary thrombus. Obesity and the presence of a family history of coronary heart disease were more common in the group of patients with a non-high platelet indices than in the group of patients with a high platelet indices, similar to the group based on the degree of intracoronary thrombus. These baseline characteristics are consistent with the study by Wang, J. et al. 2019 [20], Ulucan et al. [18], Bekler et al., 2015 [10], and Rechcński, T. et al. (2013) [21]. Studies on PDW as a predictor of impaired reperfusion and long-term mortality in STEMI patients undergoing primary PCI by Huczek et al. and Vakili et al. also showed similar characteristics [22]

Only 4% of STEMI patients with high platelet indices had comorbid atrial fibrillation and no comorbid Chronic Heart Failure, CKD and stroke, with similar characteristics found among the high coronary thrombus grade group. The patients' mean LVEF and TAPSE were 42% and 1.9 cm, respectively, and all patients had RWMA (regional wall motion abnormality) from echocardiographic examination. Of the 71 samples, 42 patients (59.25) with MACE, 29 patients (40.8%) without MACE, of all patients with MACE, 5 patients (7%) experienced cardiovascular death during treatment. Of all types of MACE, AHF was dominant in 15 patients (21.1%), followed by cardiogenic shock in 41 patients (57.7%), then malignant arrhythmia in 15 patients (21.1%) and finally cardiovascular death.

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 PDW values or high and low MPV values as in the studies of Ulucan et al., 2016 [18], Vagdatli et al., 2010 [23], and Wang, J. et al. 2019 [24], where in this study the mean age, LVEF, TAPSE and duration of taking DAPT or anticoagulant drugs were similar 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 mellitus were higher in the group of patients with MACE than the group of patients not with MACE. Whereas diabetes mellitus, obesity, family history of coronary heart disease on the contrary were more dominant in the group of patients without MACE.

In this study, all patients with first-time use of acetosal, clopidogrel, enoxaparin, with the mean duration of drug use from blood collection to complete blood examination in the emergency room was slightly longer in the group of patients with high platelet indices and high intracoronary thrombus grade than those without (1.43±1.67 and 1.20±0.41; p=0.492 for platelet indices, 1.45±1.63 and 1.13±0.34; p=0.347 for intracoronary thrombus).

From the bivariate analysis of all variables grouped by groups with and without CHD, only smoking, coronary angiography results in addition to the independent variables studied, namely platelet indices and intracoronary thrombus significantly affect CHD. While the variables of patient age, gender, dyslipidemia, diabetes mellitus, hypertension, obesity, family history of coronary heart disease, killip class, STEMI region, atrial fibrillation, Chronic Heart Failure, LVEF, LV diastolic, TAPSE, RWMA, TIMI post-action flow, history of taking acetosal, clopidogrel, enoxaparin and duration of medication did not significantly affect MACE. The insignificant effect of patient age in this study can be explained because the age range of the study sample was short, in other words, the age of the patients was very similar in both the MACE and no MACE groups. The mean LVEF and TAPSE of patients in this study were also similar between the groups with and without LVEF, resulting in an insignificant effect. 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 was similar between the groups with and without MACE, making the effect also statistically insignificant. The duration of antiplatelet and anticoagulant drug consumption and the duration between the onset of STEM and drug consumption were also analyzed in this study, and it was found that the mean duration of drug consumption until the patient was taken for blood tests in the emergency room was slightly higher in the group of patients with MACE than without MACE (1.45±1.74 hours and 1.20±0.41; p=0.460). Meanwhile, the duration of drug consumption from the onset of STEMI in the group of patients with MACE was dominant with a shorter duration of <6 hours, but it was not statistically significant with p=0.095.

The relationship between PDW and traditional CHD risk factors is still not fully known. A review of various journals by Gasparyan et al. in 2011 on the relationship of PDW with thrombosis and inflammation put forward the results of his analysis

that traditional CHD risk factors affect PDW indirectly through the inflammatory process, through the role of cytokine mediator IL-1 encouraging the bone marrow to produce high PDW and then implicated in the thrombosis process [25]. Chu et al. in their meta-analysis of 16 cross-sectional studies involving 2,809 research subjects in 2009 found that PDW did not correlate with traditional risk factors for CHD, so high PDW is thought to contribute to cardiovascular events through a separate mechanism [11].

The PDW cut-off point value in this study aims to predict outcomes to obtain an optimal relationship between sensitivity and specificity. The high PDW value obtained had the highest accuracy value as a predictor of major cardiovascular events. This was easily demonstrated with the ROC.

The AUC value for PDW obtained in this study is 89.2% and for MPV is 90.1%, which has strong validity, respectively with a Standard Error of 0.054; (KI 95% 0.786-0.999; p value <0.0001) and Standard Error 0.046; (KI 95% 0.812- 0.990; p value <0.0001). The cut-off value of PDW in this study was 11.25 fl, i.e., high PDW≥ 11.25 fl and low PDW <11.25 fl based on a sensitivity value of 90.5% and specificity of 89.7%. Cut-off values that correlate PDW and STEMI events vary from study to study. And the cut-off value of MPV in this study was 10.15 fl, namely high MPV≥ 10.15 fl and low MPV <10.15 fl, also based on a sensitivity value of 90.5% and specificity of 89.7%.

Cut-off values linking PDW and STEMI events vary from study to study. The study conducted by Tomasz et al. in 2013 found a value of 16 to distinguish high and low PDW in STEMI patients. The study conducted by Mustafa et al. in 2014 found a value of 16.8 to distinguish high and low PDW in STEMI patients. And another study conducted by Ulucan et al. in 2016 found a value of 13.7 to distinguish high and low PDW in STEMI patients, where all of these values were determined by scoring or ROC curves [18].

Similarly, for MPV, a small case series study by Boos et al. in 2002 found a value of 8.5 fL to distinguish high and low MPV in IMA patients. A meta-analysis of 16 cross-sectional studies by Chu et al. in 2009 linking MPV values with increased risk of IMA found a cut-off value of 8.48 fl as the cut-off for high and low MPV. Of the 16 studies used in the meta-analysis, the MPV cut-off varied from a low of 6.5 fL to a high of 11.7 fL [11]. In another large meta-analysis in 2014 by Sansanayudh et al. of 40 studies and involving more than 12,000 research subjects linking MPV with CHD found a cut off value of 7.3 [26]

Various factors have been known to influence PDW. These factors include malignancy, DIC, sepsis, aplastic anemia, ITP and thrombocytosis. Most PDW studies in the literature do not include these factors in the exclusion criteria of the study subjects, while in this study these factors have been controlled as exclusion criteria.

This study used Ethylenediaminetetraacetic acid (EDTA) as anticoagulant in whole blood sampling tubes. Most other PDW and MPV studies also use the same type of anticoagulant. In 2006, Dastjerdi et al. conducted a study comparing the results of PDW examinations using EDTA and citrate anticoagulants. It was found that PDW examined with citrate tubes was lower [27].

Due to the involvement of various variables that can affect the value of PDW and MPV, it is recommended that each laboratory create its own cut-off point value. [30]. In this study, the cut-off points for PDW and MPV were obtained from the ROC curve. A value of 11.25 was obtained as the optimal cut-off point in stating high and low PDW, and a value of 10.15 fl as the optimal cut-off point in stating high and low MPV. What distinguishes this study from previous studies, in this study using the independent variable in the form of platelet indices, which is obtained from high PDW and/or MPV values based on the cut-off point obtained from the ROC curve. From this study of 71 patients 46 patients (64%) with high platelet indices and 25 patients (35.2%) with non-high platelet indices.

This study represents the concept of platelet characteristics in the cytemic circulation that are prone to thrombotic, namely in the form of a high platelet indices, combined with intracoronary local conditions in the form of a high intracoronary thrombus grade in predicting intrahospital MACE, showing that a high platelet indices is proven to be an independent predictor of major cardiovascular events during hospitalization in STEMI patients after primary percutaneous coronary intervention with an unadjusted hazard ratio of 46.24 (KI 95% 6.30-339.28; p value = 0.001). This means that STEMI patients after primary percutaneous coronary intervention with high platelet indices have a risk of experiencing major cardiovascular events during hospitalization that is almost 46 times greater than the group of patients with a non-high platelet indices. And high intracoronary thrombus grade was shown to be an independent predictor of major cardiovascular events during hospitalization in STEMI patients after primary percutaneous coronary intervention with an unadjusted hazard ratio of 39.0 (KI 95% 5.32-286.146; p value = 0.001). This means that STEMI patients after primary percutaneous coronary intervention with high intracoronary thrombus grade have an almost 39-fold greater risk of experiencing major cardiovascular events during hospitalization than the group of patients with non-high intracoronary thrombus grade.

After controlling for confounding variables on multivariate analysis, high platelet indices were shown to be an independent predictor of MVC with an adjusted hazard ratio of 38.13 (95% CI 5.16-282.03; p value <0.001). This means that a high platelet indices are an independent predictor of major cardiovascular events with an almost 38-fold greater risk than a non-high platelet indices.

And high intracoronary thrombus grade was shown to be an independent predictor of MVC with an adjusted hazard ratio of 31.67 (95% CI 14.28-234.54; p value = 0.001). This means that high intracoronary thrombus grade is an independent predictor of the occurrence of major cardiovascular events with a 31-fold greater risk than intracoronary thrombus that is not high in the influence of platelet indices.

In this study, the effect of high platelet indices is stronger as a predictor of MTC than the intracoronary thrombus grade can be explained by the first theoretical basis of STEMI is a condition caused by total occlusion of the coronary blood vessels, of course, most tend to have a high intracoronary thrombus grade (TIMI thrombus grade 3 to 5), thus making the data characteristics of this study tend to be relatively more homogeneous with a high intracoronary thrombus grade compared to the predictor of circulating platelet indices more heterogeneous. Both studies were single-center and involved relatively small sample sizes, so the sample distribution was better for the platelet indices predictor than the degree of intracoronary thrombus, which tended not to vary too much in the MACE group or not. In STEMI, there is rupture of the atherosclerotic plaque, which will stimulate a series of platelet activation. High platelet activation plays a crucial role in the pathogenesis of thrombus formation due to atherosclerotic plaque rupture. Measurement of platelet activation is believed to provide an index of the functional capacity of platelets. There is increased platelet activation during acute coronary syndrome, and measurement of platelet activation and/or platelet aggregation may provide prognostic information in patients at risk for cardiovascular events.

Previous studies have shown a strong relationship between function and platelet size. This is because large platelets, which are produced from activated megakaryocytes in the bone marrow, are more reactive than normal platelets. Consequently, larger, hyperactive platelets play an important role in accelerating intracoronary thrombus formation and propagation, promoting thrombotic events. Various studies have attempted to find the best platelet indices parameter that can describe the increase in platelet activation. Of all the platelet indices parameters, PDW can reflect changes in both the level of platelet stimulation and the speed of platelet production [28]. Other studies have shown a significant association between PDW and IMA and cardiovascular events [11,29,30]. High platelet distribution width will depict high platelet activation in IMA patients, higher potential for thrombosis, and more severe infarction, so PDW is expected to play a role as a predictor of major cardiovascular events in IMA patients.

The observation time in this study was during the patient's treatment in the hospital, which illustrates the short-term prognosis of STEMI patients. From the literature search by researchers, there have been no studies similar to this study, but the results obtained in this study are in accordance with previous studies that used PDW as a short-term prognostic factor in myocardial infarction patients.

A study by Ulucan et al. in 2016 in 320 patients with IMA found that patients with high PDW (cut off 13.7) had a 2-fold risk of mortality during hospitalization in patients with IMA [18]. The role of PDW in post-IMA morbidity by Vakili et al. in 2008 using a population of 203 STEMI patients found that high PDW at baseline may act as a predictor of impaired reperfusion and major cardiovascular events during hospitalization after primary PCI with an OR of 2.49, respectively [22]. A 2013 study by Tomasz et al. in 538 IMA patients found that high PDW was significantly associated with an increased risk of post-IMA mortality during hospitalization with an OR of 2.96 [21].

Prognostic studies during hospitalization and long-term care by Ulucan et al. 2016 in their study using PDW as a predictor of major cardiovascular events and coronary end flow in 320 IMA patients who underwent pharmacological revascularization or PCI therapy found that high PDW was a predictor of cardiovascular events in-hospital and long-term care after IMA with an OR of 1.8. [24]. Another study by David, et al. (2013) in a study of 119 patients with IMA, first found that PDW was a strong predictor of mortality within 1-year post IMA with an OR of 1.2. [31]. Considering that a risk value above 2.0 is considered significant, PDW is a good prognostic marker in predicting the occurrence of cardiovascular events in post-IMA patients. As good prognostic markers, PDW and MPV can be used as secondary prevention modalities in patients with IMA.

The interaction of platelet indices with intracoronary thrombus grade on MTC during hospitalization in STEMI patients undergoing primary percutaneous coronary intervention was determined by structural equation modeling analysis. In this study, it was found that the incidence of MCI during hospitalization in STEMI patients with the presence of two predictors together, namely high platelet indices and with high intracoronary thrombus grade, was dramatic when compared with the absence of both conditions or one of these predictors. Patients with a non-high platelet indices and a non-high intracoronary thrombus grade had almost no incidence of MCI during hospitalization, whereas in the presence of one predictor, a high degree of intracoronary thrombus, without a high platelet indices, 16.7% experienced MCI during hospitalization, whereas in the presence of one predictor, a high platelet indices, the incidence of MCI was 25%, and STEMI patients with a high platelet indices and high intracoronary thrombus grade experienced MCI during hospitalization was 95.2%. The tendency of STEMI patients with high platelet indices to experience MACE during hospitalization is 17 times the condition of high intracoronary thrombus grade expressed in Mantel-Haenzel Common Estimate 17.480 (95% KI 4.457 - 1346.906; Cochran's and Mantel-Haenszel p value <0.001.

This is the specificity of this study compared to previous studies that assessed predictors of MCH with platelet indices values or PDW and/or MPV and the intracoronary thrombus grade individually as predictors. While this study assessed both predictors simultaneously and found high platelet indices and high intracoronary thrombus grade as independent predictors of the incidence of MACE during hospitalization. It turned out that the presence of both conditions of high platelet indices and intracoronary thrombus degree showed a stronger predictor. The combination of the two predictors obtained sensitivity and specificity values of 95.2% and 93.1%, respectively, and an AUC value based on the ROC curve of 0.942, which is much better than the separate predictors of platelet index and intracoronary thrombus. The AUC value, which is quite strong, has the potential for bias. Still, theoretically, in conditions where platelets are more reactive, especially combined with conditions of high intracoronary thrombus grade, thrombotic events tend to be higher, so that complications, in this case, MACE during hospitalization also tend to be higher, a study from Attumalil 2022 [19], Ulucan et al., 2016 [18] and Chu, S.G. et al. 2010 [11] and distinguishes this research is that this research predictor uses a composite of PDW and MPV components so that it has the potential for the AUC to be stronger.

After correlation with factors other than the main predictors of the effect on MACE with the Cox regression backward log-rank model, it was found that in addition to the main predictors studied, there were other factors that also significantly influenced the incidence of hospitalized MACE, namely smoking and CAD3VD coronary angiography results. Theoretically, smoking is associated with the incidence of intracoronary thrombus and MVC during hospitalization with its pathomechanism through various pathways. Smoking increases serum LDL- cholesterol and triglyceride concentrations and decreases serum HDL-cholesterol, increases free radical-induced coronary endothelial damage, and vascular inflammation. [35]. Smoking through its nicotine content, activates the sympathetic nervous system (SNS), increases the rate-pressure product (RPP) causing increased myocardial oxygen demand, coronary artery vasoconstriction, increased blood carboxyhemoglobin levels, reduced myocardial oxygen delivery [32]. So, related to the goal of risk stratification and prevention of MACE, as clinicians, we always educate to stop smoking in STEMI patients to prevent MACE-related complications of STEMI. Similarly, family support education is also not to smoke, considering that smoking can be active or passive.

Lesion complexity in the form of CAD 3VD significantly affected MCH after covariate cox regression. There was a change in hazard value and significance from unadjusted to adjusted in CAD2VD. This finding is supported by the study of Ulucan et al., 2016 in Turkey which found that complex lesions (multi-vessel disease) significantly affect long-term (4 years) MACE [24]. Before covariates, 2VD CAD had a higher incidence of MCI compared to 3VD CAD which clinically we might assume to have more severe disease. However, the limitation of this study is that the sample was not differentiated by the percentage of stenosis severity angiographically, it could be that although 2VD CAD has more severe stenosis and even a higher degree of intracoronary thrombus. Coronary evaluation in this study is also without physiological intervention studies in this case FFR (fraction flow reserve) or imaging interventions such as IVUS (Intravascular ultrasound) or OCT (Optical coherence tomography) that can evaluate even though CAD 3VD may be physiologically FFR shows a value >0.8 which is not significant stenosis or through IVUS or OCT shows structurally insignificant stenosis, while CAD 2VD may be in this patient almost most of them are really significant stenosis. Similarly, when the sample size is relatively small and from one center, the distribution of 3VD, 2VD and 1VD CAD groups is not balanced, which may be possible when the sample size is larger and multi-center studies provide more appropriate results.

Various studies have found an association between PDW and CHD. It is also known that PDW is higher in IMA compared to patients without IMA. Several studies have also found an association between high PDW and the rate of recurrent stenosis after coronary angioplasty and morbidity after NSTEMI [25,33]. To avoid the influence of reperfusion therapy masking the role of platelet indices and intracoronary thrombus on the incidence of FM, in this study, reperfusion therapy was excluded from the study sample from the beginning. Inflammatory processes and thrombosis seem to have a significant role in correlating PDW values with post-IMA cardiovascular events. Hypothesized by Azab et al. that high PDW, high MPV with low platelet count is a markers of increased platelet activity and aggregation. Low platelet count is associated with high expression of glycoprotein VI and an increase in various inflammatory markers [33]. Tsiara et al. (2003) also revealed that high PDW, high MPV and low platelet count have stronger platelet aggregation, thus playing a major role in the thrombosis process [34].

Overall, the clinical significance of the results of this study can recommend clinicians, especially interventionists, to risk stratify the incidence of intrahospital MACE in STEMI patients, mainly primary percutaneous coronary intervention, including the incidence of high degrees of intracoronary thrombus can also be prevented in addition to intrahospital MACE by considering the use of stronger antiplatelets such as GP IIbIIIa, preparation for the possibility of thrombus aspiration or thrombectomy in patients with high platelet index at the first hospital admission as also recommended by previous studies from PDW and MPV predictors separately. Indeed, there are not many studies related to PDW and MPV specifically related to GPIIbIIIa in preventing intracoronary thrombus burden and intrahospital MACE. We need to know that GPIIbIIIa drugs, in this case, do not directly reduce the platelet indices value because the

platelet indices are only a biomarker of circulation (predictor). Still, the high platelet reactivity described by the biomarker is handled more aggressively and optimally so that it can inhibit the expression of GPIIbIIIa on the platelet cell membrane and break the natural journey toward intracoronary thrombus formation and ultimately prevent STEMI MACE during hospitalization.

This study has limitations that should be considered, namely, the MACE follow-up period in this study is only during hospitalization, which does not describe the prognosis of patients after hospitalization, making it difficult to generalize the results of this study to STEMI patients as a whole. Therefore, research can be developed with a more extended follow-up period until post-hospitalization so that the prognosis of 30-day, six-month, one-year, or five-year MACE can also be assessed in STEMI patients after primary percutaneous coronary intervention based on a high platelet index and high intracoronary thrombus grade. This study did not include a sedentary lifestyle as one of the confounding factors. This study also did not include patients who underwent previous reperfusion therapy. Anticoagulant therapy in all patients was the same as enoxaparin, so it is less able to explain the risk of MACE during treatment if previously failed fibrinolytic or who received anticoagulant therapy in the form of UFH instead of enoxaparin.

CONCLUSION

High platelet indices and high intracoronary thrombus grade can be used as additional information for risk stratification of in-hospital MACE of STEMI patients post-primary PCI, especially when both variables were combined.

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