Research Article

In-Hospital Major Adverse Cardiac Events Factor Predictors on ST-Elevation Myocardial Infarction after Primary Percutaneous Coronary Intervention at dr. Cipto Mangunkusumo General Hospital

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Abstract

Major Adverse Cardiac Events (MACE) are the main causes to increase mortality in ST-Elevation Myocardial Infarction (STEMI) patients who undergo Primary Percutaneous Coronary Intervention (PPCI). In-hospital MACE inducing factor predictors identification is expected to enhance STEMI patients' care and outcome. This study aims to identify in-hospital MACE factor predictors in STEMI patients with PPCI treatment at RSCM. Retrospective cohort study by tracing medical records on patients with PPCI treatment at RSCM from January 2015 - March 2020. The chi-squared bivariate analysis concluded between predictor factors; age, smoking, hypertension, diabetic Mellitus, chronic kidney disease, time-to-treatment, Killip class, left ventricle ejection fraction (LVEF) and LDL cholesterol level. Logistic regression is used in multivariate and prediction model analysis on variables with p<0,25 in bivariate analysis. This study involves 291 patient subjects. The occurrence of MACE is 43.3% on patients age > 60 years (29,6%), smoking (61,2%), hypertension (50,9%), diabetes mellitus (36,1%), chronic kidney disease (6,2%), Killip class II-IV (32,2%), LVEF > 50% (57%) dan cholesterol LDL level > 100 mg/dl (79,4%). Median time-to-treatment is 528 (379-730) minutes. Age, Killip class, and LVEF influences in-hospital MACE during PPCI with OR (95% CI) consecutively are 2,15 (1,22-3,79), 4,34 (2,49-7,56) and 2,88 (1,72-4,82). MACE prediction model in this study produces area under curve (AUC) 0,729 (95% CI 0,67-0,78). In-hospital MACE on STEMI patients after PPCI occurrence is 43.3%, influenced by age, Killip class, and LVEF.

Keywords: *major adverse cardiac events, primary percutaneous coronary intervention, myocardial infarction.*

Faktor Prediktor *Major Adverse Cardiac Events* Selama Perawatan pada Pasien ST-Elevasi Miokard Infark yang Menjalani Intervensi Koroner Perkutan Primer di RSUPN dr. Cipto Mangunkusumo

Abstrak

Major Adverse Cardiac Events (MACE) merupakan penyebab utama meningkatnya mortalitas pada pasien ST-Elevasi Miokard Infark (STEMI) yang menjalani intervensi koroner perkutan primer (IKPP). Identifikasi faktor prediktor yang mempengaruhi terjadinya MACE selama perawatan diharapkan dapat meningkatkan perawatan dan luaran klinis dari pasien STEMI. Penelitian ini bertujuan untuk mengetahui faktor prediktor MACE selama perawatan pada pasien STEMI yang dilakukan IKPP di RSCM. Studi kohort retrospektif dengan menelusuri rekam medis pasien yang menjalani IKPP di RSCM periode Januari 2015-Maret 2020. Dilakukan analisa bivariat antara faktor prediktor usia, status merokok, hipertensi, diabetes mellitus, penyakit ginjal kronik, time-to-treatment, kelas killip, fraksi ejeksi ventrikel kiri (FEVK) dan kadar kolesterol LDL dengan kejadian MACE selama perawatan pada pasien STEMI yang menjalani IKPP, menggunakan metode Chi-square. Analisa multivariat dan analisa model prediksi dilakukan dengan metode regresi logistik terhadap variabel dengan nilai p= <0,25 pada analisa bivariat.Didapatkan subyek sebanyak 291 pasien untuk diteliti. Major Adverse Cardiac Events selama perawatan didapatkan sebesar 43,3% dengan usia >60 tahun (29,6%), status merokok (61,2%), hipertensi (50,9%), diabetes mellitus (36.1%), penyakit ginjal kronik (6,2%), kelas Killip II-IV (32,2%), FEVK > 50% (57%) dan kadar kolesterol LDL > 100 mg/dl (79,4%). Median time-to-treatment didapatkan sebesar 528 (379-730) menit. Usia, kelas killip dan FEVK mempengaruhi kejadian MACE selama perawatan dengan OR (IK 95%) masing-masing 2,15 (1,22-3,79), 4,34 (2,49-7,56) dan 2,88 (1,72-4,82). Model prediksi MACE selama perawatan pada pasien STEMI yang menjalani IKPP memiliki nilai area under curve (AUC) 0,729 (IK 95% 0,67-0,78). Major Adverse Cardiac Events (MACE) selama perawatan

Kata kunci: *major adverse cardiac events, intervensi koroner perkutan primer, infark miokard.*

Introduction

Cardiovascular disease is the highest cause of death in the world among non-communicable diseases, with mortality rate of 126 per 100,000 people (15.2 million from 56.9 million deaths in 2016).[1] Coronary heart disease has increased in prevalence to more than from 1.5 times in a decade (16% in 1992 to 26.9% in 2001).[2] In the cardiology intensive care unit (ICCU) at dr. Cipto Mangunkusumo General Hospital/Rumah Sakit Umum Pusat Nasional dr. Cipto Mangunkusumo (RSCM) in 2008-2012, 1,298 patients were treated with chest pain, and up to 950 (73.7%) were diagnosed with acute coronary syndrome (ACS).[3] The most common type of ACS (41.2%) is ST elevation myocardial infraction (STEMI), followed by unstable angina pectoris (UAP) at 40.5% and non-ST elevation myocardial infraction (NSTEMI) at 18.3%. Meanwhile, another study conducted at the RSCM in 2011 reported the proportion of deaths in STEMI patients was 18.6%.[4] The mortality rate of STEMI patients after primary percutaneous coronary intervention (PPCI) during treatment at RSCM in August 2013 - August 2014 was 3.8% (95% CI 2.6-5).[5]

Primary percutaneous coronary intervention (PPCI) is the treatment of choice in the management of patients with acute STEMI which significantly reduces mortality and morbidity compared to fibrinolytics as a reperfusion strategy.[6] Clinical outcomes in STEMI patients are influenced by the occurrence of complications known as major adverse cardiac events (MACE), which consists of left ventricular dysfunction, recurrent ischemia, early reinfarction, severe coronary disease, stroke and malignant arrhythmias.[7]

The occurrence of MACE in STEMI patients is important in determining medical management, especially the duration and intensity of hospitalization, as well as optimizing appropriate therapy during treatment. Various kinds of risk factors that contribute to the incidence of MACE from several studies are clinical characteristics, demographics, comorbidities, and lifestyle during MACE complications.

Thrombolysis in myocardial infarction (TIMI) risk stratification has been widely used to predict mortality during treatment and 30 days in STEMI patients. TIMI, which was derived from a clinical cohort trial based on 8 clinical predictor factors, consists of age, diabetes, hypertension or angina, systolic blood pressure, heart rate, Killip classification, body weight, anterior ST segment elevation or left bundle-branch block (LBBB) and time to reperfusion therapy >4 hours.[8] However, the independent risk factors for STEMI currently available have mostly focused on death during treatment or 30 days as outcome and have not taken into account other major cases, such as MACE after the PCI and possible long-term outcomes.

In developing countries, there is a wide variation in the provision of health services. It is often a challenge to provide the best treatment strategies recommended in international guidelines. We need to examine the clinical predictors of MACE incidence in different populations, especially in Indonesia. Thus, we will develop a novel and easy predictor model of MACE risk factors in STEMI patients undergoing PPCI, such as heart failure, cardiogenic shock, malignant arrhythmia, recurrent myocardial infarction, and stroke at RSCM.

Methods

This was a prognostic-based retrospective cohort study. Secondary data was obtained from the medical records of STEMI patients who had undergone PPCI who at RSCM and in January 2015 to March 2020. The subjects were STEMI patients who had been diagnosed in the emergency room with an onset of ≤12 hours, had undergone PPCI, and can be followed up. Exclusion criteria were patients with severe comorbidity including acute stroke, liver cirrhosis, acute complications of diabetes mellitus, sepsis, chronic inflammatory disease, or malignancy, patients who were pregnant or lactating, and patients with incomplete medical record.

The variables examined included age, smoking status, hypertension, diabetes mellitus, chronic kidney disease, time-to-treatment, Killip class, left ventricle ejection fraction (LVEF) and LDL cholesterol levels. All research subjects will be observed during treatment to see the outcome in the form of MACE. Data were analyzed by univariate, bivariate and multivariate analysis. The results were presented as frequency distribution table. Numerical data were presented as mean and standard deviation if normally distributed, or otherwise as median and range. Bivariate analysis was performed using the chi-square test. The relative risk (RR) and confidence interval (CI) values of each independent variable were analyzed in relation to the dependent variable. Multivariate analysis was performed using logistic regression.

To produce a model prediction for MACE during the treatment of STEMI patients treated by PPCI,

calibration and discrimination tests were carried out by assessing the area under curve (AUC). The data was analyzed by SPSS version 20 program. This research has passed the ethical review of the Health Research Ethics Committee, Faculty of Medicine, Universitas Indonesia with letter number KET-891/UN2.F1/ETIK/PPM.00.02/2021.

Results

We calculated a minimal number of research subjects of 238 people based on a 37.78% MACE frequency in STEMI patients from previous study. Of the total 408 STEMI patients who underwent PPCI, 291 patients met the criteria to participate in the study, and 117 patients did not have complete medical record data.

Table 1. Characteristics of Research Subjects

Characteristics	N = 291
Age (years), Median (RIK)	54 (49-61)
Age Group, n (%)	
Age < 60 years	205 (70.4)
Age ≥ 60 years	86 (29.6)
Smoking, n (%)	
Yes	178 (61.2)
No	113 (38.8)
Hypertension, n (%)	
Yes	148 (50.9)
No	143 (49.1)
Diabetes Mellitus, n (%)	
Yes	105 (36.1)
No	186 (63.9)
Chronic Kidney Disease, n (%)	
Yes	18 (6.2)
No	273 (93.8)
Time-to-treatment, Median, n (%)	528 (379-730)
Killip's Class	
Killip I	197 (67.7)
Killip II	39 (13.4)
Killip III	24 (8.2)
Killip IV	31 (10.7)
Killip's Class	
Killip I	197 (67.7)
Killip II-IV	94 (32.3)
LVEF, n (%)	
< 50 %	125 (43)
≥ 50 %	166 (57)
LDL Cholesterol (mg/dl), n (%)	
≤ 100	60 (20.6)
> 100	231 (79.4)
MACE, n (%)	
Yes	126 (43.3)
No	165 (56.7)
MACE, n (%)	
Malignant arrhythmia	22 (7.6)
Heart failure	107 (36.8)
Cardiogenic shock	56 (19.2)
Recurrent myocardial infarction	7 (2.4)
Stroke	12 (4.1)

Table 1 shows the occurrence of MACE is 43.3% with a proportion of patients aged >60 years (29,6%), patients who smoked (61,2%), had hypertension (50,9%), diabetes mellitus (36,1%), chronic kidney disease (6,2%), Killip class II-IV (32,2%), LVEF >50% (57%) and cholesterol LDL level of >100 mg/dl (79,4%). Median time-to-treatment is 528 (379-730) minutes. The predictor factors associated with the presence of MACE in STEMI patients undergoing PPCI were time-to-treatment, Killip II-IV, LVEF <50% and LDL cholesterol levels >100 mg/dl (Table 2).

There were three variables in the multivariate analysis, namely age, Killip class and LVEF which achieved statistical significance for the occurrence of MACE during treatment in STEMI patients undergoing PPCI (Table 3). Using 3 predictor variables which were significant in logistic regression analysis, we obtained a probability equation model as following: age <60 years=0; age >60 years=1, Killip class I=0; class Killip class II-IV=1; LVEF <50%=1; LVEF >50%=0. The prediction model analysis obtained has an AUC value of 0.729 with a 95% CI of 0.670-0.788. The internal validation of the prediction model was carried out using the Bootstrapping method. After validation, the Hosmer-Lameshow test was obtained for the occurrence of MACE, with p=0.208.

Discussion

MACE in 126 subjects was 43.3%, higher than the results of Tsai et al.[9] study, which found the occurrence of MACE in STEMI patients undergoing PPCI of 36.7%. This result emphasizes the importance of identification and early risk stratification in the management of STEMI and an integrated approach in the initial risk stratification assessment. Age > 60 years had an OR of 2.25 (95% CI 1.29-3.92). In Morrow et al,[10] the MACE rate in the elderly was 5% and the risk of MACE was increased in elderly patients with an OR of 3.54 (95% CI 2.36-5.30). The increasing life expectancy and the mean age of STEMI patients are increasing, which affects the prognosis of STEMI patients.

Old age strongly predicts MACE occurrence in STEMI patients undergoing PPCI. Elderly patients undergoing PPCI have other comorbidities such as hypertension and diabetes mellitus which are associated with a poorer prognosis than younger patients. Older adults also often experience complications of heart failure and cardiogenic shock which increase the risk of MACE.[11, 12]

Table 2. Major Adverse Cardiac Events Based on Characteristics of the Subjects

Characteristics	MACE		RR (CI 95%)	p
	Yes, n (%)	No, n (%)		
Age Group				
≥60 years	46 (53.5)	40 (46.5)	1.37 (0.95-1.97)	0.088
<60 years	80 (39)	125 (61)		
Smoking				
Yes	82 (46.1)	96 (53.9)	1.18 (0.82-1.70)	0.368
No	44 (38.9)	69 (61.1)		
Hypertension				
Yes	70 (47.3)	78 (52.7)	1.20 (0.85-1.71)	0.292
No	56 (39.2)	87 (60.8)		
Diabetes Mellitus				
Yes	42 (40)	63 (60)	0.88 (0.61-1.28)	0.521
No	84 (45.2)	102 (54.8)		
Chronic Kidney Disease				
Yes	12 (66.7)	6 (33.3)	1.59 (0.88-2.89)	0,123
No	114 (41.8)	159 (58.2)		
Time-to-treatment (minutes), median (RIK)	579 (390-784)	483 (375-699)	-	**0,034***
Killip Class				
I	63 (32)	134 (68)	2,09 (1,47-2,97)	**<0,001**
II-IV	63 (67)	31 (33)		
LVEF (%)				
<50	74 (59,2)	51 (40,8)	1,89 (1,44-2,47)	**<0,001**
≥50	52 (31,3)	114 (68,7)		
LDL cholesterol. (mg/dL)				
>100	36 (60.0)	24 (40.0)	1.54 (1.18-2.00)	**0.005**
<100	90 (39.0)	141 (61.0)		

Chi-square test; **Mann Whitney test*

Table 3. Major Adverse Cardiac Events Based on Age, Killip and LVEF

Characteristics	p	OR (CI 95%)
Age	0.008	2.15 (1.22-3.79)
Killip	<0.001	4.34 (2.49-7.56)
LVEF	0.001	2.88 (1.72-4.82)

Killip class II-IV has an OR of 4.71 (95% CI 2.72-8.16) and p<0.001. El-Menyar et al.[13] reported an increase in the risk of MACE following the increase in Killip class. In Killip class II OR was 2.1 (95% CI 1.25-3.69), Killip class III OR was 6.1 (CI 95% 3,41-10,86) and Killip IV class OR was 28 (95% CI 15,24-54,70). Patients with higher Killip class had more severe angiographic coronary artery disease, left ventricular hypertrophy and more extensive myocardial infarction. In advanced Killip class, the use of additional therapies such as beta blockers, angiotensin converting enzyme blockers and nitrates decreases due to unstable hemodynamic conditions causing higher MACE in STEMI patients with more advanced Killip class.

LVEF <50% had an OR of 1.890 (95% CI 1.44-2.47) and p <0.001. Alidoosti et al.[14] reported that left ventricular dysfunction or reduced LVEF increased the occurrence of MACE with HR of 2.07 (95% CI 1.03-4.16), p = 0.04. Ye et al.[15] found that LVEF was a predictor factor for the occurrence of MACE in PPCI patients with OR of 1.15, (95% CI 1.08-1,33) and p=0.011. In this meta-analysis, which involved 10,347 patients with preserved LVEF and 31,625 patients with reduced LVEF, it was found that patients with reduced LVEF had a significantly increased risk of death (p=0.05).[16, 17]

Time-to-treatment was significantly associated with MACE occurrence during treatment in STEMI patients who underwent PPCI with a median of 579 (390-784) minutes, compared to those without MACE with a median of 483 (375-699) minutes. In this study, the median time-to-treatment was more prolonged than in several countries: 3.9 hours at

the National Registry of Myocardial Infarction in the United States 2020,[18] 2.15 hours in The Japanese Acute Myocardial Infarction Registry 2013,[19] and 4.6 hours in The Korea Acute Myocardial Infarction Registry 2008.[20] Song et al.[21], also found a median time-to-treatment of 5.5 hours (3.75-8.50) hours in STEMI patients undergoing PPCI. Longer time-to-treatment was associated with broader infarct size, more severe transmural necrosis, and microvascular obstruction.[22] The independent effect of time-to-treatment on MACE occurrence was challenging to be analyzed—first, sample size and lack of long- term follow-up may limit the ability to find a relationship between time-to-treatment and MACE. Second, time-to-treatment may not be accurate enough as it relies heavily on the patient's memory which may lead to bias; and third, patients arriving late may be at a greater risk of death, weakening the time-to-treatment power of MACE.[19]

LDL cholesterol level > 100 mg/dl was significantly associated with the occurrence of MACE with RR of 1.54 (95% CI 1.18-2.00), p=0.005, similar to Sud et al.[23] who found STEMI patients with elevated LDL cholesterol levels >100 had a higher risk of developing MACE with an HR of 1.78 (95% CI 1.64-1.94). The present study demonstrated that improved cholesterol management after PCI, routine screening of LDL cholesterol levels and increased use of statin therapy, could improve outcomes in STEMI patients.

Our multivariate analysis yielded three significant variables: age, Killip class, and LVEF. These three variables had a statistical significance of 0.008, <0.001 and 0.001, respectively. The ROC curve analysis found an AUC of 0.729, indicating a 72.9% ability to discriminate predictor factors against MACE during treatment in STEMI patients undergoing PPCI9%, which is a good discriminatory ability.

The TIMI risk score for STEMI also predicts factors that influencing the 30-day outcome of STEMI patients with an AUC of 0.784. In The TIMI Risk Score for STEMI, mortality predictor factors included: age 65-74 years (score 2), age >74 years (score 3), history of diabetes mellitus/hypertension or angina (score 1), blood pressure systolic <100 (score 3), heart rate >100 (score 2), Killip class II-IV (score 2), body weight <67 kg (score 1), anterior ST elevation or LBBB (score 1) and time-to-treatment >4 hours (score 1). With a total score of 0, the risk of mortality within 30 days was 0.8% and with a score of >8, the risk increased to 35.9%. The prediction model of this study performs quite well compared to The TIMI Risk Score for STEMI which has a larger number of samples.

Smoking in this study was not found to be significantly associated with the presence of MACE. Similar results were found in the study of Pinto et al.[24] Weisz et al.[25] analyzed the CADILLAC study, and demonstrated that mortality in STEMI patients was not associated with smoking. Basic clinical differences such as younger age in STEMI patients and lower prevalence of comorbidities and risk factors in the smoking population with STEMI may explain the smoking paradox.

Hypertension was also not found to be significantly associated with the presence of MACE during the treatment of STEMI patients undergoing PPCI. Similar results were found by Huang et al.[26], with no significant difference in the occurrence of MACE during treatment in STEMI patients. The use of antihypertensive drugs such as angiotensin converting-enzyme blockers and beta blockers in the adequate management of STEMI can be cardioprotective for the occurrence of MACE.

Diabetes mellitus was also not significantly associated with MACE, similar to the study by Akhtar et al.[27], which showed that DM was not an independent predictor of MACE occurrence in STEMI patients. It is well known that the inflammatory state and changes in glucose homeostasis in DM can cause endothelial dysfunction even in the absence of significant coronary artery stenosis, such as in acute myocardial infarction with multiple coronary artery stenosis and thrombus, which also play a role in the outcome in STEMI patients. Furthermore, changes in endothelial function can lead to restenosis after revascularization by PCI and may increase thrombus formation. Control of inflammatory status is the right choice of therapy to improve the outcome of cardiovascular disease. Hypoglycemic drugs with anti-inflammatory properties can improve the condition by stabilizing coronary plaque.[28] In the management of STEMI patients with DM, glycemic control has been shown to reduce thrombus burden and increase myocardial repair.[29, 30]

CKD was not associated with the presence of MACE during the treatment of STEMI patients undergoing PPCI. The results of this study differ from those of Sattar et al.[31] which showed that CKD is an independent predictor of the occurrence of MACE, especially cardiogenic shock and heart failure, during treatment in STEMI patients. CKD is associated with increased inflammatory factors, abnormal apolipoprotein levels, coagulopathy, anemia, left ventricular hypertrophy and increased arterial calcification.[32]

The limitation of this study is its retrospective design; the possibility of information bias is quite large because the researcher cannot control the quality of data that has been carried out by others in the past.

Conclusion

The proportion of MACE during treatment in STEMI patients undergoing PPCI was 43.3%. Age, Killip class and LVEF were predictors of MACE occurrence during treatment in STEMI patients undergoing PPCI. Prediction model of MACE during treatment in STEMI patients: age <60 years = 0; age >60 years = 1, Killip class I = 0; Killip class II-IV= 1; LVEF <50% = 1; LVEF > 50% = 0. With the performance of the prediction model, it is quite good with a Hosmer-Lameshow test value of p=0,208, and the predictive model discrimination ability is quite good with an AUC of 0,729 (CI 95% 0,67-0,78).

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