Predictors of major adverse cardiac events during 7-days period in acute coronary syndrome patients who had percutaneous coronary intervention in Cipto Mangunkusumo National Hospital, Jakarta

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ABSTRACT

Background: Major adverse cardiac events (MACE) increase the morbidity and mortality of patients with acute coronary syndrome (ACS). Data are lacking on MACE occurrence in patients with ACS after percutaneous coronary intervention (PCI). This study aims to find out the predictors of MACE during 7 days in ACS patients who had PCI.

Methods: The study design was unmatched case-control. The study included 461 patients with ACS who were hospitalized in the intensive cardiology care unit in Cipto Mangunkusumo Hospital from January 1st, 2015 until November 30th, 2017. Age, female sex, diabetes mellitus, hypertension, heart failure, kidney function disorder, cardiogenic shock, ejection fraction ≤ 40%, left main (LM) coronary artery stenosis, arrhythmia, 3-vessel coronary artery stenosis, and left anterior descending (LAD) artery stenosis were included in the analysis as predictors of MACE.

Results: Cardiogenic shock (OR = 10.65, p = 0.001), LAD stenosis (OR = 15.23, p = 0.02), ejection fraction ≤ 40% (OR = 10.8, p = 0.00), 3-vessels or more coronary artery stenosis (OR 3.47, p = 0.01), heart failure (OR = 3.1, p = 0.02), and renal function disorder (OR 4.76, p = 0.00) were proven as predictors of MACE during 7-days period in ACS patients who had PCI. Female sex, cardiogenic shock, LAD stenosis, and ejection fraction ≤ 40% were independent predictors of MACE in ACS patients who had PCI, with OR values of 6.33 (95%CI 1.32–30.50), 17.56 (1.85–167.06), 26.61 (1.38–513.81), and OR 7.6 (1.86–31.09), respectively.

Conclusion: Cardiogenic shock, LAD stenosis, ejection fraction ≤ 40%, ≥ 3 vessels stenosis, heart failure, and renal function disorder were predictors of MACE during 7 days in ACS patients who had PCI.

Keywords: acute coronary syndrome, major adverse cardiac events, percutaneous coronary intervention, predictors.

INTRODUCTION

Cardiovascular diseases include coronary heart disease (CHD) and acute coronary syndrome (ACS), in addition to other conditions. Cardiovascular diseases are the leading cause of death worldwide. Even though the mortality rate due to CHD decreases, death from CHD is still the leading cause. A report by World Health Organization (WHO) estimated that around 16.7 million population died due to cardiovascular diseases every year and 7.3 million death occurred due to CHD every year. Death due to cardiovascular diseases is larger than the total sum of 4 main causes of death, namely, cancer, chronic obstructive pulmonary disease (COPD), accident, and diabetes mellitus. Based on the report of the Ministry of Health in 2010, the mortality rate due to heart diseases was still 8.7%. Available data in the intensive cardiology care unit (ICCU) of Ciptomangunkusumo Hospital (RSCM) in 2001-2005 showed the prevalence of ACS increases every year. ACS is an emergency in cardiovascular diseases. Patients with definitive ACS with ST-segment elevation that occurred less than 12 hours should have reperfusion therapy with primary percutaneous coronary intervention (PCI). Patients with non-ST segment elevation or unstable angina pectoris based on the risk assessment are classified into those who need: emergency invasive strategy, initial invasive strategy, and conservative strategy. Revascularization in patients with ACS and CHD can be conducted by coronary artery bypass graft (CABG) or PCI. MACE consists of acute myocardial infarction, ischaemic stroke, coronary arterial occlusion, and death. Detection and intervention of predictive factors for MACE are critical to increasing health levels and life expectancy. Assessment of predictors after a procedure is very important for counseling patients and their families. The prognosis of patients after PCI is important for guiding the operator to perform the procedures. The study by Panduranga et al. in Oman showed that MACE occurrence in hospitals was 3.6% with an in-hospital mortality rate of 1.8%. The CADILLAC Risk Score study by Halkin A et al. in
2005 reported MACE occurrence in hospitals in patients who had PCI was 3% with a mortality rate of 2.4% in primary angioplasty in myocardial infarction. A study in non-ST elevation myocardial infarction (NSTEMI) patients in Thailand by Wongpraparut reported the occurrence of MACE was 5.6% with a 3.1% mortality rate. The study by Park et al. showed the occurrence of MACE was 11.6%.

Based on this description, the authors intended to study the factors that might become predictors of MACE during 7 days in ACS patients who had PCI in Cipto Mangunkusumo National Hospital, Jakarta, Indonesia.

METHODS

An unmatched case-control study design and unbiased was used to evaluate the factors predicting MACE during 7 days in ACS patients who had PCI. The populations were ACS patients who had PCI in RSCM Jakarta. The subjects of this study were ACS patients who received stenting in their coronary arteries. The cases were those who experienced MACE in 7 days after stenting. The criteria of MACE consist of acute myocardial infarction, ischemic stroke, coronary arterial occlusion, and death. The controls did not experience MACE during the same period. Exclusion criteria were ACS patients who had CABG, suffered from severe sepsis, were in hemodialysis treatment, and who suffered from malignancy. The diagnostic criteria for kidney dysfunction in this study are if creatinine clearance < 60 ml/minute and/ or creatinine level > 2 mg/dl. Also, the diagnostic criteria used for cardiogenic shock are being diagnosed if systolic is less than 90 mmHg or MAP <65 mmHg and O2 saturation is less than 95%.

The study was conducted in ICCU, ICU of Integrated Cardiac Care, and Integrated Cardiac Care ward in RSCM. The minimal sample size was determined to be similar to a case-control study by Wolfram et al. with OR value of 4.24. Estimated proportion of risk factor exposure in those who were exposed was 25%, with a confidence level of 95% (Z = 1.96) and power of 80% for the 2-sided alternative hypothesis. The minimum sample size needed was 34 subjects who experienced MACE and 34 subjects who did not experience MACE.

This study was approved by Permanent Committee for Ethical Medical Research, Faculty of Medicine, Universitas Indonesia No. 1109/UN2.F1/ETIK/2017. All medical record data would be kept confidential.

The study was conducted from January 1st, 2015 until November 30th, 2017 in RSUPN Dr. Cipto Mangunkusumo Jakarta. The study was conducted by collecting data from medical records.

The results of the study were presented descriptively. Bivariate analysis was conducted by classifying the exposed and non-exposed according to the study variables with their respective measurement scale. The chi-square test or Fisher’s exact test was used to assess the statistical significance of each variable. Odds ratios (ORs) were estimated at significance level α = 0.05 and a confidence interval of 95% (95%CI) using SPSS version 24. Multivariate analysis was conducted with stepwise logistic regression analysis.

RESULTS

732 ACS patients were treated in the intensive care unit. A total of 461 patients had PCI. During the period of this study, ACS patients who had PCI and experienced MACE were 37 patients. This is shown in Figure 1.

The results showed that MACE occurrence in ACS patients who had PCI was 8.02%. During this study, subjects who satisfied the inclusion criteria were 74 subjects, consisting of 32 (43.2%) STEMI patients, 33 (44.6%) NSTEMI patients, and 9 (12.2%) unstable angina pectoris patients. Based on the components of MACE, there were 19 (51.4%) recurrent infarctions, 9 (24.2%) early death, 7 (19%) strokes, and 2 (5.4%) revascularization with PCI. To assess the predictors of MACE, we estimated the OR values with their confidence intervals. The estimations are shown in Table 1.

Bivariate analysis showed that ejection fraction ≤ 40% had an OR value of 10.8 (95%CI = 3.18-36.8, p = 0.00). Heart failure was a predictor of MACE with OR 3.1 (95%CI = 1.19- 8.09). Three coronary artery vessel stenosis had an OR value of 3.47 ((95%CI = 1.32-9.08).

![Figure 1. Subjects of the study.](image-url)
Renal dysfunction is a predictor of MACE with OR 4.76 (95%CI = 1.72-13.6). LAD stenosis is a predictor of MACE with OR 15.23 (95%CI = 1.85-125.4). Cardiogenic shock is a predictor of MACE with OR 10.65 (95%CI = 2.21-51.31). Variables of age ≥ 60 years old, female sex, diabetes mellitus, left main coronary artery stenosis, hypertension, and urgent PCI gave a p-value > 0.05.

Multivariate analysis was conducted, and the independent predictors of MACE in hospitals are shown in Table 2. The table showed that shock, LAD stenosis, ejection fraction ≤ 40%, female sex, and the interaction between ejection fraction ≤ 40% and LAD stenosis were independent predictors of MACE during 7 days in ACS patients who had PCI.

**DISCUSSION**

The results of this study showed the occurrence of MACE in the intensive care unit in patients who had PCI was 8.02%. In this study, there were 32 (43.2%) STEMI patients and 42 (56.8%) NSTEMI and unstable angina pectoris patients. The total number of subjects with STEMI diagnosis was quite large because the revascularization guideline recommends that not all NSTEMI patients and unstable angina pectoris should be treated with PCI.

Similar results were reported by Wongpraparat in Thailand, with a proportion of 5.6%. This study was conducted in patients who were mostly NSTEMI who had PCI in 29 cardiac catheterization centers. Almost a similar number was reported by Moeswir et al., who reported a proportion of 9.21%. The difference with this study was that all subjects had ACS. A study by Panduranga et al. in Oman reported a smaller proportion (3.6%) with an in-hospital mortality rate of 1.8%. Difference with the study by Panduranga was that the study was conducted in all patients who had PCI. A higher number was reported by Park et al. MACE occurred in the proportion of 11.6%. Ehsan et al. in Bangladesh conducted a study on TIMI score and MACE during 30 days in Bangladesh. MACE occurrence in unstable angina pectoris and NSTEMI patients were 10.6%, while in STEMI patients was 11.6%.

In this study, the age variable gave an OR value of 0.58 (0.23-1.46) and p = 0.24. This result showed that there was no evidence that an age of more than 60 years was associated with MACE. This was different from the results of Singh et al. study which showed the value of OR 3.16. These studies gave different results because, in Singh’s study, the subjects were more than 80 years old. Other studies showed different results due to the age of the subjects being over 65 years old. Another factor that might cause this is the patients’ functional status.

The female sex gave the OR value of 2.71 (0.83-8.78) and p = 0.09. In multivariate analysis, the adjusted OR was 6.33 (p = 0.022). Similar results were reported by Berger et al., with OR value of 1.91 (95%CI 1.83-2.00). An increase in the risk of MACE in females is often due to lower functional status compared to males. In older age, females would have estrogen deficiency which raises the risk of damage to coronary arteries. Other factors assumed to affect this are the higher proportion of microvascular dysfunction, diffuse stenosis, and erosion of plaques in women. Other factors that might also affect this are irregular antiplatelet use and a higher number of stenosis in women.

In this study, diabetes mellitus gave the OR value of 2.01 (0.69-4.33) and p = 0.24. Diabetes mellitus was not proven to be a predictive factor for MACE due to prolonged thin-cap fibroatheroma. A study by Santos et al. showed that MACE occurred after 1 year (OR 2.61, p = 0.027). Another factor that might affect this is the occurrence of thrombosis due to the increase in advanced glycation end products (AGEs) that are affected by insulin resistance and glucose level, while another more important factor is the mean amplitude of glycemic excursions (MAGE). In the report by Mi et al., MAGE is more important than blood glucose level during treatment.

Hypertension gave the OR value of 2.01 (0.77-5.23) and p = 0.15. This is different from Tsai et al. study on MACE occurring in 12 months, with an HR value of 1.73 (1.06-2.21). The results are different because Tsai’s study was conducted until 12 months. This might be because MACE
occurs due to chronic inflammation, and plaque formation needs other factors aside from hypertension that stimulates inflammation and the ability of fibrinolytic mechanism. Other factors assumed to affect this is the use of antihypertensive drugs which improve oxygen consumption and the neurohumoral system, and improve the perfusion to the coronary artery.

Ejection fraction ≤ 40% gave an OR value of 10.8 (3.18-36.8) and p = 0.02. Similar results were reported by Halkin et al. with OR value of 4.67 (p = 0.0001) and Wongpraparut et al. with OR value of 6.5 (p = 0.005). In low ejection fraction conditions, the vascular dysfunction is more severe and will give impact the extent of the area which is damaged.15,16

Heart failure gave the OR value of 3.1 (1.19-8.09) and p = 0.02. Congestion is due to the decrease in ejection fraction. The ejection fraction is the indicator of the extent of the damaged myocardium.30 A study by Burjonropa showed similar results.31

Renal function disorder was a predictor of MACE with OR value of 4.76 (1.72-13.16). This result is consistent with reports by Kassain et al.32 and Almeida et al.33 In renal function disorder, there was sympathetic and renin-angiotensin systems activation.34,35 In CKD patients, apolipoprotein A1 decreases and there is an increase in homocysteine, lipoprotein, fibrinogen, and C-reactive protein. This can trigger atherosclerosis.36

Three or more artery coronary vessel stenosis was associated with MACE with OR value of 3.47 (1.32-9.08) and p = 0.01. This study is consistent with Halkin et al., who reported that 3 coronary artery stenosis increased 2.2 times the risk of MACE.15 Stenosis in many arteries is associated with the extent of areas in which the perfusion is disturbed. Perfusion disturbance will affect the hemodynamic condition and leads to a decrease in ejection fraction and triggers chronic inflammation that will eventually cause MACE.36

LM coronary artery stenosis gave an OR value of 2.61 (0.91-7.51) and p = 0.07. LM coronary artery stenosis and MACE are not significantly associated, and it is assumed that not all patients with LM coronary artery stenosis had PCI. In PCI, the SYNTAX score is calculated. In LM coronary artery stenosis, the score will be high. If the SYNTAX score is more than 33, the best choice is CABG.37

In this study, LAD stenosis was associated with MACE with an OR value of 15.23 (1.85-125.4) and p = 0.02. The result shows a significant association between LAD stenosis and MACE. This study is consistent with a report by Sadria.38 LAD provides the highest blood flow to the left ventricle. The function of the left ventricle is to maintain blood flow to the entire body. A disturbance in LAD flow will lead to a decrease in the function of the left ventricle.

Arrhythmia gave an OR value of 2.47 (0.89-6.86) and p = 0.08. This shows that arrhythmia and MACE were not significantly associated. In large STEMI, the risk of fatal arrhythmia is quite high. Appropriate management will overcome arrhythmia.

Primary or urgent PCI gave the OR value of 0.52 (0.21-1.31) and p = 0.163. This is different from other reports.11,18 Other studies were conducted as multicenter studies. Another factor that could affect the association was the fact that patients might refuse to have PCI. Furthermore, RSCM is a national referral hospital, so primary PCI will be conducted mostly in peripheral network hospitals.

In multivariate analysis, female sex was the predictor of MACE with adjusted OR 6.33 (p = 0.021). In patients who had cardiogenic shock, the adjusted OR was 17.56 (p = 0.013). In cardiogenic shock, the hemodynamics is unstable. LAD stenosis gave an adjusted OR of 26.61 (p = 0.03). Ejection fraction ≤ 40% gave an adjusted OR of 7.6 (p = 0.005) and the interaction between ejection fraction ≤ 40% and LAD stenosis gave an adjusted OR of 6.38 (p = 0.00).

From the logistic regression equation, it can be concluded that independent predictive factors for MACE in ACS patients who had PCI are female sex, cardiogenic shock, LAD stenosis, ejection fraction ≤ 40%, and interaction between ejection fraction ≤ 40% and LAD stenosis. This equation can predict a total of 79.7%, and it can predict 81.1% MACE occurrence. It also predicts the probability of non-occurrence of MACE (78.4%).

Several variables are not significantly associated with MACE in multivariate analysis. They are age ≥ 60 years old, diabetes mellitus, hypertension, heart failure, renal disorder, left main coronary artery stenosis, 3 vessels disease stenosis, fatal arrhythmia, and primary PCI. Heart failure was not proven to independently predict MACE. Three vessels disease stenosis was not independently proven as a predictor of MACE, probably because PCI was conducted in the culprit lesion. This study is consistent with a report by Querella et al.39 In patients with arrhythmia, angiography and PCI were conducted, so that the success rate of PCI will improve prognosis.37

Based on this study, strict monitoring should be conducted in patients who are female, who have renal dysfunction, 3 coronary artery stenosis, LAD stenosis, ejection fraction ≤ 40%, and cardiogenic shock before PCI in ACS patients. In coronary angiography, if LAD stenosis and 3 coronary artery stenosis are found, stricter monitoring is needed after PCI. A study on MACE in STEMI and NSTEMI patient groups needs to be conducted. A cohort prognostic study on MACE occurrence in ACS patients who had PCI is needed. To increase the precision of the confidence interval, a case-control study with a cases-to-controls ratio of more than 1 or a cohort study needs to be conducted.

This study had some strengths and limitations. The strength of this study is the fact that this is the first study on MACE in ACS patients who had PCI in Indonesia. The limitation of this study is the study design, which is unmatched case-control. In this study, not all predictors for MACE were included. The study was conducted on primary and urgent PCI, so the results might be different from other studies. This study was conducted in ACS patients, while the pathophysiology and management of STEMI, NSTEMI, and unstable angina pectoris are different.

CONCLUSION

Heart failure, renal dysfunction, 3 coronary artery stenosis, LAD stenosis, cardiogenic shock, and ejection fraction ≤ 40% are predictors of MACE during 7-days period in ACS patients who had PCI.
Female sex, cardiogenic shock, ejection fraction ≤ 40%, LAD stenosis, and the interaction between LAD stenosis and ejection fraction ≤ 40% are independent predictors of MACE during 7 days in ACS patients who had PCI.

CONFLICT OF INTEREST

The authors have no conflict of interest

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ETHICAL STATEMENT

This study was approved by Permanent Committee for Ethical Medical Research, Faculty of Medicine, Universitas Indonesia No. 1109/UN2.F1/ETIK/2017.

AUTHOR CONTRIBUTION

All authors contributed equally to this study

REFERENCES


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