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The effect of infection on mortality in acute coronary syndrome patients at Dr. Sardjito General Hospital, Yogyakarta

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ABSTRACT

Ischemic heart disease is the second most significant health burden in Indonesia and the world. The prevalence of coronary heart disease patients in Yogyakarta is predicted to experience a continuous increase. In Sardjito Hospital, mortality rate of acute coronary syndrome (ACS) patients reaches 15%, with pneumonia infection identified as one of the predictors. Despite this high mortality rate, there is a lack of studies addressing the contribution of infectious comorbidities to mortality incidence among ACS patients. This study aimed to investigate the e ffect of infectious comorbidities on the incidence of mortality among ACS patients and its mortality rate in Sardjito Hospital. This study used a cross-sectional design in 794 patients diagnosed with ACS and registered in the SCIENCE registry from January to December 2022 at Sardjito Hospital. The analysis was conducted using the Chi-square method to determine the effect of infectious comorbidities on mortality among ACS patients and a logistic regression test to evaluate the correlation between variables. Based on bivariate analysis, it was found that infectious comorbidities increased mortality rate among ACS patients (p<0.001, OR=2.22[1.46-3.38]), reaching 5.2%. The bivariate analysis between confounding factors and outcome of patients showed that obesity, dyslipidemia, and revascularization significantly influenced the results of ACS patients. Based on multivariate analysis, it was discovered that infectious comorbidities, obesity, diabetes, dyslipidemia, and revascularization had a significant association with mortality of patients with ACS. Furthermore, infectious comorbidities increased the odds of mortality for ACS patients by 2.04 times. Infectious comorbidities increased the incidence of mortality in ACS patients by 2.04 times with mortality rate of 5.2%.

ABSTRAK

Penyakit jantung iskemik merupakan beban penyakit kedua di Indonesia dan dunia. Angka pasien penyakit jantung koroner di Yogyakarta pun diprediksikan akan terus meningkat. Tingkat mortalitas pasien sindrom koroner akut (SKA) di RSUP Dr.Sardjito mencapai 15% dengan salah satu prediktor mortalitasnya adalah infeksi pneumonia. Dari angka kematian yang cukup besar tersebut, belum ada studi yang membahas mengenai kontribusi komorbid infeksi terhadap kejadian mortalitas pasien sindrom koroner akut. Mengetahui pengaruh komorbid infeksi terhadap kejadian mortalitas pasien SKA dan mengetahui tingkat mortalitasnya di RSUP Dr.Sardjito. Penelitian ini menggunakan desain studi uji potong lintang (*cross sectional*) pada 794 pasien yang terdiagnosis sindrom koroner akut dan terdaftar di registri SCIENCE periode Januari-Desember 2022 RSUP Dr.Sardjito. Penelitian dilakukan menggunakan metode *Chi-square* untuk melihat pengaruh komorbid infeksi terhadap mortalitas pasien SKA dan uji regresi logistik untuk mengetahui korelasi antarvariabel. Berdasarkan analisis bivariat ditemukan bahwa komorbid infeksi meningkatkan kejadian mortalitas pasien SKA (p<0,001, OR=2,22[1,46-3,38]) dengan tingkat mortalitas mencapai 5,2%. Berdasarkan hasil analisis bivariat antara faktor perancu dengan luaran pasien, ditemukan bahwa riwayat obesitas, dislipidemia, dan revaskularisasi berpengaruh terhadap luaran pasien sindrom koroner akut secara signifikan. Sementara itu, berdasarkan analisis multivariat ditemukan bahwa komorbid infeksi, obesitas, diabetes, dislipidemia, dan revaskularisasi memiliki hubungan dengan kejadian mortalitas pasien SKA secara signifikan. Komorbid infeksi meningkatkan peluang kejadian mortalitas pasien SKA sebesar 2,04 kali. Komorbid infeksi meningkatkan kejadian mortalitas pasien SKA sebanyak 2,04 kali secara dependen dengan tingkat mortalitas sebesar 5,2%.

Keywords:
ischemic heart disease;
acute coronary syndrome;
comorbid infection;
in hospital mortality;
SCIENCE registry

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INTRODUCTION

Cardiovascular disease is the leading cause of death globally, followed by ischemic heart disease, particularly in developing countries,[1] including in Indonesia.[2] Meanwhile, the prevalence of coronary heart disease patients in Yogyakarta is predicted to experience a continuous increase.[3] Ischemic heart disease initiates with an imbalance between the supply and demand of oxygen to the heart due to occlusion of atherosclerotic plaque, spasm of blood vessel muscles, blockage by embolism, or arterial thrombus.[4] Consequently, acute coronary syndrome (ACS) arises, presenting a spectrum of clinical symptoms ranging from STEMI (ST-segment elevation myocardial infarction), NSTEMI (Non ST-segment elevation myocardial infarction), to UAP (unstable angina pectoris).[4]

Approximately 11.1% of ACS patients had nosocomial infection and 7% of patients suffered from sepsis.[5,6] Infection, such as pneumonia play a significant role in increasing mortality risk of cardiovascular disease patients admitted to the Cardiac Intensive Care Unit (CICU). Consequently, infectious comorbidities are included in the components of the mortality of patients risk scoring system.[7,8] When patients develop infection after ACS event, infection-causing pathogens, such as bacteria, can invade the ruptured plaque.[9] This results in an increased inflammatory response causing the infarct area to expand, leading to sepsis in patients.[6] Mortality rate of ACS patients is significantly high, reaching 52%. Meanwhile, in Dr. Sardjito General Hospital, Yogyakarta mortality rate of patients with cardiovascular disease reaches 15%, with pneumonia being one of the predictors.[7,9] Despite these high mortality rates, there is a lack of studies investigating the contribution of infectious comorbidities to mortality rate of ACS patients.

MATERIAL AND METHODS

Study design

This study used an analytical observational method with a cross-sectional design to evaluate the comparison of mortality rates of ACS patients accompanied by infectious comorbidities at Dr. Sardjito General Hospital, Yogyakarta from January to December 2022. The secondary data were obtained from the SCIENCE registry (Sardjito Cardiovascular Intensive Care) of the Dr. Sardjito General Hospital.

Protocol of study

This study followed the protocol in the SCIENCE registry and the protocol has received ethical approval from the Medical and Health Research Ethics Committee of the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada with ethical clearance number KE/FK/0311/EC/2023.

The inclusion criteria were patients diagnosed with ACS, while those aged <18 y.o. with incomplete data were excluded. The data collected included demographic (age, gender, and patients risk factors), clinical (diagnosis of ACS, diagnosis of infection, pneumonia, urinary tract infection, and sepsis), and outcome of patients (mortality).

The dependent and independent variables in this study were mortality of patients and infectious comorbidities, respectively. Meanwhile, the confounding variables were smoking, dyslipidemia, hypertension, obesity, diabetes mellitus, and revascularization.

Statistical analysis

The data collected were processed with IBM SPSS and bivariate analysis using the Chi-square method was performed to determine the effect of infectious comorbidities on mortality of patients. Chi-square analysis was also carried out to determine the effect of confounding variables on mortality of patients. A $p < 0.05$ was considered as statistically significant. All bivariate analysis results with a $p < 0.25$ were subjected to further multivariate analysis in the form of regression analysis to determine the likelihood of mortality in ACS patients based on predictor variables such as infectious comorbidities and other confounding factors.

RESULTS

The secondary data in the SCIENCE registry showed that there were 797 patients diagnosed with ACS between January and December 2022. A total of 3 patients with incomplete data were excluded from this study, resulting in a final sample size of 794 patients.

Analysis of baseline characteristics in TABLE 1 showed that the sample was predominantly male (76.2%), aged ≥ 60 years (53.7%), classified as obese based on body mass index (39.9%), diagnosed with IMAEST (70%), received revascularization procedures (84%), and experienced cardiogenic shock (19.4%). The mean age of the sample was 60 years with a standard deviation of 11.57 and a variance of 133.97, showing that the age variation of the sample was wide. Additionally, only 18.6% of patients in the population had infectious comorbidities with the most common infection being pneumonia (14.1%). Based on risk factors for heart disease, more than half of the sample had a history of hypertension (61.1%) and smoking (59.7%).

Bivariate analysis showed that mortality rate of ACS patients with infectious comorbidities was 5.2% (TABLE 2). It was indicated that infectious comorbidities significantly increased mortality rate of ACS patients [$p<0.001$, OR=2.22 (1.46-3.38)].

Bivariate analysis was also performed between confounding variables and mortality of outcomes of patients. The results showed that history of obesity ($p=0.011$), dyslipidemia ($p=0.019$), and revascularization ($p=0.002$) significantly influenced the outcomes of ACS patients (TABLE 3).

The results of bivariate analysis with a significance value <0.25 were further examined for correlation with the dependent variable using logistic regression analysis. This was carried out to determine whether infectious comorbidities served as an independent factor influencing mortality incidence of ACS patients. Based on bivariate analysis, the variables of obesity ($p=0.011$), diabetes ($p=0.074$), dyslipidemia ($p=0.019$), revascularization ($p=0.002$), and the presence of comorbid infection ($p<0.001$) met the criteria for logistic regression analysis to determine the correlation with the dependent variable.

TABLE 1. Baseline characteristics of patients (n=794)

Variable	n (%)
Sex	
• Male	605 (76.2)
• Female	189 (23.8)
Age [(mean ± SD); variance]	[(60.68 ± 11.57); 133.97]
• < 60	368 (46.3)
• ≥ 60	426 (53.7)
BMI Classification	
• Underweight	37 (4.7)
• Normal	265 (33.4)
• Overweight	175 (22.0)
• Obesity	317 (39.9)
Risk factors	
• History of coronary heart disease (MI, CABG, angioplasty)	164 (20.7)
• Smoking	474 (59.7)
• History of ischemic heart disease	88 (11.1)
• Hypertension	485 (61.1)
• Diabetes	230 (29.0)
• Dyslipidemia	101 (12.7)
Type of ACS Disease	
• STEMI	556 (70.0)
• NSTEMI	185 (23.3)
• UAP	53 (6.7)
• Infectious Comorbidities	148 (18.6)
• Pneumonia	112 (14.1)
• UTI	29 (3.7)
• Sepsis	6 (0.8)
• Mortality of patients	136 (17.1)
Revascularization	
• Yes	667 (84.0)
• No	127 (16.0)
• Presence of shock	168 (21.1)
• Cardiogenic shock	154 (19.4)
• Septic shock	13 (1.6)
• Hypovolemic shock	1 (0.1)

TABLE 2. Chi-square analysis of the presence of infectious comorbidities on outcome of patients

	Outcome of patients		p	OR (95%CI)
	Mortality [n (%)]	Alive [n (%)]		
Infectious comorbidities				
• Yes	41 (5.2)	107 (13.5)	<0.001	2.22 (1.46-3.38)
• No	95 (12.0)	551 (69.4)		
Total	136 (17.1)	658 (82.9)		

TABLE 3. Chi-square analysis of confounding factors on mortality of ACS patients

Variable	Outcome of patients		p
	Mortality [n (%)]	Alive [n (%)]	
Obesity	41 (5.2)	276 (34.8)	0.011
Smoking	79 (9.90	395 (49.7)	0.674
Hypertension	81 (10.2)	404 (50.9)	0.689
Diabetes	48 (6.0)	182 (22.9)	0.074
Dyslipidemia	9 (1.1)	92 (11.6)	0.019
Revascularization	102 (12.8)	565 (71.2)	0.002
Total	136 (17.1)	658 (82.9)	

TABLE 4. Results of binary logistic regression analysis on mortality of ACS patients

Variable	OR (95% CI)	p
Infectious comorbidities	2.04 (1.32-3.14)	0.001
Obesity	0.65 (0.43-0.98)	0.042
Diabetes	1.52 (1.01-2.27)	0.044
Dyslipidemia	0.43 (0.21-0.89)	0.024
Revascularization	0.59 (0.37-0.94)	0.025

Multivariate analysis showed that all variables, namely infectious comorbidities(p=0.001),obesity(p=0.042), diabetes (p=0.044), dyslipidemia (p=0.024), and revascularization (p=0.025) had a significant association with mortality incidence of ACS patients (TABLE 4). However, only infectious comorbidities (OR=2.04) and diabetes (OR=1.52) could increase the chance of mortality for ACS patients. Based on the results, in ACS patients with infectious comorbidities, the chance of mortality was 2.04 times higher than in ACS patients without infection.

DISCUSSION

This study showed that there were 148 patients (18.6%) who had infectious comorbidities with mortality rate of 5.2%. Infectious comorbidities had the significant effect on increasing mortality incidence of ACS patients with mortality rate of 41 patients (p<0.001). Several mechanisms were identified through which infection increased incidence of mortality in ACS patients. This included an increase in systemic inflammatory conditions that have previously occurred in ACS patients, affecting the elevation of pro-inflammatory cytokines, hypercoagulation status, and excessive vasodilation. Hypercoagulable status in patients is caused by increased interaction between immune cells and tissue factors capable of causing DIC (disseminated intravascular coagulation).[10] Furthermore, excessive vasodilation is triggered by the inflammatory response, which is associated with cardiogenic shock, a condition prone to occur in myocardial infarction patients as a form of body decompensation to the shock.[11] Both DIC and excessive vasodilation were found to cause impaired hemodynamics and perfusion to organs resulting in organ dysfunction and shock.[11]

Mortality in ACS patients are usually caused by complications such as acute heart failure, cardiogenic shock, sepsis shock, and arrhythmias.[12] Myocardial infarction causes failure to the heart's pumping function, so the heart cannot pump blood adequately to the rest of the body, hence hypoperfusion occurs.[13] Initially, the body will compensate for the hypoperfusion condition by activating sympathetic responses, which can later lead to an increase in pressure in the left ventricle, followed by pulmonary vascular congestion, then an increase in right ventricular pressure followed by vascular congestion throughout the body.[13] This leads to heart failure, hemodynamic dysfunction (cardiogenic shock) and damage to various organs.[20] Comorbid infections in ACS patients will worsen the complications of cardiogenic shock by 20-30% due to hyperinflammation that causes excessive vasodilation and worsening of hemodynamic disturbance in the body.[11]

Impaired perfusion to various organs can also occur due to infection, which is called sepsis shock.[11] As many as 7% of patients with a primary diagnosis of acute myocardial infarction develop sepsis.[6] Comorbid infection, which is the cause of sepsis, affects the outcome of acute coronary syndrome patients through the increased of systemic inflammatory response (hyperinflammation), enlargement of myocardial infarction area, activation of coagulation, and invasion of atherosclerotic plaque by infectious bacteria.[6]

In this study, obesity significantly influenced mortality of ACS patients (p=0.011) and was a protective factor for mortality of patients (OR: 0.65; 95% CI: 0.43-0.98). Generally, obesity causes various changes in cardiac work and endothelial function due to increased oxidative stress from the release of pro-inflammatory cytokines by adipose tissue.[14] These changes in endothelial and cardiac function lead to increased atherosclerosis formation, resulting in

a higher risk of ACS in obese patients.[14] Although the risk of ACS is increase in obese patients, mortality rate among patients is lower compared to normal and underweight BMI group.[15] Further studies found that the obesity paradox phenomenon only occurred in short-term outcome of patients. This showed that obesity would reduce the risk of poor prognosis in the short term (30 d), while long-term (30 d to 1 yr) prevalence is characterized by a worse prognosis than patients without obesity.[16]

Obesity is associated with various conditions that pose a risk for cardiovascular disease such as dyslipidemia.[17] Dyslipidemia is characterized by an imbalance in lipid profile of a person, where HDL levels in the blood are low, while LDL and triglyceride levels are high.[17] In this study, there were 101 patients (12.7%) who had dyslipidemia, and the incidence of mortality was relatively low, occurring in 9 out of the total sample (1.1%). The condition of dyslipidemia influenced mortality incidence of ACS patients significantly (p=0.019) and was a protective factor for mortality of patients with ACS (OR: 0.43; 95% CI: 0.21-0.89). Although obesity and dyslipidemia are different, 60-70% of obese patients have dyslipidemia.[18]

A total of 84% of patients in this study received revascularization, which affected mortality incidence of ACS patients (p=0.002), acting as a protective factor (OR: 0.59; 95% CI: 0.37-0.94). Since almost all patients received revascularization procedures, the risk of associated infection increased. Post-revascularization infection arise due to instrumentation when performing PCI (Percutaneous Coronary Intervention) procedures. This includes access to the vasculature, repetitive injections in the same location, and the duration of the procedure, contributing to the risk of infection to increase.[19]

In this study, 230 patients (29%) were identified with diabetes. The results showed that diabetes did not affect the incidence of mortality in ACS patients (p=0.074). However, multivariate analysis showed that diabetes increased the odds of mortality in ACS patients by 1.52 times. In diabetic patients, vascular endothelial dysfunction occurs due to decreased synthesis of potent vasodilators, namely nitrogen monoxide (NO), caused by reduced eNOS (endothelial nitric oxide synthase). This phenomenon led to impaired vasodilatory function of coronary vessels, resulting in high smooth muscle cell proliferation, leukocyte adhesion, and platelet aggregation in coronary vessels.[18] The condition of insulin resistance that appeared in type two DM patients also caused the energy efficiency of the heart to decrease.[20] This study has a limitation, such as not being able to examine the effect of specific infections on the mortality of ACS patients.

CONCLUSION

In conclusion, infectious comorbidities increased mortality rate of ACS patients by 2.04 times (p=0.001; 95%CI: 1.32-3.14) with mortality rate of 5.2%. It is recommended, ACS patients with comorbid infections should receive more attention considering the influence of comorbid infections on patient mortality.

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