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Association between the level of high-sensitivity troponin I (Hs-Trop I) and major adverse cardiovascular events in patients with acute myocardial infarction of segment elevation (STEMI) with primary percutaneous coronary intervention (PCI)

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ABSTRACT

ST-segment elevation myocardial infarction (STEMI) is a condition which increases the risk of developing major adverse cardiovascular events (MACEs). For patients with STEMI, an efficient method of risk stratification is necessary in order to evaluate the clinical outcome. Troponin has been commonly used in the diagnosis of both STEMI and NSTEMI. The use of high sensitivity assays of troponin has been extensively studied in order to measure the size of myocardial damage caused by STEMI. This study aimed to investigate the association between the level of high sensitivity troponin I (Hs-Trop I) and the incidence of MACEs in patients with primary percutaneous coronary intervention (PCI) in Dr. Sardjito General Hospital, Yogyakarta, Indonesia. It was a cross-sectional observational analytic study involving a total of 195 patients. Data were obtained from both the SCIENCE (Sardjito Cardiovascular Intensive Care) registry and the medical record of Dr. Sardjito General Hospital. Pearson's Chi square test to evaluate the association between variables was applied. To determine the effect of confounding variables, a multivariate analysis was used. A significant difference in the baseline characteristics between the supramedian and inframedian Hs-Trop I groups (cutoff value of 2063.8 ng/mL) in age, onset, total ischemic time, wire crossing time and the smoking history of both groups was observed. Bivariate analysis showed a significant associations between Hs-Trop I and MACEs (p = 0.033), acute heart failure (p = 0.009) as well as mortality (p = 0.024). Meanwhile, no significant association between Hs-Trop I and cardiogenic shock (p = 0.977) and malignant arrythmia (p = 0.551) was reported. Furthermore, multivariate analysis showed Hs-Trop I, age and wire crossing time were significantly associated with the incidence of MACEs (p = 0.045). In conclusion, there is a significant association between the Hs-Trop I levels and the MACEs events in STEMI patients with primary PCI in Dr. Sardjito General Hospital, Yogyakarta, Indonesia.

ABSTRAK

Infark miokardium akut dengan elevasi segmen ST (IMA-EST) adalah kondisi yang meningkatkan risiko kejadian kardiovaskular mayor (KKM). Metode stratifikasi risiko efisien diperlukan untuk menilai luaran klinis pasien IMA-EST. Salah satu biomarker yang banyak digunakan untuk mendiagnosis baik IMA-EST dan IMA-nonEST adalah troponin. Penggunaan metode penetapan troponin sensitifitas tinggi banyak diteliti sebagai salah satu biomarker yang akurat dalam menilai luas kerusakan miokardium akibat IMA-EST. Penelitian ini bertujuan untuk mengkaji hubungan antara kadar *Hs-Trop I* pasien IMA-EST yang dilakukan intervensi koroner perkutan (IKP) primer pada saat admisi

Keywords:
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dengan insidensi dari KKM selama durasi perawatan di RSUP Dr. Sardjito Yogyakarta, Indonesia. Penelitian ini merupakan penelitian observational analitik dengan desain potong lintang. Sebanyak 195 pasien diikutsertakan dalam penelitian ini, data pasien diperoleh dari instalasi catatan medis RSUP Dr. Sardjito dan registry SCIENCE (*Sardjito Cardiovascular Intensive Care*) secara *consecutive sampling*. Analisis dilakukan dengan uji Chi-Square pada variabel *Hs-Trop I* dan insidensi KKM. Analisa multivariat dilakukan dengan membuat model multivariat regresi logistik. Perbedaan yang signifikan ditemukan pada karakteristik dasar subjek penelitian yang dibagi berdasarkan nilai *Hs-Trop I* menjadi kelompok supramedian dan inframedian (*cutoff* 2063.8). Ditemukan perbedaan usia, onset, *total ischemic time*, *wire crossing time*, dan status merokok pada kedua kelompok. Pada analisis bivariat, ditemukan hubungan signifikan antara *Hs-Trop I* dengan KKM (p = 0,033), gagal jantung akut (p = 0,009), dan mortalitas (p = 0,024), tidak ada hubungan yang signifikan antara *Hs-Trop I* dengan syok kardiogenik (p = 0,977) dan aritmia maligna (p = 0,551). Pada analisis multivariat regresi logistik, ditemukan variabel *Hs-trop I*, usia, dan *wire crossing time* memiliki hubungan yang signifikan terhadap insidensi KKM (p = 0,045). Penelitian ini menunjukkan adanya hubungan yang signifikan antara kadar *Hs-Trop I* admisi pasien dengan insidensi dari KKM pada pasien IMA-EST yang menjalani IKP Primer di RSUP Dr. Sardjito, Yogyakarta.

INTRODUCTION

Acute coronary syndrome (ACS) is a term used to describe a range of conditions associated with sudden, reduced blood flow to the heart. It is one of the main health problems due to its high mortality and morbidity, including its high numerical value and medical costs. Worldwide, ACS is the leading cause of death and loss of disability-adjusted life years (DALYs). Most of ACS happens in low-middle income countries, such as Indonesia and other South East Asian countries.[1]

Acute myocardial infarction with ST-segment elevation (STEMI) is one of the clinical conditions of ACS. This STEMI is characterized by an increase in the ST segment in two leads on electrocardiography (ECG) examination and an increase in biomarkers of cardiac muscle cell necrosis (CK-MB, troponin, and others).[2] Patients with STEMI are at a high risk of experiencing post-infarction major adverse cardiovascular events (MACEs) with an incidence of 4.2-5%.[3]

Troponins are biomarkers released by the heart muscle when there are damages and death to these cells. Since early 2000, these biomarkers have been used and recommended for evaluating the diagnosis of patients with acute myocardial infarction (AMI). In the recent years, a method of accurately measuring the troponin levels has been discovered, in the form of high sensitivity troponin I (Hs-Trop I) assays. It is capable of detecting elevation of cardiac troponin to the 99th percentile of the upper reference limit, which in turn will be able to detect signs of myocardial ischemia and/or infarction earlier in the progression of the disease when compared to conventional troponin assays that have a less sensitive detection of early ischemia and infarction. Other cardiac biomarkers such as CK-MB, lactate dehydrogenase, and myoglobin are not preferred due to their low sensitivity and low specificity towards the myocardium.[4]

Furthermore, the measurement of high-sensitivity troponin (Hs-Trop I) is considered as a standard clinical practice in the management of patients with ACS. Therefore, Hs-Trop I admission data are easy to discover and obtain. The risk assessment methods for post-MI sequelae such as the global registry of acute coronary events (GRACE) and the thrombolysis in myocardial infarction (TIMI) risk score require a lot of patient

data combination and increase in the delay to treatment time in STEMI patients. This is in accordance with this study which suggests that there is a need for a risk stratification method which is fast, simple, and easy to use in clinical settings. This study aimed to investigate the association between the Hs-Trop I levels taken at admission and the MACEs prevalence that occurred during the treatment of STEMI patients with primary PCI.

MATERIALS AND METHODS

Study design

This was an observational analytic study with a cross-sectional design using the data obtained from patients diagnosed with STEMI since August 2019 to December 2020 from the Sardjito Cardiovascular Intensive Care (SCIENCE) registry and the medical records installation at Dr. Sardjito General Hospital, Yogyakarta, Indonesia. The protocol of the study was approved by the Medical and Health Research Ethics Committee, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada/Dr. Sardjito General Hospital, Yogyakarta (ref. KE/FK/0558/EC/2019).

Patients

A total of 195 patients met the inclusion and exclusion criteria needed to be involved in this study. The prevalence of MACEs including acute heart failure, cardiogenic shock, malignant arrhythmias, and patient mortality during the treatment duration at the hospital were considered as the dependent variables. Meanwhile, the independent variable was the patient's Hs-Trop I levels taken at admission. There were also several variables assessed for their effect in this study, namely age, onset, patient risk factors (smoking habits, diabetes mellitus, hypertension, stroke history) and length of treatment (wire crossing time, total ischemic time). The target population of this study were patients diagnosed with STEMI while the sample population were STEMI patients that underwent primary PCI reperfusion in Dr. Sardjito General Hospital, Yogyakarta.

The study subjects were the source population that met the criteria and data collection was carried out using consecutive sampling techniques until the sample size was met. Inclusion criteria for the subjects were: (1) STEMI patients with complaints of chest pain <12 h, (2) 30-75 y.o. and (3) with reperfusion therapy in the form of primary PCI with the results of TIMI Flow 3. Meanwhile, the exclusion criteria for the subjects were as follows: (1) history of chronic kidney failure stage >IV, defined as patients with GFR <15 (2) a history of chronic heart failure before a heart attack and (3) patients with malignancy. Samples were obtained using the consecutive sampling method until the minimum size of 142 was met.

Data collection

Hs-Trop I levels were determined using the VIDAS® Hs-trop I kit with a value range of 1.5-40,000 ng/L. The data obtained from 195 patients were analyzed and divided into two groups based on a median value of 2063.8 ng/L, namely the supramedian and inframedian groups. Furthermore, bivariate categorical analysis was used to assess the association between Hs-Trop I and MACEs.

Data analysis

Statistical analysis was performed using SPSS software while the association between the two variables was assessed through bivariate Pearson's Chi-square test for data with normal distribution or the Fisher exact test for data with an abnormal distribution. In addition, an odds ratio (OR) of each variable

was analyzed. Multivariate logistic regression analysis was used to examine the effect of confounding variables. Analyzed variables that fulfills statistical significance with a p of < 0.25 would be included in multivariate analysis to be further analyzed for variable independent factor.

RESULTS

Characteristics of patients

A total of 195 patients were involved in this study consisted of 171 male (87.7%) and 24 females (12.3%). The mean age of patients was 57.18 ± 8.29 y.o. The median value of the Hs-Trop I level was 2063.8 ng/L. Among the patients, 64 patients (32.8%) had type 2 diabetes melitus, 115 patients (59%) had hypertension, and 18 patients (9.2%) had a history of stroke attack. A total of 130 patients smoked cigarettes (66.7%), this study did not further differentiate whether the patient was an ex-smoker or an active smoker. The median wire-crossing time of patients was 145 min, with 124 patients (63.6%) classified as not have the ideal wire-crossing time.

TABLE 1. Characteristics of patients

Variables	Total (n=195)
Age (mean ± SD, y.o.)	57.18 ± 8.29
Gender [n (%)]	
• Male	171 (87.7)
• Female	24 (12.3)
Cardiovascular Profile	
• Hs-Troponin I [median (range)]	2063.8 (2.7-40000)
- Supramedian [n (%)]	98 (50.3)
- Inframedian [n (%)]	97 (49.7)
• Onset [median (range) min]	360 (60-660)
• Wire Crossing Time [median (range) min]	145 (45-1020)
- Non-Ideal (>120 min) [n (%)]	124 (63.6)
- Ideal (<120 min) [n(%)]	71 (36.4)
• Total Ischemic Time [median (range) min]	490 (212-1200)
Comorbidity	
• Diabetes Mellitus [n (%)]	64 (32.8)
• Hypertension [n (%)]	115 (59.0)
• Stroke History [n (%)]	18 (9.2)
• Smoking Habits [n (%)]	130 (66.7)
Clinical Outcomes	
• MACEs [n (%)]	79 (40.5)
- Acute heart failure [n (%)]	34 (17.4)
- Cardiogenic Shock [n (%)]	28 (14.4)
- Malignant arrhythmias [n (%)]	54 (27.7)
- Mortality [n (%)]	17 (8.7)

*MACEs = major adverse cardiovascular events

Character of study subjects based on Hs-Trop I

The results of univariate analysis showed a significantly different in onset, wire crossing time ($p < 0.001$) and total ischemic time ($p = 0.023$) between supramedian and inframedian were observed (TABLE 2). Furthermore, a significantly different between ideal/non-ideal categories of the wire crossing time was reported (p=0.022). However, the comorbidities such as diabetes mellitus, hypertension, stroke and smoking habits were not significantly different ($p> 0.05$). Furthermore, variables with p value < 0.25 i.e. age, onset, wire crossing time, total ischemic time and smoking habits were continued for bivariate analysis before being declared as confounding variables and included in the logistic regression multivariate analysis with the main variable (troponin status).

TABLE 2. Characteristics of study subjects based on Hs-Trop I levels

Variables	Supramedian (n=98)	Inframedian (n=97)	P value
Age (mean ± SD, y.o.)	58.06 ± 8.46	56.29 ± 8.06	0.136**
Gender [n (%)]			
• Male	88 (89.8)	83 (85.6)	0.369
• Female	10 (10.2)	14 (14.4)	
Cardiovascular profile			
• Onset [median (range) min]	420 (60-660)	270 (60-660)	0.000*
• Wire Crossing Time [median (range) min]	152.5 (45-703)	134 (48-1020)	0.023*
- Non-Ideal (>120 min) [n (%)]	70 (71.4)	54 (55.7)	0.022*
- Ideal (<120 min) [n(%)]	28 (28.6)	43 (44.3)	
• Total Ischemic Time [median (range) min]	566.5 (224-1123)	415 (212-1200)	0.000*
Comorbidities			
• Diabetes Mellitus [n (%)]	34 (34.7)	30 (30.9)	0.575
• Hypertension [n (%)]	58 (59.2)	57 (58.8)	0.952
• Stroke History [n (%)]	11 (11.2)	7 (7.2)	0.334
• Smoking Habits [n (%)]	70 (71.4)	60 (61.9)	0.156**

Nonparametric data analyzed with Mann-Whitney test. Categorical data was analyzed with Chi-square test; *significant at $p < 0.05$; ** significant at $p < 0.25$

Association between Hs-Trop I and MACEs

A significantly association between Hs-Trop I levels with the overall MACEs prevalence (OR= 1.872; 95%CI: 1.048 – 3.343; p = 0.033), the incidence of acute heart failure (OR= 2.822; 95%CI: 1.268 – 6.281; p = 0.009), and the mortality (OR=3.556; 95% CI: 1.116-11,327; p = 0.024]. Patients with supramedian level of Hs-Trop I are at 1.872 times risk of having MACEs, 2.822 times risk to experience an acute heart failure, and 3.556 times risk of a death compared to those with inframedian of Hs-Trop I (TABLE 3). However, no association between Hs-Trop I levels with the incidence of cardiogenic shock (OR=0.988; 95% CI: 0.440-2.200; p = 0.977], and the malignant arrythmias (OR=1.210; 95% CI: 0.646 - 2.270; p = 0.511].

TABLE 3. Chi-Square analysis between the level of Hs-Trop I with MACEs

Variables		MACEs		p	OR (95% CI)
		Yes [n (%)]	No [n (%)]		
Hs-Troponin I	Supramedian	47 (48)	51 (52)	0.033	1.872 [1.048 – 3.343]
	Inframedian	32 (33)	65 (67)		
		Acute Heart Failure			
	Supramedian	24 (24.5)	74 (74.5)	0.009	2.822 [1.268 – 6.281]
	Inframedian	10 (10.3)	87 (89.7)		
		Cardiogenic Shock			
	Supramedian	14 (14.3)	84 (85.7)	0.977	0.988 [0.44 – 2.2]
	Inframedian	14 (13.9)	83 (83.1)		
		Malignant Arrythmias			
	Supramedian	29 (29.6)	69 (70.4)	0.551	1.210 [0.646 – 2.27]
	Inframedian	25 (25.8)	72 (74.2)		
		Mortality			
	Supramedian	13 (13.3)	85 (86.7)	0.024	3.556 [1.116 – 11.327]
	Inframedian	4 (4.1)	93 (95.9)		

P value calculated using Pearson's Chi Square, significant on $p < 0.005$.

Multivariate analysis and logistic regression model

Bivariate analysis showed only the wire crossing time was associated to the MACEs incidence ($p < 0.05$), whereas the total ischemic time ($p = 0.373$), the onset ($p = 0.738$), the age ($p= 0.149$) and the smoking habits ($p = 0.180$) were not associated to the MACEs incidence (TABLE 4).

TABLE 4. Feasibility of multivariate analysis

Variables	P*
Age	0.149
Smoking habits	0.180
Wire crossing time	
▪ Dichotomous variable	0.04
▪ Continuous variable	0.028
Onset	0.738
Total ischemic time	0.373

Nonparametric variables were analyzed with Mann-Whitney U test, while categorical variables were analyzed with Pearson's chi square test. *included on multivariate analysis at $p \leq 0.25$

The unadjusted model in this study only tested the Hs-Trop I level and MACEs using logistic regression (TABLE 5). These results showed a significant association between Hs-Trop I and MACEs (OR= 1.872; 95%CI: 1.048-3.343; p=0.034). Model A involved the wire crossing time (dichotomous) and age variable, therefore, the effect of Hs-Trop I on MACEs was adjusted to the presence of these two variables (TABLE 5). These results showed that Hs-Trop I levels still had a significant association with the incidence of MACEs and had an effect on the variable of wire crossing time and patient age (OR=1.848; 95%CI: 1.015-3.366; p=0.045).

TABLE 5. Multivariate logistic regression model

	Risk of MACEs		
	OR	95% CI	p
Unadjusted (Hs-Trop I)	1.872	1.048 – 3.343	0.034
Model A (Hs-Trop I, wire crossing time, age)	1.848	1.015 – 3.366	0.045

*Significant on $p < 0.05$

DISCUSSION

The association between Hs-Trop I and MACEs

Among 195 patients involved in this study, 98 patient were categorized as supramedian Hs-Trop I group and 97 patients were categorized as inframedian Hs-Trop I group. A significant association between the Hs-Trop I and MACEs was observed (TABLE 3). In previous study, a positive association between troponin levels with infarct area in patients with STEMI was reported.[5] Furthermore, another study investigated the infarct area and the extent of damage to the myocardium by comparing the size of the infarct area with the total left ventricular myocardial mass (LVMM). They are the main predictors of the MACEs incidence in STEMI patients with primary PCI, with hazard ratio (HR) of 1.03 times [95% CI 1.01-1.06] ($p < 0.001$). In addition, it was discovered that an infarct size of ≥15% LVMM had a significant negative linear association ($r^2 = 0.66$; $p < 0.001$) with left ventricular ejection fraction (LVEF), which was discovered for every 5% increase in infarct size, followed by a 6.1% decrease in LVEF.[6,7] This decrease in left ventricular ejection fraction is believed to be the cause of the post-infarction sequelae, such as mortality and MACEs.[8,9]

In sub-analysis, a significant association was observed between the supramedian Hs-Trop I with mortality and the incidence of acute heart failure which is common in ischemic/infarction cases in the myocardium (TABLE 3). This causes a decrease in myocardium contractility and leads to hemodynamic instability.[10] Generally, the association between Hs-Trop I levels and mortality may be seen in the decline in cardiac function. It was discovered that a decrease in left ventricular ejection fraction had a significant association with patient mortality. Meanwhile, patients with higher troponin levels on admission had a higher mortality rate as well.[8,11] An insignificant association was also discovered between Hs-Trop I with the incidence of cardiogenic shock and malignant arrhythmias, a condition caused by a single point and not serial troponin measurements. As

described in the previous section, serial measurements of Hs-Trop I describe the progression of myocardial damage over time intervals.[12]

Association between Hs-Trop I, age, and wire crossing time on the incidence of MACEs

The association between the increase in baseline troponin levels (both troponin I and troponin T isoforms) and age has been widely discussed in previous studies. A positive association between troponin levels and age has been reported.[13-15] An increase in Hs-Trop I levels when measured in serial caused long wire crossing times. However, because the measurements in this study were carried out during admission, the low Hs-Trop I condition in detected admission may increase if the subject's wire crossing time was not ideal. Therefore, both of them may influence each other and also affect the outcome, namely the incidence of MACEs.[16] It was also discovered that delayed STEMI treatment performed by primary PCI had a significant association with large infarct size and decreased left ventricular function.[17] Serial measurements of Hs-Trop I show a stronger association between these three variables.[12]

Comparison of Hs-Trop I levels to established risk score

Thrombolysis in myocardial infarction (TIMI) risk score and global registry of acute cardiac events (GRACE) risk score are the main risk scoring system used as a risk stratification method to differentiate patients into low, intermediate, or high-risk cardiac complications. Although they provide a high degree of risk stratification of the patients, they were developed by enrolling patients from North America, South America, and Europe.[18] It is not entirely clear whether the two risk scoring systems provide a good insight to Asian, especially Indonesian patients.

Elevated Hs-Trop I levels was one of the criteria included in GRACE risk score to stratify the risk of the patient. However, the system does not include the troponin levels to the incidence of MACEs. This study may help close the gap by providing the quantitative range of Hs-Trop I that is associated with a higher prevalence of MACEs.

Study limitations

This study has several limitations, such as data obtained from a single-center, Hs-Trop I measurements carried out in a single point unable to show a causal association between the two variables investigated. This study could not examine the incidence of MACEs due to it being a cross-sectional in design. A cohort study is required to determine MACEs incidence and its relation to the level of Hs-Trop I in patients with STEMI.

CONCLUSION

In conclusion, the Hs-Trop I at the time of patient admission, has a significant association with the incidence of MACEs occurring during the hospitalization duration of STEMI patients with PCI at Dr. Sardjito General Hospital, Yogyakarta.

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