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ORIGINAL PAPERS

The Role of High Sensitivity C-Reactive Protein as a Predictor in Outcome ST - Elevation Acute Myocardial Infarction Patients Underwent the Primary Percutaneous Coronary Intervention

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Abstract

Background: The role of inflammation is an important part for the process of acute myocardial infarction. Inflammation of blood vessel walls and inflammatory response are considered as the main pathogenesis of atherothrombosis in ST elevation of myocardial infarction. Hs-CRP can measure the inflammatory response after acute myocardial infarction thereby providing prognosis for major adverse cardiovascular event.

Objective: This study aims to the serum levels of Hs-CRP at admission as a predictor of a Major Adverse Cardiovascular Event (MACE), including cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke, stent thrombosis in STEMI patient who underwent primary percutaneous intervention (PPCI) during hospitalization and 30 days after primary percutaneous coronary intervention.

Methods: This study was a prospective observational cohort study. Subjects were patients with a diagnosis of onset <24-hour STEMI and underwent treatment at the Cardiovascular Care Unit and cardiovascular ward Dr. Soetomo Hospital, Surabaya. ELISA test is carried out to measure serum levels of Hs-CRP from peripheral blood samples taken at admission. Based on the level of hs-CRP subjects were divided into two groups, namely groups with hs-CRP <2 mg / l and hs-CRP levels ≥ 2 mg/l. Subjects were then observed during treatment and assessed the appearance of major adverse cardiovascular event.

Results: The subjects of this study were 61 patients, patients with hs-CRP level ≥2 mg/l were higher risk of major adverse cardiovascular event with 19,158 fold (OR 19.158; p = 0.006, 95% CI) than patient with hs-CRP < 2 mg/l. Hs-CRP levels had a weak positive relationship with cardiovascular mortality (RR 0.274, p = 0.033, 95% CI). Patient with Hs-CRP ≥ 2 mg/l have higher risk of cardiovascular mortality 3.514 fold than Hs-CRP < 2 mg/l (Odds ratio 3.514, p = 0.252, IK 95%).

Conclusion: There is weak positive correlation between hs-CRP and mortality of the patients with STEMI. The patients with hs-CRP ≥ 2 mg/l have 19 folds higher than Hs-CRP < 2 mg/l with significant statistic.

Keywords: Inflammation, Acute Myocardial Infarction with ST-segment elevation, hs-CRP, mortality, major adverse cardiovascular event.

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INTRODUCTION

ST-elevation myocardial infarction (STEMI) mortality is influenced by many factors, including advanced age, killip class, treatment time window, management strategy, previous myocardial infarction, diabetes mellitus, kidney failure, number of coronary vascular lesions, and left ventricular systolic function measured by measuring ventricular ejection fraction[1]. Several studies have emphasized the acute fall in STEMI and the long-term mortality associated with the reperfusion therapy used, percutaneous coronary intervention (PCI), current antithrombotic therapy, and secondary prevention[2].

Inflammation is an important phase of all phases, including the short-term prognosis after myocardial infarction. Inflammation of the vessel wall and the inflammatory response are considered to be the main pathogenesis of atherothrombosis in myocardial infarction. In recent years, many inflammatory biomarkers have been studied to determine whether increased levels of these molecules are associated with a poor prognosis in patients with myocardial infarction. Several studies have shown a relationship between C-Reactive protein (CRP) and recurrence in acute coronary syndrome patients[3,4]. Early in acute myocardial infarction, CRP levels may be in response to an inflammatory response of myocardial ischemia and not chronic vascular inflammation[5]. This emphasizes that CRP levels are a simple marker of a potential myocardial ischemia inflammatory response and provides prognostic information on the risk of death. So that CRP measurement can be used as a risk stratification and management tool in very high-risk patients that affect the clinical outcome of STEMI[6].

Many studies are concerned with the prognostic value of high-sensitivity C-reactive protein (hs-CRP) as a predictor of rehospitalization in patients with acute myocardial infarction. Hs-CRP has been shown to be associated with clinical outcomes in hospitals such as death, myocardial infarction and angina. It can be useful as a risk biomarker in patients with myocardial infarction[7,8]. Hs-CRP is related to the duration and number of cigarettes consumed each day[9]. A study conducted by Raposeiras-Roubin et al. found that higher Hs-CRP levels are a predictor of acute myocardial infarction in the hospital[10]. Other study data suggest that hs-CRP levels as predictors are still conflicting because there are studies that show no significant relationship between Hs-CRP levels and STEMI patients who die or survive hospitalization[11].

The relationship between hs-CRP levels and clinical outcomes of patients with STEMI in Indonesia has not been known. Acute myocardial infarction is associated with extensive myocardial inflammation and causes a systemic inflammatory response. Hs-CRP can measure the inflammatory response in response to tissue damage after acute myocardial infarction, thereby providing a short-term prognosis and reducing the risk of death. This study can help us understand the prognostic significance of Hs-CRP levels in acute myocardial infarction. For further research this emphasizes the inflammatory process. It is hoped that hs-CRP levels can provide prognostic information based on the risk of death; besides, CRP in patients with acute myocardial infarction is a strong univariate predictor of mortality.

MATERIALS AND METHODS

Participants

The population of the research subjects were patients who came to the emergency room of Dr. Soetomo General Academic Hospital after being diagnosed with STEMI. 61 subjects were included in this study. Data collection was carried out by directly meeting patients who came to the emergency departments of Dr. Soetomo General Academic Hospital. Primary data were obtained by interviewing and examining patients, including physical, laboratory, and other supporting examinations, at the emergency departments of Dr. Soetomo General Academic Hospital. Secondary data is obtained from patient medical records. Then the patient is followed during treatment in the hospital. The sample in this study was venous blood from STEMI patients who were taken by purposive sampling; that is, every patient who met the research criteria was included as a research subject until they met the specified number of samples. Patients with STEMI are new patients at the hospital emergency room. Dr. Soetomo Surabaya General Academic Hospital, who met the following study criteria: Inclusion Criteria: Male and female Patients who met the STEMI diagnostic criteria with an onset of less than 24 hours Age 18 years with various risk factors such as previous history of myocardial infarction, hypertension, diabetes mellitus, smoking, dyslipidemia, and family history of coronary heart disease Exclusion criteria: heart failure with functional classification class III-IV; acute liver failure;

decreased kidney function; kidney failure; patients with renal transplants; sepsis; severe neurological disorder; muscular dystrophy; bacterial, viral, or parasitic infection; infections under antibiotic treatment; Individuals taking anti-inflammatory drugs, which include steroid or non-steroidal anti-inflammatory drugs (NSAIDs); and septic shock.

Ethical Approval

We have conducted an ethical approval base on the Declaration of Helsinki with registration research at the Health Research Ethics Committee in the Dr. Soetomo General Academic Hospital, Surabaya, Indonesia (1470/KEPK/IX/2019).

Study Design

This research is an analytic observational study using a prospective cohort study.

Meansurenment of High sensitivity C-Reactive Protein (hs-CRP)

Serum Separator Tube (SST) tubes to accommodate blood samples, tools, and materials for hs-CRP examination are Roche/Hitachi Cobas C systems. A 3 mL sample of venous blood was collected in a vacuum tube serum separator tube (SST). Maximum sample stability: 11 days at room temperature (15–25 oC), 2 months at 2–8 oC, and 3 years at -15 oC.

Statistical Analysis

The data obtained will go through the process of coding, entry, cleaning, and editing, then be processed using the statistical package for social sciences (SPSS) 17 statistical software, and the results will be presented in the form of tables and graphs. The data obtained will be processed using SPSS version 17. Statistical analysis using descriptive statistics and inferential statistics Categorical data are presented in the form of frequency distributions, the mean, and the standard deviation. Comparison test using the Wilcoxon test and chi square. Regression test using the regression log.

RESULT

Characteristics of participant

Study subjects were divided based on hs-CRP value and the presence or absence of major adverse cardiovascular events (MACE). The description of the characteristics of the 61 patients with a diagnosis of STEMI who became the study sample was mostly male: 42 people (68.9%), while 19 people (31.1%) were women with an age range between 40 and 85 years (56.28 9.48 years). Most of the study subjects received PPCI therapy—as many as 61 people (100%). The decision to select a reperfusion procedure was based on hospital management guidelines and was not determined by this study. Most of the subjects experienced anterior-type PPCI, which included STEMI anterior (41.67%), inferior 6 (9.8%), inferior-posterior 8 (13.1%), and inferior-RV 5 (8.2%). The main risk factor was hypertension (24 people), followed by diabetes mellitus (20 people), smoking (10 people), dyslipidemia (7 people), and family history (2 people). Some subjects have a combination of several risk factors. The length of time from the attack of acute myocardial infarction to arrival at the the emergency room ranged from 1–48 hours with an average of 7.77 hours, while the length of stay ranged from 1–26 days with an average of 5 days. The ejection fraction ranges from 24 to 59%, with an average of 47.19%. For serum creatinine, with a range of 0.65 to 4.24 and an average of 1.35 mg/dl. Tables 5.1 and 5.2 showed several significant differences in subject characteristics between the hs-CRP groups, including: smoking risk factors (P = 0.026), IMA location (p = 0.000), KILLIP class (0.003), and coronary lesions.

The basic characteristics of the other study subjects were not statistically different between groups based on hs-CRP levels either. During hospitalization, 11 patients died, with an overall mortality rate of 18.1%. Additionally, 21 patients with heart failure (34.4 %), 24 patients with MACE were observed out of 61 patients. Data on the distribution of results from measuring hs-CRP levels in the study and during hospitalization of the 61 study subjects are summarized in the Table 1.

Table 1. Demographic Characteristics Frequency distribution of study variables based on gender, hypertension, diabetes mellitus, dyslipidemia, smoking habits, family history, hs-CRP concentration, and cardiovascular risk.

Table 1. Demographic Characteristics Frequency distribution of study variables based on gender, hypertension, diabetes mellitus, dyslipidemia, smoking habits, family history, hs-CRP concentration, and cardiovascular risk.

	Variable	Total (%)	P value
Gender	Laki-laki	42 (68.9%)	0.003*
	Perempuan	19 (31.1%)	
Hipertensi	No	37 (60.7%)	0.096*
	Yes	24 (39.3%)	
Diabetes mellitus	No	41 (67.2%)	0.007*
	Yes	20 (32.8%)	
Dyslipidemia	No	54 (88.5%)	0.000*
	Yes	7 (11.5%)	
Smoking habit	No	51 (83.6%)	0.000*
	Yes	10 (16.4%)	
Family History	No	59 (96.7%)	0.000*
	Yes	2 (3.3%)	
Concentration Hs-CRP	Hs CRP < 2	14 (23.0%)	0.000*
	Hs CRP ≥ 2	47 (77.0%)	
Infarction history	No	61 (100.0%)	***
	Yes	0 (0.0%)	
Revascularization history	No	61 (100.0%)	***.
(CABG dan PCI)	Yes	0 (0.0%)	
Mortality	No	50 (81.9%)	0.000*
	Yes	11 (18.1%)	
Non-fatal MI	No	61 (100 %)	0.000*
	Yes	0 (0.0 %)	
Heart Failure	No	40 (65.6%)	0.015*
	Yes	21 (34.4%)	
Stroke	No	52(85.2%)	0.000*
	Yes	9(14.8%)	
Location MI	STEMI Anterior	41 (67.2%)	0.000**
	STEMI Inferior	6 (9.8%)	
	STEMI Inferior Posterior	8 (13.1%)	
	STEMI Inferior-RV	5 (8.2%)	
	STEMI Inferior -RV-Posterior	1 (1.6%)	
Coronary Lesion	One Vessel disease	35 (57.4%)	0.249*
	Multiple Vessel disease	26 (42.6%)	
Killip	1	52 (85.2%)	0.000**
	2	2 (3.3%)	
	3	1 (1.6%)	
	4	6 (9.8%)	
MACE	No	37 (60.7%)	
	Yes	24 (39.3%)	

*chi Square Test, **one sample kolmogorov smirnov test, *** This variable is constant. Chi-Square Test cannot be performed

Table 2. Demographic characteristics based on variables with hs-CRP levels

Characteristics < 2 mg/l(N=14)		Mean	hs-CRP	Hs-CRP ≥ 2 mg/l(N=47)
Age (years)		56.28	56.29	56.28
Sistolic		132.16	133.71	131.70
Diastolic		83.72	82.29	84.15
Pulse Frequency		85.19	78.86	87.09
Respiration		19.75	19.71	19.77
Triglycerides		115.46	135.57	109.47
Blood sugar		185.59	201.07	180.98
Total Cholesterol		156.54	179.86	149.59
HDL		64.26	78.57	60.00
LDL		100.93	113.14	97.29
Length of treatment	**(day)**	5.36	5.07	5.45
Onset of chest pain	**(hour)**	7.77	5.64	8.40
ejection fraction		47.19	49.3	47.53
Serum creatinine		1.35	1.24	1.39
Gender	Laki-laki (%)	68.9	85.7	63.8
	Perempuan(%)	31.1	14.3	36.2
Hypertension	No (%)	60.7	64.3	59.6
	Yes (%)	39.3	35.7	40.4
Diabetes Mellitus	No (%)	67.2	57.1	70.2
	Yes %)	32.8	42.9	29.8
Dyslipidemia	No (%)	88.5	85.7	89.4
	Yes (%)	11.5	14.3	10.6
Smoke	No (%)	83.6	64.3	89.4
	Yes (%)	16.4	35.7	10.6
Family History	No (%)	96.7	92.9	97.9
	Yes (%)	3.3	7.1	2.1
History of infarction	No (%)	100.0	100.0	100.0
	Yes (%)	0	0	0
History hospitalization	No (%)	100.0	100.0	100.0
	Yes (%)	0	0	0
Mortality	No (%)	81.9%	92,9%	78,7%
	Yes (%)	18.1%	7,1%	21,3%
Non-fatal MI	No (%)	100	100	100
	Yes (%)	0	0	0
Heart failure	No (%)	65.6	92.9	57.4
	Yes (%)	34.4	7.1	42.6
Non-fatal Stroke	No (%)	85.2	78.6	87.2
	Yes (%)	14.8	21.4	12.8
Location MI	STEMI Anterior	67.2	64.3	68.1
	STEMI Inferior	9.8	28.6	4.3
	STEMI Inferior	13.1	7.1	14.9
	Posterior			
	STEMI Inferior-RV	8.2	0	10.6
	STEMI Inferior -RV-	1.6	0	2.1
	Posterior			
Coronary Lesion	One Vessel disease(%)	57.4	57.1	57.4
	Multiple Vesseldisease (%)	42.6	42.9	42.6
Killip	1 (%)	85.2	85.7	85.1
	2 (%)	3.3	0	4.3
	3 (%)	1.6	7.1	0
	4 (%)	9.8	7.1	10.6

* Chi-Square Tests, ** Wilcoxon Ranks Test,*** no statistisc are computed

Relationship between hs-CRP levels and mortality during hospitalization STEMI patientsThe Spearman's rho test was used to analyze the correlation between hs-CRP levels and mortality during hospitalization, which can be seen in Table 3.

Table 3. The relationship between Hs-CRP levels and mortality during hospitalization in IM-EST patients

			Hs-CRP	Mortality
Spearman's rho	Hs-CRP	Correlation Coefficient	1.000	**.274***
		Sig. (2-tailed)		
		N		
	Mortality	Correlation Coefficient	**.274***	1.000
		Sig. (2-tailed)	.033	
		N	61	61
*. Correlation is significant at the 0.05 level (2-tailed).				

The table above explains that there is a low and weak positive correlation between hs-CRP and mortality, with a correlation value of 0.274 (p = 0.033). The analysis of hs-CRP category as a predictor of mortality during hospitalization in IMA-EST, a partially bivariate analysis was performed to obtain the odds ratio (OR). The results of the analysis are presented in Table 4.

Table 4. Hs-CRP levels as a predictor of mortality during hospitalization in IMA-EST patients

	B	S.E.	Wald	df	p	OR
Category Hs-CRP	1.257	1.097	1.312	1	0.252	3.514
Constant	-3.822	2.106	3.293	1	0.070	0.22

The Table above explains that people with hs-CRP levels 2 mg/l are more at risk of experiencing an incident of mortality by 3.514 times compared to people who have HS CRP levels 2 mg/l, which is not statistically significant. (Odds ratio 3.514, p = 0.252, CI 95%).

Examination Results of hs-CRP Levels with MACE During Hospitalization and 30 Days of STEMI Patients.

Table 5. HS-CRP levels as a predictor of MACE during hospitalization

	B		S.E.	Wald	df		p		OR
Category Hs-CRP		2.953	1.079	7.482		1		.006	19.158
Constant		-5.518	2.097	6.925		1		.008	.004

The Table 5 above explains that based on the variable in the equation table, the independent variable (hs-CRP) has a P value of Wald test (Sig) 0.05, which is equal to 0.006, meaning that the hs-CRP variable has a significant influence on Y (major adverse cardiac events (MACE)) with p = 0.006, 95% CI. Individuals with hs-CRP levels 2 are more at risk of experiencing major adverse cardiac events (MACE) incidents by 19.158 times compared to people who have hS-CRP levels 2 mg/l (OR 19.158; p = 0.006, CI 95%).

DISCUSSION

In this study, the majority were male as many as 42 people (68.9%), while there were 19 women (31.1%) with an age range between 40 and 85 years (56.28 ± 9.48 years). This is in accordance with a study by Jarayaj et al., which explains that the prevalence of myocardial infarction (MI) is higher in men in all specific age groups than in women. In addition, based on a national survey in England, in 2014, the prevalence of MI was 640,000 cases in men and 275,000 cases in women. This represents approximately 915,000 people who have MI in the UK. The prevalence of MI in men is about three times higher than in women in the UK. The age-specific prevalence of MI extends from 0.06% of men < aged 45 years to 2.46% of those ≥ aged 75 years[12]. Study from Dharma, Iwan et al, of a total of 1126 STEMI who underwent PPCI between 2008-2013, the mortality of STEMI patients who underwent PPCI during working hours was 15% with HR 0.77; CI 95 % interval 0.52-1.16. While those outside working hours are around 19%. This is almost the same as the mortality rate of STEMI patients undergoing PPCI at Dr. Soetomo General Academic Hospital, with a mortality rate of 18%[13]. hs-CRP levels measured during acute coronary syndromes, which were associ-

ated with cardiovascular events. They suspected that elevated hs-CRP levels after ACS were associated with the risk of MACE, cardiovascular death, and all other causes of death. This is in line with this study's analysis of measured serum hs-CRP levels in STEMI patients as a predictor of the clinical outcome of STEMI undergoing primary percutaneous coronary intervention[14].

Major cardiovascular events are a major cause of mortality and morbidity in patients with STEMI. Several dozen relevant articles report that MACE and its components are considered primary endpoints. A study analysis of the Vista trial 16, found the incidence of MACE to be 4.2% to 51% regardless of the mode of treatment and follow-up from the time STEMI was diagnosed. In our study, Hs-CRP levels had a weak positive association with mortality. Individuals with Hs-CRP levels more than equal to two are more at risk of experiencing an incident of mortality as much as 3.514 times compared to individuals who have Hs-CRP levels <2 mg/l, and statistically, hs-CRP levels have no significant effect as a predictor of mortality. This is in accordance with a study by Zebrack et al. It was reported that CRP levels were not associated with death or recurrent coronary events in patients with MI[15-16]. Our study differs from Sibele et al. in their retrospective cohort study, 118 STEMI patients were analyzed, with 20 patients dying. There is a strong relationship between hs-CRP levels and mortality during hospitalization, which suggests that Hs-CRP can be used as a marker of myocardial ischemia's inflammatory response, which provides prognostic information related to the risk of death. According to the study, the results of the logistic regression test showed that every 1 mg/dl increase in hs-CRP increased the risk of death by 15% (p = 0.0017)[17]. Another study from Mahmoud and colleagues with 448 subjects with IMA.

hs-CRP levels are checked within 12–24 hours of symptom onset. The results of this study found 4 patients who died (3%) with low hs-CRP, while 15 patients had hs-CRP in the middle quadrant, and 33 patients had high Hs-CRP levels. In multivariate analysis, high Hs-CRP levels or above quadrants were associated with mortality 30 days after STEMI. With RR 3.0; 95 % CI; 1.3-7.2; p = 0.01) and the occurrence of heart failure. (OR 2.6; 95%, CI; 1.5-4.6 p= 0.0006. According to Suleiman et al., CRP levels are not associated with post-infarction angina, recurrent myocardial infarction and the need for revascularization, but patients with Hs-CRP levels within 12-24 hours of chest onset pain is an independent marker of 30 days of death and the occurrence of heart failure in patients with AMI. This study suspects that hs-CRP levels are associated with an inflammatory process associated with the extent of infarction and post-infarction ventricular remodeling. This study is different from our study regarding mortality[18].

Carrero al. reported that hs-CRP levels were a high predictor of the incidence of death and MACE where hs-CRP levels > 2 mg/l had a 1.42-fold risk of mortality compared to hs-CRP <2 mg/L (95% CI, 1.31-1.53) while Hs-CRP levels > 2 mg/l had a 1.28 higher risk of MACE[19]. Regarding MACE, this study is in line with our research that Hs-CRP levels have a significant effect on MACE, with an RR of 1.065 (95% CI). and Hs-CRP levels have a positive relationship with major cardiovascular events. Individuals with Hs-CRP levels more than equal to 2 are more at risk of experiencing MACE as many as 19,158 times compared to individuals who have hs-CRP levels less than 2.

The presence of environmental, genetic, and comorbid factors, such as cardiovascular risk factors, can influence hs-CRP levels[20]. Studies from Yousuf Omair show that cardiovascular risk factors affect the hs-CRP cutoff point, such as metabolic syndrome, diabetes mellitus, hypertension, use of oral contraceptives, dietary patterns, and smoking. Likewise, race or ethnicity in individual populations affects hs-CRP levels, which vary. hs-CRP levels were found in African Americans, followed by Hispanics, South Asians, or East Asians. Based on the NHANES (National Health and Nutrition Examination Survey) analysis, hs-CRP levels ranged from 0.1 to 296 mg// (mean 4.3; median 2.1) Hs-CRP levels were higher in women than men and would increase with age. The average Hs-CRP was 3.5 mg/l in 20–29-year-olds versus 5.7 mg/l in 70–79-year olds[21].

Study Limitations

The limitations of this study included: the value of dissolved hs-CRP serum levels in the subjects studied was not compared to the control group, the number of samples used was small with an unequal proportion between subjects who experienced MACE and subjects who did not experience MACE, and the study time was short.

CONCLUSION

This study shows that hs-CRP is able to predict mortality and MACE in hospital care. Individuals with hs-CRP levels ≥ 2 mg/l had a risk of 3 times the risk

of mortality, which was not statistically significant and almost 19 times the occurrence of MACE compared to Hs-CRP levels < 2 mg/l which was statistically significant.

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