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Procalcitonin and Troponin-I as Predictor of Mortality in Acute Myocardial Infarction Patients

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ABSTRACT

Acute Myocardial Infarction (AMI) is known as one of the leading causes of death worldwide, including Indonesia. Procalcitonin is an inflammatory marker that has been recognized as a predictor of mortality in sepsis patients. However, the role of procalcitonin as a predictor of mortality in AMI patients has not been widely studied. Troponin-I has been recognized as a biomarker of AMI. However, it remains unclear whether troponin-I can also act as a biomarker to predict the death of AMI patients. This study aimed to determine the role of procalcitonin and troponin-I as predictors of mortality in AMI patients. A 5-month analytical observational study was performed on AMI patients who were admitted to Dr. Saiful Anwar Hospital, Malang. Patients with sepsis or infection were excluded. Among 51 research subjects, there was a significant difference in median procalcitonin and troponin-I levels between deceased and surviving patients ($p<0.05$). Procalcitonin level with a cut-off of 2.16 ng/mL had a sensitivity of 77% and specificity of 87%. Troponin-I level with a cut-off of 3.1 ng/mL had a sensitivity of 61% and specificity of 84%. The odds ratio of procalcitonin to mortality was 17.78 ($p=0.001$), but no significance was found in troponin-I. Procalcitonin was correlated with mortality ($r=0.519$, $p=0.005$). Therefore, it was concluded that procalcitonin could be used to predict mortality in AMI patients.

Keywords: Procalcitonin, troponin-I, acute myocardial infarction, mortality

INTRODUCTION

Acute Myocardial Infarction (AMI) is one of the leading causes of death. In the United States, the estimated incidence of Acute myocardial infarction is 605,000 cases per year, with 20% of patients dying within one year of the event.[1,2] Acute myocardial infarction occurs due to atherosclerosis, which causes a decrease in coronary perfusion. This condition reduces oxygen supply to the myocardial tissue, resulting in cardiac ischemia. Complications may occur immediately or later after myocardial infarction.[3]

Cardiovascular Disease (CVD), especially coronary heart disease, is the primary cause of mortality globally. An estimated 17.9 million people died from CVD in 2019, representing 32% of global deaths. Over three-quarters of CVD deaths take place in low- and middle-income countries.[4,5] Based on the 2018 National Health Survey data, the incidence of heart and blood vessel disease in Indonesia is increasing from year to year.[6]

The inflammatory processes that play a role in the pathophysiology of atherosclerosis and myocardial infarction are the basis for an increase in inflammatory markers. In acute myocardial infarction, muscle cells of the heart undergo necrosis. Cell necrosis has been known to cause inflammatory conditions. The inflammatory response to myocardial ischemia determines the extent of the damaged area and causes left ventricular remodeling after AMI.[7]

There are several known inflammatory biomarkers. One of the recently discovered inflammatory biomarkers is procalcitonin. Procalcitonin is a peptide precursor of the calcitonin hormone, consisting of 116 amino acids. In a healthy person, procalcitonin is formed in the thyroid C cells from the CALC-1 gene, which is then converted into the calcitonin hormone (32 amino acids), kata-calcitonin (21 amino acids), and N-terminal procalcitonin (57 amino acids). The role of procalcitonin testing in AMI has not been widely studied.[8,9] Therefore, this study aimed to determine the role of procalcitonin as a predictor of mortality in AMI patients.

The use of biomarkers is one of the approaches to diagnosing AMI. Cardiac troponin-I is a biomarker that has been used extensively to diagnose AMI. Troponin-I is a regulatory protein found in thin filaments of the contractile apparatus of cardiac muscle. Its level is not commonly detected or even

relatively low in normal individuals; however, its status can reach 20 fold-increase in the condition of AMI. Troponin-I is more specific for myocardial tissue because it is not found in skeletal muscles.[10] High level of cardiac troponin-I in the blood is thought to represent pervasive heart muscle damage; therefore, it is expected to determine the risk of death in patients with AMI. This study aimed to assess the role of troponin-I as a predictor of mortality in AMI patients.

METHODS

This research was an analytical observational cohort study with a consecutive sampling of AMI patients who were admitted to Dr. Saiful Anwar Hospital, Malang. The study was conducted for five months, from January to May. Research subjects were male or female AMI patients aged 40 years or above. The diagnosis of AMI was made from the clinical symptom of typical angina, electrocardiography (ECG) with an ST wave elevation that describes the diagnosis for STEMI, and ST depression or T inversion, which describes the diagnosis for Non-ST Elevation Myocardial Infarction (N-STEMI), and increased cardiac troponin-I level.[11] The cut-off level of troponin-I for the diagnosis of AMI was ≥ 1.0 ng/mL. Exclusion criteria were AMI patients with sepsis based on diagnosis from clinicians and/or Sequential Organ Failure Assessment (SOFA) score of ≥ 2.[12] In addition, all patients were analyzed for the serum levels of troponin-I and procalcitonin at admission. According to the Helsinki Declaration, the research processes were carried out according to the Health Research Ethics Committee of Dr. Saiful Anwar Hospital Malang number 400/286/K.3/302/2019.

Troponin-I levels were measured in this study using the sandwich immunochromatography method (AIM Troponin I Q-Rapid Test) and Easy Reader for the quantification. In contrast, the procalcitonin levels were measured using Electro Chemiluminescence Immunoassay (ECLIA) method and Cobas e411 analyzer. All laboratory analyses were carried out in the Central Laboratory of Dr. Saiful Anwar Hospital, Malang.

The data from this study were analyzed using the Mann-Whitney U test and Spearman correlation test. In addition, procalcitonin and cardiac troponin-I levels as a predictor of mortality were analyzed by Receiver Operating Characteristics (ROC) curve and odds ratio. A p-value <0.05 was stated significantly. The patient's mortality was assessed on the last day of hospitalization.

RESULTS AND DISCUSSIONS

A total of 103 AMI patients were measured for cardiac troponin-I and procalcitonin levels during five months of research. Fifty-two people were excluded due to sepsis and/or infection, leaving 51 people included in this study. Among 51 participants, 13 people passed away (25.5%), and 38 survived (74.5%). The median procalcitonin level of the deceased patients was higher than the median in those who survived. Similar results were also found in the median troponin-I level, higher in deceased patients than those who survived. The median troponin-I and procalcitonin levels are listed in Table 1.

A diagnostic test was performed in this study to determine the cut-off level of procalcitonin and troponin-I to increase mortality risk. The test results showed that procalcitonin levels with a cut-off of

Table 1. Median troponin-I and procalcitonin levels

	Non-Survivor (n=13)	Survivor (n=38)	p-value
Procalcitonin	8.19 ng/mL (0.02–73.63)	0.28 ng/mL (0.03–27.39)	0.001*
Troponin-I	8.2 ng/mL (1.0–84.7)	5.8 ng/mL (1.0–41.6)	0.045*

*significant at p<0.05

Table 2. diagnostic test of procalcitonin and troponin-I for mortality risk

	Area Under Curve	p-value	Cut-Off (ng/mL)	Sensitivity	Specificity
Procalcitonin	0.804	0.001*	2.16	77%	87%
Troponin-I	0.641	0.106	3.1	61%	84%

*significant at p<0.05

2.16 ng/mL increased mortality risk with a sensitivity of 77% and specificity of 87% (Table 2). The levels of troponin-I with a cut-off of 3.1 ng/mL had a sensitivity of 61% and specificity of 84%, despite its insignificance (Table 2). The ROC curves of procalcitonin and troponin-I can be seen in Figures 1 and 2.

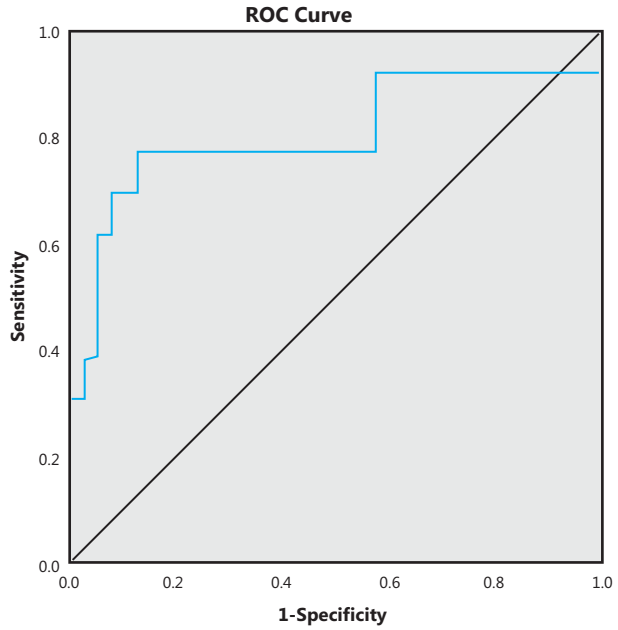

Figure 1. The ROC curve of procalcitonin (AUC=0.804)

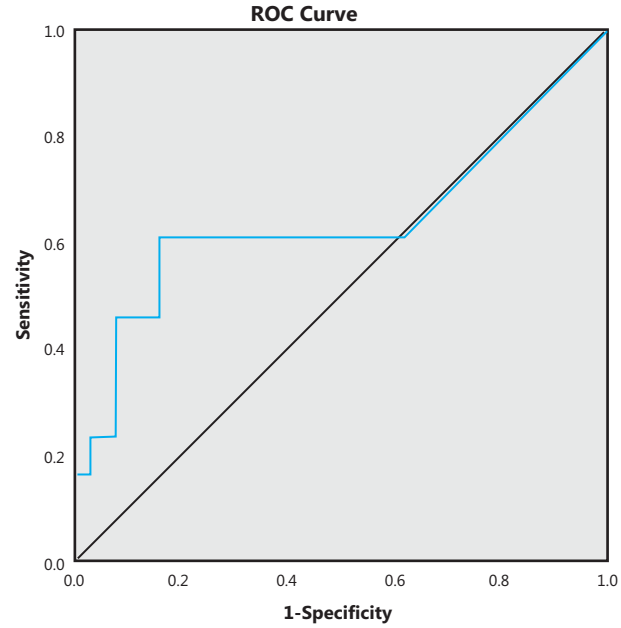

Figure 2. The ROC curve of troponin-I (AUC=0.641)

The calculation of the odds ratio of procalcitonin to mortality was 17.78 (p=0.001; 95% CI=1.448–4.308), while troponin-I was not significant (Table 3). Furthermore, the Spearman correlation test showed that procalcitonin had a moderate correlation with mortality (r=0.519, p=0.005).

Table 3. The odds ratio of procalcitonin and troponin-I

	Cut-Off (ng/mL)	Odds Ratio	p-value
Procalcitonin	2.16	17.78	0.001*
Troponin-I	3.1	3.46	0.45

*significant at p<0.05

Several studies regarding procalcitonin and troponin-I have been conducted. Procalcitonin is known to be a general inflammatory marker protein. In healthy individuals, all procalcitonin produced by thyroid C cells will be converted into calcitonin, resulting in low levels of procalcitonin in the blood (<0.05 ng/mL). However, procalcitonin is released by various tissues into the bloodstream in inflammatory conditions.[13] Increased levels of procalcitonin are also found in conditions of infection or sepsis.[14] The production of procalcitonin in inflammatory conditions occurs through direct mechanisms induced by Lipopolysaccharide (LPS) or toxic metabolites from microbes, and indirect mechanisms induced by various inflammatory mediators such as Interleukin (IL)-6, Tumor Necrosis Factor (TNF)-α, etc.[15] Troponin-I, which is known as a biomarker of myocardial infarction, can also be increased in non-cardiovascular conditions, such as in sepsis.[3,16] For these reasons, patients with sepsis or infection were excluded in this study to rule out the possibility of increased procalcitonin due to inflammation and infection other than cardiac ischemia.[8]

This study aimed to determine if high levels of procalcitonin and troponin-I can predict the risk of death in AMI patients or if any of those parameters can increase the risk of death in AMI patients. From the results of this study, it was known that there was a significant difference in procalcitonin levels between AMI patients who passed away and those who survived. Procalcitonin levels with a cut-off of 2.16 ng/mL increased the risk of mortality in AMI patients and were correlated with patient mortality. The measurement results of troponin-I levels also showed a significant difference in troponin-I levels between AMI patients who passed away and those who survived. However, its increased levels were not correlated with the risk of death in AMI patients.

Acute onset of myocardial ischemia causes damage to cell death (cardiomyocytes, endothelial cells, fibroblasts, and interstitial cells), resulting in an inflammatory response. This condition will activate proinflammatory mediators. In addition, the longer inflammatory period will lead to a more delayed healing phase of the myocardium.[7] Acute myocardial infarction is a sterile inflammatory condition with a

release of inflammatory cytokines-chemokines, platelet activation, leukocytosis, and hyperglycemia.[17] According to Dai *et al*., the levels of procalcitonin in the blood can reflect the severity of inflammation in patients with coronary heart diseases, and increased levels of procalcitonin are also associated with the prognosis of these patients.[8] Another study by Ertem *et al*. also showed similar results: procalcitonin is an inflammatory marker associated with cardiovascular disorders.[18] The production of procalcitonin in inflammatory conditions occurs through direct mechanisms induced by LPS or toxic metabolites from microbes and indirect mechanisms induced by various inflammatory mediators such as IL-6, TNF-α, and so on.[15] Increased levels of procalcitonin in this study were associated with patient severity and poor prognosis in AMI patients, which can predict the patient's risk of death.

Increased troponin-I levels in AMI conditions occurred due to myocyte damage and increased cell membrane permeability causing cardiac troponin to be released into the blood circulation, highlighting the role of troponin-I as one of the diagnostic markers in AMI.[19] In this study, troponin-I levels with a cut-off of 3.1 ng/mL were found to increase the risk of mortality in AMI patients, despite its insignificant results. This contrasts with several previous studies, which stated that troponin-I and T are correlated with short-term mortality rates and recurrent ischemic events.[20-22] This research was different from the previous research due to other measurement methods of troponin-I.

Based on the results of this study, it was suspected that increased acute inflammatory response due to heart muscle damage in AMI is more responsible for causing death than the extent of heart muscle damage, which is indicated by an increase in procalcitonin levels that is correlated with patient mortality. At the same time, there was no correlation found between troponin-I levels and patient mortality. However, this finding needs to be confirmed by performing a further study that measures other inflammatory parameters that have not been studied.

CONCLUSIONS AND SUGGESTIONS

The procalcitonin and troponin-I levels in AMI patients who passed away were higher than in those who survived. Procalcitonin can predict death in AMI patients, while troponin-I was not proven to be a predictor for death in AMI patients. Therefore, it was necessary to carry out further research by examining other inflammatory parameters in AMI patients to prove that increased inflammatory process plays a role in the death of AMI patients.

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