Role of Lactic Acid as Predictor of Mortality in Patients with Acute Myocardial Infarction

Novi Khila Firani\textsuperscript{1,2}, Theresa Sugartati Oetji\textsuperscript{1}

\textsuperscript{1}Department of Clinical Pathology, Faculty of Medicine, Brawijaya University/Dr. Saiful Anwar Hospital, Malang, Indonesia. E-mail: theresa.oetji@gmail.com
\textsuperscript{2}Department of Biochemistry and Biomolecular, Faculty of Medicine, Brawijaya University/Dr. Saiful Anwar Hospital, Malang, Indonesia

\textbf{ABSTRACT}

The hypoxic-ischemic condition causes tissue metabolic abnormalities and organ dysfunction, characterized by elevated blood lactic acid levels. It is suspected that increased lactic acid in Acute Myocardial Infarction (AMI) patients could increase mortality risk. This study aimed to determine whether increased lactic acid levels could be used as a predictor of mortality in AMI patients. The analytical observational-cohort study was performed on AMI patients who were admitted to Dr. Saiful Anwar Malang Hospital from January 2018 to December 2019. Research subjects were divided into two groups, the group of deceased and living AMI patients, who were tested for lactic acid, troponin-I, CKMB, and creatinine levels at admission. Diabetes mellitus and septic patients were excluded. For analysis of lactic acid as a predictor of mortality, ROC curve analysis and odds ratio were used. There found that lactic acid levels in the deceased AMI patients group were higher compared to that of the living AMI patients (\(p < 0.05\)). The sensitivity and specificity values of lactic acid as a predictor of mortality in AMI patients at a cut-off of 3.5 mmol/L were 66.7\% and 80\%, respectively. Odds ratio analysis showed that AMI patients with lactic acid levels more than 3.5 mmol/L had 8 times greater mortality risk than those whose level less than 3.5 mmol/L. It was concluded that lactic acid level can be used as an indicator to predict the mortality of AMI patients.

\textbf{Keywords:} Lactic acid, predictor, mortality, acute myocardial infarction

\textbf{INTRODUCTION}

Coronary heart disease is the leading cause of death at all ages after stroke, with a prevalence of 12.9\%. This is based on the results of a survey by Indonesian Ministry of Health’s Sample Registration System (SRS) in 2014.\textsuperscript{1} Basic Health Research or Riset Kesehatan Dasar (Riskesdas) data in 2013 also showed that the highest prevalence of cardiovascular disease in Indonesia was coronary heart disease, with a percentage of 1.5\%.\textsuperscript{2} The World Health Organization (WHO) in 2012 stated that approximately 17.5 million people died from cardiovascular disease or equal to 31\% of total 56.5 million deaths.\textsuperscript{3} More than 3/4 of deaths from cardiovascular disease occur in developing countries. Of the total deaths due to cardiovascular disease, 7.4 million (42.3\%) were caused by coronary heart disease and 6.7 million (38.3\%) were caused by stroke.\textsuperscript{3}

Coronary heart disease is ischemic heart disease with a diverse clinical spectrum ranging from ischemia without symptoms, angina pectoris, Acute Myocardial Infarction (AMI), to sudden cardiac death. Increased markers of myocardial injury such as cardiac-Troponin I (cTnI) and other cardiac enzymes can differentiate between myocardial infarction and unstable angina.\textsuperscript{4}

AMI patients have a high risk of mortality. Previous studies stated that several biomarkers were known to be able to predict mortality of AMI patients, including cTnI, C-Reactive Protein (CRP), Interleukin (IL)-6, Creatine Kinase-MB (CKMB) enzyme, creatinine, and HbA1c.\textsuperscript{6-10} Lactic acid is known as a biomarker that can act as a predictor of mortality in septic patients.\textsuperscript{11} Lactic acid is a metabolic product under anaerobic conditions.\textsuperscript{12} Hypoxic-ischemic condition causes metabolic abnormalities in tissue and organ dysfunction, which cause an increase in lactic acid level. Increased lactic acid can be found in patients with a critical illness, cardiogenic shock, and poor prognosis.\textsuperscript{13} The role of lactic acid as a predictor of mortality in AMI patients in Indonesia has not been widely studied. This study aimed to determine the role of lactic acid as a predictor of mortality in AMI patients in Dr. Saiful Anwar Hospital, Malang to help clinicians in management of AMI patients.
METHODS

This research was an analytical observational-cohort study on AMI patients who were treated at Dr. Saiful Anwar Hospital, from January 2018 to December 2019. The research subjects were selected through consecutive sampling. Subjects were male or female patients aged 40 years or above, and diagnosed with AMI, which included ST-Elevation Myocardial Infarction (STEMI) and Non-ST-Elevation Myocardial Infarction (NSTEMI) based on clinical symptoms, Electrocardiography (ECG), and laboratory tests of cTnI ≥ 1µg/L. Diabetes mellitus and septic patients were excluded. The research procedures were performed according to the Helsinki Declaration and approved by Health Research Ethics Committee of Dr. Saiful Anwar Hospital, Malang with number 400/286/K.3/302/2019.

All patients were tested for cTnI, CKMB, creatinine, HbA1C, and the lactic acid levels at admission. The test specimens were serum for cTnI, CKMB enzyme, creatinine, and lactic acid. EDTA blood specimens were used for HbA1C test. cTnI levels were measured with Sandwich Immunochromatography method (AIM Troponin I Q-Rapid Test), which was analyzed using Easy Reader. CKMB, creatinine, and lactic acid levels were measured using the enzymatic method and analyzed using Cobas 6000. HbA1c levels were measured using the Ion-Exchange High-Performance Liquid Chromatography method and analyzed using Bio-Rad D-10. All laboratory tests were carried out in the Central Laboratory of Dr. Saiful Anwar Hospital, Malang.

The research subjects were divided into two groups, AMI patients who died in treatment (deceased group) and patients who survived (living group). Mann-Whitney U test and Spearman correlation test were used for statistical analysis. The potential of lactic acid as a predictor of mortality was analyzed using Receiver Operating Characteristics (ROC) curve and odds ratio, p-value < 0.05 was stated as significant.

RESULTS AND DISCUSSION

There were 180 subjects with AMI during the study period. A total of 117 patients (65%) who had diabetes mellitus or sepsis were excluded. The characteristics of research subjects can be seen in Table 1.

According to the results of this study, the average age of AMI patients treated at Dr. Saiful Anwar Hospital, Malang was around 61-63 years old. It shows that the incidence of AMI increases in old age. These results were similar to studies conducted by Hai et al., suggesting that the mean age of the study population of the acute coronary syndrome was 65 years. Gender had no significant difference in this study; however, it appeared that the proportion of deceased patients were higher in females. It was thought because they were menopausal female. In menopausal female, the incidence of AMI are increased due to the absence of estrogen’s protective effect against atherosclerosis.

A previous study by Julie et al. suggested that elevated cTnI was associated with an increased risk of death due to increase of cTnI indicating turnover and apoptosis of myocytes. Therefore, it is related to the degree of myocardial damage. In this study, deceased AMI patients had higher cTnI but lower CKMB levels than those of living patients; however, none of them were statistically significant. These results were probably due to the variation of the time interval between the onset of symptom and blood sampling for cTnI and CKMB levels measurement for each research subject. A previous study showed that cTnI increased in 4-12 hours after onset of symptom, reached the peak in 12-24 hours,

Table 1. Characteristics of subjects

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Deceased Patients</th>
<th>Living Patients</th>
<th>Unit</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age*</td>
<td>63.36±11.14</td>
<td>61.87±12.25</td>
<td>years</td>
<td>0.61</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td>0.59</td>
</tr>
<tr>
<td>Male</td>
<td>9 (27.3%)</td>
<td>19 (63.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>24 (72.7%)</td>
<td>11 (36.7%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactic acid</td>
<td>4.20 (2.90-8.05)</td>
<td>2.70 (2.25-3.10)</td>
<td>mmol/L</td>
<td>0.001**</td>
</tr>
<tr>
<td>cTnI</td>
<td>12.60 (1.95-23.60)</td>
<td>8.70 (3.15-23.30)</td>
<td>µg/L</td>
<td>0.75</td>
</tr>
<tr>
<td>CKMB</td>
<td>95 (56.50-253.23)</td>
<td>127 (48.50-343.75)</td>
<td>U/L</td>
<td>0.86</td>
</tr>
<tr>
<td>HbA1C</td>
<td>5.80 (5.50-6.05)</td>
<td>5.95 (5.50-6.20)</td>
<td>%</td>
<td>0.55</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.61 (1.00-2.94)</td>
<td>1.25 (0.92-1.84)</td>
<td>mg/dL</td>
<td>0.23</td>
</tr>
</tbody>
</table>

*Mean±SD, SD: Standard Deviation  
** statistically significant
and disappeared within 5-7 days, while CKMB increased 3-6 hours after onset of symptom, reached the peak in 12-24 hours, and returned to normal within 12-48 hours.\textsuperscript{17} Prospective multicenter SYCOMORE study about the prognostic significance of renal insufficiency in patients characterized by acute coronary syndrome stated that renal function was independently associated with hospital mortality.\textsuperscript{18} Previous studies also showed that increased creatinine levels were associated with the impaired myocardial flow and poor prognosis in AMI patients.\textsuperscript{19} Kidney disorders cause the development of arteriosclerosis through increased fibrinogen, homocysteine, lipoprotein-a, intermediate-density lipoprotein, oxidized low-density lipoprotein, and decreased high-density lipoprotein.\textsuperscript{20} In this study, creatinine levels between the deceased and the living AMI patients showed no significant difference, excluding the possibility of death due to renal insufficiency.

The results of the ROC curve analysis for lactic acid in this study showed the ability of lactic acid as a predictor of mortality in AMI patients with Area Under Curve (AUC) of 0.733 (Figure 1). The sensitivity and specificity values of lactic acid with a cut-off of 3.5 mmol/L as a predictor of mortality in AMI patients were 66.7% and 80%, respectively.

![Figure 1. ROC curve of lactic acid (AUC=0.733)](image)

The results of the Spearman correlation test showed that there was a significant relationship between lactic acid level and mortality ($p=0.001$) with a moderate level of correlation (0.430). Odds ratio analysis showed that AMI patients with lactic acid levels more than 3.5 mmol/L had 8 times greater mortality risk than AMI patients with lactic acid levels less than 3.5 mmol/L (95% CI=2,531–25,284).

From these results, it was suggested that the increased level of lactic acid was correlated with poor tissue perfusion. According to Martin \textit{et al.}, lactic acid concentration could provide additional prognostic information in STEMI patients in addition to signs of hypoperfusion, systolic blood pressure, and Left Ventricular Ejection Fraction (LVEF). The lactic acid level was also independently associated with 30-day mortality. Hemodynamic instability and clinical signs of peripheral hypoperfusion increased to more than 40% in subjects with lactic acid concentrations ≥ of 5 mmol/L.\textsuperscript{21}

In this research have found that lactic acid can be used as a predictor of mortality in AMI patients at a cut-off of 3.5 mmol/L, with sensitivity and specificity values of 66.7% and 80%, respectively. Odds ratio analysis showed that AMI patients with lactic acid levels more than 3.5 mmol/L had 8 times mortality risk greater than AMI patients whose levels of less than 3.5 mmol/L. These findings indicated that high levels of lactic acid can be used as a prognostic biomarker to predict mortality in AMI patients. This phenomenon explained that ischemic conditions can cause tissue hypoperfusion, resulting in abnormalities of cell metabolism, which is characterized by an increase in lactic acid level. When myocardial ischemia occurs, Adenosine Triphosphate (ATP) levels can be maintained by increased glycolysis but at the expense of limited glucose and glycogen stores. Glucose utilization is increased more than 10-fold in ischemic/hypoxic conditions of cardiac myocytes followed by accumulation of lactic acid. When the oxygen supply is limited, the reoxidation of Nicotinamide Dinucleotide Dehydrogenase (NADH) to Nicotinamide Dinucleotide (NAD+) in the mitochondria during glycolysis is altered, and NADH is re-oxidized by the reduction of pyruvate to lactic acid, allowing glycolysis to continue.\textsuperscript{22}

Although glycolysis can occur under anaerobic conditions, the amount of ATP formed per oxidized glucose molecule is limited, allowing more glucose to be metabolized under anaerobic conditions.\textsuperscript{22} Acidic conditions due to increased levels of lactic acid is worsened when the ATP level begins to decrease. If ATP is depleted during ischemia, necrosis will occur due to a passive loss of the transmembrane ion gradient, and it is followed by cell swelling and loss of membrane integrity. The cell death program (apoptosis) is an active process that consumes energy that requires ATP. Therefore, the cell death program pathway becomes unsuccessful and replaced by necrotic cell death due to decreased ATP levels.\textsuperscript{22}

The clinical value of lactic acid levels has been studied in critical care patients. Measurement of
blood lactic acid can be used as an indicator of hemodynamic disturbances and as a predictor of outcome in various forms of shock. In patients with cardiogenic shock, several studies have shown a significant increase in lactic acid levels. AMI can cause cardiogenic shock, resulting in impaired tissue perfusion. When tissue perfusion is impaired, oxygen delivery will decrease and induces myocyte to undergo anaerobic glycolysis. The anaerobic glycolysis produces lactic acid from pyruvate rather than oxidizing pyruvate for energy production in mitochondria. In patients with ischemic heart disease, the amount of lactic acid released by the myocardium is associated with the severity of coronary artery disease.22

Vermeulen et al. conducted a study about arterial lactic acid levels in patients with STEMI before Percutaneous Coronary Intervention (PCI). They measured hemodynamic parameters and other characteristics of patients at admission. They found that elevated arterial lactic acid levels measured before PCI were associated with hypotension, higher heart rate, and diabetes. They also found that elevated lactic acid levels were associated with worse outcomes including increased 30-day mortality and larger infarct size.22 In our study, diabetic patients were excluded; therefore, it could be considered that lactic acid was an independent predictor of mortality on AMI.

CONCLUSION AND SUGGESTION

Increased levels of lactic acid more than 3.5 mmol/L can be used as an indicator to predict mortality in AMI patients, with a sensitivity and specificity of 66.7% and 80%, respectively. AMI patients with lactic acid levels more than 3.5 mmol/L have 8 times greater risk of mortality than AMI patients with lactic acid levels less than 3.5 mmol/L. However, further research is needed to improve the sensitivity and specificity value of lactic acid as a predictor of mortality in AMI patients.

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REFERENCES