Hyperlactatemia as Predictor Mortality Within 30 Days After Acute Myocardial Infarction

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Abstract

Acute myocardial infarction (AMI) is a major cause of morbidity and mortality in deleveloped countries and an important health problem in developing countries. Generally, hyperlactatemia is an anaerob metabolism product as a result of indeaquate tissue oxygenation. Myocardial ischemia will cause decrease of ATP formation from phosporylation oxydation and pyruvate conversion into lactate in sitosol with very high speed that cause tissue lactate accumulation. Hyperlactatemia is a metabolic stress marker and its severity level associated with increase morbidity and mortality. Serial lactate levels measurement will give more advantage than only one time. The aim of this study is to investigate hyperlactatemia as mortality predictor 30 days post AMI. This study was a prospective cohort observational study and 121 acute myocardial infarction patients were included as subjects with consecutive sampling. Lactat levels measurement used capillary blood when the patients admitted and 2 hours after using Accutrend lactate meter. ROC curve was used to determine hyperlactatemia level. Patients were followed until 30 days to evaluate mortality. The result of this study was hyperlactatemia with lactate levels ≥ 4,4 mmol/L was a threefold mortality predictor 30 days after AMI (HR=3,33, 95% CI 1,084-10,210, p value= 0,036) and Killip class (HR: 2,814, 95% CI: 1,786-4,435; p <0,001) and hemoglobin levels (HR: 0,810, 95% CI: 0,672-0,978; p = 0,28) as a confounding factors. Hyperlactatemia is a mortality predictor 30 days after acute myocardial infarction. Beside of that, Killip class and hemoglobin levels are confounding factors.

Keywords: acute myocardial infarction; hyperlactemia; mortality

Coronary Heart Disease (CHD) or cardiovascular disease is currently one of the leading and first causes of death in developed and developing countries, including Indonesia. Thirty (30) days hospital mortality after acute myocardial infarction was estimated at 7.99% (1). Establishing the diagnosis of IMA with several classifications is carried out by conducting anamnesis, physical examination, electrocardiogram (ECG), and cardiac marker examination. The diagnosis of IMA will be more difficult in patients with non specific chest pain or atypical (2). ECG sensitivity using ischemia criteria (ST depression and T inversion) in determining IMA was only 16%. Likewise, the sensitivity of peak troponin-I levels is only 40%. Most laboratory tests performed such as myoglobin, Creatinin Kinase type MB (CK-MB), and troponin rely heavily on damage to heart muscle cells that undergo ischemic and result in damage or necrosis of heart muscle cells so that they release enzymes into serum and do not take into account the measurement of physiological changes that occur in the heart (3, 4). Lactic acid is a product of anaerobic glycolysis that increases under tissue hypoperfusion. Regional stages of hypoperfusion are often found in acute myocardial infarction despite normal blood

pressure circumstances. In basal conditions, the myocardium obtains or extracts lactate from and into circulation, but in ischemia conditions this ability will be disrupted, so myocardial ischemia can cause increased lactate levels in circulation through these two mechanisms (5). The sensitivity of initial lactate performance to myocardial infarction is said to be 88%. With this high enough sensitivity, lactate can be used as a parameter in the management and triage of patients with chest pain presentation (5). This study was conducted to determine the role of lactate as a predictor of 30 days mortality after IMA.

1. Method

This study is an observational study with a prospective cohort design from November 2014 to February 2015 with 121 IMA samples (STEMI & NSTEMI) taken by consecutive sampling at PJT Sanglah Hospital Denpasar. The diagnosis of IMA was established using WHO criteria where patients with chronic kidney and liver disease, sepsis, diabetic ketoacidosis, history of malignancy and use of antiretrovirals were not included in the study.

The patient's lactate level was checked at the beginning diagnosis of IMA and 2 hours after treatment using a portable Accutrend lactate meter, battery-powered reflectance photometer manufactured by Roche Diagnostics, Mannheim, Germany (POC device) where capillary blood is taken from the tips of fingers or toes that are not fitted with infus. Patients are followed 30 days from the first diagnosis to determine the outcome of mortality by various causes where hospital mortality is obtained from medical records and out-of-hospital mortality is obtained by telephone to family or patients themselves.

Data analysis was carried out using the Stata E 12 program which was carried out in several stages, at the first is univariate analysis, determining ROC curves, bivariate and last with multivariate analysis. The cut of point to determine hyperlactatemia is done by creating a curve receiver operating characteristic (ROC). Lactate levels which are numerical variables are then changed to hyperlactatemia categorical variables and not based on the cut of point value of ROC. Bivariate analysis was used to determine the effect of hyperlactatemia on mortality using the Kaplan-Meier survival estimation method and a logrank test. Variables with categorical data scales were performed Chi Square test. Variables with numerical data scales are tested for normality with the Saphiro Wilk Normality Test. The normally distributed variable ($p > 0.05$) was analyzed by an independent t-test. While the variables are not normally distributed ($p < 0.05$) a non-parametric test (two group mean comparison test) is carried out. The multivariate analysis used to determine the effect of hyperlactatemia on mortality is the Cox Proportional Hazard Model where a global test was previously carried out to determine whether or not proportional hazard assumptions are met. The variables included in the multivariate test are variables with a value of $p<0.25$. The P value that is considered meaningful is ≤ 0.05.

2. Result

Total 121 IMA patients, 84 (69%) STEMI patients, and 37 (31%) NSTEMI patients were included in the study from November 2014-February 2015. The characteristics of patients shown in tables 1, 2 and 3 are grouped based on hyperlactatemia or not. The ROC curve for determining the cut point of hyperlactatemia is shown in figure 1.

Table 1 Characteristics Subjects Based on Demographics, Clinical Presentation and Reperfusion Therapy

Characteristic	Total (n=121)	Hyperlactatemia	
		Yes (n=27)	No (n=94)
Demographic			
Man	103 (85,12%)	20 (74,07%)	83 (88,30%)
Woman	18 (14,88%)	7 (25,93%)	11 (11,70%)
Age (years), average ± SD	59,07±12,14	60,59±12,93	58,64±11,94
Characteristics at emergency			
Onset of chest pain			
≤12 hr	86 (71,07%)	19 (70,37%)	67 (71,28%)
>12 hr	35 (28,93%)	8 (29,63%)	27 (28,72%)
Diagnosis			
STEMI	84 (69,42%)	17 (62,96%)	67 (71,28%)
NSTEMI	37 (30,58%)	10 (37,04%)	27 (28,72%)
Killip			
I	79 (65,29%)	9 (33,33%)	70 (74,47%)
II	17 (14,05%)	3 (11,11%)	14 (14,89%)
III	8 (6,61%)	1 (3,70%)	7 (7,45%)
IV	17 (14,05%)	14 (51,85%)	3 (3,19%)
Reperfusion			
Thrombolytics			
Yes	47 (38,84%)	4 (14,81%)	43 (45,74%)
No	74 (61,16%)	23 (85,19%)	51 (54,26%)
PCI			
Yes	1 (0,83%)	1 (3,70%)	0 (0,00%)
No	120 (99,17%)	26 (96,30%)	94 (100,00%)

Table 2 Characteristics Subjects Based on Laboratory

Characteristics	Total (n=121)	Hyperlactatemia	
		Yes (n=27)	No (n=94)
WBC (µL), average ± SD	12,96±4,55	13,45±4,32	12,82±4,62
Hemoglobin (mg/dL), average ± SD	14,03±2,24	13,37±2,98	14,22±1,96
Albumin (g/dL), average ± SD	3,75±0,47	3,62±0,59	3,78±0,43
Random blood sugar (mg/dL), average ± SD	171,20±79,15	166,38±73,64	172,58±80,98
pO2 (mmHg), rerata ± SD	135,95±36,01	125,85±41,56	138,85±33,94

Table 3 Characteristics Subjects Based on Cardiovascular Risk Factors

Characteristics	Total (n=121)	Hyperlactatemia	
		Yes (n=27)	No (n=94)
Family history			
Yes	11 (9,09%)	3 (11,11%)	8 (8,51%)
No	110 (90,91%)	24 (88,89%)	86 (91,94%)
Dyslipidemia			
Yes	60 (49,59%)	14 (51,85%)	46 (48,94%)
No	61 (50,41%)	13 (48,15%)	48 (51,06%)
Hypertension			
Yes	54 (44,63%)	11 (40,74%)	43 (45,74%)
No	67 (55,37%)	16 (59,26%)	51 (54,26%)
Diabetes			
Yes	36 (29,75%)	6 (22,22%)	30 (31,91%)
No	85 (70,25%)	21 (77,78%)	64 (68,09%)
Smoking			
Yes	69 (57,02%)	13 (48,15%)	56 (59,57%)
No	52 (42,98%)	14 (51,85%)	38 (40,43%)

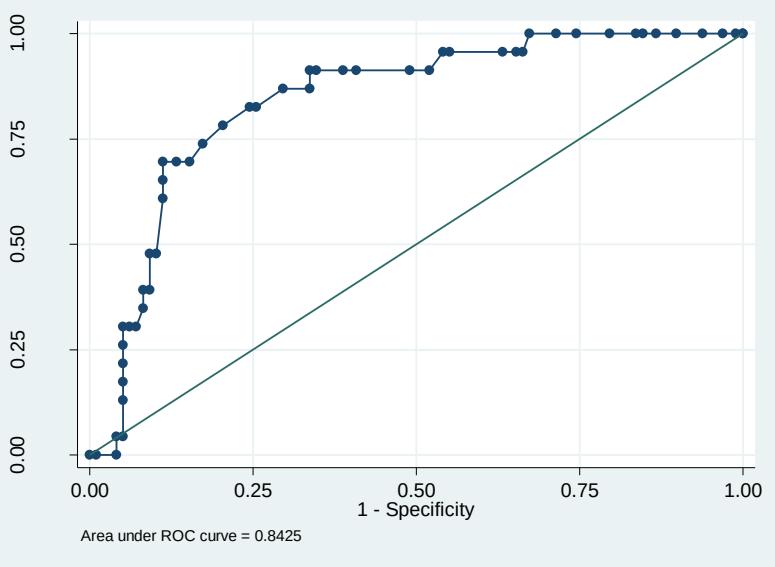

Figure 1. The ROC Curve in Determining the cutt of point Hyperlactatemia Area Under Curve (AUC) is 0.8425, Standard Error 0.0418, (95% CI = 0.76059-0.92442).

Based on the results of the ROC curve analysis, the best cutt of point value in expressing hyperlactatemia as a predictor the outcome of mortality and obtained the optimal relationship both in terms of sensitivity and specificity was at a lactate level of 4.4 mmol / L. The effect of hyperlactatemia on mortality is shown in figure 2. Kaplan-Meier's survival estimation

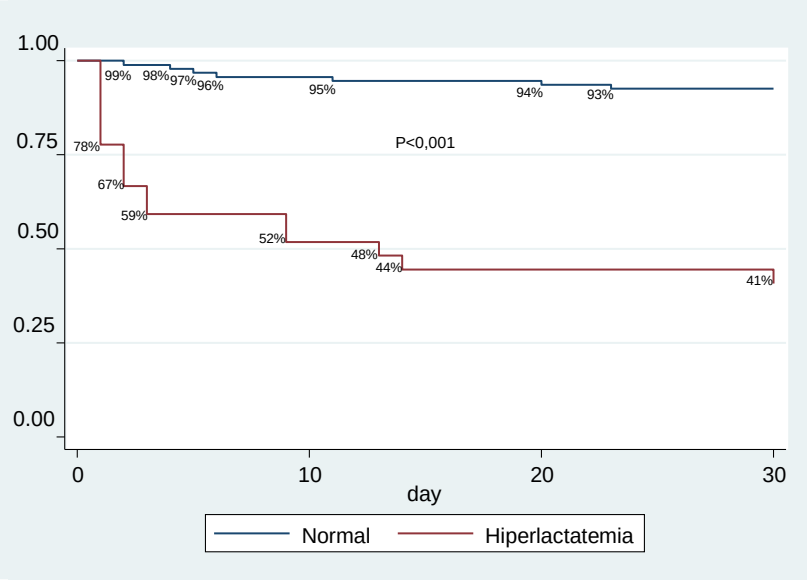

Figure 2 Kaplan Meier Survival Estimation Curve 30-day Post-IMA Mortality Curve Based on Hyperlactatemia

After the Logrank test, it was found that the survival rate between patients with hyperlactasemia and without hyperlactasemia was significantly different with a p value of <0.0001. The independent effect of hyperlactasemia on momortality is seen with a hazard ratio value of 14.5 (HR = 14.5, 95% CI = 5.639 – 41.640, p < 0.0001) shown in table 4 below.

Table 4 Hazard Ratio (HR) of 30-day Post-IMA Mortality with Hyperlactatemia and Without Hyperlactatemia

Variable	Number of mortality	Number of person-time	IR	HR	95% CI	P value
Hyperlactatemia						
• Yes	16	423	0,038	14,5	5,639-41,640	<0,0001
• No	7	2681	0,003	Ref		

Variables that have a P<0.25 value including sex, killip class, thrombolytic therapy, percutaneous coronary intervention (PCI), albumin levels and blood hemoglobin are included in the multivariate analysis shown in the following table.

Table 5 Basic Model of Cox Proportional Hazards Regression Analysis of Hyperlactatemia as a Predictor 30-day Mortality Post-IMA

Variable	HR	CI	P
Hyperlactatemia	3,47	1,167-10,320	0,025
Gender	0,38	0,138-1,035	0,058
Killip	2,74	1,700-4,412	<0,001
Thrombolytic (Streptokinase)	0,16	0,020-1,265	0,082
PCI	0,89	0,105-7,481	0,913
pO2	0,99	0,984-1,005	0,316
Albumin	1,51	0,558-4,068	0,419
Hemoglobin	0,84	0,693-1,013	0,068

Table 6 Final Model of Cox Proportional Hazards Regression Analysis of Hyperlactasemia as a Predictor 30-day Mortality Post-IMA

Variable	HR	95% CI	P
Hyperlactatemia	3,33	1,084-10,210	0,036
Gender	0,395	0,143-1,094	0,074
Killip	2,814	1,786-4,435	<0,001
Hemoglobin	0,810	0,672-0,978	0,028

After multivariate analysis, the effect of hyperlactatemia on mortality was 3 fold compared to no hyperlactatemia (HR = 3.33, 95% CI = 1.084-10.210, p = 0.036) and it was also found that the Killip class variable (HR: 2.814, 95% CI: 1.786-4.435; p <0.001) and blood hemoglobin levels (HR: 0.810, 95% CI: 0.672-0.978; p = 0.28) as confounding variables of the study.

3. Discussion

The main result of myocardial ischemic is mitochondrial metabolic dysfunction due to decreased oxygen delivery to tissues, resulting in decreased ATP formation from postforylated oxidation. A decrease in ATP formation aerobically will cause an increase in the glycolysis process and an increase in glucose uptake by mitochondria and glycogen breakdown. Unlike heart conditions with normal blood flow, during ischemia pyruvate produced through the process of glycolysis cannot be completely oxidized in mitochondria, and there is a conversion of pyruvate to lactate in the cytosol at a high rate resulting in an increase in tissue lactate (6). Hyperlactatemia is a marker of metabolic stress and its severity associated with increased morbidity and mortality (7). In this study, there were 27 patients with hyperlactatemia and 94 patients without hyperlactatemia and there where 23 patients died (16 hyperlactatemia and 7 without hyperlactatemia). The cutt of point value obtained from the ROC curve is 4.4 mmol / L as the best cutt of point in expressing hyperlactatemia. The cut of point value is almost the same as several other studies including Jansen et al in 2008, Jhamb et al in 2011, Henning et al in 1982, and Vermeulen et al in 2010 (8-11).

In this study, the effect of hyperlactatemia on mortality was 3 fold compared to without hyperlactatemia (HR = 3.33, 95% CI = 1.084-10.210, p = 0.036) and it was also found that the Killip class variable (HR: 2.814, 95% CI: 1.786-4.435; p <0.001) and blood hemoglobin levels (HR: 0.810, 95% CI: 0.672-0.978; p = 0.28) as confounding variables.

IMA patients will experience impaired circulation regulation. The process begins with anatomical or functional obstruction of the coronary arteries resulting in regional myocardial ischemia if ischemia persists at infarction. If the infarction is extensive enough, it will result in suppression of left ventricular function so that it will decrease the volume of the cup and increase the final filling pressure of the diastolic. A decrease in the volume of a heavy left ventricle will lower aortic pressure (decrease in systemic perfusion) and result in a decrease in blood pressure which will aggravate the decrease in coronary perfusion pressure so that it will aggravate the ischemic myocardium and initiate the occurrence of vicious circle. Increased diastolic filling pressure of the left ventricle leads to pulmonary congestion which further aggravates hypoxemia and

myocardial ischemia. Secondary systemic inflammation due to the infarction process results in the release of cytokines resulting in vasodilation and decreased systemic vascular resistance so as to reduce systemic perfusion and reduce coronary perfusion pressure which will aggravate ischemia. The vicious circle will cause a decrease in perfusion at the tissue level. Hypoxia and lactic acidosis worsen myocardial contractility where all these mechanisms will result in death in IMA patients (12). From this explanation, it is suspected that both ischemic coronary arteries and heart failure due to IMA will cause perfusion disorders in the heart and all tissues which will result in changes in aerobic metabolism to anaerobic metabolism which will increase lactate production in tissues with various metabolic consequences so that all these conditions will eventually result in death in IMA patients. Lazzeri found that elevated lactate levels were associated with hospital mortality of STEMI patients with PCI only in patients with classes III and IV (OR, 1.17; 95% CI, 1.05-1.30; P=0.03) (13). Shabbir et al obtained a significantly increased IMA Mortality with an increase in Killip class (class III and IV) (P = 0.000) (14). In anemia, hyperlactatemia will occur through the mechanism of increased production due to an increase in glycolysis speed, resulting in an imbalance between the formation of ATP and AMP and also caused by a decrease in clearance (15). Ceyhan et al found a linear negative correlation between lactate levels and hemoglobin levels ($r = -0.6213$; $p < 0.005$), where hypoxemia caused by anemia is thought to cause an increase in lactate levels. Some potential mechanisms that can worsen the prognosis of IMA patients with anemia include sympathetic activity, left ventricular hypertrophy, impaired ability of the heart to tolerate hemoglobin levels. Excessive increase in hemoglobin is also associated with poor cardiovascular prognosis where high blood viscosity and increased thrombus formation are said to be underlying mechanisms (16). Sabatine et al found in STEMI patients 30 days mortality was higher in patients with hemoglobin levels < 14 g/dL or >17 g/dL. In NSTEMI patients, mortality, infarction and ischemia increased with a decrease in hemoglobin levels < 11g/dL or an increase in > 16g/dL (17).

4. Conclusion

Hyperlactatemia is a predictor of mortality 30 days after IMA, where Killip Class and blood hemoglobin levels are confounding variables of the study. Similar studies can be done with longer mass follow-up, so that the long-term prognosis of IMA patients can also be assessed based on lactate levels. Further research can be conducted to assess the independent effect of lactate on mortality by excluding confounding variables. Interventional studies can be conducted that aim to determine whether the administration of more aggressive medical therapy or early intervention measures can improve the outcomes of patients with high lactate levels.

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