



RELATIONSHIP BETWEEN SERUM HOMOCYSTEINE LEVEL WITH THE SEVERITY OF ACUTE MYOCARDIAL INFARCTION ASSOCIATED WITH GENSINI SCORE

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DOI: 10.5281/zenodo.3612054

Abstract

Background

Coronary Arterial Disease (CAD) is currently one of the main and first causes of death in developed and developing countries, including Indonesia. Acute myocardial infarction (AMI) is a common cardiac emergency caused by unstable ischemic syndrome. In practice, abnormalities are diagnosed and assessed based on clinical evaluation, electrocardiogram, biochemical testing, invasive and non-invasive imaging, and pathological evaluation. Homocysteine is an amino acid that has a sulfur group involved in the methionine cycle, namely in the remethylation pathway and the transsulfuration pathway. The function of this cycle is to donate the methyl groups needed by various body molecules and the synthesis of glutathione.

Method

This is an analytic observational research with cross-sectional approaches. A total of 50 subjects with acute myocardial infarction, serum homocysteine levels were examined as well as coronary angiography examination. The severity of acute myocardial infarction was assessed by a Gensini score which was then statistically analyzed. Data were analyzed using computer statistical software.

Results

Median Gensini score was 52 (6-94). From laboratory tests, the average serum homocysteine level was $10.28 \pm 4.61 \mu\text{mol} / \text{L}$. Using the Spearman correlation, the correlation between serum homocysteine levels and Gensini scores was $p = 0.001$ with $r = 0.445$.

Conclusion

From the results of the study concluded that there was a significant relationship between serum homocysteine levels with the severity of acute myocardial infarction associated with Gensini scores.

Keywords: Coronary arterial disease, acute myocardial infarction, Homocysteine, Gensini score.

Introduction

Acute myocardial infarction is an event of myocardial necrosis caused by an unstable ischemic syndrome. In practice, the disorder is diagnosed and assessed on the basis of clinical evaluation, the electrocardiogram (ECG), biochemical testing, invasive and noninvasive imaging, and pathological evaluation.^{1,2}

Homocysteine (Hcy) is a detrimental intermediate of cellular metabolism in the human body. An increased level of Hcy in the blood is an indicator of a high risk of stroke. Even more dangerous is the increased risk of stroke compared with the normal population when both blood pressure and Hcy increase.³⁻⁵

This study aims at assessing the role of serum homocysteine levels in predicting degree or severity in patients with acute myocardial infarction.

Methods

This study is an observational cross-sectional study which was performed at Haji Adam Malik General Hospital Medan with permission from Research Ethics Committee of the Faculty of Medicine, Universitas Sumatera



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Utara-RSHAM. Subjects were recruited from April to July 2019 consecutively. The inclusion criteria were patients who were clinically confirmed as acute myocardial infarction and undergoing percutaneous coronary intervention. While exclusion criteria were patients who are receiving methotrexate, carbamazepine, phenytoin, nitrogen oxides, anticonvulsants, 6-azauridine triacetate and patient who refuse to take part in the study.

Study Procedure

Subject's clinical and demographic characteristics who admitted in the ER with acute myocardial infarction as working diagnose were recorded. Blood samples were taken from all subjects upon admission. The samples were then placed in clot activator containing tubes to get the serum and were stored at optimal temperature and kept freeze until examination. Serum Homocysteine levels were studied using Homocysteine Kit by Abbott with chemiluminescence microparticle immunoassay (CMIA) principle. Gensini scores were assessed based on the results of percutaneous coronary intervention.

Statistical analysis

Categorical variables are presented by number or frequency (n) and percentage (%). Numerical variables are represented by mean and standard deviation for normally distributed data, if data not normally distributed, the data shown by median. To compare serum homocysteine levels between low gensini scores (1-29) groups and high gensini scores (> 30) group, Mann Whitney test was conducted. To see the correlation between serum homocysteine levels and gensini scores the Spearman correlation test was used. Receiver Operating Characteristic (ROC) analysis were used to determine the optimal cut-off value for Homocysteine, then Area Under Curve (AUC) were analyzed to assess the prognostic significance. All the data were analyzed using computer statistic software, the value of $p < 0.05$ was said to be statistically significant.

Result

A total of 50 patients with acute myocardial infarction were included in this study. Most of the subjects were men (80%) with average age of 57,34 years old. Subjects with majority of traditional cardiovascular risk factors were seen in this study, such as obesity with overweight, history of hypertension, 70% with history of diabetes mellitus and 62% were smoker, abnormal lipid profile and glucose metabolism profile. Subject with ST-segment elevation myocardial infarction (STEMI) were 60%, and the rest were diagnosed with Non ST-segment elevation myocardial infarction (NSTEMI). Laboratory data and other findings of the subject of this study are presented in table 1.

Table 1. Baseline Characteristics

Variabel	(n:50)
Age (years)	57.34±8.74
Male sex (n,%)	40 (80%)
BMI, kg/m ²	28,4 ± 3,7
Diabetes Mellitus	28 (56%)
Hypertension	23 (46%)
Smoking	35 (70%)
Family History	24 (48%)
Diagnosis	
STEMI	29 (58%)
NSTEMI	21 (42%)
Laboratory Characteristics	
Hb (g/dL)	12,8 ± 2,5
Leukocyte (x10 ³ μL)	12.480 (5.730 – 28.120)
Thrombocyte (x10 ³ μL)	220 (77 – 754)
Fasting blood Glucose Levels (mg/dL)	117(68-370)



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HbA1C (%)	7.2(5-11.6)
Triglycerida (mg/dL)	147(46-347)
HDL (mg/dL)	36.70±12.41
LDL(mg/dL)	129(52-197)
Ureum (mg/dL)	30.04±11.36
Creatinine (mg/dL)	1 (0,54 – 11,2)
PTX3 (ng/mL)	3,1 (0,27 – 10,76)
Homocysteine (µmol/L)	10.28±4.61
Gensini Score	52(6-94)

Mann Whitney U test was used to assess the comparison of Homocysteine levels with the severity of AMI associated with the Gensini score, the value of $p = 0.003$ was obtained (Tabel 2). This shows that there is a significant difference between Homocysteine levels in groups with low gensini scores (mild atherosclerosis) and groups with high gensini scores (severe atherosclerosis)

Table 2. Comparison of Homocysteine IMA levels with the severity of IMA associated with Gensini scores

Variable	Severity of AMI		P
	(Gensini score 1-29)	(Gensini score ≥ 30)	
Homocysteine (µmol/L)	7.67(2.42-16.19)	10.84(4.19-21.93)	0.003*

*Mann Whitney U tests

Table 3. Correlation of Homocysteine levels with severity of IMA is associated with Gensini scores

Variable	p	r
Homocysteine (µmol/L)	0.001*	0.445
Gensini score		

*Spearman correlation test

A ROC analysis was performed to identify serum Homocysteine levels of $>9,19\mu\text{mol/L}$ at admission as the optimal cut-off to predict in-hospital MACEs with a sensitivity of 72%, specificity of 72% (AUC 0,757, 95% CI 0,608 – 0,905 $p=0.003$) (Figure 2).

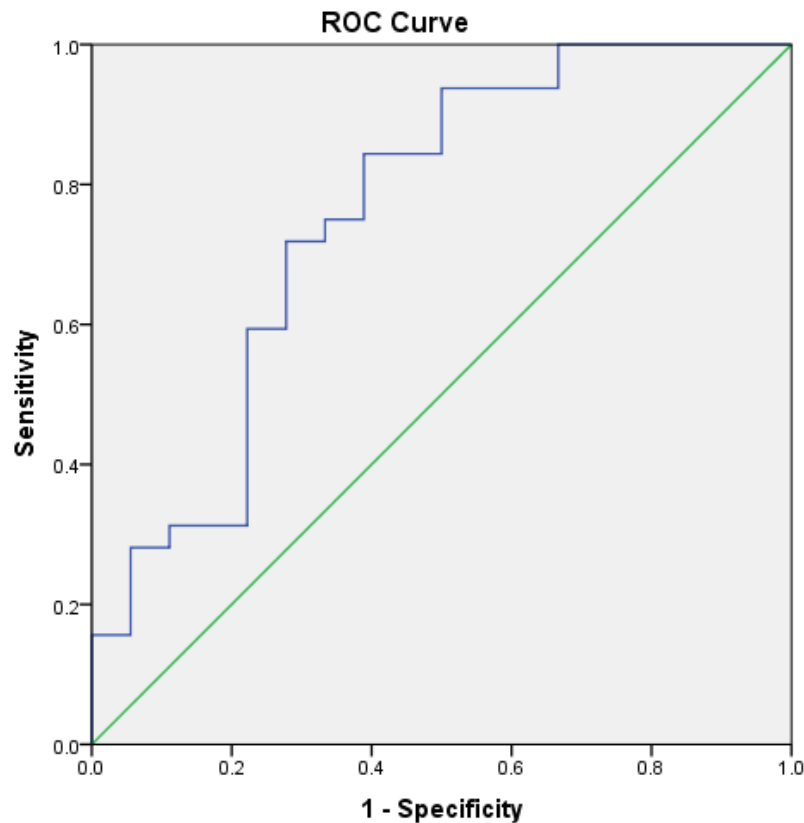


Figure 1. Receiver-operating characteristic curve analysis to assess the performance of Homocysteine rerum on the severity of IMA associated with Gensini Score

Discussion

Acute myocardial infarction occurs due to plaque rupture due to the process of atherosclerosis. Atherosclerosis is a chronic travel process that involves the interaction of various inflammatory processes.⁶ Homocysteine is a sulfur-containing amino acid formed after methionine demethylation, belonging to the intermediate product of the methionine cycle. The earliest reports of metabolic disorders originated from observations of homocystinuria in patients with congenital cystathionine synthase deficiency.⁷ Since then, scientists have also found several other metabolic changes in HCY metabolism of enzymes or coenzymes caused by metabolic disorders. In recent years, with improvements in measurement techniques, HCY in various forms has been measured in normal human plasma and found to be a potential effective factor in the treatment of several ailments including cardiovascular, cerebrovascular and peripheral vascular diseases. HCY metabolic disorders have been found in patients suffering from chronic renal insufficiency, psoriasis and vitamin B12 deficiency as well.⁸⁻¹³

This research is a prospective cohort study to find out the relationship between serum homocysteine levels and Gensini score based on percutaneous coronary intervention in patients with acute myocardial infarction. This research was conducted at RSUP Adam Malik Medan from April to July 2019 and involved 50 samples that met the inclusion and exclusion criteria. Acute myocardial infarction patients in this study consisted of STEMI and NSTEMI.

Based on the results of laboratory examination and coronary angiography examination, it was found that there were significant differences in Homocysteine levels between the IMA group with low Gensini score and the IMA group with High Gensini Score ($p = 0.003$). Likewise, when analyzing the correlation between Homocysteine levels and the severity of the IMA associated with the Gensini score, a significant value with



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moderate relationship strength was obtained ($p = 0.001$, $r = 0.445$). This is in accordance with research conducted by Shenoy which conducted a study of the relationship of serum homocysteine levels with the severity of CAD in Indians. In that study also found a significant correlation between serum homocysteine levels and the severity of CAD based on Gensini scores.¹⁴ Research conducted by Naghshtabrizi regarding Homocysteine levels in patients with CAD who underwent angiography also showed consistent results, where in the study there were significant differences in homocysteine levels between patients with normal patients, Single Vessel Disease, 2 Vessel Disease, and 3 vessel diseases with a p value <0.001 . In that study also found the highest Homocysteine levels in the group with 3 vessel diseases compared with other groups.¹⁵ Research conducted by Kabir on CAD sufferers in Bangladesh also gave almost the same results, where the highest homocysteine levels were found in the group with 3 vessel diseases compared with other groups $p = 0.001$.¹⁶

This is because Homocysteine can cause endothelial dysfunction which is thought to occur mainly from oxidative stress. Research has shown that homocysteine suppresses nitric oxide vasodilators by increasing levels of dimethylarginine asymmetric (ADMA), a strong inhibitor of nitric oxide synthase (eNOS). This mechanism can explain changes in vascular endothelium and changes in platelet coagulation that trigger cardiovascular disease. In various in vitro studies, homocysteine has been shown to trigger the proliferation of vascular smooth muscle cells. The arterial lumen space will be narrower by increasing the smooth vascular proliferation usually considered a dangerous effect for CAD. It also has a role in increasing the activity of HMG CoA reductase which in turn increases cholesterol synthesis. Increased cholesterol levels increase atherosclerosis and risk factors for CAD.¹⁷⁻¹⁹

Homocysteine discrimination performance to determine the degree of severity of myocardial infarction was presented with an AUC value of 75.7% (95% CI = 0.608 - 0.905) which showed moderate discrimination quality. In this study, the cut off point of Homocysteine to predict the severity of IMA with severe atherosclerosis based on Gensini score was $9.19 \mu\text{mol} / \text{L}$. The results of this study show differences with previous studies such as the study conducted by Liu et al (2018) who conducted research on Homocysteine levels in predicting major cardiac events. In that study, the AUC value for homocysteine and GRACE score was 83% in predicting major cardiac events (Liu et al., 2018). Research conducted by Li regarding initial levels of admission to Homocysteine ED in IMA patients in China shows a cut-off value of $17.55 \mu\text{mol} / \text{L}$ with 53% sensitivity and 20% specificity in predicting cases of IMA that can perform spontaneous reperfusion.³ Another homocysteine study conducted by Cesari on homocysteine in cases of CHD with cardiac function associated with risk of death showed the AUC value of homocysteine levels was 62.4% in predicting a decrease in the ejection fraction of poor left ventricles.²⁰ This difference lies in the expected outcome, race and scoring used. This causes this study to have a cutoff value for Homocysteine levels that are lower than other studies.

Conclusion

There was a significant correlation between the severity of the IMA which was associated with the Gensini score. Serum homocysteine levels might be used as a marker to determine high-risk patients with acute myocardial infarction.

Limitation and Suggestion

There is some limitation of this study such as limited sample, no further follow-up after the patient discharged, no sub-group analysis and variation of timing when collecting blood samples for serum homocysteine levels. Further studies may recruit more sample that represent population with longer follow-up, so the exact prognostic significance of serum homocysteine may be useful.

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