



Effect of Homocysteine and Mean Platelet Volume on Jenkins Modified Gensini Score in Acute Myocardial Infarction

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ABSTRACT

Introduction: Coronary heart disease is a leading cause of death in developing countries. The world health organization (WHO) estimates that by 2020 the incidence of coronary heart disease will increase from 7.1 million to 11.1 million. Atherosclerosis is the main cause of coronary heart disease. Several studies reported risk factors for atherosclerosis include smoking, hypertension, diabetes and homocysteine levels. In addition to risk factors such as atherosclerosis, platelets have an important role in developing coronary heart disease in the form of acute coronary syndromes. Increased platelet activity as measured by mean platelet volume (MPV) also increases the incidence of acute coronary syndrome. This study aims to determine the relationship between homocysteine levels and mean platelet volume to the severity of coronary stenosis in patients with acute coronary syndrome.

Method: This is an observational study with a cross-sectional approach and was carried out in June—August 2018. The number of samples in this study were 47 patients. All study subjects who met the inclusion criteria were taken history and physical examination including age, sex, weight, height, blood pressure, history of dyslipidemia, history of diabetes, history of hypertension, and routine laboratory examinations. After that, the subject who met the inclusion criteria had blood samples examination for homocysteine levels and MPV, and

then underwent coronary angiography examination and performed an assessment of the severity of coronary stenosis through Jenkins modified gensini score. Finally, statistical analysis was performed to find correlation between plasma homocysteine and mean platelet volume with Jenkins modified gensini score.

Result: From a total of 47 subjects, 30 patients (64%) were male with an average age of nearly 60 ± 10 years. The value of the lipid profile, cardiac parameters are generally within normal limits. There is an increase in leukocytes above the upper limit value with an average value of $11,600 /\mu\text{L}$. The average value of whole serum homocysteine in the patient is at $12 \mu\text{mol/L}$ with a deviation levels of about $3.1 \mu\text{mol/L}$, while the MPV value is at $9.8 \pm 0.7 \text{ fL}$. In this study, we found that an increase in homocysteine levels of $1 \mu\text{mol/L}$ causing the possibility of individuals experiencing coronary artery stenosis with a gensini score of > 13 by 2-fold. The association between MPV and the severity of coronary artery stenosis showed patients with MPV $9.6-10.5 \text{ fL}$ experienced a reduction in severe lesion odds of $1.000-0.021$ compared to $\leq 9.5 \text{ fL}$. There is a positive relationship between homocysteine levels and the severity of coronary artery stenosis, but the relationship between MPV and severity of coronary artery stenosis has not been fully answered with available data.

Keywords: acute myocardial infarction, homocysteine, mean platelet volume, modified Gensini score

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ABSTRAK

Pendahuluan: Penyakit jantung koroner merupakan penyebab utama kematian di negara berkembang. *The world health organization* (WHO) memperkirakan pada tahun 2020 angka kejadian penyakit jantung koroner akan meningkat dari 7,1 juta ke 11,1 juta. Aterosklerosis adalah salah satu penyebab penyakit jantung koroner. Pada beberapa penelitian melaporkan faktor risiko terjadinya aterosklerosis diantaranya seperti merokok, hipertensi, diabetes dan kadar homosistein. Selain faktor risiko seperti aterosklerosis, trombosit mempunyai peran penting dalam terjadinya penyakit jantung koroner seperti sindroma koroner akut. Peningkatan aktivitas trombosit yang diukur dengan *mean platelet volume* (MPV) juga meningkatkan angka kejadian sindrom koroner akut. Penelitian ini bertujuan untuk mengetahui hubungan kadar homosistein dan *mean platelet volume*

terhadap derajat keparahan stenosis koroner pada pasien sindroma koroner akut.

Bahan dan Metode: Desain penelitian ini adalah observasional dengan pendekatan potong lintang dan dilakukan pada bulan Juni - Agustus 2018. Jumlah sampel pada penelitian ini adalah 47 pasien. Semua subjek penelitian yang memenuhi kriteria inklusi dilakukan anamnesis dan pemeriksaan fisik meliputi usia, jenis kelamin, berat badan, tinggi badan, tekanan darah, riwayat dislipidemia, riwayat diabetes, riwayat hipertensi, dan pemeriksaan laboratorium rutin. Setelah itu dilakukan pengambilan sampel darah untuk pemeriksaan kadar homosistein dan MPV, pemeriksaan angiografi koroner dan dilakukan penilaian derajat keparahan stenosis koroner melalui skor gensini modifikasi Jenkins. Kemudian dilakukan analisis korelasi

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plasma homosistein dan *mean platelet volume* dengan skor gensini modifikasi Jenkins.

Hasil: Dari total 47 subjek penelitian, didapatkan 30 pasien (64%) laki-laki dengan usia rata-rata pada subjek penelitian hampir 60 ± 10 tahun. Nilai profil lipid, parameter jantung pada umumnya dalam batas normal. Terdapat peningkatan leukosit di atas nilai maksimum dengan nilai rata-rata 11.600 /mL. Nilai rata-rata homosistein serum keseluruhan pasien berada pada 12 $\mu\text{mol/L}$ dengan tingkat deviasi sekitar 3,1 $\mu\text{mol/L}$, sedangkan nilai MPV berada pada $9,8 \pm 0,7$ fl.

Pada penelitian ini menunjukkan peningkatan kadar homosistein 1 $\mu\text{mol/L}$ menyebabkan kemungkinan individu mengalami stenosis arteri koroner dengan skor modifikasi gensini > 13 sebesar dua kali lipat. Hubungan MPV dengan keparahan stenosis arteri koroner memperlihatkan pasien dengan MPV 9,6-10,5 fl mengalami reduksi odd lesi berat sebesar 1,000 - 0,021 dibandingkan $\leq 9,5$ fl. Terdapat hubungan yang positif antara kadar homosistein dengan keparahan stenosis arteri koroner, akan tetapi hubungan MPV dan keparahan stenosis arteri koroner belum terjawab penuh dengan data yang ada.

Kata Kunci: Infark Miokard Akut, *homocysteine*, *mean platelet volume*, *modified Gensini score*

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INTRODUCTION

Coronary heart disease is the leading cause of death in developing countries.¹ The world health organization (WHO) estimates that the incidence of coronary heart disease will increase from 7.1 million to 11.1 million in 2020.² Three-quarters of deaths from coronary heart disease in the world are in developing countries.³ The research conducted at RSUP Prof. Dr. R. D. Kandou Manado found 55 cases of acute coronary syndrome (SKA) in 2006; 104 cases in 2007; 166 cases in 2008; 251 cases in 2009; and 354 cases in 2010.⁴ Risk factors and characteristics such as family history, obesity, dyslipidemia, smoking and the process of atherosclerosis are strong predictors of SKA.⁵

Atherosclerosis is one of the causes of SKA. Atherosclerosis affects both genetic and environmental factors. Some studies report an increase in homocysteine associated with the occurrence of early atherosclerosis. McCully also reported that atherosclerosis accompanied by arterial thrombosis was closely related to hyperhomocysteinemia, so in this study it was concluded that the presence of hyperhomocysteinemia increased 13% risk of SKA in the future.⁶

Homocysteine is a sulfhydryl amino acid, a compound formed in the metabolism of essential amino acids methionine, many of which come from animal protein. Increased homocysteine levels cause atherothrombosis. Homocysteine causes oxidative stress, endothelial dysfunction and triggers thrombosis. Epidemiological studies show an increase in plasma homocysteine associated with the incidence of coronary heart disease, stroke and peripheral vascular disease.⁷

Platelets have a central role in the occurrence of SKA associated with plaque rupture in atherosclerosis which causes the formation of intracoronary thrombus which triggers SKA. Increased

platelet activity is associated with a higher risk of SKA. Mean platelet volume (MPV) is the average size of platelets in the blood. MPV values reflect activation of platelets.^{8,9} Increased MPV happens in patients with several cardiovascular risk factors such as smoking, diabetes, and hypertension. A study by Chu et al. showed that an increase in MPV in patients with acute coronary syndrome increases the risk of death.¹⁰⁻¹³

Several studies have shown that increased homocysteine level is an independent factor that is closely related to the severity of lesions.¹⁴⁻¹⁶

Research on the relationship between homocysteine levels and mean platelet volume with the severity of coronary stenosis in patients with acute coronary syndrome is still a controversial. This makes the authors interested in examining the relationship between homocysteine levels and mean platelet volume to the severity of coronary stenosis in patients with acute myocardial infarction in Indonesia.

By knowing the relationship between homocysteine levels and the mean platelet volume with the severity of coronary stenosis in acute myocardial infarction patients, it is expected that the results of this study can be used to help manage patients in the context of primary and secondary prevention of acute myocardial infarction with progression of cardiovascular disease especially the severity of coronary artery stenosis. It is expected that the results of this study can provide additional information on the large increase in homocysteine and MPV levels in acute myocardial infarction and its role in the progression of cardiovascular disease, especially the severity of coronary stenosis to support the hypothesis of the possibility of elevated homocysteine and MPV levels leading to increased coronary stenosis.

METHODOLOGY

Research design

This study is an observational study with a cross-sectional approach in terms of sampling and data collection. The research was carried out in the Department of Cardiology and Vascular Medicine in the Prof. Dr. R. D. Kandou Hospital, Manado, North Sulawesi, Indonesia. The research was conducted from May to July 2018.

Patient

The accessible population of the study was patients with acute myocardial infarction in the emergency department, intensive cardiac care unit, coronary catheterization laboratory and in the inpatient room of Prof. Dr. R. D. Kandou Hospital Manado. Each patient who fulfills the diagnosis criteria of acute myocardial infarction and study inclusion criteria, and does not meet one of the exclusion criteria, will be asked for informed consent to become a research sample.

The inclusion criteria in this study were individuals with acute myocardial infarction (NSTEMI or STEMI), and these individuals were willing to undergo homocysteine, MPV and coronary angiography. The exclusion criteria were stable angina pectoris, unstable angina pectoris, stroke patients, chronic renal failure (CKD-EPI <60 ml/min/1.73 m²), history of malignancy, unwillingness to take part in the study, and non-cooperation patients.

Sample size

The sample size was calculated using the formula for correlation coefficients based on Hulley and Cummings. The minimum sample number obtained from the formula was 47 patients.

Stages of research

After obtaining ethical clearance from Prof. Dr. R. D. Kandou Hospital, this study was conducted in four stages. The first stage is population selection and to those who fulfill the inclusion criteria, informed consent is obtained. The second stage is history taking, physical examination, laboratory test, coronary angiography. The third stage was carried out by Jenkins modification score analysis. The fourth stage is data processing and analysis.

Statistical analysis

The relationship between the two main independent variables, homocysteine and mean platelet volume, with the outcome of the Jenkins modified gensini score as a measure of the severity of coronary artery stenosis in this study was analyzed using a logistic regression model. Modeling results at the univariable (without controlling for other

variables) and multivariable levels complement each other in answering the research questions previously formulated. The choice of control or confounding variables in the multivariable model is based primarily on the importance of getting a relationship between the two main independent variables with the Jenkins modified gensini score, besides looking at the results of univariate analysis and the relative effects of these variables on homocysteine and mean platelet volume. The regression modeling results are reported as odds ratio (OR), lower and upper limit of 95% confidence intervals, CI, and p values.

The description of the research variables is carried out in both univariate and bivariate. Univariate analysis includes assessing the distribution of each variable, including the normality of numerical variables. This evaluation is carried out using graphs such as histograms, boxplots, and density curves, in addition to the Shapiro-Wilk normality test. In the category variable, the distribution is done through a frequency table. The concentration and distribution values are calculated according to the type of variable and distribution normality for numerical ones. For numerical variables with normal distributions, values are given in the form of mean and standard deviation (SD). If distribution abnormalities can be proven, the median value and interquartile range (IQR) are used. For categorical variables, the values displayed are absolute frequencies and percentages. Descriptive bivariate analysis assessed differences in each variable by sex. Tests are carried out by the T test or the Mann-Whitney U test for numerical variables, and the chi-square test for categorical variables.

Most research data management is done in the R statistical software version 3.5.1 application, which is also the main tool for statistical analysis. The R version used in the study has a number of routine procedures for descriptive tabulation and regression modeling.

RESULTS

Basic characteristics of patients

This study was conducted from May to July 2018 to patients with acute myocardial infarction. The characteristics of all research subjects are shown in the characteristics table of patients with acute myocardial infarction. Subjects are generally almost 60 years old with a deviation of around 10 years with 30 people (64%) of whom are men and the rest are women. Lipid profile values such as total cholesterol, HDL, LDL, and triglycerides are generally within normal limits. Similarly, the two kidney function parameters, namely blood urea and creatinine levels, which respectively had a median of 31.0

Table 1 Characteristics of patients with acute myocardial infarction in the study, in mean SD, median (Q1;Q3), dan n (%)

Characteristics	Total (n = 47)		Women (n = 17)		Men (n = 30)		p ^a
	Mean ± SD	Median (Q1;Q3)	Mean ± SD	Median (Q1;Q3)	Mean ± SD	Median (Q1;Q3)	
Age (years old)	58.8 ± 9.7	*	58.2 ± 10.8	*	59.1 ± 9.1	*	0.763
Hemoglobin (mg/dL)	14.2 ± 2.3	*	14.0 ± 1.8	*	14.2 ± 2.5	*	0.751
Leucocytes (x103/μL)	*	11.6 (9.1 ; 13.5)	*	11.6 (9.1 ; 13.6)	*	11.6 (9.0 ; 13.3)	0.690
Thrombocyte (x103 μL)	268.6 ± 70.4	*	292.8 ± 67.9	*	254.8 ± 69.2	*	0.075
Cholesterol (mg/dL)	179.9 ± 46.6	*	194.6 ± 58.8	*	171.6 ± 36.6	*	0.104
HDL (mg/dL)	*	38.0 (35.0 ; 42.5)	*	40.0 (37.0 ; 43.0)	*	37.0 (32.8 ; 41.5)	0.055
LDL (mg/dL)	*	108.0 (85.5 ; 148.0)	*	139.0 (101.0 ; 170.0)	*	103.5 (84.2 ; 138.0)	0.078
Triglycerides (mg/dL)	*	117.0 (95.0 ; 145.5)	*	136.0 (105.0 ; 156.0)	*	112.0 (93.2 ; 144.8)	0.611
Creatinine (mg/dL)	*	1.0 (0.9 ; 1.2)	*	1.0 (0.9 ; 1.0)	*	1.1 (0.9 ; 1.3)	0.114
Ureum (mg/dL)	*	31.0 (25.5 ; 40.5)	*	31.0 (26.0 ; 41.0)	*	30.5 (25.5 ; 39.8)	0.973
Homocysteine (μmol/L)	12.0 ± 3.1	*	10.9 ± 3.0	*	12.6 ± 3.0	*	0.072
MPV (fL)	9.8 ± 0.7	*	9.6 ± 0.7	*	9.9 ± 0.7	*	0.225
≤ 9.5 fL	19 (40%)	*	8 (47%)	*	11 (37%)	*	0.776
9.6-10.5 fL	21 (45%)	*	7 (41%)	*	14 (47%)	*	
>10.5 fL	7 (15%)	*	2 (12%)	*	5 (17%)	*	
Jenkins Modified Gensini Score	16.1 ± 4.4	*	16.5 ± 3.6	*	15.9 ± 4.8	*	0.656
≤ 13	12 (26%)	*	4 (24%)	*	8 (27%)	*	>0.100
>13	35 (74%)	*	13 (76%)	*	22 (73%)	*	

Note: SD standard deviation, Q1 quartile I, Q3 quartile III, HDL high-density lipoprotein, LDL low-density lipoprotein, MPV mean platelet volume. ^aT test or Mann-Whitney U on numerical variables, test χ^2 on categorical variables

Table 2 Logistic regression models for Jenkins modified gensini score with homocysteine levels and mean platelet volume as predictors

Variable	Odds Ratio, OR			
	Score >13 (severe lesion) vs Score 1-13 (mild or moderate lesion)			
	Univariate Model		Multivariate Model ^a	
	OR (95% CI)	p	OR (95% CI)	p
Homocysteine (μmol/L)	12.80 (0.998; 1.641)	0.052	2.287 (1.247; 4.193)	0.008
MPV				
≤ 9.5 fL	1.000		1.000	
9.6-10.5 fL	0.5333 (0.128; 2.225)	0.388	0.021 (0.001; 0.596)	0.024
> 10.5 fL	1.6 (0.147; 17.411)	0.700	1.726 (0.025; 117.462)	0.800

Note: CI confidence interval, MPV mean platelet volume. ^aMultivariate regression analysis controls the variability of age, hemoglobin level, creatinine level, and interaction between serum cholesterol and triglyceride levels.

(IQR 25.5; 40.5) mg / dL and 1.0 (IQR 0.9; 1.2) mg / dL. The overall hemoglobin level of patients is not problematic. The leukocyte count is slightly above the maximum limit value with a median of around 11,600 /μL. Platelet counts are generally relatively normal.

In the main variables of the study, the mean blood homocysteine levels of all patients were as high as 12.0 μmol / L with a variation of approximately 3. μmol / L, while the mean platelet volume was at 9.8 ± 0.7 fL. When using classification according to the categories used in the regression analysis,

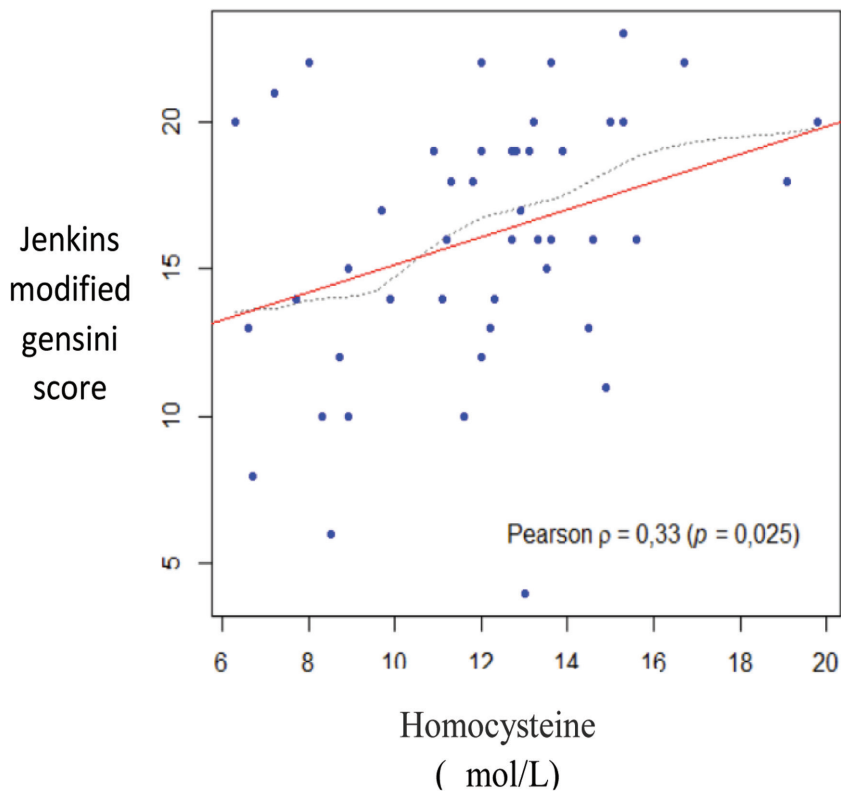


Figure 1 Scatterplot of relationship between homocysteine and Jenkins modified gensini score. The red line is the fit least square curve, while the gray line is the curve of local regression (loess)

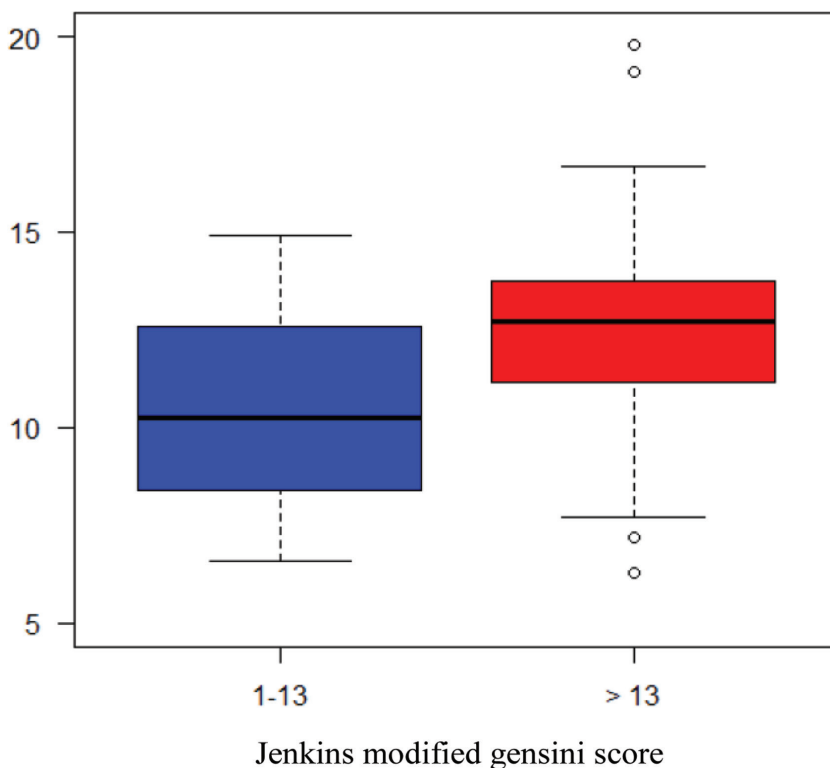


Figure 2 Boxplot of relationship between homocysteine and Jenkins modified gensini score

85% of patients have a mean platelet volume of less than 10.5 fL (Figure 5). All patients had a mean Jenkins modified gensini score with a deviation of slightly above 4 units. Based on grouping the severity of coronary artery stenosis, the majority of patients had severe lesions with a ratio of about 7 to 3 compared to those with mild/ moderate lesions. It should be noted that all patients in this study had a Jenkins modified gensini score above zero, with minimum and maximum values 4 and 23, respectively.

The stratification of patients according to sex in the next section of the characteristics table of patients with acute myocardial infarction shows no statistical differences between the number of men and women on other research variables. The p-value for all patient characteristics was quite large compared to the expected significance level, $\alpha = 0.05$. Blood homocysteine levels in men appeared slightly higher ($p = 0.072$), but the difference is only around $2 \mu\text{mol} / \text{L}$. The quantity of mean platelet volume and Jenkins modified gensini score in both genders is similar, even after the two variables are grouped according to categories in the regression analysis.

Blood homocysteine levels, mean platelet volume and their relationship with Jenkins modified gensini score

Preliminary analysis of the relationship between blood homocysteine levels and Jenkins modified gensini score as a measure of the severity of coronary artery stenosis, as well as between the mean platelet volume and Jenkins modification score or category scale that visually does not change existing correlations (figure 1 shows). However, the correlation between the mean platelet volume and Jenkins modification score requires a more thorough interpretation. On the scatterplot, the relationship between mean platelet volume and Jenkins modification score clarify this complexity (figure 3 shows). The least square fit curve in the image captures the global tendency of the relationship between these two variables as a negative correlation. But the picture shown by the local regression or loess curve reveals a more accurate state. At the mean platelet volume ≤ 9.5 fL, the relationship tends to be negative (higher mean platelet volume, lower Jenkins modification gensini score), where this tendency disappears slightly at the mean platelet volume between 9.6 and 10.5 fL. In this interval the distribution of the Jenkins modified gensini score appears to be quite even so that the relationship between the two variables is relatively constant as indicated by the loess curve. For the mean values

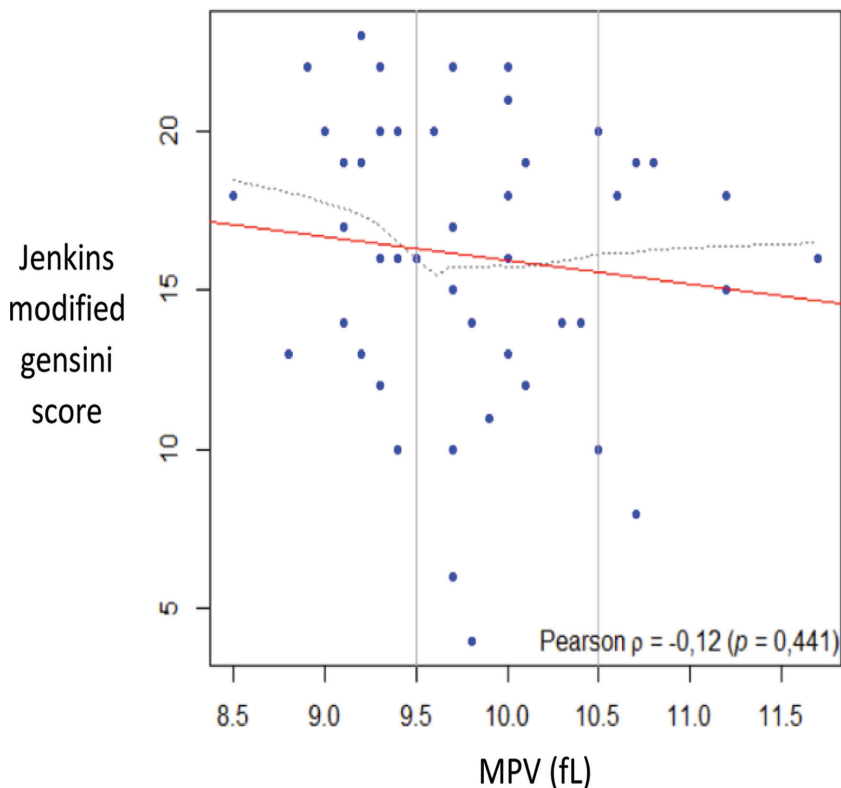


Figure 3 A scatterplot showing relationship between mean platelet volume and Jenkins modified gensini score. The red line is the least fit square curve, while the gray dash is the loess curve

of higher platelet volume, the relationship with the Jenkins modified gensini score begins to change in quality (tends to be positive).

The boxplot about relationship between homocysteine and Jenkins modified gensini score (figure 2 shows) presents the results of the Jenkins modified gensini score modeling by including blood homocysteine levels and mean platelet volume as the main independent variables in the multivariable model. Before other variables are controlled, these two regression predictors do not show a statistically significant relationship. After age, hemoglobin levels, creatinine levels, and serum cholesterol and triglyceride levels were controlled for their effect on outcomes, the relationship that had been visually demonstrated earlier on the scatterplot about the relationship between homocysteine and Jenkins modified gensini score shifted. The logistic regression model for the Jenkins modified gensini score with homocysteine levels and mean volume platelets as predictors showed that for every one $\mu\text{mol/L}$ increase in homocysteine in the blood, the likelihood of individuals experiencing coronary artery stenosis with a Jenkins modification score above 13 rose more than double (95% CI 1.2; 4.2 and $p = 0.008$) after the effects of other variables were controlled. In the same situation,

the relationship between mean platelet volume and Jenkins modified gensini score needs to be divided into two parts: Patients with mean platelet volume between 9.6 and 10.5 fL experience reduced odds of severe lesions (Jenkins modified gensini score > 13) on average by 1,000-0,021 or about 98% ($p = 0.024$) compared to those with a mean platelet volume of 9.5 fL. Conversely, patients with acute myocardial infarction with a mean platelet volume above 10.5 fL tend to increase the odds of severe lesions almost two times, but the relationship is not statistically significant ($p > 0.05$).

DISCUSSION

The study involved 47 patients with acute myocardial infarction including 34 male patients (64%) and 13 female patients. This is in accordance with the research conducted by Sorensen NA et al. and Ayach Bi et al. about the characterization of acute coronary syndromes with the percentage of patients with male sex more than women.^{17,18} Patients in this study had an average age of around 60 ± 10 years. This is consistent with the research conducted by Sorensen et al.¹⁷ with the median age of 61 patients in the study, $p = 0.001$. In the values of lipid profiles such as total cholesterol, HDL, LDL, and triglycerides in general are within normal limit, as well as two-parameter of kidney function namely blood urea and creatinine levels, which respectively had median of 31.0 (IQR 25.5; 40.5) mg / dl and 1.0 (IQR 0.9; 1.2) mg / dl. In this study, the patients had increased leukocytes, slightly above the upper limit with a median of around 11600 / μL . This is in accordance with the research conducted by Munir et al.,¹⁹ and Nunez et al.,²⁰ There was an increase in the number of leukocytes in the incidence of acute coronary syndromes. Increased leukocytes are a sign of infection or inflammation associated with atherogenesis and plaque rupture is formed. So this examination of leukocytes is an independent factor in long-term mortality in acute coronary syndromes. In a study conducted by Nunez et al., The increase in leukocytes was strongly associated with coronary heart disease. Which is a sign of triggered systemic inflammatory response.²⁰

The mean homocysteine levels in this study were 12.0 $\mu\text{mol/L}$ with a variation of approximately 3.1 $\mu\text{mol/L}$. In a study conducted by Auer et al., there was an increase in homocysteine on the first day with a median of 11.9 $\mu\text{mol/L}$ (10.7-12.6).²¹ Research by Astoni et al.²² reported that in the group who died of coronary heart disease, levels were found tHcy averaged 13.1 $\mu\text{mol/L}$. Homocysteine causes an increase in tissue damage more than the effect of prothrombotic state. In several studies,

it was shown that homocysteine adversely affects endothelial vasodilation, thus limiting coronary flow reserves during acute coronary occlusion. However, the concentration of homocysteine can be lowered with folic acid and vitamin B6.²³ Authors hope that there will be further studies in finding out the effects of Vitamin B6 and folic acid in the progressivity of acute coronary syndromes.

The mean value of platelet volume in acute myocardial infarction was 9.8 ± 0.7 fL, this is similar to the study conducted by Erkus et al. which reported higher MPV in acute myocardial infarction compared to the control group (10.7 ± 1.7 fL versus 8.8 ± 1.5 fL; $p < 0.001$).²⁴ In this study, patients had a modified gensini score of 16 ± 4 units, based on the classification of the severity of coronary artery stenosis, the majority of patients had severe lesions with a ratio of about 7 to 3 compared to mild or moderate lesions. This is in accordance with the study conducted by Zhenhong et al. which reported that patients with acute coronary syndrome had severe lesions with gensini score above 20.²⁵

Stratification of patients according to gender showed no difference in the number of men and women towards other research variables. The quantity of mean platelet volume and gensini scores in both gender is relatively similar, even after the two variables are grouped according to the categories in the regression analysis. This is similar to the study from Park et al.²⁶ which reported no significant difference between both genders in mean platelet volume. In this study, homocysteine levels between women and men did not appear to be statistically significant with the mean value of homocysteine levels in men compared to women was differed around $2 \mu\text{mol/L}$. This is similar to the study conducted by Vigo and colleagues who found no significant difference in homocysteine levels between men and women, which was $2.5\text{-}3 \mu\text{mol/L}$.²⁷

Blood homocysteine levels and mean platelet volume and their relationship with Jenkins modified gensini score

The relationship between homocysteine levels and the severity of lesions assessed by Jenkins modified gensini score seemed linear and positive. This is in accordance with the study by Boers et al.²⁸ which reported high plasma homocysteine levels associated with coronary atherosclerosis, also found an increased incidence of myocardial infarction compared to the control group. The study by Nygard et al.²⁹ reported homocysteine levels of 9-14.9 increased the incidence of coronary heart disease by 8.9%, while an increase of > 15 could cause an increased incidence of coronary heart disease by 24.7%. Authors concluded that

increased homocysteine levels had association with an increase in the severity of lesions assessed by the Jenkins modified gensini score. This study also showed an increase in blood homocysteine levels of $1 \mu\text{mol/L}$ caused the possibility of individuals experiencing coronary artery stenosis with over 13 gensini score as much as twice, this was obtained after the effects of other variables were controlled.

The relationship indicated by the mean platelet volume and Jenkins modified gensini score requires a more accurate interpretation. The picture shown on the local regression or loess curve illustrates a more accurate result. At the mean platelet volume of ≤ 9.5 fL, the existing relationship tends to have a higher mean platelet volume compared to the lower Jenkins modified gensini score, where this tendency disappears slightly when the mean platelet volume between 9.6 and 10.5 fL. In this interval, the distribution of the Jenkins modified gensini score appears to be quite even so that the relationship between the two variables is relatively constant as indicated by the loess curve. For the mean values of higher platelet volume, the relationship with the Jenkins modified gensini score begins to change in quality (tends to be positive). This is consistent with a study conducted by Symth et al., which reported that MPV was positively associated with the severity of stenosis in coronary arteries.³⁰ Higher MPV values had a high Jenkins modified gensini score and had more severe and critical lesions simultaneously. Moreover, the study by Murat et al. reported an association between platelet size and the severity of coronary heart disease.¹⁶ The relationship between increased MPV, platelet count, and atherosclerosis severity can be explained by increased metabolic and enzymatic platelet activation and increased mediator secretion by thrombocytes. More severe coronary heart disease causes an increase in the generation of larger platelets with a larger and higher MPV in forming atherosclerotic plaques and can lead to the evolution of atherosclerosis.

Patients with a mean platelet volume between 9.6 and 10.5 fL experienced a reduction in the odds of severe lesions (Jenkins modified gensini score > 13) averaging 1.000 - 0.021 or about 98% ($p = 0.024$) compared to those with mean platelet volume of 9,5 fL; In contrast, patients with acute myocardial infarction with a mean platelet volume of > 10.5 fL tended to have increased the odds of severe lesions almost double, but this relationship did not reach statistical significance ($p > 0.05$). This result is in accordance with the research conducted by Rahmawati et al.³¹ and Sayin et al.³² that there was no relationship

between Jenkins modified gensini score and the mean platelet volume, which may be because the sample size in both studies was less than 100 subjects. In contrast, the research conducted by Reddy et al. showed association between mean platelet volume and gensini score. To note, the study by Reddy et al.³³ was a case-control study with research subjects consist of 173 cases and 191 controls.³³ In this study, we found no significant positive relationship between the mean platelet volume and gensini score.

CONCLUSION

From this study, it can be concluded that: (1) there is a correlation between blood homocysteine levels and the severity of coronary artery stenosis as measured by the Jenkins modified gensini score; (2) there is a relationship between mean platelet volume with the severity of coronary artery stenosis as measured by Jenkins modified gensini score; and (3) the relationship between blood homocysteine levels and severity of coronary artery stenosis has a positive relationship whereas correlation between mean platelet volume and severity of coronary artery stenosis cannot be answered with existing data.

We suggest further research is needed by increasing the number of samples to determine the relationship between mean platelet volume and severity of coronary artery stenosis, regarding blood homocysteine levels that are affected by vitamin B6 and folic acid which can reduce atherosclerosis. We also suggest a research with a bigger sample size to find the relationship between homocysteine levels and the severity of coronary artery stenosis.

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