

# Media Medika Muda

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Volume 2, Nomor 2

ARTIKEL ASLI

Mei – Agustus 2016



## RELATIONSHIP BETWEEN HOMOCYSTEINE PLASMA LEVELS AND AREA OF MYOCARDIAL INJURY IN ACUTE CORONARY SYNDROMES

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### ABSTRACT

**Background:** Increased homocysteine plasma levels are associated with increased thrombosis. Acute coronary syndromes (ACS) is the process of thrombosis in coronary arteries induced by atherosclerosis plaque ruptures, fissures or erosion. The purpose of this study is to analyze the relationship between increased levels of homocysteine in the blood and the area of ischemic injury in myocardium of patients with ACS.

**Methods:** In the frame of Cardio Metabolic Investigation (Carmetin); a cross-sectional study was done among ACS patients (n=40) admitted at Dr. Kariadi Hospital from August to November 2009. Serum homocysteine were obtained by Enzyme Linked Immuno Assay (ELISA) at the arrival. Myocardial injury area were assessed indirectly by levels of cardiac Troponin I (cTnI) at the time of arrival and 24 hours later. Homocysteine levels were divided into quintiles.

**Results:** There were twenty seven male patients (67.5%) and thirteen female patients (32.5%). Eighteen patients (45%) had a negative cTnI (defined as cTnI  $\leq$  0.10 ng/ml), while twenty two patients had positive cTnI (55%) at arrival. At the peak levels, only one patients had a negative cTnI levels. There is significant relationship between homocysteine level and the peak of cTnI level ( $p=0.048$ ). Homocysteine levels were significantly higher in cTnI positive than cTnI negative patients ( $p<0.01$ ).

**Conclusion:** The increased of homocysteine plasma level is associated with increased of myocardial injury area in ACS patients.

### ABSTRAK

Latar belakang:

Metode:

Hasil:

Simpulan:

Kata kunci:

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## INTRODUCTION

Epidemiological studies indicate that increased plasma homocysteine concentrations are associated with increased risk of atheromatous formation in the blood vessels and risk of thrombosis. Coronary artery disease includes either atheromatous lesion formation or thrombosis triggered by plaque rupture, process in patients with acute coronary syndrome.<sup>1,2</sup>

Previous study reported that elevated levels of plasma homocysteine play role as independent risk factor of coronary artery disease.<sup>3</sup> Clear evidence was more prominent in patients with congenital disease of homocystinuria, where cystathionine enzyme  $\beta$ -synthase or methylene tetrahydrofolate reductase were not expressed genetically for homocysteine metabolism. This situation causes increased plasma homocysteine levels and affect the occurrence of atherosclerosis in most blood vessels in the early life.<sup>4</sup> Nygard, O et al in his study proved that elevated levels of plasma homocysteine is a predictor of mortality in patients with proven CHD who underwent catheterization.<sup>5</sup>

Atheromatous lesions mechanism for increased plasma homocysteine is still unclear, but the elevated homocysteine plasma levels and an increased risk of thrombotic have been proven through in vitro and in vivo research, and a lot of researches were done to find the relationship between homocysteine with the factors involved in the coagulation cascade. Homocysteine inhibits expression of trombomodulin on endothelial cell surface, inhibits activation of protein C, induces tissue factor activity, promotes expression of clotting factors II, V, X, and XII, inhibits the binding of antitrombin III and endothelium, reducing the number of receptors on the endothelial tissue plasminogen activator, increasing the binding of lipoprotein (a) to fibrin, enhancing platelet aggregation. The combination of these disturbances will result in increased thrombogenesis.<sup>6,7,8</sup>

Acute coronary syndrome (ACS) consist of ST-segment elevation Myocardial Infarction (STEMI), Non-ST Segment Elevation Myocardial Infarction (NSTEMI) and Unstable angina pectoris (UAP) is a process of thrombus formation in coronary arteries, which is triggered by atherosclerotic plaque rupture, erosion or fissure. The process of atherosclerotic plaque rupture exposing the tissue with blood flow, then the effect is followed by activation of the coagulation cascade to form thrombus.<sup>9</sup>

The aim of this study is to investigate the relationship between homocysteine levels and myocardial injury area of ACS patients.

## METHODS

### Type and Research Design

This study is a part of Cardiometabolic Investigation (Carmetin), the design was cross-sectional of consecutive patients ( $n=40$ ), admitted at the Coronary Care Unit, Cardiac Center of Kariadi Hospital Semarang. Laboratory analysis was done at GAKY Laboratory of Kariadi Hospital Semarang. The study began from August to November 2009.

### Measurement of injured myocardial area and homocysteine

Homocysteine levels were taken from venous blood. Myocardial infarction area was measured indirectly using the levels of cardiac troponin I (cTnI) at admission and 24 hours later. Serum stored in -20C temperatures before measured by the method of enzyme link immune assay (ELISA).

### Data Analysis

Univariate analysis performed to determine the proportion of descriptions, rates, and the standard deviation of each group. Value of troponin I is in the form of quantitative. The data is then divided into 5 homocysteine quintile, the differences between the categories were tested by using Chi Square test. To test the normality of data, one sample Kolmogorov-Smirnov was used. If there is a normal distribution, independent t-test was conducted for two variables and analysis of variance (ANOVA) for more than two variables, whereas if the data distribution is not normal non-parametric test Kruskal-Wallis is used. Data analysis was using SPSS for Windows.

## RESULTS

The number of subjects in this study was 40 patients. Most of the patients were male with age average of 56.3 years. Of 40 subjects of research, the mean homocysteine levels were in quintile 4. At the time of arrival 18 patients were diagnosed with UAP and Non-STEMI as differential diagnose (cTnI <0.1 mcg/liter) while 22 patients were diagnosed with myocardial infarction (cTnI > 0.1 mcg / liter). Of 18 patients with UAP on arrival, 17 patients experienced myocardial infarction by serial measurement of enzyme cTnI. Hypertension is the traditional risk factors that are most commonly found in this study, as much as 62.5% (Table 1).

**Table 1.** Basic characteristic of the study group

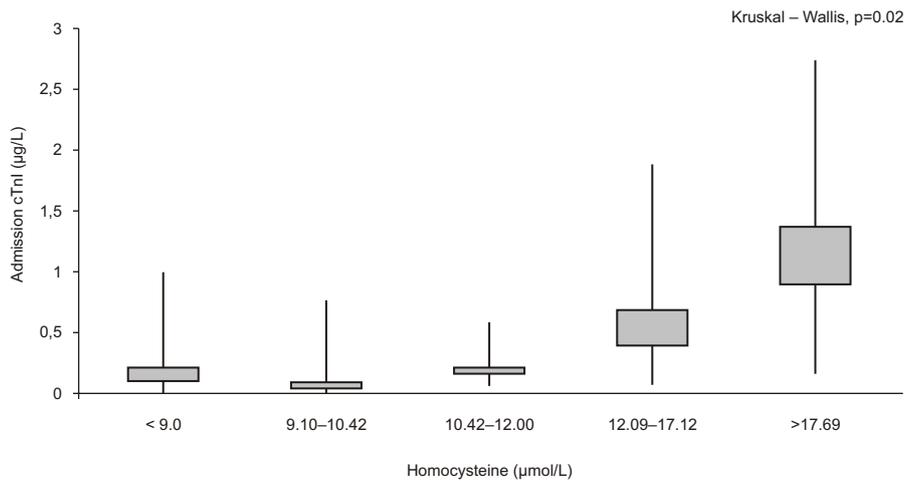
Variabel Studi	All n = 40
Age (years)	56.33 ± 10.6
Male (% total)	67.5 %
Hypertension (% total)	62.5 %
Diabetes mellitus (% total)	20 %
Current smoking (% total)	55 %
Dyslipidemia (% total)	45 %
Homocysteine (µmol/liter)	14.03 ± 8.89
Admission cTnI (µg/liter)	0.7 ± 2.33
Admission cTnI > 0.1 µg/liter (% total)	55 %
Peak cTnI (µg/liter)	2.76 ± 8.48
Peak cTnI > 0.01 µg/liter (% total)	97.5 %

The relationship between homocysteine levels with cTnI levels was first done by dividing plasma

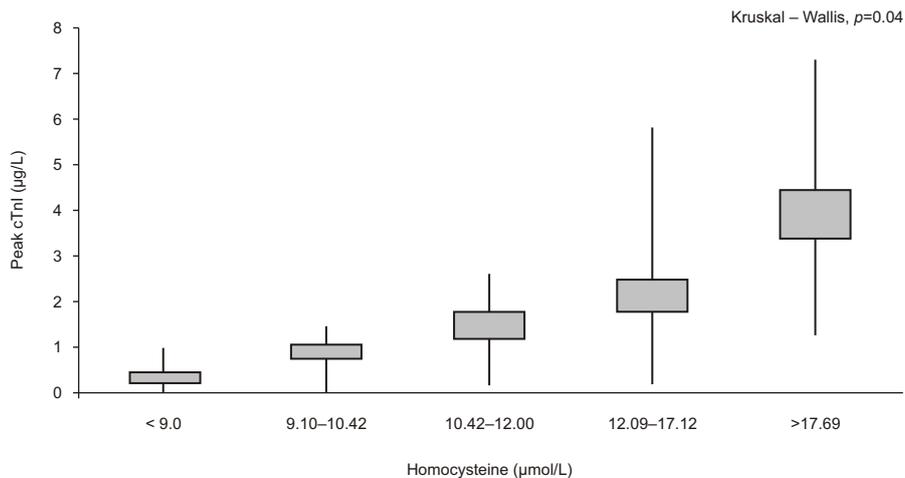
homocysteine levels into quintiles. Figure 1 shows the relationship between the levels of early cTnI with homocysteine levels. There is a significant relationship between the increasing of initial cTnI and homocysteine quintile. (0.15, 0.04, 0.22, 0.69 and 1.3 µg/liter in each quintile homocysteine, Kruskal-Wallis,  $p=0.02$ ).

The relationships between homocysteine concentrations with cTnI still visible on the cTnI peak levels. Figure 2 illustrates the significant relationship between the increase in average peak levels cTnI and homocysteine levels (0.43, 1.05, 0.74, 1.87, and 4.5 µg/liter in each quintile homocysteine, Kruskal-Wallis,  $p=0.04$ )

There is significant difference in homocysteine concentration between admission cTnI negative and cTnI positive in all patients ( $9.6\pm 2.1$  vs  $17.63\pm 10.6$  µmol/liter, respectively,  $p<0.01$ ). Significant



**Figure 1.** Admission cTnI levels by quintiles of homocysteine



**Figure 2.** Peak cTnI Levels by quintiles of homocysteine

difference also seen in homocysteine concentration between peak cTnI negative patients and cTnI positive patients ( $14.22 \pm 8.93 \mu\text{mol/liter}$  vs  $6.7 \mu\text{mol/liter}$ , respectively,  $p < 0.01$ ).

## DISCUSSION

The main purpose of this study is to indicate the relationship between elevated levels of homocysteine with peak cTnI levels of ACS patients. It is assumed that homocysteine as the independent variable and cTnI as dependent variable. There may be arguments that say otherwise. But homocysteine levels did not fluctuate in a few days in patients with acute coronary syndrome.<sup>10</sup>

Although thrombosis is important in the pathophysiology of coronary artery occlusion, myocardial infarction area depends on the interaction of several other factors, such as the duration of ischemia, atherosclerotic plaque characteristics, coronary artery spasm, and collateral flow.<sup>9</sup> Homocysteine can increase the area of infarction injury through its prothrombotic capabilities.<sup>13</sup> Experimental and clinical evidence indicates that homocysteine affect endothelial-dependent vasodilation, and as a result coronary flow becomes limited.<sup>8</sup>

Relationships between homocysteine and cTnI levels are significant both in admission as well as peak cTnI. This fact indicates a consistent relationship between homocysteine with myocardial infarction area. cTnI levels began to rise within 3 to 6 hours to reach the top in 12 and stayed till 4 days. Damage due to necrosis of ischemic myocardium specifically known indirectly through measuring levels of troponin T or I, which under normal circumstances is one of the contractile proteins within cardiac muscle cells. Lysis of myocardium resulted in the issuance of cardiac troponin T or I into the circulation. Today, this marker is used as a standard in determining myocardial infarction because this biomarker specificity and sensitivity are very high, even small areas of necrosis can be detected. Research says that there is an existence of a strong relationship between levels of cardiac troponin T or I with area that experienced extensive necrosis.<sup>9,11,12</sup>

Currently several imaging techniques, including thallium sestamibi, positron emission tomography, and contrast-enhanced magnetic resonance imaging (CE-MRI) are used for quantification of infarct size. Estimation of infarction area could be measured indirectly using cTnI. Previous study had already found correlation between infarct size and cTnI measured 72–96 hours after myocardial infarction.<sup>12</sup>

Homocysteine levels can be lowered by folic acid supplementation, vitamin B12 and vitamin B6 or a combination of nutritional intervention consists of these three vitamins. Those vitamins act on homocysteine utilization has been reported have an effect on cardiovascular risk reduction. Homocysteine is a methylation reaction product which will be converted to methionine with methyltetrahydrofolate assistance, this conversion requires a coenzyme, while vitamin B6 is needed for other mechanisms of homocysteine utilization. Further research is needed to assess the therapeutic effect of homocysteine reduction on the area of myocardial infarction or intervention through these three vitamin diet (alone or combination) or by supplementation.<sup>14</sup>

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