



# The Correlation between Serum Amyloid A, Mean Platelet Volume, and Creatine Kinase Myocardial B in Acute Coronary Syndrome

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## Abstract

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**BACKGROUND:** Atherosclerosis causes acute myocardial necrosis and inflammation characterized by increased mean platelet volume (MPV) and serum amyloid A (SAA). Creatine Kinase Myocardial Band (CKMB) is known as myocardial necrosis marker commonly used in daily practice to help diagnosing acute coronary syndrome.

**AIM:** The purpose of this study was to determine the correlation between MPV, SAA, and CKMB in patients with acute coronary syndrome.

**METHODS:** An analytic observational study with a cross-sectional approach was conducted from May to July 2019. This study involved 32 patients with ACS at the Emergency Department of Dr Kariadi Public Hospital. The inclusion criteria of this study were patients with chest pain, aged 30–75 years, and normal body temperature while the exclusion criteria were malignancy, undergoing chemotherapy/radiation, renal failure, hypertension, and liver disease. Examination of CKMB was done using the spectrophotometry method, MPV value was measured using a hematology analyzer, and SAA level was measured using the ELISA method. Statistical test was done using Spearman correlation.

**RESULTS:** The median (min-max) of MPV and SAA values was 9.85 (2.78-11.7) fL and 40.454 (5.879–66.059)  $\mu\text{g/ml}$ , while the mean  $\pm$  SD (min-max) value of CKMB was  $115.47 \pm 155.97$  (10–608) U/L. The correlation coefficient between CKMB level with MPV and SAA levels were  $r = -0.244$  ( $p = 0.179$ ) and  $r = 0.442$  ( $p = 0.011$ ), respectively.

**CONCLUSION:** There was a significant positive moderate correlation between CKMB and SAA levels which could be used as a marker of acute inflammation in ACS, whereas inflammatory marker of MPV did not have a significant correlation.

## Introduction

Acute coronary syndrome (ACS) is a condition that occurs due to decreased blood flow to the coronary arteries, causing the malfunction of heart muscle with the final consequence of death. The prevalence of coronary heart disease in Indonesia according to the Basic Health Research held by Indonesian Ministry of Health in 2018 was 0.5% or an estimated 883,447 cases of all non-communicable disease patients [1]. According to the American Heart Association (AHA), men and women (age > 50 years) have the same prevalence of coronary heart disease (CHD) as they aged [2]. Acute coronary syndrome manifests as unstable angina pectoris (UAP), non-ST elevation myocardial infarction (N-STEMI), and ST elevation myocardial infarction (STEMI) [3].

Some of diagnostic tools of ACS are creatine kinase MB (CKMB) level measurement and electrocardiographic examinations. CKMB assay is widely used in clinical assessment. CKMB concentration increases begin 3–6 h after damage occurs and reaches the peak between 12 and 24 h forward. CKMB examination has been widely accepted and become

the gold standard for determining the diagnosis of ACS more than 20 years [4].

Mean platelet volume is the average volume of platelets in the peripheral blood circulation. Increased MPV indicates increased metabolic and enzymatic activity, thereby facilitating the formation of intracoronary thrombi. There is a significant difference in MPV in ACS patients that is greater than in non-ACS [5], [6], [7]. The advantages of this parameter examination are that it is relatively affordable, easy to do and available in daily practice. The increase in MPV is directly proportional to the increase in troponin levels so that it can be used as an independent predictor in early detection of ACS [6], [7].

Serum Amyloid A (SAA) consists of an acute phase reactant protein produced by the liver that appears as an acute inflammatory response. SAA levels can increase 1000 times in patients with atherosclerotic plaque and patients with high cardiovascular risk. The higher SAA level in a person increases the risk of cardiovascular disease [6], [7]. A meta-analysis of 26 studies found that high SAA levels were significantly associated with an increased risk of developing coronary heart disease. SAA levels have a positive correlation with C-Reactive Protein (CRP), fibrinogen and Inter Leukin 6 (IL-6), and negatively correlated with High Density

Lipoprotein (HDL) [8]. The SAA levels play a role in the pathophysiology of atherosclerosis. SAA was found as an apolipoprotein in HDL particle and also plays a role in cholesterol transport under physiological stress. SAA has been shown to be chemotactic for monocytes and polymorphonuclear leucocyte (PMN) thus participates in enhancing the migration of monocytes and PMN to inflamed tissues during an acute phase response [9], [10].

Apart from SAA, platelets also have an important role in ACS, especially in atherothrombosis. Plaque rupture is followed by platelet activation, thrombus formation, and coronary artery occlusion. Platelet activation changes the platelet shape and size which can lead to an increase in the MPV value. Atherosclerotic plaque can cause coronary artery occlusion. Increased CK-MB concentrations were found in the occlusion state which was released by necrotic heart muscle as is the case with ACS. Research on the relationship between MPV and SAA levels as a marker of acute inflammation with CKMB levels in ACS needs to be done further which can be used as clinical and biomolecular markers. The purpose of this study was to determine the correlation between MPV, SAA, and CKMB in patients with acute coronary syndrome.

## Methods

This research was an observational analytic study with a cross-sectional design and consecutive sampling method. This research was conducted from May 2019 to April 2020 at Dr. Kariadi Public Hospital Semarang. The CKMB and MPV examinations were performed at the Laboratory of Dr. Kariadi Public Hospital Semarang. The SAA level examination was performed at the Iodine Deficiency Disorders (IDD) Laboratory of the Medical Science Faculty of Diponegoro University (MSFDU) Semarang. This study involved 32 patients who met the inclusion and exclusion criteria. The inclusion criteria of this study were patients with chest pain, aged 30–75 years, normal body temperature (temperature 36.5°C–37.2°C), and willing to participate in this study by signing an informed consent. The exclusion criteria were patients with malignancy, undergoing chemotherapy/radiation, acute or chronic renal failure (serum creatinine level > 2.0 mg/dL), history of hypertension, and history of liver disease.

SAA levels were measured using an enzyme-linked immunosorbent assay (ELISA) method. The normal reference value for SAA is <10 mg/L. MPV measurements were measured using the Sysmex XN-1000 hematology analyzer. MPV normal value is 7.2–11.7 fL. CK-MB levels were determined using the clinical chemical photometry method of dimension RxL max, the normal value of CK-MB was 7–25 U/L.

The data normality test was performed by the Shapiro–Wilk test while the relationship between variables was performed by the Spearman test. The

result of statistical test is significant if  $p < 0.05$ . Ethical clearance was obtained from the Ethical Committee for Medical and Health Research, Faculty of Medicine, Diponegoro University Semarang on December 29, 2019, with No.521/EC/KEPK/FK UNDIP/XII/2019.

## Results

This study involved 40 subjects of ACS patients, as many as eight subjects were excluded from this study because they did not comply with the inclusion criteria where three subjects had fever, two subjects died, and three subjects were over 70 years old. Screening results obtained 32 samples that met the inclusion and exclusion criteria and were willing to sign an informed consent.

Data on the characteristics of research subjects are shown in Table 1.

**Table 1: The characteristics of the study subjects**

Variable	F	%	Mean ± SD (min-max)	Median (min-max)
Age (years)			60.00 ± 9.17 (33–74)	
Sex				
Male	23	71.9		
Female	9	28.1		
Weight (kgs)			76.00 ± 11.70 (60–95)	
Height (cms)			160.19 ± 4.99 (150–170)	
BMI (kgs/m <sup>2</sup> )			29.76 ± 5.27 (20.76–40)	
Diagnosis				
UAP	7	21.9		
STEMI	15	46.9		
NSTEMI	10	31.3		
Systolic blood pressure (mmHg)			137.75 ± 14.19(110–165)	
Diastolic blood pressure (mmHg)			88.44 ± 6.32 (80–100)	
Ureum (mg/dl)			44.41 ± 22.41 (15–96)	
Creatinine (mg/dl)			1.74 ± 3.00 (0.5–1.8)	
Random blood sugar (mg/dl)			186.13 ± 103.14 (85–420)	
AST (U/l)			25.06 ± 4.41 (16–32)	
ALT (U/l)			44.88 ± 10.00 (25–59)	
HDL (mg/dl)			45.12 ± 18.26 (18–95)	
LDL (mg/dl)			107.47 ± 39.72 (67–202)	
Cholesterol (mg/dl)			183.00 ± 53.08 (104–320)	
Triglyceride (mg/dl)			127.87 ± 56.61 (67–256)	
CKMB (U/L)			115.47 ± 155.97 (10–608)	
SAA (mg/L)				40.624 (5.879–66.059)
MPV (fL)				9.85 (2.78–11.7)

F: Frequency; min: Lowest value; max: Highest value.

There is a moderate positive correlation between SAA and CKMB and there is no significant correlation between MPV and CKMB, as shown in Table 2.

## Discussion

Thirty-two subjects in this study were acute coronary syndrome patients. Fourteen subjects had

**Table 2: The correlation between SAA, MPV, and CKMB**

Variable	CKMB (U/L)	
	r	p
SAA (mg/L)	0.442	0.011*
MPV (fl)	-0.244	0.179

\*p < 0.05.

normal body mass index (43.8%), 11 subjects were overweight (34.4%), and seven subjects were obese (21.9%). There were 13 subjects with dyslipidemia (40.6%), 12 subjects with hypertension (37.5%), and eight subjects with hyperglycemia (25%).

Platelets play role in pathogenesis of ACS since the thrombus formation when plaque rupture occurs and also in the progression of infarct. The MPV represents the volume of platelet and remains constant within 4 months, so it can reflect the previous status of patients and may be clinically useful in predicting the onset of ACS. Increasing of MPV may increase adhesivity and tendency of platelet aggregation so that the risk of intracoronary thrombus formation becomes higher. Increased MPV was an indicator for larger and more active platelet, but the prognostic value of MPV still remained to be controversial [11], [12].

There was no correlation between MPV and CKMB in ACS patients in this study. Our study obtained a normal MPV value (9.85) with a reference value of 4–11 fL. The MPV was not correlated with CKMB because the MPV of 29 subjects in this study were normal, but their CKMB levels were increased. Another study also showed that there was no relationship between MPV levels and lesions in acute coronary syndrome ( $p = 0.068$ ) [13]. Another research by De Luca *et al.* also showed that MPV was not correlated with the severity of coronary artery disease in ACS [14].

There was moderate positive correlation between SAA and CKMB in ACS. This condition shows that the increase in SAA levels is directly proportional to the severity of infarct, indicated by increase in CKMB levels. Inflammation that occurs in ACS will cause SAA to be synthesized and produced by the liver in response to the rising of pro-inflammatory cytokine, IL-6. Research by Cabala also showed a positive relationship between SAA and cardiac biomarkers ( $r = -0.39$  and  $p = 0.01$ ) in ACS [15].

Atherosclerosis is the disease primarily responsible for most ACS cases. Atherosclerosis is formed due to plaque which affects the normal mechanism of blood vessels so that occlusion occurs. Coronary artery occlusion will lead to myocardial infarction and extensive muscle tissue necrosis, in which CKMB is released into the bloodstream. The increase in CKMB reflects the process of myocardial damage [16], [17].

This situation will also stimulate an acute inflammatory process characterized by the release of pro-inflammatory cytokines (IL-1, IL-6, and IL-8), tumor necrosis factor (TNF  $\alpha$ ) which will be responded by the liver by producing acute phase proteins, including SAA. The SAA levels can increase by 1000 times, 4–6 h after the inflammatory stimulus, thus making SAA as sensitive marker for inflammatory responses [15], [18].

It is necessary to conduct other studies observing another clinical marker that can be used

to assess acute inflammation in ACS patients. These clinical markers should be easy to check and available at any health facility. However, our research was conducted on ACS subjects with various comorbidity, such as hypertension, kidney disease, and obesity, so it is necessary to do research on ACS with fewer comorbidity.

## Conclusion

There was a significant positive moderate correlation between CKMB and SAA levels which could be used as a marker of acute inflammation in ACS, whereas inflammatory marker of MPV did not have a significant correlation

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