

# Correlation Between AIP, SAA, MPV and Stenosis Degree in Coronary Artery Disease

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## ABSTRACT

**Background:** Dyslipidemia and inflammation play an important role in stable coronary artery disease (CAD) which are marked by atherogenic index of plasma (AIP), serum amyloid A (SAA) and mean platelet volume (MPV) on atherosclerosis formation. The degree of stenosis is measured by visual evaluation of the percentage reduction of coronary diameter relative to adjacent normal segments.

**Aim:** To determine the correlation between AIP, SAA, MPV and degree of stenosis in patients with stable CAD.

**Method:** An observational, analytic study with cross sectional design was carried out in 31 patients with stable CAD at Kariadi Hospital who were willing to sign an informed consent. Triglyceride and HDL were measured by clinical chemistry analyzer to evaluate AIP, while SAA was measured by ELISA method and MPV was measured by hematology analyzer. The stenosis degree was measured by coronary angiography. Spearman test was done for data analysis with  $p < 0.05$  was considered statistically significant.

**Results:** The values of AIP, SAA and MPV were  $0.49 \pm 0.23$ ;  $31.87 \pm 11.41$  mg/ml; and  $10.13 \pm 1.19$  fl respectively, while the median (minimum-maximum) stenosis was 80(20-100)%. The correlation between AIP, SAA and MPV with stenosis degree were  $r = 0.44$ ,  $p = 0.01$ ;  $r = 0.54$ ,  $p < 0.01$ ;  $r = 0.53$ ,  $p < 0.01$ ; respectively.

**Conclusion:** There is significant moderate positive correlation between AIP, SAA, MPV and the stenosis degree in patients with stable CAD. The elevated of AIP, SAA and MPV is directly proportional to the severity of coronary stenosis degree.

**Keywords:** AIP, SAA, MPV, stenosis degree.

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## INTRODUCTION

One of the foremost and first causes of death in both developed and developing countries is cardiovascular disease.<sup>1,2,3</sup> In 2012, an estimated 17.5 million of people die caused by cardiovascular disease. The deaths caused by coronary artery disease (CAD) is estimated at 7.4 million of the total deaths.<sup>4</sup> WHO estimated that there were around 20 million deaths from cardiovascular disease in 2015.<sup>5</sup> Prevalence of CAD diagnosed by doctors in Indonesia according to Indonesian Basic Health Research 2013 was about 0.5% or an estimated 883,447 people.<sup>3</sup>

Coronary artery disease is a cardiovascular disease caused by narrowing of the coronary arteries due to atherosclerosis process. One manifestation of CAD is stable CAD that refers to patients with a diagnosis of CAD who are not experiencing changes in acute symptomatic status.<sup>6</sup> Dyslipidemia can cause activate the formation of atherosclerosis in the coronary arteries. Stable CAD is known as chronic inflammation. Various studies have proven that inflammation symptoms are associated with severity of stable CAD and a worsening cardiovascular outcome.<sup>7</sup>

Plasma atherogenic lipids represent atherosclerotic plaque formation. Measurement of plasma atherogenic lipids is expressed by the atherogenic index of plasma (AIP). This parameter generated from the calculation of logarithms (triglycerides/HDL). The atherogenic index of plasma is a ratio of small dense lipoprotein with HDL fraction that reflect atherosclerosis. A high AIP value indicates an increase in small and dense LDL proportions.<sup>8,9</sup> Research conducted by Dobiasova et al.<sup>10</sup> on CAD patients who had received statin therapy for three

years showed significant differences in AIP values between groups without stenosis and groups with stenosis.

Serum amyloid A (SAA) is produced by the liver as an acute and chronic inflammatory response. Some of evidence reveal that SAA involved in pathophysiology of coronary stenosis, namely SAA is found as apolipoprotein in HDL molecules and shows a chemotactic effect on monocytes.<sup>11</sup> A research by Sudana et al.<sup>12</sup> showed that SAA levels between subjects with coronary stenosis and without coronary stenosis were significantly different.

Platelets are effective markers of the atherosclerotic process. Platelets can interact with endothelial cells and leukocytes because platelets express adhesion molecules and secrete various chemokines and cytokines. Larger platelets contain denser granules and produce more thromboxane A<sub>2</sub>, which is more thrombogenic than small platelets.<sup>13,14</sup> Mean platelet volume (MPV) is a sign that indicates platelet function and activity.<sup>15</sup> Research by Ekici et al.<sup>16</sup> proved a significant positive correlation between MPV and the severity of stenosis in CAD patients evaluated by angiography.

Some previous studies only used one or two laboratory parameters and one clinical parameter, whereas this study uses three laboratory parameters and one clinical parameter, namely AIP values, SAA levels, MPV values, and coronary stenosis levels in the study population with stable CAD patients. Many studies investigated the correlation of laboratory parameters with the complexity of coronary lesions from coronary angiography results using Syntax scores and Gensini scores, but only limited studies determined the correlation between laboratory parameters with quantitative degrees of stenosis based on the percentage obtained from coronary angiography.

The objective of this study is to determine the correlation between AIP, SAA, MPV and the coronary stenosis degree in stable CAD. These laboratory parameters are expected to detect early coronary lesions in CAD, which are non-invasive examination. Furthermore, determination of the stenosis degree in this study was based on the percentage of the coronary stenosis degree quantitatively obtained from the coronary angiography.

## MATERIAL AND METHODS

An observational, analytic study with cross sectional design was carried out in Central General Hospital Dr. Kariadi Semarang. Research subjects consist of patients with a diagnosis of stable CAD who would undergo coronary angiography. The subjects were determined by consecutive sampling in February 2018. The patients were those who met the inclusion and exclusion criteria of the study. Inclusion criteria included stable CAD patients aged over 40 years old, normal body temperature, normal liver function and had never undergone Percutan Coronary Intervention. Patients who were experiencing an attack of acute coronary syndrome, active smokers, coronary angiography examination showed normocoronary (0% stenosis), patients who took clopidogrel, patients with malignancy or a history of chemotherapy and undergoing chemotherapy were not included in this study.<sup>16,17,18</sup> As many as 31 research subjects were agree to join this study and suitable with the study criterias.

Complete blood count examination with Sysmex XN-1000 and clinical chemistry examination with Dimension RxL Max were carried out in the Laboratory of Central General Hospital Dr. Kariadi Semarang. Examination of SAA levels with the ELISA method was done in the GAKI Laboratory Faculty of Medicine Diponegoro University. Coronary angiography was performed in Central General Hospital Dr. Kariadi Semarang. The degree of coronary stenosis was expressed as a percentage and was measured by visual evaluation of the percentage reduction of coronary diameter relative to adjacent normal segments. Coronary angiography and its readings were performed by two Cardiologists.

The independent variables were AIP, SAA and MPV values, while the dependent variable was the coronary stenosis degree. Data were analyzed by using the Spearman correlation to determine correlation AIP, SAA, MPV and the stenosis degree in stable CAD patients. Statistical results were significant if  $p < 0.05$ . This research had received an Ethical Clearance from the Health Research Ethics Commission of Medical Science Faculty of Diponegoro University/Central General Hospital Dr. Kariadi Semarang. Informed consent signed by all research subjects.

## RESULTS

This study involved 31 people consisting of 19 men (61%) and 12 women (39%). Table 1 shows the characteristics of research subjects. The average age of the research subjects was  $56.74 \pm 7.11$  years. The mean of MPV values, AIP levels and SAA levels in the study subjects were

$10.13 \pm 1.19$  fl,  $0.49 \pm 0.23$  and  $31.87 \pm 11.41$  ng/ml, respectively. The degree of stenosis had a median of 80% with a range of 20-100%. Shapiro-Wilk test was used to determine the normality of the data. Data which were normally distributed included age, systolic pressure, BMI, hemoglobin, leukocytes, platelets, MPV, SGPT, triglycerides, HDL, AIP and SAA. Data that were not normally distributed consisted of diastolic pressure, fasting plasma glucose, cholesterol, LDL and stenosis degree.

Most of the subjects in this study were stable CAD patients with risk factors as can be seen from table 2. They were dyslipidemia, hypertension, history of active smokers and diabetes mellitus. Research subjects who were accompanied by dyslipidemia were 16 persons (51.6%), subjects with hypertension were 14 persons (45.2%), subjects with a history of active smokers were 14 persons (45.2%) and subjects with diabetes mellitus were 13 persons (41.9%).

Bivariate correlation test of AIP, SAA and MPV with stenosis degree by using Spearman correlation were shown in table 3. The correlation test between AIP, SAA and MPV with stenosis degree showed a significant moderate positive correlation with  $r = 0.44$ ,  $p = 0.01$ ;  $r = 0.54$ ,  $p < 0.01$ ;  $r = 0.53$ ,  $p < 0.01$ ; respectively.

Table 1. Characteristics of research subjects

Subject Characteristics	Average $\pm$ SD	Median (min-max)
Age (Year)*	56.74 $\pm$ 7.11	57 (43-78)
BMI (kg/m <sup>2</sup> )*	24.83 $\pm$ 3.41	24.7 (17.0-31.2)
Systolic pressure (mmHg)*	133.48 $\pm$ 18.59	135 (100-170)
Diastolic pressure (mmHg)	79.52 $\pm$ 8.59	80 (65-100)
Hb (g/dl)*	14.31 $\pm$ 1.91	13.90 (10.0-18.70)
Leukocyte count (x10 <sup>3</sup> / $\mu$ l)*	8.27 $\pm$ 1.77	8.05 (4.65-11.80)
Platelet count (x10 <sup>3</sup> / $\mu$ l)*	268.35 $\pm$ 66.44	259 (164-454)
MPV (fl)*	10.13 $\pm$ 1.19	10.20 (6.90-12.20)
SGPT (U/l)*	24.8 $\pm$ 5.7	25 (15 - 34)
Fasting plasma glucose (mg/dl)	147.97 $\pm$ 58.76	137 (93-390)
Cholesterol (mg/dl)	174.84 $\pm$ 49.20	156 (104-283)
LDL (mg/dl)	114.97 $\pm$ 36.36	106 (60-190)
Triglycerides (mg/dl)*	124.77 $\pm$ 44.90	116 (60-216)
HDL (mg/dl)*	39.68 $\pm$ 12.17	40 (13-67)
AIP*	0.49 $\pm$ 0.23	0.44 (0.15-0.99)
SAA (ng/ml)*	31.87 $\pm$ 11.41	31.02 (14.43-56.23)
Degree of stenosis (%)	63.87 $\pm$ 23.33	80 (20-100)

\* Normal distribution data with  $p > 0.05$  using Shapiro-Wilk SD: Standard Deviation, min: lowest value, max: highest value

Table 2. Stable CAD risk factors of subjects

Risk factor	n	%age
Dyslipidemia	16	51.6
Hypertension	14	45.2
Active smoker history	14	45.2
Diabetes mellitus	13	41.9

Table 3. Correlation between AIP, SAA, MPV and coronary stenosis degree

Paramater	Coronary Stenosis Degree	
	r	p*
AIP	0.44	0.01
SAA	0.54	< 0.01
MPV	0.53	< 0.01

\*Significant correlation if  $p < 0.05$

## DISCUSSION

The mean age of the study subjects was 56.74 years old with a standard deviation of 7.11. The youngest age was 43 years old and the oldest was 78 years old. This is in accordance with Basic Health Research 2013, the prevalence of CAD increases along with age.<sup>3</sup> Increased age is associated with changes in structure in the coronary arteries, namely the arterial wall becomes more rigid. Moreover, changes in molecular biology in elderly patients also cause arterial endothelial dysfunction.<sup>19</sup> The study subjects consisted of 19 (61%) men and 12 (39%) women. The effect of estrogen protects women from the risk of CAD. Inflammation is an important element of atherosclerotic pathogenesis. The estrogen cause an increase in expression of superoxide dismutase and inhibit NADPH oxidase, thereby it reduces oxidative stress.<sup>20</sup>

Some research subjects have risk factors for CAD, namely dyslipidemia, hypertension, history of active smokers and diabetes mellitus. The role of dyslipidemia is very important in the atherosclerosis process that triggers CAD.<sup>9</sup> High blood pressure for a long time can damage blood vessel walls and make blood vessels more susceptible to plaque constriction and buildup associated with atherosclerosis. CAD is one of the macrovascular complications of diabetes mellitus.<sup>21</sup> Exposure to cigarette smoke molecules causes blood vessel walls to release inflammatory mediators and cytokines which indirectly cause damage to the blood vessel walls. Research subjects were currently not smoking because researchers exclude subjects who were active smokers to reduce the bias of examination results of AIP and MPV values.<sup>12,16,22</sup>

The result of the correlation test between AIP value and the coronary stenosis degree in this study was a significant moderate positive correlation. This value indicated an increase in AIP value is directly proportional to the severity of coronary stenosis degree. The migration of plasma lipids to the tunica intima layer is an important process in the formation of atherosclerosis. Atherogenic dyslipidemia that has been known includes an increase in triglycerides, an increase in free fatty acids, a decrease in HDL cholesterol and an increase in small dense LDL.<sup>8,9,10</sup>

AIP values were obtained from  $\log(TG/HDL)$ . The AIP parameter is an indicator of the ratio of small dense lipoprotein with HDL fractions that reflects the presence of atherosclerosis.<sup>8,23</sup> Small and dense LDL molecules tend to be atherogenic because they stay longer in the plasma, making it easier to bind to the scavenger receptor. Scavengers receptors that have been bound to LDL will be taken to macrophages in the arterial wall layer and then undergo oxidation to form foam cells and eventually form atherosclerotic plaques.<sup>8,9</sup> This is in accordance with the study by Dobiasova, *et al.*<sup>10</sup> which proved that AIP values

between groups without coronary stenosis and groups with coronary stenosis were significantly different.

The results of the correlation test between SAA levels and the coronary stenosis degree in this study were significant moderate positive correlation. This value indicated that the increase in SAA levels was directly proportional to the severity of coronary stenosis degree. Chronic inflammatory condition that occurred in stable CAD caused SAA to be synthesized and secreted by the liver in response to cytokines produced by macrophages, interleukin-6.<sup>12</sup>

Serum amyloid A removes apo A-1 from HDL to form larger and denser HDL molecules, thereby reducing the ability to catalyze cholesterol esterification. The SAA-HDL bond is unable to prevent LDL oxidation, even strengthens the appearance of foam cells and then it becomes fatty streak which is the beginning of the development of coronary stenosis. SAA molecules can be distributed also in LDL particles, the interactions between SAA and LDL catalyzed by reactive oxygen species. Early onset of plaque with extracellular lipid content and small cholesterol ester and thick fibrous capsules with stable plaque characteristics lead to stable CAD with elevated SAA levels. This research results were in accordance with the research of Sudana, *et al.* which proved that SAA levels between groups of subjects with coronary stenosis and without coronary stenosis were significantly different. SAA was present at every stage of atherosclerosis development. SAA levels in coronary stenosis will be higher than are not stenosis.<sup>12,24,25</sup>

The results of the correlation test between MPV value and coronary stenosis degree in this study were significant moderate positive correlation. This value indicated an increase in MPV value directly proportional to the severity of coronary stenosis degree. The platelet indices are an important marker for evaluating platelet function and screening for risk factors for certain diseases including Stable CAD. The MPV is one of examination of the platelet indices and currently MPV examination has become a routine check.<sup>15</sup>

MPV value as a marker of platelet activity and its function, it can assess platelet aggregation, platelet factor 4, thromboxane A2 formation and  $\beta$ -thromboglobulin secretion.<sup>16</sup> Critical platelet surface molecules are needed to interact with leukocytes, endothelial cells, and matrix molecules thus affecting atherogenesis.<sup>14,15</sup> The increase of MPV causes a prothrombotic condition as well as expression of molecular adhesions, such as p-selectin and glycoprotein IIb/IIIa and release of  $\beta$ -thromboglobulin. Inflammatory conditions that occur in stable CAD caused the platelet size formed tended to be larger.<sup>9,14</sup> The results of this study were in accordance with the study by Ekici *et al.*<sup>16</sup> who reported a positive significant relationship between MPV and severity of stenosis in CAD patients evaluated by angiographic examination based on Syntax scores and Gensini scores.

## CONCLUSION

There was significant moderate positive correlation between AIP, SAA, MPV and stenosis degree in stable CAD patients. The elevated of AIP, SAA and MPV was

directly proportional to the severity of coronary stenosis degree. A further study is needed to analyze the parameters of AIP, SAA and MPV as a diagnostic marker of coronary stenosis.

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