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The Correlation between Neutrophil Lymphocyte Ratio, C-reactive Protein, and Serum Amyloid a with the Degree of Stenosis in Acute Coronary Syndrome

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Abstract

BACKGROUND: Inflammation plays a central role in the pathophysiology of acute coronary syndrome (ACS), involving neutrophils as non-specific markers of inflammation and lymphocytes as regulatory markers, measured in the form of neutrophil lymphocyte ratio (NLR). C-reactive protein (CRP) plays a role in the blockage of heart arteries and serum amyloid A (SAA) plays a role in the pathophysiology of coronary stenosis.

AIM: The study aimed to determine the correlation between NLR, CRP, and SAA levels with the degree of coronary artery stenosis in ACS.

METHOD: The design of this study was cross-sectional. The target population in this study was patients with ACS in Dr. Kariadi Hospital Semarang. We performed an NLR measurement with a hematologic analyzer, CRP, and SAA levels using the ELISA method, and coronary angiography using the Gensini score. Furthermore, we also performed the Spearman correlation test between variables.

RESULTS: The median (min; max) values of NLR, CRP, SAA levels, and Gensini score were 4.39 ± 0.48 (0.36; 18.17); 8.63 ± 2.22 (5; 105.11) mg/dL; 36.859 (3.909–69.724); 65 (6–178), respectively. The correlation between NLR, CRP, and SAA levels with the Gensini scores was r = 0.064, p = 0.595; r = 0.240, p = 0.044; r = −0,164, p = 0.171, respectively.

CONCLUSION: CRP measurement could be used as a marker of inflammation in ACS to manage the inflammation process. Furthermore, SAA levels were clinically useful biomolecular parameters in evaluating acute inflammation in ACS, although it did not correlate with the Gensini scores.

Introduction

Acute coronary syndrome (ACS) is a major health problem in both developed and developing countries [1], [2]. The prevalence of coronary heart disease (CHD) in Indonesia, according to the Basic Health Research of Health Research and Development Agency in 2013, was 0.5% or 883,447 cases of all non-communicable disease patients. The prevalence of ACS in Central Java was 0.5% or 120,447 cases [3]. Based on the American Heart Association (AHA) data, men and women (aged >50 years) have the same prevalence of CHD as they age [4], [5].

ACS is a cardiac emergency with clinical manifestations of chest pain or other symptoms as a result of myocardial ischemia. Clinical manifestations of ACS could be unstable angina pectoris, non-ST-elevation myocardial infarction (NSTEMI), and ST-elevation myocardial infarction (STEMI) [6]. According to the AHA, the American College of Cardiology, and the European Society of Cardiology, the diagnosis of ACS can be established based on history taking, 12-Lead ECG examination, and increased cardiac markers. The diagnosis of ACS made when two out of three criteria met [4], [6], [7].

Inflammation plays a central role in the pathophysiology of ACS. ACS is often associated with atherosclerotic plaque rupture and total or partial occlusions of arterial infarction [8]. Increased inflammatory markers, especially C-reactive protein (CRP), are associated with an increased risk of cardiovascular events. Previous studies showed that CRP was not only a marker of inflammation but also having an active role in atherogenesis [9]. Haidari *et al*. investigated the correlation between CRP serum levels and CHD by angiography of 450 individuals. CRP levels in patients with CHD were significantly higher than the patients in the control group (2.14 mg/L vs. 1.45 mg/L), and this correlation indicated an inflammatory process in CHD [10], [11].

Neutrophil lymphocyte ratio (NLR) is a combination of inflammatory markers, consisting of neutrophils as non-specific markers of inflammation and

lymphocytes as regulatory markers. NLR has a better predictive value compared to total leukocyte count or neutrophil type count as a marker of cardiovascular disease and has been introduced as a potential marker for detecting inflammatory processes in cardiac abnormalities and as a predictor of long-term mortality in ACS patients [12].

Serum amyloid A (SAA) consists of an acute phase reactant protein produced by the liver as an acute and chronic inflammatory response. The production of SAA is due to the response to cytokines of IL-6 whose levels can increase 1000 folds [13], [14]. SAA played a role in the pathophysiology of atherosclerosis and coronary stenosis. Some studies also found SAA as apolipoprotein in HDL particles and played a role in the acute modification of cholesterol transport during physiological stress. SAA also showed the chemotactic effects on monocytes. Previous studies showed that there were significant differences in SAA levels between subjects with coronary stenosis and without coronary stenosis [13], [14], [15].

The process from atherosclerosis to the occurrence of ACS is chronic inflammation. Therefore, we used the laboratory parameters of NLR, CRP, and SAA in the study as inflammatory markers of ACS. These parameters were related to the occurrence of atherosclerosis. NLR can be an important measure of inflammation in ACS due to its cost-effectiveness, availability, and easy calculation. Furthermore, NLR, CRP, and SAA measurements are non-invasive laboratory tests expected to detect the early occurrence of chronic processes in stable CHD. Determination of the degree of stenosis used in this study was quantitatively obtained from the results of coronary angiography or cardiac catheterization and calculated using the Gensini score. The score was easy to calculate and more applicable. Based on these theories, the study aimed to determine the correlation between NLR, CRP, and SAA levels with the degree of coronary artery stenosis in ACS.

Methods

This study was an analytical observational study with a cross-sectional design conducted at Dr. Kariadi Hospital Semarang from April to September 2019. The subjects of the study were 32 patients diagnosed with ACS by Cardiologists and underwent coronary angiography. There were many refusals of the ACS patient to join this research so that the sample number was small. We performed consecutive sampling on subjects who met the inclusion and exclusion criteria of the study. The inclusion criteria were man, normal body temperature, and underwent coronary artery angiography. The exclusion criteria were a history of cancer, underwent chemo/radiotherapy, past infection, history of ACS, history of liver disease, coagulation impairment, hypercholesterolemia, and autoimmune. We collected the data from history taking, physical examination, ECG examination, angiography examination, and laboratory examination. We also measured urea and creatinine levels to ensure the study subjects did not experience impaired kidney function that could affect SAA levels.

NLR was the result of a comparison between absolute neutrophil count and absolute lymphocyte count. The measurements of absolute neutrophil count and absolute lymphocyte count were performed using a Sysmex XN-1000 hematology analyzer (Sysmex, Japan). We measured the CRP serum levels using the hsCRP ELISA method, expressed in mg/L units. The measurement of the CRP serum levels was performed using an i-Chroma device with a reference value of <5 mg/L (Boditech Med Inc., South Korea). Furthermore, we measured the SAA serum levels using the ELISA method (AssayMax™ Human SAA ELISA Kit, Assay Pro). The SAA serum levels were expressed in μg/mL units with the reference values of ≤6 μg/mL. The degree of coronary artery stenosis obtained from coronary angiography was expressed based on the Gensini score, which is interpreted by two Cardiologists after conducting an agreement test.

We processed the data using SPSS and conducted a normality test. The correlation between variables was analyzed using the Spearman test. Statistical test results were significant if the $p < 0.05$. This study obtained ethical approval from the Ethics Commission of the Faculty of Medicine of the Diponegoro University. All of the participants gave written consent to participate in this study.

Results

During the study, we found 32 subjects, consisting of 27 (84.4%) men and 5 (15.6%) women. A total of 12 (37.5%) subjects had a diagnosis of NSTEMI and 20 (62.5%) subjects had a diagnosis of STEMI. The mean age of the study subjects was 58.8 ± 11.12 years with a range of 32-73 years. Table 1 shows the characteristics of the study subjects.

We classified the severity of coronary lesions into mild, moderate, and severe based on the modified Gensini score. There were 5 (16%) subjects with mild coronary lesions, 10 (31%) subjects with moderate coronary lesions, and 17 (53%) subjects with severe coronary lesions, as presented in Table 2.

Most of the study subjects were STEMI patients (62.5%) with risk factors of smoking, hypertension, diabetes mellitus, and dyslipidemia.

Table 1: The characteristics of the subjects of the study

Parameter	Mean±SE	Median (Min–Max)
Age (years)	60±1.20	
Total cholesterol (mg/dl)		185 (150–250)
Triglycerides (mg/dl)		142 (100–255)
LDL (mg/dl)	120±3.95	
HDL (mg/dl)		37 (30–57)
Systole (mmHg)		137 (90–178)
Diastole (mmHg)		82.5 (59–110)
Urea (mg/dl)		32 (13–96)
Creatinine (mg/dl)	1.1±0.24	
Random blood glucose (mg/dl)		160 (87–420)
ANC	9.37±0.43	
ALC		1.82 (0.54–12.01)
NLR		4.39 (0.36–18.17)
CRP levels (mg/dl)		8.63 (5–105.11)
SAA levels		36.859 (3.909–69.724)
Gensini score		65 (6–178)
Troponin		18.29 (0.045–50)

Comments: SE, Standard error; min: minimal value; max: maximal value. NLR: Neutrophil lymphocyte ratio, CRP: C-reactive protein, SAA; Serum Amyloid A.

Among the subjects of the study, 15 (46.87%) were smokers, 18 (56.25%) had dyslipidemia, 19 (59.37%) had hypertension, 6 (18.75%) had hyperglycemia, and 12 (37.5%) had a history of diabetes mellitus. Table 3 shows the distribution of risk factors in the subjects of the study.

Table 2: The degree of coronary artery stenosis

Degree of coronary artery stenosis	Number	Percentage
Mild	5	16
Moderate	10	31
Severe	17	53

We performed a bivariate correlation test between NLR, CRP, and SAA parameters with the degree of stenosis using the Spearman correlation test. Table 4 shows the results of the correlation test.

Table 3: The risk factors of ACS

Risk factors	Number (patients)	Percentage
Dyslipidemia		
Yes	18	56.25
No	14	43.75
Hyperglycemia		
Yes	6	18.75
No	26	81.25
Hypertension		
Yes	19	59.37
No	13	40.63
Smoking		
Yes	15	46.87
No	17	53.13
Diabetes mellitus		
Yes	12	37.5
No	20	62.5

ACS: Acute coronary syndrome.

The result of the Spearman correlation test showed no correlation between NLR and the degree of stenosis ($r = 0.064$; $p = 0.595$). In the other hand, the Spearman correlation test between CRP levels and the degree of stenosis showed a weak positive correlation ($r = 0.240$; $p = 0.044$). The correlation test between SAA levels with the degree of stenosis using the Spearman correlation test showed $r = -0.164$ with a $p = 0.171$, meaning that there was no correlation between them.

Table 4: The correlation between NLR, CRP, and SAA levels with the Gensini score

Parameters	Gensini score	
	r	p
NLR	0.064	0.595
CRP levels	0.240	0.044
SAA levels	−0.164	0.171

The correlation was significant if $p<0.05$. NLR: Neutrophil lymphocyte ratio, CRP: C-reactive protein, SAA: Serum Amyloid A.

Discussion

The mean age of the study subjects was 58.8 ± 11.12 years, with the youngest age was 32 years, and the oldest was 73 years. This result was consistent with the results of the 2013 Basic Health Research, in which the prevalence of ACS increased with age [3]. Increased age is associated with structural changes in the coronary arteries, in which the arterial walls become stiffer. Furthermore, the changes in molecular biology in elderly patients also cause arterial endothelial dysfunction. The study subjects consisted of 27 (84.4%) men and 5 (15.6%) women, which indicated that the incidence of ACS was more common in men than in women. This result was consistent with the study of Montalescot *et al*. (2013), in which 83.7% of the ACS cases found in men [16]. Men tend to have a greater risk of CHD than women in adulthood. The incidence of ACS in premenopausal women was lower than those in men and postmenopausal women due to their hormonal factors. Premenopausal women had endogenous estrogen, which provided a protective effect against CHD [17]. Some study subjects had risk factors of ACS, namely smoking, diabetes mellitus, hypertension, hyperglycemia, and dyslipidemia. The result of the study found that 19 (59.37%) of the subjects had hypertension. The mean systolic pressure of the subjects was 136.37 ± 25.25 mmHg with a median of 137 (90–178) mmHg, while the mean diastolic pressure was 84.53 ± 15.09 mmHg with a median of 82.5 (59–110) mmHg. Chronic high blood pressure can damage blood vessel walls and make it more susceptible to narrowing and plaque deposition, which is associated with atherosclerosis [8].

CHD is a macrovascular complication of diabetes mellitus. Atherosclerotic lesions in diabetes mellitus occur due to hyperglycemia, which causes endothelial dysfunction. The hyperglycemia state will increase the tendency for oxidative stress and an increase in oxidized LDL, which is more atherogenic [18], [19]. The mean fasting blood glucose level of the study subjects was 153.17 mg/dl, with a median of 160 (87–420) mg/dl. In this study, 12 (37.5%) subjects had type 2 diabetes mellitus.

The role of dyslipidemia is essential in the process of atherosclerosis, which triggers the occurrence of ACS. Dyslipidemia, defined as abnormalities in lipid metabolism, is characterized by an increase or decrease in plasma lipid fractions. Lipid fraction abnormalities include an increase in total cholesterol, LDL cholesterol, and triglycerides levels and decreased HDL levels [20]. The measurement of lipid profiles in the study showed that 18 (51.6%) subjects had dyslipidemia. Grundy *et al*. (2009) showed strong evidence of a correlation between LDL cholesterol and cardiovascular events.

The study included 15 (46.87%) subjects with a history of active smoking, all of whom were

men. Smoking is a strong risk factor of ACS due to its ability to accelerate the process of atherosclerosis through several mechanisms. Exposure to cigarette smoke molecules causes blood vessel walls to release inflammatory mediators and cytokines, which indirectly cause damage to blood vessel walls. The study did not base the subjects on one risk factor only. Some subjects had more than one risk factor of ACS that was different from each other and caused the diverse conditions of the subjects.

We used Troponin I examination as a diagnostic criterion in study subjects with a mean value of 20.20 ± 19.26 μg/L. The results of NLR examination of the study subjects showed an average of 6.10 ± 3.98. Coronary angiography examination aimed to demonstrate the coronary anatomy and the degree of lumen obstruction of the coronary arteries. The results could identify coronary lesions starting from the location, length, diameter, and shape of the arteries, the degree of coronary lumen obstruction, the characteristics of the obstruction including atheroma, thrombus, dissection, spasm or bridging, and assessing the blood flow. Moreover, it could assess the presence of coronary artery collaterals. The Gensini scores divided the degree of stenosis into mild (Gensini score of 1–30), moderate (Gensini score of 30–60), and severe (Gensini score of >60). The mean Gensini score in this study was 70.53 ± 38.49.

The correlation test between NLR and the degree of coronary stenosis in this study showed no correlation (r = 0.064; p = 0.595). This result could be explained because the modified Gensini score was the percutaneous coronary intervention system. The modified Gensini score is the most comprehensive coronary artery bypass grafting score in assessing the severity of coronary lesions because it includes the number of stenotic arterial segments, the degree of arterial lumen stenosis, and the location of the stenotic segment. It includes eight coronary artery segments grouped by its severity of occlusion (score 1 for stenosis of <50%, score 2 for stenosis of 50–74%, score 3 for stenosis of 75–99%, and score 4 for total occlusion). Each blood vessel segment, whose degree of stenosis has been measured, is added up, then multiplied by the value determined according to the area of the coronary arteries involved (the left main coronary artery × 5; the proximal left anterior descending [LAD] coronary artery × 2.5; the proximal circumflex artery × 2.5; mid LAD × 1.5; right coronary artery, distal LAD, posterolateral artery, and obtuse marginal artery × 1; other segments × 0.5). The Gensini score assessment divided the degree of stenosis into mild (score of 1–6), moderate (score of 7–13), and severe (score of >13) [21].

Li *et al*. (2018) showed that the NLR level was significantly higher in the chronic occlusion group compared to those in the acute coronary stenosis group, as in ACS [22]. Furthermore, the inflammatory process in the course of the disease occurred in all coronary arteries from the main artery, the arterial branches to the distal arteries. Both inflammations that occurred locally in the coronary arteries and that occurred systemically played roles in the destabilization and rupture of atherosclerotic plaque that could cause acute cardiovascular events [8]. The criteria based on the number of damaged blood vessels or the degree of stenosis of the blood vessels could not systematically reflect the severity of the disease. These reasons caused no correlation between NLR and the degree of stenosis in this study.

The correlation test between CRP levels and the degree of coronary stenosis in this study showed a weak positive relationship (r = 0.240; p = 0.044). This value indicated that an increase in CRP levels was directly proportional to the severity of coronary stenosis. CRP is one of the substances found in atherosclerotic lesions in the tunica intima along with monocytes, monocyte-derived macrophages, and lipoproteins, which shows that CRP is directly related to the process of atherosclerosis [23], [24]. The study conducted by Habib and Masri in 2013 on 87 CHD patients showed that there was a positive correlation between CRP and the severity of stenosis (r = 0.423; p = 0.018) [25]. In the other hand, the study conducted by Mansoor *et al*. (2014) reported that patients with high CRP levels were at risk for severe coronary lesions during early adulthood. The study also used the Gensini score (p < 0.01, r = 0.6692) [26].

The correlation test between SAA levels and the degree of coronary stenosis in this study showed no correlation (r = −0.164; p = 0.171). SAA, in theory, plays a role in the pathophysiology of coronary stenosis. SAA is an acute-phase protein produced by the liver in response to inflammation, whose levels can increase 1000 folds. This study found extremely high SAA levels. However, it was not correlated to the degree of coronary stenosis, although the percentage of patients with moderate and severe stenosis was 84%. Despite the absence of a correlation between high SAA levels and the degree of stenosis, the finding of high SAA levels in ACS needs special attention. SAA can be found as apolipoprotein in HDL molecules and shows chemotactic effects on monocytes and T lymphocytes. SAA molecules allow vascular damage and induce matrix metalloproteinase expression, which causes atherosclerosis [27], [28].

SAA removes Apo A-1 from HDL to form larger and denser HDL molecules, thereby reducing the ability to catalyze cholesterol esterification. SAA-HDL bond is not able to prevent LDL oxidation and even strengthens the formation of foam cells, which then becomes a fatty streak at the beginning of the development of coronary stenosis. SAA molecules can be distributed not only in HDL but also in LDL particles. The oxidative interactions between SAA and LDL form the binding of SAA to LDL, which is catalyzed by ROS. The early appearance of stable plaque with a small extracellular lipid content

and cholesterol ester and thick fibrous capsule leads to stable coronary with increased SAA levels [27], [28].

This study did not investigate each type of ACS, which might provide different information compared to the overall analysis. It needed a larger size of the sample in the analysis of each type of ACS. This study did not analyze the comorbid factor presented in the subjects, so further study is required. Finally, further study was needed to investigate the correlation between inflammatory parameters and other cardiac stenosis scoring systems.

Conclusion

CRP examination could be beneficial as a marker of acute inflammation in the condition of ACS to manage the inflammation process.

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