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Relationship of Troponin I with Neutrophil Lymphocyte Ratio and Serum Amyloid A in Acute Coronary Syndrome

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Abstract

BACKGROUND: Acute coronary syndrome (ACS) is the leading cause of death in the world. It can initiate an acute inflammatory process by inducing proinflammatory cytokines at the cellular level measured by neutrophil lymphocyte ratio (NLR), at the biomolecular level characterized by serum amyloid A (SAA) production in liver. The relationship of elevated troponin I levels as a marker of heart muscle necrosis with NLR and SAA as inflammatory markers needs further discussion.

AIM: The purpose of this study was to determine the relationship between cardiac necrosis markers and inflammatory parameters in ACS.

METHODS: An analytic observational study with a cross-sectional approach was conducted from March to May 2019. This study involved 32 patients with ACS at the Emergency Department of Dr. Kariadi Hospital, with the onset of attacks of 4−6 h which met the inclusion and exclusion criteria. Examination of troponin I level was done using the ELFA method, NLR value was measured using a hematology analyzer, and SAA level was measured using the ELISA method. Statistical test was done using Spearman correlation. $p < 0.05$ was considered significant.

RESULTS: The median (min-max) of troponin I, NLR, and SAA values was 0.617 (0.001−40,000) μg/L, 4.92 (1.38−18.16), and 40.454 (5.879−66.059) μg/ml, respectively. The correlation of troponin I level with NLR and SAA was $r = 0.180$, $p = 0.243$ and $r = 0.655$, $p = 0.000$.

CONCLUSIONS: There was a significant positive moderate relationship between troponin I level and SAA which could be used as a marker of acute inflammation in ACS, whereas cell inflammation marker of NLR did not provide a significant meaning.

Introduction

Cardiovascular disease is a major health problem in both developed and developing countries. It is estimated that more than 20 million people worldwide die from heart disease and stroke by the year 2030 [1]. Acute coronary syndrome (ACS) is a term for group of symptoms that arise from acute ischemia of heart muscle, related to occlusion of coronary arteries, which cause troponin release into the bloodstream [2], [3], [4]. It also stimulates acute inflammation characterized by the release of proinflammatory cytokines. They can be detected by increase in neutrophil lymphocyte ratio (NLR) at cellular level, which is less-invasive, cost-effective, easily available and calculated, and also increase in serum amyloid A (SAA) at biomolecular level [5], [6], [7].

This study analyzed the relationship between cardiac necrosis markers (troponin I) and inflammatory markers (NLR and SAA) in ACS. It can be useful to evaluate the inflammatory process of ACS related to troponin I and of course the intervention of the inflammation.

Methods

This study was an observational analytic study with a cross-sectional design conducted at Dr. Kariadi Hospital, Semarang in March–May 2019. All subjects of the study were requested to give written informed consent and patients' identities were confidential. This study was approved by the Health Research Ethics Committee of Dr Kariadi Hospital, Semarang.

The subjects of the study were 32 patients with ACS diagnosed by cardiologists. The subject sampling was done using consecutive sampling method who met the inclusion and exclusion criteria of the study. The inclusion criteria were chest pain for the 1st time

4−6 h after onset, age 30−65 years old, normal body temperature (36.5°C−37.2°C). The patients who were not willing to participate in this study, died before angiography, had malignancy, under chemo/radiotherapy program, had acute/chronic kidney failure, had previous myocard infarct, and liver disease were excluded from this study. Data were collected from history taking, physical examination, ECG examination, and laboratory examination.

Troponin I level contained in blood serum was measured by ELFA method with a reference >0.3 μg/L. NLR value was the result of a manual calculation of the ratio between absolute neutrophil counts and absolute lymphocyte counts. Absolute neutrophil counts and absolute lymphocyte counts were examined using a Sysmex XN-1000 hematology analyzer with a reference >5.25. Serum SAA level was examined by ELISA method, expressed in μg/L with a reference ≥ 325 μg/L. Data were analyzed using a computer program, and data normality test was done using Shapiro-Wilk test. Bivariate analysis was performed to determine the relationship of troponin I with NLR and SAA on the ACS. Statistical test results were significant if $p < 0.05$.

Results

The characteristics of the data are shown in Table 1.

Table 1: The characteristics of the study subjects

The characteristics of the subjects	Median (min - max)
Age (years)	60 (33−74)
Body weight (kg)	68 (53−82)
Height (cm)	161,50 (155,00177,00)
Body mass index (kg/m^2)	24,84 (21,78−29,72)
Random blood glucose (mg/dL)	169 (85,00−420,00)
AST (U/L)	22,15 (11,18−35,41)
ALT (U/L)	24,75 (17,89−39,97)
Urea (mg/dL)	32 (19,00−50,00)
Creatinine (mg/dL)	1,2 (0,50−2,00)
Total cholesterol (mg/dl)	156 (104−283)
Low-density lipoprotein (LDL) (mg/dL)	106 (60−190)
Triglycerides (mg/dl)	116 (60−216)
High-density lipoprotein (HDL) (mg/dL)	40 (13−67)
Leukocyte count (10^3/uL)	9,44 (5,62−19,15)
Absolute neutrophil counts (/μL)	8,071 (2,770−15,810)
Absolute lymphocyte counts (/μL)	2,421 (0,540−9,790)
Neutrophil lymphocyte ratio (NLR)	4,913 (1,38−18,16)
CKMB (U/L)	39 (10−608)
Troponin I (μg/L)	0,617 (0,001−40,000)
Serum amyloid A (SAA) (μg/L)	40454 (5879−66059)

Min: Lowest value; max: highest value.

Characteristics of the data were presented in the form of median with maximum and minimum values, because most of the parameters in the characteristic of the data were not normally distributed. From all the study subjects, 13 (40.6%) of them had dyslipidemia, 12 (37.5%) of them had hypertension, and 8 (25%) of them had hyperglycemia. Based on the body mass index, 14 (43.8%) subjects were normal, 11 (34.4%) subjects were overweight, and 7 (21.9%) subjects were obese. The distribution of risk factors in the subjects of this study is shown in Table 2. Analysis of the correlation between troponin I level with NLR and SAA was performed using the Spearman test presented in Table 3.

Table 2: Risk factors of ACS

Risk factors	Number (people)	Percentage
Body mass index		
Normal	14	43,8
Overweight	11	34,4
Obese	7	21,9
Dyslipidemia		
Yes	13	40,6
No	19	59,4
Hyperglycemia		
Yes	8	25
No	24	75
Hypertension		
Yes	12	37,5
No	20	62,5

Table 3: The correlation between troponin I with NLR and SAA

Cardiac cell necrosis markers	Inflammation markers	
	NLR	SAA
Troponin I		
r	0.180	0.655
p	0.243	0.000*

*Significant if $p < 0.05$

The correlation between troponin I level and NLR reached $r = 0.180$ with $p = 0.243$ which meant that there was no relationship between troponin I level and NLR in ACS. The correlation between troponin I level and SAA reached $r = 0.655$ with $p = 0.000$ which meant that there was a moderate positive relationship between troponin I level and SAA in ACS.

Discussion

The relationship between troponin I and NLR

The results of NLR and troponin I levels in this study exceeded the reference values and indicated the inflammatory state in the ACS. The presence of troponin I in serum indicates damage of heart muscle. The American Heart Association defines acute myocardial infarction (AMI) as evidence of heart muscle necrosis that is known by detecting troponin I level [4]. The process of AMI is followed by an accumulation of neutrophils in an ischemic area and areas, where reperfusion occurred will release proteolytic enzymes or reactive oxygen species (ROS) and cause damages to the surrounding myocytes, thereby aggravating heart muscle ischemia and expanding infarction areas through microvascular occlusion [8]. Lymphopenia in ACS is caused by an increase in endogenous cortisol that occurs during acute stress of ACS [9]. The conclusion from the condition of neutrophilia and lymphopenia is that the greater the area of necrosis, the greater the response of leukocytes at the local or systemic level [8], [9], [10].

This study showed an increase in NLR, accompanied by an increase in troponin I levels.

However, this relationship was not statistically significant. It was known that there had been no studies which showed that troponin I and NLR levels did not increase in ACS patients. Nalbant *et al*. reported that NLR and troponin levels increased in ACS patients [11]. Korkmaz *et al*. also stated that there was an increase in NLR levels in patients with ACS compared to the control group and stated that it was a marker of the onset of coronary ischemia [12]. This increased NLR and troponin I levels were supporting the theory that the increase in NLR was a marker of inflammation in patients with ACS. Tehto *et al*. also stated that an increase in absolute neutrophil counts did not only gave an idea of inflammation but also influenced the instability of atherosclerotic plaque [13].

This study showed that there was no relationship between troponin I and NLR levels, which could be caused by a marked increase in troponin I level during an acute attack not followed by a corresponding increase in NLR level. Nugroho *et al*. found that in acute inflammation, there was an increase in the average level of leukocytes over time. It showed that in 48 h after chest pain, leukocytes increased by 29.7% compared to the 1st h after chest pain [14]. In this study, vein blood sampling was carried out at 4−6 h after the onset of chest pain based on the history of the patient so that an increase in troponin level had not been followed by a marked increase in NLR level.

The undetectable increase in NLR level could be caused by an acute inflammatory reaction in AMI, causing neutrophil migration from blood circulation to heart muscle. However, it was not accompanied by bone marrow response yet. As a result, neutrophils in circulation were not detected and their value was low (neutropenia) which could be shown by the number of leukocytes and neutrophils which did not increase. At the beginning of the ACS, the body immune system was activated and cells that were mainly recruited in this initial process were neutrophils. This explained the increase in neutrophils in tissues that had not been measured in circulation [15], [16]. The response of increased neutrophils in ischemic tissue due to inflammation depended on individual genetic variations. These differences could be explained by the presence of different genomic characteristics in each individual in metabolic and inflammatory regulation so that the response to stress in critical illness would form a different inflammatory response [17], [18], [19].

The relationship between troponin I and SAA

There was a moderate positive relationship between troponin I level and SAA in ACS. This value showed that the increase in SAA was directly proportional to the increasing severity of infarction which was characterized by increased levels of troponin I level. Inflammatory reactions that occur in ACS caused SAA to be synthesized and secreted by the liver in response to inflammatory cytokines (IL-6). This was similar to the study of Zairis *et al*. and Cabala *et al*. which showed that there was a relationship between troponin I level and SAA in patients with ACS [20], [21].

The condition of ACS is related to the occlusion of coronary arteries that cause AMI and extensive tissue muscle necrosis, wherein the case of cardiac necrosis troponin I is released into the bloodstream. The presence of troponin I in serum shows that heart muscle damage has occurred. This situation will also stimulate the acute inflammatory process marked by the release of proinflammatory cytokines (IL-6) which will be responded to by the liver with the production of acute reactant phase proteins, one of which is SAA, in which level can increase as much as 1,000 times 4−6 h after the inflammatory stimulus, thus making SAA as a sensitive marker of the inflammatory response. SAA level increases during the acute incidence of heart muscle infarction within 24 h and peaks within 3 days after the onset of chest pain [22], [23]. Serum amyloid A can be used as a marker of acute inflammation in patients with ACS that has only occurred within 4−6 h of chest pain.

However, there were some limitations in our study. First, this study did not classify subjects based on the degree of coronary artery stenosis and the extent of infarction lesions that can describe different degrees of inflammation. Stenosis areas of the coronary arteries are related to the area of infarction in heart muscle, the greater the narrowing of the coronary arteries, the wider the area of infarction, and the higher the troponin level and the more neutrophils are recruited in the blood vessels that have stenosis. Second, this study did not measure proinflammatory cytokines level such as, IL-1, IL-6, IL-8, TNF-α, I-CAM levels, V-CAM levels, E-selectin, and P-selectin, as inflammatory mediators so their exact levels were still unknown, which could affect NLR. Further, research needs to be done with subjects classification based on the degree of coronary artery stenosis and the extent of infarction lesions, also examine the proinflammatory cytokines level that has been described above.

Conclusions

There was a moderate positive relationship between troponin I and SAA; therefore, SAA could be used in evaluating the inflammatory condition of ACS patients with 4−6 h of onset. This was in contrast to the NLR which cannot be used as a cell inflammation marker to evaluate inflammation in ACS with 4−6 h of onset.

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