



Original Research

Correlation of Neutrophil-Lymphocyte Ratio, Vessel Score based on Sullivan Scoring System, and Troponin in Acute Coronary Syndrome PatientsChelssi Gloria Tessari^{1*}, Achmad Lefi² , Yetti Hernaningsih³ ¹Medical Undergraduate, Study Program, Faculty of Medicine, Universitas Airlangga.²Department of Cardiology and Vascular Medicine, Faculty of Medicine, Universitas Airlangga, RSUD Dr. Soetomo, Surabaya.³Department of Clinical Pathology, Faculty of Medicine, Universitas Airlangga, RSUD Dr. Soetomo, Surabaya.

ARTICLE INFO

Article history:

Submitted 03 January 2022

Reviewed 15 May - 15 August 2022

Revised 21 September 2022

Accepted 20 September 2022

Available online 30 September 2022

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2018@fk.unair.ac.id*Keywords:*Acute Coronary Syndrome
Neutrophil-Lymphocyte
Troponin I
Sullivan Score
Vessel Score

ABSTRACT

Acute Coronary Syndrome (ACS) is one of the highest causes of death globally, with the number of deaths reaching more than 9 million people in 2016. Therefore, a fast and accurate ACS diagnosis is needed. This study aimed to determine the relationship between the neutrophil-lymphocyte ratio, the number of coronary artery lesions evaluated by angiography, and troponin I in ACS patients **Material and Methods:** This research is an analytic observational with a retrospective cross-sectional design. Sampling was carried out using a total sampling technique and obtained 87 samples that met the inclusion and exclusion criteria for the 2019-2020 period at Dr. Soetomo Regional General Hospital Surabaya. The correlation between the number of coronary artery lesions and the neutrophil-lymphocyte ratio to troponin I levels were respectively analyzed using chi-square and spearman-rho with SPSS ver. 25. **Results:** The results showed a moderately significant correlation between the neutrophil-lymphocyte ratio and troponin I levels ($p = 0.003$, $r_s = 0.319$). While the correlation analysis between the number of coronary artery lesions and the vessel score on troponin I showed insignificant results ($p = 0.525$), which means that the number of coronary artery lesions was not correlated with troponin I. **Conclusion:** This study concludes a significant correlation with moderate correlation between the neutrophil-lymphocyte ratio and troponin I. However, there is no significant correlation between the number of coronary artery lesions assessed by the Sullivan and troponin I levels.

Introduction

ACS is one of the leading causes of death globally, with the number of deaths reaching more than 9 million people in 2016 [1]. Therefore, prompt and accurate diagnosis is essential to reduce ACS morbidity and mortality. Examining the cardiac biomarkers could be considered as assistance to

examine the patient showing symptoms of ACS so that we can take further action as soon as possible. The gold standard of cardiac biomarkers is cardiac troponin because it has a very high specificity for myocardial cells compared to other biomarkers [2,3]. In addition to non-invasive methods such as

cardiac biomarkers, invasive methods such as cardiac catheterization can also be helpful in the ACS diagnosis. This process of catheterization is known as coronary angiography. The pathogenesis of ACS is motivated by the formation of atherosclerotic plaques in the coronary arteries. An inflammatory process initiates the process of atherosclerosis due to damage to the intima layer of blood vessels [4]. This inflammatory process in the coronary arteries involves neutrophils, T cells, mast cells, and dendritic cells that will infiltrate the intima layer of damaged blood vessels. This ongoing severe inflammatory process involving leukocytes and platelets as the primary key can disrupt atherosclerotic plaques and cause ischemia of cardiac cells. Neutrophils disrupt atherosclerotic plaques by releasing proteolytic enzymes, arachidonic acid derivatives, and superoxide radicals [5]. Because of this, inflammatory marker substances and blood cells that play a role in the inflammatory process, such as the neutrophil-lymphocyte ratio, are considered to play a role as markers of ACS in patients.

In contrast to neutrophils that negatively impact atherosclerotic plaques, lymphocytes have protective properties against atherosclerotic plaques. This protective property is due to the role of T-helper 2 cells, which can suppress the expression of IFN- γ , which plays a role in intracellular lipid deposition and foam cell formation

in endothelial lesions [6]. In addition, T-helper 17 cells also have atheroprotective properties in advanced atherosclerosis [7]. T-regulatory cells also have this atheroprotective property that can suppress the inflammatory process [8,9]. According to research by Kafkas et al. (2012) and Alfakry et al. (2012), increased inflammatory markers can associate with clinical coronary syndrome severity and recurrence in ACS. [10,11]

Research by Ndrepepa et al. (2011) and Samman Tahhan et al. (2018) showed a positive correlation between highly sensitive troponin and the severity of coronary artery narrowing as measured using the Gensini score through angiographic procedures [12,13]. Dur et al. (2017) reported a high neutrophil-lymphocyte ratio as an independent predictor of the severity and complexity of coronary atherosclerosis and correlated with CKMB and troponin levels in ACS patients. [14]

Compared with previous studies, the researcher wants to prove a relationship between the neutrophil-lymphocyte ratio and the number of coronary artery lesions with troponin I levels. The neutrophil-lymphocyte ratio was chosen as a variable because it is cheap, easy to practice in daily clinical practice, and has a role as an independent predictor on the severity of coronary atherosclerosis and troponin levels. Troponin I was chosen because it is the most specific and most recommended biomarker in diagnosing ACS

compared to other biomarkers, particularly because troponin is not elevated in patients with kidney disease, polymyositis, and dermatomyositis. In contrast, troponin T is elevated in these conditions [15]. In assessing the severity of the lesion based on the number of coronary artery lesions, the researcher chose vessel score as the scoring system that was quantified from the angiographic examination of ACS patients.

Material and Methods

This study is an observational analytic study with a cross-sectional design. The researcher used the total sampling technique in this study. The research sample was all medical records of patients with Acute Coronary Syndrome (ACS) at Dr. Soetomo Regional General Hospital, Surabaya, from November 2019 to December 2020 and have met the inclusion criteria. Patients with incomplete medical records, suffering from hematologic, autoimmune, infectious, and inflammatory diseases, and undergoing immunosuppressive treatment were excluded from this study. Health Research Ethics Commission of RSUD Dr. Soetomo Surabaya has approved the ethics of this research (ref. no: 0262/LOE/301.4.2/XII/2020), and the identity of the research sample is guaranteed to be confidential.

Age, gender, type of ACS, vessel scores, neutrophils, lymphocytes, and troponin I samples were obtained from medical records. Troponin I was

examined using the SNIBE MAGLUMI series using the Sandwich Chemiluminescent Immunoassay (CLIA) method. The neutrophil-lymphocyte ratio was obtained from the division between neutrophil and lymphocyte levels. The variables of this study consist of the independent and dependent variables. The independent variables were the neutrophil-lymphocyte ratio and the number of coronary artery lesions, while the dependent variables were troponin I and ACS. The correlation between the two variables was carried out using SPSS version 25 with the chi-square method to find the correlation between the number of coronary artery lesions to troponin I and the spearman rho method to find the correlation between the neutrophil-lymphocyte ratio to troponin I. The results of the analysis were significant if the p-value < 0.05.

Result

Basic Characteristics of Research Sample

In this study, 87 samples (69 STEMI, 6 NSTEMI, and 12 STEAM) met the inclusion criteria. The age range of the dominating research subjects was 51-60 years, with 28 samples (32.18%), and most of the patients were male (83.21%).

Table 1. Demographic Characteristics of the Research Sample

Characteristics	n (%)
Sex	
Male	75 (83.21%)
Female	12 (13.79%)
Age (years), (Mean \pm SD)	54.40 \pm 10.40
ACS type	
STEMI	69 (79.31%)
NSTEMI	5 (6.90%)
UAP	9 (13.79%)
Vessel score	
0 VD	4 (4.60%)
1 VD	43 (49.43%)
2 VD	24 (27.58%)
3 VD	16 (18.39%)
Lab [Median (Min-Max)]	
Neutrophil	78.60 ¹ (48.40 ¹ -93.40 ¹)
Lymphocyte	14.30 ¹ (4.70 ¹ -43.80 ¹)
Neutrophil-lymphocyte ratio	5.65 (1.11-18.85)
Troponin I	7.32 ² (0.00 ² -187.41 ²)

¹ % (percentage)

² ng/mL (nanogram per milliliter)

Based on the results of angiography, the study sample was divided into four categories based on the vessel score, namely 0 VD (no vessel with >70% stenoses), 1 VD (presence of >70% stenosis in 1 main coronary artery), 2 VD (presence of >70% stenoses in 2 main coronary arteries), and 3 VD (presence of >70% stenoses in 3 main coronary

arteries) [16]. The angiography results were then grouped into simple lesions (vessel scores 0 VD and 1 VD) and multiple lesions (vessel scores 2 VD and 3 VD). Furthermore, the type of ACS was associated with the patient's angiography results, as shown in Table 2.

Table 2. Distribution of Sample Angiography Results Based on Type of ACS Suffered.

	Simple Lesion	Multiple Lesion	Total
STEMI	39	30	69
NSTEMI	2	4	6
UAP	6	6	12
Total	47	40	87

Neutrophil-Lymphocyte Ratio Value

The neutrophil-lymphocyte ratio used in this study is the neutrophil and lymphocyte value of the patient at the first examination since the patient came to the hospital. The neutrophil-lymphocyte ratio was categorized into < 3 and ≥ 3 .

Table 3. Frequencies of Neutrophil-Lymphocyte Ratio

	Max Value.	Min Value.	Frequencies	
			< 3	≥ 3
Neutrophil-lymphocyte ratio	18.85	1.11	13 (14.94%)	74 (85.06%)
Total			87 (100%)	

Troponin I

Troponin I categorized into < 0.1 and ≥ 0.1 . The troponin I used in this study is the troponin I at the first examination since the patient came to the hospital. The frequency of troponin I can be seen in Table 4

Table 4. Frequencies of Troponin I

	Max Value.	Min Value.	Frequencies	
			$< 0.1^*$	$\geq 0.1^*$
Troponin I	187.41*	0.000002*	16 (18.39%)	71 (81.61%)

Total	87 (100%)
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*ng/mL (nanogram per milliliter)

Correlation of the number of coronary artery lesions based on the Vessel Score with the Troponin I in ACS Patients

Based on the data that has been collected, it was found that in patients with simple lesions, there were 7 patients (14.89%) with troponin levels < 0.1 ng/mL and 40 patients (85.11%) with troponin levels ≥ 0.1 ng/mL. Meanwhile, in patients with multiple vessel disease, there were 9 patients (22.50%) with troponin levels < 0.1 ng/mL and 31 patients (77.50%) with troponin levels ≥ 0.1 ng/mL. Then a correlation test was performed using the chi-square analysis method on vessel score category data and troponin I category data, and the results were not significant, $p=0.525$ ($p > 0.05$).

Correlation of Neutrophil-Lymphocyte Ratio Value to Troponin I Value in ACS Patients

The correlation analytical test between the neutrophil-lymphocyte ratio, which categorized into neutrophil-lymphocyte ratio < 3 and ≥ 3 , and troponin I level was done using the spearman's rho analysis method. After the correlation test was carried out on the two variables, significant results were obtained ($p=0.003$) with a correlation coefficient of 0.319 which means the strength of the correlation is moderate.

Discussion

The majority of the sample in this study were male (75 patients [86.21%]). Research by Yadav et al. (2010) stated that of the 200 research subjects with ACS, 144 (72.00%) of them were male, and 56 (28.00%) were female with a ratio of male and female ACS patients of 2.57:1 [17]. Males are 10-15 times more likely to develop heart disease because of the gradual decline in estrogen levels after puberty, while, as is well known, estrogen is associated with an atheroprotective role. It can increase high-density lipoprotein (HDL) levels and reduce low-density lipoproteins (LDL). In addition, estrogen also has antioxidant, vasoprotective, and antithrombotic effects.[18,19]

The dominating age category was patients aged 51-60 years (28 patients [32.18%]). Yadav et al. (2010) also showed that the research sample was dominated by ACS patients aged 51-60 years (46 patients [23.00%]).[17]

Based on the ACS category and type of coronary artery lesion, this study was dominated by STEMI patients with simple lesions (42 patients [48.28%]), followed by STEMI patients with multiple lesions (31 patients [35.63%]), then followed by UAP patients with simple lesions and multiple lesions respectively were two patients (2.30%) and three patients (3.45%), and NSTEMI patients with simple lesions and multiple lesions were respectively three patients (3.45%) and six patients (6.90%).

Research by Khan (2016) found that from the 50 STEMI patients and 50 NSTEMI patients who were the subjects in the study, 80% of STEMI patients suffered from simple vessel disease, and 80% of NSTEMI patients suffered from multiple vessel disease.[20]

After analyzing the cross-tabulation results between the number of coronary artery lesions and troponin I level in ACS patients, the results were not significant between these two variables ($p = 0.525$). This indicates that the number of lesions in the coronary arteries is not associated with troponin I level.

A study by Apriliani (2019) also found no significant relationship between troponin I level and the degree of arterial stenosis. The degree of stenosis means the number of coronary vessels involved. Thus, based on this study, troponin I levels were not associated with the number of lesions in the coronary arteries[18]. Mahajan et al. (2006) showed that patients with elevated troponin I levels were not always associated with coronary artery lesions. In his study, an increase in troponin I levels was found, but no coronary artery lesions were found by angiography.

These patients tend to have a higher-than-normal Left Ventricular Ejection Fraction (LVEF) despite a low prevalence of risk factors for atherosclerosis. Elevated troponin I levels in these patients can be caused by several causes, such as tachycardia,

myocarditis, pericarditis, severe aortic stenosis, gastrointestinal bleeding, sepsis, left ventricular hypertrophy, severe Congestive Heart Failure (CHF), stroke, electrical trauma, contusion myocardium, hypertensive emergencies, myocardial bridging, pulmonary embolism, diabetic ketoacidosis, Chronic Obstructive Pulmonary Disease (COPD) exacerbations, and coronary spasm.^[21]

The findings in this study and the research conducted by Apriliani (2019) are different from the findings in the research conducted by Cardoso et al. (2018) and Iriana, Nurulita, and Rauf (2019), which showed a correlation between high sensitive troponin and severity of stenosis in coronary artery disease (CAD) ^[19,21]. The difference in the results of this study can be caused because the two studies used hs-Troponin I, which has very high sensitivity compared to troponin I ^[19]. In addition, research by Laufer et al. (2010) showed that troponin levels in the blood could be elevated even in patients with mild CAD, and this troponin increase is not always accompanied by myocardial infarction. An increase in troponin found in patients with severe lesions and patients with mild lesions is thought to occur when the metabolic demands of the heart exceed the oxygen supply to the heart ^[23]. Rittersma et al. (2005) stated that in patients with acute myocardial infarction treated for thrombectomy, 50% of them had old thrombi visible at the lesion site. This

indicates that thrombi formation at the site of atherosclerotic lesions is not a rare occurrence and is not always accompanied by clinically manifest plaque rupture and vascular occlusion. The release of thrombi in small coronary vessels is a potential cause of micro-injury to the myocardium. In 25-40% of cases, this thrombus formation is caused by plaque erosion, not by plaque rupture. Furthermore, microinjury resulting from the thrombus can activate caspase-3 in myocytes and result in the breakdown of troponins and their release into the blood circulation.^[24]

Based on the Spearman's rho correlation analysis results between the neutrophil-lymphocyte ratio and troponin I level in patients with ACS, the p-value is significant ($p=0.003$) with a correlation coefficient of 0.319, which means that there is a moderate and unidirectional significant relationship. Research by Korkmaz et al. (2014) showed that the neutrophil-lymphocyte ratio tends to be higher in the troponin I positive group of patients ^[25]. Research by Oztürk et al. (2013) showed an increase in NLR values in the group of patients with NSTEMI when compared to the control group.^[26]

Atherosclerosis is characterized by a low-grade, chronic arterial wall inflammation^[27]. The inflammatory process is considered to play an essential role in the pathogenesis of the atherosclerosis process and the complications that accompany it. Unstable atherosclerotic and

ruptured plaques experienced a higher increase in neutrophils than stable atherosclerotic plaques.^[28]

Meanwhile, low lymphocyte levels are a common finding in ACS patients and are associated with increased mortality risk ^[29]. The neutrophil-lymphocyte ratio is considered a promising marker of inflammation and has been used in some cases to predict undesirable events. Lesions in the endothelial area of coronary blood vessels are exacerbated by risk factors, such as smoking, hypercholesterolemia, hypertension, and diabetes, causing dysfunction of the vascular endothelium. This endothelial dysfunction will form a chemotactic gradient that attracts leukocytes, especially neutrophils, from the bloodstream to the lesion area^[30]. The production of neutrophils by the bone marrow, which G-CSF and IL-23 control, will increase because of the inhibition of the cholesterol efflux mechanism of myeloid progenitors. Disturbance in CXCL12-CXCR4 also induces neutrophilia^[31]. Neutrophils that increase and infiltrate the lesion area will attract and produce pro-atherogenic proteins, such as myeloperoxidase, alpha-defensins, cathelicidins, LL37, and S100A8/A9.^[32]

Neutrophils also play an essential role in the process of plaque rupture through the release of proteolytic enzymes, arachidonic acid derivatives, and superoxide radicals. Elevated neutrophils are associated with poorer angiographic outcomes,

larger infarct size, and short-term prognosis in STEMI myocardial infarction. Neutrophils mediate the inflammatory response to myocardial infarction damage through several biochemical mechanisms leading to further tissue damage. While neutrophils are increased, lymphocytes have relative lymphopenia in response to stress, which is characterized by an increase in endogenous cortisol and is an early marker of acute myocardial infarction.

The decrease in lymphocytes mainly occurred in CD4+ and CD4+/CD8+ ratios. In addition, ACS patients also have decreased CD4+CD25+ regulatory T cells in the acute phase caused by increased oxidized-LDL and were associated with plaque instability and ACS severity^[33]. This severe inflammatory process with leukocytes, especially neutrophils, as the primary key will continue until tissue ischemia causes damage to heart cells. Myocardial ischemia activates caspase 3, an enzyme that breaks down troponin into fragments that can cut the sarcolemma of myocardial cells so that troponin is detected in the blood ^[18]. This explains why the neutrophil-lymphocyte ratio is correlated with troponin I.

Acknowledgement

The author wishes to thank everyone who has helped the research process, in particular to the dean of the Faculty of Medicine Universitas Airlangga, the director of the Regional General Hospital Dr. Soetomo Surabaya, head and staff of the ITKI Regional General Hospital Dr. Soetomo Surabaya, head and staff of PPJT Regional General Hospital Dr. Soetomo Surabaya, and the head and staff of The Health Research Ethics Commission of Regional General Hospital Dr. Soetomo Surabaya, so the author can complete this research without any hindrance.

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