RELATIONSHIP OF EPICARDIAL ADIPOSE TISSUE THICKNESS AND NEUTROPHIL TO LYMPHOCYTE RATIO WITH CORONARY LESION SEVERITY IN STABLE CORONARY HEART DISEASE

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ABSTRACT

Introduction*: Stable angina pectoris (SAP) is the one of the leading causes of death in men and women from every major ethnic group. Several studies have shown that the neutrophil to lymphocyte ratio (NLR) is a systemic inflammatory marker associated with cardiovascular events. Epicardial adipose tissue (EAT) has been considered to have an important role in cardiovascular physiology and pathogenesis. This study aimed to investigate the relationship of EAT thickness and NLR with coronary lesion severity in patients with stable coronary heart disease.* ***Methods:*** *This study was a cross-sectional study conducted at Department of Cardiology and Vascular of Kandou General Hospital, Manado, North Sulawesi, Indonesia, from May to August 2019. The population were patients with SAP who underwent coronary angiography procedures. The relationship between the EAT and NLR and the SYNTAX score were evaluated on a bivariate and multivariate level. Results: A significant linear relationship between EAT thickness and SYNTAX score was found (Pearson r = 0.32; p = 0.014). In addition, after controlling for sex and NLR, the correlation between EAT thickness and SYNTAX score increased to almost 0.7 points for each millimeter increase in EAT (95% CI 3.45 - 10.25; p <0.001). There was no significant correlation found between NLR and SYNTAX score both before and after controlling the confounding variables.* ***Conclusion****: There was a significant correlation found between EAT thickness and coronary lesion severity based on the SYNTAX score. In contrast, there was no significant correlation found between the NLR and the severity of coronary lesions.*

Keywords*: Stable angina pectoris, epicardial adipose tissue thickness, neutrophil-to-lymphocyte ratio, severity of coronary lesions, SYNTAX score*

ABSTRAK

Pendahuluan: Angina pektoris stabil (APS) adalah salah satu penyebab kematian tertinggi di antara pria dan wanita di berbagai etnis. Beberapa studi menunjukkan bahwa rasio netrofil terhadap limfosit (NLR) merupakan penanda inflamasi sistemik yang berhubungan dengan kejadian kardiovaskular. Ketebalan jaringan adiposa epikardial (EAT) juga memiliki peran penting pada fisiologi dan patogenesis penyakit kardiovaskular. Studi ini bertujuan untuk menilai hubungan ketebalan EAT dan NLR terhadap severitas lesi pada pasien APS. **Metode**: Studi ini merupakan studi potong lintang yang dilakukan di Bagian Kardiologi dan Kedokteran Vaskular RSUP Prof. Dr. R. D. Kandou, Manado dari Mei hingga Agustus 2019. Subjek penelitian ini adalah pasien APS yang menjalani pemeriksaan angiografi koroner. Hubungan antara ketebalan EAT dan NLS terhadap skor SYNTAX dievaluasi menggunakan korelasi bivariat dan multivariat. Hasil: Terdapat hubungan antara ketebalan EAT dengan skor SYNTAX (r=0,32; p=0,014). Setelah melakukan penyeseuaian jenis kelamin dan NLR, setiap peningkatan satu milimeter ketebalan EAT meningkatkan hampir 0,7 skor SYNTAX (95%CI 3,45 – 10,25; p<0,001). **Simpulan**: Terdapat hubungan signifikan antara ketebalan EAT dengan severitas lesi koroner yang diukur menggunakan skor SYNTAX. Sebaliknya, tidak ditemukan hubungan antara NLR dengan skor SYNTAX.

Kata Kunci: Angina pektoris stabil, ketebalan jaringan adiposa epikardial, rasio netrofil terhadap limfosit, severitas lesi koroner, skor SYNTAX

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INTRODUCTION

Atherosclerosis, the main cause of coronary heart disease (CHD), is a chronic inflammatory process that may lead to the formation of unstable atherosclerotic plaques. Patients with complaints of chest pain with stable atherosclerotic plaques are also known as stable angina pectoris (SAP). CHD is the leading cause of death in men and women from every major ethnic group in the United

States. In 2014, more than 600,000 Americans were estimated to have a new coronary event and more than 300,000 had recurrent CHD events. Between 2013 and 2030, the medical costs of CHD are projected to increase by almost 100% and highlight the growing health and socio-economic problems.[1], [2] Hence, CHD prevention strategies play a critical role. 1-3 There are more than 17 million deaths each year due to cardiovascular events in the world. Several risk factors such as hypertension, diabetes, smoking, acute, and chronic inflammation are known to play a role in disease pathogenesis and generating interest to investigate for various markers of inflammation. The inflammatory process is thought to play a fundamental role in atherosclerosis both as a trigger and a role in its progression.[3], [4]

Recent studies on atherosclerotic plaques suggested a more complex pathophysiology in which the inflammatory process plays an important role in the onset and progression of the disease. This is evidenced by an increase in several inflammatory markers associated with increased morbidities in CHD patients. The release of various cytokines by local inflammatory cells leads to activation of endothelial cells and changing their natural anticoagulant properties. These inflammatory cytokines also increase endothelin release by endothelial cells resulting in local vasoconstriction. A number of cells, including neutrophils, monocytes, lymphocytes, and eosinophils play a role in the pathogenesis of coronary artery disease. Coronary vascular endothelium is damaged by neutrophils through adherence-dependent mechanisms involving selectin molecules. This results in the release of free oxidative radicals and proteases and also aggregates to occlude the vasa vasorum.4 Some studies have shown that the neutrophil to lymphocyte ratio (NLR) is a systemic inflammatory marker associated with cardiovascular events such as stable, unstable CHD, as well as decompensated heart failure.[5]

Epicardial adipose tissue (EAT) is located between the myocardium and is surrounded by the visceral pericardium, accounting for nearly 15% of the total heart weight. EAT

acts as brown fatty tissue and protects the heart and coronary arteries against hypothermia. EAT is an immunological organ that is metabolically active with the potential to interact with myocardial cells. Inflammatory infiltration into these tissues have been observed in CHD patients. EAT and myocardium share the same microcirculation, hence cytokines can diffuse directly into the arterial and myocardial circulation via capillaries (paracrine and vasocrine secretion processes). Therefore, EAT has been considered to have an important role in cardiovascular physiology and pathogenesis.[6]–[8]

The thickness of EAT and NLR are both potential markers of the severity of coronary artery lesions. Both parameters can be obtained through a non-invasive, widely available modalities. Therefore, this study aimed to investigate the relationship of EAT thickness and NLR with coronary lesion severity in patients with stable coronary heart disease.

METHODS

This study was a cross-sectional study conducted at Department of Cardiology and Vascular of Kandou General Hospital, Manado, North Sulawesi, Indonesia. The study was conducted for 3 months from May to August 2019.

The population were patients with stable angina pectoris (SAP) who underwent coronary angiography procedures in the inpatient unit. SAP patients was defined as asymptomatic or stabilized post-acute coronary syndrome patients. Patients with SAP who underwent echocardiography, treadmill, coronary computed tomography (CT) scan, and coronary angiography with sinuses rhythm and were willing to participate were included in this study. The exclusion criteria included (1) patients with chronic pulmonary disease, obesity, skin diseases, mass in the thoracic cavity, etc. which complicate echocardiography examination or cause a poor echo window; (2) patients with moderate-severe valvular heart disease; (3) patients with ventricular or supraventricular arrhythmias on resting ECG records, including atrial fibrillation; (4) Immunocompromised patients (elderly, diabetes mellitus, and HIV); (5) Acute heart failure patients; (6)

patients with acute coronary syndromes requiring therapy for revascularization of either primary or early PCI; (7) patients with a history of PCI or previous bypass surgery; (8) uncooperative patients. With the significance level and the power of study determined at 5% and 20%, respectively, a minimum of 44 study subjects were obtained from calculation.

This study obtained the approval from Kandou General Hospital Ethical Committee. Patients presented with SAP were subjected to history taking, physical examination, electrocardiography, laboratory and echocardiography. Subsequently, patients who met the study criteria were asked for informed consent. Patients who were willing to participate then underwent a coronary angiography examination.

Body weight was measure by a calibrated analog scale while height measurements was conducted using measuring board. Complete blood analysis including leukocyte (eosinophils, lymphocytes, neutrophils, monocytes) was conducted with Cobas Integra® 400 plus analyzer. EAT thickness measurement was conducted using a Philips EPIQ 5 echocardiography device with a S5-1 transducer with a frequency range of 1-5 MHz. The severity of coronary lesions were evaluated with cardiac catheterization video data analyzed using the SYNTAX score through the assistance provided on the website of http://www.syntaxscore.com/calculator/syntaxscore/frameset.htm. Other demographic data were obtained from medical records.

The relationships between the EAT and NLR and the SYNTAX score were evaluated on bivariate and multivariate level. A multivariable linear regression model was used to assess the partial relationship between EAT, NLR, and SYNTAX scores. The regression modeling results were reported as changes in the SYNTAX score for each unit change in EAT or NLR, lower and upper limits of the confidence interval (CI) of 95%, and p-value. All data analysis were conducted using R statistical software version 3.5.2.

RESULTS

A total of 61 study subjects were obtained from June to August 2019. Table 1 demonstrated the

characteristics of study subjects. The proportion of male patients (n=40) were almost twice of female patients (n=21). Mean age, EAT thickness, uric acid levels, high-density lipoprotein (HDL) showed statistically significant differences between male and female. The mean age was significantly higher in female subjects than male subjects (mean 64.2 ± 6.8 vs 57.0 ± 8.0, respectively; p = 0.001). The median EAT thickness in female subjects was significantly higher compared to male subjects (0.8; IQR 0.4 - 0.9 vs 0.5; IQR 0.3 – 0.7, respectively; p = 0.025). In terms of the severity of coronary artery lesions, patients were generally classified as having a low mortality risk with a median SYNTAX score below 22, even though a quarter of these patients scored over 30. Male subjects had lower serum HDL levels than female subjects (33.0; IQR 29.0 – 36.0 vs 40.0; IQR 35.0 - 44.0, p = 0.008).

Figure 1 presents a graph of bivariate relationship between EAT and NLR thickness and coronary artery lesion severity measured using the SYNTAX score. The two scatterplots showed a linear relationship between the thickness of the EAT and the SYNTAX score as well as between the NLR and the SYNTAX score. However, only the thickness of EAT showed a significant correlation (Pearson r = 0.32; p = 0.014). It is further confirmed by the regression models in Table 2.

Table 2 illustrates that changes in the SYNTAX score were not associated with NLR both in the univariate model (p = 0.302; 95% CI -2.20 - 6.9) and multivariate model (p = 0.975; 95% CI -3.97 - 4.10). In contrast, before adjustments, each millimeter increase in the mean EAT thickness increased the SYNTAX score by more than 0.4 points. After controlling for sex and NLR, the correlation between EAT thickness and SYNTAX score increased to almost 0.7 points for each increase in EAT (95% CI 3.45 - 10.25; p <0.001).

DISCUSSION

To the authors' knowledge, this is the first study that investigated the relationship of EAT and NLR towards coronary lesion severity in Indonesia. This study included a total of 61 subjects with predominance of male (65.57%) subjects over female

(34.43%) subjects. American Heart Association (AHA) in 2019 stated that the prevalence of coronary heart disease in people aged >20 years were 7.4% in men and 6.2% in women in the United States population. In patients with stable angina pectoris, it was found that patients aged >45 years showed a predominance of male (370,000) over female (195,000).[9], [10] The National Health and Nutrition Examination Survey (NHANES, 2013- 2016) data showed the incidence of male and female with CHD to be 19.7% and 12.6% in patients aged >60 year.[10] The NLR parameter was shown to have no correlation with SYNTAX score thereby was not included into the regression equation.

This study exhibited a linear relationship between EAT thickness and SYNTAX score with a significant correlation (Pearson r = 0.32; p = 0.014). After controlling for sex and NLR, the correlation between EAT thickness and SYNTAX score increased to almost 0.7 points for each millimeter increase in EAT (95% CI 3.45 - 10.25; p <0.001). Similarly, Wang et al. [11] showed a significant correlation between the thickness of EAT and the SYNTAX score. Chaitanya et al [12] further demonstrated that EAT thickness of > 7 mm showed a positive significant correlation with the severity of lesions in the SYNTAX score, with an area under the curve (AUC), sensitivity, and specificity of ≥ 5 mm, 69.2%, and 33%, respectively.

In brief, this study showed no significant differences in bivariate relationships. This might be due to difference in subject's age, cut-off values in some regions (some studies from the western region reported a ratio of 2.5 - 5, tended to be higher in Asian populations, but it was proven that several studies had opposite results) [13], a relatively small sample size, as well antibiotics or corticosteroids prescription for several comorbidities that might affect the hematological results.[14]
This study showed no significant correlation between NLR and SYNTAX score both before and after controlling the confounders. Derya et al. [15] (r= 0.534, p <0.001) and Kim Bong et al. [16] (r = 0.353, p <0.001) showed significant correlations between EAT and NLR in hypertensive population.

Hypertension is a well-known triggering factor of cardiovascular disease. Increased production of reactive oxygen species (ROS) is known to occur in the elderly, and is associated with persistent inflammation and progression to a chronic disease. Increased production of proinflammatory factors is a characteristic feature of cardiac pathophysiology in the elderly, including high levels of interleukin-6 (IL-6), tumor necrosis factor-α (TNFα), and C-reactive protein (CRP).[9] Increased chronic proinflammatory factors is expected to have an effect on the EAT thickness and NLR.[3]

CONCLUSION

There was a significant correlation found between EAT thickness and coronary lesion severity based on the SYNTAX score. In contrast, there was no significant correlation found between the NLR score and the severity of coronary lesions based on the SYNTAX score. Further studies with a larger population, well-selected populations, and minimum confounding factors are needed to investigate the thickness of the EAT and coronary lesions based on the SYNTAX score. In addition, the cut-off value of the EAT thickness in predicting the presence or absence of coronary lesions also requires further investigations.

What is already know on this topic

- Some studies have shown that the neutrophil to lymphocyte ratio (NLR) is a systemic inflammatory marker associated with cardiovascular events such as stable, unstable CHD, as well as decompensated heart failure
- Therefore, EAT has been considered to have an important role in cardiovascular physiology and its disease pathogenesis
- The EAT thickness and NLR are both potential markers of the severity of coronary artery lesions that can be obtained through a non-invasive, widely available modalities

What this study adds

- A significant linear relationship between EAT thickness and SYNTAX score was found (Pearson r = 0.32; p = 0.014).

- After controlling for sex and NLR, the correlation between EAT thickness and SYNTAX score increased to almost 0.7 points for each millimeter increase in EAT (95% CI 3.45 - 10.25; p <0.001)
- There was no significant correlation found between NLR and SYNTAX score both before and after controlling the confounding variables

Competing interests

The authors declare no competing interest.

Authors' contributions

Darwin Indra designed and conducted the concepted study, analyzed and interpreted the data as well as prepared the manuscript. Lucia Panda and Edmond Jim helped in interpreting data and revising the manuscript. All authors approved the final version of the manuscript.

Table 1. Characteristics of study subjects

Variables	Total (n=61)		Sex				p^a
			Female (n=21)		Male (n=40)		
	μ ± SD	Med (Q1;Q3)	μ ± SD	Med (Q1;Q3)	μ ± SD	Med (Q1;Q3)	
Age (year)	59.5 ± 8.3	*	64.2 ± 6.8	*	57.0 ± 8.0	*	0.001
BMI (kg/m^2)	26.3 ± 3.5	*	26.0 ± 3.2	*	26.4 ± 3.6	*	0.694
Uric acid (mg/dl)	7.2 ± 1.8	*	6.4 ± 1.7	*	7.7 ± 1.7	*	0.011
NLR	*	2.0 (1.6 ; 2.5)	*	1.8 (1.6 ; 2.1)	*	2.1 (1.6 ; 2.6)	0.108
HbA1C (%)	*	6.5 (5.8 ; 8.4)	*	6.1 (5.8 ; 7.3)	*	6.5 (5.8 ; 8.6)	0.271
eGFR (ml/men/1.72 m^2)	72.7 ± 22.7	*	67.7 ± 21.8	*	75.3 ± 23.0	*	0.215
Cholesterol (mg/dl)	164.5 ± 46.1	*	168.9 ± 48.3	*	162.2 ± 45.3	*	0.593
HDL (mg/dl)	*	34.0 (30.0 ; 40.0)	*	40.0 (35.0 ; 44.0)	*	33.0 (29.0 ; 36.0)	0.008
LDL (mg/dl)	*	90.0 (70.0 ; 115.0)	*	100.0 (80.0 ; 131.0)	*	83.5 (68.0 ; 107.2)	0.114
Triglyceride (mg/dl)	*	143.0 (104.0 ; 203.0)	*	154.0 (110.0 ; 211.0)	*	119.0 (101.2 ; 184.0)	0.205
EF	*	62.0 (56.0 ; 70.0)	*	65.0 (59.0 ; 71.0)	*	61.2 (55.5 ; 68.2)	0.240
EAT	*	0.6 (0.4 ; 0.8)	*	0.8 (0.4 ; 0.9)	*	0.5 (0.3 ; 0.7)	0.025
SYNTAX score	*	18.0 (6.0 ; 30.0)	*	12.0 (3.0 ; 37.5)	*	23.0 (9.5 ; 29.1)	0.538

SD = standard deviation, Med = median, Q1 quartile I, Q3 quartile III, BMI = body mass index, NLR = neutrophil to lymphocyte ratio, eGFR = estimated glomerulus filtration rate, HDL = high density lipoprotein, LDL = low density lipoprotein, EF = ejection fraction, EAT = epicardial adipose tissue.

[a] = T test or Mann-Whitney U according to the normality of the distribution.

Table 2. Linear regression model of SYNTAX score with EAT thickness and NLR as the main covariates

Variables	SYNTAX score chages			
	Univariate model		Multivariate model[a]	
	β (95% CI)	*p*	β (95% CI)	*p*
Age	-0.15 (-0.63; 0.32)	0.526	*	
Male vs female	1.67 (-6.54; 9.88)	0.685	-5.49 (-12.90; 1.93)	0.153
BMI	0.10 (-1.03; 1.24)	0.856	*	
AU	1.79 (-0.35; 3.92)	0.099	*	
HbA1C	0.38 (-1.66; 2.43)	0.709	*	
eGFR	-0.13 (-0.30; 0.04)	0.138	*	
Cholesterol	0.07 (-0.01; 0.16)	0.087	*	
HDL	-0,36 (-0.80; 0.08)	0.103	-0.92 (-1.36; -0.49)	<0.001
LDL	0.04 (-0.06; 0.14)	0.406	*	
Triglyceride	0.00 (-0.05; 0.06)	0.916	*	
EF	-0.38 (-0.67; -0.10)	0.008	*	
NLR	2.39 (-2.20; 6.97)	0.302	0.06 (-3.97; 4.10)	0.975
EAT	4.42 (0.93; 7.91)	0.014	6.85 (3.45; 10.25)	<0.001

Note: CI = confidence interval, BMI = body mass index, NLR = neutrophil to lymphocyte ratio, eGFR = estimated glomerulus filtration rate, HDL = high density lipoprotein, LDL = low density lipoprotein, EF = ejection fraction, EAT = epicardial adipose tissue.

Figure 1. Scatter plot demonstrating the relationship between EAT Thickness, NLR and SYNTAX Score

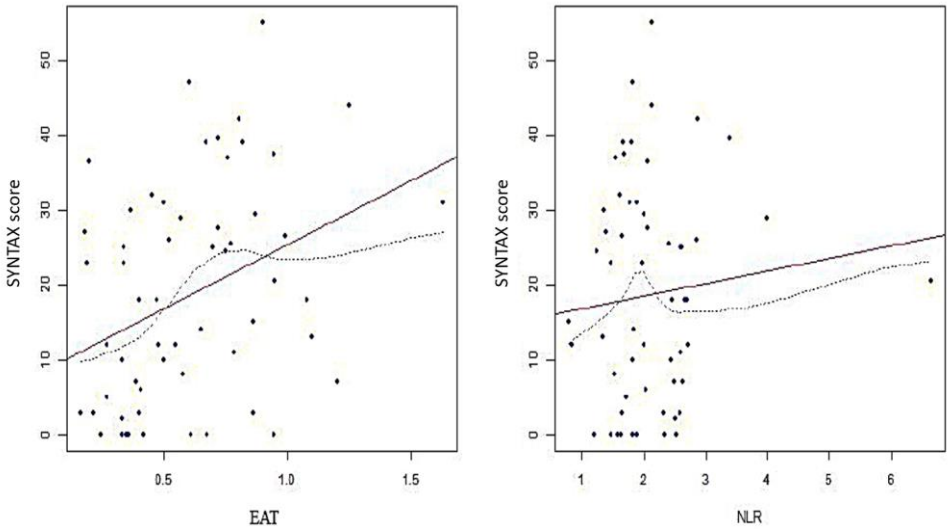

Figure 1. Scatterplot of the relationship between EAT thickness, NLR and SYNTAX Score. The Pearson correlation coefficient values were 0.32 (p = 0.014) and 0.13 (p = 0.302), respectively. EAT = Epicardial Adipose Tissue; NLR = Neutrophil to Lymphocyte Ratio

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