The Association of Platelet-Lymphocyte Ratio and Carotid Intima-Media Thickness in Systemic Lupus Erythematosus Patients

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Abstract

The platelets-lymphocytes ratio (PLR) is one of the inflammatory markers of atherosclerosis. Atherosclerosis is common among patients with compromised immune systems, including those with systemic lupus erythematosus (SLE). The occurrence of atherosclerosis at an early age (accelerated atherosclerosis) will increase the mortality and morbidity of SLE patients. The aim of this study was to assess the relationship between PLR and carotid intima-media thickness (CIMT) in patients with SLE. A cross-sectional study was carried out at Dr. Zainoel Abidin Hospital, Banda Aceh from July to December 2020. The PLR was determined by dividing the platelet count by lymphocyte count using a calculator during regular hematological examinations, while CIMT was measured using B Mode Doppler ultrasonography (USG). Other hematological parameters such as hemoglobin, hematocrit, erythrocyte, leucocyte, and diff count were also evaluated. Data analysis was performed using SPSS software. Fisher's exact test was employed to determine significant association between PLR and CIMT, and $p < 0.05$ was considered statistically significant. A total of 33 SLE patients were enrolled in the study 2 of them (6%) showed an increased CIMT, with an average age of 53.5 ± 2.12 years and diagnosis duration of 78 (12-144) months. Increased PLR was observed in 54.5% (18) of the patient, where one of them was noticed the thickening of the carotid intima-media as well. However, the result of Fisher's exact analysis suggested no significant relationship between PLR and CIMT in the patients with SLE ($p = 1,000$).

Keywords: Atherosclerosis, platelet to lymphocyte ratio, tunica intima thickness, systemic lupus erythematosus

1. Introduction

Atherosclerosis is one of the leading causes of vascular disease worldwide. The main clinical manifestations include ischemic heart disease, ischemic stroke, and peripheral arterial diseases. Despite a dramatic decline in the incidence and mortality from ischemic stroke and vascular disease has been depicted in most low-, middle-, and high-income countries for several past decades, mortality from ischemic heart disease has been reportedly more variable. Some countries reported decreased probability, while others reported an increase, especially in Eastern Europe and Asia [1]. In the UK, CHD remains the biggest killer although the rate of death from coronary heart disease (CHD) has been decreasing slowly in younger age groups. Approximately 80.000 deaths (ratio of 2:1 male vs female) were reported in 2010 due to CHD. CHD has also been the most common cause of death in other European countries, causing more than 681.000 deaths per year in the European Union [2]. In Indonesia, the estimated prevalence of CHD was 0.5%, affecting approximately 883.447 people [3].

Atherosclerosis is common among patients with compromised immune systems. In systemic lupus erythematosus (SLE), atherosclerosis can occur at a relatively young age of onset (accelerated atherosclerosis), resulting in high rates of morbidity and mortality as a result of cardiovascular disorders. An increased risk of cardiovascular diseases in SLE patients was first reported in 1976. In the study regarding the bimodal mortality pattern of SLE, infection and cardiovascular disorders were suggested as the main causes of morbidity and mortality among SLE patients [4]. The prevalence of carotid plaque was also reportedly twice higher in SLE patients compared to those of the normal population, along with faster plaque progression and rapid destruction of the vascular wall due to the ineffectiveness of the repair mechanism [5, 6].

A study reported a significantly higher carotid intima-media thickness (CIMT) in patients with SLE compared to the controls [7]. CIMT has been suggested as an early marker of subclinical atherosclerosis [8]. Inflammation plays a central role both in the initiation and in the development of the atherosclerotic process [9]. Platelet to lymphocyte ratio (PLR) has been widely recognized as a common biomarker of inflammation and is often used to predict disease activities in patients with SLE [10, 11]. In addition, PLR was independently and positively associated with the severity of atherosclerosis. PLR is an expensive and easy-to-apply indicator for predicting the severity of coronary heart disease (CHD) [7, 9, 10, 12, 13]. In Indonesia, however, studies regarding the association of PLR and

CIMT in SLE patients are still limited. Therefore, this study sought to evaluate the relationship between PLR and CIMT among the patients with SLE.

2. Methods

A cross-sectional study was conducted among registered systemic lupus erythematosus (SLE) patients at Dr. Zainoel Abidin Hospital, Banda Aceh from July to December 2020. The patients aged over 18 years, diagnosed with LES according to American College of Rheumatology (ACR) 1997 criteria, and undergoing outpatient treatment in rheumatology division of internal medicine were included in the study. On the other hand, the patients who were pregnant, had severe LES or LES accompanied by thrombocytopenia, had chronic kidney disease undergoing hemodialysis treatment, and those with malignancy were excluded. Ethical Approval was obtained from the Institutional Review Board of Faculty of Medicine, Universitas Syiah Kuala/ Dr. Zainoel Abidin Hospital Banda Aceh (085/EA/FK-RSUDZA/2020).

Two variables were used in the study: independent (the platelets-lymphocytes ratio, PLR) and dependent (the carotid intima-media thickness, CIMT). The PLR was determined by dividing the platelet count by lymphocyte count using a calculator during a routine blood screening. Other hematological parameters such as hemoglobin, hematocrit, erythrocyte, leucocyte, and diff count were also evaluated. CIMT was measured using B Mode Doppler ultrasonography (USG) at several anatomical points on the carotid artery. CIMT values of <0.9 mm was considered normal; > 0.9 mm (thickened); and >1.2 mm (atherosclerosis plaque) (24). Several demographic (age, gender) and clinical characteristics (duration of disease diagnosis, medicamentosa, and comorbidities) of the patients were also recorded.

Data analysis was performed using SPSS software. Categorical variables were expressed as number and percentage (%), while quantitative variables were presented as mean ± SD (standard deviation) and median range (min-max). Univariate analysis was done to provide the distribution of frequency of each tested variable, whereas bivariate analysis using Fisher's exact test was performed to identify the association between PLR and the CIMT. Variables examination was done at a 95% confidence interval and a p-value of ≤ 0.05 was considered statistically significant.

3. Result

A total of 33 SLE patients were included in the study and most of them (48.4%) aged between 26-35 years. The patients' characteristics based on the carotid intima-media thickness are presented in Table 1. The vast majority of patients (31 participants, 94%) had a normal CIMT, whereas 2 (6%) patients were found with thickened carotid intima-media, with an equal contribution between males and females (50% each). There was a significant difference in ages between those who have normal and thickened tunica intima (p-value <0,001) with an average age gap of 20.92 years. The thickening of tunica intima occurred in the patients between 44-55 years of age (mean: 53 years). No significant difference was noticed between the two groups in terms of gender, duration of the disease diagnosis, and medicamentosa. The average duration of the disease diagnosis was 24 months in the patients with a normal CIMT and 78 months in those with thickened intima-media. The PLR median was found higher, but not statistically significant, in the patients with normal CMIT (normal: 209 vs thickened: 129.26) (Table 1). There was also no significant difference (p-value > 0.05) in all of the hematological parameters between the two groups of the patients (normal and thickened tunica intima) (Table 2).

The association between the PLR and CIMT is shown in Table 3. Most of the patients (51.5%) with elevated PLR had a normal CIMT. There was only 1 patient (3%) found with an increased PLR along with the thickening of the carotid intima-media. Fisher's exact analysis suggests no significant relationship between the PLR and CIMT (p-value = 1.000) among the patients with SLE in the present study.

4. Discussion

We conducted a cross-sectional study among the systemic lupus erythematosus (SLE) patients at Dr. Zainoel Abidin Hospital, Banda Aceh. SLE is a complex autoimmune disease with unknown etiology, yet presents with highly variable prognoses and clinical manifestations [14]. Our data suggested that women and those aged between 26-35 (mean age: 32.6 years) were more likely to suffer from SLE (Table 1). Previous studies have reported that the common ages for women diagnosed with SLE were 30-40 years [15], with the peak incidence occurring in the late (60 years) age group [16]. Age has been recognized as one of the multifactorial etiologies in SLE and is presumably associated with the use of hormonal contraception at both productive and menopause periods, causing the alteration in the hormonal mechanisms [15, 17].

Table 1. Baseline characteristics of the patients based on tunica intima thickness

Characteristics	Tunica Intima Thickness		P-value
	Normal	Thickened	
Gender, n (%)			0.335
Male	5 (16.1)	1 (50)	
Female	26 (83.9)	1 (50)	
Age (year), mean ± SD	32.6 ± 7.83	53.5 ± 2.12	<0.001*
Age groups (year), n (%)			0.001*
18 – 25	5 (16.1)	0	
26 – 35	15 (48.4)	0	
36 – 45	9 (29)	0	
46 – 55	2 (6.5)	2 (100)	
Duration of the diagnosis (month), Median (min-max)	24 (1-96)	78 (12-144)	0.545
Medicamentosa, n (%)			0.118
Mycophenolate Mofetil	4 (12.9)	1 (50)	
Mycophenolate mofetil + Methylprednisolone	18 (58.1)	-	
Leflunomide + Methylprednisolone	1 (3,2)	-	
Cyclosporine	1 (3.2)	1 (50)	
Cyclosporine + Methylprednisolone	3 (9.7)	-	
Hydroxychloroquine	1 (3.2)	-	
Methylprednisolone	3 (9.7)	-	
Comorbidities, n (%)			0.006*
Hypertension	1 (3.2)	2 (100)	
None	30 (96.8)	0	
PLR, median (min-max)	209 (76–520.8)	129.26 (35.18 – 223.3)	1.000

Table 2. Hematological examinations of the patients

Characteristics	Tunica Intima Thickness		P-value
	Normal	Thickened	
Hemoglobin, mean ± SD	11.7 ± 1.62	12.5 ± 0.98	0.482
Hematocrit, mean ± SD	38.4 ± 3.26	42.5 ± 0.7	0.097
Erythrocyte, mean ± SD	4.3 ± 0.63	4.3 ± 0.14	0.989
Leucocyte, mean ± SD	6,879.7 ± 3043.07	8,650 ± 2474.87	0.429
Thrombocyte, mean ± SD	283,716.9 ± 114,428.12	233,000 ± 41,012.19	0.542
Eosinophil, median (min-max)	0 (0 – 2)	0 (0 – 1)	0.496
Basophil, median (min-max)	0 (0 – 1)	0 (0)	0.379
Band neutrophil, median (min-max)	1 (0 – 3)	1 (1 – 2)	0.18
Segmented neutrophil, median (min-max)	64 (19 – 84)	52 (38 – 66)	0.385
Lymphocyte, median (min-max)	24 (8 – 72)	36 (17 – 55)	0.428
Monocyte, median (min-max)	8 (2 – 26)	12 (10 – 14)	0.184

Table 3. The association between the PLR and the CIMT in the patients with SLE

		Carotid arterial tunica intima-media		P-value*
		Thickened	Normal	
PLR, n (%)	Increased	1 (3)	17 (51.5)	1.000
	Normal	1 (3)	14 (42.5)	

**Fisher's* exact test

Studies have reported a higher risk of atherosclerosis in individuals with SLE [10, 18, 19]. Atherosclerosis is associated with the thickening or narrowing of the arteries as a result of plaque buildup [10, 20]. In SLE patients, atherosclerosis can also occur at a relatively young age (20-29 years) due to the early onset of vascular damage [21, 22]. In our study, however, the thickening of the intima-media was observed in the age group of 46-55 years (mean:

53.5 years), and a significant difference in age was depicted between the patient with normal and thickened intima-media (p-value < 0.001) (Table 1). Age has been significantly associated with the development of atherosclerosis in SLE patients as it affects the progressivity of plaque, tunica intima thickness, and coronary arterial calcium [21, 23, 24], and the risk increases at the age of over 45 years in males and over 55 years in females [18, 25]. Other studies suggested that the highest prevalence occurred in the age group of 30-49 and the risk was twice to five times higher in the late-onset SLE [21, 26]. The exacerbation of various atherogenic risk factors in the elderly has contributed to the development of atherosclerosis in patients with SLE [22].

PRL has been considered a potential biomarker of inflammation and is associated with the severity of atherosclerosis [9, 11, 13]. Palette plays an important role in the early process of plaque formation, while lymphocytes serve as a marker of chronic inflammation. Our data revealed that more than half of the patients (18 out of 33, 54.5%) had an increase in PLR (Table 3). The exacerbation in PLR provides an overview of the inflammation and stability of atherosclerotic plaques, as well as indicates the activities of SLE disease itself [11]. Studies have demonstrated that PLR increased in patients with coronary heart disease, aortic stenosis, heart failure, renal failure, malignancy, and SLE [27, 28]. Elevated platelet count or platelet activation contribute to the atherosclerosis onset and development, and decreased lymphocyte count has been reportedly related to major negative cardiovascular events in patients with coronary heart disease [29].

Furthermore, platelets are associated with the pathogenesis of SLE. Compared to healthy individuals, platelet activation is higher in SLE patients as a result of increased production of thromboxane and β-thromboglobulin. Platelet and lymphocyte levels tend to decrease in SLE patients, and thrombocytopenia is one of the criteria indicating disease progression and poor prognosis. A low platelet count is presumably caused by the presence of platelet sequestration in blood vessels due to the presence of immune complexes in the circulation [30, 31]. The condition of lymphopenia in SLE patients is related to the presence of systemic inflammatory response in the pathogenesis of the disease. Thus, there is a relationship between platelet and lymphocyte levels with the overall pathogenesis of SLE [30].

CIMT has been widely recognized as a marker of subclinical atherosclerosis. CIMT examination is useful for predicting the incidence of atherosclerosis and cardiovascular events. It has been suggested as a risk factor for cardiovascular disease and potentially indicates the progression of atherosclerosis within blood vessels [8, 32]. A significant difference in CIMT between SLE patients and control (patients without SLE) has been reported [33]. In addition, CIMT was found to be positively correlated with PLR in hemodialysis patients, and PRL has been suggested as one of the independent predictors of CIMT [34]. Other studies exhibited a significant relationship between lymphopenia and CIMT progression ($p < 0.05$) in SLE patients. Lymphopenia in SLE has been associated with disease activity and the use of glucocorticoid and methotrexate therapy [24]. Long-term treatment with high-dose steroids can trigger the exacerbation of SLE and enhance the risk of cardiovascular complications in the patients [26]. History of lupus nephritis and the use of higher doses of corticosteroids also increased the development of CIMT in SLE patients [24, 35].

In the current investigation, 2 out of 33 SLE patients (6%) had a rise in CIMT, and one of them was discovered with exacerbated PLR as well (Table 3). However, unlike those reported in previous studies, the result of Fisher's exact analysis suggested no significant association between PLR and CIMT in the patients with SLE in the current investigation ($p > 0.05$) (Table 3). In addition, PLR median was found higher in SLE patients with normal CIMT compared to those with thickened carotid intima-media (normal: 209 vs thickened: 129.3). The use of different therapies for SLE treatment and different number of samples utilized in the current study might have contributed to these contrary findings [36].

5. Conclusion

In total, 33 SLE patients were enrolled in the study and more than 50% had increased PLR levels. Most of the patients (94 %) also showed a normal thickness of the carotid tunica intima (< 0.9 mm). However, one patient was found with an increased level of PLR along with the thickening of the tunica intima. The result of Fisher's exact test suggests no significant association between the PRL and CIMT in the patients with SLE (p-value > 0.05). Further investigation or a prospective cohort study regarding the correlation between PLR and CIMT involving a larger number of samples should be conducted to obtain a more definitive conclusion.

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