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Indah Fitri Lestari Saragih
Department of Internal Medicine, Faculty of Medicine, North Sumatera University Medan, Indonesia

Blondina Marpaung
Department of Internal Medicine, Rheumatology Division of North Sumatera University Medan, Indonesia

Savita Handayani
Department of Internal Medicine, Hematology and Oncology Division of North Sumatera University Medan, Indonesia

Corresponding Author:
Indah Fitri Lestari Saragih
Department of Internal Medicine, Faculty of Medicine, North Sumatera University Medan, Indonesia

Assessment of the differences between mean platelet volume (MPV) and platelet distribution width (PDW) values in flare and non-flare groups in Systemic Lupus Erythematosus (SLE) patients

Indah Fitri Lestari Saragih, Blondina Marpaung, Savita Handayani

Abstract
Systemic Lupus Erythematosus (SLE) is an autoantibodies process against the cell nuclei and immune complex that will activate the inflammatory system causing the excitatory threshold of platelet activation to be lower. Increase of significant mortality due to active disease (flare) SLE needs special attention. Study of the association of Mean Platelet Volume (MPV) and Platelet distribution width (PDW) as a marker to predict SLE activity was still controversial. On the other hand, MPV and PDW can be calculated easily in routine and low-cost laboratory tests. This study assesses the differences between Mean Platelet Volume (MPV) and Platelet Distribution Width (PDW) values in flare and non-flare groups in SLE patients. We found a significant difference in MPV values between flare compared to non-flares groups. Based on Receiver Operating Characteristic (ROC) curve showed an optimal cutoff value for MPV in the flare group is 9.15 fl and high sensitivity (90.6%). We recommend MPV value for initial screening in the detection of active (flare) SLE.

Keywords: systemic lupus erythematosus, MEX-SLEDAI, mean platelet volume, platelet distribution width

1. Introduction
Systemic Lupus Erythematosus (SLE) is an autoimmune disease signed with the absence of autoantibodies against cell nuclei and immune complexes that will activate the inflammatory system, thereby causing damage to the targeted organs[1-2]. The CDC Lupus registry estimates an annual prevalence from 2002-2004 in Asia (94.7 and 56.2 per 100,000 people, respectively). The yearly incidence of different racial/ethnic groups from 2002-2004 was significantly higher for blacks than whites for Asians, the incidence being 4.2 and 3.8 per 100,000 people, respectively. SLE was identified as the cause of death, with an average of 2,061 deaths per year over the seven years [3]. Late diagnosis, poor therapeutic adherence, and persistent SLE disease activity play a significant role in the prognosis of SLE patients [4]. The MEX-SLEDAI Index evaluates SLE activity in the last ten days with 85.7% sensitivity and 100% specificity. The Mex-SLEDAI has scores from 0 to 24[5]. The pathogenesis of SLE disease is not yet fully known. Antinuclear antibodies (ANA) and Anti-Ds-DNA antibodies are the disease's hallmark and shall be the initial test performed in SLE. Autoantibodies may be associated with a particular clinical subset of SLE, while others may serve as a marker of disease activity [6]. Several studies found that platelets have an important role to play in inflammatory processes and immune responses[7-9]. Hematologic manifestation can occur in SLE were anemia, leukopenia secondary to neutropenia, lymphopenia, and thrombocytopenia can be mild or severe [6]. These hematologic abnormalities are due to several immune and nonimmune mediated mechanisms. It was associated with excessive production of cytokines, antibodies, immune complexes, growth factor deficiencies, increased peripheral accumulation, a decreased life span, reduced neutrophil functions, gastrointestinal losses, and toxicity of medication [7]. SLE affects the numbers, ratios, and volumes of peripheral blood cells involving Mean platelet volume (MPV) is a parameter of a complete blood cell count (CBC) [7]. Platelets (PLT) play a role in inflammatory reactions and immune response. Platelet distribution width (PDW) that shows the heterogeneity in PLT morphology is clinically related to PLT activation. Several studies have reported that MPV and PDW are useful markers of SLE disease activity was still controversial [7,10-14]. The low cost and widely available examinations, make this study focus on how MPV and PDW affect SLE disease activity [10].

2. Materials and methods

2.1 Materials

This study used a cross-sectional design inclusion 64 respondents were selected consecutively in June 2020 among SLE patients who came to H. Adam Malik Hospital. Inclusion criteria were: men and women who were not pregnant aged > 18 years, patients diagnosed with SLE according to updates of the American College of Rheumatology (ACR) revised criteria for the classification of SLE in 1997, each respondent were assessed the course of SLE disease activity by scoring MEX-SLEDAI. The MEX-SLEDAI score ranges from 0 to 32; SLE flare (active) is defined as a MEX-SLEDAI score >5 and SLE remission or inactivity score ≤2. All respondents provided informed consents, and cooperative. The exclusion criteria included SLE patients with a massive stress (severe trauma, surgery, cardiac shock, burns), severe renal insufficiency (GFR) <30 ml/min), cirrhosis of the liver, having hematological disorders such as ITP, microtiter hypochromic anemia, macrocytic anemia, or other diseases that directly affect platelet size and volume such as hypertension, diabetes mellitus, obesity, dyslipidemia, and sepsis. This study had an ethical clearance approval from the Medical Faculty of North Sumatera University Health Research Ethical Committee. In this study, we assessed the course of SLE disease activity by scoring MEX-SLEDAI. Patients who had their venous blood drawn for complete blood count (CBC). CBC was analyzed using an automated hematology analyzer Sysmex XN-1000, then MPV and PDW were noted. The normal value of PDW is 10.0 - 18.0% with a decrease in value (PDW <10.0%) and an increase (PDW> 18.0%). MPV has a normal value of (6.5-9.5 fl) by indicating a decrease in value (MPV <6.5 fl) and an increase (MPV> 9.5 fl). The research data were processed using SPSS 20th.

2.2 Mathods

Analysis data used univariate analysis to represent frequency distribution of gender, age, MEX-SLEDAI score, platelet count, ANA test, and anti-dsDNA.The bivariate analysis uses to find out the difference in MPV and PDW values between flare and non-flare groups in SLE patients using the Mann-Whitney test. The data were considered as significant if the p-value was <0.05.

3. Results & discussion

3.1 Results

Table 1: Characteristics of research subject

Variable	Flare (n=32)	Non-Flare (n=32)	*P-Value*
Sex, n(%)			0.302
Male	3 (9.3)	1 (3.1)	
Female	29 (90.7)	31 (96.9)	
Age, Median (min-max) years	26 (18-45)	30 (19 -53)	0.463
Trombocytes	260156 ±92286	268968 ±85114	0.86
MEX-SLEDAI, Median (min-max)	12 (6-21)	2 (1-2)	<0.001*
Anti dsDNA, Median (min-max)	190 (13.2-886.0)	55.6 (23.2-570.0)	0.005*
ANA Test, Median (min-max)	107.5 (11.0-257.0)	62.7 (14.0-268.0)	0.113

Anti dsDNA: Antibodi Anti-double stranded DNA; ANA: Antinuclear Antibodies test; *p<0.05

The characteristic of research subject (table 1) in the flare group showed the most commonly were female 29 (90.7%) with an age range of 18–45 years, average platelet count (260156), median MEX-SLEDAI score=12, Anti-ds DNA level 190 (13.2-88.0) and ANA test level 107.5 (11.0-257.0).

In the non-flare group, the majority were female 31 (96.9%) with an age range of about the same as flares group of 19 – 53 years, average platelet count (268.968), median MEX-SLEDAI score=2, the Anti-ds DNA level 55.6 (23.2-570.0) and ANA tests 62.7 (14.0-268.0).

Based on the frequency distribution of respondent characteristics between the SLE flare group and the non-flare group, the Mann-Whitney test showed significant difference in the MEX-SLEDAI score (p<0.001) and Anti ds DNA (p=0.005).

Table 2: The Relationship of MPV, PDW levels to flare and non-flare SLE groups

Variable	Flare (n=32)	Non-Flare (n=32)	*P-Value*
MPV, Mean ± SD	9.03±2,02	10.350 ± 1.09	0,002*
PDW, Mean ± SD	11.75±3,14	10.560 ± 2.13	0,083

MPV: Mean Platelet Volume; PDW: Platelet Distribution Width, *p<0.05

MPV and PDW as a biomarker for the course of SLE in table 2 shows a significant difference in the mean MPV value in the flare group higher than the non-flare group [(9.020 + 2.010 vs. 10.35 ± 1.09) fl, (p = 0.002)]. Eventhough the mean value of PDW was not statistically significant.

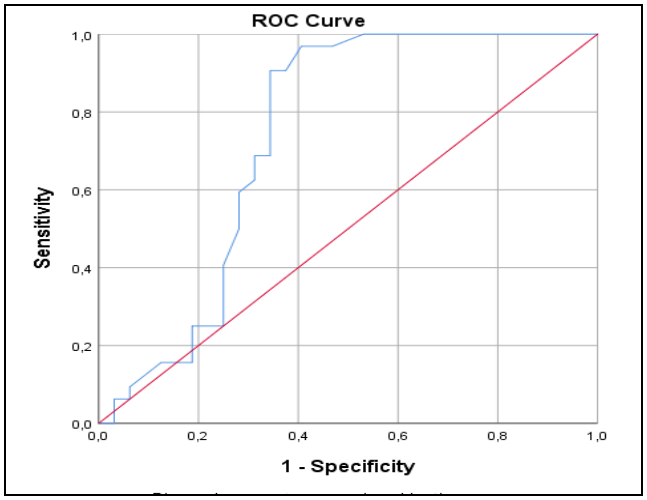

Fig. 1 ROC curve of MPV levels in the flare group.

3.2 Discussion

Most of the respondents with SLE were female. In general, SLE affects females most commonly than males with a ratio (12: 1) [15]. This fact associated with hormonal impact is a significant risk factor for SLE. Estrogens and prolactin induce autoimmunity and increase the B-cell activation factor production and modulate lymphocyte and pDC activation. In contrast, androgens are considered protective in SLE [6]. Several studies also found that the majority of SLE patients

were female such as study in Colombia (84.5%), Sweden (87%), and Jakarta (98.4%) [16-18]. The age range of respondents with SLE in the flare group was 26 (18-45) years in line with other studies that found almost the same that the median age of SLE group was 47 years, (18-64) years, and 19 - 50 years[11,19-20].

The laboratory results showed that the mean platelet count was lower in the flare group than in the non-flare SLE group (260156 ± 92286 vs. 268968 ± 85114). In line with the previous study showed that the platelet count was lower in the flare group SLE (268.88 ± 870.02 vs. 271.72 ± 698.07)[11]. However, another study found that the SLE in the non-flare group had a lower value than the flare group (244.0 ± 49.5 vs. 270.0 ± 105700)[12].

There was a significant difference in the value of Anti dsDNA between the SLE flare group and the non-flare group [190 (13.2-886) vs. 55.6 (23.2-570), (p = 0.005)]. Gheita *et al*. showed the same result, where the mean value of anti dsDNA increased significantly compared to the control group based on SLE disease activity criteria with SLEDAI and SLICC/ACR scores [(133.2 ± 100.50 vs. 22.03 ± 17.20) IU/mL, (p<0.0001)][21]. Study Narayanan K. also showed a significant positive correlation between the Anti-dsDNA value and the SLEDAI score (p=0.01)[22].

The antinuclear antibody (ANA) is a general term for autoantibodies against various nuclear components that can be seen in all kinds of rheumatic diseases. Anti-double-stranded DNA (ds-DNA) dsDNA antibodies are useful in confirming the diagnosis in the clinical settings when SLE is likely to be the diagnosis, because high concentrations of anti-ds-DNA antibodies are almost exclusively present in SLE patients, anti-ds-DNA antibodies are SLE-specific. Qu *et al*. showed a sensitivity of ANA (95.36%) and specificity of the anti-ds-DNA antibody (96.90%) in SLE diagnosis. ANA has the highest sensitivity in the diagnosis of SLE, but its specificity is the worst. Otherwise, anti-ds-DNA antibody has the lowest sensitivity for SLE diagnosis, but the highest specificity. Eventhough, they have limited usefulness in monitoring disease activities and in predicting flares [23,24].

Complete blood count parameters provide a significant marker of systemic inflammation. PDW and MPV became popular and vital markers of platelet activation. Studies with SLE showed lower MPV scores and higher PDW scores in patients and a positive relationship between PDW and disease activity [10,25]. In contrast, a study in DLE patients found no significant difference between PDW and MPV levels in the healthy control group [19].

MPV has been considered a reliable marker to indicate platelet activation and inflammation. Decreased MPV levels were observed in patients with SLE associated with an active inflammatory state associated with disease activity [25]. Decreasing MPV value is caused by large consumption and activated platelets in the place of extravascular inflammation [13]. This study found MPV in SLE respondents was significantly lower in the flare than in the non-flare group [(9.02 + 2.01 vs. 10.35 ± 1.09) fl (p=0.002). In line with others studies such as Safak *et al*., [(7.66 ± 0.89 vs. 8.62 ± 1, 06) fL, (p<0.0001)][25], Hartmann *et al*., [(10.0 ± 0.7 vs. (10.7 ± 1.0) fl, (p = 0.005)][12], Garcia *et al* [(7.16 ± 1.39 vs. 8.16 ± 1.50) fl (p=0.005)][11] and Chen *et al* [(10.74 ± 0.94 vs. 11.09 ± 1.14), p<0.001][10].

The amount of inflammation affected the decreasing MPV values in RA and SLE patients due to the high consumption of large platelets in the area of inflammation (p<0.004)[13]. The MPV value showed a significantly higher amount in SLE patients than RA [(9.5 ± 1.7 vs. 8.7 ± 1.6) fl, p<0.05)][7]. On the other hand, another study stated that the results were different obtaining a higher MPV value in the flare than non-flare in juvenile SLE patients statistically significant (p=0.001) and also positively correlated with SLEDAI scores (p=0.01, r=0.55)[14]. Study Islamoglu *et al*. found no significant difference in MPV value between patients with Discoid Lupus Erythematosus (DLE) and the control group (p=0.160), where the limitation of the study was a retrospective design that collected minimal data on a patient[19].

Based on this study, the PDW value was higher in the flare group compared with the non-flare group but not statistically significant [(11.75 ± 3.14 vs. 10.56 ± 2.13), (p = 0.083)]. In line with study Sherif *et al*., showed that the difference of PDW values in 80 (mild - severe) flares compared to non-flare SLE patients with controls group were mild flare (13.35 ± 2.27), moderate flare (13.81 ± 2.98), severe flare (12.68 ± 3.06) non flare group (12.94 ± 3.0) and control group (14.27 ± 2.17) statistically not significant (p=0.367)[20]. The study of Islamoglu *et al*. also showed no significant difference in PDW value between DLE patients and the control group [(16.4 ± 2.7 vs. 16.4 ± 0.78) (p=0.988)][19].

In contrast, Chen *et al*. found that the PDW value in SLE was significantly increased in the flare compared to the non-flare SLE group [(14.31 ± 2.90 vs. 12.15 ± 1.55), (p<0.001)], but the limitation of the study was the relatively small number of samples, which affects external validation[10]. In comparison, the study of He *et al*. (2020) obtained higher PDW values in SLE patients with Pulmonary Arterial Hypertension (PAH) than SLE without PAH. PDW and MPV values have a negative correlation between platelet counts and PDW (r = -0.770; p <0.05), MPV (r=-0.523; p <0.05), in other words, the lower of platelet count correlate in increasing PDW and MPV values in dengue shock syndrome and DHF respondents[26].

Characteristic signs of chronic inflammatory disease were abnormal immune system regulation, and persistent inflammation affects the hematopoiesis system. Peripheral blood cell changes use to diagnose disease activity and several collagen diseases such as RA, SLE, and Sclerosis [7]. Platelets can form ROS (reactive oxygen species). Oxidative stress plays a role in the inflammatory process, will activate platelets so that platelets have a primary role in the pathophysiology of disease [27]. Other platelet function markers such as PDW, can represent the heterogeneity of platelet morphology and are clinically associated with platelet activation. Also, MPV assesses the platelet size most frequently used. These parameters evaluate in routine blood tests [10].

The heterogeneity of MPV and PDW values may be due to differences in patient clinical characteristics, treatment strategies, race, and sex comparisons. The mechanism of decreasing MPV value in flare group SLE patients was associated with the release of proinflammatory platelet bioactive molecules. Excess production of proinflammatory cytokines can suppress the bone marrow, followed by the creation of smaller platelet sizes. The increase in MPV in SLE patients in the flare group tends to be associated with vascular events, thrombocytopenia, and condition after receiving treatment [20].

Mean platelet volume in the flare group SLE respondents had a cutoff of 9.15 fl with sensitivity (90.6%) and specificity (66%). Previous studies had cutoff value results for MPV in the flare SLE group, such as the Hartman *et al*. 9.85 fl with sensitivity (61%) specificity (24%) [12], Garcia *et al*. 8.32 fl

with sensitivity (86%) and specificity (41%)[11], Yavuz *et al*. 8.4 fl with sensitivity (75%) and specificity (90%)[14]. The limitations of this study were the delayed time between sampling and examination of the sample, small amount number of samples, and do not involve observation of the history of drug use and treatment activities in disease so that it can bias the results of the study.

4. Conclusions

This study concludes that the mean MPV value has a significant difference between a flare and non-flare group of SLE. The AUC curve shows an optimum cutoff value of the flare group (9.15 fL) and high sensitivity. We recommend MPV for initial screening in the detection of active (flare) SLE.

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