Correlation Between Mex-Sledai and Mean Platelet Volume In Systemic Lupus Erythematosus Patients

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ABSTRACT

Background. Systemic lupus erythematosus (SLE) is a chronic autoimmune disease which has a variety of clinical phenotypes with a complex clinical course. The clinical phenotypes are highly variable which can be characterized by acute attacks, active periods, controllable or remission. Mean platelet volume (MPV) is a straightforward accessible indicator of platelet activity and is associated with systemic inflammation. The routine usage of MPV as markers for disease activity in SLE remains problematic. Early detection of disease progression is pivotal in the management of SLE for obtaining better outcomes. Objective. The study aimed to confirm that the measurement of the disease severity in patients with SLE using Mex-SLEDAI has a negative correlation with the decrease of MPV value. Methods. This cross-sectional analytic descriptive study was conducted using secondary data from the medical records of patients with SLE older than 18 years of age who were not taking antiplatelets in the Internal Medicine policlinic of Dr. Sardjito General Hospital in 2018. Patients with a previous history of cardiovascular and cerebrovascular events, malignancies, receiving a treatment for infections, including sepsis, chronic infections (i.e. tuberculosis, cytomegalovirus, herpes simplex, herpes zoster), HIV, hepatitis B or hepatitis C, and incomplete data of medical record were excluded. The correlation between SLEDAI Mex and MPV values was evaluated using the Spearman’s correlation test. Results. Sixty-seven subjects (65 women, 2 men) aged 34 ± 11 years were recruited in the study. The median duration of diagnosis was 38.2 ± 45.7 months. Arthritis, skin rash and photosensitivity were identified in 81.1%, 53.7%, and 46.3% of patients, respectively. The Mex-SLEDAI score ranged from 0 to 16. The average of MPV value is 9.73 ± 1.21 fL. A significant correlation between MPV and SLEDAI Mex was observed (p = 0.03 (p <0.05), r = -0.255). Conclusion. The more severe SLE disease activity (based on the Mex-SLEDAI scoring), the more negative correlation with the MPV value.

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with a variety of clinical phenotypes. SLE is more common in women than men, with a ratio of around 6: 1. Black people have the highest incidence and prevalence of SLE worldwide, followed by Asian and then the white group. A United States study reported an increase in the incidence of SLE between 1950 and 1992. This increase might be partly due to the improvement of ability to diagnose SLE. Reported values for the incidence and prevalence of SLE vary widely around the world with an overall incidence ranging from 0.3-31.5 cases per 100,000 population per year, and prevalence of 3.2-517.5 cases per 100,000 population. The prevalence of SLE has been reported in several countries, including 37-97.5 cases per 100,000 population in Taiwan, 43 cases per 100,000 population in Thailand, and 14 cases per 100,000 population in Japan.
population in Malaysia, and 19.3-92.8 cases per 100,000 population in Australia².

SLE disease trends in hospital inpatients in Indonesia increased from 2014-2016. In 2014, there were 1,169 cases with 110 fatalities and the number was increased to 2,166 cases with 550 fatalities in 2016. A study reported that deaths occurred in 1 out of 4 people being hospitalised due to SLE. Therefore, due to its high mortality, establishing an early detection of SLE progression is required³. Cardiovascular disease, infection, and various diseases related to major organs such as the kidneys, brain and lungs are considered the cause of death among SLE patients⁴.

Clinical manifestations of SLE vary depending on the organ involved with a complex clinical course. The clinical phenotypes are highly variable which can be characterized by acute attacks, active periods, controllable or remission. Disease activity is defined as reversible clinical and laboratory manifestations, reflecting the immunological and inflammatory manifestations of an organ involvement due to lupus at a certain time point. Assessment of disease activity is expected to be practically applicable, allowing an easy and inexpensive data collection and uncomplicated interpretation. SLE disease activity can be assessed by a scoring system named Mexican systemic lupus erythematosus disease activity index (MEX-SLEDAI)⁵.

Mean platelet volume (MPV) is a straightforward accessible indicator of platelet activity and is associated with systemic inflammation. MPV examination can be performed although laboratory blood tests are measured using a rapid and inexpensive tool such as automatic blood counter⁶. During platelet activation due to inflammation, the platelet morphology reshapes from discoid to spherical and increases its volume (higher MPV value) to obtain a larger surface. A larger platelet size indicates a more active functional, metabolic and enzymatic activities. The activated platelets contain more granules, consisting of essential compounds which are stimulated during platelet activation. Therefore, MPV can be applied as a marker of platelet function and activation. Platelet size depends on the intensity of systemic inflammation, inversely proportional to MPV levels in high and low degree of inflammation and in anti-inflammatory treatment. In a high-grade systemic inflammatory disease such as SLE, MPV level is generally smaller than healthy people⁷.

The routine usage of MPV as markers for disease activity in SLE remains problematic. Early detection of disease progression is pivotal in the management of SLE for obtaining better outcomes. The study aimed to confirm that the measurement of the disease severity in patients with SLE using Mex-SLEDAI has a negative correlation with the decrease of MPV value.

Behçet’s disease is a rare disorder that causes blood vessel inflammation throughout body. The disease can lead to numerous signs and symptoms, include mouth sores, eye inflammation, skin rashes and lesions, and genital sores. Treatment involves medications to reduce the signs and symptoms of Behçet’s disease and to prevent serious complications, such as blindness. Steroids and immunosuppressive agents are drugs of choice. The presence of infections makes the management become dilemmatic.

**Method**

This cross-sectional analytic descriptive study was conducted using secondary data from the medical records of patients in the Internal Medicine policlinic of Dr. Sardjito General Hospital in 2018. The SLEDAI Mex was selected as an independent variable and the MPV value was chosen as the dependent variable. The confounding variables in this study were diabetes mellitus, hypertension, infection, smoking, cerebrovascular or cardiovascular disorders, malignancy and depression. Confounding variables were partially controlled by the restriction method. The other variables which could not be
controlled were evaluated using specific analysis (adjustment).

Large calculation formula was determined based on the sample size formula for correlative research with the value of r was the expected occurrence. Based on the formula studied by Yavuz and Aydin Ece, r value of this study was 0.55, resulting the minimum sample size of 338. The inclusion criteria used in this study included outpatients aged more than or equal to 18 years with a final diagnosis of SLE and did not consume anticoagulants and or antiplatelet. Exclusion criteria applied in this study included patients with a previous history of cardiovascular and cerebrovascular events, malignancies, receiving a treatment for infections, including sepsis, chronic infections (i.e. tuberculosis, cytomegalovirus, herpes simplex, herpes zoster), HIV, hepatitis B or hepatitis C, and incomplete data of medical record were excluded. The correlation between SLEDAI Mex and MPV values was evaluated using the Spearman’s correlation test. A p value ≤0.05 with 95% confidence interval (CI) was considered significant.

**Result**

This cross-sectional analytic descriptive study involved 72 patients with SLE in the Outpatient Installation of Department of Internal Medicine of Dr. Sardjito General Hospital in 2018. Five patients were excluded due to infection (3 patients) and incomplete medical records (2 patients) (figure 1).

![Figure 1. Study Flow chart](image)

The average age of SLE patients recruited in this study was $34 \pm 11$ years. There was a considerable difference in the number of subjects based on sex with a female predominance of 97% (65 out of 67 subjects). The mean duration of patients being treated with SLE was $38.2 \pm 45.79$ months. Several clinical manifestations of SLE were documented in this study, including arthritis (81.1%), skin rash (53.7%), photosensitivity (46.3%), alopecia (41.8%), oral or nasal ulcers (38.8% ), lupus nephritis (31.3%), hemolytic anemia (19.4%), neuropsychiatric (19.4%), serositis (14.9%), thrombocytopenia (10.3%) and leukopenia (9%).

Laboratory findings from the subjects showed mean of hemoglobin levels of $11.7 \pm 1.85$ g/dL, platelets levels of $311 \pm 117 \times 10^3 \mu L$, and MPV values of $9.73 \pm 1.21$ fL. SLE disease activity assessed in this study using Mex-SLEDAI resulted a mean value of 5.9 (0-16). Confounding variables in this study were documented from people with diabetes mellitus (1.5%), hypertension (6.1%) and smoking (3%) (table 1). Furthermore, subjects with depression were evaluated using the Beck Depression Index showing an average score of 13.4 ± 9.8.
Table 1. Basic characteristics of research subjects

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (in years old), mean±SD</strong></td>
<td>34 ± 11</td>
</tr>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Female</td>
<td>65 (97)</td>
</tr>
<tr>
<td><strong>Disease duration (in months), mean±SD</strong></td>
<td>38.2 ± 45.79</td>
</tr>
<tr>
<td><strong>Mex-SLEDAI score, median (Min-Max)</strong></td>
<td>5.9 (0-16)</td>
</tr>
<tr>
<td><strong>BDI Score, mean ± SD</strong></td>
<td>13.4 ± 9.8</td>
</tr>
<tr>
<td><strong>Comorbidity</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>4 (6.1)</td>
</tr>
<tr>
<td>Diabetes Mellitus, n (%)</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>Smoker, n (%)</td>
<td>2 (3)</td>
</tr>
<tr>
<td><strong>Early Manifestation, n(%)</strong></td>
<td></td>
</tr>
<tr>
<td>Malar rash</td>
<td>36 (53.7)</td>
</tr>
<tr>
<td>Photosensitivity</td>
<td>31 (46.3)</td>
</tr>
<tr>
<td>Oral Ulcer</td>
<td>26 (38.8)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>28 (41.8)</td>
</tr>
<tr>
<td>Arthritis</td>
<td>55 (81.1)</td>
</tr>
<tr>
<td>Lupus nephritis</td>
<td>21 (31.3)</td>
</tr>
<tr>
<td>Hemolytic anemia</td>
<td>13 (19.4)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>6 (9)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>7 (10.4)</td>
</tr>
<tr>
<td>Serositis</td>
<td>10 (14.9)</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td>13 (19.4)</td>
</tr>
<tr>
<td><strong>Laboratory Results, Mean ± SD</strong></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin, g/dl</td>
<td>11.7 ± 1.85</td>
</tr>
<tr>
<td>Leukocyte, $10^3/\mu$L</td>
<td>7.46 ± 4</td>
</tr>
<tr>
<td>Thrombocyte, $10^3/\mu$L</td>
<td>311 ± 117</td>
</tr>
<tr>
<td>Mean Platelet Volume, fL</td>
<td>9.73 ± 1.21</td>
</tr>
</tbody>
</table>

The degree of SLE disease activity was measured using the Mex-SLEDAI. The scores were made in numerical form to assess its correlation with MPV values as shown in figure 2. A significant correlation between MPV and Mex SLEDAI was observed ($p = 0.03$, $r = -0.255$).
Analysis of the MPV value on each Mex-SLEDAI component showing leukopenia or lymphopenia (n=34 (50%), p=0.67), hemolysis or thrombocytopenia (n=29 (43%), p=0.281), arthritis (n=26 (38%), p=0.308), kidney disorders (n=22 (32%), p=0.342), mucocutaneous disorders (n=20 (29%), p=0.314), neurological disorders (n=3 (4%), p=0.604), vasculitis (n=3 (4%), p=0.27), myositis (n=2 (3%), p=0.792), and fever or fatigue (n=2 (3%), p=0.394).

Analysis of confounding variables in the study resulted in no correlation between MPV values and selected variables as follows: smoking (p = 0.792), diabetes mellitus (p = 0.446); hypertension (p = 0.761) (table 2); and depression as measured by Beck's Depression Inventory (BDI) scores with MPV value (p = 0.082, r = -0.172) (figure 3).

Table 2. Relationship between Confounding Variables and MPV

<table>
<thead>
<tr>
<th>Mean Platelet Volume</th>
<th>Mean</th>
<th>Standard Deviation</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoker</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9.95</td>
<td>.35</td>
<td>0.792</td>
</tr>
<tr>
<td>No.</td>
<td>9.72</td>
<td>1.23</td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>8.80</td>
<td></td>
<td>0.446</td>
</tr>
<tr>
<td>No.</td>
<td>9.74</td>
<td>1.22</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>9.55</td>
<td>.38</td>
<td>0.761</td>
</tr>
<tr>
<td>n No.</td>
<td>9.74</td>
<td>1.26</td>
<td></td>
</tr>
</tbody>
</table>
Multivariate analysis was carried out to determine the variables which could be predictors of disease activity as measured by Mex-SLEDAI. Depression (measured by BDI) and the degree of SLE disease activity (measured by Mex-SLEDAI) with p <0.25 in the bivariate test were further analysed using multivariate approach. Both BDI and Mex-SLEDAI have no significant effects on the MPV values. Both of these variables only contributed an influence of 6.7%, whereas the remaining were influenced by other factors.

<table>
<thead>
<tr>
<th>Regression coefficient</th>
<th>95.0% Confidence Interval for B</th>
<th>R²</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Constant)</td>
<td>10.277</td>
<td>0.000</td>
</tr>
<tr>
<td>Mex-SLEDAI</td>
<td>-0.054</td>
<td>0.129</td>
</tr>
<tr>
<td>BDI</td>
<td>-0.017</td>
<td>0.263</td>
</tr>
</tbody>
</table>

Table 3. Multivariate analysis of SLE disease activity and depression for MPV

Discussion

The recruited subjects in this study consisted of 2 male subjects and 65 female subjects, with an average age of 34 years. In accordance with available epidemiologic data, SLE is more often found in women and in the productive age. In this study, the musculoskeletal manifestation such as arthritis was the most common manifestation observed at the time of diagnosis (83.9%). The finding was relatively similar with previous studies which reported an average occurrence in 81.1% of cases9.10. A study conducted by Mok and Lau suggested malar rash as the second most common mucocutaneous manifestation (56%). Interestingly, the current study indicated skin rash as the most reported mucocutaneous manifestation by 53.7%, followed by photosensitivity (46.3%), alopecia (41.8%), and oral or nasal ulcers (38.8%) 10.

The current study also suggested nephritis ranked third most common clinical manifestations by 31.3%. A previous study performed by Salido and Reyes reported the incidence of nephritis in third place in most Asian countries, except in Singapore and India ranked first and second, respectively11.
haematological findings were identified in the current study, including haemolytic anemia (19.4%), thrombocytopenia (10.4%), and leukopenia (9%). These findings were relatively lower than those from other Asian countries as reported by Salido and Reyes (26-83.8%) and even inversely proportional with a Saudi Arabian study reporting an average of 82.7%.\textsuperscript{11,12} Compared to a Malaysian study, the incidence of neuropsychiatry in this study was relatively lower than the Malaysian report by 19.4% and 23%, respectively. However, the incidence of serositis identified in the current study was higher than the Malaysian study by 14.9% and 6%, respectively\textsuperscript{13}.

Numerous studies showed different variations and dominant manifestations. The association between countries, regions, and races was not clearly reported. Therefore, it is difficult to determine a clear correlation between race and SLE events. Epidemiological variations from different studies might be caused by differences in study populations (communities or hospitals), data collection methodologies, and unstandardized diagnostic facilities\textsuperscript{11}.

Platelets play an active role in inflammation. Platelets are actively involved not only in thrombosis, but also in immune system. The granules contained in platelets have an essential role in the interaction of platelets with other key components in inflammation, including leukocytes, complement, endothelial, nitric oxide and vascular. The larger platelets contain more granules and other molecules than the normal-sized platelets\textsuperscript{7}.

MPV has been reported with various findings in autoimmune diseases such as inflammatory bowel disease, ulcerative colitis, Crohn's disease, and rheumatoid arthritis. Kapsoritakis et al. demonstrated MPV differences in patients with active and non-IBD. In the ulcerative colitis group and Crohn's disease, MPV in active patients was lower than in inactive groups by 8.5 fl vs 9.0 fl and 7.8 fl vs 8.9 fl, respectively. The other hemostasis markers were also increased compared to healthy controls\textsuperscript{14}. On the contrary, Liu et al. showed higher MPV in patients with Crohn's disease compared to normal subjects, but the disease activity was not assessed\textsuperscript{15}.

Regarding the role of platelets in inflammation, MPV is considered to be a parameter for assessing disease activity in SLE. Disease activity is a clinical and laboratory manifestation arising from an inflammation. Mex-SLEDAI was selected as an instrument in this study to assess disease activity because it was practical and economical. Compared to other instruments, Mex-SLEDAI uses more clinical parameters than laboratory parameters. Therefore, serological parameters such as anti-dsDNA and complement are not assessed. Yavuz and Ece showed higher MPV values in juvenile SLE patients than controls\textsuperscript{8}. Bora Ayna et al. suggested the mean MPV value (SLEn + = 9.1 ± 2.2, S = 0.001) and the NLR value (SLEn + = 5.9 ± 5.9, S = 2.6 2.5, p <0.001) were significantly higher in the lupus nephritis group compared to the lupus group without kidney involvement\textsuperscript{16}.

The current study also demonstrated a significant negative correlation between MPV and Mex-SLEDAI (p = 0.033, r = -0.255). It indicates that the higher the Mex-SLEDAI score the lower the MPV value. Thrombopoiesis is influenced by inflammation. Therefore, during the inflammation, the immune system produces more platelets with larger size, which ultimately increase the MPV value. The degree of inflammation affects the platelets distribution. In severe inflammation, more platelets are recruited to the site of inflammation leaving reduced number of circulating platelets with smaller size resulting a low MPV value\textsuperscript{17}.

A decrease in platelet size is also associated with the release of platelet micro particle (PMP) into the extracellular space. Lood et al. reported a decrease in platelet size associated with increased platelet activation which promotes the degree of inflammation in lupus patients with increased formation of
circulating platelet micro particles \( (p < 0.0001, r = -0.46) \)\(^{18}\).

Several studies documented a lower MPV size was more associated to active lupus patients than those without flare. Delgado-Garcia et al. showed a significant decrease of MPV in active compared to inactive lupus patients \( (7.16 \pm 1.39 \text{ vs } 8.16 \pm 1.50, p = 0.005) \)\(^{19}\). MPV had a correlation not only with SLE disease activity as measured by SLEDAI but also with other markers of biological activity (i.e. ESR, CRP levels, proteinuria). Safak et al. demonstrated similar findings showing a decrease in MPV size in the active lupus group\(^{20}\).

The reasons for platelet size being uniformly decreased and its association to platelet activation in SLE remain unclearly understood. After platelet activation, platelets transform its shape, with \( \alpha \)-granules (containing P-selectin) and dense bodies (containing serotonin) fusing with the plasma membrane and releasing their contents, contributing to local prothrombotics and initiating the inflammation. Alteration of platelets morphology and additional granular membranes which amalgamate with the plasma membrane are considered to increase the platelet size. However, exocytosis of solid granules containing serotonin has also been shown in platelet activation, indicating that not all platelet activation will cause fusion of the granule plasma membrane and an increase in platelet size. Furthermore, it has been shown that after the release of PMP ecotosomes, platelet size will decrease. In platelet apoptosis, the release of PMPs is concurrently occurred with the reduced platelet size\(^{17,18}\).

MPV is also affected by depression, diabetes mellitus, hypertension, and smoking. There was no significant correlation observed between MPV values and several variables, including depression \( (p = 0.08) \), smoking \( (p = 0.792) \), diabetes mellitus \( (p = 0.446) \), and hypertension \( (p = 0.761) \). The multivariate analysis showed that BDI with Mex-SLEDAI did not significantly influence the MPV values. Both of these variables only contributed an influence of 6.7%, the remaining were influenced by other factors.

**Conclusion**

The more severe SLE disease activity (based on the Mex-SLEDAI scoring), the more negative correlation with the MPV value. For the further studies, it is recommended to use other devices (such as SLEDAI) to assess disease activity which also assess serological activity and use more specific platelet activation markers (such as \( \beta \)-thromboglobulin).

**References**


