

## Immature Platelet Fraction in Patients with SLE-related Thrombocytopenia

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### ABSTRACT

Systemic lupus erythematosus (SLE) is an autoimmune disease which causes chronic inflammation and may impact various organs. Hematologic abnormality, including thrombocytopenia, is a common clinical manifestation in SLE, ranging between 7-30%. Thrombocytopenia in SLE has been proven to correlate with a more active disease and a worse prognosis. Most of the time, it gets hard to determine the underlying cause of thrombocytopenia. Immature platelet fraction (IPF) examines immature thrombocyte at peripheral blood and can be used to determine whether thrombocytopenia happens because of a decreased production or increased peripheral thrombocyte destruction. This study was done to evaluate immature platelet fraction value in SLE patients with thrombocytopenia. This was a cross-sectional descriptive observational study. Sample was taken from SLE inpatients and outpatients at Dr. Hasan Sadikin Bandung Hospital. There were 24 subjects included in this study, which counts 7.4% of SLE population. The mean platelet count was  $56,870 \pm 28,933 /\text{mm}^3$ . IPF values ranged from 0.9-3.2%, with median 5.7%. The median IPF in moderate-severe thrombocytopenia group was 7.5%, higher than that of mild thrombocytopenia group (4.2%). It can be concluded that IPF values were increased in most SLE patients with thrombocytopenia compared to normal population. It suggests that increased platelet destruction plays an important role in the pathogenesis of SLE thrombocytopenia. A wide range of IPF values shows multifactorial nature of thrombocytopenia causes in SLE patients.

**Keywords:** SLE, thrombocytopenia, IPF

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### ABSTRAK

Systemic lupus erythematosus (SLE) merupakan penyakit autoimun yang menyebabkan inflamasi kronis dan mengenai berbagai organ tubuh. Kelainan hematologi, termasuk trombositopenia, merupakan manifestasi klinis yang umum pada SLE, berkisar 7-30%. Trombositopenia pada SLE telah terbukti berhubungan dengan penyakit yang lebih aktif dan prognosis yang lebih buruk. Seringkali sulit untuk menentukan penyebab yang mendasari terjadinya trombositopenia. Immature platelet fraction (IPF) mengukur trombosit muda di darah perifer dan dapat digunakan untuk menentukan apakah trombositopenia terjadi akibat produksi yang kurang atau karena peningkatan destruksi perifer trombosit. Penelitian ini diadakan dengan tujuan untuk mengetahui gambaran IPF pada SLE dengan trombositopenia. Penelitian ini adalah penelitian yang bersifat observasi deskriptif potong lintang. Sampel diambil dari pasien SLE rawat jalan maupun rawat inap di RSUP Dr. Hasan Sadikin Bandung. Didapatkan 24 subjek yang diikutsertakan dalam penelitian ini, yaitu sebesar 7,4% dari populasi SLE. Nilai rata-rata trombosit subjek penelitian sebesar  $56.870 \pm 28.933 /\text{mm}^3$ . Nilai IPF berkisar 0,9 hingga 3,2%, dengan median 5,7%. Median nilai IPF pada kelompok trombositopenia sedang-berat sebesar 7,5%, lebih tinggi dibanding pada kelompok trombositopenia ringan (4,2%). Dapat disimpulkan bahwa IPF meningkat pada sebagian besar pasien SLE dengan trombositopenia dibandingkan dengan populasi normal, menunjukkan peningkatan destruksi perifer trombosit memegang peranan penting pada patogenesis trombositopenia SLE. Kisaran IPF yang lebar menunjukkan penyebab trombositopenia pada SLE yang bersifat multifaktorial.

**Kata kunci:** SLE, trombositopenia, IPF

## **1. Introduction**

Systemic lupus erythematosus (SLE) is an autoimmune disease that causes chronic inflammation and affect various organ of the body.<sup>1</sup> Haematological involvement is common and included in both American College of Rheumatology (ACR) and Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE. This includes autoimmune haemolytic anemia (AIHA), leucopenia, and thrombocytopenia.<sup>2,3</sup>

Thrombocytopenia is a common clinical manifestation of SLE, ranging from 7-30%.<sup>4</sup> Thrombocytopenia in SLE has been shown to be associated with higher disease activity and worse prognosis.<sup>5,6</sup> However, given the number of potential etiologies of thrombocytopenia in SLE patients, it is often difficult to determine the underlying cause.<sup>4</sup> Bone marrow examination is usually indicated. This procedure has some limitations; it is invasive and sometimes difficult to interpret. The immature platelet fraction (IPF) is a parameter that measures the number of reticulated platelets in peripheral blood, using hematology analyser Sysmex XE-series. This parameter can be used to help determine whether thrombocytopenia is secondary to low-platelet production or increased platelet turnover.<sup>7</sup> There have been many studies conducted on IPF level, such as in ITP, aplastic anemia, and post chemotherapy cytopenia. Until recently, there has not been any report about IPF in SLE patients. The aim of this study is to evaluate IPF level in thrombocytopenia SLE.

## **2. Methods**

This study used a descriptive, cross-sectional study design. This study was conducted in RSUP Dr. Hasan Sadikin. SLE patients with thrombocytopenia were enrolled in this study from August to December 2016. All participants were given informed consent and voluntarily participated in this study. The study was conducted with the approval by the Ethical Committee on Health Research, RSUP Dr. Hasan Sadikin Bandung Number LB.04.01/A05/EC/268/VIII/2016.

## **Data Collection Procedures**

Participants were interviewed and asked to complete a set of questionnaires that contained three sections: **(1)** Baseline and clinical information form; **(2)** Mex-SLEDAI scoring; **(3)** SLICC/ACR damage index scoring. Routine hematological counts and IPF value were also measured on the same day.

**(1)** Baseline data included age and gender. Clinical data included duration of SLE diagnosis, organ involvement, ANA pattern examination, medical treatment and comorbidities.

**(2)** Mex-SLEDAI, a modified version of SLEDAI, was used to measure disease activity of SLE. The score ranges from 0 to 32, with higher score imply greater disease activity. Patients with score less than 2 are said to have clearly inactive disease, those scoring between 2 and 5 are categorized as probable active, while those scoring more than 5 are said to be clearly active.<sup>8</sup>

**(3)** SLICC/ACR damage index was developed to assess the accumulated damage in patients with SLE. This instrument includes assessment of 12 organ systems and records damage occurring in SLE patients regardless of its cause. It may result from previous disease activity, from medication, or from intercurrent illness. To avoid confusion between active inflammation and damage, an item has to be present for at least 6 months to be included in the damage index.<sup>9</sup>

## **3. Results**

There were 24 subjects included in this study. Of 24 patients, 14 (58.3%), 7 (29.2%), and 3 (12.5%) had mild (platelet counts  $>50,000/\text{mm}^3$ ,  $<100,000/\text{mm}^3$ ), moderate (platelet counts  $>20,000/\text{mm}^3$ ,  $\leq 50,000/\text{mm}^3$ ), and severe thrombocytopenia (platelet count  $\leq 20,000/\text{mm}^3$ ). Patients were divided into 2 thrombocytopenia groups according to severity: mild and moderate-severe.

Participants' baseline characteristics are summarized in Table 1. The median age was 31 years old and 91.7% were women.

**Table 1. Baseline Characteristics**

	All n=24	Mild thrombocytopenia n=14	Moderate-severe thrombocytopenia n=10
Age (years), median (min – max)	31 (16 – 64)	33 (22-64)	29 16-36)
Gender, n (%)			
Male	2 (8.3)	2 (14.3)	0 (0.0)
Female	22 (91.7)	12 (85.7)	10 (100.0)

The clinical characteristics of the patients were shown in Table 2. The median SLE duration was 12 months. The most detected ANA pattern was homogenous. Besides hematology, patients also had other organs involvement: mucocutaneous, musculoskeletal, and renal. Most patients had Mex-SLEDAI score >5 that showed increased disease activity.

**Table 2. Clinical Characteristics**

	All n=24	Mild thrombocytopenia n=14	Moderate-severe thrombocytopenia n=10
SLE duration (months), median (min – max)	12 (0 – 180)	38 (0-156)	4 (0-180)
ANA pattern, n (%)			
- <i>Speckled</i>	4 (16.6)	3 (21.4)	1 (10.0)
- Homogenous	6 (25)	3 (21.4)	3 (30.0)
- Cytoplasmic	1 (4.2)	1 (7.1)	0 (0.0)
- No data	13 (54.2)	7 (50.0)	6 (60.0)
Organ involvement, n (%)			
- Mucocutaneous	21 (87.5)	14 (100.0)	7 (70.0)
- Musculoskeletal	18 (75)	11 (78.6)	7 (70.0)
- Renal	24 (100.0)	11 (78.6)	7 (70.0)
- Hematology	7 (29.2)	14 (100.0)	10 (100.0)
- Neuropsychiatry	2 (8.3)	4 (28.6)	3 (30.0)
- Vasculitis	2 (8.3)		0 (0.0)
- Serositis		2 (14.3)	2 (20.0)
- Serositis		0 (0.0)	
Drugs, n (%)			
- Azathioprine	5 (20.8)	5 (35.7)	0 (0.0)
- Cyclophosphamide	1 (4.2)	0 (0.0)	1 (10.0)
Comorbidities, n (%)			
- Sepsis	5 (20.8)	2 (14.3)	3 (30.0)
- Chronic liver disease	1 (4.2)	0 (0.0)	1 (10.0)

MEX-SLEDAI, median (min – max)	10 (3 – 28)	11 (3-28)	10 (4-9)
- <2	(n=0)		
- 2-5	(n=5)		
- >5	3 (3-5) (n=19)	(n=4) 3(3-5) (n=10)	(n=1) 4 (n=9)
SLICC/ACR <i>damage Index</i> , median (min – max)	1 (0 – 7)	1 (0-7)	2 (0-2)

Table 3 shows hematology finding measured by Sysmex XE-series hematology analyzer. Majority of patients (79.2%) had anemia. The hemoglobin level in moderate-severe thrombocytopenia group was lower than that in the mild group.

**Table 3. Hematology Parameter**

	All n=24	Mild thrombocytopenia n=14	Moderate-severe thrombocytopenia n=10
- Hb (g/dL), mean ± SD	9.5 ± 2.9	10.3 ± 2.7	8.4 ± 2.8
- WBC (/mm <sup>3</sup> ), median (min-max)	5.920 (380 – 41.320)	6.130 (1.490 – 14.200)	5.920 (380 – 41.320)
- Platelet (/mm <sup>3</sup> ), mean ± SD	56.870 ± 28.933	4.2 (1.0 – 32.0)	7.5 (0.9 – 20.2)
- IPF (%), median (min-max)	5.7 (0.9 – 32.0)	3.490 (630-18.792)	10 (180-4.082)
- A-IPF (/mm <sup>3</sup> ), median (min-max)	2.588 (180-18.792)		

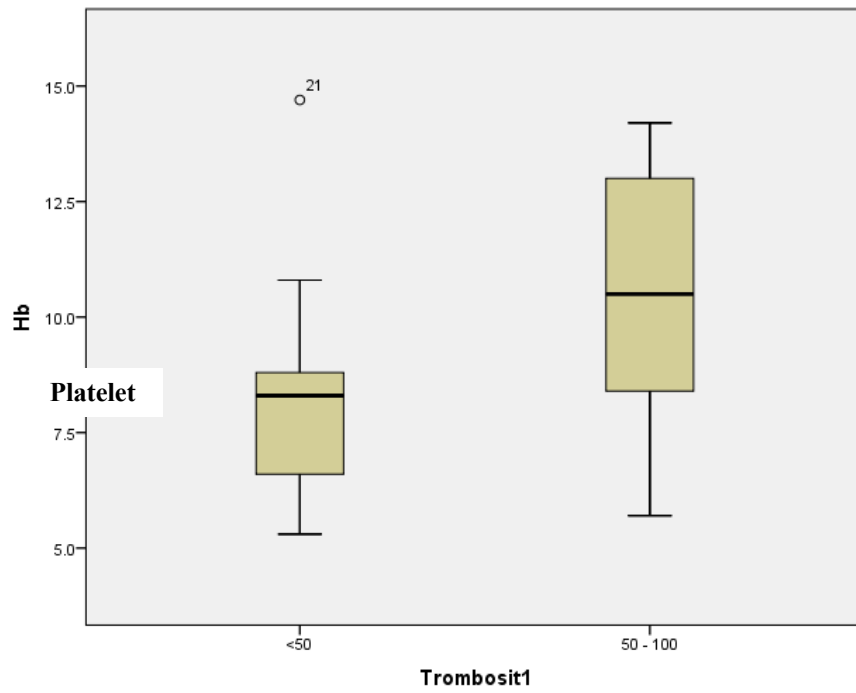


Figure 1. Hemoglobin level in mild and moderate-severe thrombocytopenia groups

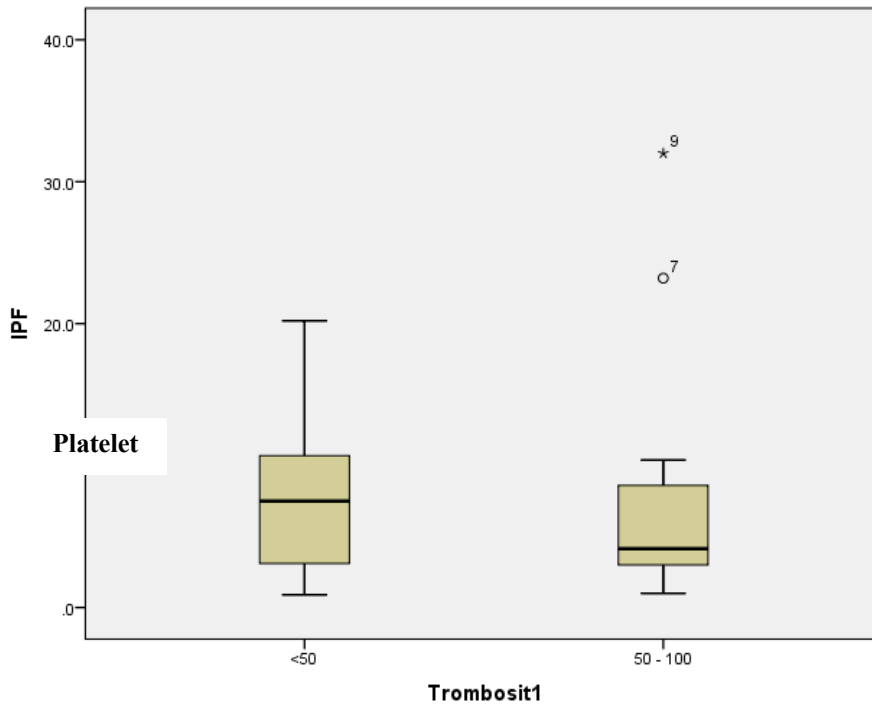


Figure 2. IPF level in mild and moderate-severe thrombocytopenia groups

#### **4. Discussion**

This is the first reported study that evaluates IPF value in SLE thrombocytopenia patients. We found the proportion of SLE patients that had thrombocytopenia was 7.4%. This is consistent according to known literature, which says that it ranges from 7-30%. As reported in other studies, we found that the proportion of severe thrombocytopenia group was the lowest compared to mild and moderate group.<sup>10</sup>

Thrombocytopenia could occur in any phases of SLE disease courses. Broadly, it is divided into 2 categories. The first one has thrombocytopenia as a part of a generalized exacerbation of SLE. Usually these patients have acute onset, severe, but respond well to corticosteroid treatment. The other group has more chronic form of thrombocytopenia, less related to disease activity and typically less responsive to corticosteroid therapy.<sup>2</sup> In this study we found that majority (58.3%) SLE thrombocytopenia patients had disease duration of more than 6 months.

We recorded ANA patterns of the patients. From available data, the majority of SLE thrombocytopenia patients had homogenous pattern. This is consistent with study by Ghrahani, which reported that SLE patients with homogenous pattern have a higher hematology involvement risk.<sup>11</sup>

Previous studies found that thrombocytopenia in SLE is related with higher disease activity.<sup>5</sup> In this study we found 75% patient had Mex-SLEDAI score >5 that shows active disease. In moderate-severe thrombocytopenia group, 90% patients had active disease; compared with 71.4% patients in mild group.

Immature platelet fraction is good parameter that reflects megakaryocytes activity in bone marrow. Briggs et al reported the IPF reference range in healthy individuals was 1.1-6.1%, with a mean of 3.4%.<sup>7</sup> In Indonesia, Novita reported a reference range of 0.64-3.2%.<sup>12</sup> In this study we found IPF in SLE thrombocytopenia patients ranged from 0.9-3.2% with median 5.7%. A wide variation in IPF values shows the multifactorial causes of thrombocytopenia in

SLE patients. Median IPF in moderate-severe thrombocytopenia group was higher than the mild group (7.5% vs 4.2%). This shows a negative correlation between platelet count and IPF. The lower platelet count, the higher IPF value, which shows increased thrombopoiesis activity.

There are several limitations in this study that should be considered. First, the current study is a descriptive study. There is no analysis on factors that affect platelet and IPF level in SLE patients. Future studies with multivariate analysis are needed. A further limitation of the current study is the subjects of this study are cross-sectional in nature, only included patients who had thrombocytopenia at the time of sampling. There was no serial platelet examination and outcome follow-up on the patients. Another limitation is limited number of subjects. For a better analysis, we suggest multicentre study involving more patients.

#### **5. Conclusion**

IPF values were increased in most SLE patients with thrombocytopenia compared to normal SLE population. It suggested that increased platelet destruction plays an important role in the pathogenesis of SLE thrombocytopenia. IPF in moderate-severe thrombocytopenia group was higher than the mild group and it shows an increase thrombopoiesis activity. A wide range of IPF values shows multifactorial nature of thrombocytopenia causes in SLE patients. IPF could be routinely ordered in SLE thrombocytopenia patient to determine the need of bone marrow examination.

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