

The Pattern of Hematological Manifestations in Systemic Lupus Erythematosus Patients at Dr. Soetomo General Academic Hospital Surabaya

Shakila Zuleika Putri Maharani^a, Yuliasih^b, Paulus Budiono Notopuro^{c*}, Lita Diah Rahmawati^b

*paulus-b-n@fk.unair.ac.id

^aMedical Program, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia

^bDepartment of Internal Medicine, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia – Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

^cDepartment of Clinical Pathology, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia – Dr. Soetomo General Academic Hospital, Surabaya, Indonesia

Abstract

Systemic Lupus Erythematosus (SLE) is an autoimmune illness with a broad range of clinical manifestations, one of which is hematological manifestations that cause high morbidity and mortality if there is a delay in diagnosis. This research was conducted to analyze the pattern of hematological manifestations of SLE patients. This research was a descriptive retrospective study. A total of 106 patients with systemic lupus erythematosus met the inclusion criteria. Patients were dominated by a female (94.34%) and the age group of 18 - 27 years old (46.23%). The average hemoglobin level of the sample was 8.16 g/dl with anemia in 99 patients (93.4%), which was morphologically dominated by normochromic normocytic anemia in 61 patients (57.55%). The mean platelet count of the sample was $192.77 \times 10^3/\mu\text{L}$ and thrombocytopenia was found in 26 patients (24.53%). The mean lymphocyte count of the sample was $1.03 \times 10^3/\mu\text{L}$ and lymphopenia was found in 26 patients (79.25%). The mean leukocyte count in the sample was $7.53 \times 10^3/\mu\text{L}$ and leukopenia was found in 22 patients (20.75%). This study concludes that SLE patients are dominated by females aged 18 – 27 years old and the most frequent hematological abnormalities are anemia (morphologically dominated by normochromic normocytic anemia), thrombocytopenia, lymphopenia, and leukopenia.

Keywords: Systemic lupus erythematosus; anemia; thrombocytopenia; leukopenia; lymphopenia

1. Introduction

An autoimmune illness known as Systemic Lupus Erythematosus (SLE) showed a variety of manifestations, from minor to fatal involving various body organs [1]. Hematological manifestations of SLE that are often found are anemia, leukopenia, and thrombocytopenia[2]. Thrombocytopenia and lymphopenia are hematological manifestations that lead to severe lupus and increase mortality and morbidity if not treated properly[3][4]. Zhao et al. reported that thrombocytopenia is a bad prognostic indicator where SLE patients with severe thrombocytopenia will experience a decreased long-term survival rate[5]. Hematological manifestations are often not suspected as manifestations of SLE if this condition only appears in a single organ without being accompanied by other organ abnormalities, causing delays in diagnosis[6]. This condition will worsen SLE disease activity which causes high morbidity and mortality.

In 2017, Sufian et al. reported that out of 89 active SLE patients, 77 (85.4%) patients had hematological manifestations consisting of anemia (77.5%), thrombocytopenia (17.9%), lymphopenia (17.9 %), autoimmune hemolytic anemia (AIHA) (10.1%), neutropenia (19.1%), and pancytopenia (5.6%)[7]. Studies in Saudi Arabia, Pakistan, and Nigeria reported conditions similar to Sufian et al., who found anemia as the most hematological manifestations[8][9][10]. Miranda-

Hernández et al. reported the opposite situation with Sufian et al., who found thrombocytopenia in 63.1% of patients[11]. Skare et al. and Koh et al. also reported a different condition from Sufian et al., who found leukopenia as the most common hematological manifestation[12][13]. Trilistyoati's research at Dr. Soetomo Surabaya in 2018 found hematological abnormalities in the form of anemia (73.71%), thrombocytopenia (33.86%), lymphopenia (76.89%), and leukopenia (32.67% of 273 SLE patients[14].

Anemia, leukopenia, lymphopenia, thrombocytopenia, and pancytopenia were several hematological abnormalities of SLE. Suppression of the bone marrow brought on by an influx of pro-inflammatory cytokines, the formation of antibodies against each blood cell, chronic disease, and bleeding can result in hematologic abnormalities. White blood cell abnormalities often occur in SLE patients, including leukopenia and lymphopenia caused by decreased bone marrow production. In comparison, thrombocytopenia can occur due to impaired platelet production in the bone marrow[15].

The goal of this research was to analyze the pattern of hematological abnormalities in individuals with SLE.

2. Methods

This research was a descriptive retrospective study used a total sampling collection technique. All individuals with SLE who fit the American College of Rheumatology (ACR) 1997 criteria and underwent complete blood count at Dr. Soetomo General Academic Hospital Surabaya from January 2019 – June 2021 were included as the study's subjects. This study has been authorized by Dr. Soetomo General Academic Hospital Surabaya's academic ethics committee with number 0654/LOE/301.4.2/X/2021.

One hundred and six patients met the inclusion criteria, systemic lupus erythematosus patients based on the 1997 ACR criteria with complete medical record data. Using Microsoft Excel, this study analyzed age, gender, hemoglobin level, platelet count, leukocyte count, and lymphocyte count and presented a distribution frequency table converted into a descriptive form.

3. Results and Discussion

This study included one hundred and six systemic lupus erythematosus patients who fit the inclusion criteria.

Table 1. Characteristics of patients

	Category	Frequency (n)	Percentage (%)
Gender	Male	6	5.66%
	Female	100	94.34%
Age (years old)	18-27	49	46.23%
	28-37	36	33.96%
	38-47	16	15.09%
	>47	5	4.72%

Gender distribution of patients was dominated by a female with 100 patients (94.34%). This study's results followed several previous studies, which also found that female dominate by female patients's gender[7][13][16]. Incidence rates based on gender varied in different countries. This

gender difference is thought to be due to sex hormone factors in the pathogenesis of SLE that affect SLE activity, where prolactin and estrogen hormones are found to be high in women with SLE.[17][18]

Most patients were in the 18-27 age group with 49 patients (46.23%). Similar studies were found in the study of Hamijoyo et al. and Sufian et al., where most SLE patients were between the ages of 21-30 years old and 21 – 25 years old sequentially[7][16]. SLE is more prevalent during the reproductive age, with the mean age at diagnosis varying from 24 to 32 years and presenting a more severe manifestation and prognosis[19].

Table 2. Mean blood cells count of patients

Blood Cells	Mean
Hemoglobin (g/dl)	8.16
Thrombocyte ($10^3/\mu\text{L}$)	192.77
Lymphocyte ($10^3/\mu\text{L}$)	1.03
Leukocyte ($10^3/\mu\text{L}$)	7.53

Table 3. Hematological manifestations of patients

Haematological Manifestations	Frequency (n)	Percentage (%)
Anemia	99	93.4%
Hypochromic Microcytic Anemia	24	22.64%
Normochromic Normocytic Anemia	61	57.55%
Autoimmune Haemolytic Anemia (AIHA)	6	5.66%
Thrombocytopenia	26	24.53%
Thrombocytosis	6	5.66%
Lymphopenia	26	24.53%
Lymphocytosis	3	2.83
Leukopenia	22	20.75%
Leukocytosis	21	19.81%

This study found that the average hemoglobin level in SLE patients was 8.16 g/dl. This hemoglobin level is below the normal range, which indicates anemia. This result is in accordance with the data on the frequency of patients with anemia, about 99 patients (93.40%). The prevalence of SLE patients with anemia in this study supported by Sufian et al., Khan et al., and Oguntona, where anemia is the most common hematological manifestation, respectively[7][8][9]. Chronic inflammation, infection, renal insufficiency, and bleeding are some mechanisms that influence the decrease in hemoglobin levels. Immunological or non-immunological factors can induce anemia in SLE patients[20]. Immunological factors such as cytokine activation, suppression of erythroid progenitor cell proliferation, and antibodies to erythropoietin can induce a decrease in hemoglobin levels. Non-immunological factors that can cause a decrease in hemoglobin levels are NSAIDs and long-term steroid therapy in SLE patients which can cause gastrointestinal bleeding[21].

According to morphology, normochromic normocytic anemia in 61 patients (57.55%) was the most frequent hematological manifestation of anemia which is strongly connected to anemia of chronic disease[22]. Similar results by Rouf et al., Usman et al., and Uskudar Teke et al. also found SLE patients with normochromic normocytic anemia in most of the sample[7][22][23]. Long-term

inflammation and systemic disease are the most typical causes of normochromic normocytic anemia[24]. In contrast, hypochromic microcytic anemia is thought to arise due to iron deficiency that is frequently present in SLE patients. The increasing number of patients treated with steroids and NSAIDs can predispose blood loss in the upper gastrointestinal tract and cause hypochromic microcytic anemia[25].

Autoimmune Hemolytic Anemia (AIHA) is not a common condition that occurs in SLE patients[25]. This study showed only 6 out of 106 SLE patients with AIHA (5.66%). Gormezano et al. stated that the prevalence of SLE patients with AIHA ranged from 4% to 10% of adult SLE patients[25]. The destruction of erythrocytes can cause AIHA in SLE through autoantibodies to antigens on the surface of erythrocytes[25].

The mean platelet count in SLE patients found in this study was $192.77 \times 10^3/\mu\text{L}$, classified in the normal range and supported by several previous study research by Lu et al., Samohvalov, and Njoroge, who found the mean platelet count in SLE patients within the normal range[25][26][27]. Most patients with SLE have platelet counts in the normal range due to a generalized reactive response to chronic inflammation and blood transfusion therapy in SLE patients[20][25]. Thrombocytopenia was the most common hematological manifestation based on the platelet count in this study with 26 patients (24.53%). Thrombocytopenia affects 10% to 25% of SLE patients, supported with a study in Saudi Arabia, Turkey, and Tunisia[10][25][28]. Thrombocytopenia is hypothesized to be induced by autoantibodies that destroy platelets and consumption of platelets in the periphery[28].

According to this study, the average lymphocyte count was $1.03 \times 10^3/\mu\text{L}$. Most SLE patients have low lymphocyte counts below the normal range. Lu et al. and Samohvalov found similar results on the low mean lymphocyte count in SLE patients[26][27]. SLE patients with lymphocyte count below the normal range was in accordance with the data of SLE patients with lymphopenia in this study, as many as 84 patients or 79.25%. These results were supported by data of lymphopenia in SLE ranging from 15% to 82%[29]. The appearance of lymphopenia is significantly associated with SLE disease activity, infection, lupus nephritis, complement consumption, cytotoxic agents, and high doses of steroids and cyclophosphamide[30][31].

According to this study, the average leukocyte count in SLE patients was $7.53 \times 10^3/\mu\text{L}$, which was classified in the normal range. This result is supported by the finding of Lu et al., Samohvalov, and Njoroge, who also found the mean leukocyte count in SLE patients was in the normal range[25]–[27]. The most common hematological manifestation based on the leukocyte count was leukopenia in 22 patients (20.75%). These results were lower than the frequency of SLE patients with leukopenia, which ranged from 22% to 41.8%[29]. Leukopenia reflects SLE disease activity, bone marrow suppression due to immunosuppressants, or other medical conditions[32]. Neutropenia, lymphopenia, or a mix of the two may precede the appearance of leukopenia[33]. SLE patients with leukopenia have increased thrombocytopenia, lymphopenia, and hemolytic anemia[12].

This study has several limitations. The sample used in this study was heterogeneous because it was not exclude the therapeutic variable and history of hematology disease which can affect the hematological manifestations that occur in the sample.

4. Conclusion

This study concludes that females in the age group of 18 – 27 dominate systemic lupus erythematosus patients. Anemia (morphologically dominated by normochromic normocytic anemia), thrombocytopenia, lymphopenia, and leukopenia are SLE's most prevalent hematological manifestations. Suggestions for further research to conduct research with specific patient selection.

Acknowledgements

The author seek to express their greatest appreciation to the health research ethics committee's staff and medical record data officers for their help during data collection so that this research can take place and achieve its objectives.

References

- [1] K. Tselios and M. B. Urowitz, "Cardiovascular and Pulmonary Manifestations of Systemic Lupus Erythematosus," *Current Rheumatology. Review*, vol. 13, no. 3, pp. 206–218, 2017.
- [2] F. Bashal, "Hematological Disorders in Patients with Systemic Lupus Erythematosus," *Open Rheumatol J.*, vol. 7, no. 1, pp. 87–95, 2013, doi: 10.2174/1874312901307010087.
- [3] J. Merayo-Chalico, D. Gómez-Martín, A. Piñeirúa-Menéndez, K. Santana-de Anda, and J. Alcocer-Varela, "Lymphopenia as risk factor for development of severe infections in patients with systemic lupus erythematosus: A case-control study," *Quarterly Journal of Medicine*, vol. 106, no. 5, pp. 451–457, 2013.
- [4] J. Li, Z. Pan, H. Liu, F. Ding, Q. Shu, and X. Li, "Retrospective analysis of the risk of hemorrhage associated with moderate and severe thrombocytopenia of 173 patients with systemic lupus erythematosus," *Medicine (United States)*, vol. 97, no. 27, 2018, doi: 10.1097/MD.00000000000011356.
- [5] J. Zhao *et al.*, "Chinese SLE Treatment and Research group (CSTAR) registry VII: Prevalence and clinical significance of serositis in Chinese patients with systemic lupus erythematosus," *Lupus*, vol. 25, no. 6, pp. 652–657, 2016, doi: 10.1177/0961203315625460.
- [6] P. K. Sasidharan, M. Bindya, and K. G. Sajeeth Kumar, "Hematological Manifestations of SLE at Initial Presentation: Is It Underestimated?," *ISRN Hematology.*, vol. 2012, pp. 1–5, 2012.
- [7] A. B. M. A. Sufian, M. A. Kashem, and S. Biswas, "Pattern of hematological manifestations in patients with systemic lupus erythematosus attending in a tertiary care hospital," *J Med.*, vol. 18, no. 2, pp. 86–91, 2017, doi: 10.3329/jom.v18i2.33686.
- [8] A. Khan *et al.*, "Clinical manifestations of patients with Systemic Lupus Erythematosus (SLE) in Khyber Pakhtunkhwa," *J Pak Med Assoc.*, vol. 67, no. 8, pp. 1180–1185, 2017.
- [9] S. A. Oguntona, "Haematological Manifestations of Systemic Lupus Erythematosus at a Tertiary Rheumatology Clinic," *Saudi J Med.*, vol. 3, no. 8, pp. 453–458, 2018, doi: 10.21276/sjm.2018.3.8.6.
- [10] A. Aleem, A. S. Al Arfaj, N. Khalil, and H. Alarfaj, "Haematological abnormalities in systemic lupus erythematosus," *Acta Reumatol Port.*, vol. 39, no. 3, pp. 236–241, 2014.
- [11] D. Miranda-Hernández *et al.*, "Active haematological manifestations of systemic lupus erythematosus lupus are associated with a high rate of in-hospital mortality," *Lupus*, vol. 26, no. 6, pp. 640–645, 2017, doi: 10.1177/0961203316672926.
- [12] T. Skare, R. Damin, and R. Hofius, "Prevalence of the American College of Rheumatology hematological classification criteria and associations with serological and clinical variables in 460 systemic lupus erythematosus patients," *Brazillian Journal of Hematology and*

Hemotherapy, vol. 37, no. 2, pp. 115–119, 2015.

- [13] J. H. Koh *et al.*, “Clinical characteristics and survival of 413 patients with systemic lupus erythematosus in southeastern areas of South Korea: A multicenter retrospective cohort study,” *Int J of Rheum Dis*, vol. 23, no. 1, pp. 92–100, 2020, doi: 10.1111/1756-185X.13761.
- [14] D. Trilistyoati, “Profil Klinis Dan Kejadian Infeksi Penderita Systemic Lupus Erythematosus Di Irna Medik Smf Ilmu Penyakit Dalam Rsud Dr. Soetomo Tahun 2016,” *Universitas Airlangga*, 2018.
- [15] A. Velo-García, S. G. Castro, and D. A. Isenberg, “The diagnosis and management of the haematologic manifestations of lupus,” *J Autoimmun*, vol. 74, pp. 139–160, 2016.
- [16] L. Hamijoyo *et al.*, “The clinical characteristics of systemic lupus erythematosus patients in Indonesia: a cohort registry from an Indonesia-based tertiary referral hospital,” *Lupus*, vol. 28, no. 13, pp. 1604–1609, 2019, doi: 10.1177/0961203319878499.
- [17] J. P. Nusbaum, J. S., Mirza, I., Shum, J., Freilich, R. W., Cohen, R. E., Pillinger, M. H., ... Buyon, “Sex Differences in Systemic Lupus Erythematosus,” *Mayo Clin Proc*, vol. 95(2), 384, 2020.
- [18] G. G. Song and Y. H. Lee, “Circulating prolactin level in systemic lupus erythematosus and its correlation with disease activity: A meta-analysis,” *Lupus*, vol. 26, no. 12, pp. 1260–1268, 2017, doi: 10.1177/0961203317693094.
- [19] G. J. Pons-Estel, M. F. Ugarte-Gil, and G. S. Alarcón, “Epidemiology of systemic lupus erythematosus,” *Exp Rev Clin Immun*, vol. 13, no. 8, pp. 799–814, 2017, doi: 10.1080/1744666X.2017.1327352.
- [20] K. M. Hamza and Z. M. Bashir, “Hematological Profile of Sudanese Patients with Systemic Lupus Erythematosus,” *Clin Med Journal*, vol. 2, no. 4, pp. 40–45, 2016.
- [21] P. C. Ratnadi, K. Suege, and N. M. R. A. Rena, “Hubungan antara kadar hemoglobin dengan tingkat keparahan penyakit pasien systemic lupus,” *E Journal Medika Udayana*, vol. 5, no. 2, pp. 1–13, 2016.
- [22] S. Y. Usman, L. Hamijoyo, and A. Tjandrawati, “Two Years Profile of Anemia in Systemic Lupus Erythematosus Patients at West Java’s Top Referral Hospital, Indonesia,” *Althea Med J*, vol. 4, no. 2, pp. 157–162, 2017.
- [23] H. Uskudar Teke, D. Uskudar Cansu, and C. Korkmaz, “Detailed features of hematological involvement and medication-induced cytopenia in systemic lupus erythematosus patients: single center results of 221 patients,” *Eur J Rheumatol*, vol. 4, no. 2, pp. 87–92, 2017, doi: 10.5152/eurjrheum.2017.160086.
- [24] G. Yilmaz and H. Shaikh, “Normochromic Normocytic Anemia,” *StatPearls*, 2020.
- [25] J. W. Njoroge, “Haematological Parameters in Systemic Lupus Erythematosus Patients at Kenyatta National Hospital, Nairobi,” *University of Nairobi*, 2016.
- [26] W. Lu, Y. Zhong, Y. Zhang, Z. Liu, and L. Xue, “The Clinical Characteristics of Leukopenia in Patients with Systemic Lupus Erythematosus of Han Ethnicity in China: A Cross-Sectional Study,” *Rheumatol Ther*, vol. 8, no. 3, pp. 1177–1188, 2021, doi: 10.1007/s40744-021-00336-6.

- [27] E. Samohvalov and S. Samohvalov, "The Pattern of Anemia in Lupus," *Curr Top in Anemia*, 2018.
- [28] M. Jallouli *et al.*, "Clinical implications and prognostic significance of thrombocytopenia in Tunisian patients with systemic lupus erythematosus," *Lupus*, vol. 21, no. 6, pp. 682–687, 2012, doi: 10.1177/0961203312438630.
- [29] L. Carli, C. Tani, S. Vagnani, V. Signorini, and M. Mosca, "Leukopenia, lymphopenia, and neutropenia in systemic lupus erythematosus: Prevalence and clinical impact-A systematic literature review," *Seminars in Arthritis and Rheumatism*, vol. 45, no. 2, pp. 190–194, 2015, doi: 10.1016/j.semarthrit.2015.05.009.
- [30] S. Faddah, M. Elwakd, A. Aboelenein, and M. Hussein, "Lymphopenia and systemic lupus erythematosus, a preliminary study: Correlation with clinical manifestations, disease activity and damage indices," *Egyptian and Rheumatologist*, vol. 36, no. 3, pp. 125–130, 2014.
- [31] N. Sobhy, M. H. Niazy, and A. Kamal, "Lymphopenia in systemic lupus erythematosus patients: Is it more than a laboratory finding?," *Egyptian Rheumatologist*, vol. 42, no. 1, pp. 23–26, 2020.
- [32] K. Lertchaisataporn, N. Kasitanon, S. Wangkaew, S. Pantana, W. Sukitawut, and W. Louthrenoo, "An evaluation of the association of leukopenia and severe infection in patients with systemic lupus erythematosus," *J Clin Rheumatol*, vol. 19, no. 3, pp. 115–120, 2013, doi: 10.1097/RHU.0b013e318289bb9b.
- [33] K. Newman, M. B. Owlia, I. El-Hemaidi, and M. Akhtari, "Management of immune cytopenias in patients with systemic lupus erythematosus - Old and new," *Autoimmun Rev.*, vol. 12, no. 7, pp. 784–791, 2013.