

The Role of Neutrophil-to-Lymphocyte Ratio as A Potential Biomarker of Erythema Nodosum Leprosum Disease Severity: A Retrospective Study

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Background: Erythema nodosum leprosum (ENL) is an acute immunologic complication of multibacillary leprosy (MB) that causes systemic inflammation in various organs. It is a major factor contributing to morbidity, mortality, and financial hardship. ENL is diagnosed clinically, and objective indicators for severe conditions remain unexplored. Simple blood biomarkers that differentiate between different ENL disease severity levels are required. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) have been widely studied as severity biomarkers of numerous neoplastic and inflammatory disorders.

Objective: We examined NLR and PLR values at various ENL severities and their role as severe disease indicators for ENL.

Methods: This cross-sectional retrospective study examined 246 patients with multibacillary leprosy—with and without ENL reactions and aged 18 and above—and calculated their NLR and PLR values. Then, we compared patients with mild and severe disease states to those without ENL. The severity classification was based on the ENLIST ENL Severity Score (EESS). To determine the NLR and PLR cutoff points of mild and severe ENL, a receiver operating characteristic (ROC) curve was constructed.

Results: The NLR value for severe ENL was significantly higher than that for mild ENL ($p < 0.05$), with a severe disease cutoff point of 5.71 (95.7% sensitivity, 68.7% specificity). No significant differences were found in PLR between patients with mild and severe ENL.

Conclusion: While PLR is not an effective assay for evaluating ENL severity, NLR is a potential biomarker for severe ENL reactions in patients with multibacillary leprosy.

Key Words: Erythema nodosum leprosum, Neglected disease, Neutrophil-to-lymphocyte ratio, Platelet-to-lymphocyte ratio, Severity

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INTRODUCTION

Erythema nodosum leprosum (ENL) is an immunologic reaction that develops as a multibacillary (MB) leprosy complication, affecting the skin, nerves, and other organs. A systematic review of field studies showed the incidence of ENL ranging from 1 to 8 per 100 person-years¹. An Indonesian hospital study revealed that 33.4% of MB leprosy patients experienced an ENL reaction² and that these patients were susceptible to nerve injuries, potentially leading to significant disability, morbidity, socio-economic burdens, and reduced quality of life¹. ENL can manifest as mild (46.2%) to severe (5.38%) inflammatory conditions³. Clinical manifestations of severe inflammation may be invisible; however, cell-level changes are occurring by this time. Objective markers that predict subclinical inflammatory progression of ENL are needed to prevent prolonged treatment time and predict clinical worsening⁴.

Among the various simple blood test parameters, the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are uniquely associated with systemic inflammation⁵. They are used as systemic inflammatory markers to predict prognosis and evaluate severity. These ratios are considered relatively stable and more accurate than absolute neutrophils (ANC), absolute lymphocytes (ALC), or platelet (PLC) counts⁶.

ENL can be characterized through neutrophil activities. A recent study found that peripheral neutrophil counts, mainly low-density (LDN), tend to be elevated, particularly in cases of severe ENL⁷. Platelets, or thrombocytes, actively participate in inflammatory responses by creating microthrombi that aid in trapping pathogens during the cellular immune response⁸. Patients with ENL often demonstrate increased T-helpers, reduced T-cytotoxic lymphocytes, and higher T-helper-to-T-lymphocyte ratios than controls; usually, these are the only lymphocytes involved in ENL.

Increases in NLR and PLR were previously associated with ENL incidence in patients with MB leprosy⁹. The NLR has a diagnostic accuracy of 78% for leprosy reactions¹⁰. Further, NLR and PLR have been widely studied as biomarkers for various systemic inflammatory diseases, including ulcerative colitis, rheumatoid arthritis, asthma, systemic lupus erythematosus, infection, and various malignancies.

NLR can predict clinical outcomes and severity in individuals with bacteremia or community-acquired pneumonia^{10,11}. However, NLR and PLR have not been explored as biomarkers of ENL severity and prognosis. The identification of accurate biomarkers will improve our ability to evaluate disease progression and therapy outcomes. NLR and PLR are available

and readily obtained within standard clinical practice settings. Therefore, this study investigated the use of NLR and PLR in different disease severities and assessed the significance of NLR and PLR as biomarkers for severe ENL.

MATERIALS AND METHODS

1. Study design

This cross-sectional retrospective study was carried out at the Leprosy Division of Dr. Soetomo General Academic Hospital in Surabaya, Indonesia. The data was gathered from the medical records of individuals with multibacillary leprosy who visited the hospital between January 2017 and December 2021.

2. Patient selection

The study included patients 18 years and older who were diagnosed with multibacillary leprosy based on clinical and laboratory examination. Hematological data was obtained from the patient's complete blood count test on the day of diagnosis. Patients with HIV, autoimmune diseases, diabetes mellitus, other mycobacteriosis, Lucio's phenomenon, type 1 leprosy reaction, and other conditions were excluded. Patients administered steroids or other immunosuppressive medications within the previous two weeks were also excluded.

3. Variables and definitions

The patient-related variables we collected included age, sex, body weight, height, leprosy type (according to Ridley-Jopling classification), bacterial index (BI), morphological index, onset of MDT therapy, ENL status, severity score (ENLIST ENL Severity Score [EESS]), and complete blood count results at the first outpatient visit.

Physicians experts in leprosy diagnosis and treatment diagnosed all cases of ENL upon observing a sudden eruption of tender papules, nodules, or plaques plus three key symptoms (tender enlarged nerves, arthritis, lymphadenitis, increased loss of sensation or muscle power, epididymal-orchitis, edema of the face or extremities, and a positive Ryrie or Ellis test, and iridocyclitis or episcleritis). ENL severity was classified according to the EESS, which includes 10 variables worth 0~3 points and is used to classify ENL as mild (< =8 total points) or severe (> 8 total points).

Body weight and height were used to calculate each patient's body mass index (BMI) and assess their nutritional

status. Skin smears from three distinct body sites were used to calculate all morphological and microbiological indexes. ANC, the ALC of peripheral blood, and the PLC and the ALC quotient were used to calculate the NLR and PLR, respectively.

4. Statistical analysis

For quantitative data that followed a normal distribution or did not, the mean (\pm standard deviation) or median (minimum-maximum), respectively, were used to tabulate the data. The Kolmogorov-Smirnov test was utilized to assess the normality

of the distribution. The percentage of the total qualitative data value was calculated. The nonparametric Kruskal-Wallis test was employed to determine the association between the hematologic variable and the severity of ENL, as all examined parameters exhibited a nonnormal distribution. Spearman's rho correlation test was used to analyze the relationship between NLR and ENL severity and PLR and ENL severity. Furthermore, a receiver operating characteristic (ROC) curve was generated to assess the sensitivity and specificity of NLR and PLR as biomarkers for severe ENL.

Table 1. Clinical characteristics and demographics of multibacillary leprosy patients

Characteristics		Non-ENL	Mild ENL	Severe ENL	n (%)
Gender	Male	149 (72.0)	13 (81.3)	14 (60.9)	176 (71.5)
	Female	58 (28.0)	3 (18.8)	9 (39.1)	70 (28.5)
Age	18~44	136 (65.7)	11 (68.75)	18 (78.3)	165 (67.07)
	45~59	52 (25.1)	3 (18.7)	4 (15.4)	59 (23.9)
	>60	19 (9.2)	2 (12.5)	1 (4.4)	22 (8.94)
BMI	<i>Underweight</i>	19 (9.2)	1 (6.3)	3 (13.0)	23 (9.3)
	Normal	119 (57.5)	10 (62.5)	12 (52.2)	141 (57.3)
	<i>Overweight</i>	36 (17.4)	4 (25.0)	6 (26.1)	46 (18.7)
	Obese (Grade I)	28 (13.5)	1 (6.3)	1 (4.3)	30 (12.2)
	Obese (Grade II)	5 (2.4)	0 (0)	1 (4.3)	6 (2.4)
Leprosy type (Ridley-Jopling classification)	BB	114 (55.1)	1 (6.3)	0 (0)	115 (46.7)
	BL	54 (26.1)	7 (43.8)	10 (43.5)	71 (28.9)
	LL	39 (18.8)	8 (50.0)	13 (56.5)	60 (24.4)
BI	0	98 (47.3)	2 (12.5)	0 (0)	100 (40.7)
	1~2	56 (27.1)	10 (62.5)	15 (65.2)	81 (32.9)
	≥ 3	53 (25.6)	4 (25.0)	8 (34.8)	65 (26.4)
MI	0	104 (50.2)	7 (43.8)	14 (60.9)	125 (50.8)
	1~4	69 (33.3)	8 (50.0)	6 (26.1)	83 (33.7)
	≥ 5	34 (16.64)	1 (6.3)	3 (13)	38 (15.4)
Onset of MDT treatment	New	187 (90.3)	10 (62.5)	11 (47.8)	208 (84.6)
	On MDT therapy	3 (1.4)	1 (6.3)	2 (8.7)	6 (2.4)
	RFT	0 (0)	2 (12.5)	5 (21.7)	7 (2.8)
	<i>Drop Out</i>	11 (5.3)	2 (12.5)	4 (17.4)	17 (6.9)
	Relapse	6 (2.9)	1 (6.3)	1 (4.3)	8 (3.3)

BI: Bacterial index; BMI: Body mass index; MDT: Multidrug therapy; MI: Morphological index; RFT: Release from treatment

RESULTS

1. Demographic study

There were 425 patients who visited the Leprosy Division between January 2017 and December 2021 (Table 1); 246 (average age 38.13 ± 14.47 years, 71.5% male, 28.5% female) patients with multibacillary leprosy met all inclusion and exclusion criteria. Of these, 39 (15.9%) had an ENL reaction, including 16 classified as mild (6.5%) and 23 as severe (9.3%). Most ENL patients, regardless of disease severity, were male (81.3% of mild patients and 60.9% of severe patients), aged 18~44 years (68.75% of mild and 78.3% of severe), and multidrug therapy-naïve (62.5% of mild and 47.8% of severe). Mild (50.0%) and severe (56.5%) ENL was primarily observed in patients with lepromatous leprosy. Most patients with mild (62.5%) and severe (65.2%) ENL had a BI of 1~2 (62.5%

of mild and 65.2% of severe) normal nutritional status, as indicated by a normal BMI (mild: 62.5%; severe: 52.2%). Mycobacterial indexes of 1~4 were primarily found in patients with mild ENL (50.0%).

2. NLR and PLR analysis

The median ALC and ANC were substantially higher ($p = 0.001$) in ENL patients with severe disease than in mild or non-ENL controls (Table 2). Compared to mild and non-ENL group patients, severe ENL patients had significantly lower ANC ($p = 0.001$). No statistically significant between-group differences were found for PLC ($p = 0.055$).

Table 3 shows a significant difference ($p = 0.001$) in median NLR between the non-ENL controls and ENL groups (mild and severe), which also reflected in Fig. 1A. Patients with severe ENL had a considerably higher median NLR ($p = 0.001$) than

Table 2. Blood count of leukocytes, neutrophils, and lymphocytes among multibacillary leprosy patients with and without ENL reaction

Blood count	Non-ENL	Mild ENL	Severe ENL	p value*
Leukocytes	7,580 (4,630~22,510)	11,190 (4,200~25,080)	17,500 (7,910~51,100)	0.001
Neutrophils	4,980 (2,010~19,540)	8,675 (1,790~22,440)	16,130 (6,260~48,650)	0.001
Lymphocytes	1,710 (590~4,040)	1,755 (680~2,950)	1,120 (470~2,530)	0.001
Platelet	300,000 (116,000~751,000)	350,000 (176,000~697,000)	416,000 (129,000~909,000)	0.055

Values shown median (minimum - maximum)

*Non-parametric Kruskal-Wallis test

Table 3. The NLR and PLR value of MB leprosy patient with and without ENL

	Non ENL	ENL (Mild + Severe)	Mild ENL	Severe ENL	$P_1^{(a)}$	$P_2^{(a)}$	Correlation coefficient: ρ value ^(b)
NLR	2.49 (0.86~14.46)	8.01 (0.94~49.64)	4.94 (0.94~22.90)	12.35 (3.13~49.64)	0.001	0.001	0.532; $\rho=0.001$
PLR	169.89 (61.14~766.33)	259.38 (59.66~1,172.34)	226.08 (59.66~670.59)	292.17 (87.76~1,172.34)	0.001	0.189	0.300; $\rho=0.001$

Values shown median (minimum - maximum)

^(a)Non-parametric Kruskal-Wallis test

^(b)Spearman's rho correlation test

P_1 : P value between Non-ENL and ENL group

P_2 : P value between mild and severe ENL group

ENL, erythema nodosum leprosum. NLR, neutrophil-to-lymphocyte ratio. PLR, platelet-to-lymphocyte ratio

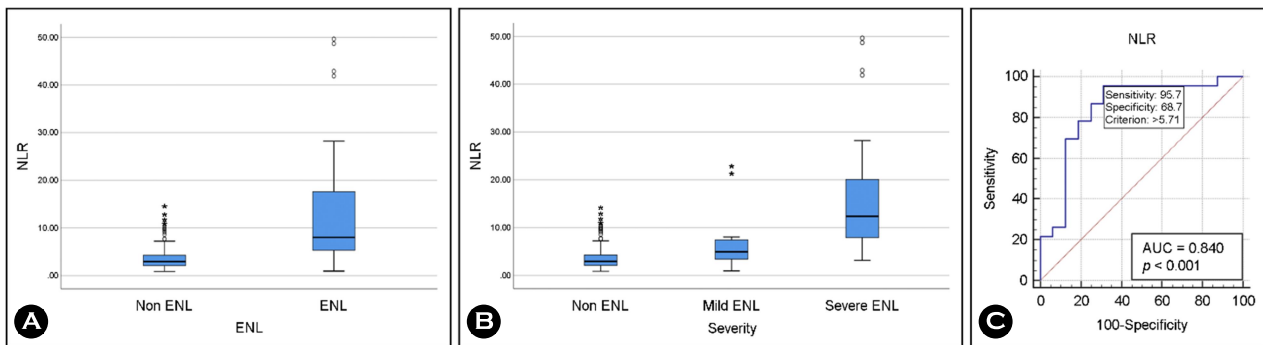


Fig. 1. NLR value of ENL patients (A) Comparison of NLR values between ENL and non-ENL groups (B) Comparison of NLR values at various degrees of ENL disease severity (C) Receiver operating characteristic (ROC) curve of NLR for severe ENL

their mild ENL counterparts (Fig. 1B). Compared to patients in the ENL (mild and severe) groups, the median PLR of non-ENL patients was substantially lower. Nevertheless, there was no apparent distinction in the median PLR between patients with mild and severe ENL ($p = 0.189$).

ENL disease severity was positively correlated with PLR ($r = 0.300$) and NLR ($r = 0.532$). Among patients with severe ENL, the areas under the curve for PLR (0.625) and NLR (0.840) suggest that PLR is a poor indicator of severe disease but that NLR has modest utility. Fig. 1C shows the NLR cutoff value for severe ENL, which was 5.71 (sensitivity 95.7%, specificity 82.5%). The PLR cutoff value for severe ENL was 365.31 (sensitivity 39.1%, specificity 93.7%).

DISCUSSION

Inflammatory and immune responses, including innate and adaptive immunity, significantly influence ENL pathophysiology. Tumor necrosis factor (TNF)- α and other cytokines—including immune complexes, neutrophils, and different subtypes of lymphocytes such as B cells, T cells, helper T cells (Th)-17, and regulatory T cells (Treg)—are immunological ENL response indicators¹². NLR reflects the equilibrium between two facets of the immune response and may serve as a possible signal for identifying ENL. Tanojo and colleagues previously examined NLR and PLR in 182 consecutive patients with MB leprosy. Patients with an ENL reaction had a higher NLR (8.19 [2.9~21.46]) than patients without an ENL reaction (2.93 [0.86~12.85]) ($p < 0.005$)⁹. The present study's findings are essentially in line with those of Tanojo et al.'s investigation. Another similar study found increased NLR values in patients with leprosy reactions, especially those with type 2 or ENL¹⁰.

NLR reflects an increase in neutrophils and a reduction in

lymphocytes. Across the board, lower NLR indicates conserved immunological balance and is typically associated with a favorable prognosis¹³. NLR increases in response to systemic inflammation¹⁰, and higher NLR is linked to increases in mortality¹⁴, exacerbations, dyspnea, and disease severity scores. It can even increase the risk of death from other inflammatory illnesses like COPD¹⁵.

The current study is the first to investigate whether the NLR can predict disease severity in ENL. Therefore, it is not possible to compare our results with previous ones. According to our current understanding of the immunological response in the ENL reaction, the study's findings demonstrate that severe cases are associated with high ANC and low ALC. Therefore, it seems reasonable that patients with severe disease would also present a high NLR. We confirmed this positive relationship between NLR and ENL severity, particularly in the patients with the most severe disease. In this study, the severe ENL group had a considerably higher median NLR (12.35 [3.13~49.64]) than the mild ENL group (4.94 [0.94~22.90]) ($p < 0.005$). Thus, NLR can determine ENL severity, with a cutoff value 5.71 (i.e., 95.7% sensitivity and 68.7% specificity) for severe disease.

Neutrophils are histological markers of ENL and release mediators that promote inflammation¹². Increased NLR strongly correlates with systemic inflammation and indicates neutrophil-mediated, nonspecific acute inflammatory responses. The superficial part of the neutrophil consists of cell surface receptors, namely CD64 (Fc γ RI). The cell surface receptor CD64 (Fc γ RI) expression is low in resting neutrophils; however, its expression increases when gram-negative bacteria stimulate the cells. Additionally, CD64 is an early biomarker and severity predictor for ENL. *In situ* and circulating neutrophils in ENL express CD64, but this is not true in patients with nonreactive leprosy¹⁶. Most TNF- α and IL-8 linked to tissue

damage in ENL are produced by neutrophils, which is in line with CD64's involvement in the elevation of proinflammatory cytokine production¹⁷.

Lymphocytes comprise various cell subtypes with unique roles in the adaptive immune response. Stress increases specific cell subtypes while decreasing others to maintain homeostasis. This agrees with our finding that there is no noticeable distinction between mild ENL and non-ENL. A prior retrospective analysis shows that ALC alone cannot distinguish between ENL and non-ENL⁹. In patients with more severe inflammation, inflammatory process dysregulation can produce uncontrolled, persistent inflammation and additional tissue injury. We found patients with severe ENL had significantly lower ALC (1.120 [470~2.350]) than their mild counterparts (1.755 [680~2.950]) ($p < 0.05$). The low lymphocyte count in the severe ENL group was proportionate to the high NLR value observed in the same group, reflecting an immune imbalance that likely produced more severe inflammation¹⁸.

PLR is increasingly considered a novel systemic inflammatory marker. Its application was first documented in neoplastic disease—including hepatocellular carcinoma and breast cancer—as a prognostic factor¹⁹. Platelets significantly impact immunomodulatory and inflammatory processes by triggering inflammatory cytokine release²⁰ and interacting with various bacteria and immune cells, such as macrophages, T lymphocytes, neutrophils, and natural killer cells, to initiate or exacerbate inflammation²¹. Increased PLC is highly correlated with increased systemic inflammation, potentially influencing the course and prognosis of numerous conditions, including diabetes mellitus and atherosclerosis^{20,21}.

PLR can distinguish between MB leprosy patients with ENL reactions and those without ENL. The PLR value of the ENL patients (169.89 [61.14~766.33]) was significantly higher as compared to those without an ENL reaction (259.38 [59.66~1,172.34]) ($p = 0.001$). PLR may also serve as a diagnostic marker for the ENL reaction in patients with MB leprosy¹³. Nevertheless, we found that PLR did not correlate with ENL disease severity. The median PLR values were statistically similar in patients with mild (226.08 [59.66~670.59]) and severe (292.17 [87.76~1,172.34]) disease ($p = 0.189$).

The involvement of platelets in ENL pathogenesis needs to be better understood. A previous study found that patients with ENL had increased fibrinogen and platelet titers, prolonged activated partial thromboplastin time (aPTT), and increased platelet activation. Increased PLC was seen in the early stages of the ENL reaction²². We found that the severity of the ENL reaction increased in conjunction with increases in PLC; however, this relationship was non-significant ($p = 0.055$). This result might support the insignificant difference

in PLR value between mild and severe ENL mentioned before.

There are several limitations to our investigation. Based on administrative data, this retrospective, single-center study included a small number of patients in the case group. The complete blood count was evaluated in all MB leprosy patients who made their first visit to our outpatient clinic without distinguishing the chronicity of the ENL reaction. Disease biomarkers may be reflected differently in acute and chronic ENL. The inability to suppress the inflammatory response will progress from acute to persistent or chronic inflammation. Moreover, we did not assess the therapy outcome in the ENL patient. Therefore, further prospective investigations with follow-up periods are necessary to evaluate these parameters as treatment outcome predictors.

CONCLUSION

The NLR can help identify patients with severe inflammation as it closely correlates with ENL severity. This simple and easy method with relatively high sensitivity and specificity can support clinicians in detecting severe ENL in MB leprosy patients. PLR was not a useful biomarker of ENL severity. Future, well-powered, and prospective studies are necessary to confirm our findings.

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CONFLICT OF INTEREST

In relation to this article, we have no conflict of interest to declare.

DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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ETHICAL APPROVAL STATEMENT

The study was approved by the Ethics Committee of Dr. Soetomo General Academic Hospital, Surabaya (IRB No. 1146/LOE/301.4.2/XI/2022). This study was conducted in accordance with the principles of the Declaration of Helsinki.

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