INTRODUCTION

Leprosy is a chronic granulomatous infectious disease that attacks the peripheral nerves, skin, and other organs except for the central nervous system. Leprosy is caused by the Mycobacterium leprae, which can survive and proliferate in macrophages and Schwan cells of the peripheral nerves. These bacteria attack the peripheral nerves and cause muscle weakness and loss of sensation in the hands, feet, and eyes, leading to ulceration and deformity.

One of the most important problems during the clinical course of leprosy is the emergence of acute inflammation episodes, defined as reactions. Leprosy reactions are one of the main causes of nerve damage, leading to impaired nerve function, deformity, and disability. Leprosy reactions can be classified into 3 types: type 1 reaction or Reversal Reaction (RR), type 2 reaction or Erythema Nodosum Leprosum (ENL), and Lucio phenomenon.

Type 2 or ENL reaction is a type III hypersensitivity reaction, according to Coombs and Gell, which causes an antigen-antibody immune complex reaction and involves the complement immune system. The Erythema Nodosum Leprosum International Study (ENLIST) Group has created an objective measure, the ENLIST ENL Severity Measure (EES), which is the first ENL severity scale verified globally, to standardize the categorization.

One of the characteristics of ENL patients is neutrophilic leukocytosis, which is a sign of systemic inflammation. The neutrophil-lymphocyte ratio (NLR) has been identified as a distinct and consistent marker indicating the underlying inflammatory response among the different metrics used to monitor neutrophil levels. Study by Gomes et al in 2020 regarding the diagnostic value of NLR in patients with leprosy reactions, statistically, NLR was also found to be higher in patients with type 2 reactions compared to type 1 reactions, with a significance value of p-value<0.001. Based on this, this study aimed to evaluate the relationship between neutrophil-lymphocyte ratio and ENLIST ENL severity scale in type 2 leprosy reactions.

METHODS

Study Design
Thirty patients from H. Adam Malik General Hospital, Dr. Pirngadi General Hospital, and Sumatera Utara University Hospital were included in this analytic observational study that used a cross-sectional methodology and consecutive sampling techniques from September 2021 to December 2022. Leprosy patients with type 2 reactions and ages under 18 meet the inclusion requirements. Each participant signed an informed consent form. Subjects with other infectious and inflammatory illnesses, autoimmune
disorders, and malignancies were excluded. A dermatological examination and history collection identified type 2 leprosy responses.

**Data Collection**
Dermatology and Venereology Polyclinic H. Adam Malik General Hospital, Dr. Pirngadi General Hospital, and Universitas Sumatera Utara Hospital Medan were the data collection sites. The Clinical Pathology Laboratory of Universitas Sumatera Utara Hospital Medan examined blood samples. Researchers have studied the medical history, paying particular attention to the primary symptom of leprosy response type 2, evaluating the severity using the ENLIST ENL severity scale, and doing a full blood count to examine the neutrophil-lymphocyte ratio in a blood sample.

**Data Analysis**
Statistical Package for the Social Sciences (SPSS) processed the acquired data. In this study, a descriptive test was used to assess the properties of one variable using univariate analysis. By using the Spearman correlation test to evaluate the significance (p) and the correlation (r), bivariate analysis was used to examine the relationship between the neutrophil-lymphocyte ratio and the ENLIST ENL severity scale in type 2 leprosy responses. Statistical significance was defined as a p-value ≤0.05.

**RESULTS**

**Characteristics of the patients**
In this study, the demographic characteristics of type 2 leprosy reactions subjects were highest in the age group of <40 years (73.33%) and male gender (66.67%) (Table 1). The mean value of the neutrophil-lymphocyte ratio was 7.60 ± 3.58 (Table 2).

The mean EESS score was 7.97 ± 1.73, with the highest degree of severity being mild (60%). Table 3 shows the severity of type 2 leprosy reactions based on EESS.

A correlation analysis was performed using the Pearson correlation method because the neutrophil-lymphocyte ratio and ENLIST ENL severity scale data were normally distributed. The statistical analysis found a significant positive strong correlation between the neutrophil-lymphocyte ratio and ENLIST ENL severity scale in type 2 leprosy reactions (p<0.001; r=0.653). The results of the correlation can be seen in Table 4.

**DISCUSSION**
A study by Fransisca et al in 2021 reported that most patients with type 2 leprosy reactions were found at the age of <40 years, 39 people (61.9%). A study by Baima de Melo et al in 2020 which located at Brazil also reported that the most common age group was 31–49 years, with 11 people (42.3%) of the 26 people. These results are consistent with this study; the age group <40 years has more type 2 leprosy reactions (Table 1). One of the risk factors that can trigger a type 2 leprosy reaction is age <40 years. This is related to the factors of productive age and high work activity that trigger stress or physical and mental exhaustion. In addition, the multiplication of *M. leprae* is slow, and the average incubation period is 5 years; symptoms can appear within 1–20 years, so that onset usually occurs in adults aged 20–30 years.

Agusti et al in 2018 and Saraswati et al in 2019 reported that the dominant distribution of patients with type 2 leprosy reactions was found in males, with the distribution of each study 74 people (69.8%) and 24 people (68.6%). A study conducted by Listiawan in Surabaya also reported distribution of most patients with type 2 leprosy reactions was found in males, (85.7%) compared to women (14.3%). In this study, it was found that 20 subjects (66.67%) were male (Table 1).

It is suspected that because of the high workload and the responsibility of men as the backbone of the family and the inability to work effectively due to leprosy, it is often associated with risk factors for type 2 leprosy reactions to stress.

A study by Gomes et al in 2020 reported that the mean value of NLR in type 2 leprosy reactions was 9.7 ± 3.4. The mean value of NLR in this investigation was 7.60 ± 3.58 (Table 2). The neutrophil-lymphocyte ratio is a specific

**Table 1. Characteristics of subjects based on gender and age group**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Type 2 Reaction (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>20</td>
</tr>
<tr>
<td>Female</td>
<td>10</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>&lt;40 years</td>
<td>22</td>
</tr>
<tr>
<td>≥40 years</td>
<td>8</td>
</tr>
</tbody>
</table>

**Table 2. Characteristic of the neutrophil-lymphocyte ratio value**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean</th>
<th>Standard Deviation</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NLR</td>
<td>7.60</td>
<td>3.58</td>
<td>0.251</td>
</tr>
</tbody>
</table>

*Analysis was carried out using the Saphiro-Wilk test. The result was considered significant if the p-value ≤0.05.

**Table 3. The severity of type 2 leprosy reactions based on EESS**

<table>
<thead>
<tr>
<th>The severity of type 2 leprosy reactions</th>
<th>n (%)</th>
<th>Mean±SD</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>18 (60.0)</td>
<td>7.97±1.73</td>
<td>0.999</td>
</tr>
<tr>
<td>Severe</td>
<td>12 (40.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Analysis was carried out using the Saphiro-Wilk Test. The result was considered significant if the p-value ≤0.05.

**Table 4. Correlation of RNL and EESS in type 2 leprosy reactions**

<table>
<thead>
<tr>
<th>Variable</th>
<th>r</th>
<th>EESS</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>NLR</td>
<td>0.653</td>
<td>&lt;0.001*</td>
<td></td>
</tr>
</tbody>
</table>

*Analysis was carried out using the Pearson Correlation Test. The result was considered significant if the p-value ≤0.05.
biodemarker that determines the proportion of neutrophils to lymphocytes. This is because a pro-inflammatory state caused by neutrophils characterizes the early stage of infection. Through phagocytosis processes, the release of antimicrobial peptides, and the generation and release of cytokines, neutrophils serve as the first line of defense in an immune response to infections. The mechanism behind the rise in NLR levels in type 2 leprosy responses is unknown. Several factors have been known to determine the increase in false RNL values, such as hematological disorders, HIV, acute myocardial infarction, type 2 diabetes, malignancy, and emotional stress. This can explain the results with different ranges in each study.10

Baima de Melo et al in 2020 assessed the severity of type 2 leprosy reactions using the EESS and showed outcomes with a mild of 46.2% and a severe of 53.8%.14 In this study, the severity of all subjects was 7.97 ± 1.73, with the most severe category being mild, 18 patients (60.0%) (Table 3). ENLIST ENL Severity Scale (EESS) was developed by the Erythema Nodosum Leprosum International Study Group (ENLIST) in 2017 to assess the severity of type 2 leprosy reactions objectively. This scale contains 10 points, including pain assessment using a visual analog scale (VAS), fever (in °C), number of ENL lesions, inflammation of ENL lesions, the extent of ENL lesions, peripheral edema, bone pain, inflammation of joints, and digits due to ENL, lymphadenopathy due to ENL, and nerve tenderness due to ENL. Each point is assessed on a scale of 0–3 with an interpretation of a total EESS score of ≤8 as mild ENL and a score >8 as severe ENL.10

The link between NLR and EESS in type 2 leprosy patients was significant (p-value<0.001) based on the Pearson correlation test of 30 research samples. The correlation coefficient (r) obtained was 0.653, showing a high positive association (Table 4). This research is the first study that learns the correlation between NLR and EESS. A study by Schmitz et al in 2016 reported that the cell surface expression of CD64 (FcγRI) on circulating neutrophils is significantly increased in type 2 leprosy reactions. A higher CD64 in circulating neutrophils is associated with the severity of type 2 leprosy reactions.21 This suggests that the role of neutrophils in the secretion of proinflammatory cytokines during episodes of type 2 leprosy reactions supports systemic inflammation in this disease. In addition, the histopathological picture of a type 2 leprosy reaction shows dominantly neutrophils in the granuloma, so it is considered a type 2 leprosy reaction characteristic. Circulating neutrophils, as well as neutrophils in a type 2 leprosy reaction lesion, are known to express CD64, which is not found in leprosy patients without a reaction and leprosy reaction type 1.8 Research by Gomes et al in 2020 explained that neutrophilia was found in type 2 leprosy reactions proving that the highest average NLR was found in this condition. In contrast, the conditions associated with neutrophils are irrelevant in type 1 leprosy reactions. This explains the reason for the absence of a relationship between NLR in type 1 leprosy reactions.

In addition, a factor that can affect the degree of severity of a type 2 leprosy reaction is the ENL lesion. Research conducted by Baima de Melo et al in 2020 found a relationship between the number and extent of ENL lesions and their severity.14 Clinically, ENL lesions were subcutaneous erythematous nodule lesions with a more than 1 cm diameter that felt painful. In general, the pathogenesis of erythema nodosum is thought to be a hypersensitivity reaction in response to an antigen that causes neutrophilic panniculitis. Neutrophil recruitment results in the formation of reactive oxygen species, TNF-α production, macrophage inhibitory factor production, and granuloma formation.22 This may explain the relationship between RNL and EESS in type 2 leprosy reactions. This study still has several limitations, such as not including any other compounding variables that might affect the result and using a small sample, which could affect the representation of the development toward the entire population.

CONCLUSION

There was a strong correlation between NLR and EESS in type 2 leprosy reactions. Further studies are needed to validate these findings with cohort design, using more samples and including other compounding variables to obtain more representative results.

ACKNOWLEDGMENTS

We would like to convey our appreciation to the Director of the Department of Dermatology and Venereology at the Universitas Sumatera Utara Faculty of Medicine and the Universitas Sumatera Utara Hospital.

FUNDING

No specific funding was received for this study.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTION

All authors contributed equally with regards to this research.

ETHICAL CONSIDERATION

The Research Ethics Commission of the Universitas Sumatera Utara Faculty of Medicine and the Universitas Sumatera Utara Hospital have given their clearance for this study with the ethical clearance number letter: 51/KEPK/USU/2022

REFERENCES

ORIGINAL ARTICLE


