ORIGINAL ARTICLE

# Neutrophil to Lymphocyte Ratio in Pulmonary Tuberculosis Patients with and without Diabetes Mellitus and Human Immunodeficiency Virus Co-Infection Comorbidities

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**ABSTRACT**

**Introduction:** Tuberculosis (TB) remains a leading cause of mortality in Indonesia. The presence of diabetes mellitus (DM) and human immunodeficiency virus (HIV) co-infection comorbidities is a double burden. In TB patients, the neutrophil to lymphocyte ratio (NLR) is an inflammatory marker and may indicate disease progression and immune system status. This study aimed to describe the NLR in pulmonary TB patients with and without DM and HIV co-infection comorbidities.
**Methods:** This study used a quantitative descriptive method with a cross-sectional approach. A total sampling technique was used, resulting in a sample of 159 participants. Data were collected from medical records.
**Results:** Among 108 newly diagnosed pulmonary TB patients in this study, 42 patients (38.9%) had a normal NLR (0.78-3.53), while 66 patients (61.1%) had an increased NLR (>3.53). Of the 28 TB patients with DM comorbidity, 12 patients (42.9%) had a normal NLR, while 16 patients (57.1%) had an increased NLR. Among the 23 TB patients with HIV co-infection comorbidity, four patients (17.4%) had a normal NLR, while 19 patients (82.6%) had an increased NLR.
**Conclusion:** The results showed that pulmonary TB patients with and without DM and HIV co-infection comorbidities had a high NLR.

## INTRODUCTION

Tuberculosis (TB) is a chronic infectious disease caused by the bacterium *Mycobacterium tuberculosis* (MTB) due to its high transmission rate through droplet nuclei.[1] It is often accompanied by comorbidities and co-infections, such as diabetes mellitus (DM) and human immunodeficiency virus (HIV). Diabetes mellitus is a metabolic disorder characterized by hyperglycemia due to inadequate insulin production or the inability of the body to use insulin effectively.[2] The most common co-infection in TB patients is HIV, one of the most common health problems in the world. It is a ribonucleic acid (RNA) virus that attacks the human immune system by targeting white blood cells, thereby increasing susceptibility to infections.[3,4]

According to the 2022 Global TB Report, 90% of TB infections affect the lungs, with more than nine million new cases annually.[5] Southeast Asia accounts for the highest incidence (45%), followed by Africa (23%), and the West Pacific (18%). More than one million deaths occur among HIV-negative TB patients, and more than 180,000 deaths occur among HIV-positive patients.[5] In addition, 1.5 million people are affected by TB accompanied by DM.[5] Indonesia ranks second in the world for the highest number of TB cases, following India.[5] According to the Ministry of Health in

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2021, there were 969,000 confirmed cases and 93,000 deaths each year, with TB cases accompanied by DM increasing by 10-15%.[6] The Health Service of Ambon reported 932 TB cases in 2022 and 1,414 TB cases in 2023, including 41 TB-HIV co-infection cases and 82 TB-DM cases.

The prevalence of TB cases has significant socioeconomic impacts. Sihaloho, *et al*. (2021) found a correlation between TB and poverty, with factors including poor nutritional intake, inadequate environment, and lack of access to health services.[7] The burden of TB can lead to reduced productivity and loss of income, thereby exacerbating global poverty.[7] This underscores the importance of the diagnosis and treatment of TB.

Tuberculosis diagnosis can be confirmed through rapid molecular testing (Gene-Xpert) using sputum samples. The bacterial load in the sample affects the quality of the test, as a higher bacterial load indicates greater virulence and increased resistance. *Mycobacterium tuberculosis* replicates in macrophages and neutrophils, with its growth controlled and regulated by T lymphocytes. Therefore, TB is often associated with hematological abnormalities such as lymphopenia and neutrophilia.[8]

The neutrophil to lymphocyte ratio (NLR) is an inflammatory marker that can be used in identifying infections, such as TB, monitoring disease progression, guiding treatment, and predicting prognosis. Neutrophil to lymphocyte ratio testing is more affordable and accessible than other markers, such as procalcitonin and C-reactive protein (CRP), which are more expensive and not available in all hospitals. Increased neutrophil counts indicate non-specific destructive inflammation, while decreased lymphocyte counts indicate an impaired immune system. Tuberculosis patients with DM and HIV co-infection comorbidities may exhibit NLR variations.[9]

In TB cases with or without comorbidities and co-infections, NLR can serve as a prognostic indicator. A study by Sallatu, e*t al*. (2019) suggested that pulmonary TB patients with positive results of acid-fast bacilli (AFB) had higher neutrophil and lower lymphocyte counts compared to those with negative results.[10] Azab, *et al*. (2014) and Coşkun, *et al*. (2014), as cited by Cahyadi, *et al*. (2018), found that NLR tends to decrease in HIV infection but increase in DM and TB.[11] Similarly, Shojaan, *et al*. (2023) identified increased NLR among TB patients.[12] Furthermore, Kurniawati, *et al*. (2022) found increased NLR among TB patients with HIV co-infection.[13] This study aimed to describe the NLR in pulmonary TB patients with and without DM and HIV co-infection comorbidities.

## METHODS

This study used a quantitative descriptive method with a cross-sectional approach. Data were collected from April to May 2024 at Bhayangkara Hospital, Ambon. The sampling technique used in this study was total sampling. The study population consisted of confirmed new cases of pulmonary TB, TB patients with comorbid DM, and TB patients with HIV co-infection through NLR testing at Bhayangkara Hospital, Ambon. Neutrophil to lymphocyte ratio testing was performed at the initial hospital admission of the patients. For patients with comorbidities and co-infections, NLR values were included regardless of whether they had received treatment or not.

This study did not use serial NLR data as it focused on evaluating NLR at the time of initial hospital admission. Although NLR values may fluctuate during the course of inflammation or infection, the data collected upon admission were considered representative for evaluating the patient's initial condition and their relationship with other research variables. Serial measurements would require a different study design with repeated measurements, which is beyond the scope of this study. Data were collected from medical records of the patients spanning January 2022 to December 2023. The data included sex, age, symptoms, NLR, comorbidities, and co-infections. All data were processed using Microsoft Excel and Statistical Package for Social Sciences (SPSS) to calculate and analyze the NLR.

## RESULTS

This study included 108 new cases of pulmonary TB, 28 TB patients with DM, and 23 TB patients with HIV co-infection. A total of 159 patients met the inclusion criteria (Table 1).

**Table 1.** Characteristics of patients

| Description | N=159 | % |
|---|---|---|
| **Sex** | | |
| Male | 95 | 59.7 |
| Female | 64 | 40.3 |
| **Age (years old)** | | |
| 17-25 | 33 | 20.8 |
| 26-45 | 54 | 33.9 |
| >46 | 72 | 45.3 |
| **Diabetes mellitus** | 28 | 17.6 |
| **Human immunodeficiency virus** | 23 | 14.5 |

The result showed that the majority of patients were male, with females representing a smaller proportion. Most patients were over 46 years of age.

**Table 2.** Characteristics of patients

| Description | TB n=108 | TB-DM n=28 | TB-HIV n=23 |
|---|---|---|---|
| **Respiratory** | | | |
| Cough | | | |
| Dry | 20 | 5 | 2 |
| Phlegm | 54 | 15 | 7 |
| Blood | 11 | 2 | 4 |
| Dyspnea | 32 | 7 | 7 |
| **Systemic** | | | |
| Fever | 15 | 3 | 2 |
| Weight loss | 7 | 0 | 4 |
| Malaise | 15 | 14 | 15 |
| Sweating | 3 | 0 | 1 |

TB: tuberculosis; DM: diabetes mellitus; HIV: human immunodeficiency virus

Table 2 presents the clinical manifestations observed in the three patient groups, namely, respiratory and systemic symptoms. Respiratory symptoms included dry cough, bloody cough, and phlegm cough, while systemic symptoms included fever, weight loss, malaise, and sweating.

**Table 3.** Neutrophil to lymphocyte ratio in pulmonary tuberculosis patients

| | | Frequency (f) | Percentage (%) |
|---|---|---|---|
| **Neutrophil to lymphocyte ratio** | Normal 0.78-3.53 | 42 | 38.9 |
| | Increase >3.53 | 66 | 61.1 |
| **Total** | | 108 | 100.0 |

Table 3 shows that among 108 new pulmonary TB cases, 66 patients (61.1%) had an increased NLR, while 42 patients (38.9%) had a normal NLR.

**Table 4.** Neutrophil to lymphocyte ratio in pulmonary tuberculosis patients with comorbid

| | | Frequency (f) | Percentage (%) |
|---|---|---|---|
| **Neutrophil to lymphocyte ratio** | Normal 0.78-3.53 | 12 | 42.9 |
| | Increase >3.53 | 16 | 57.1 |
| **Total** | | 28 | 100.0 |

Table 4 shows that among 28 TB patients with DM comorbidity, 16 patients (57.1%) had an increased NLR, while 12 patients (42.9%) had a normal NLR.

**Table 5.** Neutrophil to lymphocyte ratio in pulmonary tuberculosis patients with human immunodeficiency virus co-infection

| | | Frequency (f) | Percentage (%) |
|---|---|---|---|
| **Neutrophil to lymphocyte ratio** | Normal 0.78-3.53 | 4 | 17.4 |
| | Increase >3.53 | 19 | 82.6 |
| **Total** | | 23 | 100.0 |

Table 5 shows that among 23 TB patients with HIV co-infection, 19 patients (82.6%) had an increased NLR, while four patients (17.4%) had a normal NLR.

## DISCUSSION

Table 1 shows the characteristics of 159 patients involved in this study. The majority of TB patients were males. This finding aligns with a study by Sunarmi and Kurniawaty (2022), who reported 63 male patients out of 99 patients.[14] This contributed to a risky lifestyle among males, such as smoking. In addition, TB was more prevalent in the elderly population, as the risk of infection tends to be higher compared to the young population. Aging is associated with immunodeficiency, leading to a higher risk of TB among the elderly. These findings are in line with a study by Simmons et al. (2021), who found that progressive inflammation in aging contributes to immunosenescence in the elderly population.[15] Similarly, Li, *et al.* (2015) found that NLR had a positive correlation with age.[16]

Table 2 shows the symptoms in the three patient groups. Respiratory symptoms were reported by all patient groups: 93.5% in new pulmonary TB cases, 89.3% in pulmonary TB with DM comorbidity, and 87% in pulmonary TB with HIV co-infection. These symptoms included dry cough, phlegm cough, and bloody cough. Cough serves as a natural defense mechanism of the respiratory tract, triggered by irritants or infections such as MTB, which activate nociceptive neurons in the lungs.[17,18] Other respiratory symptoms, such as shortness of breath and rhonchi, were also found in the patients.

Dyspnea may result from pleural effusion arising from a slow-type hypersensitivity reaction to MTB in the pleural cavity in infected individuals or granuloma rupture that causes bacilli to invade the pleural cavity, thus increasing pleural fluid. This can lead to pulmonary compression associated with severe inflammation, shortness of breath, and coughing. When dyspnea develops, abnormal mucus secretion may occur, causing respiratory symptoms such as wheezing and persistent coughing. This is similar to the study by Luies and du Preez (2020), who reported that in 85% of pulmonary cases, excessive mucus secretion due to dyspnea resulted in wheezing and coughing, which is usually accompanied by sputum and generally lasts for three weeks or more.[19] Furthermore, hemoptysis may occur due to broncholithiasis, a condition commonly found in TB patients, which exacerbates coughing and results in direct lung damage.[20]

In addition to respiratory symptoms, systemic symptoms such as fever, weight loss, sweating, and malaise were observed in 47.2% of pulmonary TB patients, 67.9% of pulmonary TB patients with DM

comorbidity, and 78.3% of pulmonary TB patients with HIV co-infection. *Mycobacterium tuberculosis* infection activates inflammatory cytokines that can cause fever. Fever typically begins with a heat production phase involving skin vasoconstriction, shivering, which serve to retain heat. The hypothalamus responds by increasing body temperature, after which homeostasis between heat production and excretion can be achieved. Therefore, the body stops shivering and returns to normal temperature. Skin vasodilation facilitates heat dissipation through sweating. In pulmonary TB, fever tends to occur at night. Consequently, the onset of night sweats is associated with the body's circadian rhythm. Additionally, cortisol-induced glucocorticoids, which modulate innate and adaptive immunity, play a role in suppressing fever. A decrease in these hormones at night can be a contributing factor to night sweats.

Weight loss in pulmonary TB patients could be associated with a lack of leptin, a hormone that plays a role in weight regulation. A lack of plasma leptin levels can affect fat metabolism and suppress appetite. This finding aligns with a study by Mexitalia, *et al*. (2017), which suggested that leptin plays a role in the cellular immune response to MTB.[21] A decrease in leptin concentration before treatment typically leads to hunger, while an increase in leptin levels after the intensive treatment is associated with weight gain. In patients with HIV co-infection, the virus may damage intestinal cells, resulting in the flattening of villi and malabsorption of carbohydrates and fats. Malaise experienced by these patients may be attributed to an inflammatory response that activates various cytokines such as interleukin-1 (IL-1), IL-2, tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ), which can act directly on muscle cells, stimulating muscle protein degradation and contributing to muscle weakness, weight loss, and fatigue. In addition, in patients with DM comorbidity, high glucose levels interfere with the body's ability to convert glucose into energy due to cells not getting enough glucose. Furthermore, because patients with HIV are immunocompromised, the ongoing immune response to infection contributes to fatigue.

Table 3 shows the results of NLR testing in 108 patients with newly diagnosed pulmonary TB. The results showed that 66 patients (61.1%) had an increased NLR (>3.53), while 42 patients (38.9%) had a normal NLR (0.78 - 3.53). This can be attributed to the immune system's response in cases of infection, where neutrophils are mobilized to combat MTB. As a result, patients with pulmonary TB may experience neutrophilia, neutropenia, lymphopenia, and lymphocytosis. These results are in line with a study by Hanum, *et al*. (2023) in Jambi, who found that 12 patients undergoing treatment for less than two months had a mean NLR of 3.68, indicating an elevated level.[22] The NLR as an inflammatory marker tends to decrease as treatment progresses. However, it is often elevated during the initial stages. Furthermore, the presence of anemia in some patients may contribute to increased NLR. This is similar to a study by Iqbal, *et al*. (2020), as cited by Hanum, *et al*. (2023), which reported that 78% of their study participants with anemia had an increased NLR.[22,23]

Table 4 shows the NLR in 28 TB patients with DM comorbidity. The results showed that the number of female TB patients with DM comorbidity was higher than that of male patients at Bhayangkara Hospital, Ambon, between 2022 and 2023. The NLR among these patients was found to be increased (>3.53) in 57.1% of cases, while 42.9% had normal NLR (0.78-3.53). In patients with DM, increased NLR is often associated with leukocytosis, which can occur in response to hyperglycemia. These findings align with a study by Mahajan, *et al*. (2023), who reported that among TB 58 patients with DM comorbidity, 34 had an increased NLR, while the remaining 24 had a normal NLR.[24] The increase in NLR was associated with poor blood glucose control, and this study observed a higher proportion of female patients than male patients. Similarly, a study by Dewi (2018), which categorized patients into groups with controlled and uncontrolled DM, found that TB patients with uncontrolled DM had NLR values greater than four.[25]

Table 5 shows the NLR in 23 TB patients with HIV co-infection. The results showed that the number of male TB patients with HIV co-infection was higher than that of female patients, with most patients being adults. These characteristics are in line with a study by Gumilang, *et al*. (2022), who reported that HIV-TB cases were more common in male patients (19.7%) compared to female patients (13.79%), with the age group most affected being 26-45 years old.[26] In this study, the NLR was increased in 19 patients (82.6%) and normal in four patients (17.4%). The increased NLR may be attributed to a reduction in cluster of differentiation 4 (CD4) in HIV patients, leading to a decrease in lymphocyte levels, while neutrophil levels may increase or remain, thereby increasing NLR. These findings are similar to a study by Miyahara, *et al*. (2019), who identified that NLR in pulmonary TB patients with HIV co-infection was higher than that of those without HIV co-infection.[27] This is associated with the CD4 count of HIV patients. Similarly, a study by Sulastri, *et al*. (2021) found that TB patients with HIV co-infection had significantly higher NLR values compared to those with or without pulmonary TB (6.05±2.67).[28]

## CONCLUSION

The results showed that pulmonary TB patients with and without DM and HIV co-infection comorbidities had an increased NLR.

## LIMITATIONS OF THE STUDY

During the data collection process, a significant number of respondents did not meet the inclusion criteria, and additional time was required to locate the address of one respondent. The geographical conditions in the working area of Air Besar Health Center also posed challenges. The area is vast, with narrow roads that pass through mountains and forests, which contributed to delays in data collection.

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**Conflict of Interest**
The authors declared there is no conflict of interest.

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**Authors' Contributions**
Conceived and designed the study, conducted the research, collected and analyzed the data, manuscript writing and preparation: SFN. Provided academic guidance, critical feedback, conceptual supervision throughout the research process, and assisted in the development of the theoretical framework: RRL. Offered methodological guidance, oversight during the research implementation, and contributed to the refinement of the research objectives and structure: YNU. Provided revisions and suggestions to improve the overall quality of the study: VZL. Funded the publication costs and supported the dissemination of the study: VT. Offered critical insights and suggestions for revision and ensured accuracy and academic integrity: RA. Reviewed the manuscript: VZL, VT, RA. All authors contributed and approved the final version of the manuscript.

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