ORIGINAL ARTICLE

# Neutrophil-Lymphocyte Ratio and Nutritional Status as Parameters of Sputum Conversion in MDR-TB Before & After 3 Months of Anti-TB Treatment

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**ABSTRACT**

**Introduction:** The prolonged duration of tuberculosis (TB) treatment has led to an increase in non-compliance among TB patients undergoing anti-TB treatment, consequently leading to treatment failure and drug resistance, notably multidrug-resistant TB (MDR-TB). Individuals with poor nutritional status may elevate the risk of delayed sputum conversion in MDR-TB patients. The neutrophil-lymphocyte ratio (NLR) represents a laboratory parameter with the potential as a prognostic indicator in patients suspected of TB infection.
**Methods**: This was an analytical study with a cross-sectional design. The sample was drawn from the medical records of MDR-TB patients at Haji Adam Malik General Hospital, Medan, from October 2022 to March 2023, resulting in a total of 83 samples. Data analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 25 software, and bivariate analysis was conducted using paired t-tests.
**Results:** Out of 83 MDR-TB patients, 50 patients (60.2%) were males. Based on nutritional status before three months of anti-TB treatment, the most common nutritional status was normal with 22 patients (26.5%) and severely underweight with 36 patients (43.4%). Following three months of anti-TB treatment, the majority had normal, totaling 39 patients (47%). A total of 67 patients (80.7%) experienced sputum conversion. The results indicated a significant difference between NLR before and after three months of anti-TB treatment ($p = 0.000$), as well as a significant difference between nutritional status before and after three months of anti-TB treatment ($p = 0.012$) at Haji Adam Malik General Hospital, Medan.
**Conclusion:** Significant differences were observed in NLR and nutritional status before and after three months of anti-TB treatment.

## INTRODUCTION

The causative agent of tuberculosis (TB) is the infectious bacterium *Mycobacterium tuberculosis* (MTB). The disease primarily targets the lungs and is transmitted through individuals diagnosed with active TB who expel mycobacteria in their sputum.[1] In 2022, there was a significant worldwide improvement in the number of those identified with and treated for TB following two years of disruption caused by COVID-19, which helped mitigate the pandemic's adverse impacts on the mortality and morbidity rates of TB. The global count of newly diagnosed people with TB stood at 7.5 million in 2022, yet the worldwide goals for TB have not been achieved or are not being followed with efficiency.[2] In 2020, the World Health Organization (WHO) estimated that the global incidence of TB reached 10 million cases, resulting in 1.5 million deaths. Consequently, TB became the 13$^{th}$ leading cause of death worldwide and the 2$^{nd}$ leading cause of infectious disease-related deaths after COVID-19.[3] According to the WHO Global Tuberculosis Report 2022, the regions with the highest number of TB cases include Southeast Asia (45%), Africa (23%), Western Pacific (18%), Eastern Mediterranean (8.1%), America (2.9%), and Europe (2.2%). Indonesia, with a prevalence rate of 9.2%, is among the top 30 countries with the highest incidence of TB, reporting 351,936 TB cases in 2020. The Ministry of Health of the Republic of Indonesia detected a prevalence of TB in 2022, amounting to 969,000 cases, indicating a 61.98% increase compared to the previous year. This puts Indonesia as the

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second highest contributor of TB cases in the world behind India (28%).[1]

TB can be cured through uninterrupted routine treatment following the directly observed treatment short-course (DOTS) standard, involving the treatment of anti-TB drugs (ATDs) for six months.[4,5] The prolonged duration of TB treatment leads to the emergence of non-compliance among TB patients in adhering to anti-TB treatment, potentially causing the progression of pulmonary TB to drug-resistant TB (DR-TB), which prolongs the TB treatment duration. DR-TB is a state in which MTB, the bacteria responsible for TB, become resistant to ATDs and cannot be eradicated using first-line ATDs. This problem may be caused by human behavior, specifically the insufficient treatment of TB patients or the transmission of infection from DR-TB patients.[1,6] Significant factors contributing to the failure of TB treatment include inappropriate guidelines, non-compliance with medication regimens, poor knowledge, lack of treatment monitoring, unavailability of specific medications, inadequate medication access, insufficient care support, mental health conditions, and malnutrition.[1,6]

Malnourished individuals can experience immune system disorders, which will increase the risk of contracting the disease. One parameter that can be utilized to determine an individual's nutrition status is the body mass index (BMI), which is used to classify nutritional status based on the calculation of whether a person's weight is insufficient or excessive.[7] Patients who maintain a healthy body weight are at a reduced risk of developing multidrug-resistant TB (MDR-TB), in contrast to those who are underweight or overweight, according to Song, *et al*. (2021).[8]

The neutrophil-lymphocyte ratio (NLR) is an inflammatory biomarker that may identify bacteremia infection in patients by considering the levels of the immune system, namely neutrophils and lymphocytes. An increased NLR indicates an increase in pro-inflammatory cytokines that work to enhance the response during inflammation.[9,10] Sormin, *et al*. (2018) found significant differences in NLR values in patients with pulmonary TB and DR-TB.[11] This relates to a decrease in $CD8^+$ T cell counts in DR-TB control which was found to increase the risk of TB in DR-TB patients.

In other cytokines, such as TNF-α, which plays an important part in cellular defense against intracellular pathogens, it was found that patients treated with TNF-α antagonists were more at risk for TB infection. Meanwhile, neutrophils with lower plasma levels of HNP1-3 are linked to MDR-TB.[11] Another study by Cahyadi, *et al*. (2018) obtained results indicating a decrease in NLR after undergoing intensive phase therapy, indicating an improvement in the body's immune response following anti-TB treatment.[9]

This study aimed to determine NLR and nutritional status as parameters for sputum conversion in MDR-TB therapy before and after three months of anti-TB treatment at Haji Adam Malik General Hospital, Medan.

## METHODS

### Collecting Samples

This study was conducted at Haji Adam Malik General Hospital, Medan, from September to October 2023. The population of this study comprised all MDR-TB patients undergoing treatment between October 2022 and March 2023 at Haji Adam Malik General Hospital, Medan, who had met the inclusion criteria: MDR-TB patients aged ≥18 years old who had undergone anti-TB treatment for a minimum of three months. The exclusion criteria included patients suffering from extrapulmonary TB. The sampling technique used in this study was total sampling. A total of 83 samples were obtained. The research instrument used in this study was the medical records of MDR-TB patients at Haji Adam Malik General Hospital, Medan. This study was ethically approved by the Faculty of Medicine, Universitas HKBP Nommensen, Medan, Indonesia (no. 530/KEPK/FK/IX/2023).

### Nutritional Status Evaluation

Nutritional status was measured using medical record data, specifically weight and height. The BMI was calculated by dividing weight in kilograms by height in meters squared. The Ministry of Health of the Republic of Indonesia classified BMI values into the following categories: severely underweight (<17.0), underweight (17-<18.5), normal (18.5-25.0), overweight (>25.0-27.0), and obese (>27.0).[12]

### NLR Value

NLR value was obtained using laboratory data from medical records, including absolute neutrophil and lymphocyte values. It can be determined by dividing the absolute neutrophil count by the absolute lymphocyte count.[10,13]

### Data Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS). Univariate analysis was performed by describing the frequency distribution of the variables to be processed and investigated. The Kolmogorov-Smirnov test was used to perform normality testing. Data were considered normally distributed if a p-value for a given variable was greater

than 0.05. Otherwise, it was considered to be abnormally distributed. The paired t-test was employed to conduct the bivariate analysis. Significance was considered if the p-value < 0.05.

## RESULTS

### Sample Characteristics

The characteristics of the research subjects were differentiated based on sex, nutritional status before three months, nutritional status after three months, and sputum conversion after three months. The data on characteristics indicated that there were 50 males (60.2%), while 33 were females (39.8%). Before three months of anti-TB treatment, 29 patients (34.9%) were found to have underweight nutritional status. After three months of anti-TB, the majority had normal and underweight nutritional status, each with the same number, totaling 27 patients (32.5%). The majority of MDR-TB patients experienced sputum conversion, with 67 patients (80.7%) after 3 three months, while 16 patients (19.3%) did not experience sputum conversion (Table 1).

Furthermore, a comparison test between variables was performed using a paired sample t-test. The statistical analysis revealed that the NLR before three months had a mean value of 3.9212, while the NLR after three months had a mean of 2.5672. There was a significant difference between the NLR before and after three months of anti-TB treatment (p = 0.000) (Table 1).

The mean nutritional status value before three months of anti-TB treatment was 20.8779, whereas compared to after three months of anti-TB treatment was 21.1615. The results of this study showed that there was a statistically significant difference in nutritional status between before and after three months of TB treatment (p = 0.012) (Table 1).

**Table 1.** Sample characteristics

| Characteristics | Male (n(%)) | Female (n%)) |
|---|---|---|
| **Nutritional Status before 3 Months** | | |
| Severely underweight | 11 (22%) | 11 (33%) |
| Underweight | 5 (10%) | 2 (6%) |
| Normal | 22 (44%) | 14 (43%) |
| Overweight | 5 (10%) | 3 (9%) |
| Obese | 7 (14%) | 3 (9%) |
| **Nutritional Status after 3 Months** | | |
| Severely underweight | 8 (16%) | 8 (24.5%) |
| Underweight | 6 (12%) | 5 (15%) |
| Normal | 23 (46%) | 16 (48.5%) |
| Overweight | 6 (12%) | 1 (3%) |
| Obese | 7 (14%) | 3 (9%) |
| **Sputum Conversion after 3 Months** | | |
| Converted | 40 (80%) | 27 (81.8%) |
| Not converted | 10 (20%) | 6 (18.2%) |
| **Total** | 50 (60.2%) | 33 (39.8%) |

**Table 2.** Statistical description of NLR before and after 3 months of anti-TB treatment

| Characteristics | Mean | p-value |
|---|---|---|
| NLR before 3 Months | 3.9212 | 0.000 |
| NLR after 3 Months | 2.5672 | 0.000 |
| Nutritional status before 3 months | 20.8779 | 0.012 |
| Nutritional status after 3 months | 21.1615 | 0.012 |

NLR = Neutrophil-lymphocyte ratio

## DISCUSSION

Based on the WHO Global Tuberculosis Report 2023, the majority of individuals who acquire the disease (approximately 90%) are adults, with a higher incidence among males than females.[2] Based on the results of the analysis in Table 1, it was found that most of the MDR-TB patients were males, namely 50 patients (60.2%). The results of this study are in line with the study by Revi, *et al*. (2020), proving that men are more susceptible to being infected with TB than women.[14] Novitasari (2020) stated that there was a significant relationship (p = 0.002) between sex and pulmonary TB in Indonesia, with an odds ratio (OR) of 1.46 (95% CI: 1.16 – 1.84), indicating that males are 1.46 times more likely to experience pulmonary TB.[15] The increased incidence of TB among males can be attributed to their widespread smoking habit. Cigarettes contain toxins that pose a threat to health and increase vulnerability to different diseases, including infection with MTB.[16] However, this is not in line with the study by Sutrisna, *et al*. (2022), who stated that women are more infected with MDR-TB than men.[17] Agustian, *et al*. (2022) also mentioned that there was no correlation between sex and the occurrence of pulmonary TB (p = 0.483).[18]

This study shows that there was a significant difference (p = 0.000) between NLR before and after three months of anti-TB treatment. This is in line with the study by Cahyadi, *et al*. (2018), who stated that there was a decrease in NLR after intensive phase treatment which showed an improvement in the body's immune response after undergoing anti-TB treatment in drug-susceptible TB (DS-TB) (p < 0.001).[9] Wicaksono (2018) also demonstrated that there was a decrease in NLR in MDR TB patients who received anti-TB treatment (p = 0.006).[19] Harun, *et al*. (2021) also mentioned an increase in neutrophil percentage, a decrease in lymphocyte percentage, and an increase was found in NLR among positive acid-fast bacilli (AFB) compared with negative AFB in DS-TB.[20]

After intensive treatment for TB, patients had decreased NLR values due to a rise in lymphocyte counts and a decrease in neutrophil numbers. Neutrophils are the body's first line of defense, working to phagocytize pathogenic microorganisms. This explains why early stages of MTB infection exhibit greater neutrophil levels.[9] Furthermore, it has been shown that a higher level of neutrophil (neutrophilia) independently correlates with mortality in patients receiving TB treatment, as well as an increased risk of cavity formation and lung tissue damage, indicating a positive correlation between the neutrophil count and bacillary load in TB.[21,22]

Based on the results of the statistical description of nutritional status, there was a significant difference between nutritional status before and after three months (p = 0.012), with a mean value of nutritional status before three months found to be 20.8779 and a mean value after three months 21.1615. The results of this study align with the study by Huda, *et al*., which showed that there were changes in BMI before and after treatment, where there was an increase in BMI after treatment (p = 0.00).[23,24] Puspita, *et al*. also stated that, for DS-TB patients who have been given anti-TB for two months, their nutritional status will improve in line with anti-TB treatment.[24] Novitasari (2020) stated that the OR of patients with underweight nutritional status was 2.86 (95% CI: 2.19 – 3.73), meaning those with underweight nutritional status had 2.86 times more likely to develop DS-TB compared to those with normal and obese nutritional status.[15] Another study by Luthfi (2018) obtained that, among the 75 (56.5%) patients who initially had underweight (BMI <18.5), 9.5% experienced an improvement to acceptable nutritional status (BMI ≥18.5), 27% lacked relevant data, and 63.5% remained unchanged.[25]

All patients who experienced from underweight to acceptable nutritional status experienced successful sputum conversion following the complete intensive phase treatment. Out of the group of patients who remained underweight in nutritional status after two months of intensive phase treatment, a total of 5 (10.6%) patients reported experiencing sputum conversion failure.[25] This study believes that changing from an underweight status to one that has acceptable nutrition shows the positive effects of the consumed treatment. Certain patients who have not experienced changes in their nutritional status may require a longer period of time for them to improve their BMI and nutritional status.

The relationship between sputum conversion and changes in nutritional status during treatment can be considered mutual. Specifically, improvements in the patient's nutritional status led to an improvement in their immune system, and so does the nutritional status which, in turn, helps the conversion. Clinical symptoms, including anorexia, will decrease as a result of sputum conversion, which implies a significant reduction in the bacterial load within the patient. As a result, patients will experience an improvement in their nutritional status.[25]

Sputum conversion status is a major determinant of treatment duration and outcome in MDR-TB patients. In this study, 67 patients (80.7%) had sputum conversion after three months of anti-TB treatment, and 16 patients (19.3%) had no conversion. There were six patients with underweight nutritional status who did not convert compared to normal, overweight, and obese nutritional status. This is in line with the study by Santy, *et al*. (2020), which stated that MDR-TB patients with normal BMI experienced more sputum conversion (58.3%) compared to underweight BMI.[26] Study by Luthfi (2018) stated that patients with acceptable nutritional status (BMI ≥18.5) had a 1.106 times higher risk of experiencing successful conversion compared to patients with underweight (BMI <18.5) at the beginning of diagnosis (95% CI: 0.932 - 1.108).[25] This statistical analysis indicates that there was no significant difference between the two groups (p > 0.05).[25]

Delayed sputum conversion leads to prolonged treatment and increases the risk of treatment failure, drug side effects, and drug resistance, which contribute to longer sputum conversion times. Thus, the risk of treatment failure will lead to increased mortality risk. Among 16 patients who did not experience sputum conversion after three months, it was found that 9 patients experienced conversion in the 4$^{th}$ month, 3 patients in the 5$^{th}$ month, and 4 patients in the 6$^{th}$ month with an average NLR obtained of 2.8950065. Suryana, *et al*. (2022) stated that there was no relationship between high NLR before receiving treatment and delayed sputum conversion (95% CI: 0.71-15.91, p-value = 0.125).[27] The study indicates that NLR is a non-

specific inflammatory marker, meaning that other conditions like diabetes mellitus (DM), human immunodeficiency virus (HIV), or malnutrition could have an impact on the high level of NLR.[27]

There were 16 patients who did not experience sputum conversion, underweight nutritional status was found in 4 patients, normal in 7 patients, overweight in 2 patients, and obese in 3 patients. Low or underweight (BMI <18.5) was associated with an increased risk of delayed sputum conversion (p = 0.041), according to the study by Suryana, *et al*. (2022).[27] This was found because patients with low BMI had lower levels of pro-inflammatory cytokines and higher levels of regulatory cytokines. On the contrary, patients with higher BMI provide a protective effect against the progression of TB.

Despite the advantageous impact of reducing the risk of infection and progression of TB, a high BMI was additionally linked to a greater vulnerability to DM. A recent study has demonstrated an association between BMI and TB-related inflammatory cytokines. The levels of pro-inflammatory (IFN-γ, TNF-α, IL-22, IL-1α, IL-1β, and IL-6) cytokines in the blood are lower in people with low BMI but higher in regulatory (IL-10, TGF-β, IL-5, and IL-13) cytokines. This study showed a direct relationship between the levels of pro-inflammatory cytokines in the bloodstream and high BMI (ranging from 25 to 29.9) and an inverse relationship between the levels of anti-inflammatory cytokines in the bloodstream and low BMI. The data indicate that BMI may act as a protective mechanism against the progression of TB infection to disease by altering the cytokine surroundings of an individual.[27] Nakao, *et al*. (2019) also mentioned that pulmonary cavitation in TB patients may be linked to malnutrition and increased the severity of inflammation.[28] The study underscores the fact that immunological and nutritional status serves as straightforward and significant markers in TB patients.[28]

## CONCLUSION

There was a statistically significant difference in nutritional status before and after three months of anti-TB treatment (p = 0.012) and in NLR before and after three months of anti-TB treatment (p = 0.000). A total of 67 patients (80.7%) underwent sputum conversion after three months of anti-TB treatment, while 16 patients (19.3%) failed to undergo sputum conversion. After three months of anti-TB treatment, the average NLR for the 16 patients who did not experience sputum conversion was 2.8950065, with the average conversion occurring in the 4$^{th}$ month. Among these patients, 4 were underweight, and 7 had a normal nutritional status. The findings of this study may provide insights into clinical care interventions for TB patients. However, further investigation is necessary to confirm the findings of this study. The outcome of this study is expected to be utilized as a screening tool for challenging diagnostic cases when gold standard methods are difficult to get.

## FUTURE RECOMMENDATION

Future research can be considered regarding the comparison of NLR in MDR-TB patients with other variables, and further observations can be made regarding the factors that affect changes in NLR values in MDR-TB patients.

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**Conflict of Interest**

The authors declared there is no conflict of interest.

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**Authors' Contributions**

Designed the study: PMR, JCS, and SS. Performed the statistical analyses and participated in sample collection: PMR, JCS, and SS. Drafted the manuscript: PMR. Editing: PMR. Contributed to the manuscript revision: PMR, JCS, and SS. All authors contributed and approved the final version of the manuscript.

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