INDONESIAN HEALTH JOURNAL

Volume 5 Number 3, October 2026
pp. 899-916
E-ISSN: 2963-3036
DOI: 10.58344/ihj.v5i3.948

Baseline Neutrophil-to-Lymphocyte Ratio, Monocyte-to-Lymphocyte Ratio, and Systemic Immune-Inflammation Index Predict Second-Month Sputum Conversion and Treatment Outcomes in Drug-Resistant Tuberculosis: A Retrospective Cohort Study

Nurhidayah Asjuh*, Dyara Aqeela Fathin
Universitas Negeri Makassar, Indonesia
Email: dyasjuh@gmail.com*, dyara.aqeela@gmail.com

Keywords:
drug-resistant tuberculosis; neutrophil-to-lymphocyte ratio; monocyte-to-lymphocyte ratio; systemic immune-inflammation index; prognosis; sputum conversion

Abstract

Drug-resistant tuberculosis (DR-TB) remains a major public health challenge, highlighting the need for accessible prognostic biomarkers. This study evaluated the associations of baseline neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and systemic immune-inflammation index (SII) with second-month sputum conversion and treatment outcomes. A retrospective cohort study included 36 adults who initiated DR-TB treatment at Nene Mallomo Hospital, Indonesia, between January 2023 and June 2026. Baseline inflammatory biomarkers were calculated from pretreatment complete blood count results. Statistical analyses included the Mann–Whitney U test, receiver operating characteristic (ROC) curve analysis, and logistic regression. Sputum conversion was evaluated in 31 patients, while the mortality analysis included 24 patients. Baseline NLR was significantly higher among patients with delayed or absent sputum conversion than among those who achieved early conversion ($p = 0.048$), whereas differences in MLR and SII were not statistically significant. All three biomarkers were significantly elevated among patients who died compared with those who survived. NLR demonstrated the highest observed discriminatory ability for mortality (area under the curve [AUC] = 0.836), followed by MLR (AUC = 0.813) and SII (AUC = 0.766). These findings suggest that elevated systemic inflammatory markers were associated with unfavorable treatment outcomes. However, the small sample size and wide confidence intervals limited the precision and generalizability of the results. Baseline NLR may serve as a potential marker for early risk stratification, although its independent prognostic value remains unconfirmed. Larger prospective multicenter studies are warranted to validate these findings, establish clinically relevant cutoff values, and assess the predictive performance of these biomarkers across diverse DR-TB populations

INTRODUCTION

Tuberculosis (TB) remains a major global public health challenge associated with substantial morbidity and mortality (Wang et al., 2025). One of the primary obstacles to TB control is the emergence of drug-resistant tuberculosis (DR-TB), which requires more complex management, may involve prolonged treatment, and is generally associated with lower treatment success rates than drug-susceptible TB. Although advances in therapeutic regimens, including the combination of bedaquiline, pretomanid, linezolid, and moxifloxacin (BPaLM), have provided more effective treatment options for eligible patients, treatment responses

among individuals with DR-TB remain variable. Several factors may influence treatment outcomes, including drug resistance patterns, nutritional status, comorbidities, treatment regimens, bacterial burden, medication adherence, and individual inflammatory and immune responses (Kementerian Kesehatan Republik Indonesia, 2023a, 2023b, 2025; World Health Organization, 2025).

In DR-TB management, early identification of patients at increased risk of unfavorable treatment outcomes is essential for optimizing clinical monitoring and therapeutic decision-making. Prognostic biomarkers that are inexpensive, readily available, and easily incorporated into routine clinical practice are particularly valuable in resource-limited healthcare settings. Complete blood counts (CBCs) offer a practical approach to assessing systemic inflammatory responses because they are widely available and provide hematological parameters without requiring specialized laboratory procedures. Among the increasingly investigated inflammatory biomarkers derived from CBC results are the neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and systemic immune-inflammation index (SII) (Chen et al., 2026; Wang et al., 2019).

The NLR and MLR are calculated by dividing the absolute neutrophil and monocyte counts, respectively, by the absolute lymphocyte count, whereas the SII is calculated by multiplying the platelet count by the neutrophil count and dividing the result by the lymphocyte count. These indices reflect different aspects of systemic inflammatory and immune responses and can be calculated using routinely available hematological measurements. Consequently, they have attracted increasing attention as potential biomarkers for assessing disease severity, monitoring treatment responses, and predicting clinical outcomes (Chen et al., 2026; Wang et al., 2019). In the present study, baseline NLR, MLR, and SII values were derived from CBC measurements obtained before the initiation of DR-TB treatment.

From an immunological perspective, Mycobacterium tuberculosis infection activates both innate and adaptive immune responses. Increased neutrophil, monocyte, and platelet counts, accompanied by reduced lymphocyte counts, may indicate heightened systemic inflammation and alterations in cellular immune regulation. An elevated NLR may reflect an imbalance between neutrophil-mediated inflammatory activity and lymphocyte-associated adaptive immune responses. Similarly, an increased MLR may indicate changes in monocyte activity relative to lymphocyte availability, whereas the SII integrates platelet, neutrophil, and lymphocyte counts to provide a broader measure of systemic inflammatory status. These hematological changes may reflect the complex interactions between host immune responses, inflammatory activity, and disease progression (Alwi et al., 2024; Greer et al., 2014; Ji et al., 2025; Sormin et al., 2018; Suryana et al., 2022; Yaja et al., 2026; Yin et al., 2017).

Excessive systemic inflammation may be associated with greater tissue damage, increased mycobacterial burden, and unfavorable treatment responses. Previous studies have reported associations between elevated NLR, MLR, and SII values and disease severity, delayed sputum conversion, unfavorable therapeutic responses, and poorer clinical outcomes among patients with tuberculosis. NLR has also been investigated as a potential biomarker for assessing disease severity and monitoring treatment responses, while MLR and other hematological indices have demonstrated potential utility in predicting early microbiological outcomes. Nevertheless, the magnitude and consistency of these associations may vary

according to patient characteristics, disease severity, treatment regimens, and the timing of biomarker measurements (Adane et al., 2022; Bastard et al., 2019; Chen et al., 2026; Ji et al., 2025; Kissling et al., 2023; Liu et al., 2025; Omair et al., 2024; Suryana et al., 2022; Wang et al., 2019; Yaja et al., 2026; Yu et al., 2023).

Sputum conversion is an important microbiological indicator used to monitor treatment responses in patients with pulmonary DR-TB. Earlier sputum conversion may indicate a favorable response to antimicrobial therapy, whereas delayed or absent conversion may suggest persistent mycobacterial activity and an increased risk of unfavorable outcomes. However, sputum conversion alone does not fully determine long-term treatment success because clinical outcomes are also influenced by treatment adherence, drug resistance patterns, comorbidities, and other patient-related factors (Centers for Disease Control and Prevention, 2024; Kementerian Kesehatan Republik Indonesia, 2025). In addition to microbiological conversion, final treatment outcomes, including cure, treatment completion, treatment failure, death, and loss to follow-up, provide important measures for evaluating the effectiveness of DR-TB management (Kementerian Kesehatan Republik Indonesia, 2023a, 2025).

Although previous studies have investigated inflammatory biomarkers in tuberculosis, evidence simultaneously examining baseline NLR, MLR, and SII in relation to early sputum conversion and treatment outcomes among patients with DR-TB remains limited, particularly in Indonesia. This research gap is especially relevant to regional healthcare facilities, where accessible prognostic indicators may support clinical risk assessment without substantially increasing diagnostic costs. Existing evidence suggests that hematological biomarkers may have prognostic value; however, their discriminatory performance, optimal cutoff values, and clinical applicability require further evaluation in DR-TB populations. In particular, evidence from South Sulawesi remains insufficient to establish whether these routinely available inflammatory indices can reliably identify patients at increased risk of delayed microbiological conversion or unfavorable treatment outcomes (Adane et al., 2022; Chen et al., 2026; Fritschi et al., 2023; Kissling et al., 2023; Liu et al., 2025; Omair et al., 2024; Suryana et al., 2022; Wang et al., 2019; Yaja et al., 2026; Yu et al., 2023).

Nene Mallomo Hospital in Sidenreng Rappang, South Sulawesi, Indonesia, provides treatment services for patients with DR-TB using various therapeutic approaches, including the BpaLM regimen and other short- and longer-duration treatment regimens. Evaluating baseline inflammatory biomarkers in this clinical population may provide context-specific evidence regarding the relationships between pretreatment systemic inflammation, early microbiological responses, and subsequent treatment outcomes. The novelty of this study lies in the simultaneous assessment of three routinely available hematological indices and their discriminatory performance for clinically relevant outcomes within a regional Indonesian DR-TB population. Such evidence may contribute to the identification of potentially useful risk stratification markers, although their clinical application would require further validation in larger and more diverse patient populations.

Accordingly, this retrospective cohort study aimed to evaluate the associations of baseline NLR, MLR, and SII with second-month sputum conversion and treatment outcomes among patients with DR-TB treated at Nene Mallomo Hospital, Sidenreng Rappang, between January 2023 and June 2026. Specifically, the study sought to compare baseline inflammatory

biomarker levels across patient outcome groups, assess their discriminatory performance using receiver operating characteristic (ROC) curve analysis, and identify potential cutoff values for distinguishing patients at increased risk of unfavorable outcomes. The findings were expected to provide preliminary evidence regarding the prognostic potential of these hematological indices and inform future investigations into accessible, cost-effective approaches to risk assessment and treatment monitoring in DR-TB management.

METHOD

Design, Location, and Research Time

This observational analytical study employed a retrospective cohort design and was conducted at Nene Mallomo Hospital, Sidenreng Rappang, Indonesia, using medical records of patients with drug-resistant tuberculosis (DR-TB) from January 2023 to June 2026.

Population and Sample

The study population was all RO TB patients who started treatment at Nene Mallomo Sidenreng Rappang Hospital during the study period. Sampling was carried out using the total sampling method, namely all patients who met the inclusion criteria and did not meet the exclusion criteria during the study period were included as samples.

For the analysis of the relationship between inflammatory biomarkers and second-month sputum conversion, the study subjects must meet the criteria: age ≥18 years; diagnosed with TB RO according to the guidelines; have a complete blood test result before starting treatment so that NLR, MLR, and SII can be calculated; and have sputum examination results in the first and second month evaluations. Patients with incomplete initial laboratory data, no required sputum test results, or incomplete medical records are excluded from the analysis.

For treatment outcome analysis, subjects must have complete blood test data before treatment and have a definitive treatment outcome according to the WHO definition and the Technical Guidelines for TB RO Management, namely cured, treatment completed, treatment failed, died, or lost to follow-up. Patients who are still undergoing treatment until the end of the study period or do not have a definitive outcome are not included in the treatment outcome analysis.

Research Variables

The main independent variables are the initial NLR, the initial MLR, and the initial SII. The dependent variables consisted of second-month sputum conversion and treatment outcomes. Variables considered as confounding factors included age, sex, body mass index (BMI), nutritional status, diabetes mellitus, HIV, previous TB treatment history, treatment regimen, initial germ load, and degree of drug resistance.

NLR: Initial NLR is defined as the comparison of the absolute neutrophil count to the absolute lymphocyte count based on a complete blood test before the patient starts RO TB therapy.

NLR = Neutrophil absolut / Lymphocyte absolute.

The value used is the baseline value before treatment.

MLR: Initial MLR is defined as a comparison of absolute monocyte count to absolute lymphocyte count based on a complete blood test prior to TB RO therapy.

MLR = Monocyte absolut / Lymphocyte absolute.

The value used is the baseline value before treatment.

SII: Early SII is a systemic inflammatory index calculated based on the number of platelets, absolute neutrophils, and absolute lymphocytes.

SII = (Platelets × Neutrophil absolut) / Lymphocytes absolut.

The SII value used is the value before the patient starts RO TB therapy.

Sputum conversion: The second month of sputum conversion is defined based on the change in the results of the sputum examination to be negative at the evaluation of the second month of treatment according to the monitoring of the TB RO program. Sputum conversion is used as an indicator of microbiological response to treatment (Centers for Disease Control and Prevention, 2024; Kementerian Kesehatan Republik Indonesia, 2025). Early sputum conversion, if the negative results from follow-up are not one and two negative, whereas late conversion is considered late if the results are converted negative after the first and second months in a row.

Treatment outcomes: Treatment outcomes are determined based on the WHO definition and Technical Guidelines for the Management of TB RO, which consists of cured, treatment completed, treatment failed, died, and lost to follow-up. Treatment success is a combination of patients who are declared cured and patients who complete treatment (Kementerian Kesehatan Republik Indonesia, 2023a, 2025). In this journal, treatment outcomes are treatment success and died.

Data Collection

Data were obtained retrospectively from the medical records and databases of the RO TB Program, including demographic characteristics, weight, height, BMI, nutritional status, comorbidities, treatment regimen, complete blood test results before therapy, sputum test results during monitoring, and treatment outcomes. NLR, MLR, and SII are calculated based on the results of complete blood tests obtained before the patient starts treatment for RO TB, so that the three biomarkers represent an initial inflammatory condition or baseline.

Statistical Analysis

Data analysis was conducted using IBM SPSS Statistics. Univariate analysis is used to describe the characteristics of the research subject. Normally distributed numerical variables are presented as averages ± standard deviations, while non-normally distributed numerical variables are presented as medians and minimum–maximum ranges. Categorical variables are presented as frequency and percentage.

Bivariate analysis was performed to assess the relationship of each inflammatory biomarker with second-month sputum conversion and treatment outcomes. For numerical variables that are not normally distributed, the Mann–Whitney U test is used. Categorical variables are analyzed using the Chi-square test or Fisher's Exact Test if the Chi-square requirements are not met. The p-value of <0.05 is considered statistically significant.

Receiver Operating Characteristic (ROC) analysis was performed to evaluate the discriminating capabilities of NLR, MLR, and SII and determine the optimal cut-off value based on the Youden Index. The parameters evaluated included Area Under the Curve (AUC), sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV).

Multivariate analysis was performed using binary logistic regression. Variables with a $p<0.25$ value in bivariate analysis or variables that are considered clinically relevant are

considered to be included in the multivariate model. The results of the analysis are presented in the form of Odds Ratio (OR), 95% Confidence Interval (CI), and p value.

RESULTS AND DISCUSSION

Characteristics of Research Subjects

The total number of TB RO patients from January 2023 to June 2026 is 36 people, the data that has a complete NLR, MLR, SII is 36 people, the second month conversion analysis is 31 people, and the outcome analysis is carried out by 26 people. Characteristics of all patients who met the study criteria (table 3.1). A total of 36 patients with Drug-Resistant Tuberculosis (TB RO) met the research criteria. The mean age of patients was 48.9 ± 15.4 years, with a median of 48 years (range 22–84 years). Most of the patients were male (61.1%). The average weight is 47.0 ± 11.0 kg, height 1.62 ± 0.08 m, and BMI 17.88 ± 3.65 kg/m². Based on the WHO classification, 61.1% of patients were in the underweight category, 33.3% had normal BMI, and 5.6% were overweight. Most patients did not have diabetes mellitus (83.3%) or HIV coinfection (100% HIV negative). The most widely used treatment regimen was BpaLM (41.7%), followed by long-term regimens (36.1%) and short-term regimens (22.2%).

Table 1 Basic Characteristics of Drug-Resistant Tuberculosis Patients (n = 36)

Characteristics	Results
Number of subjects	36
Age (years)	
Red ± SD	48.9 ± 15.4
Median (Min–Max)	48 (22–84)
Gender, n (%)	
Male	22 (61,1)
Women	14 (38,9)
Weight (kg)	
Red ± SD	47.0 ± 11.0
Median (Min–Max)	46,5 (29–80)
Height (m)	
Red ± SD	1.62 ± 0.08
Median (Min–Max)	1,62 (1,42–1,82)
Body Mass Index (kg/m²)	
Red ± SD	17.88 ± 3.65
Median (Min–Max)	16,91 (11,92–27,04)
BMI category (WHO), n (%)	
Underweight (<18.5 kg/m²)	22 (61,1)
Normal (18.5–24.9 kg/m²)	12 (33,3)
Overweight (25.0–29.9 kg/m²)	2 (5.6)
Obesity (≥30.0 kg/m²)	0 (0,0)
Comorbidities, n (%)	
Diabetes mellitus (+)	6 (16,7)
Diabetes mellitus (−)	30 (83,3)
HIV (+)	0 (0,0)
HIV (−)	36 (100)
Treatment regimen, n (%)	

BpaLM	15 (41,7)
Long-term	13 (36,1)
Short-term	8 (22,2)

The Relationship of Biomarkers to Sputum Conversion

1. NLR

Based on the data, there were 32 patients, with the division: early conversion (K1 + K2) 23 patients, late conversion/no conversion (K3 + K4 + K−) 9 patients, but 1 patient had a blank NLR value, so the Mann–Whitney analysis used 23 vs 8 patients (n = 31).

The results of the Mann–Whitney test showed that the initial NLR value in the group of patients with early sputum conversion (K1–K2) was significantly lower than in the group with late or no sputum conversion (K3–K4–K−). The median initial NLR in the early conversion group was 3.93 (IQR 2.82–6.61), while in the late-conversion group it was 6.23 (IQR 4.69–12.52). The difference is statistically significant (U = 48.0; Z = −1.99; p = 0.048).

Table. 2 Comparison of Initial NLR Based on Second Month Sputum Conversion Status

Variable	Early conversion (F1–K2) n=23	Late conversion (K3–K4–K−) n=8	p*
Early NLR	3,93 (2,82–6,61)	6,23 (4,69–12,52)	0,048

Table 3 The data is presented as a median (IQR).
Mann–Whitney test results

Statistics	**Value**
n Early group	23
n Late group	8
Mann–Whitney U	48,0
Z	−1.99
p-value	**0,048**

The value **of p = 0.048** indicates that this result **is statistically meaningful** (α = 0.05)

2. MLR

Based on the analyzed data (n = 31; early conversion = 23 patients, late conversion = 8 patients), the results of the initial MLR analysis are as follows.

Table 4 Comparison of Initial MLR Based on Second Month Sputum Conversion Status

Variable	**Early conversion (F1–K2) n=23**	**Late conversion (K3–K4–K−) n=8**	**p***
Early MLR	0,46 (0,30–0,83)	0,68 (0,58–0,91)	0,203

The data is presented as a median (IQR).
Mann–Whitney test results

Statistics	Value
n Early conversion	23
n Late conversions	8
Mann–Whitney U	63,0
Z	−1.29
p-value	**0,203**

Analysis using the Mann–Whitney test showed that the median initial MLR in the early sputum conversion group (K1–K2) was 0.46 (IQR 0.30–0.83), while in the late sputum conversion group (K3–K4–K−) was 0.68 (IQR 0.58–0.91). Although the group with late conversion had a tended higher MLR value, the difference was not statistically significant (U = 63.0; Z = −1.29; p = 0.203).

3. SII

Based on the analyzed data (31 patients who met the analysis; early conversion = 23 patients, late conversion = 8 patients), the results of the SII (Systemic Immune-Inflammation Index) analysis are as follows.

Table 5 Comparison of Initial SIIs Based on Second Month Sputum Conversion Status

Variable	Early conversion (F1–K2) n=23	Late conversion (K3–K4–K−) n=8	p*
Early SII	1.311.898 (867.895–2.505.766)	2.158.825 (1.860.270–4.801.982)	0,067

The data is presented as a median (IQR).
Mann–Whitney test results

Statistics	Value
n Early conversion	23
n Late conversions	8
Mann–Whitney U	51,0
Z	−1.83
p-value	**0,067**

Analysis using the Mann–Whitney test showed that the median initial SII in the group with early sputum conversion (K1–K2) was 1,311,898 (IQR 867,895–2,505,766), while in the group with late or no sputum conversion (K3–K4–K−) it was 2,158,825 (IQR 1,860,270–4,801,982). The group with late conversion had higher SII values, but the difference did not reach statistical significance (U = 51.0; Z = −1.83; p = 0.067).

Biomarker	Higher median on late conversions	p-value	Interpretation
NLR	Yes	**0,048**	**Significant**
MLR	Yes	0,203	Insignificant
SII	Yes	0,067	There is a tendency, not yet significant

All three biomarkers showed higher values in the group with late sputum conversion. However, only NLR showed a statistically significant relationship, so in this data NLR appears to be the most promising inflammatory biomarker for predicting delayed sputum conversion in drug-resistant TB patients. SII shows a fairly strong trend (p = 0.067) and has the potential to be significant in studies with larger sample counts.

The Relationship of Biomarkers to Treatment Outcomes

Analysis of the relationship between biomarkers of routine blood results and treatment outcomes there were 27 patients with the following distribution: Treatment completion: 17 patients, Died: 8 patients, LTF (Lost to Follow-up): 3 patients. For prognostic analysis, LTF is not included in the primary analysis of outcomes because the final outcome is unknown. The following analysis compares Finished treatment and Death. Based on biomarker data and analysis outputs, analysis was carried out on patients with definitive outcomes, namely: Completed treatment of 16 patients, died, 8 patients, total analysis of 24 patients.

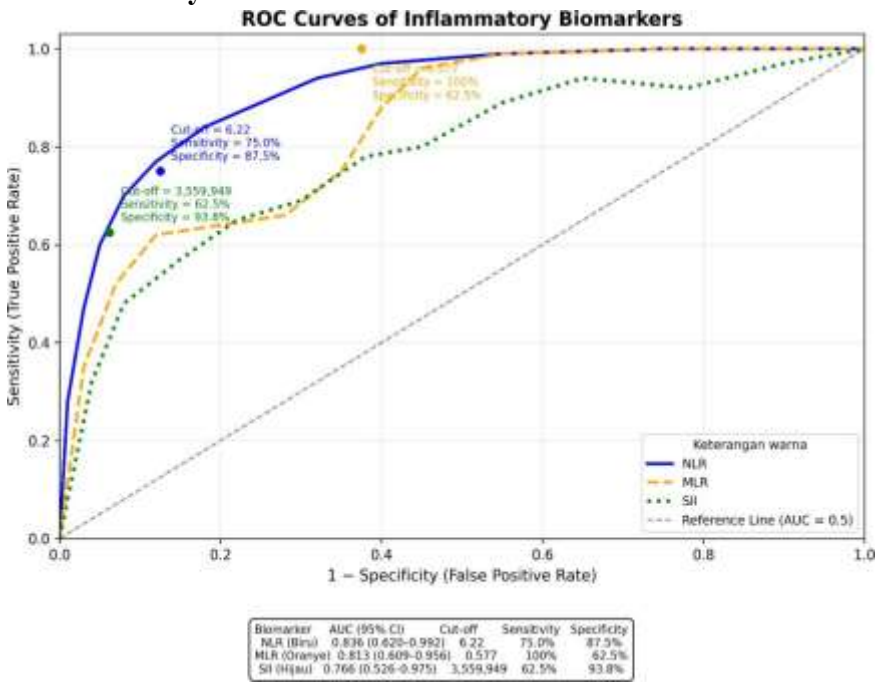
Table. 7 Comparison of Early Inflammatory Biomarkers Based on Treatment Outcomes

Variable	Completion of treatment (n=16)	Died (n=8)	p*
Early NLR	3,77 (2,77–5,99)	10,04 (5,79–16,74)	0,007
Early MLR	0,45 (0,31–0,80)	0,93 (0,66–1,19)	0,013
Early SII	1.270.863 (863.222–1.976.317)	3.867.854 (1.556.915–6.509.583)	0,038

The median initial NLR in patients who died was significantly higher than in patients who completed treatment (10.04 vs 3.77). The difference was statistically significant (p = 0.007). These findings suggest that an increase in NLR before starting therapy is associated with a worse risk of treatment outcomes. Biologically, a high NLR reflects a predominance of the neutrophil inflammatory response accompanied by a decreased lymphocyte immune response, which may describe more severe disease and lower infection elimination ability. The median initial MLR was also higher in the group that died than in the group that successfully completed treatment (0.93 vs 0.45), with a statistically significant difference (p = 0.013). These results suggest that increased MLR is related to poorer treatment outcomes. High MLR values reflect increased monocyte activity against lymphocytes, which indicates chronic inflammation and dysregulation of the immune response in drug-resistant TB. The median initial SII in the group that died was almost three times higher than in the group that completed treatment (3,867,854 vs 1,270,863). The difference was also statistically significant (p = 0.038). This

suggests that high SII is associated with an increased risk of death during treatment. Because SII combines platelet, neutrophil, and lymphocyte counts, these biomarkers describe systemic inflammation more comprehensively than NLR or MLR individually.

ROC Analysis ROC Analysis Chart



ROC analysis was conducted to evaluate the ability of early NLR, MLR, and SII to predict mortality in drug-resistant tuberculosis patients. NLR showed good discriminating ability with an AUC value of 0.836 (95% CI: 0.620–0.992), with an optimal cut-off value of 6.22 which provided a sensitivity of 75.0% and a specificity of 87.5%. MLR also has good discriminating ability (AUC 0.813; 95% CI: 0.609–0.956) with a cut-off of 0.577, sensitivity of 100%, and specificity of 62.5%. Meanwhile, SII had an AUC value of 0.766 (95% CI: 0.526–0.975), with a cut-off of 3,559,949, a sensitivity of 62.5%, and a specificity of 93.8%. These results show that NLR is the biomarker with the best predictive ability of mortality outcomes in this study.

Logistic regression using categorical biomarkers

Table 8 Logistic regression using categorical biomarkers

Variable	OR	95% CI	p
NLR >9.25	13,0	1,70-99,38	0,013
MLR >0.577	Cannot be estimated	Complete separation	----
SII >3.559.949	7,22	1,08-48,48	0,042

Logistic regression analysis showed that NLR and SII were significant predictors of mortality in drug-resistant tuberculosis patients. Patients with an initial NLR value above the cutt off had a 13.00-fold chance of death compared to patients with an NLR value below the

cut-off point (OR = 13.00; 95% CI: 1.70–99.38; p = 0.013). In addition, patients with initial SII values above the cut-off point had a 7.22-fold chance of death compared to patients with SII values below the cut-off point (OR = 7.22; 95% CI: 1.08–48.48; p = 0.042). On the other hand, the OR for MLR cannot be estimated using conventional logistic regression because there is complete separation, i.e. the distribution of data causes one of the predictor categories to separate the outcome perfectly so that the estimation of the model parameters becomes unstable.

The OR results appear to be very large and the confidence interval is quite wide because the number of deaths is only 8 patients. Therefore, these results should be interpreted as exploratory findings and need to be validated in studies with larger sample sizes.

Characteristics of TB RO patients

Subject characteristics. The average age of RO TB patients in this study was 48.9 ± 15.4 years, which suggests that most patients are of productive age. These findings are in line with the World Health Organization's report that drug-resistant tuberculosis is more common in the productive age group due to high exposure to infection, mobility, and previous medical history. The dominance of male patients (61.1%) is also consistent with various studies that report that men have a higher risk of developing TB and RO TB due to exposure to risk factors such as smoking, alcohol consumption, and delays in seeking treatment.1,14

Most of the patients in this study were underweight (61.1%) with an average BMI of 17.88 kg/m². Malnutrition is known to be closely related to cellular immunity disorders which play an important role in the elimination of Mycobacterium tuberculosis. The research of Nurfitriyana et al. also showed that BMI and NLR can be used as simple indicators to assess inflammatory status as well as monitor the development of treatment responses in tuberculosis patients (Nurfiyana & Amien, 2026). Similar results were reported by Regina et al, who found that nutritional status and NLR were associated with sputum conversion rate in MDR patients (Regina et al., 2024). In addition, Tan et al. reported that nutritional status is one of the factors influencing the prognosis of TB patients.

The majority of patients did not have diabetes mellitus (83.3%) or HIV coinfection. This is in contrast to some reports that suggest diabetes increases the risk of active TB and slows the response to therapy. 35,36 However, in this study, the low distribution of comorbidities allowed the interpretation of the relationship between inflammatory biomarkers and outcomes to be less influenced by confounding factors.

Sputum conversion

As many as 80.5% of patients have experienced early sputum conversion, while 63.9% have achieved sputum conversion in the second month. These figures show that most patients respond well to the therapy. According to WHO and the Technical Guidelines for the Management of Drug-Resistant TB of the Ministry of Health of the Republic of Indonesia, sputum conversion is one of the important indicators to assess the success of the initial response to therapy and is the basis for evaluating the sustainability of treatment (Kementerian Kesehatan Republik Indonesia, 2025; World Health Organization, 2025). This study is in line with Bastard et al, stating that the conversion of culture in the second month is an acceptable prognostic marker to assess the success of treatment of TB RO, It may even potentially be used as a surrogate marker in clinical trials (Bastard et al., 2019). Therefore, the successful early

sputum conversion in most patients in this study demonstrated a good initial response to the given treatment regimen.

Treatment Outcomes

In this study, treatment success was 59.2%, while 40.7% experienced an unfavorable outcome. This figure is still lower than the global target for the success of drug-resistant TB treatment according to the World Health Organization. The high proportion of unfavorable outcomes was mainly due to mortality (22.2%) and loss to follow-up (8.3%). These findings are in line with Jie et al's suggestion that inflammatory status before treatment is able to predict therapeutic outcomes by decreasing patient survival rates (Ji et al., 2025). In addition, Yue et al, report that inflammatory biomarkers can predict the survival status of RR/MDR-TB patients, so monitoring of inflammatory biomarkers during therapy is expected to be able to identify patients at risk of adverse outcomes early (Yu et al., 2023).

The Relationship of Early Sputum Conversion to Treatment Outcomes

In this study, no significant relationship was found between early sputum conversion and treatment outcomes (Fisher's Exact Test $p = 0.157$). However, descriptively it can be seen that 64.0% of patients who experienced early sputum conversion achieved treatment success, while all patients who did not experience early conversion experienced unfavorable outcomes.

The insignificance of these results may be due to the small sample size, especially in the group that did not experience early conversion consisting of only two patients. This condition causes the statistical power to be low so that the actual relationship may not be statistically detectable (type II error). In addition, as many as nine patients are still undergoing treatment so they cannot be included in the final outcome analysis, which further reduces the number of samples analyzed.

However, the results of this study still show a tendency that patients who experience early sputum conversion have better treatment outcomes than patients who do not experience early conversion. These findings are in line with the research of Bastard et al which shows that sputum conversion is an indicator of microbiological response to therapy, as the study states that second-month culture conversion is a prognostic marker of the success of RO TB treatment (Bastard et al., 2019). These findings are also consistent with the recommendations of WHO and the Indonesian Ministry of Health which place sputum conversion as an important indicator in the evaluation of drug-resistant TB treatment response (Kementerian Kesehatan Republik Indonesia, 2025; World Health Organization, 2025).

Relationship of Biomarkers to NLR Sputum Conversion

This study showed that an increase in NLR before treatment was related to delayed sputum conversion in drug-resistant TB patients. Biologically, higher NLR reflects a heavier systemic inflammatory response as well as an imbalance between neutrophil and lymphocyte activity, so it may be related to a higher disease burden and a slower treatment response. These results support the potential of NLR as a simple prognostic biomarker for predicting sputum conversion rate in RO TB patients. An increase in NLR describes neutrophilia, lymphopenia, which reflects systemic inflammation and a decrease in adaptive immune response. In drug-resistant TB, the condition is associated with a higher bacilli load, wider lung damage, and longer sputum conversion time.

The results of this study are in line with Suryana et al. who reported that high levels of NLR before treatment were associated with delayed sputum conversion in tuberculosis patients (Suryana et al., 2022). Similar findings were also reported by Regina et al., suggesting that NLR can be used as a simple parameter to predict sputum conversion in MDR-TB patients after three months of therapy (Regina et al., 2024). In addition, Yin et al. reported that an increase in NLR before treatment was associated with risk retreatment in tuberculosis patients (Yin et al., 2017). The results of this study are also supported by Koeswaya et al. who found that NLR correlates with bacillus load in drug-resistant TB patients (Koeswaya et al., 2026).

MLR

The results showed a tendency to increase MLR in patients with slower sputum conversion. However, in this study, the difference has not reached statistical significance. This indicates that early MLR cannot yet be used as a strong predictor of sputum conversion rate, although biologically increased MLR may reflect the activation of innate inflammatory and immune responses in drug-resistant TB patients. High MLR indicates greater monocyte activation. Monocytes are the main site of Mycobacterium tuberculosis replication, so increased MLR is often associated with more severe chronic inflammation. The results of this study are in line with Wang et al. who suggest that MLR can be used to monitor tuberculosis therapy response during treatment (Wang et al., 2019). Omair et al.'s study also reported that MLR decreased with the success of therapy, although its predictive strength was lower than that of NLR (Omair et al., 2024). Meta-analysis by Adane et al. concluded that MLR has potential as a biomarker of TB, but its accuracy is still affected by population heterogeneity and sample size research (Adane et al., 2022).

SII

This study showed a tendency that patients with higher initial SII experienced slower sputum conversion. However, the relationship was not statistically significant in this study ($p > 0.05$). The insignificance of the results is likely to be influenced by the relatively small sample size, so the power of statistical tests is limited. Because of the combination of the three inflammatory components, the SII usually has better predictive capabilities than each single parameter. The results of this study are in line with a systematic review by Fritschi et al. which reported that complete blood count-based biomarkers, including SII, have potential as indicators of diagnosis, therapy monitoring, and prognosis of tuberculosis (Fritschi et al., 2023). Similar findings were also reported by Kissling et al. who concluded that peripheral blood cell ratio is an easily usable inflammatory biomarker in clinical practice, although evidence regarding SII as a predictor of sputum conversion is still needed Further research (Kissling et al., 2023).

Descriptively, patients with slower sputum conversion tend to have higher NLR, MLR, and SII values than patients with early conversion. These findings indicate that an increase in systemic inflammatory biomarkers at the beginning of treatment may be related to delayed sputum conversion in drug-resistant TB patients

The relationship of biomarkers to treatment outcomes

The data in the study showed that the patients who died had the characteristics of more severe leukocytosis, dominant neutrophils, and lymphopenia, resulting in a much higher NLR, followed by an increase in MLR, and especially a sharply increased SII. These findings are

consistent with many studies on drug-resistant TB, that severe systemic inflammatory activation is associated with a poor prognosis. Thus NLR, MLR, and especially SII appear to be much higher in patients who die than in patients who complete treatment, while hemoglobin and platelet levels are relatively similar. These findings support the hypothesis that routine blood count-based inflammatory biomarkers have the potential to be predictors of drug-resistant TB treatment outcomes. These results are consistent with the study of Ji et al. which showed that an increase in blood inflammatory status is associated with a decrease in survival rates in tuberculosis patients (Ji et al., 2025). The study of Yu et al. also reported that inflammatory biomarkers, including NLR and MLR, are independent predictors of survival in rifampicin/multidrug-resistant tuberculosis patients (Yu et al., 2023). In addition, Chen et al. reported that NLR is an easy-to-use biomarker to predict patient prognosis tuberculosis (Chen et al., 2026). Similar findings were also reported by Han et al. suggesting that increased NLR was associated with poorer clinical outcomes in patients with miliary tuberculosis (Han et al., 2018).

All three early inflammatory biomarkers (NLR, MLR, and SII) showed a meaningful association with drug-resistant TB treatment outcomes. Patients who died had higher values of all three biomarkers than patients who successfully completed treatment. These results support that NLR, MLR, and SII have the potential to be simple prognostic biomarkers for predicting drug-resistant TB treatment outcomes, with NLR showing the strongest statistical association

Best biomarkers

Logistic regression analysis showed that NLR was the biomarker with the strongest prognostic ability to die in drug-resistant tuberculosis patients. Patients with an initial NLR value of >9.25 had a 13.0-fold odds of death compared to patients with an NLR of ≤9.25 (OR = 13.0; 95% CI: 1.70–99.38; p = 0.013). The magnitude of the OR value suggests that an increase in NLR at the beginning of treatment is closely related to an increased risk of poor treatment outcomes. Although the confidence interval is still quite wide due to the limited number of samples and the incidence of death, the entire range of intervals is above the 1 number so the relationship remains statistically significant.

These results are also consistent with ROC analysis which shows that NLR has the highest area under the curve (AUC) value compared to other biomarkers. Thus, NLR not only has a strong association with death, but also has the best discriminating ability to distinguish between patients at risk of death and patients who successfully complete treatment. The consistency between the results of the Mann–Whitney assay, ROC analysis, and logistic regression strengthens the evidence that NLR is the best prognostic biomarker in this study.

SII also showed a meaningful association with mortality (OR = 7.22; 95% CI: 1.08–48.48; p = 0.042). This suggests that systemic inflammation involving neutrophils, lymphocytes, and platelets also plays a role in the prognosis of drug-resistant TB patients. Nevertheless, the associative strength of SII is lower than that of NLR, as demonstrated by the smaller OR value and lower discriminatory ability of the ROC. These findings indicate that the addition of platelet components to the SII did not provide an improvement in predictive ability compared to NLR in this study population.

In contrast to NLR and SII, the OR for MLR cannot be estimated because there is complete separation in the logistic regression model. This condition occurs when the

distribution of data causes one of the predictor categories to separate the outcomes perfectly, so that the estimation of the model parameters becomes unstable. Therefore, the inability to obtain OR in MLR cannot be interpreted as having no association with prognosis. On the other hand, the results of the ROC analysis show that MLR still has good discrimination capabilities. Thus, the failure of the OR estimate in the MLR reflects more statistical limitations due to the small sample size than the absence of the prognostic value of the biomarker.

The results of this study show that NLR is the most superior prognostic biomarker compared to MLR and SII in drug-resistant tuberculosis patients. In addition to being readily available from routine blood tests at no additional cost, NLR exhibits the best discriminating ability, the greatest risk association with death, and simple clinical interpretation. Therefore, NLR has the potential to be used as an early biomarker for risk stratification of drug-resistant TB patients so that patients with high NLR can be identified earlier and obtain more intensive clinical monitoring and intervention during treatment.

These findings suggest that early inflammatory biomarkers could potentially be used as predictors of prognosis in drug-resistant TB patients, with NLR as the biomarker with the best predictive performance. These results are in line with a systematic review by Kissling et al. which concluded that NLR is the most consistent biomarker for assessing inflammation and tuberculosis prognosis (Kissling et al., 2023). Chen et al.'s research also showed that NLR has a good ability to discriminate against the clinical outcomes of tuberculosis patients (Chen et al., 2026). In addition, Ji et al. reported that increased NLR was associated with decreased survival in TB patients during the follow-up period (Ji et al., 2025). Nevertheless, The relatively wide confidence interval suggests that these results are still influenced by a limited number of samples, thus requiring confirmation through prospective studies with a larger number of subjects.

Clinical Implications

The results of this study support the importance of monitoring inflammatory biomarkers (NLR, MLR, and SII) along with the evaluation of sputum conversion as part of routine monitoring of RO TB patients. Hematology biomarker testing is relatively inexpensive, easy to perform, and available in almost all healthcare facilities, so it has the potential to be an aid in identifying patients at risk of delayed therapeutic response or unfavourable outcomes (Ferisa et al., 2026; Ji et al., 2025; Yaja et al., 2026; Yu et al., 2023). However, studies with larger sample sizes and prospective designs are still needed to confirm the role of these biomarkers as independent predictors of the success of drug-resistant TB treatment.

Strengths and limitations of research

The strength of this study is that it uses three inflammatory biomarkers at once (NLR, MLR, and SII), and examines two important clinical outcomes, namely second-month sputum conversion and treatment outcomes, in addition to data from real-world clinical practice. The limitations of the study were due to the retrospective design, which was in a single-center and not all patients had treatment outcomes as some were still undergoing therapy, and not all confounding factors such as micronutrient nutritional status or adherence to therapy could be evaluated

CONCLUSION

This retrospective cohort study suggested that baseline inflammatory biomarkers were associated with microbiological responses and mortality among patients with drug-resistant tuberculosis (DR-TB) at Nene Mallomo Hospital. A higher baseline neutrophil-to-lymphocyte ratio (NLR) was significantly associated with delayed or absent sputum conversion by the second month of treatment, whereas the monocyte-to-lymphocyte ratio (MLR) and systemic immune-inflammation index (SII) showed no statistically significant associations with this outcome. All three biomarkers were significantly elevated among patients who died compared with those who completed treatment. NLR demonstrated the highest observed discriminatory performance for mortality, followed by MLR and SII, although these findings did not establish the predictive superiority of any individual biomarker. Overall, the results highlighted the potential utility of routinely available hematological indices for early risk stratification in DR-TB management. However, the small sample size, retrospective study design, and imprecise estimates limited the strength of the conclusions regarding their independent prognostic value and clinical applicability.

Future research should involve larger, prospective, multicenter cohorts with standardized definitions of sputum conversion, consistent laboratory measurement units, and comprehensive follow-up to validate these associations. Subsequent analyses should account for potential confounding factors, including nutritional status, diabetes mellitus, baseline mycobacterial burden, drug resistance patterns, treatment regimens, and medication adherence. Proposed biomarker cutoff values should undergo rigorous verification and external validation before clinical implementation. Furthermore, statistical approaches appropriate for small samples and sparse outcome events should be employed to minimize unstable estimates and address potential complete separation in regression models. Longitudinal assessments of NLR, MLR, and SII may help determine whether changes in these biomarkers provide additional prognostic information beyond baseline measurements. Further investigations should also evaluate whether incorporating these inflammatory indices into established clinical prediction models improves prognostic accuracy, facilitates individualized treatment monitoring, and ultimately contributes to better patient outcomes.

REFERENCES

Wang, J., Yuan, B., Fang, Y., Zhao, C., Liu, J., & Xiong, K. (2025). Post-tuberculosis morbidities and their associated mortality: moving from challenges to solutions. *European Respiratory Review*, *34*(178), 250148.

Adane, T., Melku, M., Ayalew, G., Bewket, G., Aynalem, M., & Getawa, S. (2022). Accuracy of monocyte to lymphocyte ratio for tuberculosis diagnosis and its role in monitoring anti-tuberculosis treatment: Systematic review and meta-analysis. *Medicine, 101*(44), Article e31539. https://doi.org/10.1097/MD.0000000000031539

Alwi, I., Setiati, S., Syam, A. F., Sudoyo, A. W., Simadibrata, M., & Nasution, S. A. (Eds.). (2024). *Buku ajar ilmu penyakit dalam* (Ed. ke-7, Jilid II). Interna Publishing.

Bastard, M., Sanchez-Padilla, E., Hayrapetyan, A., Kimenye, K., Khurkhumal, S., Dlamini, T., Fadul Perez, S., Telnov, A., Hewison, C., Varaine, F., & Bonnet, M. (2019). What is the best culture conversion prognostic marker for patients treated for multidrug-resistant tuberculosis? *The International Journal of Tuberculosis and Lung Disease, 23*(10), 1060–1067. https://doi.org/10.5588/ijtld.18.0649

Centers for Disease Control and Prevention. (2024). *2021 state and city TB report: Sputum culture conversion*. Centers for Disease Control and Prevention.

Chen, J., Wang, D., Deng, B., Wang, C., Tang, S., Chen, L., & An, Q. (2026). Neutrophil-to-lymphocyte ratios as easy-to-use biomarkers for the diagnosis of active tuberculosis in children and adolescents. *Frontiers in Cellular and Infection Microbiology, 16*, Article 1743922. https://doi.org/10.3389/fcimb.2026.1743922

Ferisa, N. P., Dalimunthe, W., Pratita, W., Harahap, J., Lubis, M., & Meirina, F. (2026). NLR (neutrophil-to-lymphocyte ratio), MLR (monocyte-to-lymphocyte ratio) and NMLR (neutrophil-monocyte-to-lymphocyte ratio) as biomarkers for establishing the diagnosis of tuberculosis in children. *Indonesian Journal of Global Health Research, 8*(1), 957–962. https://doi.org/10.37287/ijghr.v8i1.476

Fritschi, N., Vaezipour, N., Buettcher, M., Portevin, D., Naranbhai, V., & Ritz, N. (2023). Ratios from full blood count as markers for TB diagnosis, treatment, prognosis: A systematic review. *The International Journal of Tuberculosis and Lung Disease, 27*(11), 822–832. https://doi.org/10.5588/ijtld.22.0598

Greer, J. P., Arber, D. A., Glader, B., List, A. F., Means, R. T., Jr., Paraskevas, F., & Rodgers, G. M. (Eds.). (2014). *Wintrobe's clinical hematology* (13th ed.). Wolters Kluwer/Lippincott Williams & Wilkins.

Han, Y., Kim, S. J., Lee, S. H., Sim, Y. S., Ryu, Y. J., Chang, J. H., Shim, S. S., Kim, Y., & Lee, J. H. (2018). High blood neutrophil-lymphocyte ratio associated with poor outcomes in miliary tuberculosis. *Journal of Thoracic Disease, 10*(1), 339–346. https://doi.org/10.21037/jtd.2017.12.65

Ji, Y., Xie, Q., Wei, W., Huang, Z., Liu, X., Ye, Q., Liu, Y., Lu, X., Lu, Y., Hou, R., Zhang, Q., Xu, Y., Yuan, J., Lu, S., & Yang, C. (2025). Association between blood inflammatory status and the survival of tuberculosis: A five-year cohort study. *Frontiers in Immunology, 16*, Article 1556857. https://doi.org/10.3389/fimmu.2025.1556857

Kementerian Kesehatan Republik Indonesia. (2023a). *Buku pegangan pengendalian tuberkulosis resistan obat dengan paduan BPaLM*. Direktorat Jenderal Pencegahan dan Pengendalian Penyakit, Kementerian Kesehatan Republik Indonesia.

Kementerian Kesehatan Republik Indonesia. (2023b). *Petunjuk teknis pengobatan tuberkulosis monoresisten INH di Indonesia*. Direktorat Jenderal Pencegahan dan Pengendalian Penyakit, Kementerian Kesehatan Republik Indonesia.

Kementerian Kesehatan Republik Indonesia. (2025). *Petunjuk teknis penatalaksanaan tuberkulosis resistan obat*. Kementerian Kesehatan Republik Indonesia.

Kissling, M., Fritschi, N., Baumann, P., Buettcher, M., Bonhoeffer, J., Naranbhai, V., & Ritz, N. (2023). Monocyte, lymphocyte and neutrophil ratios – Easy-to-use biomarkers for the diagnosis of pediatric tuberculosis. *The Pediatric Infectious Disease Journal, 42*(6), 520–527.

Koeswaya, M. D., Marliana, N., Abror, Y. K., & Kurniati, I. (2026). Correlation between neutrophil-to-lymphocyte ratio and molecular test Ct category in patients with drug-resistant tuberculosis. *Jurnal Riset Kesehatan Poltekkes Depkes Bandung, 18*(1), 433–440. https://doi.org/10.34011/juriskesbdg.v18i1.3284

Liu, Y., Li, M., Ding, Y., Gao, Y., Li, T., Wang, X., & Zheng, M. (2025). Clinical utility of monocyte-to-lymphocyte ratio and prognostic nutritional index in diagnosing smear-negative pulmonary tuberculosis with negative IGRA results. *Infection and Drug Resistance, 18*, 5731–5743. https://doi.org/10.2147/IDR.S554475

Nurfiyana, W., & Amien, A. Z. (2026). Analysis of the relationship between neutrophil-lymphocyte ratio (NLR) values and body mass index in tuberculosis patients. *Jurnal Kesehatan, 17*(1), 52–58. https://doi.org/10.26630/jk.v17i1.5529

Omair, M., Baig, M. S., Farooqui, W. A., Kousar, S., Noori, M. Y., Zeehan, N., Khan, A., Isa, S., Kamran, D. S., Bari, M. F., & Mehmood, M. (2024). Relationship of neutrophil lymphocyte ratio, monocyte lymphocyte ratio and neutrophil monocyte ratio with treatment response in pulmonary tuberculosis patients during intensive phase treatment. *BMC Infectious Diseases, 24*, Article 615. https://doi.org/10.1186/s12879-024-09454-2

Regina, P. M., Silaen, J. C., & Sembiring, S. (2024). Neutrophil-lymphocyte ratio and nutritional status as parameters of sputum conversion in MDR-TB before & after 3 months of anti-TB treatment. *Jurnal Respirasi, 10*, 137–142.

Sormin, D. E., Siagian, P., Sinaga, B. Y. M., & Eyanoer, P. C. (2018). Neutrophyl lymphocyte ratio pada pasien tuberkulosis paru dan tuberkulosis resisten obat. *Jurnal Respirologi Indonesia, 38*(3), 177–180.

Suryana, K., Dharmesti, N. W. W., & Rai, I. B. N. (2022). High pretreatment level of neutrophil to lymphocyte ratio, monocyte to lymphocyte ratio and other factors associated with delayed sputum conversion in patients with pulmonary tuberculosis. *Infection and Drug Resistance, 15*, 5455–5462. https://doi.org/10.2147/IDR.S380166

Wang, W., Wang, L. F., Liu, Y. Y., Yang, F., Zhu, L., & Zhang, X. H. (2019). Value of the ratio of monocytes to lymphocytes for monitoring tuberculosis therapy. *Canadian Journal of Infectious Diseases and Medical Microbiology, 2019*, Article 3270393. https://doi.org/10.1155/2019/3270393

World Health Organization. (2025). *Global tuberculosis report 2025*. World Health Organization.

Yaja, H., Kashyap, B., & Kotru, M. (2026). Utility of hematological indices in predicting the sputum conversion at the end of the intensive phase of treatment for patients with pulmonary TB. *Annals of Pathology and Laboratory Medicine, 13*(3), A153–A162. https://doi.org/10.21276/apalm.3789

Yin, Y., Kuai, S., Liu, J., Zhang, Y., Shan, Z., Gu, L., Huang, Q., Pei, H., & Wang, J. (2017). Pretreatment neutrophil-to-lymphocyte ratio in peripheral blood was associated with pulmonary tuberculosis retreatment. *Archives of Medical Science, 13*(2), 404–411. https://doi.org/10.5114/aoms.2016.60822

Yu, Q., Luo, H., Hu, S., Sun, D., Nie, Q., & Yan, J. (2023). The survival analysis of rifampicin/multidrug-resistant tuberculosis patients based on the levels of inflammatory biomarkers: A retrospective cohort study. *Frontiers in Cellular and Infection Microbiology, 13*, Article 1118424. https://doi.org/10.3389/fcimb.2023.1118424