

## Neutrophil-Lymphocyte Ratio Against Pulmonary TB Retreatment at Sanjiwani Gianyar Regional Hospital, 2020-2022

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### ABSTRACT

**Background:** Tuberculosis (TB) is one of the main causes of death and the highest cause of death caused by infection. Distinguishing between pulmonary TB that has been cured and completed treatment from retreatment TB based only on history, physical examination, laboratory examination and radiological findings is often difficult because pulmonary TB is often non-specific and the sensitivity of sputum microscopic examination for BTA bacteria is 50-60%. Neutrophil Lymphocyte Ratio (NLR) is considered to have a stronger discriminatory ability in predicting bacteremia than discrimination based on neutrophilia or lymphocytopenia alone. **Method:** This research uses analytical research methods with a case-control design because measurements are carried out at the same time. This study uses secondary data obtained from the medical records of patients who experienced TB in the period from January 2020 to May 2022. **Results:** In this study, the average age of cases was  $48 \pm 17$  years and that of controls was  $52 \pm 14$  years. Based on the receiver operating characteristics (ROC) curve, it was found that the best NLR cut-off was 3.2 with a sensitivity of 92% and a specificity of 32%. Based on chi-square analysis, it was found that the NLR cut-off of 3.2 was significantly correlated with the incidence of retreatment with  $P=0.009$ . **Conclusion:** The neutrophil-lymphocyte ratio (NLR) with a cut-off of 3.2 can be used as a useful indicator in tuberculosis (TB) retreatment.

**Keywords:** bacteremia; laboratory examination; lymphocytopenia; neutrophil-lymphocyte ratio; tuberculosis

### INTRODUCTION

Tuberculosis (TB) is a Mycobacterium tuberculosis infection that can affect the lungs and other organs and tissues. The spread of TB occurs from one individual to another when an infected person coughs or sneezes, releasing bacteria into the air which is then inhaled by other people [1]. Prolonged exposure is required for someone to become infected with TB, so transmission usually occurs from close family members or work colleagues, not from people you don't know intimately. Even though TB is a disease that is easily transmitted, transmission does not occur easily between humans. If not treated properly, TB can become a potentially fatal disease. Globally, TB is one of the main causes of infection resulting in death [2].

In 2019, tuberculosis (TB) remained the most common cause of death from a single infectious pathogen. Globally, approximately 10.0 million people were diagnosed with TB that year, and there were approximately 1.2 million TB deaths in individuals not infected with HIV, as well as an additional 208,000 deaths in individuals living with HIV. Of the total, 88% were adult patients and 12% were patients under 15 years of age [3]. The Southeast Asia region had the highest number of TB cases in 2019, accounting for 44% of total cases

worldwide, followed by Africa (25%) and Western Pacific (18%). Smaller percentages are found in the Middle East (8.2%), America (2.9%), and Europe (2.5%). Eight countries, such as India, Indonesia, China, the Philippines, Pakistan, Nigeria, Bangladesh and South Africa, contribute two-thirds of the total TB cases globally [4].

Indonesia faces a significant burden of tuberculosis (TB), with an estimated 845,000 cases occurring in 2020 and 357,199 new cases reported. The impact of TB in Indonesia is something that deserves attention. In 2021, the Southeast Asia region accounts for almost half of the total TB cases worldwide, and Indonesia is included in 22 countries with a high level of TB burden. TB is ranked second as the main cause of death in adults in Indonesia, after cardiovascular disease. Every year, around 500,000 new TB cases are reported in Indonesia, causing 175,000 deaths. The prevalence of TB varies across geographic regions, with a prevalence rate of approximately 759 cases per 100,000 population based on bacteriological evidence [5].

Pulmonary tuberculosis retreatment refers to the treatment of patients who have previously undergone TB treatment but experienced a relapse or did not respond to treatment.

Distinguishing between pulmonary TB that has been cured and completed treatment from retreatment TB based only on history, physical examination, laboratory examination and radiological findings is often difficult because pulmonary TB is often non-specific and the sensitivity of sputum microscopic examination for BTA bacteria is 50-60%. The physiological immune response of circulating leukocytes to various inflammatory stress conditions characterized by an increase in neutrophil count and a decrease in lymphocyte count has long been known. An increase in total WBC and neutrophils is an inflammatory reaction mainly caused by bacterial infection. Lymphocytopenia has also long been used as a diagnostic marker for bacterial infection. Therefore, the Neutrophil Lymphocyte Ratio (NLR) is considered to have a stronger discriminatory ability in predicting bacteremia than discrimination based on neutrophilia or lymphocytopenia alone [6].

From the description above, it is known that the role of NLR as an inflammatory biomarker in various systemic diseases ranging from cardiovascular to oncological diseases has been widely studied and has better accuracy and sensitivity values than other routine parameters such as WBC count, CRP, neutrophil count, lymphocyte count, procalcitonin. From various studies, the use of NLR in respiratory diseases has also been proven as a better inflammatory marker.

#### METHOD

This research uses analytical research methods with a case-control design because measurements are carried out at the same time. This study uses secondary data obtained from the medical records of patients who experienced TB in the period from January 2020 to May 2022. The sample in this study was all pulmonary TB patients who had a history of previous OAT treatment at Sanjiwani Gianyar Regional Hospital in the period January 2020 to 2022 and who met inclusion and exclusion criteria.

Data processing starts from the editing process because at this stage the researcher will check the medical records to assess whether there is incomplete data. Then proceed with coding, namely assigning a code to each data manually before processing it with a computer. The next stage is entry, namely entering the medical record data into the computer after all the medical record guidelines have been recorded. Next is data cleaning, namely checking all data that has been entered into the computer to avoid errors in data entry. Then the data is saved in the saving process and the final stage is data analysis.

Data analysis used SPSS version 25. To look for significant differences between retreatment TB cases and the control group, a Pearson  $\chi^2$  test was carried out. In bivariate analysis, odds ratios (OR) were calculated with a 95% confidence level (CI) to evaluate factors associated with retreatment TB cases and controls. Meanwhile, multivariate analysis was used to obtain a corrected odds ratio (AOR) with a 95% confidence level (CI) to determine factors associated with TB retreatment. It is important to note that a p-value  $< 0.05$  was considered statistically significant for all analyzes performed.

#### RESULTS

In this study, there were 50 research subjects with 25 control patients who were defined as tuberculosis patients who recovered without retreatment and 25 case-patients, namely tuberculosis patients who were undergoing retreatment. Patient characteristics are shown in table 1. In a study involving 50 subjects, patient characteristics can be described as follows: The average age of patients was 53 years with an age range between 38 to 60 years. The majority of patients are men, as many as 30 out of 50 patients (60%). Blood analysis results showed that the average neutrophil level was 76, with a range between 68.1 to 83.6. In addition, the average lymphocyte level in patients was 14, with a range between 9.8 to 20.8. The patient's NLR (Neutrophil-Lymphocyte) Ratio was 5.4, with a range from 3.2 to 8.4. There were 19 patients (38%) who had a history of diabetes mellitus (DM), while the other 31 patients (62%) had no history of DM. Of all the patients, 23 of them (46%) had positive TCM (Molecular Rapid Test) results, while 27 other patients (54%) had negative results on this test.

In correlation analysis using the Chi-Square test on two groups of patients, namely cases (N=25) and controls (N=25), several significant findings were found. First, there is a strong and significant relationship between the level of NLR (Neutrophil-Lymphocyte Ratio) and patient status. More specifically, case patients had a higher level of NLR ( $\geq 3.2$ ) than control patients, with a highly significant difference ( $p = 0.009$ ), indicating that NLR may be an important indicator in identifying potential cases. However, in terms of patient age, gender, and HIV status, the results of Chi-Square analysis showed that there was no significant relationship between these factors and patient status. Patient age in the categories  $< 40$  years, 40-59 years, and  $\geq 60$  years, male gender, and HIV status did not influence the differences between cases and controls, with p values greater than 0.05.

**TABLE 1:** Characteristics of Research Subjects.

Parameter	Subject (n=50)
Age (Year)	53 (38-60)
Male	30 (60%)
Neutrophil	76 (68.1-83.6)
Lymphocyte	14 (9.8-20.8)
NLR	5.4 (3.2-8.4)
DM	
Yes	19 (38%)
No	31 (62%)
TCM	
Positive	23 (46%)
Negative	27 (54%)

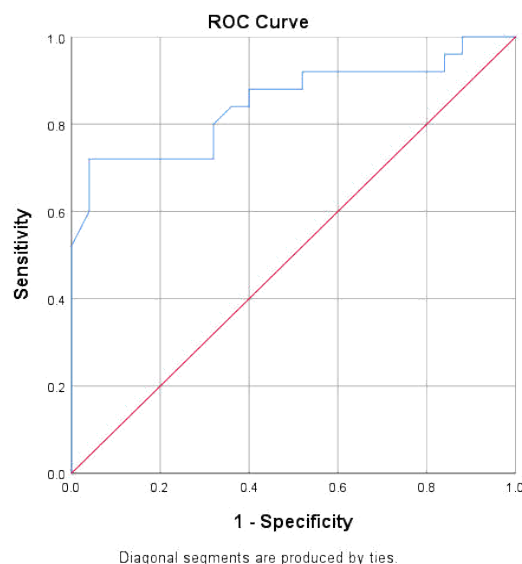
**TABLE 2:** Characteristics of Research Subjects.

Characteristics	Case (N=25)	Control (N=25)	P
NLR			
≥ 3.2	23	15	0.009
< 3.2	2	10	
Age (Year)			
< 40	8	4	0.5
40-59	11	14	
>= 60	6	7	
Male	13	17	0.19
HIV	5	4	0.5
DM	14	5	0.009
TCM positive	11	12	0.5

\*DM = Diabetes Mellitus.

Results also showed a significant association between a history of diabetes mellitus (DM) and TB re-treatment (p = 0.009). Meanwhile, the results of the TCM (Rapid Molecular Test) test did not influence the differences between the two groups of patients, with a p-value = 0.5. These results provide important insights in understanding the characteristics and associated factors of cases and controls in this study. Based on the receiver

operating characteristics (ROC) curve, the best NLR cut-off was 3.2 with a sensitivity of 92% and a specificity of 32% as shown in Figure 1. Patients with NLR ≥ 3.2 were seen in 23 case patients and 15 control patients and NLR <3.2 was obtained. in 2 case patients and 10 control cases. Based on chi-square analysis, it was found that the NLR cut-off 3.2 was significantly correlated with the incidence of TB retreatment with P=0.009.



**FIGURE 1:** ROC curve of NLR of retreated and non-retreated TB patients.

The results of multivariate analysis using a logistic regression model showed that HIV status, age, Rapid Molecular Test (TCM) and gender did not have a significant relationship with cases. The strongest factors related to cases were a history of diabetes mellitus (DM) and Neutrophil-Lymphocyte Ratio (NLR). Both have high and statistically significant ORs. History of DM has an adjusted OR of 2.3 with (p-value 0.024), while NLR has an adjusted OR of 2.7 with (p-value 0.008). The analysis is shown in Table 3.

**TABLE 3:** Multivariate analysis with adjusted odds ratio.

Variables	OR	p	aOR	p
HIV	1.3	0.7	1.4	0.157
Age	1.2	0.75	0.41	0.68
Gender	0.51	0.3	1.8	0.075
DM	5.1	0.008	2.3	0.024
NLR	7.6	0.007	2.7	0.008
TCM	0.85	0.78	0.43	0.653

## DISCUSSION

Retreatment for tuberculosis (TB) is treatment given to patients who have previously undergone TB treatment but experienced a relapse or did not respond to initial treatment. These cases include individuals who restarted treatment after experiencing a relapse or failure of previous treatment, as well as those who returned with a new episode of TB after completing previous treatment [7].

In patients with a history of first-line TB treatment, treatment should be based on individual susceptibility test results. Health facilities need to carry out drug sensitivity testing. Further treatment is adjusted according to the results of the sensitivity test. This treatment approach aims to effectively treat TB and prevent further recurrence [8].

The success rate of treatment in TB retreatment cases is an important indicator in evaluating the effectiveness of TB control programs. As determined by the World Health Organization (WHO), the treatment success rate for retreatment cases is calculated based on the proportion of patients who recovered or successfully completed treatment among those registered as retreatment cases. This metric provides insight into overall treatment outcomes in retreatment cases [9].

Various risk factors contribute to the emergence of TB retreatment cases. Factors such as age, gender, HIV status, and comorbidities such as schizophrenia have been identified as potential risk factors. In this study, it was found that the average age of patients was 53 years with an age range of 38 to 60 years. The majority of patients are men, as many as 30 out of 50 patients (60%). A study conducted by Agyare stated that the majority of TB retreatment patients were in the age range of 31-40 years and 41-50 years [10]. This shows that individuals in the productive age group are the ones most frequently infected with TB in the area.

However, the chances of treatment success were better for respondents aged less than or equal to 20 years (5.57) and 51-60 years (2.06). Based on this evidence, there could be an increased economic burden as most TB patients are in an age group that may be unable to work due to the disease [11].

With increasing age, TB retreatment rates are higher in men. This difference is most striking in the 40-59-year age group. A similar increase in the incidence of TB in aging men has been seen in other studies. Higher TB rates in elderly men compared to women are associated with higher prevalence rates of infection in men from early adulthood due to higher exposure opportunities [12].

Research by Peters., et al which examined communities with a high burden of TB and HIV, found that TB retreatment consistently contributed to more than a quarter of the TB disease burden over a 10-year period. The overall risk of TB retreatment in HIV-positive patients is twice as high as in HIV-negative patients [13]. In this case, there was no correlation between HIV patients and the incidence of TB retreatment, this could be due to the sample size tending to be small and not describing the HIV-infected population as a whole.

The role of white blood cells in the systemic inflammatory response to infection is critical. When an infection occurs, the number of neutrophils in the blood circulation increases while the number of lymphocytes decreases. Neutrophilia is considered a common indicator of infection, but absolute lymphocytopenia is rarely used as a marker in the management of infectious diseases. However, recent studies have shown that absolute lymphocytopenia has the potential to predict the presence of bacteremia and the severity of some infectious diseases [14].

The use of neutrophil to lymphocyte ratio as a combined parameter is increasingly popular in various clinical situations. Initially, this ratio was studied as a marker of infection and was found to have a strong correlation with disease severity and treatment outcomes [15]. In patients with advanced pulmonary tuberculosis, the ratio of neutrophils to lymphocytes is reported to be significantly higher compared with patients with milder TB severity. In addition, the ratio of neutrophils to lymphocytes can also be used as an indicator to potentially differentiate tuberculosis from community-acquired pneumonia. by bacteria (CAP) as well as sarcoidosis [16]. Recently, the ratio of neutrophils to lymphocytes was proposed as a simple marker that can differentiate severe bacterial infections from viral infections. Other studies have also examined the use of the neutrophil to lymphocyte ratio in certain clinical conditions, as well as its use as an independent predictor of survival in patients with various conditions, ranging from oncological to cardiovascular diseases [17].

In this study, it was found that the best NLR cut-off was 3.2 with a sensitivity of 92% and a specificity of 32%. Based on chi-square analysis, it was found that the NLR cut-off 3.2 was significantly correlated with the incidence of TB retreatment with  $P=0.009$ . Research by Yin, et al states that a high neutrophil-to-lymphocyte ratio (NLR) in peripheral blood is associated with an increased risk of TB retreatment, along with other risk factors such as age over 60 years, smoking history, and the presence of early cavitation on photographs chest x-ray. This study implies that NLR can be used as a marker to identify those at high risk of TB retreatment and help reduce the burden of disease through risk factor intervention. According to the article, the best cutoff value for NLR was 2.53, with a sensitivity of 70.6% and a specificity of 45.4% [18].

This study also showed a significant relationship between the history of diabetes mellitus (DM) and TB re-treatment ( $p = 0.009$ ). This is in line with research conducted in Taiwan which included 760 patients with TB retreatment showing that DM increased the incidence of re-treatment for TB (HR 1.96) [19].

The strength of this research is that this research is the first research to discuss the use of NLR as an indicator of TB retreatment. However, this research also has several limitations, namely the sample size tends to be small so it cannot describe the real population. This study also did not directly examine the population of TB patients with HIV.

## CONCLUSION

Based on this research, it can be concluded that the neutrophil-lymphocyte ratio (NLR) with a cut-off of 3.2 can be used as a useful indicator of TB retreatment. The results of the analysis showed that high NLR and the presence of diabetes mellitus were significantly associated with cases of TB retreatment. This NLR ratio can provide information about inflammation and immune responses in the body associated with TB retreatment. The use of NLR as an indicator can help in identifying risk factors and monitoring patients who require retreatment. However, further research is needed to validate and confirm these findings and identify deeper associations between NLR and TB retreatment.

## CONFLICT OF INTEREST

The author declares that there is no conflict of interest related to the publication of this research article.

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