Exploration of The Neutrophil-to-Lymphocyte Ratio as an Indicator of Inflammation with Hemoglobin and Creatinine Levels as an Illustration of Kidney Function in Tuberculosis Cases

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Abstract

Tuberculosis (TB) remains a major global health challenge, consistently ranking among the leading causes of morbidity and mortality worldwide. Its chronic progression, ease of airborne transmission, and potential to induce systemic inflammation and multi-organ involvement underscore the urgency of timely diagnosis and monitoring of disease progression and treatment response. In this context, the neutrophil-to-lymphocyte ratio (NLR) has emerged as a simple and cost-effective biomarker of systemic inflammation. This study aimed to investigate the association between NLR and two key clinical parameters, haemoglobin and creatinine levels, as indicators of anemia and renal function, respectively, in TB patients. A descriptive analytical observational study with a cross-sectional design was conducted at the Immunology Laboratory of the Faculty of Health Sciences, Maarif Hasyim Latif University, from August 2024 to January 2025. The study sample comprised 80 adult TB patients, and data were analyzed using Spearman's rank correlation via SPSS version 25. Results revealed a statistically significant weak negative correlation between NLR and hemoglobin levels ($p = 0.040$, $r = -0.230$), suggesting that heightened inflammation may be associated with lower hemoglobin levels, potentially due to inflammation-induced anemia. In contrast, the correlation between NLR and creatinine levels was not statistically significant ($p = 0.303$, $r = 0.117$), indicating a weak and clinically inconclusive relationship between systemic inflammation and renal function in patients without evident kidney disorders. These findings underscore the potential utility of NLR as an early marker of inflammation-related anemia in TB patients. However, NLR alone may be insufficient for assessing renal function, highlighting the need for complementary diagnostic parameters in future research. Overall, NLR offers promise as a clinical evaluation tool in TB management, particularly in resource-limited settings.

Keywords: ***Neutrophil-to-Lymphocyte Ratio (NLR), Tuberculosis, Inflammatory Biomarkers, Anemia, Kidney Function.***

INTRODUCTION

Tuberculosis (TB) remains a major cause of global morbidity and mortality, caused by the bacillus *Mycobacterium tuberculosis* (Mtb), which is highly transmissible via respiratory droplets. It is estimated that one in four individuals worldwide harbors an immunological response to Mtb, which may remain latent or progress to active disease(Gill et al., 2022a). According to the World Health Organization (WHO), TB ranks as the 13th leading cause of death globally and the second most deadly infectious disease after COVID-19. In 2021, Southeast Asia accounted for 45% of newly reported TB cases(Min et al., 2023); (WHO, 2025). Indonesia is among the countries with the highest TB burden, reporting approximately 845,000

cases of morbidity and 98,000 TB-related deaths, yet only 67% of identified cases received treatment (Devi et al., 2024).

An estimated one-quarter of the global population carries a latent Mycobacterium tuberculosis (Mtb) infection, which, under immunocompromised conditions, may transition from an asymptomatic dormant state to active, transmissible disease(Alsayed & Gunosewoyo, 2023). Extensive research over the past two decades on host–pathogen interactions, alongside post-mortem studies of lung lesions from TB patients, has demonstrated that clinical manifestations of TB pathology largely result from damage to the surrounding tissue network caused by uncontrolled inflammation triggered by the host immune response to Mtb(Hunter, 2020) (McCaffrey et al., 2022). To minimize tissue damage and excessive inflammation, regulating the host's immunological response is essential. Upon inhalation, Mtb enters the alveolar regions of the lungs, where it is primarily engulfed by *alveolar macrophages* (AM) via receptor-mediated *phagocytosis*(Strong et al., 2022). However, Mtb-containing phagosomes evade clearance and proliferate within host macrophages by inhibiting key innate effector processes, including *phagosome* maturation, *lysosomal* fusion, *autophagy*, and the generation of reactive oxygen and nitrogen species(Shamaei & Mirsaeidi, 2021). Through *interleukin-1* (IL-1)-mediated inflammasome signalling, AMs harbouring live Mtb migrate to the lung's interstitial space—the principal site of chronic infection(DesJardin et al., 2002).

Further inflammation is driven by *proinflammatory cytokines* secreted by infected alveolar macrophages (AMs), notably tumor necrosis factor (*TNF*) and *interleukin-6* (IL-6), along with chemokines that recruit additional immune cells to the developing *granuloma*—including *monocytes*, *neutrophils*, natural killer cells, and $\gamma\delta$ T cells(Zha et al., 2022). According to (Vega et al., 2021),

Tuberculosis is an infectious disease whose pathophysiology is predominantly marked by an inflammatory response, often resulting in hematological abnormalities. Disease progression and prognosis largely depend on the host's immune dynamics. White blood cell (WBC) populations are fundamental components of the systemic inflammatory response to infection. Standard differential panel (SDP) counts serve as common indicators of inflammation, and emerging research suggests that various *leukocyte* ratios may play critical roles in chronic inflammatory conditions. Patients with severe tuberculosis frequently exhibit haematological changes such as *anaemia*, elevated erythrocyte sedimentation rate (ESR), and *thrombocytosis*. Under immunological stress, circulating leukocytes typically respond by increasing neutrophil production while reducing lymphocyte counts—a physiological adaptation to infection(Aktas, 2021).

The peripheral blood neutrophil-to-lymphocyte ratio (NLR) serves as a representative marker of systemic inflammatory response and is associated with the prognosis of various acute and chronic diseases or clinical disorders. It reflects the relative proportions of circulating neutrophils and lymphocytes(Chen et al., 2024). Despite its clinical relevance, comprehensive research exploring the comorbidity of tuberculosis (TB) with other bacterial infections using NLR values and red blood cell changes remains limited (Fu et al., 2025). Patients with active TB often present with reduced hemoglobin levels, and anemia has been identified as the most prevalent comorbidity, affecting approximately 61.53% of TB patients. The decline in hemoglobin during Mycobacterium tuberculosis (Mtb) infection significantly impacts treatment outcomes and overall quality of life(Dasaradhan et al., 2022).

Tuberculosis (TB) infection is known to induce systemic inflammation, including chronic inflammatory anemia, which arises from shortened erythrocyte lifespan, impaired iron incorporation into erythrocytes, and reduced sensitivity to erythropoietin(Chhabra et al., 2021a). Anti-TB medications, while essential for disease control, may adversely affect kidney function. Despite these side effects, discontinuation is not advisable due to the risk of developing drug-resistant bacterial strains that are more difficult to treat. Serum creatinine serves as a standard biomarker for detecting renal impairment(Arif et al., 2023).

The novelty of this study lies in its integrative approach to evaluating the neutrophil-to-lymphocyte ratio (NLR) as a marker of systemic inflammation and its concurrent association with hemoglobin and creatinine levels. This dual-parameter analysis provides insights into potential renal dysfunction and anemia in TB patients. By simultaneously examining the relationships between NLR and two key clinical indicators—hemoglobin and creatinine—this study contributes to a growing body of literature exploring the diagnostic potential of NLR in tuberculosis. It offers new perspectives on utilizing NLR not only as a marker of inflammation but also as an early predictor of organ impairment, particularly in TB patients undergoing long-term treatment.

This study aims to investigate the neutrophil-to-lymphocyte ratio (NLR) as an indicator of systemic inflammation in tuberculosis (TB) cases and to examine its relationship with hemoglobin and creatinine levels as markers of renal function. Specifically, the research evaluates the potential utility of NLR as an inflammatory biomarker for clinical monitoring of TB patients and explores its correlation with other hematological and biochemical parameters that reflect physiological and renal status. The goal is to provide a more comprehensive understanding of the systemic condition of individuals affected by TB.

METHODS

This study employed a descriptive analytical research design with a cross-sectional approach, conducted from August 2024 to January 2025 at the Immunology Laboratory, Faculty of Health Sciences, Maarif Hasyim Latif University. The study population comprised 100 patients diagnosed with tuberculosis (TB). Purposive sampling was used, with inclusion criteria of adult patients aged 19–60 years, without comorbidities, who had been undergoing anti-TB treatment for more than one year but less than three years. The selection of this 1–3 year treatment window reflects the study's emphasis on long-term anti-TB therapy, a period in which chronic inflammatory responses, and their clinical manifestations, such as anemia and potential renal dysfunction, are more likely to emerge. Exclusion criteria included pulmonary TB patients who had received treatment for less than one month, those with comorbidities, and pediatric patients. After applying these criteria, a total of 80 eligible participants were included in the study. The research aimed to evaluate the correlation between neutrophil-to-lymphocyte ratio (NLR) values and indicators of inflammation-related anemia (hemoglobin levels), as well as renal function (creatinine levels) in TB patients.

A 5 mL blood sample was collected from each patient via the antecubital vein by an experienced medical laboratory technician. Two millilitres were transferred into an EDTA-coated tube, homogenized, and used for complete blood count (CBC) analysis. The remaining 3 mL was placed into a serum separator tube, allowed to clot for 30 minutes, and centrifuged at 2200 rpm for 10 minutes. The resulting serum was used to assess creatinine levels.

NLR and *hemoglobin* values were determined from the CBC, which included lymphocyte and neutrophil counts obtained using an automated CBC analyzer. The neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the total number of segmented neutrophils by the total number of lymphocytes (NLR = segmented neutrophils / lymphocytes). Serum creatinine levels were measured using an automatic biochemical analyzer, with a normal reference range of 0.5–0.9 mg/dL, to evaluate renal function.

All clinical laboratory testing and result interpretation were conducted in accordance with the manufacturer's instructions and standard operating procedures. Spearman's Rho correlation test was employed due to the non-normal distribution of the data, which renders parametric methods such as Pearson's correlation unsuitable for this analysis. Spearman's Rho is appropriate for evaluating the strength and direction of relationships between numerical variables that are either not normally distributed or measured on an ordinal scale. The level of

statistical significance (α) applied in this study was 0.05, indicating that a relationship between variables was considered statistically significant if the p-value was less than 0.05.

The collected data were processed and presented through descriptive narratives, tables, and graphical visualizations. Numerical variables—including NLR values, hemoglobin levels, and creatinine levels—were summarized using means and standard deviations, while demographic data were reported as percentages. The relationships among NLR, haemoglobin, and creatinine levels were analysed using Spearman's Rho, with all statistical procedures performed in SPSS version 25.0.

RESULTS

Analysis of clinical data from 80 patients with *tuberculosis* (TB) revealed a mean *neutrophil-to-lymphocyte ratio* (*NLR*) of 3.82. The mean *hemoglobin* level was 12.8 g/dL, while the mean serum *creatinine* level was 1.2 mg/dL. The association between *NLR* and *hemoglobin* levels, assessed using the Spearman's rank correlation test, showed a statistically significant negative correlation (p = 0.040; r = –0.230). In contrast, the correlation between *NLR* and serum *creatinine* was not statistically significant (p = 0.303; r = 0.117).

Tabel 1. The association between *NLR* and *hemoglobin* levels

Variable	Spearman's r	p-value
Hemoglobin	-0.230	0.040
Creatinine	0.117	0.303

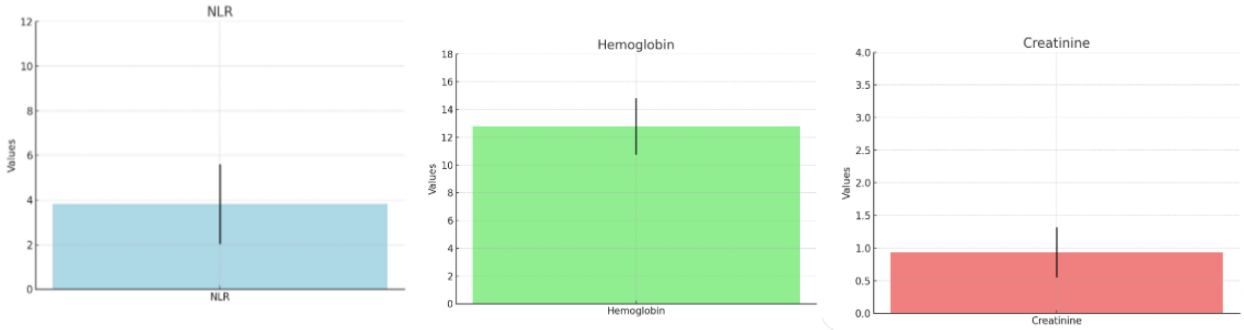

Figure 1. Descriptive statistics of research parameters

The diagram above shows the average values of NLR, *hemoglobin* (Hb), and *creatinine*, with error bars represented by black lines indicating the standard deviation. This provides a visual representation of the data's distribution and variability.

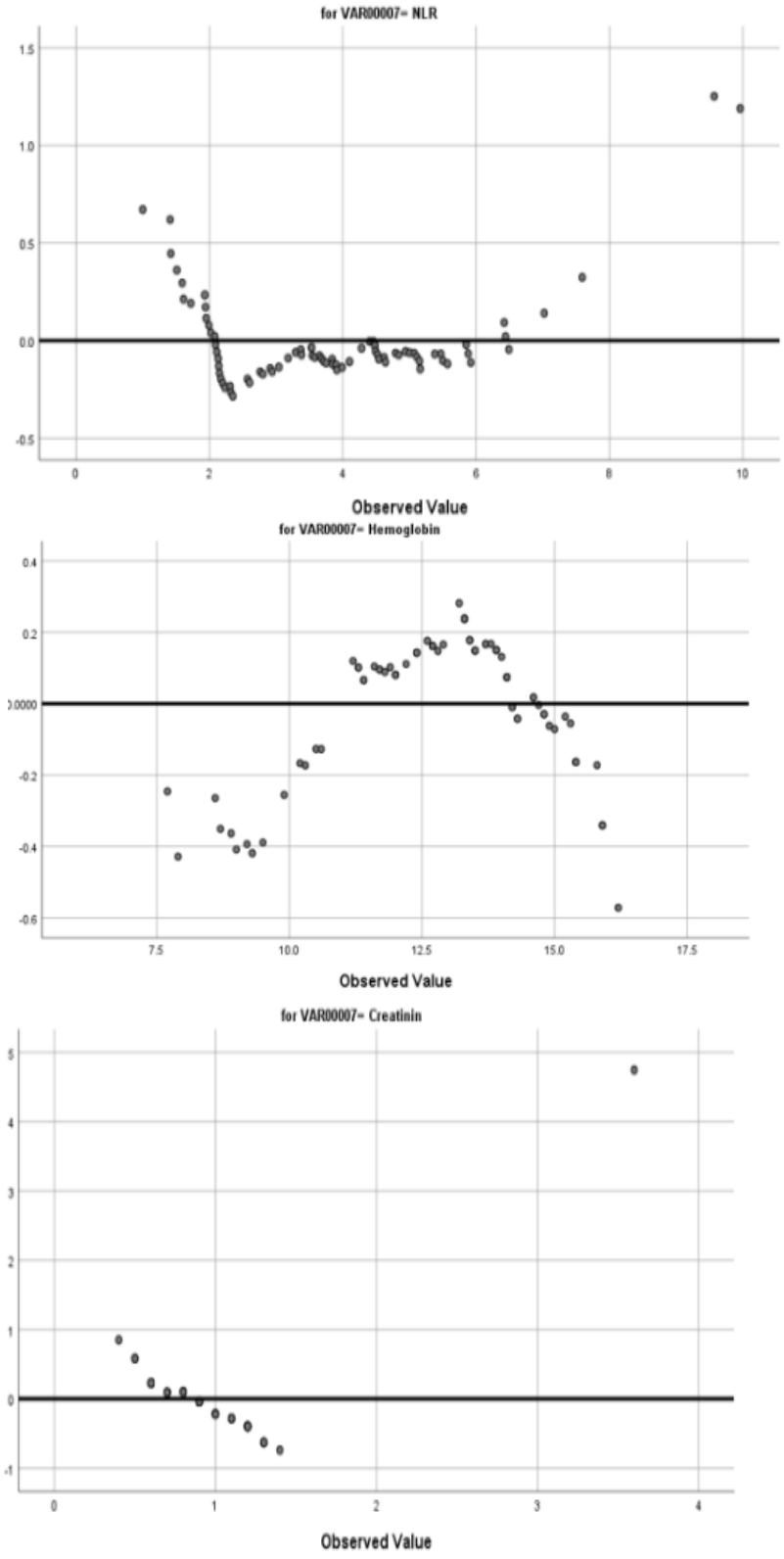

Figure 2. Distribution of NLR, Hemoglobin and Creatinine data

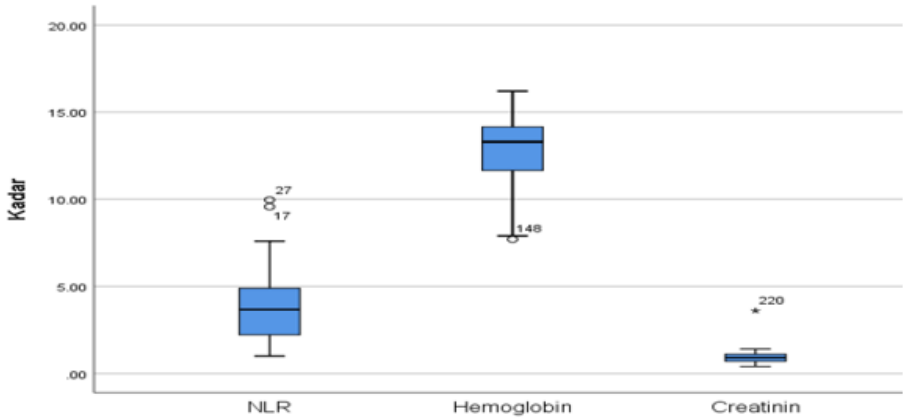

Figure 3. Box plot of research data

The NLR and hemoglobin parameters demonstrated a statistically significant relationship, with a weak negative correlation coefficient, suggesting that an increase in NLR may be associated with a tendency for hemoglobin levels to decrease, and vice versa (Temizhan et al., 2022). In contrast, the analysis of NLR and creatinine showed no statistically significant relationship; however, a weak positive correlation was observed based on the correlation coefficient (r = 0.117), indicating a possible trend in which higher NLR values may be accompanied by increased creatinine levels.

DISCUSSION

Effect of Neutrophil to Lymphocyte Ratio (NLR) and Hemoglobin Levels

This study reveals a significant relationship between the neutrophil-to-lymphocyte ratio (NLR) and hemoglobin levels in tuberculosis (TB) patients, with a p-value of 0.040 and a weak negative correlation coefficient (r = –0.230). These results suggest that an elevated NLR tends to be associated with reduced hemoglobin levels. This relationship can be attributed to the systemic inflammatory response in TB, where heightened neutrophil activity and diminished lymphocyte counts reflect chronic immune activation. Such inflammation affects iron metabolism and erythropoiesis, ultimately leading to decreased hemoglobin concentrations.

From a pathophysiological standpoint, chronic inflammation due to Mycobacterium tuberculosis infection stimulates the release of proinflammatory cytokines, including interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). These cytokines promote the production of hepcidin, a key regulatory hormone of iron metabolism. Elevated hepcidin levels result in decreased intestinal iron absorption and increased iron sequestration within macrophages, impairing iron availability for erythropoiesis and contributing to the development of inflammatory anemia. These findings align with previous studies (Chhabra et

al., 2021; Ashenafi et al., 2023; Alshuweishi et al., 2023; Taniguchi et al., 2024; Akase et al., 2020), which similarly reported anemia in TB as a consequence of sustained inflammation that disrupts red blood cell production.

Moreover, anemia in TB patients is frequently normocytic and normochromic due to inflammation but can be aggravated by factors such as malnutrition, micronutrient deficiencies, or adverse effects of prolonged treatment. These conditions often contribute to significant declines in hemoglobin levels, a clinical concern that is often overlooked in routine TB management. In this context, NLR presents as a simple yet informative hematological marker that may provide early insight into a patient's inflammatory status and the potential for developing anemia. This study reinforces the utility of NLR as a preliminary screening tool for identifying TB patients at risk for inflammation-related anemia, particularly in resource-limited healthcare settings.

A substantial decrease in hemoglobin levels can adversely affect quality of life and treatment outcomes, manifesting in fatigue, immunosuppression, and delayed recovery. Therefore, the observed association between elevated NLR and lower hemoglobin supports the inclusion of NLR in routine laboratory evaluations for TB patients. These findings also justify targeted nutritional interventions or hematinic supplementation in individuals presenting with low hemoglobin and high NLR values.

Finally, the study encourages future research to explore the mechanistic link between inflammation and anemia in TB through the assessment of additional biomarkers such as ferritin, transferrin saturation, and serum hepcidin levels. Combining NLR with other diagnostic indicators may enhance the accuracy of inflammatory anemia detection and improve clinical management strategies for TB. This work contributes meaningfully to the development of cost-effective, accessible hematological screening tools, especially within primary care settings in regions with high TB prevalence.

Effect of Neutrophil to Lymphocyte Ratio (NLR) and Creatinine Levels

This study found no statistically significant relationship between neutrophil-to-lymphocyte ratio (NLR) values and creatinine levels in patients with tuberculosis (TB), yielding a p-value of 0.303 and a weak positive correlation coefficient ($r = 0.117$). Although the direction of correlation suggests that higher NLR values may be associated with increased creatinine levels, the relationship is too weak to be considered consistent or clinically meaningful. These results indicate that variations in systemic inflammatory response, as

represented by NLR, do not necessarily reflect changes in kidney function—particularly among TB patients without evident renal impairment.

Creatinine, a waste product of muscle metabolism excreted by the kidneys, is commonly used to assess glomerular filtration rate. However, creatinine levels may remain within the normal range during early stages of kidney damage, especially in individuals with differing muscle mass. Conversely, NLR reflects systemic inflammation but does not directly measure renal excretory capacity. This physiological distinction may explain the lack of correlation. These findings are consistent with studies by Devi (2024) and Gao et al. (2024), which note that a relationship between NLR and creatinine becomes apparent primarily in patients with chronic kidney disease or overt renal decompensation.

Furthermore, participants in this study did not exhibit significant renal dysfunction, with most presenting creatinine levels within the normal range (mean: 1.2 mg/dL), suggesting preserved kidney function despite TB-related inflammatory states. In such populations, NLR may have limited utility as a predictor of renal impairment. However, in cohorts at higher risk of kidney failure or severe infection (e.g., sepsis), NLR may prove valuable as a prognostic indicator of multisystem involvement.

It is important to note that creatinine-based assessment has limitations, as serum levels are affected by factors such as age, gender, hydration status, and muscle mass. Therefore, future studies should consider additional indicators of renal function, such as estimated glomerular filtration rate (eGFR), Cystatin C, or proteinuria, to better detect subclinical kidney damage not captured by creatinine alone.

In summary, while NLR has demonstrated its value as an inflammation marker associated with haemoglobin levels, its role in predicting renal function in TB patients appears limited. These findings underscore the importance of adopting a multimodal approach to evaluating organ function in chronic disease contexts. Going forward, combining NLR with more specific and sensitive renal biomarkers may enhance diagnostic accuracy and inform clinical decision-making in TB care.

CONCLUSION

This study identified a statistically significant but weak negative correlation between the neutrophil-to-lymphocyte ratio (NLR) and hemoglobin levels in TB patients, suggesting a potential role of systemic inflammation in inflammation-induced anemia. No significant association was observed between NLR and serum creatinine levels, indicating limited utility of NLR in assessing renal function.

NLR may serve as a low-cost biomarker for detecting anemia in TB patients,

particularly in resource-constrained settings. However, for evaluating renal function, more sensitive indicators—such as the estimated glomerular filtration rate (eGFR)—should be prioritized. Policy-level efforts should consider integrating NLR into TB clinical guidelines, improving laboratory infrastructure at the primary care level, and strengthening the training of health personnel. Further large-scale studies are essential to validate these findings and to explore the use of comprehensive inflammatory markers in the clinical management of TB.

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