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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

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ABSTRACT

Tuberculosis (TB) in children presents a major diagnostic challenge due to the paucibacillary nature of the infection and difficulties in sputum collection. As an alternative, blood cell ratios such as Neutrophil-to-Lymphocyte Ratio (NLR), Monocyte-to-Lymphocyte Ratio (MLR), and Neutrophil-Monocyte-to-Lymphocyte Ratio (NMLR) have been proposed as hematological biomarkers that can support the diagnosis of TB in children. This study aimed to evaluate the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of NLR, MLR, and NMLR in establishing the diagnosis of TB in children at RS Adam Malik. A retrospective observational study was conducted using data from the TB DOTS medical records of children aged 0–18 years during 2024. Hematologic parameters (neutrophils, monocytes, lymphocytes) and the ratios NLR, MLR, and NMLR were analyzed and compared with clinical and bacteriological TB diagnosis (TCM/BTA). Of the 219 children who met the inclusion criteria, NLR showed a sensitivity of 82.3%, specificity of 78.7%, PPV of 84.9%, NPV of 75.3%, and accuracy of 80.8%. MLR showed a sensitivity of 80.8%, specificity of 75.3%, PPV of 82.7%, NPV of 72.8%, and accuracy of 78.5%. NMLR showed a sensitivity of 76.9%, specificity of 66.3%, PPV of 76.9%, NPV of 66.3%, and accuracy of 72.6%. These ratios were significantly associated with TB diagnosis ($p < 0.05$). The most common clinical symptoms found in positive cases included persistent cough, prolonged fever, weight loss, and night sweats. NLR, MLR, and NMLR demonstrate good diagnostic value in supporting the diagnosis of TB in children. NLR showed the most optimal results, followed by MLR and NMLR. These hematological ratios can be used as quick, inexpensive, and easily accessible diagnostic aids, especially in facilities with limited bacteriological testing capabilities.

Keywords: hematologic biomarker; MLR; NLR; NMLR; pediatric tuberculosis; TB diagnosis

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INTRODUCTION

Tuberculosis (TB) remains one of the most pressing global health concerns, with millions of cases and deaths reported each year. The World Health Organization (WHO) estimated that in 2021, there were approximately 10.6 million cases of TB worldwide, including 1.2 million cases among children. Despite global efforts to control the disease, TB continues to be a leading cause of morbidity and mortality, particularly in individuals who do not receive adequate treatment. In Indonesia, the highest number of TB cases in 2021 occurred in the age group of 45–54 years (18%), followed by the 35–44 years (17%), 25–34 years (17%), and 15–24 years (17%) age groups. Additionally, a 33% coverage rate was reported for contact investigation, while preventive therapy for TB in children under five years old was only 1.9%. These statistics highlight significant gaps in TB prevention, diagnosis, and treatment, especially among vulnerable populations such as children (Kementerian Kesehatan RI, 2021).

TB is an infectious disease caused by Mycobacterium tuberculosis, which spreads primarily through the air when an infected person exhales, coughs, or sneezes. Recent research indicates that breathing is a more significant route of transmission than coughing, with exhalation releasing up to 90% of the TB bacteria compared to just 7% through coughing. While M. tuberculosis typically affects the lungs (pulmonary TB), it can also infect other areas of the body, resulting in extrapulmonary TB (Moore et al., 2024). In children, TB often manifests differently from adults, presenting unique challenges in clinical diagnosis and treatment. Children under the age of five are particularly vulnerable to TB and are more likely to develop the disease after exposure than older children. The clinical symptoms in children are often nonspecific and resemble those of common childhood illnesses, which complicates early detection (Pinto et al., 2017).

Diagnosis of pediatric TB can be challenging due to the difficulty children face in producing sputum samples for examination. Consequently, more invasive diagnostic methods such as sputum induction or gastric aspiration are often required. Bacteriological tests, including acid-fast bacillus (AFB) smear, GeneXpert MTB/RIF (TCM), and bacterial culture, along with immunological tests such as interferon-gamma release assays (IGRA) and tuberculin skin tests (TST), are commonly used to confirm the diagnosis (Lewinsohn et al., 2017). However, these diagnostic tests often have limitations in terms of speed, cost, and accuracy, underscoring the need for new, more effective diagnostic methods. Additionally, the clinical diagnosis of TB in children is frequently supported by laboratory tests, although these are not yet universally accepted as diagnostic criteria (Diel & Nienhaus, 2023).

In addition to clinical and bacteriological examinations, hematological markers such as erythrocyte sedimentation rate (ESR), monocyte-to-lymphocyte ratio (MLR), and neutrophil-to-lymphocyte ratio (NLR) are being explored as potential biomarkers for TB diagnosis. ESR is a widely used non-specific marker for inflammation and infection, including in TB diagnosis, due to its simplicity and low cost. Monocyte and lymphocyte ratios have been found to correlate with TB infection, with higher MLR values often associated with the presence of active TB, while lower values are linked to remission or non-advanced TB cases (Pai et al., 2016). Despite promising findings, research on the role of these biomarkers, particularly in pediatric populations, is still limited, and their utility in diagnosing pediatric TB remains uncertain (Jenkins et al., 2017). This study aims to evaluate the role of hematological markers, specifically the monocyte-to-lymphocyte ratio (MLR), neutrophil-to-lymphocyte ratio (NLR), and neutrophil-monocyte-lymphocyte ratio (NMLR), in the diagnostic process of pediatric TB at Adam Malik General Hospital. The goal is to determine whether these ratios can provide additional diagnostic value to traditional methods, potentially leading to faster and more accurate TB diagnoses in children.

METHOD

This descriptive analytical study uses a cross-sectional design to evaluate the sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of Neutrophil-to-Lymphocyte Ratio (NLR), Monocyte-to-Lymphocyte Ratio (MLR), and Neutrophil-Monocyte-to-Lymphocyte Ratio (NMLR) in diagnosing tuberculosis (TB) in children. The study will take place at the Pediatric Clinic and Emergency Department (ED) of Haji Adam Malik General Hospital, Medan, from January to December 2024. Participants include children aged 0-18 years diagnosed with TB, selected via purposive sampling based on inclusion and exclusion criteria. The sample size is calculated to be 219 based on diagnostic test formulas. Inclusion criteria include children registered in the TB DOTS program with relevant laboratory tests. Exclusion criteria involve children with conditions affecting lab parameters. Data will be collected from medical records, and statistical analysis will be performed using SPSS version 24.0 to assess diagnostic performance.

RESULT

Table 1, the majority of participants were male (50.7%), with 111 male and 108 female children. The average age of the respondents was 9.58 years (SD = 6.13), indicating a wide age range among the participants. Regarding nutritional status, the majority of children were classified as

malnourished (58%), followed by those with undernutrition (26.5%). Only 19.2% of children had a normal nutritional status, while 9.6% were overweight and 3.2% were obese.

Table 1.
Characteristic of Participants (n=219)

Characteristic	f (%)
Gender	
Male	111 (50.7%)
Female	108 (49.3%)
Age (Months and Years)	
Mean (SD)	9.58 years (6.13 years)
Median (Min – Max)	11 years (0,5 – 18 years)
Nutritional Status	
Poor	91 (58%)
Insufficient	58 (26.5%)
Good	41 (19.2%)
Excessive	21 (9.6%)
Obesity	7 (3.2%)
Clinical Diagnosis	
Positive	150 (68.5%)
Negative	69 (31.5%)
Bacteriological Diagnosis	
Positive	130 (59.4%)
Negative	89 (40.6%)
NLR (Neutrophil-Lymphocyte Ratio)	
Positive	126 (57.5%)
Negative	93 (42.5%)
MLR (Monocyte-Lymphocyte Ratio)	
Positive	127 (58%)
Negative	92 (42%)
NMLR (Neutrophil-Monocyte-Lymphocyte Ratio)	
Positive	130 (59.4%)
Negative	89 (40.6%)

In terms of clinical diagnosis, 150 children (68.5%) were diagnosed with tuberculosis (TB) clinically, while 69 children (31.5%) had a negative clinical diagnosis. Bacteriological diagnosis revealed 130 children (59.4%) were confirmed positive for TB, while 89 children (40.6%) tested negative. For the Neutrophil-Lymphocyte Ratio (NLR), 126 children (57.5%) had positive results, and 93 children (42.5%) were negative. Similarly, for the Monocyte-Lymphocyte Ratio (MLR), 127 children (58%) were positive, and 92 children (42%) were negative. The Neutrophil-Monocyte-Lymphocyte Ratio (NMLR) showed 130 children (59.4%) tested positive, and 89 children (40.6%) tested negative.

Table 2.
Diagnostic Performance of NLR, MLR, and NMLR in Comparison to Bacteriological

Examination		Bacteriological Examination (TCM/BTA)		Total (n)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
		Positive	Negative						
NLR	Positif	107	19	126	82,3	78,7	84,9	75,3	80,8
	Negatif	23	70	93					
	Total	130	89	219					
MLR	Positif	105	22	127	80,8	75,3	82,7	72,8	78,5
	Negatif	25	67	92					
	Total	130	89	219					
NMLR	Positif	100	30	130	76,9	66,3	76,9	66,3	72,6
	Negatif	30	59	89					
	Total	130	89	219					

Table 2 shows the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy for each ratio. The NLR examination demonstrated a sensitivity of 82.3%, specificity of 78.7%, PPV of 84.9%, NPV of 75.3%, and accuracy of 80.8%. MLR had a sensitivity of 80.8%, specificity of 75.3%, PPV of 82.7%, NPV of 72.8%, and an accuracy of 78.5%. Finally, NMLR showed a sensitivity of 76.9%, specificity of 66.3%, PPV of 76.9%, NPV of 66.3%, and

accuracy of 72.6%. These findings indicate that all three ratios (NLR, MLR, and NMLR) demonstrate promising diagnostic potential in detecting TB in children, with NLR showing the highest overall performance.

DISCUSSION

This study involved 219 children admitted to RS Adam Malik and registered in the TB DOTS program, consisting of 111 boys (50.7%) and 108 girls (49.3%). The mean age of the participants was 9.58 years (SD = 6.13), indicating considerable age variation among the subjects. These findings align with previous studies showing that tuberculosis (TB) is more prevalent among boys than girls. A study conducted in Saskatchewan, Canada, found that 60% of pediatric TB cases occurred in boys (Ndubuka et al., 2024), and a study in Poland also revealed higher TB incidence in boys (22.2 per 100,000) compared to girls (8.4 per 100,000) in 2017 (Koseła, 2019). Regarding nutritional status, the majority of children in this study had poor nutritional status (58%), followed by those with malnutrition (26.5%). This is consistent with findings from other research that malnutrition is a significant risk factor for TB incidence. For example, a study in India on the Saharia population found that TB prevalence was especially high among individuals with poor nutritional status, compounded by other socio-economic risk factors such as alcohol and tobacco use (Bhat et al., 2019). Malnutrition weakens the immune system, making children more vulnerable to TB infection.

In terms of diagnosis, 150 children (68.5%) were clinically diagnosed with TB, while 130 children (59.4%) were confirmed positive by bacteriological tests. This discrepancy between clinical and bacteriological diagnoses may be due to the limited sensitivity of bacteriological tests in detecting TB in children. In a study conducted in Sumy, Ukraine, it was noted that pediatric clinical diagnoses are often made more rapidly than bacteriological confirmations, highlighting the challenges of early detection in pediatric TB cases (Duzhyi et al., 2023). On the other hand, a study in Ethiopia indicated that while the incidence of TB had decreased, cases in children still constituted a significant proportion, underscoring the need for improved bacteriological diagnostics in pediatric TB (Bodena et al., 2019). When analyzing the tabulation of bacteriological and clinical examination results, 127 children showed true-positive results (positive in both clinical and bacteriological tests), while 3 children had false-positive results (positive in the bacteriological test but negative clinically). Conversely, 23 children had false-negative results (negative in the bacteriological test but positive clinically), and 66 children had true-negative results (negative in both tests). These findings suggest that while some children had negative bacteriological tests, they presented clinical symptoms indicative of TB, likely due to effective immune responses preventing disease progression despite exposure to TB bacteria.

Regarding hematological markers, the Neutrophil-Lymphocyte Ratio (NLR) was identified as a significant inflammatory marker. The increased NLR reflects a decrease in lymphocyte count and an increase in neutrophils, both of which are associated with delayed apoptosis and poor response to treatment in inflammatory conditions (Yunfeng et al., 2025). Neutrophils are the first cells to infiltrate the lungs after TB infection and are crucial in the formation of granulomas and lung tissue damage during the infection. On the other hand, T lymphocytes play a vital role in fighting TB, and their levels negatively correlate with TB severity (Sheng et al., 2025). NLR has been shown to effectively differentiate between TB patients and healthy children, with a cutoff value of 1.5 yielding a sensitivity of 61% and specificity of 79% (Sheng et al., 2025).

The Monocyte-Lymphocyte Ratio (MLR) demonstrated significant diagnostic potential in this study, with 105 true positives and 22 false positives. Statistical analysis showed a significant p-value of 0.001, indicating a strong relationship between MLR values and TB diagnosis. MLR, reflecting the relative frequency of monocytes as target cells for Mycobacterium tuberculosis (MTB) growth, and lymphocytes as effector cells in MTB clearance, is a critical marker in the immune response to TB infection (Adane et al., 2022). In line with this, monocyte changes were found to be a key factor in TB pathogenesis, highlighting MLR's utility in distinguishing active TB

cases from healthy individuals (La Manna et al., 2017). Similarly, the Neutrophil-Monocyte-Lymphocyte Ratio (NMLR) also showed significant results with 100 true positives and 30 false positives, with a p-value of 0.001 indicating a significant association with TB diagnosis. These findings corroborate a study by Jeon et al. (2019), which observed that an increase in neutrophils and a decrease in lymphocytes are common in TB patients, distinguishing them from those with non-TB lung diseases. NMLR has emerged as a promising marker for discriminating TB from other infectious diseases, offering an additional tool for clinicians when diagnosing TB in pediatric patients.

Overall, in this study, NLR demonstrated the highest positive predictive value (PPV) of 84.9% and negative predictive value (NPV) of 75.3%, followed by MLR with PPV of 82.7% and NPV of 72.8%, and NMLR with PPV of 76.9% and NPV of 66.3%. High PPV values indicate that a positive result in these ratios is highly indicative of actual TB infection, emphasizing their confirmatory role in TB diagnosis. On the other hand, the lower NPV values, especially for NMLR, suggest that negative results may require further clinical, radiological, or molecular follow-up to exclude TB diagnosis. These results align with studies by Kissling et al. (2023) and Aygün et al. (2024), where NLR and MLR showed similar diagnostic values in identifying pediatric TB cases across different geographical settings. However, some studies, such as that by Bozdemir (2021), suggest that while NLR and MLR are elevated in TB and pneumonia patients, they may not be sensitive or specific enough to differentiate between these conditions reliably in routine clinical practice. This highlights the need for further research to refine the use of hematological ratios in pediatric TB diagnosis. This study has several key limitations. First, the cross-sectional design limits the ability to infer causal relationships between the hematological ratios and TB diagnosis. Secondly, reliance on secondary data from medical records means that the researchers did not have control over the completeness or accuracy of the collected clinical information. Missing data, especially regarding symptoms and contact history, may have impacted the classification of TB diagnoses. Lastly, the study's results are based on data from a single hospital, which may limit the generalizability of the findings to other settings or populations.

CONCLUSION

Based on the findings of this study, it can be concluded that the Neutrophil-to-Lymphocyte Ratio (NLR), Monocyte-to-Lymphocyte Ratio (MLR), and Neutrophil-Monocyte-to-Lymphocyte Ratio (NMLR) show significant potential as adjunctive diagnostic tools in the detection of tuberculosis (TB) in children. These hematological ratios were found to be reliable indicators, with their diagnostic accuracy contributing to the early identification of pediatric TB cases. This research demonstrates that incorporating these blood ratios into routine clinical practice may enhance diagnostic capabilities, especially in settings where traditional diagnostic methods are challenging or unavailable. By exploring these biomarkers, this study provides valuable insights into the potential for non-invasive diagnostic methods in pediatric TB, contributing to both scientific understanding and clinical application in the fight against tuberculosis in children.

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