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The Potential of Leukocyte Ratio to Differ Pediatric Tuberculosis from Bronchopneumonia

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ABSTRACT

Introduction: Differentiating between TB and pneumonia is crucial to avoid treatment delays. Delayed diagnosis can result in reduced patient survival rates, increased treatment expenses and prolonged treatment durations. Several leukocyte ratios such as Neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), platelet-lymphocyte ratio (PLR), monocyte-lymphocyte ratio (MLR) will be compared to confirm whether it can be used to distinguished pulmonary tuberculosis from community-acquired pneumonia.

Material and Methods: Retrospective study of 100 children aged 1-12 years who were treated at RSUD Dr. Haryoto Lumajang, period 1 January 2019 – 1 January 2023. Data on age, gender, diagnosis and laboratory results were obtained from medical records.

Results: Of the 100 children included 50 had TB disease and 50 had pneumonia. The mean of neutrophil counts was significantly higher in the control group compared to the case group. NLR and MLR ratio were statistically significant. NLR were both statistically significant in both <5 years old and >5 years old, but MLR were not significantly different in both age groups. A significant but weak positive correlation was found between tuberculosis (case) group, pneumonia (control) group, and age of children (r=0.132; p=0.048). Younger children (less than 5 years old) had 0.571-fold odds for tuberculosis infection compared to the older children.

Conclusion: NLR hold promise as readily accessible diagnostic biomarkers for distinguishing children with TB disease from those with pneumonia.

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INTRODUCTION

Mycobacterium tuberculosis (TB) is a contagious bacterial infection primarily affecting the lungs. Individuals infected with TB bacteria may not exhibit any symptoms, and those with active TB need an extended treatment regimen [1]. Globally, 7.5 million people were newly diagnosed with TB in 2022, 12% were children (aged 0-14 years). Indonesia is accounted for 10% of the world's TB cases, the second highest in the world [2]. The manifestations of TB encompass a diverse array of symptoms, the most common in children are persisting and not resolving cough, prolonged fever, anorexia, failure to thrive, unusual fatigue [1].

Timely identification of TB is crucial for effective treatment, improved survival outcomes, and preventing the spread of Mycobacterium tuberculosis. However, existing diagnostic methods often prove inefficient in promptly diagnosing pulmonary conditions. Traditional approaches such as sputum smear tests and various diagnostic tools, including blood tests, have been employed for early detection. The drawback lies in the time-consuming nature of both blood and sputum tests, with analyses often extending over prolonged periods. Furthermore, delays within healthcare systems and obstacles in obtaining timely laboratory results are common occurrences [3]. Previous research indicates that the accurate diagnosis of TB may take up to 45 days, with a reported median delay of 9.9 weeks for TB detection [4].

Some symptoms of TB overlap with those of other lung-related illnesses, such as pneumonia—a lung infection caused by bacteria, viruses, or fungi.

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Pneumonia shares similar symptoms with pulmonary TB (PTB), and experiments conducted by infectious disease experts reveal a tendency to interchangeably misdiagnose TB and pneumonia [5]. Pinto et al. have verified the prevalence of misdiagnosis. Therefore, distinguishing between TB and non-tuberculous pneumonia becomes imperative to avoid treatment delays, subsequently leading to diminished patient survival rates, escalated treatment costs, and prolonged treatment durations [5].

In a 2013 investigation, Yoon et al. demonstrated that the Neutrophil-Lymphocyte Count Ratio serves as a valuable diagnostic test for precisely identifying pneumonia or tuberculosis in adults (age >18years old) [6]. The treatment for one of these conditions can influence the diagnosis of the other. For instance, managing patients with pneumonia may impede the prompt diagnosis of tuberculosis in regions where tuberculosis is prevalent [7]. Liu et al. employed MRI images and deep learning techniques to differentially diagnose pneumonia and tuberculosis [8]. A framework for distinguishing between pneumonia and tuberculosis was proposed using neural networks and chest X-ray images [9]. Another study detailed the clinical and microbiological features, radiological patterns, and treatment outcomes of individuals aged one to 17 with pneumonia attributed to tuberculosis [10]. Wei et al. conducted an investigation to definitively distinguish acute tuberculosis pneumonia (TP) from community-acquired pneumonia [11].

The main aim of this study is to propose a method for differential diagnosis of TB and pneumonia. Several leukocyte ratios such as Neutrophil-lymphocyte ratio (NLR), lymphocyte-monocyte ratio (LMR), platelet-lymphocyte ratio (PLR), monocyte-lymphocyte ratio (MLR) will be compared to confirm whether it can be used to distinguished pulmonary tuberculosis from community-acquired pneumonia.

MATERIAL AND METHODS

This research is a retrospective study of 100 children aged 1-12 years who were treated at RSUD Dr. Haryoto Lumajang, period 1 January 2019 – 1 January 2023. Data on age, gender, diagnosis and laboratory results were obtained from medical records. A complete blood test is performed at the first visit. Exclusion criteria for patients who are known to have multiple organ sources of infection include UTI, CNS infections, Typhoid, DHF, as well as patients with blood disorders (HIV, leukemia, thalassemia, ITP) and chronic diseases.

Patients were divided into two groups: case group consisting of 50 children with pulmonary tuberculosis and control group consisting of 50 children with bronchopneumonia. Platelet count, neutrophil count, lymphocyte count, and monocyte count, as well as their percentages were measured from peripheral venous blood samples collected in EDTA tubes. NLR is calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. LMR is calculated by dividing the number of lymphocytes by monocytes, PLR is calculated by dividing the number of platelets by lymphocytes and MLR by dividing the number of monocytes by lymphocytes.

Data are presented as mean and standard deviation, or frequencies and percentages as appropriate. Data are not normally distributed; therefore, the Mann-Whitney U test was used to analyze the data. Significant association was defined as $p < 0.05$. The contingency coefficient was used to measure the association between nominal variables. In addition, logistic regression was used to measure the odds ratios and their 85% confidence intervals (CIs) for risk estimation. Significant association were defined as $p<0.05$.

RESULTS

A total of 100 children were included in our study, 50 children with pulmonary tuberculosis in case group and 50 children with pneumonia in control group. The laboratory parameters in the case and control groups were shown in **Table 1.** The mean of neutrophil counts was significantly higher in the control group compared to the case group. The mean of other laboratory parameters in both groups was not statistically significant.

NLR and MLR ratio were statistically significant. NLR and MLR were further evaluated between children aged less than 5 years old and more than 5 years old in case and control group (**Table 2**). NLR were both statistically significant in both <5 years old and >5 years old, but MLR were not significantly different in both age groups. A significant but weak positive correlation was found between tuberculosis (case) group, bronchopneumonia (control) group, and age of children ($r=0.132$; $p=0.048$). Younger children (less than 5 years old) had 0.571-fold odds for tuberculosis infection compared to the older children (**Table 3**).

DISCUSSION

Diagnostic potential of ratios derived from Complete Blood Count (CBC), including NLR, LMR, PLR, and MLR, was suggested from decades ago for TB, but this concept has recently regained attention. In many scenarios, TB is only considered in symptomatic children exhibiting symptoms like fever, cough, and failure to thrive. The findings of this study reveal that NLR is lower in children with TB disease and outperforms other ratios. Specifically, the absolute

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Table 1. Laboratory Parameters in Case and Control Groups

Laboratory Parameters (SI)	Case (n=50)	Control (n=50)	Mann-whitney U (p-value)
Platelet count (10^3 cells/L)	287100 (±93363)	327760 (±140863)	0.229
Neutrophils count (10^3cells/L)	4168(±3313)	7072 (±4958)	0.001
Lymphocytes count (10^3cells/L)	3686 (±2139)	3609 (±1921)	1.000
Monocytes count (10^3cells/L)	1151(±748)	1189 (±633)	0.350
Neutrophils to lymphocyte ratio (NLR)	1.41 (± 1.02)	2.35 (± 1.89)	0.005
Lymphocyte to monocyte ratio (LMR)	3.99 (±2.51)	3.58 (±1.88)	0.508
Platelet to lymphocyte ratio (PLR)	115.99 (±111.68)	130.83 (±177.42)	0.866
Monocyte to lymphocyte ratio (MLR)	0.44 (± 0.46)	1.80 (± 2.39)	0.000

values were expressed as mean ± standard deviation. SI = international system of units

Table 2. NLR and MLR Ratio in Case and Control Group Aged <5 and >5 Years Old

Laboratory Parameters (SI)	n	Case	n	Control	*p-value*
Neutrophils to lymphocyte ratio (NLR)					
<5years old	31	1.05 (± 0.76)	35	1.32 (± 0.76)	0.011
>5years old	19	1.94 (± 1.07)	15	2.35 (± 1.89)	0.036
Monocyte to Lymphocyte ratio (MLR)					
<5years old	31	4.46 (± 2.14)	35	4.67 (± 2.36)	0.179
>5years old	19	2.72 (± 2.10)	15	3.27 (± 1.45)	0.789

values were expressed as mean ± standard deviation. SI = international system of units

Table 3: Contingency Coefficient Analysis of Case-Control Groups and Age of Children

Groups	Age Range			Coefficient Correlation	p-value	Odds Ratio	95% Confidence Interval	
	<5 Yo	>5 Yo	Total				Lower	Upper
Case	36	34	70					
Control	76	41	117	0.132	0.048	0.571	0.312	1.044
Total	112	75	187					

neutrophil count in the case group alone exhibited a significantly lower count compared to other parameters.

Neutrophils play a crucial role in the innate immune system, contributing significantly to host defense by migrating to the site of injury, inducing the secretion of various inflammatory cytokines, engaging in phagocytosis, and generating reactive oxygen species [12]. NLR is a measure that reflects the ratio of neutrophil count to lymphocyte count, serving as an easily accessible, calculable, and cost-effective parameter [13]. Numerous studies have demonstrated a connection between elevated NLR and chronic inflammation observed in conditions such as cardiovascular disease, diabetes mellitus, and malignancies [14–18]. Moreover, platelets may contribute to inflammation by storing pro-inflammatory and regulatory mediators in their granules, releasing them at the site of inflammation upon platelet activation. Activated platelets can also facilitate the entry of neutrophils into lesions [19].

The immune mechanisms elucidating the findings in our study stem from recent evidence highlighting the significant role of innate immunity in TB disease [20]. In both human in vitro and mouse in vivo models, persistent infection with Mycobacterium tuberculosis is demonstrated in hematopoietic stem cells within the

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bone marrow. Consequently, M. tuberculosis promotes the development of progenitor cells towards the myeloid lineage, thereby stimulating the generation of monocytes and neutrophils over the lymphoid lineage [21]. These underlying mechanisms may lead to an increase in neutrophil and monocyte counts and a decrease in lymphocyte counts, resulting in lower NLR, MLR, and Neutrophil-Monocyte-to-Lymphocyte Ratio (NMLR) associated with TB disease. Our study shown a consistent result with this previous study, regarding NLR and MLR.

In a study assessing adults with TB disease and other respiratory infections, including viral pneumonia, bacterial pneumonia, aspiration pneumonia, and empyema, lower NLR, and MLR were found in patients with TB compared to those with other respiratory infections [22]. Two additional studies comparing adults with TB to those with community-acquired bacterial pneumonia reported conflicting results, with one showing lower NLR and the other showing higher NLR in TB patients compared to controls [6,23].

In contrast to these conflicting results in adults, our study demonstrated lower ratios in children with TB compared to children with pneumonia. Possible explanations for these differences include variations in age, disparities in the pathophysiology of TB between children and adults, and differences in the causative pathogens for respiratory tract infections in younger age groups [24,25]. The findings in our study suggest an association between NLR with TB disease. These biomarkers could potentially be utilized early in the diagnostic evaluation of children with respiratory symptoms to assess the likelihood of TB disease. Additionally, in children with a positive immunodiagnostic test and only minor or absent symptoms, these ratios may aid in distinguishing between TB disease and infection.

However, it's important to acknowledge the limitations of our study. Firstly, it relied on medical records, and the sample size was small. Therefore, a long-term, prospective, observational cohort study is warranted to validate and further explore these findings.

CONCLUSION

This research indicates that Neutrophil-to-Lymphocyte Ratios (NLR) hold promise as readily accessible diagnostic biomarkers for distinguishing children with TB disease from those with other lower respiratory tract infections. However, it's important to note that these findings need confirmation through a more extensive study sample, encompassing both low and high TB incidence settings.

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CONFLICT OF INTEREST

The authors have declared that no competing interests exist.

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