

CORRELATION BETWEEN MLR AND NLR WITH LENGTH OF STAY IN CHILDREN WITH TYPHOID FEVER

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ABSTRAK

Abstract:

Typhoid fever is a systemic infection caused by *Salmonella typhi* bacteria that predominantly affects children. Monocyte to Lymphocyte Ratio (MLR) and Neutrophil to Lymphocyte Ratio (NLR) are simple hematological parameters that potentially describe the inflammatory response. This study aims to determine the correlation between the MLR and NLR and the length of hospital stay in pediatric typhoid fever patients. This study used an analytical observational design with a cross-sectional approach and involved 48 pediatric typhoid fever patients treated at PKU Muhammadiyah Sampangan Hospital, Surakarta. Data on MLR, NLR, and length of hospital stay for pediatric typhoid fever patients were obtained from medical records. Statistical analysis was used to evaluate the correlation between variables. MLR ($p = 0.653$, $r = -0.067$) and NLR ($p = 0.231$, $r = 0.176$). These findings indicate that MLR and NLR values are not accurate predictors of length of stay in pediatric typhoid fever patients. MLR and NLR are not significantly correlated with length of hospital stay in pediatric typhoid fever patients. This study confirms that simple hematological parameters are insufficient to describe the factors affecting length of hospital stay in pediatric typhoid fever patients.

Abstrak:

Demam tifoid merupakan infeksi sistemik akibat bakteri *Salmonella typhi* yang dominan menyerang pada usia anak. Neutrophil to Lymphocyte Ratio (MLR) dan Monocyte to Lymphocyte Ratio (NLR) merupakan parameter hematologi sederhana yang berpotensi menggambarkan respons inflamasi. Penelitian ini bertujuan mengetahui korelasi antara MLR dan NLR terhadap lama rawat inap pada pasien demam tifoid anak. Penelitian ini menggunakan desain observasional analitik dengan pendekatan cross-sectional dan melibatkan 48 pasien anak demam tifoid yang dirawat di RS PKU Muhammadiyah Sampangan, Surakarta. Data MLR, NLR, serta lama rawat inap pasien demam tifoid anak diperoleh dari rekam medis. Analisis statistik digunakan untuk mengevaluasi korelasi antar variabel. Nilai MLR ($p = 0,653$, $r = -0,067$) dan NLR ($p = 0,231$, $r = 0,176$). Temuan ini menunjukkan bahwa nilai MLR dan NLR bukanlah prediktor yang akurat terhadap lama rawat inap pada pasien demam tifoid anak. MLR dan NLR tidak berkorelasi secara signifikan dengan lama rawat inap pada pasien demam tifoid anak. Penelitian ini menegaskan bahwa parameter hematologi sederhana belum cukup menggambarkan faktor yang memengaruhi lama rawat inap pada pasien demam tifoid anak.



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INTRODUCTION

Typhoid fever is a disease associated with systemic infection by *Salmonella enterica serovar typhi* bacteria, which is transmitted through the fecal-oral route, crossing the intestinal epithelium and spreading systemically and intracellularly, causing nonspecific fever symptoms. According to data from the World Health Organization (WHO) in 2019, there are 9 million cases of typhoid fever each year, resulting in an increase in the number of deaths of around 110,000 per year due to this disease. This disease has a high burden, especially in Asia and Africa, most commonly affecting infants to young adults [1].

Typhoid fever in Indonesia is more common in children than adults. Based on data from the Early Warning and Response System (SKDR) of the Ministry of Health of the Republic of Indonesia in 2025, there were 572,741 suspected cases of typhoid fever nationally. Central Java occupies the third highest level after East Java and West Java, with a total of 109,899 suspected typhoid fever cases [2]. The highest incidence rate is found in the 5-15 year age group of 180 people per 100,000 population, while at the age of >16 years only 51 people per 100,000 population, with the average age of sufferers around 10 years [3]. Another study showed that the prevalence of typhoid fever in suspected adult patients was only 4.7% of 233 cases [4].

Enforcement of the clinical diagnosis of typhoid fever is a challenge because the symptoms are not typical and often resemble other infections, so in endemic areas of fever that lasts more than one week without a clear cause, it must be suspected as typhoid until proven otherwise [5]. Laboratory examinations play an important role with various methods including peripheral blood examinations, serological tests, blood cultures, and molecular examinations. In addition, complete blood count tests are also always used, not only as a method to support diagnosis, but also as

an indicator of disease severity that is commonly carried out in primary and community hospital laboratories [6].

Neutrophil to Lymphocyte Ratio (NLR) and *Monocyte to Lymphocyte Ratio* (MLR) are important indicators in assessing inflammatory responses, including in *Salmonella infection* that causes typhoid fever. Increased NLR has been associated with a stronger inflammatory response, disease severity, as well as length of stay in pediatric patients [7], [8], [9]. MLR has been shown to be effective in distinguishing bacterial and viral infections with higher values in bacterial infections and lower values in viral infections, especially in the acute phase [10], [11].

Research related to MLR in children is still limited because most studies focus on the adult population, even though children are a vulnerable group to typhoid fever which is high prevalence in developing countries [8], [12]. Research studies on the correlation between NLR and MLR and length of hospitalization in pediatric patients have not been comprehensively studied [13]. Based on this, researchers are interested in examining the correlation between the *Monocyte to Lymphocyte Ratio* and the *Neutrophil to Lymphocyte Ratio* on the length of hospitalization in pediatric typhoid fever patients.

RESEARCH METHOD

The design of this study uses an analytical observational design with a *Cross-sectional approach*. This research was carried out at PKU Muhammadiyah Sampangan Hospital from September 2025 to November 2025. The target population in this study is child patients with typhoid fever at PKU Muhammadiyah Sampangan Hospital. The sample of this study was taken using *the consecutive sampling* technique, which is a method of sampling sequentially over a certain period of time based on criteria according to the characteristics needed in the study.

The study sample was obtained from complete patient medical record data for the period January – December 2024, including the results of the first day of hospitalization blood tests for the calculation of *Monocyte to Lymphocyte Ratio* (MLR) and *Neutrophil to Lymphocyte Ratio* (NLR) values. The research subjects were selected based on the inclusion and exclusion criteria that had been set. The inclusion criteria in this study include pediatric patients under 18 years of age who are undergoing hospitalization with a diagnosis of typhoid fever based on the results of tubex Tubex ≥ 4 examination at PKU Muhammadiyah Sampangan Hospital, and have complete medical record data. Exclusion criteria include patients who have a history of comorbidities, such as malaria or dengue fever, as well as patients with a history of hematological malignancies. The data that has been collected is then analyzed using statistical software, namely SPSS version 26. Statistical methods were used to describe the characteristics of the study subjects, including age, sex, *Monocyte to Lymphocyte Ratio* (MLR) value, *Neutrophil to Lymphocyte Ratio* (NLR) value, and Length of Stay (LOS). The normality of data distribution was tested using Shapiro-Wilk. In bivariate analysis, it was carried out using the Spearman correlation test to assess the relationship between the variables studied. A $p < 0.05$ is considered to indicate a statistically significant relationship.

RESULT AND ANALYSIS

In this study, 48 medical records have been obtained that meet the restriction criteria and can be used as the subject of this study. The characteristic distribution data can be seen from table 1.

Tabel 1.
Distribution of Research Subject
Characteristics

Variabel	n (%)	Hasil Med (min – max)
Age (year)		7,50 (1 – 7)
0 – 4	14 (29,2)	
5 – 9	12 (25)	
10 – 18	22 (45,8)	
Gender		
Male	25 (52,1)	
Female	23 (47,9)	
WBC count ($10^3/\mu\text{L}$)		5,79 (1,14 – 18, 84)
Absolute Neutrophil ($10^9/\text{L}$)		3,41 (0,61 – 12,68)
Absolute Monocyte ($10^9/\text{L}$)		0,5 (0,12 – 1,59)
Absolute Lymphocyte ($10^9/\text{L}$)		1,5 (0,11 – 5,27)
MLR		0,3 (0,09 – 7,0)
High	5 (10,4)	
Medium	17 (35,4)	
Low	26 (54,2)	
NLR		2,07 (0,32 – 68,85)
High	14 (29,2)	
Medium	27 (56,3)	
Low	7 (14,6)	
LOS		2 (2 – 5)

The results of the Shapiro-Wilk test showed that the variables MLR, NLR, and Length of stay were not normally distributed ($p < 0,05$); therefore, Spearman's correlation analysis was used. Based on the characteristic distribution data, the age distribution shows that the 10 – 18 year old age group had the highest number of typhoid fever diagnoses, at 22 (45,8%). Regarding gender characteristics, male subjects predominated, numbering 25 (52,1%). The distribution of the *Monocyte to Lymphocyte Ratio* (MLR) data shows the majority fell into the low category, totaling 26 (54,2%). The *Neutrophil to Lymphocyte Ratio* (NLR) was most frequently in the moderate category, with 27 cases (56,3%). The median Length of Stay for children with typhoid fever was 2 days, indicating that majority of participants had a short

hospital stay. it was obtained that the most age at which typhoid fever in children was 10 – 18 years old.

Tabel 2.

Bivariate analysis between MLR and NLR with length of stay

Variable	p-value	r-value
MLR	0,653	-0,067
NLR	0,231	0,176

The results of the Spearman correlation bivariate test showed that the *Monocyte to Lymphocyte Ratio* (MLR) and length of hospitalization had statistical results of $p = 0.653$ and $r = -0.067$. At a $p > 0.05$, the relationship between the two variables was declared insignificant, so that the MLR data did not provide a correlation with the length of hospitalization in pediatric patients diagnosed with typhoid fever. In the results of *Neutrophil to Lymphocyte Ratio* (NLR) and length of hospitalization, statistical results were $p = 0.231$ and $r = 0.176$. At a p value of > 0.05 , the relationship between the two variables was declared insignificant, so that NLR data in pediatric typhoid fever patients did not have a correlation with the length of hospitalization

DISCUSSION

Based on the characteristic distribution data, it was obtained that the most age at which typhoid fever in children was 10 – 18 years old. This is in line with reports based on global surveillance, typhoid fever is a major threat to children and adolescents. Global *Burden of Disease* modeling data in 2019 significantly increased in the 10-14 year old group, and then 1-4 year old children. This high vulnerability in school age groups and adolescents is mainly due to behavioral and environmental factors. Their increasingly widespread activities outside the home, such as at schools and playgrounds, as well as snacking habits in places with inadequate sanitation, dramatically increase their exposure to *Salmonella typhi* bacteria

through contaminated food or water. The immune system, which is still in the development stage, makes the body not fully optimal in fighting infections [14].

Characteristic distribution data show that the sex of males is more numerous than females. This is in accordance with research at the Lau Health Center, Maros Regency, there are findings that men have a higher susceptibility to typhoid fever than women [15]. This is not caused by biological differences or immunity, but by different behavioral factors and life habits between the two groups. Men tend to do more intense activities.

In the distribution of data on the characteristics of leukocyte count, it was found that the results of the data showed that most of the subjects were in the normal range of childhood typhoid fever. This is similar to the study conducted by children with a diagnosis of typhoid fever that has been confirmed by blood culture, the results were obtained that 73% of childhood typhoid fever cases were in the normal range (4,000 – 12,000/ μ L) for the number of leukocytes [16]. This is due to the mechanism of pathogenesis of *Salmonella typhi* that can survive inside phagocyte cells without triggering a significant increase in leukocytes, as well as factors such as previous treatment, exposure to low amounts of bacteria, and vaccination status [19].

The *Monocyte to Lymphocyte Ratio* (MLR) value recorded in the distribution of data to the dominant subject showed results in the low category. Pathophysiologically, this is initiated by the active transfer of activated monocytes from the blood circulation to target tissues such as the intestines, which leads to a decrease in their absolute amount in the blood. This displacement is often accompanied by a delayed and suboptimal monocyte activation response in the early phases of infection, as observed in individuals who develop into illness [17]. Bone marrow suppression and hemophagocytosis can also contribute to the lack of increased

monocytes in circulation [18]. Infection triggers a strong adaptive immune response, characterized by a significant increase in lymphocyte count (lymphocytosis) as part of a specific response to *Salmonella typhi*. The combination of a relative decrease in monocytes and an increase in lymphocytes results in low MLR values [18], [19].

The distribution of data on the *Neutrophil to Lymphocyte Ratio* (NLR) value showed a dominant outcome in the medium category. Pathophysiologically from the medium *Neutrophil to Lymphocyte Ratio* (NLR) value in typhoid fever, it has a unique immunomodulation mechanism mediated by Vi capsular polysaccharide in *Salmonella typhi*. Vi capsular polysaccharide acts as a major virulence factor that suppresses the innate immune response, specifically inhibiting the recognition of lipopolysaccharides (LPS) by TLR4 receptors in macrophages to reduce the production of IL-8 chemokine required against the summoning of neutrophils to infected tissues, resulting in the absence of significant neutrophilia in the periphery [20]. The condition is reinforced by the characteristic of *Salmonella typhi* infection as an obligate intracellular pathogen that persists inside phagocyte cells, so it does not necessarily trigger a massive systemic neutrophilia response. This infection causes lymphopenia due to apoptosis and lymphocyte redistribution. Neutrophilia and lymphocyte decline can produce NLR that remains in the normal range [21].

Length of hospitalization in pediatric typhoid fever patients shows an average length of hospitalization of 2 days. This is in line with research conducted at the Jakarta Islamic Hospital tends to be relatively short (1-4 days) due to the effectiveness of antibiotic treatment used [22]. In pediatric patients, it generally has a faster immune response and lower complications.

1. Relationship of MLR to Length of stay

The inability of the *Monocyte to Lymphocyte Ratio* (MLR) to predict the length of hospitalization in typhoid fever can be explained from various perspectives. Pathophysiologically, MLR simply reflects the balance between the two components of the immune system. Monocytes are not homogeneous populations, but rather are made up of functional subsets (classical, intermediate, and non-classical) with different roles in inflammatory processes. MLR only counts the total number of monocytes without distinguishing their subsets, a single measurement upon admission is not able to describe a complex acute inflammatory state. Lymphocyte counts are also easily affected by non-specific factors such as physiological stress, dehydration, or comorbidities, so their fluctuations do not necessarily reflect the degree of inflammation of typhoid itself [23], [24], [25].

This MLR ability is associated with the altered nature of the infection. Changes in the number of monocytes and lymphocytes are greatly influenced by the phase of a disease. Samples may be taken after the peak of inflammation has occurred, when the monocyte response has decreased and the lymphocytes have begun to reach normal numbers, or after the administration of therapy (such as antibiotics) that can modulate leukocyte counts rapidly. In some patients, it comes to the recovery phase when the inflammatory process has subsided. The condition results in a single MLR measurement can be at great risk for assessing the actual inflammatory condition and it is difficult to know the course of the disease related to length of stay [26].

The findings are consistent with research which states that MLR cannot be considered a specific marker for acute typhoid fever [27]. This is because the increase in MLR essentially only describes a systemic inflammatory response that is general, not a unique response to

Salmonella typhi infection. A similar pattern of increased MLR was also found in viral infections (such as Dengue or COVID-19), other bacterial infections, and non-infectious inflammatory diseases. The peculiarity of the immune response in typhoid lies in the specific functional changes of monocyte cells, which cannot be measured simply by looking at the comparison of cell counts.

2. Relationship of NLR to length of stay

These findings are in line with the results of at Dr. Soetomo Hospital Surabaya, which reported that NLR in patients with typhoid fever did not have a significant value in predicting the length of hospitalization [27]. This insignificance is due to the characteristics of typhoid fever infection itself. In contrast to other infections such as dengue or sepsis. NLR has been shown to have a prognostic value of hematologic changes in typhoid fever caused by *Salmonella typhi* more often presenting symptoms in the form of other abnormalities, such as anemia (37.5%) and thrombocytopenia (48.43%).

The pathophysiology of NLR does not show a good sensitivity as a predictor of length of hospitalization in typhoid fever because of its static characteristics and do not adequately reflect the course of a disease. In typhoid fever, NLR tends to have low values from the beginning due to neutropenia caused by bone marrow suppression and the phenomenon of hemophagocytosis. This is different from other bacterial infections that actually show an increase in NLR. These already depressed NLR values do not have a significant enough picture to be associated with clinical *outcomes* such as duration of treatment. The length of the stay is more influenced by factors such as response to antibiotics, the appearance of complications (such as intestinal perforation or encephalopathy), and the patient's comorbidity conditions [28].

Neutrophil to Lymphocyte Ratio (NLR) cannot be used as a single predictor

of length of hospitalization due to its non-specific nature. The improvement only describes the presence of generalized systemic inflammation without being able to explain the cause, severity, or the presence of specific complications (such as intestinal perforation or bleeding) that are the main determinants of the duration of treatment. The length of stay is a complex result of multiple factors such as the patient's response to antibiotics, age, nutritional status, and comorbidities. The condition of leukocytes in fluctuating typhoid fever, reinforced by the absence of a consistent and valid cut-off value, makes NLR measurements at one time unable to accurately explain the course of the disease[29].

The tendency of NLR values to remain low or stable in *Salmonella typhi* infection makes it less sensitive compared to other bacterial infections. Its predictive capacity can be optimized when combined with other clinical indicators, such as defervescence time, Dynamic inflammatory markers (such as CRP), and monitoring for potential complications during treatment [30].

CONCLUSION

Based on the results of the study, no statistically significant relationship was found between the value of Monocyte to Lymphocyte Ratio (MLR) and Neutrophil to Lymphocyte Ratio (NLR) on the length of hospitalization in pediatric patients with typhoid fever ($p > 0.05$). These results suggest that MLR and NLR cannot yet be used as a single indicator to predict the length of hospitalization in pediatric patients with typhoid fever. This study has limitations, such as a relatively small number of samples, measurement of laboratory parameters, and has not controlled confounding factors that can affect the length of hospitalization, such as the severity of the disease, nutritional status, the accuracy of antibiotic therapy, complications, and comorbidities. Therefore, further research needs to

consider a larger sample count and control of these confounding factors is needed so that the relationship between MLR and NLR with length of hospital stay is more accurate.

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