JK JURNAL KESEHATAN

The Relationship Between White Blood Cell Count and Fever Duration in Typhoid Fever Patients at Ibn Sina Hospital, Makassar City, in 2023

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Article Information

ABSTRACT

Introduction: Typhoid fever is a systemic infectious disease caused by *Salmonella Typhi*, where the endotoxin produced by the bacteria can affect leukocyte counts and fever duration. This study aimed to determine the relationship between leukocyte counts and fever duration in typhoid fever patients at Ibnu Sina General Hospital, Makassar, in 2023. **Method:** This study is an analytical observational study with a cross-sectional design and a retrospective approach. Data were obtained from 506 medical records of typhoid fever patients using total sampling technique. Data analysis used the Chi-Square test with the Fisher Exact test as an alternative and the Spearman Rho test. **Results:** The results showed that the majority of subjects were female (54.9%) with the most common age group being 11–20 years (32%). Most had normal leukocyte counts (62.3%) and experienced acute fever (86%). The Spearman Rho test indicated a statistically significant relationship between leukocyte count and fever duration (p= 0.049) with a very weak negative correlation strength (r = -0.098). **Conclusion:** Therefore, it can be concluded that there is a statistically significant relationship between leukocyte count and fever duration in typhoid fever patients at Ibnu Sina General Hospital in Makassar City in 2023, with a very weak inverse correlation.

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INTRODUCTION

Typhoid fever is an infectious disease caused by the bacterium *Salmonella Typhi*. According to *the World Health Organization* (*2020*), there were approximately 14.3 million cases and 135,900 deaths worldwide in 2017. Typhoid fever is a complex problem in developing countries, including Indonesia. Epidemiological data from the Indonesian Ministry of Health indicate that the incidence rate of typhoid fever in Indonesia is approximately 350–810 per 100,000 population. This translates to approximately 600,000–1,500,000 cases of typhoid fever annually in Indonesia. An epidemiological study in South Sulawesi Province recorded 23,271 suspected cases of typhoid fever, with 16,743 confirmed cases, the highest incidence occurring in Bulukumba District (3,270 cases), Makassar City (2,325 cases), and Enrekang District (1,153 cases) (Health Department (2015).

Typhoid fever presents with a wide range of clinical symptoms, from mild to severe. In the first week, the disease presents with symptoms such as fever, headache, dizziness, muscle pain, loss of appetite, nausea, vomiting, diarrhea, abdominal discomfort, coughing, and nosebleeds. In the second week, symptoms become more pronounced, including fever, relative bradycardia, hepatomegaly, splenomegaly, mental disturbances such as somnolence, stupor, coma, delirium, and even psychosis (Widodo 2014). The duration of fever in typhoid fever can range from acute to chronic. The duration of fever can be influenced by several factors, such as the amount of endotoxin in the body, which plays a role in determining the duration of fever. If the amount is sufficiently high in the body, it will have adverse effects that prolong the duration of fever (Hashmi and Thakur 2019). If the patient's immune system is sufficiently strong, the body's ability to combat bacterial invasion will be faster, resulting in better outcomes in temperature measurements. Typhoid fever can be diagnosed based on clinical symptoms, physical examination, and laboratory tests. Laboratory tests, including leukocyte count, are important for screening and diagnosing typhoid fever. Leukocyte count is a routine blood test used to determine normal leukocyte levels, leukopenia, or leukocytosis in cases of typhoid fever (Widat, Jumadewi, and Hadijah 2022).

Based on research conducted by Rosinta in 2015, there is a relationship between the duration of fever and leukocyte examination results in patients with typhoid fever at Al Ihsan Hospital (Rosinta et al. 2016). However, this finding differs from the study conducted by Febriani in 2021, which found no association between fever duration and leukocyte count in typhoid fever patients at Dr. Harjono S Ponogoro General Hospital (Febriani et al. 2021). However, research on this relationship is still limited in the Makassar region, particularly studies using large case data. Therefore, the researcher aims to conduct a study on "The Relationship Between White Blood Cell Count and Fever Duration in Typhoid Fever Patients at Ibn Sina Hospital, Makassar City, in 2023."

LITERATURE REVIEW

Leukocyte Count and Duration of Fever in Typhoid Fever

Changes in leukocyte counts are commonly observed in acute infections, including typhoid fever caused by *Salmonella typhi*. This infection can trigger an immune response characterized by leukocytosis; however, as the disease progresses, some studies have reported leukopenia due to bone marrow suppression by bacterial endotoxins (Hashmi and Thakur 2019; Widat et al. 2022). Bacterial endotoxins are known to play a role in the onset of fever through the activation of inflammatory mediators (Guyton and Hall 2014; Sevia Mitha et al. 2023).

Previous studies have evaluated the relationship between leukocyte counts and clinical manifestations of typhoid fever; however, the specific relationship between leukocyte change patterns and fever duration has not been extensively discussed. Therefore, this study aims to address this gap by evaluating the correlation between leukocyte counts and fever duration in typhoid fever patients to enhance clinical understanding in assessing infection progression.

METHOD

This study is an analytical observational study with a cross-sectional design and a retrospective approach. The study aims to determine the relationship between leukocyte count and fever duration in typhoid fever patients at Ibnu Sina General Hospital in Makassar City in 2023. The data used were secondary data obtained from medical records at Ibnu Sina General Hospital during the period January–December 2023. All research procedures were approved by the Research Ethics Committee of the Faculty of Medicine, University of Muslim Indonesia, with ethical approval number: 210/A.1/KEP-UMI/VI/2024.

The population in this study included all typhoid fever patients admitted to Ibnu Sina General Hospital in Makassar City during 2023, totaling 816 patients. The researcher used total sampling, so all individuals in the population who met the inclusion criteria and did not meet the exclusion criteria were included as samples.

The inclusion criteria for this study included patients with a minimum agglutinin O titer of 1/160 or a TUBEX TF result of ≥ +4, complete medical records including name, medical record number, age, gender, onset of fever, and leukocyte examination results. This study only used the results of the first hematology examination conducted within the first week of the patient's admission to the hospital. Meanwhile, exclusion criteria included patients with complications, comorbidities, or other infections such as tuberculosis, pneumonia, and immunodeficiency conditions, as well as patients who had received antibiotics prior to laboratory testing. After selection based on these criteria, 506 patient data met the criteria for analysis.

The collected data were analyzed using **SPSS** software **version 29 (*Statistical Product and Service Solutions*)**. Univariate analysis was performed to describe the frequency distribution of each study variable. Next, bivariate analysis was used to determine the relationship between leukocyte count and duration of fever. Leukocyte count in this study was categorized into three groups: decreased, normal, and increased. Meanwhile, duration of fever was categorized into three groups: acute, subacute, and chronic.

The statistical tests used in the bivariate analysis included **the Chi-square test** to examine the relationship between two categorical variables. If the Chi-square test requirements were not met, the researcher used **the Fisher's Exact Test** as an alternative. Additionally, **the Spearman Rho test** was conducted to assess the correlation between two variables, namely leukocyte count and fever duration, in numerical or ordinal form.

RESULTS AND DISCUSSION

This study utilized secondary data in the form of medical records of typhoid fever patients recorded at Ibnu Sina Hospital in Makassar City in 2023, which met the inclusion and exclusion criteria, resulting in 506 data points that were statistically analyzed.

Univariate analysis showed that the total number of study subjects was 506, consisting of 278 (54.9%) females and 228 (45.1%) males. Most subjects were in the 11–20 age group, totaling 162 (32%). Based on leukocyte count examinations, the majority of

subjects had normal leukocyte levels (315, 62.3%), while 191 (37.7%) showed abnormal levels, comprising 153 with elevated leukocytes and 38 with decreased leukocytes. Based on the duration of fever, most subjects experienced acute fever (435, 86%), followed by subacute fever (53, 10.5%), and chronic fever (18, 3.6%).

Based on the results of bivariate analysis, it was found that out of 506 study subjects with normal leukocyte counts, 256 had acute fever duration, 34 had subacute fever duration, and 17 had chronic fever duration. The number of leukocytes increased with acute fever duration in 135 subjects, with subacute fever duration in 17 subjects, and with chronic fever duration in 1 subject. The number of leukocytes decreased with acute fever duration in 36 subjects, with subacute fever duration in 2 subjects, and with chronic fever duration in none. Based on the *Fisher Exact* test results, the p-value was 0.049, which means that p < 0.05, indicating a significant relationship between leukocyte count and fever duration. Based on the *Spearman Rho* test, the correlation coefficient was -0.093, indicating a negative and very weak correlation, meaning that as the number of leukocytes increases, the duration of fever decreases, but the correlation is very weak. This indicates that there is a significant relationship between leukocyte count and fever duration in typhoid fever patients at Ibnu Sina Hospital in Makassar City in 2023, with a very weak reciprocal correlation.

Table 1. Distribution of Respondent Characteristics (N= 506)

Characteristics	Categories	Frequency (n)	Percentage (%)
Gender	Male	228	45
	Female	278	54.9
Age (years)	1–10	80	15
	11-20	162	32
	21-30	153	30.2
	31–40	46	9
	41-50	29	5.7
	51-60	28	5
	61-70	7	1.4
	71-80	1	0.2
White Blood Cell Count	Normal	315	62.3
	Elevated	153	30.2
	Decreasing	38	7.5
Duration of fever	Acute	435	8
	Subacute	53	10.5
	Chronic	18	3.6

Table 2. Relationship Between White Blood Cell Count and Fever Duration in Typhoid Fever Patients

Leukocyte Count	Duration of Fever			Total	P-value	Correlation
	Acute n (%)	Subacute n (%)	Chronic n (%)			
Normal	264 (83.8)	34 (10.8)	17 (5.4)	315 (100)	0.049*	-0.093**
Increasing	135 (88.3)	17 (11.1)	1 (6.6)	153 (100)		
Decreased	36 (94.8)	2 (5.2)	0 (0)	38 (100)		

Fisher's exact test, **Spearman's rho test*

Typhoid fever can affect anyone regardless of gender, as gender is not a primary risk factor for the disease. The condition is more closely associated with poor *personal hygiene*, poor food hygiene, and unsanitary living conditions (Febriani et al. 2021).

Transmission typically occurs through *contaminated* water, food, or food contaminated *by carriers*, which are the primary sources of infection. The differences in prevalence between women and men found in some studies across various hospitals may be due to more women seeking medical attention, or vice versa. However, it is also possible that men, or conversely, have a high incidence of typhoid fever but do not seek medical attention at hospitals (Khairunnisa, *et al.* 2020).

Typhoid fever is more common in the 11-20 age group because people in this age range often engage in outdoor activities, putting them at high risk of infection *with Salmonella typhi*, for example through consumption of food that is not hygienically prepared and poor *personal hygiene* (Hadi, Santriani, Ilma Khaerina B. Amaliyah, and Zaidan. 2020).

Leukocytes, also known as white blood cells, are part of the body's immune system. Their primary function is to protect the body from bacterial invasion or foreign substances. The normal range for leukocyte count based on age is 9,400–34,000 µL for ages 1–3 years, 4,000–12,000 µL for ages 4–11 years, for ages 12–15 years, the range is 3,500–9,000 µL, and for ages ≥16 years, the normal range is 3,500–10,500 µL (Health Promotion Team of RSST 2022). Abnormal leukocyte counts vary from none at all to an early indicator of life-threatening processes (Rice, *et al.* 2022). Leukocytosis is a condition where the leukocyte count is above the normal range. This may be due to an ongoing infection because antibiotics have not successfully killed the *Salmonella Typhi* bacteria. Factors influencing increased leukocyte counts in typhoid fever patients indicate the presence of infection in the patient's body. The increase in leukocyte counts occurs to initiate and maintain the body's defense mechanisms to combat infection (Nurmansyah, 2020). Leukopenia, on the other hand, is a condition where the leukocyte count is below the normal range. This is caused by bacterial metabolism and toxins in the bone marrow, which suppress bone marrow as the primary site of myelopoiesis. Additionally, *Salmonella Typhi* bacteria are phagocytosed by the end of the second week, although they may no longer be detected in the blood, but they remain in the bone marrow, disrupting the leukocyte formation process, resulting in leukocyte counts below the normal range (Widat et al., 2022).

Fever can be classified into acute, subacute, and chronic based on duration. Acute fever (duration <7 days) is characteristic of infectious diseases, while subacute fever (no more than 2 weeks) may be observed in typhoid fever cases. Chronic or persistent fever (duration >2 weeks) is typical of chronic bacterial infections such as tuberculosis, HIV infection, cancer, and connective tissue diseases (Ogoina, 2014). The duration of fever can be influenced by several factors, such as variations in the amount of endotoxins present in the body. If the amount of endotoxins is high in the body, it will have a negative impact, prolonging the duration of fever. If the patient's immune system is strong, the body's ability to fight bacterial invasion will be faster, resulting in better outcomes in body temperature measurements. Additionally, the duration of fever is influenced by the *Basal Metabolic Rate* (*BMR*) of the body, which is related to physiological processes and affects the amount of heat produced by each individual (Sevia, et al., 2023).

Theoretically, typhoid fever patients with elevated or decreased white blood cell counts indicate a more severe infection. This can occur due to differences in the patient's immune response and the amount of endotoxins present in the patient's body. This triggers the inflammatory process, one of which is fever (Guyton and Hall 2014; Sevia Mitha *et al.* 2023).

Fever is a term referring to an increase in body temperature caused by infection or inflammation. In response to bacterial invasion, certain phagocytic cells such as macrophages release chemical substances known as endogenous pyrogens. Heat response mechanisms are activated to cool the body through vasodilation and sweating. This

indicates that a decrease in the number of endogenous pyrogens affects the duration of fever (Lauralee, 2016).

In addition to the immune system, the amount of endotoxin also plays a role in the number of leukocytes and the duration of fever. The average amount of endotoxin that can cause infection in humans is approximately 10^3 to 10^6 organisms (Hashmi and Thakur, 2019; Paul and Bandyopadhyay, 2017). When *Salmonella typhi* bacteria enter the body, endotoxins also enter the body, increasing the number of leukocytes (leukocytosis). *Salmonella typhi* in the bone marrow affects the process of blood cell formation, particularly leukocytes (white blood cells), resulting in a decrease in leukocyte production (leukopenia). This occurs because endotoxins entering the body cause bone marrow suppression and activation of hemophagocytosis by macrophages in the bone marrow, which is the site of leukocyte formation. The amount of endotoxins also influences the amount of endogenous pyrogens released, which cause fever. A low leukocyte count indicates a high level of *Salmonella typhi* bacterial endotoxin in the body, leading to prolonged fever (Hashmi and Thakur, 2019; Khairunnisa et al. 2020). However, in this study, no decrease in leukocyte count was found with chronic fever duration because the amount of endotoxin entering the typhoid fever patients whose data were collected was unknown, and they did not have complications.

Based on the study results, a statistically significant association was found between leukocyte count and fever duration in typhoid fever patients at Ibnu Sina General Hospital, Makassar City, in 2023, although the correlation was very weak. This indicates that although the statistical relationship is significant, the biological or clinical relationship between leukocyte count and fever duration is not strong enough to serve as a single indicator for assessing the severity of typhoid infection.

These findings are consistent with several studies indicating that changes in leukocyte count can occur in Salmonella typhi infections, including both leukocytosis as a response to active infection and leukopenia due to bone marrow suppression by bacterial endotoxins (Nurmansyah et al, 2020; Widat et al, 2022) However, the duration of fever itself is not solely influenced by leukocyte count but also by various other factors such as endotoxin levels, nutritional status, individual immune response, as well as the effectiveness and timing of treatment initiation (Baratawidjaja and Rengganis, 2014; Guyton and Hall, 2014; Sevia Mitha et al, 2023)

Additionally, confounding factors such as inconsistent timing of laboratory data collection, prior use of antipyretics or antibiotics before admission, and incomplete documentation of the patient's nutritional status can influence the interpretation of the relationship between leukocyte count and fever duration. For example, patients with poor nutritional status tend to have a weakened immune response, leading to prolonged fever even with normal leukocyte counts. (Febriani et al, 2021)

This study has several limitations. The data used were derived from secondary medical records, which did not allow direct observation of patients' clinical conditions. Several important variables, such as hydration status, medication adherence, or typhoid complications, were not reported in full, despite their potential to influence fever duration. Additionally, endotoxin levels in patients were not measured, making it impossible to confirm whether prolonged fever duration is directly related to the toxin load of Salmonella typhi.

CONCLUSION

Based on the results of this study, it can be concluded that there is a significant association between leukocyte count and fever duration in typhoid fever patients at Ibnu Sina General Hospital in Makassar City in 2023, with a very weak inverse correlation. This

indicates that leukocyte count cannot be used as the sole indicator for estimating the duration of fever in typhoid fever patients. Therefore, clinical assessment of patients must continue to consider other parameters, including clinical symptoms, blood culture results, and response to therapy. Comprehensive monitoring remains crucial to prevent complications and accelerate the healing process. Recommendations **for future researchers** include conducting further studies with a larger sample size and considering other variables, such as patients' immune status, antibiotic use, and nutritional factors, to obtain a stronger understanding of the relationship between hematological parameters and fever duration.

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