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CORRELATION OF WIDAL TITER WITH THE NUMBER OF LEUKOCYTES, LYMPHOCYTES AND NEUTROPHILS IN TYPHOID FEVER PATIENTS

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ABSTRACT

Background: Typhoid fever is an acute infection caused by the bacteria Salmonella typhi. In typhoid fever patients, abnormal leukocyte, lymphocyte, and neutrophil counts are often found. Typhoid fever is prevalent in tropical regions, including Indonesia, where it ranks fifth among infectious diseases, affecting 1.6% of the general population. **Objective:** The aim of this study is to determine the correlation between Widal titer and the number of leukocytes, lymphocytes, and neutrophils in typhoid fever patients. **Methods:** The research design used quantitative analysis with a cross-sectional method. The study utilized secondary data from 30 respondents patients with typhoid fever at 'Aisyiyah Siti Fatimah Tulangan Hospital, conducted in April 2024. **Results:** The research data were analyzed using Spearman's correlation test in SPSS, and the results showed a significant correlation (p=0.014; r=-0.444) between the Widal titer for S. typhi O and S. typhi H with the leukocyte count, no significant correlation (p=0.855; r=0.035) between Widal titers for S. typhi O and S. typhi H with lymphocyte counts, and a significant correlation (p=0.023; r=-0.413) between Widal titers for S. typhi O and S. typhi H with neutrophil counts. **Conclusion:** Based on the research results, here is a significant correlation between Widal titer and leukocyte count and between Widal titer and neutrophils. There is no significant relationship between Widal titer and lymphocyte count in patients with typhoid fever.

INTRODUCTION

The World Health Organization (WHO) reported in 2023 that in 2019 there were approximately 9 million cases of typhoid fever with 110,000 deaths globally[1]. Typhoid fever is common in tropical regions, including Indonesia, where it ranks fifth as the most common infectious disease in the community, with a prevalence of approximately 1.6% of the population[2].

Typhoid fever is an acute infection caused by the bacterium Salmonella typhi[3], which activates the immune system, particularly leukocytes such as neutrophils and lymphocytes[4]. Leukocytes play an important role in the body's defense system against foreign substances or antigens. In maintaining the immune system, leukocytes activate the immune response and perform phagocytosis to engulf and destroy pathogens[5]. Lymphocytes play an essential role in the immune response to protect the body from infection. Lymphocytes are divided into two main types: T lymphocytes, which regulate cellular immunity, and B lymphocytes, which play a role in humoral immunity. Meanwhile, neutrophils are the body's first line of defense against acute infections. In addition to fighting acute infections, neutrophils also respond more quickly to inflammation and tissue damage than other types of leukocytes[6].

In diagnosing typhoid fever, a serological test using the Widal test is conducted to detect the presence of antibodies in patients with typhoid fever against Salmonella typhi antigens[3]. The Widal test was chosen as a diagnostic tool for typhoid fever

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because it is a quick, simple, and low-cost test that can detect antibodies in the body against Salmonella typhi antigens[7]. The principle of the test involves an agglutinin antibody reaction, which dilutes the flagellar (H) and somatic (O) antigens. The diagnostic value of the Widal test is determined by the rise in antibody titers in the blood for O, H, and Vi antigens[3]. In patients with typhoid fever, abnormal counts of leukocytes, lymphocytes, and neutrophils are often observed, which are caused by the lipopolysaccharide endotoxin of *Salmonella typhi* and the occurrence of margination, redistribution, and a sharp increase in apoptosis[4].

According to a study conducted by[4], A significant correlation (p = 0.006) was found between Widal titer and white blood cell count in typhoid patients, with the white blood cell count decreasing as the Widal titer increased in the test results. This condition can occur due to a decrease in the number of leukocytes in patients with typhoid fever because leukocytes play a role in fighting very high body temperatures or fighting infections. Salmonella typhi produce endotoxins in the form of lipopolysaccharides that affect and attack the bone marrow, causing a significant decrease in the number of leukocytes.

In the study of the relationship between Widal titer and lymphocyte count, it was explained in research conducted by[7]. The results showed that there was no correlation (p = 0.051) between Widal titer and lymphocyte count in typhoid fever patients. This occurred because several patients were found to have normal lymphocyte counts due to differences in the patients' immune responses and levels of resistance to the bacteria.

The results of preceding research are inconsistent by[8], who showed that there is a correlation between Widal titer and the number of lymphocytes found in typhoid fever patients with a significance value of 0.009. This occurs because Salmonella bacteria produce endotoxins that can suppress lymphocyte production in the bone marrow, resulting in lymphocytopenia in some cases of typhoid fever. Lymphocyte depletion can occur due to lymphocyte margination, lymphocyte redistribution, and increased lymphocyte apoptosis, which are common responses of the body to bacterial infection.

Previous research has discussed the relationship between Widal titer and leukocyte count, and Widal titer and lymphocyte count, with varying results. Based on the above background, further research is needed on the correlation between Widal titer and leukocyte, lymphocyte, and neutrophil counts in patients with typhoid fever.

METHODS

This study used an analytical observational research design, with a cross-sectional study design. The research was conducted at 'Aisyiyah Siti Fatimah Tulangan Hospital in April 2024. There were 30 research samples, according by[9], correlational research requires a minimum of 30 samples, while experimental research requires a minimum of 15 samples per group. which were secondary data of typhoid fever patients from February to March 2024 at 'Aisyiyah Siti Fatimah Tulangan Hospital. based on samples that met the inclusion criteria, namely typhoid fever patients with a Widal test salmolella typhi O titer of ≥ 1/160, Salmonella typhi H titer of ≥ 1/160 and aged 5–20 years. Exclusion criteria included typhoid fever patients with a Widal test titer ≤ 1/160, aged < 5 years and > 20 years. The sampling technique used purposive sampling, a method of selecting samples from a population that meets the criteria established by the researcher based on specific objectives. The study used secondary data from medical records at the 'Aisyiyah Siti Fatimah Tulangan Sidoarjo Hospital with 30 respondents. The examination of leukocyte, lymphocyte, and neutrophil counts was performed using the Sysmex XP-100 device, and the Widal test was performed using the slide test method. Data analysis was performed using the SPSS program, followed by a normality test using the Shapiro-Wilk test, and then a non-parametric test using the Spearman correlation test.

RESULTS

The research data showed that women patients tended to outnumber male patients, as many as 18 patients (60.0%) were women, while male patients amounted to 12 people (40.5%). And the majority of typhoid fever patients came from the age group of 12-16 years as many as 12 patients (40.0%)

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Table 1. The frequency distribution of patients based on Age and Gender

Variable	Number of Patients (Frequency)	Percentage (%)
Age		
5-11	10	33.4%
12-16	12	40.0%
17-20	8	26.6%
Total	30	100
Gender		
Women	18	60.0%
Men	12	40.0%
Total	30	100

Table 2. The frequency distribution of patients based on Widal titer values Antigen

Variable	Number of Patients (Frequency)	Percentage (%)
Antigen O		
1/160	10	55.6%
1/320	8	44.4%
Total	18	100%
Antigen O		
1/160	4	33.3%
1/320	8	66.7%
Total	12	100%

Based on Table 2, the number of patients who tested positive for antigen O shows that 10 patients (55.6%) had positive results on the Widal test with a titer of 1/160, and 8 patients (44.4%) had a positive titer of 1/320. For the H antigen, it shows that 4 patients (33.3%) had positive results on the Widal test with a titer of 1/160, and 8 patients (66.7%) had a positive titer of 1/320.

Table 3. Distribution of leukocyte data in samples

Variable	Mean	Normal Value
Leukocyte (sel / µL)	6.613 ± 3.120	5,000 – 10,000 cells/µL
Lymphocyte (%)	25.9 ± 13,7	25-35%
Neutrophil (%)	59.0 ± 20.4	50-70%.

Based on Table 3, the average leukocyte count is 6.613/µL ± 3.120/µL, the average lymphocyte count is 25.9% ± 13.7%, and the average neutrophil count is 59.0% ± 20.4%. The average leukocyte, lymphocyte, and neutrophil counts in typhoid fever patients fall within the normal range, with normal leukocyte values being 5,000 – 10,000 cells/µL, normal lymphocyte values 25 – 35%, and normal neutrophil values 50 – 70%.

Table 4. Correlation Widal Titer with Leukocyte, Lymphocyte, and Neutrophil Counts

Variable	Widal Titer	
Leukocytes	-0.444	0.014
Lymphocytes	0.035	0.855
Neutrophils	-0.413	0.023

From the data in Table 4, the relationship between Widal titer and leukocytes yielded a value of (r= -0.444 ; p= 0.014), indicating a moderate relationship with an inverse direction between Widal titer and leukocytes. In the relationship between Widal titer and lymphocytes, the value obtained was (r= 0.035 ; p= 0.855), indicating a weak correlation between Widal titer and lymphocytes, and the correlation between Widal titer and neutrophils yielded a value of (r = -0.413; p = 0.023), indicating a moderate correlation with an inverse relationship between Widal titer and neutrophils. A negative value indicates an inverse relationship, meaning that the higher the Widal titer, the lower the number of lymphocytes and neutrophils.

The strength of the correlation between Widal titer and leukocyte and neutrophil counts indicates a moderate correlation, while the relationship between Widal titer and lymphocyte count shows a very low correlation strength. This corresponds to the interpretation of correlation strength presented in Table 5[10].

The direction of the relationship between Widal titer and leukocyte and neutrophil counts shows a negative correlation, indicating an inverse relationship between the variables. This means that as the Widal titer increases, the leukocyte and neutrophil counts in typhoid fever patients decrease.

DISCUSION

Based on the data presented in Table 1, most patients showed that women patients tended to outnumber male patients, as many as 18 patients (60.0%) were women, while male patients amounted to 12 people (40.5%). This study is in line with[12] that the majority of respondents were female rather than male. Typhoid fever can affect anyone, both men and women, especially due to poor personal hygiene. In addition, the high number of female residents is also

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one of the factors causing a higher prevalence of typhoid fever among women.

Based on the data presented in Table 1, The majority of typhoid fever patients came from the age group of 12-16 years as many as 12 patients (40.0%). This can happen because school-aged adolescents often engage in outdoor activities that increase their risk of exposure to Salmonella typhi through contaminated food or drinks due to poor hygiene when eating, drinking, and not washing their hands properly[12].

In the diagnosis of typhoid fever, the Widal test is performed to measure the agglutination of antibodies against O antigen (somatic antigen), which is a crucial factor in determining the virulence of the bacteria, and H antigen (flagellar antigen)[3]. The results show that agglutination of O antigen is more sensitive compared to agglutination of H antigen. The higher presence of O antigen can be attributed to several factors, including the more durable structure of the antigen, a slower immune response, and the effects of infection, vaccination, and antibiotics[13].

Based on the data presented in Table 2, 10 patients (55.6%) had positive results on the Widal test with a titer of 1/160, and 8 patients (44.4%) had a positive titer of 1/320 tested positive for O antigen.

This occurs because Antigen O is a lipopolysaccharide component found in the cell wall of Salmonella typhi and is an antigen that does not require the assistance of T lymphocytes to stimulate an immune response. In other words, antigen O can directly activate B lymphocytes to produce antibodies without first undergoing T lymphocyte activation. As a result, antibodies against antigen O tend to form more quickly and appear earlier during the infection process compared to antibodies against antigen H. Consequently, antibody titer measurements for antigen O typically yield positive results earlier and more frequently than those for antigen H[14].

The results of the Widal test indicate an infection, as evidenced by a fourfold increase in the Widal titer, from 1/40 to 1/80, then to 1/160, and finally to 1/320[13]. The increase in Widal titer values corresponds with the duration of the patient's fever. For the antibody titer against O antigen, a titer of 1/320 is often found within the 6–9 day fever range. Meanwhile, the antibody titer against H antigen typically reaches 1/160, with a maximum value of 1/320 during the same fever period of 6–9 days[15]. Antibody formation begins at the end of the first week or on the sixth day after the onset of fever, rapidly increasing to a peak by the fourth week and remaining elevated for several weeks thereafter. This is the reason for the increased titer values observed in Widal test results[16].

Based on the research data, the relationship between Widal titer and leukocyte count in Table 4 shows a significant correlation. This is due to the fact that when the body experiences an infection, it suppresses leukocyte production in the bone marrow. An increase in Widal titer indicates a strong immune response. Between 15% and 25% of typhoid fever patients experience leukopenia and neutropenia[17]. A decrease in leukocyte count is known as leukopenia, which is caused by bacteria metabolizing in the bone marrow, leading to bone marrow suppression[18]. The stimulation of lipopolysaccharide (LPS) endotoxins from Salmonella typhi results in hemophagocytosis, a pathological state characterized by active macrophages or histiocytes that phagocytize leukocytes and their precursor cells in the bone marrow, resulting in leukopenia[2]. The leukocyte count in typhoid fever patients decreases as Widal titers rise, due to the endotoxins from Salmonella typhi[4]. When the leukocyte count in the blood rises or falls, it indicates an assault on the body, such as infections, chronic inflammatory diseases, parasitic infections, and others[6].

The research results regarding the relationship between Widal titer and lymphocyte count in Table 4 show no significant correlation. This is consistent with previous studies (Fitriyani et al., 2021) indicating no relationship between Widal titer and lymphocyte count, attributed to several factors, including the patient's age and the duration of fever experienced[7]. This may also be due to the fact that of the 30 respondents, 33.3% had normal lymphocyte counts and 16.7% had lymphocyte counts above normal values. This condition may be influenced by nutritional status, immunity levels, and the body's response to infection[8].

Lymphocytes are the dominant type of cell in the adaptive immune system, constituting about 25-35% of all leukocytes. Their primary function lies in the

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immune response through their ability to interact specifically with antigens. This ability is an essential part of the normal immune response, allowing the recognition of self and non-self components, making lymphocytes play a key role in the body's adaptive immune response. Before the adaptive immune system is activated, the innate immunity first responds to infectious agents. If innate immunity fails to react to the infection, the adaptive immune system will be activated to respond. Lymphocytes, which are part of the adaptive immune system, take longer to react to infections. During the typhoid fever infection phase, patients will go through several phases of fever. In the early phase of fever, the immune response of lymphocytes has not yet functioned optimally, making the relationship between Widal titer and lymphocyte count not clearly observable[16].

In the early phase of typhoid fever, *Salmonella typhi* infects the gastrointestinal tract and subsequently spreads into the bloodstream[19]. This stage is known as bacteremia stage I, occurring from days 1 to 3, while bacteremia stage II occurs from days 4 to 10 after the bacteria begin to infect[20].

The relationship between Widal titer and neutrophil count in Table 4 shows a significant correlation. The negative correlation indicates an inverse relationship between the variables, meaning that as the Widal titer increases, the neutrophil count in the patients' blood decreases. The lipopolysaccharide endotoxins from *Salmonella typhi* can lead to neutropenia, and infections in typhoid fever result in decreased neutrophil production. Neutropenia is related to leukopenia, which is a condition characterized by a decrease in leukocytes in the peripheral blood, commonly due to a reduction in neutrophil count. When the body experiences an infection, it suppresses the activity of the bone marrow, which is where neutrophils are produced, leading to decreased neutrophil production. Neutrophils, a type of leukocyte with a short lifespan, have their mortality significantly increased due to infections, which also lead to apoptosis or premature death of neutrophils[4].

The limitations of this study include the limited number of samples and types of parameters examined. In future studies, the number of samples and parameters examined for *Salmonella paratyphi* A and *Salmonella paratyphi* B can be increased.

CONCLUSION

Based on the research results, here is a significant correlation between Widal titer and leukocyte count and between Widal titer and neutrophils. There is no significant relationship between Widal titer and lymphocyte count in patients with typhoid fever

ETHICAL APPROVAL

Ethical Clearance from the Ethics Feasibility Commission for Research and Health (KKEPK) of the Faculty of Dental Medicine, Universitas Airlangga Surabaya, and has been declared ethically feasible under Number 0375 / HRECC.FODM / IV / 2024.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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AUTHOR CONTRIBUTIONS

Contributing to the preparation, writing, editing of the manuscript, and providing guidance.

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