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Association of Immunoglobulin G/ Immunoglobulin M Typhoid Expression with Neutrophil-Lymphocyte Ratio in Patients At Haji Hospital, Surabaya

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ABSTRACT Typhoid fever is one of the major bacterial infections worldwide caused by *the bacterium Salmonella enterica serovars typhi* in humans. The examination used is the rapid Typhoid test. This rapid typhoid test is used to detect antibodies to *Salmonella typhi.* The purpose of the study was to determine the results of the Neutrophil - Lymphocyte Ratio with various criteria results from the Immunoglobulin G / Immunoglobulin M Test in typhoid fever patients. This type of study is descriptive observational with selective sampling taken. The samples in this study were 28 samples conducted in April 2023 on typhoid fever patients at the Haji Hospital in East Java Province. This study used the Rapid Typhoid Test Immunochromatography method with positive Widal criteria and supporting examination using Neutrophil–Lymphocyte Ratio (NLR) with *Hematology Analyzer* tool Fluorescent Flow Cytometry method. Typhoid and NLR rapid test results are processed descriptively in tables and based on percentages. The results obtained from the rapid test were positive IgM of 29%, positive IgG of 11%, positive IgG and IgM of 3%, and negative IgG and IgM of 57%. The average NLR was 4,43% with a median of 2,85. IgG / IgM examination of NLR showed no significant association in typhoid fever patients. It is hoped that this research will be further developed using the Tubex TF examination. The community is expected to improve the cleanliness of the surrounding environment.

INDEX TERMS Typhoid Fever, IgM, IgG, NLR.

I. INTRODUCTION

Typhoid fever is one of the main bacterial infections worldwide caused by the bacterium Salmonella enterica serovars typhi in humans. Salmonella typhi bacteria have pathogenic properties that can infect humans and survive in water, soil, and food [1]. In Indonesia, typhoid fever is endemic to all tropical and subtropical regions. Salmonella typhi is most pleased with tropical climate conditions.

Cases of an increase in typhoid fever are influenced by changes in weather, one of which is the peak of the rainy season and humidity in air temperature [2]. Cases of typhoid fever have increased from year to year around 350-850/1,000 population with a prevalence of 1.6% [3]. According to the Surabaya Health Office, in 2019 diseases of the digestive system, one of which was typhoid fever, was the second case at 14.82% [4].

There are various types of tests for typhoid fever, one of which is a blood culture examination, complete blood count, and serological examination. Examinations that are often carried out are the Widal Test and Immunoglobulin G / Immunoglobulin M Test. Other supporting tests such as HA (Hemagglutinin) Test, Blood Culture Test, Typhidot Test, Tubex Test, and ELISA Test (Enzym-linked Immunobent Assay) [5].

An antibody is a protein (immunoglobulin) that the body produces in response to the ingress of an antigen that can recognize and bind to that antigen, allowing the antibody to help destroy the antigen. Antibodies are produced by plasma cells resulting from the proliferation of B lymphocyte cells due to antigenic stimulation. Antibodies that are formed bind to similar antigens that enter the body. If the antigen enters the body and the substance crosses the non-specific reaction

barrier, it will enter and bind to B-lymphocyte cells and then synthesize antibodies [6].

Before that B lymphocyte cells produce IgM immunoglobulin molecules on the plasma membrane which act as antigen receptors. The antigen stimulates the cell to form and attack the gaps in its membrane in the specific recognition area for the antigen. Lymphocytes then produce immunoglobulin for the same antigen. Salmonella typhi bacteria have several antigens that will interact with the patient's antibodies and agglutinins and cause an agglutination reaction, the antigens are referred to as O antigens (somatic), H antigens (bacterial flagella), and Vi antigens (bacterial capsules) [7].

Innate cells play a role in the early stages of infection and produce cytokines, as well as activating and accumulating inflammatory cells. There is an increase in the number of Fc receptor cells that produce cytokines for the survival of the host [8]. Lymphocytes play an important role in antigen recognition, there are two types of lymphocytes themselves, namely T lymphocyte cells and B lymphocyte cells that work to form a defense against infection [9].

When antibodies bind to pathogens, they activate complement system proteins. This activation binds to the phagocytic cell receptors at the site of infection by lysing the organism to form pores in the membrane [8]. In the Widal Test examination, the result of agglutination on the widal plate and the IgM/IgG examination showed that both results were positive due to the formation of antibodies that cause Salmonella typhi infection in the patient's body.

When Salmonella typhi enters the body, the bacteria will be destroyed by macrophages followed by an inflammatory response process, especially in the liver, spleen, lungs, and intestines. During infection, macrophages will express Toll-like receptors (TLR4) and recognize lipopolysaccharide (LPS) in the main component of the cell wall of Salmonella typhi and stimulate pathways on TLR4 to produce inflammatory cytokines [10]. These cytokines will make the body experience symptoms of chills, and nausea accompanied by headaches with an incubation period of 7 days to 14 days.

The gold standard examination for typhoid fever can use the Widal test. If seen between the two examinations, the prevalence for the Widal test is 70%, judging from the prevalence, the Widal test is relatively higher with similar antigens [11]. The widal test looks for the presence or absence of agglutination which indicates the presence or absence of antibodies in the reaction to Salmonella typhi O and H antigens. The widal test has low sensitivity and specificity by giving a negative result of 30% [12].

Examination of Immunoglobulin G and Immunoglobulin M uses the immunochromatography rapid test method which is qualitative. This examination is one of the important parameters in the detection of IgG and IgM Salmonella typhi antibodies in serum to distinguish between primary and secondary infections. This IgG IgM examination is also the main screening in determining infection with Salmonella typhi bacteria [13]. An infection has a difference between initial and frequent antibodies. Initial infection (IgM) is detected first, while frequent infection (IgG) levels increase rapidly, detected when exposed to infection again [14]. The rapid antibody test used in this study is one of several tests that have been modified to replace the widal reaction test in diagnosing typhoid fever [15].

Examination of typhoid fever usually uses the Widal test, one of the gold standard examinations, rapid IgG/IgM Typhoid examination using the Immunochromatography method. Both of these tests detect the presence of Salmonella typhi antibodies in the serum. Other supporting examinations are complete blood count using the parameter Neutrophil–Lymphocyte Ratio (NLR) fluorescent flow cytometry method. In a study that was conducted by Meiwinda, 2021 NLR is a parameter in detecting bacteremia by looking at the results of inflammation values in subjects and to express values in NLR the median range is around 3.97 and the accuracy of the results is still not quite right [16]. Neutrophils have a role in the innate response in acute infections such as typhoid fever, transmission of agents that damage the bone marrow leads to the activation of alternating production mechanisms [15].

Abnormal results in a complete blood count in patients with typhoid fever there is an abnormality in the decrease in the number of leukocytes, namely leukopenia and lymphocytosis. If it is concluded that the patient with typhoid fever with positive results, the number of neutrophils is lower than the number of lymphocytes, and the NLR value is higher. This condition predicts a critical phase of plasma leakage [17]. This study aims to find out the results of the Neutrophil-Lymphocyte Ratio with various expressions of the results of the Immunoglobulin G / Immunoglobulin M Test in typhoid fever sufferers at Haji General Hospital Surabaya.

II. METHODHOLOGY

This research is an observational descriptive study aiming to determine the Neutrophil-Lymphocyte Ratio with various result criteria from the Immunoglobulin G / Immunoglobulin M test. This research was conducted at the Cito Laboratory of Haji Hospital, East Java Province from December 2022 - April 2023. Sampling technique in the study This is *selective sampling* with positive Widal criteria. Samples were taken from 28 patients with typhoid fever. Data was collected after obtaining a letter of ethics and a research permit. Data collection used primary data and secondary data, from the results of laboratory examinations, IgG/IgM test results were obtained with many expressions and NLR values. Processing and analysis of data is done descriptively.

The serological examination is based on the detection of an antibody, namely using 2 tests, the widal examination and typhoid IgG/IgM examination. The widal examination is an examination of *the Salmonella typhi* bacterial suspension to determine the increase in O and H antibody titers in the patient's serum [18]. O antibodies appear after 6-8 days and H antibodies appear 10-12 days after the onset of the disease. This test is based on an agglutination reaction where there

are two stages, first, the antibody binds to one of the receptors (antigen binding site), and the second antibody through another receptor will interact with other antigens that have already bound to one of the antibody molecules to form antigen-antibody clumps [7].

The principle of the Widal test is that there is an agglutination reaction between *Salmonella typhi antigens* and patient agglutinins. Agglutinin titer is expressed with the highest dilution value which still shows agglutination. In general, the O-agglutinin titer is higher and faster than the H or Vi titer. In widal examination, the patient's serum contains antibodies and will react to antigens made from suspension of *Salmonella typhi bacteria* so that agglutination is formed, agglutination itself is an antibody bond with antigen so that red blood cells clump [19].

Salmonella IgM/IgG uses *a rapid test* in the form of a cassette with an immunoassay-based principle and is qualitative for the detection of antibodies to *Salmonella typhi* in serum, plasma, or blood. the sample is dripped on the cassette along the cassette, the antibody in IgM in the serum binds to the HD conjugate, and the immunocomplex is captured by the anti-human IgM antibody pre-coated membrane and forms a color line in column M, in the sense that IgM is positive. In the IgG antibody in serum binds to the HD conjugate, the immunocomplex is captured by the pre-coated reagent and forms a color line on column G, so the result shows positive IgG. Whereas column C (control) should form a red line regardless of the color of the IgM or IgG column, if the control column does not form a color line the results obtained are declared invalid. The first step is to place the rapid test cassette on the laboratory table and then purchase the patient code label. Second, put 1 drop of patient serum using a special rapid pipette and add 1 drop of diluent buffer. Results can be read in 10 to 15 minutes interpretation of results should not take more than 15 minutes. This examination is more specific and sensitive than the widal examination. When the body is infected, the body forms IgM antibody compounds which appear on days 3-5 while IgG antibodies appear on day 14 [20].

Other supporting examinations use a Complete Blood Examination by determining the Ratio of the Neutrophil-Lymphocyte value. The principle is to use a Hematology Analyzer tool using the Fluorescent Flow Cytometry method. Flow cytometry is used for the breakdown of cells and particles as they move through very small streams. The sample is adsorbed and measured, diluted to a certain ratio, and stained. The sample is then placed in a flow cell. Semiconductor laser light beams on blood cells passing through flow cells. The forward scattering light is received by the photodiode and the lateral scattering light and lateral fluorescent light are received by the photomultiplier tube.

This light is converted into electrical pulses making it possible to obtain blood cell information. The stages of the venous blood procedure are accommodated in as much as 3 mL in a vacutainer tube. The tube containing the hematology examination was immediately carried out using *a Hematology Analyzer*. Insert the vacutainer tube into the appliance and close it. The mechanism describes directly the results will appear in about 1 minute, if the results are out then they will be printed using an automatic printer [21]. after the results come out, the data will be processed using the scatter type (x, y) with variables divided into three, namely the first neutrophil results, the second lymphocyte results, and the third the results of the neutrophil-lymphocyte ratio.

III. RESULTS

The sample in the Typhoid IgG/IgM examination criteria is presented in FIGURE 1 The sample found that out of 28 patients out of 16 patients (57%) did not have the primary infection and secondary infection, 8 patients (29%) had a primary infection, 3 patients (11%) had a secondary infection and 1 patient (3%) had a secondary infection and occurred immunity (frequent).

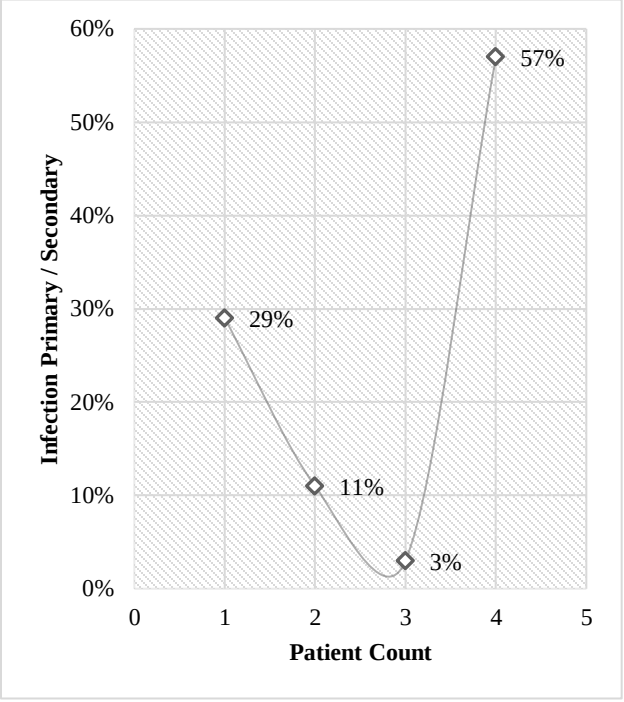

FIGURE 1. Typhoid IgG/IgM Examination Expression Results.

FIGURE 2 presents the mean value of the Neutrophil-Lymphocyte Ratio of patients with typhoid fever. From the results of the Typhoid IgG/IgM examination, the lymphocyte ratio value of 28 patients was 4.42%, exceeding the normal value limit. The average percentage of neutrophils is 64.65% and the average percentage of lymphocytes is 26.21%. Both of these average values are still within normal limits but there are still some high and low values. The results of the statistical distribution based on TABLE 1 showed that 28 patient samples were statistically analyzed to obtain an average value of the Neutrophil-Lymphocyte Ratio for typhoid fever patients at the Haji Hospital in East Java Province in 2023 of 4,43 with a median of 2,85, a standard

deviation of 5,22, the lowest value is 0,62 and the highest value is 22,12.

TABLE 1
Distribution of Descriptive Statistical Values of the Neutrophil-Lymphocyte Ratio.

Variable	N	Means	Median	SD	Min	Max
NLR value	28	4,43	2.85	5,22	0.62	22,12

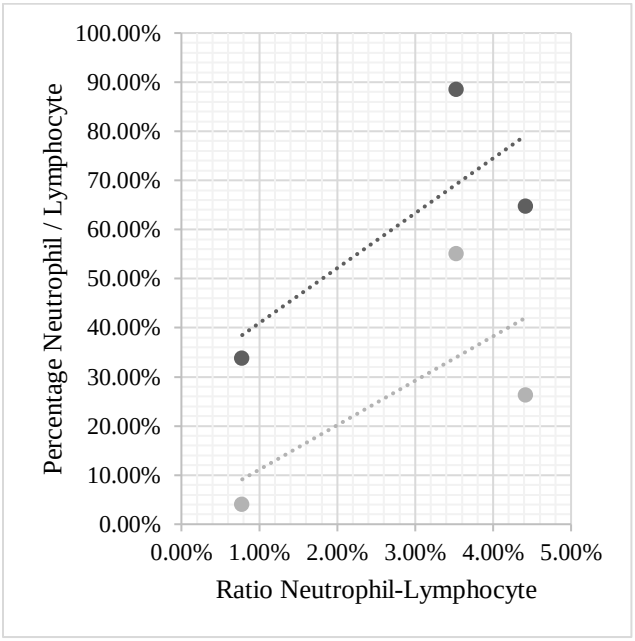

FIGURE 2. NLR (Neutrophil –Lymphocyte Ratio) Average Result Value of Typhoid Fever Patients.

IV. DISCUSSION

Based on the results of a study conducted in April-May 2023 in the cito laboratory at the Haji Hospital in East Java Province with a total sample of 28 patients. This study was divided into 4 criteria, namely negative IgG and positive IgM, positive IgG and negative IgM, positive IgG and positive IgM, and negative IgG and negative IgM. Then the results obtained were 16 people with a percentage of 57% negative, 8 people with a percentage of 29% Primary Infection (Positive IgM), 3 people with a percentage of 11% Secondary Infection (Positive IgG), and 1 person with a percentage of 3% Secondary and frequent Infections (Positive IgM) and positive IgG).

The results of the criteria from the Typhoid IgG / IgM examination of the 28 samples in total found 1 sample that rarely occurs, one of which is positive IgM and positive IgG indicating a secondary infection and frequent (repeat) occurs because when the patient is infected a primary infection (IgM) will be detected at 3-5 days after the occurrence of fever and secondary infection (IgG) will occur after 2 weeks after the patient is infected. The infection increased on the 2nd day and was followed by the emergence of IgM. The occurrence of liver complications when *Salmonella typhi bacteria* are in the liver tissue indicates that the reticuloendothelial system phagocytoses organisms and eliminates infected cells by releasing cytotoxic substances. Bacteria enter the gallbladder resulting in secondary infection in the small intestine ileum.

Both negative IgG and positive IgM results indicate a primary typhoid infection and IgG is still not formed in the critical phase on days 3-5 of fever or appears 48 hours after antigen exposure. The results of the three positive IgG and negative IgM numbers of this secondary infection are less than the primary infection, these antibodies are formed after a few days after infection and can last a long time even though the patient has recovered. As for the results of the four negative IgG and negative IgM, patients do not experience *Salmonella Typhi bacterial infection* because antibodies have not yet been formed.

Based on research conducted by Meiwinda Rizky Nurhidayah, 2021 based on the ratio between neutrophils and lymphocytes, the median for suspected typhoid was 3.97 and the range of these values was within the normal range, so NLR cannot be used as a marker of inflammation and assesses the severity of the patient's accuracy [16]. Still not enough. In another study by Cherly Sarah and Umashamkar (2016), The average NLR result in malaria was 3.9 [22]. The ratio of neutrophils to lymphocytes is also a marker of inflammation in acutely ill patients. Another study was also conducted by Nur Almatin, the results of an average NLR of 3.62 indicated inflammation, therefore the Neutrophil - Lymphocyte Ratio can be used as a marker of inflammation for monitoring healing [23].

The results of my research are that in the Neutrophil-Lymphocyte Ratio (NLR) TABLE 1 that occurs where the average percentage has been calculated as 4.43%, and the median is 2.85. The normal value of the Neutrophil - Lymphocyte Ratio (NLR) is 0.78% - 3.53% [24]. It can be seen from the results of this average that the NLR value exceeds the normal value does not mean that all NLR values are not good because some of the average values of Neutrophils and The lymphocytes of all patients had high neutrophil and lymphocyte values. In my opinion, IgG/IgM examination of the NLR value shows no significant association in typhoid fever sufferers. In comparison with the Meiwinda study, 2021 with a median result of 3.97 which is still within normal limits while for normal values the ratio is 0.78% -3.53% with the research results my NLR value is

4.43% with a median of 2.85 which is in outside the normal range, so the NLR value cannot be used as an inflammation monitoring because it causes an increase or decrease in the neutrophil value and lymphocyte value.

The increase in the NLR value is due to an increase in neutrophils due to the body's response, which induces excessive secretion of pro-inflammatory cytokines and a decrease in lymphocytes due to apoptosis but can return to normal because leukocytes are reproducing. The normal value for the percentage of neutrophils is 37% - 72.0% and the normal value for the percentage of lymphocytes is 20% - 55.0%. The average neutrophil value is 64.65% and the average lymphocyte value is 26.21% when viewed from normal values the average results of both neutrophil and lymphocyte values are still within the normal range.

A high NLR is caused by an increase in the number of neutrophils and a decrease in the number of lymphocytes and this indicates an inflammatory response (inflammation) that stimulates neutrophil cell production and accelerates lymphocyte apoptosis or may experience local inflammation or systemic inflammation [25]. Therefore NLR is used as a marker of inflammation and can also be used to assess the development of a complication in a patient.

In typhoid sufferers, the number of leukocyte cells decreases because *Salmonella Typhi bacteria* secrete exogenous pyrogenic endotoxins in the form of lipopolysaccharides which stimulate macrophages to activate white blood cells, namely neutrophils when neutrophils are in the bloodstream and reach the tissues. As a result, leukocytes in the bloodstream are reduced.

The limitation of this research is that the respondents with positive widal criteria. The weakness of the study was that not all respondents had positive Widal test results and if an IgG/IgM examination was carried out the results were also positive. The implication of this research is to add IgG/IgM examination information with NLR.

V. CONCLUSION

This study aims to find out the results of the Neutrophil-Lymphocyte Ratio with various expressions of the results of the Immunoglobulin G / Immunoglobulin M Test in typhoid fever sufferers at Haji General Hospital Surabaya. Based on the results of a study on typhoid fever sufferers conducted at Haji Hospital in East Java in 2023, it can be concluded that the average result of the Neutrophil-Imphocyte Ratio was 4.43% with a median of 2,85. The supporting examination for the diagnosis of typhoid fever carried out at Haji East Java Hospital in 2023 is an IgM/IgG Typhoid examination. In a sample of 28 patients, the first result was IgM positive IgG negative 29%, the second result was IgM negative IgG positive 11%, the third result was IgM positive IgG Positive 3%, and the fourth result IgM negative IgG negative 57%. So, IgG/IgM examination of NLR showed no significant association in patients with typhoid fever. This research can broaden scientific insights so that research can be developed further, for example through research on Tubex tf. Weaknesses of rapid IgG/IgM typhoid examination, weak positive results, and a line that does not appear too clearly so that it can cast doubt on the results of the examination.

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