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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 remains a major health concern, especially in tropical and subtropical countries such as Indonesia, where *Salmonella enterica* serovar Typhi continues to cause significant morbidity. The clinical diagnosis of typhoid fever is often supported by serological tests, including Immunoglobulin M (IgM) and Immunoglobulin G (IgG), and hematological parameters such as the Neutrophil-Lymphocyte Ratio (NLR), which reflects systemic inflammation. This study aims to assess the association between IgM/IgG expression and NLR in patients with confirmed typhoid fever. A descriptive observational study was conducted at the Cito Laboratory of Haji General Hospital, East Java, from December 2022 to April 2023. Twenty-eight patients with confirmed typhoid fever, selected through purposive sampling based on positive Widal criteria, were included in the analysis. The Typhoid IgG/IgM rapid immunochromatographic test was used to determine serological profiles, while the NLR was calculated using complete blood counts obtained via Fluorescent Flow Cytometry with a hematology analyzer. The results showed 29% of patients were IgM positive, 11% IgG positive, 3% both IgM and IgG positive, and 57% negative for both. The average NLR was 4.43, with a median of 2.85. Despite elevated NLR values, the study found no significant correlation between IgM/IgG expression and NLR, indicating that NLR may have limited diagnostic relevance for typhoid fever in this context. In conclusion, while serological testing remains vital in diagnosing typhoid fever, the NLR alone may not serve as a reliable marker of infection severity. Future studies are encouraged to explore additional biomarkers and compare them with serological responses for enhanced diagnostic accuracy.

**INDEX TERMS** Typhoid Fever, Immunoglobulin M, Immunoglobulin G, Neutrophil-Lymphocyte Ratio, Inflammatory Biomarkers

## I. INTRODUCTION

Typhoid fever remains a significant public health burden globally, particularly in tropical and subtropical regions such as Indonesia, where the disease is endemic. The causative agent, *Salmonella enterica* serovar Typhi, is a Gram-negative bacterium that can survive in contaminated water, soil, and food, allowing for widespread transmission in regions with inadequate sanitation [1]-[3]. In Indonesia, the incidence of typhoid fever is estimated to range between 350–850 cases per 1,000 population with a prevalence of 1.6% annually [4]. Surveillance data from the Surabaya Health Office revealed that typhoid fever constituted the second most common digestive disorder reported in 2019, accounting for 14.82% of cases [5].

The diagnosis of typhoid fever typically relies on serological and hematological investigations. Standard diagnostic tests include the Widal test, complete blood count (CBC), and serological detection of Immunoglobulin M (IgM) and Immunoglobulin G (IgG) antibodies against *S. typhi*. More recent diagnostic innovations include the Tubex TF test, Typhidot test, and enzyme-linked immunosorbent assays (ELISA), which aim to improve sensitivity and specificity [6]-[8]. While the Widal test remains widely used in resource-limited settings, its limitations due to cross-reactivity and low sensitivity have been well documented.

Antibody responses in typhoid fever follow a characteristic pattern: IgM antibodies emerge during the acute phase, while IgG antibodies become detectable during convalescence or reinfection [12],[13]. Serological detection of IgG/IgM using rapid immunochromatographic tests offers a more specific, albeit qualitative, assessment of *S. typhi* infection and can distinguish between primary and secondary infections [14]-[16].

In addition to serological markers, the Neutrophil-to-Lymphocyte Ratio (NLR) has gained attention as an accessible, cost-effective hematological marker for systemic inflammation and infection severity [17]. NLR represents the balance between innate (neutrophils) and adaptive

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(lymphocytes) immune responses and has been associated with prognosis in various infectious diseases [18], [19]. However, the clinical utility of NLR in typhoid fever remains poorly defined, with limited studies assessing its correlation with serological markers such as IgM and IgG levels [20].

The existing literature lacks integrative approaches that assess the relationship between immunoglobulin expression and NLR values in typhoid patients. Furthermore, while serological and hematological assessments are commonly performed independently, their combined diagnostic and prognostic potential is not yet fully elucidated. This research addresses that gap by examining the association between IgG/IgM expression and NLR in typhoid fever patients at Haji General Hospital, Surabaya.

The objective of this study is to evaluate whether there is a significant relationship between the IgG/IgM serological profile and the NLR among typhoid fever patients. This study contributes to the existing body of knowledge by:

1. Providing an integrated analysis of serological and hematological parameters in typhoid diagnosis;
2. Evaluating the diagnostic accuracy and reliability of rapid IgG/IgM testing in conjunction with NLR values;
3. Exploring the potential use of NLR as an adjunct inflammatory marker in assessing disease progression or severity in typhoid fever.

This article is structured as follows: Section II outlines the research methodology, including study design, data collection, and analytical techniques. Section III presents the findings of the IgG/IgM and NLR assessments. Section IV discusses the implications of the findings, compares them with previous literature, and outlines limitations. Finally, Section V presents the conclusion and suggests avenues for future research.

## II. METHOD

This study employed a descriptive observational design, aimed at exploring the association between Immunoglobulin G (IgG) and Immunoglobulin M (IgM) expression with the Neutrophil-to-Lymphocyte Ratio (NLR) in patients diagnosed with typhoid fever. The study was conducted at the Cito Laboratory of Haji General Hospital, East Java Province, Indonesia, over a period of five months, from December 2022 to April 2023.

### A. STUDY DESIGN AND SETTING

As an observational and cross-sectional analysis, this study focused on collecting data without influencing the natural course of disease. This design was selected to enable the evaluation of serological and hematological profiles in real-world clinical scenarios. The study site, Haji General Hospital, is a public tertiary referral hospital in Surabaya, East Java, which regularly receives patients with infectious diseases, including typhoid fever.

### B. STUDY POPULATION AND INCLUSION CRITERIA

The target population comprised adult patients clinically diagnosed with typhoid fever and confirmed through serological testing (Widal test) during the study period. The inclusion criteria were as follows:

1. Patients aged 18 years and above
2. Diagnosed with typhoid fever based on positive Widal test results,
3. Underwent both IgG/IgM rapid test and complete blood count (CBC) testing,
4. Provided written informed consent for participation.

Patients with comorbid infections or immunosuppressive conditions (e.g., HIV, cancer, or autoimmune disorders) were excluded to prevent confounding immune response interpretations.

### C. SAMPLING TECHNIQUE AND SAMPLE SIZE

The sampling method was purposive (selective) sampling, where subjects were selected based on the predefined inclusion criteria. This non-probability method was chosen due to the specificity of diagnostic criteria required. A total of 28 patients who met all inclusion criteria were enrolled. Although non-randomized, the selected sample reflects a typical clinical representation of typhoid fever cases in the setting.

### D. IgG/IgM RAPID SEROLOGICAL TESTING

Detection of anti-*Salmonella typhi* antibodies was performed using a Typhoid IgG/IgM Rapid Test Cassette, employing the immunochromatographic assay principle. This qualitative test detects antibodies in patient serum or plasma and distinguishes between IgM (indicative of acute infection) and IgG (suggestive of past or secondary infection). The procedure included the following steps:

1. A drop of serum was applied to the sample well of the cassette,
2. Followed by one drop of buffer solution,
3. The test result was interpreted within 10–15 minutes.

The test membrane contains anti-human IgM and anti-human IgG lines coated on specific regions (labeled M and G respectively), while the control line (C) validates the assay. If red lines appeared in both test and control regions, the result was considered valid. Absence of a control line rendered the test invalid and necessitated retesting [21], [22].

### E. HEMATOLOGICAL EXAMINATION AND NLR CALCULATION

A complete blood count (CBC) was performed to determine neutrophil and lymphocyte levels, from which the NLR was derived. Venous blood (3 mL) was collected from each participant using an EDTA vacutainer tube and processed immediately using a hematology analyzer equipped with fluorescent flow cytometry. The flow cytometry method involves directing a focused laser beam at blood cells in a fluid stream, enabling light scattering and fluorescence signals to be recorded by detectors. These signals provide detailed cell type differentiation, including absolute neutrophil and lymphocyte counts [23], [24].

The NLR was calculated using the following formula:
NLR=Absolute Neutrophil CountAbsolute Lymphocyte Co unt\text{NLR} = \frac{\text{Absolute Neutrophil Count}} {\text{Absolute Lymphocyte Count}} NLR = Absolute Lymphocyte CountAbsolute Neutrophil Count
Reference ranges for NLR were considered normal between 0.78 and 3.53, based on previously published clinical standards [25].

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### F. DATA PROCESSING AND ANALYSIS

All data obtained were tabulated and subjected to descriptive statistical analysis using Microsoft Excel. Categorical data, such as IgG/IgM test results, were expressed as frequencies and percentages. Numerical data, including NLR values, were presented as means, medians, standard deviations, minimum, and maximum values. No inferential or multivariate statistical tests were conducted, as the primary objective of this study was to descriptively explore potential associations, rather than to establish causal relationships.

### G. ETHICAL CONSIDERATIONS

The study was conducted following ethical principles as outlined in the Declaration of Helsinki. Ethical approval was obtained from the Health Research Ethics Committee of Haji General Hospital, Surabaya. All participants provided informed consent before inclusion in the study, and confidentiality was maintained by anonymizing patient data.

## 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).

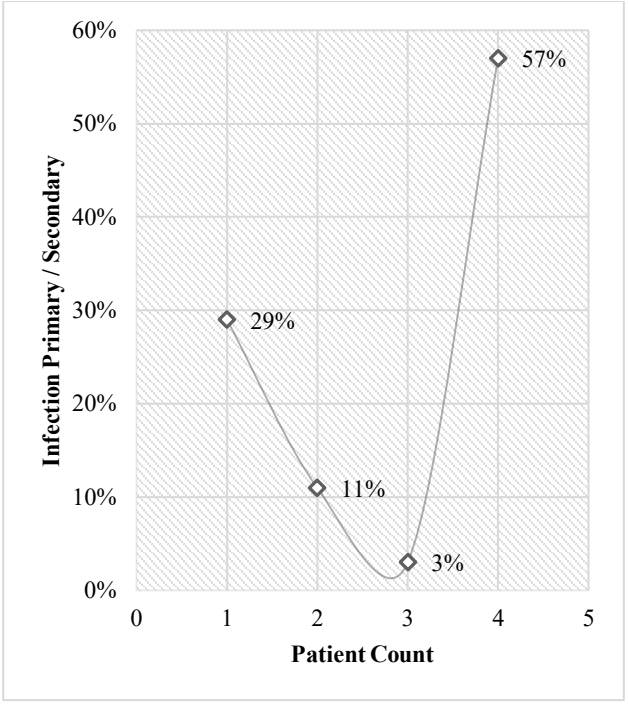


FIGURE 1. **Typhoid IgG/IgM Examination Expression Results.**

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 |

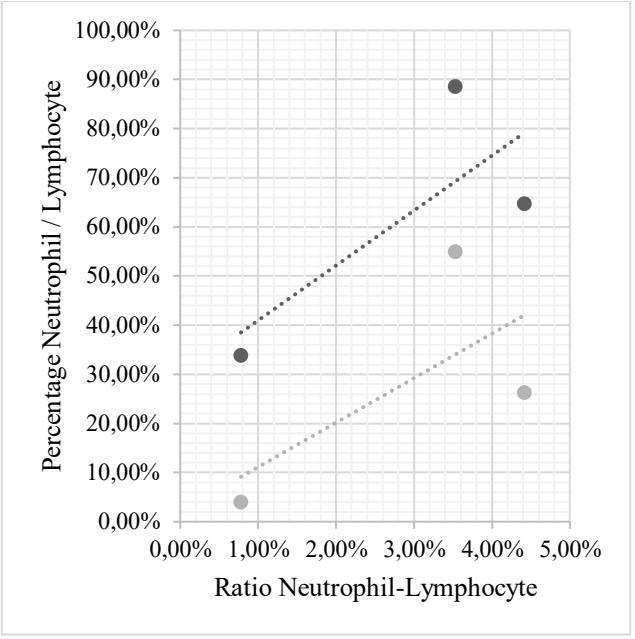


FIGURE 2. **NLR (Neutrophil –Lymphocyte Ratio) Average Result Value of Typhoid Fever Patients.**

## IV. DISCUSSION

### A. INTERPRETATION OF RESULTS

The primary objective of this study was to examine the association between Typhoid IgG/IgM serological expressions and the Neutrophil-to-Lymphocyte Ratio (NLR) in patients diagnosed with typhoid fever. Among the 28 participants, 29% demonstrated positive IgM responses indicating acute or primary infection, 11% showed IgG positivity suggestive of previous or secondary infection, 3% had simultaneous IgG and IgM positivity, and 57% were negative for both. Meanwhile, the average NLR value was calculated at 4.43, with a median of 2.85. These values fall slightly above the standard reference range for NLR in healthy individuals, which is generally considered to be 0.78–3.53 [26].

A key interpretation of this result is the trend of elevated NLR values in patients with active immune responses, as represented by IgM or IgG positivity. Neutrophils are known to increase rapidly in acute bacterial infections, while lymphocytes tend to decrease due to immunosuppression or apoptosis during infection, leading to an elevated NLR. However, in this particular cohort, despite some elevation in

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NLR, the data analysis did not demonstrate a statistically significant association between IgG/IgM expression and NLR levels. This lack of significance may be due to the limited sample size and the natural variability in immune response during the typhoid infection spectrum.

Moreover, the IgG/IgM test using immunochromatographic rapid methods remains qualitative and does not provide antibody titers, which restricts deeper quantitative interpretation. The 3% of patients exhibiting both IgM and IgG positivity may represent cases of reinfection or subacute phases, highlighting the dynamic antibody response to *Salmonella typhi*. In such instances, the immune system activates both humoral components simultaneously, which theoretically could also cause more pronounced inflammatory hematological changes. Nonetheless, the findings of this study do not support the use of NLR as a standalone inflammatory marker that can consistently reflect the serological phase of typhoid fever.

Another consideration involves the 57% of patients who were negative for both IgG and IgM yet were clinically confirmed with typhoid fever based on Widal test results. This finding raises concerns regarding the sensitivity of rapid serological testing in early or window phases of infection and underscores the limitations of antibody-based diagnostics in detecting recent infections when antibodies are yet to develop in sufficient quantities.

The range of NLR values in this study (min 0.62, max 22.12) further illustrates the interindividual variability in host immune responses. While some patients showed elevated neutrophil counts consistent with acute infection, others had normal leukocyte distributions. These observations suggest that NLR must be interpreted in conjunction with clinical features, disease duration, and other biomarkers to avoid misleading conclusions.

### *B. COMPARISON WITH OTHER STUDIES*

The results of this study are in partial agreement with previous research on the role of NLR in infectious diseases. A study by Rizky et al. reported a median NLR of 3.97 in suspected typhoid fever patients, a value that was comparable to our median of 2.85 and average of 4.43 [27]. Their study similarly concluded that NLR, although indicative of inflammation, may not serve as a reliable standalone diagnostic marker due to its overlap with other febrile illnesses.

Furthermore, Nur Almatin et al. investigated NLR as a marker in diabetic ulcer patients and reported average NLR values around 3.62, which, while elevated, did not have consistent diagnostic power across patient subgroups [28]. In line with this, our findings suggest that although NLR tends to rise in infectious states, its clinical relevance is limited without complementary diagnostic tools such as serology or molecular testing.

In malaria research, Philipose and Umashankar found that an NLR threshold of 3.9 was predictive of disease severity, particularly in complicated cases [29]. However, such thresholds cannot be directly extrapolated to typhoid fever, given the differences in pathogen biology and host immune responses. While both diseases cause systemic inflammation, the cytokine profiles and immunopathological mechanisms differ significantly.

Studies in other systemic infections such as COVID-19 have demonstrated stronger correlations between elevated NLR and disease severity. For instance, Liu et al. found that NLR was significantly higher in severe COVID-19 patients, reinforcing the marker's value in conditions with intense neutrophil activation and lymphocyte suppression [30]. However, in the context of typhoid, particularly in mild-to-moderate presentations, the NLR changes may not be sufficiently discriminatory, as reflected in our results.

Additionally, Forget et al. highlighted the broad variability in normal NLR values depending on demographic, physiological, and clinical variables [31]. This further emphasizes the need for caution when interpreting NLR values in small heterogeneous populations such as ours.

One particularly relevant comparative study by Ella et al. analyzed IgG/IgM and NLR parameters among suspected typhoid patients and concluded that while each test has diagnostic value, combining them does not significantly enhance accuracy unless supported by quantitative titer data or molecular confirmation [32]. This finding echoes the current study's conclusion that rapid tests and hematological indices need to be supplemented with more robust diagnostic modalities for accurate clinical decisions.

### *C. LIMITATIONS AND IMPLICATIONS*

This study has several limitations that may have influenced the outcomes and interpretations. First and foremost, the sample size of only 28 patients limits the generalizability and statistical power of the findings. A larger sample would enable subgroup analysis, stratification by infection stage, and more robust inferential testing.

Secondly, the non-randomized purposive sampling technique introduces selection bias. Patients were selected based on positive Widal criteria, which itself has known limitations in specificity and sensitivity [33]. The dependence on Widal for initial inclusion may have led to misclassification, particularly in patients with non-typhoidal febrile illnesses who nonetheless tested positive due to cross-reactive antibodies.

Another important limitation lies in the qualitative nature of the IgG/IgM test. Quantitative antibody titers would provide greater diagnostic precision and allow correlation with NLR levels across infection phases. The binary results (positive/negative) offered limited depth for analyzing immune response kinetics. In future studies, the use of ELISA or PCR-based diagnostics could provide enhanced sensitivity and enable definitive association between infection stage and inflammatory markers.

Additionally, the study did not control for co-infections, nutritional status, or prior antibiotic use, all of which can significantly influence leukocyte profiles and antibody production. For instance, malnutrition can suppress lymphocyte proliferation and skew NLR values, while antibiotics may blunt immune responses prior to testing.

The clinical implication of this study is that NLR, while simple and cost-effective, should not be used in isolation for diagnosing or staging typhoid fever. Its utility is best realized when interpreted alongside serological or molecular diagnostics, especially in resource-limited settings where laboratory capacity is constrained. The current findings contribute to the growing body of evidence that advocates

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for multimodal diagnostics, integrating rapid testing with hematological markers for better clinical decision-making.

Moreover, this study underscores the need for standardization of NLR reference ranges in different infectious diseases. Without clear thresholds adapted to specific pathogens and patient populations, the clinical value of NLR remains uncertain. Larger multi-center studies could help define context-specific cutoffs and validate the utility of NLR in endemic regions.

Lastly, the findings highlight the importance of public health education on early diagnosis and proper sanitation. Since typhoid remains a preventable illness, improving hygiene practices and access to clean water remain the most effective long-term strategies for disease control.

## V. CONCLUSION

This study was conducted to evaluate the association between Immunoglobulin G (IgG) and Immunoglobulin M (IgM) expression and the Neutrophil-to-Lymphocyte Ratio (NLR) in patients diagnosed with typhoid fever at Haji General Hospital, Surabaya. The main objective was to determine whether variations in humoral immune responses, as detected through rapid serological testing, corresponded with changes in hematological inflammatory markers—specifically NLR values. A total of 28 patients who met the inclusion criteria based on positive Widal test results were selected through purposive sampling. These patients underwent both serological testing using the IgG/IgM rapid immunochromatographic method and hematological testing using Fluorescent Flow Cytometry for neutrophil and lymphocyte quantification. The findings revealed that 29% of patients were IgM-positive, indicating acute or primary infection; 11% were IgG-positive, suggesting secondary or past infection; 3% were positive for both IgM and IgG, potentially reflecting reinfection or a transition phase; and 57% were negative for both antibodies, possibly due to early-stage infection or diagnostic limitations. The mean NLR value among the patient cohort was 4.43, with a median of 2.85—slightly above the standard reference range of 0.78–3.53 for healthy individuals. Despite these variations, statistical analysis demonstrated no significant correlation between NLR levels and the serological expression of IgG/IgM antibodies. This suggests that while NLR may be elevated in some cases, it does not consistently reflect the serological stage or severity of typhoid fever. These findings imply that NLR, although a cost-effective and widely accessible biomarker of systemic inflammation, may have limited diagnostic utility in isolation for typhoid fever. It is recommended that future studies involve larger, randomized populations and incorporate more sensitive and quantitative diagnostic methods such as ELISA, PCR, or Tubex TF to validate and extend these results. Further investigation into combining NLR with other hematological or biochemical markers may offer a more comprehensive diagnostic approach. Moreover, longitudinal tracking of NLR over the disease course could help determine its prognostic relevance in typhoid fever management.

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## DATA AVAILABILITY

No datasets were generated or analyzed during the current study.

## AUTHOR CONTRIBUTION

All authors contributed significantly to the conception, design, data collection, analysis, and interpretation of the study. Nur Zerlinda led the laboratory work, data collection, and manuscript drafting. Evy Diah Woelansari provided supervision, critical revision, and contributed to data interpretation and methodology refinement. Anita Dwi Anggraini assisted in literature review, validation of results, and overall manuscript review. All authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

## DECLARATIONS

### *ETHICAL APPROVAL*

The authors declare that this manuscript is original and has not been previously published or submitted elsewhere. Ethical approval for this study was obtained from the Health Research Ethics Committee of Haji Hospital, Surabaya, and written informed consent was secured from all participants. The authors report no conflicts of interest in relation to this research and confirm that there were no financial or commercial relationships that could be construed as potential competing interests.

### *CONSENT FOR PUBLICATION PARTICIPANTS.*

Consent for publication was given by all participants

### *COMPETING INTERESTS*

The authors declare no competing interests.

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