

Lymphocyte Cell Count Profile based on Widal Titer On Pediatric Typhoid Fever

Dian Nurmansyah^{1,2}, Syihab Fayumi³, Shalehatun Nisa², Puspawati^{2,4}
Maya Sasmitha², Musyirrah Mudzakkir² Muhammad Arsyad²

¹ Program Studi Doktor Kedokteran dan Ilmu Kesehatan, Fakultas Kedokteran Kesehatan Masyarakat dan Keperawatan, Universitas Gadjah Mada, Indonesia

² Program Studi Diploma III Analis Kesehatan, Fakultas Ilmu Kesehatan dan Sains Teknologi, Universitas Borneo Lestari, Indonesia

³ Departemen Anak, Rumah Sakit Umum Daerah Ratu Zalecha, Indonesia

⁴ Departemen Patologi Klinik, Rumah Sakit Umum Daerah Ratu Zalecha, Indonesia

Email: *diannurmansyah@mail.ugm.ac.id

Article Info

Article history :

Received : August 4th 2025

Revised : September 29th 2025

Accepted : September 30th 2025

Keyword :

Lymphocyte count;

Widal titer;

Pediatric typhoid fever;

Salmonella typhi

ABSTRACT

Typhoid fever remains a significant public health concern in Indonesia, which has the third-highest global case rate, with 350–810 cases per 100,000 people and a fatality rate of 3.1–10.4%, primarily due to delayed diagnosis and treatment. Children aged 5–14 years are most affected, with transmission occurring via contaminated food, water, or poor hygiene. *Salmonella typhi* invades intestinal immune tissues (Peyer's patches), triggering responses from T and B lymphocytes, though bacterial endotoxins can suppress bone marrow function, altering leukocyte levels. This study analyzed the relationship between Widal titer and lymphocyte counts in pediatric typhoid patients using a cross-sectional design. Data from 526 patients at Graha Medika Martapura Clinic and Ratu Zalecha Hospital (January 2023–February 2025) were analyzed statistically, with inclusion criteria of Widal titer $\geq 1/320$ and complete blood count results. Results showed 18.8% of patients had elevated lymphocytes, 79.3% had normal levels, and 1.9% exhibited lymphocytopenia. Higher Widal titers (1/640) correlated with lower lymphocyte counts (15.8% elevated vs. 23.0% at 1/320), suggesting immune suppression mediated by IL-6 through specific signaling pathways. Paradoxically, some cases showed lymphocytosis (18.8%), likely due to cytokine-induced immune modulation. Statistical analysis revealed a minimal correlation ($R^2=0.006$), indicating Widal titer explains only 0.6% of lymphocyte variation. These findings demonstrate that while Widal titer has limited predictive value for lymphocyte changes, immune response mechanisms, particularly involving IL-6, play a critical role in typhoid fever's hematological manifestations.

INTRODUCTION

Indonesia remains the third-highest country in the world for typhoid fever cases. The number of cases tends to increase annually. Approximately 350–810 cases per 100,000 people are reported in Indonesia, with a fatality rate of 3.1–10.4%, primarily due to delayed diagnosis and treatment (Mitha, Setyowati, Pratiwi, & Utama, 2023). The highest prevalence of typhoid fever (1.60%) occurs in children aged 5–14 years. Transmission of typhoid fever

How to cite:

Nurmansyah, D., Fayumi, S., Nisa, S., Puspawati, P., Sasmitha, M., Mudzakkir, M., & Arsyad, M. (2025). Lymphocyte Cell Count Profile based on Widal Titer On Pediatric Typhoid Fever. *Jurnal Analis Medika Biosains (JAMBS)*, 12(2). doi:<https://doi.org/10.32807/jambs.v12i2.480>

occurs through various routes, commonly known as the 5Fs (Food, Fingers, Fomites, Flies, and Feces). If a person rarely washes their hands before and after eating, poor personal hygiene allows *Salmonella typhi* bacteria to easily enter the body through the oral route (Lestari, Sukrama, & Nurmansyah, 2019).

Salmonella typhi enters the body via contaminated food or water. After passing through the stomach, the bacteria penetrate the intestinal wall and invade the gut's immune defense tissue, known as Peyer's patches. There, the bacteria are recognized by immune cells called Antigen-Presenting Cells (APCs) and combated through phagocytosis. The immune response then continues with T and B lymphocytes, white blood cells that play a critical role in fighting infections (Nurmansyah & Normaidah, 2020). Changes in leukocyte (white blood cell) levels in pediatric typhoid patients occur due to bone marrow suppression caused by endotoxins released by *Salmonella typhi* (Samatra, et al., 2017). Consequently, inflammation develops as part of the immune response (Khairunnisa, Hidayat, & Herardi, 2020). A study by Ekasari & Saroh (2021) found a correlation between Widal titer and lymphocyte count in typhoid patients. The higher the Widal titer, the lower the lymphocyte count, suggesting a suppressed immune response in severe cases.

MATERIALS/METHOD

This study employed an observational analytic design with a cross-sectional approach. The research was conducted at Graha Medika Martapura Clinic, and Ratu Zalecha General hospital at Banjar Regency, in April 2025. A total of 526 secondary data samples from pediatric typhoid patients (January 2023–February 2025) were included, selected based on the following criteria: Widal titer $\geq 1/320$ and complete blood count (CBC) results obtained simultaneously. Samples were collected using purposive sampling. Data analysis was performed statistically using SPSS version 27, with cross-tabulation and simple linear regression tests.

RESULTS AND DISCUSSION

The study results revealed that among the patients, 99 cases (18.8%) showed elevated lymphocyte counts, 417 cases (79.3%) had normal lymphocyte levels, and 10 cases (1.9%) demonstrated reduced lymphocyte counts

Table 1. Frequency of patients based on result of lymphocyte count

Category	Frequency [N]	Percentage (%)
Limfositosis	99	18,8 %
Normal	417	79,3 %
Limfopenia	10	1,9 %

Table 2. Crosstabulation beetwen widal titer and lymphocyte count on pediatric patients with typhoif fever

Widal Titer	Lymphocytosis		Normal		Limphopenia	
	N	%	N	%	N	%
1/320	51	23,0	169	76,1	2	0,9
1/640	48	15,8	248	81,6	8	2,6

Table 2 reveals that among 222 patients with a Widal antigen O titer of 1/320, 51 cases (23.0%) demonstrated elevated lymphocyte counts, 169 cases (76.1%) showed normal lymphocyte levels, and only 2 cases (0.9%) exhibited reduced counts. Meanwhile, in the 304 patients with a higher titer of 1/640, 48 cases (15.8%) had elevated lymphocytes, 248 cases

(81.6%) maintained normal levels, while 8 cases (2.6%) displayed decreased lymphocyte counts, indicating a progressive relationship between antibody titer levels and lymphocyte response pattern.

Table 3. Statistical analysis using Linear Regression between Widal titer and Lymphocyte count

Variable tested	R value	R Square
Widal Titer – Lymphocyte count	.079 ^a	.006

Table 3 reveals an R Square value of 0.006 (0.6%), indicating that the independent variable (Widal titer) accounts for only 0.6% of the variation in the dependent variable (leukocyte count). Meanwhile, Table 2 demonstrates that the majority of patients (76.1%) exhibited normal lymphocyte counts. Lymphocytes, constituting 25-35% of total leukocytes, serve as key components of the adaptive immune system (Salerno-Goncalves, Chen, Bafford, & Sztein, 2024). These cells specifically recognize antigens, enabling them to distinguish between self and foreign components. During typhoid infection, the innate immune response initially activates. If ineffective, the adaptive immune system is subsequently engaged, though this process requires more time. Notably, in early-stage typhoid fever, lymphocyte activation remains suboptimal, frequently resulting in normal lymphocyte levels (Firiyani, Pauzi, & Jiwantoro, 2021)

The study revealed that 1.9% of pediatric typhoid patients developed lymphocytopenia, which can be attributed to concurrent infections impairing bone marrow function, compromised host immunity, and direct *Salmonella typhi* invasion. The observed lymphocyte reduction in this study is partially mediated by IL-6, which inhibits lymphopoiesis through lymphocyte inflammation and exerts direct cytotoxic effects on progenitor cells, while also selectively inducing macrophages to produce IL-6, thereby triggering lymphocyte apoptosis and leading to decreased lymphocyte counts during *Salmonella typhi* infection (Kheladi, et al., 2022; Anggraini, 2023). The mechanism of IL-6-induced lymphocytopenia begins when *Salmonella typhi* enters the body: lipopolysaccharides (LPS) activate Toll-like receptor 4 (TLR4) for early infection detection, while flagellin stimulates TLR5, with both receptors initiating NF-κB signaling to induce IL-6 production (Eric, et al., 2025; Yin, et al., 2020). Research by (Zhou, et al., 2022) and (Leisman, et al., 2020) demonstrate an inverse relationship between IL-6 levels and T-cell counts, indicating that elevated IL-6 reduces lymphocyte numbers by inducing GSDME-mediated pyroptosis of T-cells while simultaneously blocking lymphopoiesis through enhanced progenitor cell expansion and suppression of lymphoid options, ultimately resulting in lymphocytopenia in pediatric typhoid patients.

However, in some cases, lymphocyte counts may paradoxically increase. Bone marrow suppression frequently occurs in typhoid fever patients, which can lead to elevated lymphocyte levels—a condition commonly referred to as lymphocytosis (Alugupalli, 2024; Cheng, et al., 2022; Firiyani, Pauzi, & Jiwantoro, 2021).

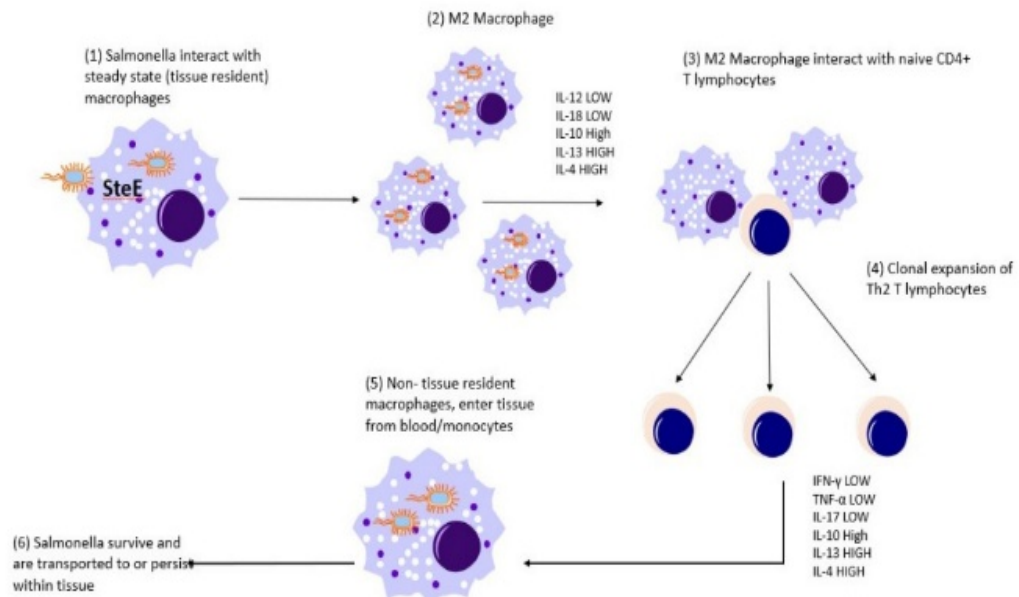


Figure 1. Lymphocytosis mechanism on typhoid fever (Alugupalli, 2024)

The illustration shown in Fig.1 demonstrates how *Salmonella typhi* bacteria are engulfed by immune cells called macrophages. Following phagocytosis, these macrophages release effector proteins like SteE, which shift their role from infection-combating (pro-inflammatory) to immune response-suppressing (anti-inflammatory). This phenotypic switch triggers macrophages to secrete cytokines that modulate other immune cells—particularly lymphocytes. These cytokines selectively inhibit the development of infection-fighting lymphocyte subsets while promoting immunosuppressive lymphocyte populations. Consequently, bacterial clearance is impaired, and uncontrolled immune cell proliferation may occur. This mechanism explains why lymphocyte counts can paradoxically increase during active infection (Foster, et al., 2021; Gonzalez, et al., 2019).

Table 3 revealed no significant correlation between Widal titer and lymphocyte counts in pediatric typhoid patients. Simple linear regression analysis indicated that Widal titer accounted for merely 0.6% of lymphocyte count variation. Nevertheless, these findings align with (Ekasari & Saroh, 2021) study, demonstrating an inverse relationship between Widal titers and lymphocyte levels - higher titers correlated with decreased lymphocyte numbers. Elevated Widal titers reflect humoral immune responses to *Salmonella typhi* antigens, which may trigger cytokine storms (particularly IL-6). This cytokine can impair leukocyte recovery, compromise immune function, and potentially increase mortality risk (Zhou, et al., 2022)(Zhou et al., 2022; Das et al., 2024), likely explaining the observed lymphocytopenia in high-titer patients.

CONCLUSIONS

The study findings revealed that pediatric typhoid patients had a mean lymphocyte count of 35.78. Additionally, the research identified relative lymphocytosis in approximately 18.8% of cases, characterized by increased lymphocyte percentage despite an overall decrease in total leukocyte count.

ACKNOWLEDGEMENTS

The authors extend their sincere gratitude to RSUD Ratu Zalecha Hospital and Graha Mandiri Clinic for their invaluable support and facilities, which were instrumental in the successful and timely completion of this research study.

REFERENCE

- Alugupalli, K. (2024). TLR4 Ligands in Typhoid Vi Polysaccharide subunit vacciness contribute to Immunogenicity. *ImmunoHorizons*, 29-34.
- Anggraini, D. N. (2023). Aspek Klinis dan Pemeriksaan Laboratorium Demam Tifoid. *Jurnal Kesehatan Tambusai*, 2641 - 2647.
- Cheng, Y., wang, Y., Wang, X., Jiang, Z., Zhu, L., & Fang, S. (2022). Neutrophil - to Lymphocyte ratio, Platelet to Lymphocyte ratio and Monocyte to Lymphocyte ratio in Depression : an updated systematic review and meta analysis . *Frontiers in Psychiatry*.
- Ekasari, Y., & Saroh, D. (2021). Hubungan titer widal dengan jumlah limfosit pada kasus demam tifoid di wilayah kerja puskesmas Sawoo. *Jurnal Analis Laboratorium Medik*, 73-74.
- Eric, M. B., Netongo, P., Kamden, S., Nzuno, C., Tcoutang, A., Berenger, T., . . . Mbacham, W. (2025). Stress mediating inflammatory cytokine profilin reveals unique patterns in malaria and typhoid fever patients. *PloS ONE*, 1-16.
- Firiyani, F., Pauzi, I., & Jiwantoro, Y. (2021). Hubungan titer widal dengan jumlah limfosit dan trombosit pada pasien demam tifoid di Puskesmas Gunungsari Lombok Barat. *Jurnal Analis Medika Biosains (JAMBS)*.
- Foster, N., tang, Y., BAchieri, A., Geng, S., Jiao, X., & Barrow, P. (2021). Revisiting persitent Salmonella infection and the carrier state : What do we know ? *Pathogens*.
- Gonzalez, Kurtz, F., Bauer, D., Hitt, R., Fitch, Wetzel, A., . . . Gunna. (2019). Establishment of Chronic typhoif Infection in a mouse carriage model involves a type 2 immune shift adn T and B cell recruitment to the Gallblader. *MBio*.
- Khairunnisa, S., Hidayat, E., & Herardi, R. (2020). Hubungan jumlah leukosit dan persentase limfosit terhadap tingkat demam pada pasien anak dengan demam tifoid di RSUD Budhi Asih Tahun 2018-Oktober. *Seminar Nasional Riset Kedokteran (SENSORIK)* (pp. 60-69). Jakarta: UPN Veteran Jakarta.
- Kheladi, M., Sameni, F., Yahyazade, S., Radandish, M., Owlia, P., Bagheri, N., . . . Aghaei, F. (2022). Covid-19 and the potetial of Janus Family kinase (JAK) pathway inhibiton: A Novel treatmenr strategy. *Frontiers in Medicine*.
- Leisman, D., Ronner, L., Pinnoti, R., Taylor, M., Sinha, P., Calfee, C., . . . Deutschman, C. (2020). Cytokine elevation in severe and critical COVID-19 : a rapid systematic review, meta-analysis ,and comparison with other inflammatory syndromes. *The Lancet Respiratory Medicine*, 1233-1244.
- Lestari, A. A., Sukrama, I. D., & Nurmansyah, D. (2019). The earthworm (*Lumbricus rubellus*) extract decreased aminotransaminasi enzyme level and number of bacterial colony in male rats infected with *Salmonella typhimurium*. *Biomedical and Pharmacological Journal*, 325-332.
- Mitha, B., Setyowati, E., Pratiwi, M., & Utama, L. (2023). Hubungan usia, jenis kelamin dan jumlah leukosit dengan durasi demam pada penderita demam tifoid anak di RSUD Kota Mataram tahun 2019-2021. *Cakrawala Medika: Journal of Health Sciences*, 131-137.

-
- Nurmansyah, D., & Normaidah. (2020). Review : Patogenesis dan Diagnosa Laboratorium Demam Tifoid. *Klinikal Sains : Jurnal Analisis Kesehatan*, 51-61.
- Salerno-Goncalves, R., Chen, H., Bafford, A. C., & Sztein, M. B. (2024). Epigenetic regulation in epithelial cells and innate lymphocyte responses to *S. Typhi* infection: insights into IFN- γ production and intestinal immunity. *Front. Immunol.*
- Samatra, D. P., GB, M. T., Sukrama, I. D., Dewi, N. W., Praja, R. K., & Nurmansyah, D. (2017). Extract of earthworms (*Lumbricus rubellus*) reduced malondialdehyde and 8-hydroxy-deoxyguanosine level in male wistar rats infected by salmonella typhi. *Biomedical and Pharmacology Journal*, 1765-1771.
- Yin, C., Liu, Z., Xian, H., Jiao, Y., Yuan, Y., Li, Y., . . . Jiao, X. (2020). Avra experts inhibition of Nf-KB pathway in its native salmonella serotype through supression of p-jnk and beclin-l molecules. *International Journal of Molecular Science*, 1-14.
- Zhou, X., Ye, G., Lv, Y., Guo, Y., Pan, X., Li, Y., . . . Lei, P. (2022). IL-6 drives T cell death to participate in lymphopenia in COVID-19. *International Immunopharmacology*.