

CORRELATION OF SEROLOGICAL MARKERS WITH HEMATOLOGICAL ALTERATION IN NS1 POSITIVE DENGUE PATIENTS

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Abstract

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Received on 2, OCT, 2025
Accepted on 20 Dec, 2025
Published on 24 Dec, 2025
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Dengue fever is caused from a viral infection from a mosquito bite that has serious impacts on the blood systems of the body, and the severity of the infection is different between first and second occurrences of the disease. As a result, features of these disease manifestations are important for fast, accurate, and efficient disease control. The current cross-sectional study aimed by observing the hematological changes,

and the changes were compared to hematological changes of serological markers (IgM and IgG) found in the blood of NS1 dengue positive patients. One hundred NS1 dengue positive patients were assessed. Kuwait Teaching Hospital Peshawar was and is the location of the study. The demographics, serological status, and hematological indices were captured and analyzed using SPSS V.27. A $p < 0.05$ was considered statistically significant. Of the study sample, 58 were male (58%) and 42 (42% of the sample) female, and the mean age was 29.1 (SD 8.9 years). The serological study found that for 42% of the study subjects, the dengue infection was primary while for the remaining 58%, the dengue infection was found to be a secondary infection. Hematological analysis presented that the majority of patients advanced thrombocytopenia (mean platelet count $103.5 \pm 45.8 \times 10^3/\mu\text{L}$) and leukopenia (mean WBC $3.3 \pm 1.3 \times 10^3/\mu\text{L}$), although red cell indices largely continued within normal

ranges. Proportional analysis recognized that secondary dengue infections were related with significantly inferior platelet (87.4 vs $125.9 \times 10^3/\mu\text{L}$) and WBC counts (3.0 vs $3.7 \times 10^3/\mu\text{L}$) associated to main infections. Association analysis further revealed a significant negative association between WBC count and both IgM ($r = -0.237$, $p = 0.018$) and IgG ($r = -0.324$, $p = 0.001$), as well as between lymphocyte count and both IgM ($r = -0.205$, $p = 0.041$) and IgG ($r = -0.279$, $p = 0.005$). Platelet amount also shows a statistically significant but weak negative association with both antibody markers.

Key words: Dengue Fever, hematological parameters, Serological markers.

Introduction:

Dengue is a major mosquito-borne viral infection that represents an important public health problem in tropical and subtropical regions. It is caused by dengue virus (DENV), a member of the genus *Flavivirus*, and is mainly transmitted by *Aedes aegypti* and *Aedes albopictus*. Dengue infection can range from a mild febrile illness to severe dengue associated with plasma leakage, bleeding, shock, and organ dysfunction. The clinical presentation may overlap with other febrile diseases, making early laboratory confirmation important for appropriate diagnosis and patient monitoring (Khan et al., 2020). Serological diagnosis of dengue commonly involves detection of nonstructural protein 1 (NS1) antigen and dengue-specific IgM and IgG antibodies. NS1 is released into the bloodstream during the early phase of infection and is therefore particularly useful for detecting acute dengue infection. IgM generally develops later during the acute phase, while IgG may indicate previous exposure or secondary infection. Because these markers appear at different stages of infection, their interpretation together with hematological parameters can provide useful information about the stage and progression of dengue (Chakraborty et al., 2024). NS1-positive patients are particularly important for studying early hematological changes because NS1 can be detected before a strong antibody response develops. The relationship between NS1 antigen and blood-cell abnormalities may be influenced by viral replication, immune response, infection history, and disease stage. A study conducted in Indonesia

demonstrated significant relationships between NS1 positivity and hematological parameters, particularly leukocyte and platelet counts, indicating that routine blood investigations may provide supportive information in NS1-positive dengue infection (Sunari et al., 2023). Thrombocytopenia is one of the most characteristic hematological abnormalities in dengue. Reduction in platelet count may result from impaired bone-marrow production, increased peripheral destruction, immune-mediated mechanisms, platelet activation, and increased platelet consumption. Platelet abnormalities may become more prominent during the critical phase and are therefore routinely monitored in dengue patients. Significant alterations in platelet count and platelet indices have been reported among dengue patients with different serological profiles (Shahila et al, 2022). Leukopenia is another common hematological finding in dengue infection. It may result from transient bone-marrow suppression, altered leukocyte production, and changes in the distribution of circulating white blood cells. Changes in lymphocyte and neutrophil counts may also occur during the course of infection. Hematological investigations have demonstrated that leukopenia and thrombocytopenia are frequently associated with laboratory-confirmed dengue infection (Ngim et al., 2021). The relationship between serological status and hematological alterations may vary according to the stage of dengue infection. Patients who are NS1 positive alone may demonstrate different hematological patterns from those who are simultaneously positive for NS1 and IgM. In particular, thrombocytopenia and leukopenia have been reported among NS1-only positive patients, while combined NS1 and IgM positivity may be associated with more pronounced platelet abnormalities (Bhattarai et al., 2023). Similar findings have shown that leukopenia may be more prominent in NS1-only patients, whereas thrombocytopenia may become more severe in patients with combined NS1 and IgM positivity (Tuladhar et al., 2024). Hematocrit, hemoglobin, and red blood cell parameters are also important in the laboratory assessment of dengue. An increase in hematocrit may occur because of plasma leakage and hemoconcentration during the critical

phase, whereas reductions in hemoglobin or hematocrit may occur because of bleeding, fluid administration, or other factors. A study investigating dengue viral load demonstrated a positive relationship between viral load and hematocrit and an inverse relationship between viral load and platelet count (Pathak et al., 2021). The association between NS1 and hematological abnormalities, however, is not always consistent. Differences may occur because of the timing of testing, disease severity, viral load, age, immune status, and whether the infection is primary or secondary. Research among adult dengue patients found that although liver enzyme abnormalities were associated with thrombocytopenia, NS1 antigen levels and leukopenia were not consistently associated with platelet reduction (Ramalingam et al., 2024). This indicates that dengue-related hematological changes are multifactorial and should not be interpreted on the basis of a single serological marker. Recent research has therefore emphasized the importance of evaluating multiple hematological parameters together with serological markers. Platelet count, WBC count, lymphocyte count, neutrophil count, hemoglobin, RBC count, and hematocrit may collectively provide a more comprehensive laboratory profile of dengue infection. Advanced hematological parameters have also been investigated for their potential role in dengue screening and prediction of platelet recovery (Juneja et al., 2025). In dengue-endemic regions such as Pakistan, investigating these relationships is particularly important because early diagnosis and monitoring are essential for reducing complications. Local studies have reported substantial thrombocytopenia and leukopenia among dengue patients and have demonstrated variations in hematological findings according to serological status (Anwar et al., 2022). Understanding the relationship between NS1 positivity and hematological alterations may therefore help clinicians recognize characteristic laboratory patterns during acute infection. Therefore, the correlation of serological markers with hematological alterations in NS1-positive dengue patients is an important area of investigation. Assessing NS1, IgM, and IgG in relation to platelet count, WBC count, differential leukocyte count,

hemoglobin, RBC count, and hematocrit may improve understanding of the hematological response to acute dengue infection. Such correlations may support early diagnosis, disease monitoring, identification of patients at increased risk of complications, and more effective clinical management of dengue patients (Sarkar et al., 2024).

Method and Material:

A descriptive cross-sectional study was conducted to determine the prevalence of hematological abnormalities and their correlation with serological markers among NS1-positive dengue patients during the acute phase of infection. The study was conducted at the Pathology Laboratory, Emergency Department, and main medical wards of Kuwait Teaching Hospital, Peshawar, over a period of six months. Patients aged 18–60 years with clinically suspected acute dengue infection and positive NS1 antigen results were enrolled after providing written informed consent. Patients with a previous history of dengue infection, other co-infections, severe infections, significant comorbidities affecting hematological parameters, pregnancy or breastfeeding, and those unwilling to participate were excluded. Approximately 5 mL of venous blood was collected aseptically into sterile EDTA-containing tubes. Each sample was labeled with a unique identification number, collection date, and time and transported to the laboratory within two hours of collection. Samples were maintained at approximately 4°C until analysis. Demographic and clinical information was collected using a pre-structured questionnaire, while laboratory results were systematically recorded in a computerized database. Dengue NS1 antigen and dengue-specific IgM and IgG antibodies were detected using an immunochromatographic test (ICT) according to the manufacturer's instructions. Where applicable, IgM and IgG antibodies were confirmed using enzyme-linked immunosorbent assay (ELISA). The serological results were classified according to NS1, IgM, and IgG positivity. Hematological parameters, including red blood cell (RBC) count, white blood cell (WBC) count, lymphocyte count, and platelet count, were analyzed using an automated Sysmex hematology analyzer according

to standard operating procedures. The sample size was estimated using Daniel's formula, $n = Z^2pq/d^2$, based on the expected prevalence, confidence level, and margin of error. Ethical approval was obtained from the relevant institutional ethical committee, and confidentiality of participants was maintained throughout the study. Data were analyzed using appropriate statistical software. Continuous variables were summarized as mean $\pm$ standard deviation, while categorical variables were presented as frequencies and percentages. Independent-samples t-test was used to compare hematological parameters between two serological groups, while one-way ANOVA followed by Tukey's post-hoc test was applied for comparisons among more than two groups. Pearson's correlation coefficient was used to determine the strength and direction of associations between IgM/IgG serological markers and hematological parameters, including RBC, WBC, lymphocyte, and platelet counts. A p -value <0.05 was considered statistically significant.

Result:

Demographic Characteristics

Table # 01: Shows a foundational overview of the 100 patients. Out of 100 patients 58 were males (58%) and 42 were females (42%). The majority of patients were (87%) which was between 18 and 45 years old. The main single group was young adults aged 18-30 years (52%), shadowed by the 31-45 years group (35%). Only 13% of patients were among 46-60 years old. The average (mean) age of all participants was 29.1 years, with a standard deviation of 8.9 years

Table no. 1 Demographic characteristics

Characteristic	Category	Frequency (n)	Percentage (%)
Gender	Male	58	58.0
	Female	42	42.0
Age Group (Years)	18-30	52	52.0
	31-45	35	35.0

	46-60	13	13.0
Mean Age ± SD		± 8.9 years	
- Acquired	35%	0%	100%

Graphic Analysis of Serological and Hematological Parameters:

Table #02: Shows the impact of the infection on the patients' blood cells. The values are presented as Mean ± Standard Deviation (SD), which shows the average and how supper out the numbers are. White Blood Cell Count (WBC) ($\times 10^3/\mu\text{L}$): 3.3 ± 1.3 (Normal: 4.0-11.0) Lymphocyte Count ($\times 10^3/\mu\text{L}$): 1.6 ± 0.7 (Normal: 1.2-3.5) Platelet amount ($\times 10^3/\mu\text{L}$): 103.5 ± 45.8 (Normal: 150-450) Red Blood Cell amount (RBC) ($\times 10^6/\mu\text{L}$): 4.7 ± 0.6 (Normal: 4.5-5.9)

Table no.2 Serological Profile and Hematologic Parameters

Parameter	Mean ± SD	Normal Range
Serological Status (ELISA		
Primary Infection (IgM+/IgG)	42 (42.0%	
Secondary Infection (IgG+)	58 (58.0%)	
Hematological Parameters		
White Blood Cell Count (WBC) ($\times 10^3/\mu\text{L}$)	3.3 ± 1.3	4.0-11.0
Lymphocyte Count ($\times 10^3/\mu\text{L}$	1.6 ± 0.7	1.2-3.5
Platelet Count ($\times 10^3/\mu\text{L}$)	103.5 ± 45.8	150-450
Red Blood Cell Count (RBC) ($\times 10^6/\mu\text{L}$)	4.7 ± 0.6	4.5-5.9

Figure #01 Shows the distribution of WBC, Lymphocyte, and Platelet amounts in Dengue NS1 patients. The dashed red lines designate the lower limits of the normal ranges. Leukopenia, lymphocytopenia, and thrombocytopenia are all depicted by the median values for all three parameters falling below their corresponding margins. The male-to-female ratio was 1.6:1, with 39% of cases being female and 61% of cases being male. The mean age of the patients was 27.8 ± 12.6 years (range 8–65 years). Teenagers and young adults (11–30 years) constituted the largest proportion (54%), while elderly patients (>60 years) were least affected (2%).

Distribution of Main Hematological Parameters in Dengue NS1 Patients

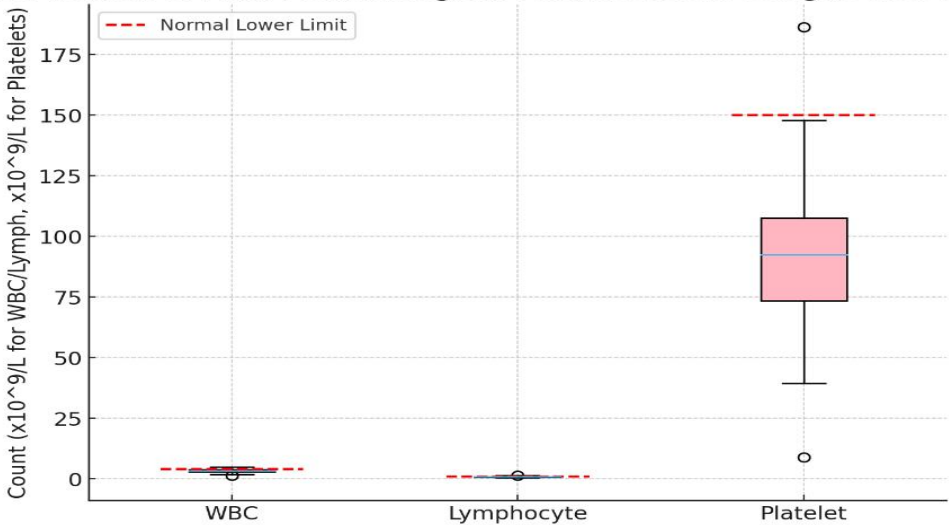


Figure
no.1

Distribution of Main Hematological Parameters in Dengue NS1 Patients:

Serological Profile

Table #04 Indicates that the mean platelet count was $128.7 \times 10^3/\mu\text{L}$, which is less than the typical reference range of $150\text{--}450 \times 10^3/\mu\text{L}$. The average TLC was $4.9 \times 10^3/\mu\text{L}$, with leukopenia present in 38% of cases. While anemia was noted in about 22% of individuals, hemoglobin and hematocrit were within reference levels for the majority of patients. 41% of patients had eosinophilia, primarily in cases of repossession.

Table no.4 shows Hematological Parameters (n=100)

Parameter	Decreased n (%)	Normal n (%)	Increased n (%)
RBC	18 (18%)	61 (61%)	21 (21%)
Hemoglobin (Hb)	22 (22%)	69 (69%)	9 (9%)
Hematocrit (HCT)	25 (25%)	66 (66%)	9 (9%)
RDW-CV	3 (3%)	62 (62%)	35 (35%)
MCV	24 (24%)	71 (71%)	5 (5%)

MCH	20 (20%)	67 (67%)	13 (13%)
MCHC	10 (10%)	79 (79%)	11 (11%)
TLC	38 (38%)	55 (55%)	7 (7%)
Neutrophil %	37 (37%)	56 (56%)	7 (7%)
Lymphocyte %	11 (11%)	69 (69%)	20 (20%)
Monocyte %	5 (5%)	91 (91%)	4 (4%)
Eosinophil %	41 (41%)	56 (56%)	3 (3%)
Platelet Count	63 (63%)	35 (35%)	2 (2%)
PDW	5 (5%)	52 (52%)	43 (43%)
MPV	3 (3%)	61 (61%)	36 (36%)
P-LCR	4 (4%)	64 (64%)	32 (32%)
Plateletcrit (PCT)	68 (68%)	28 (28%)	(4%)

Figure no.2 shows the mean WBC and platelet counts of individuals with initial and subsequent dengue infections are contrasted in a bar chart. The mean platelet count of patients with initial infection was $125.9 \times 10^3/\mu\text{L}$, which was higher than that of patients with secondary infection ($87.4 \times 10^3/\mu\text{L}$). The analysis reveals more severe platelet reduction, and increased severity in secondary dengue cases, than in primary infections. The mean WBC counts in primary and secondary infections were 3.7 and $3.0 \times 10^3/\mu\text{L}$, respectively. Thus, the degree of leukopenia is greater than in primary infections.

Mean Platelet and WBC Counts in Primary vs. Secondary Dengue Infection (n=100)

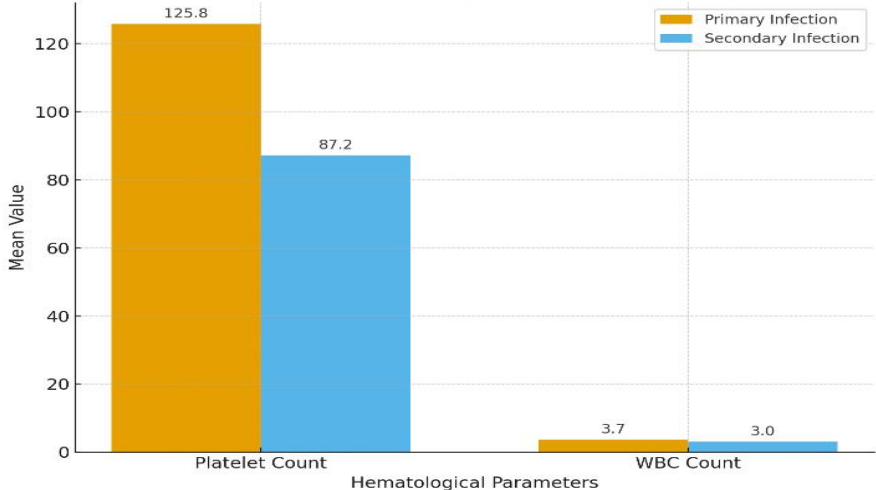


Figure no.2 Comparison of Platelet and WBC Count by Infection Type

Association Between Immunological and Blood Parameters:

The purpose of this analysis is to characterize the relationship between the levels of the two types of antibodies, IgM and IgG, and various blood parameters. The table no.5 shows correlation constants (r- values) between hematological parameters and dengue-specific antibodies (IgM = primary infection marker, IgG = secondary infection marker) along with their p-values for significance. IgM: $r = -0.237$, $p = 0.018$. Significant negative correlation. As IgM levels rise (primary dengue), WBC counts incline to reduction. IgG: $r = -0.325$, $p = 0.001$. Stronger negative association. In secondary dengue (IgG-positive), WBC counts fall even further. Leukopenia is additional pronounced in secondary dengue. Lymphocyte Count: IgM: $r = -0.205$, $p = 0.041$ Significant negative correlation, but weaker than WBC. IgG: $r = -0.278$, $p = 0.005$ Moderate negative correlation with stronger association in IgG. Lymphocyte reduction occurs in both primary and secondary dengue so in secondary cases. Platelet Count: IgM: $r = -0.038$, $p < 0.001$. Very minor correlation, but highly significant statistically. IgG: $r = -0.061$, $p < 0.001$ Over, very weak negative correlation but statistically significant. Platelet counts drop in both infections, though correlation coefficients are weak. Large sample size may explain the statistical significance despite small r- values. RBC Count: IgM: $r = -0.038$, $p = 0.708$ No significant correlation. IgG: $r = -0.061$, $p = 0.547$. No significant association. Red blood cell counts are not significantly affected by either IgM or IgG status.

Table no.5 Correlation (r) between Serological Markers and Hematological Parameters

Hematological Parameter	IgM	p-value	IgG	p-value
WBC Count	-0.237	0.018	-0.325	0.001

Lymphocyte Count	-0.205	0.041	-0.278	0.005
Platelet Count	-0.038	<0.001	-0.061	<0.001
RBC Count	-0.038	0.708	-0.061	0.547

Discussion:

In the current study found that the majority of patients were young adults between the ages of 18 to 30 (52%), followed by 31–45 year old (35%), and the 46–60-years old were the smallest group (13%). The predominance of young patients is consistent with the literature from dengue-endemic areas where the young and youths are especially affected by the disease, as they are more frequently exposed to dengue-carrying *Aedes aegypti* mosquitoes and have lower levels of immunity (WHO, 2022). The age of the unit (29.1 ± 8.9 years) is also consistent with other studies in the South Asian region which note that dengue infections are largely in the 20 to 35 year age range (Khan et al., 2019; Ahmad et al., 2018). From the study's total, 58% of the patients were of the male sex, giving a male predominance (1.6:1 sex ratio). A similar trend was observed in the region (Rasheed et al., 2021; Khan et al., 2020). The higher male presence may be a result of occupational and activity patterns, as men are generally more outdoors. Nonetheless, in the literature geographic differences in dengue disease pattern have been noted and this also relates to the underlying sampling and health-seeking behavior. The analysis showed the most constant hematologic abnormalities to be thrombocytopenia, leukopenia, and lymphocytopenia, while the counts of RBCs remained largely unchanged. Thrombocytopenia. Mean platelet counts of $103.5 \pm 45.8 \times 10^3/\mu\text{L}$ fall significantly below the expected normal range ($150\text{--}450 \times 10^3/\mu\text{L}$). It therefore confirms thrombocytopenia as a diagnostic indicator of dengue infection. Pathophysiology, thrombocytopenia occurs due to suppression of the bone marrow, peripheral destruction of the platelets, and immune-mediated clearing (Gulati & Maheshwari, 2007; Sellaheewa, 2013). This finding is clinically important as thrombocytopenia is associated with bleeding complications and increased severity of the disease. Leukopenia. The mean WBC count of

$3.3 \pm 1.3 \times 10^3/\mu\text{L}$ is below the normal of $4.0\text{--}11.0 \times 10^3/\mu\text{L}$. Leukopenia was documented in about 38% of individuals. These findings corroborate investigators (Martina et al., 2009; Ahmad et al., 2018) who showed the dengue infection peripheral and bone marrow damage to correlate with reduced WBC counts. In suspected dengue, leukopenia is commonly used as an ancillary diagnostic criterion. Lymphocytopenia. The mean lymphocyte count of $1.6 \pm 0.7 \times 10^3/\mu\text{L}$ exceeds the normal range of 1.2 to $3.5 \times 10^3/\mu\text{L}$. Lymphocytopenia is a common finding in both primary and secondary dengue and reflects dysfunctional immune responses. Findings were comparable in South and Southeast Asia (Cucunawangsih et al., 2015; Rasheed et al., 2019). On the contrary, the average RBC count ($4.7 \pm 0.6 \times 10^6/\mu\text{L}$) were within the normal range; hence, it can be concluded that anemia is not a feature of dengue. This concurs with prior studies (Martina et al., 2009), which showed that a reduction of RBC is reported only in very severe and complicated event; often due to hemorrhage or plasma leakage. Proportional analyses which highlighted the discrepancies between primary and secondary dengue. Firstly, concerning platelet counts, those with secondary infections showed even lower mean counts of ($87.4 \times 10^3/\mu\text{L}$). platelet counts in comparison to primary with ($125.9 \times 10^3/\mu\text{L}$) which evidences more severe immune-mediated destruction and thrombocytopenia. Then concerning WBC counts, those with secondary infections also had lower WBC counts of ($3.0 \times 10^3/\mu\text{L}$) compared to primary infections which had counts of ($3.7 \times 10^3/\mu\text{L}$). The finding that secondary dengue infections are more likely to present leukopenia further strengthens the case for this being a more severe form of secondary dengue. Supporting this finding and equally noting this loss of leukocytes is research done by Halstead in 2007 and Vaughn et al in 2000, to which they attribute the phenomenon to antibody-dependent enhancement (ADE). The main designs for association analysis are: Evidence of a significant negative association was shown in WBC count with IgM ($r = -0.237$, $p = 0.018$) and IgG ($r = -0.325$, $p = 0.001$). An even stronger association was shown in WBC count in individuals positive for IgG. This illustrates that there is a considerable degree of

leukopenia in secondary dengue. This pattern of association has previously been reported in South and Southeast Asia (Cucunawangsih et al, 2015; Khan et al, 2020). Significant negative correlations were shown by both IgM ($r = -0.205$, $p = 0.041$) and IgG ($r = -0.278$, $p = 0.005$), with IgG showing a higher association. This demonstrates that lymphocytopenia is a crucial characteristic of both infection types, however it is more noticeable in secondary dengue.

Platelet Count: The correlations were extremely significant ($p < 0.001$) while being modest (IgM $r = -0.038$, IgG $r = -0.061$). This demonstrates that whereas thrombocytopenia is consistently present in both groups, antibody status alone does not have a significant impact on it. The homogeneous platelet failure and sample size may be the cause of the significant statistical significance.

RBC Count: IgM and IgG did not show any significant relationships ($p > 0.5$). This reiterates that a dengue infection does not directly cause anemia. These relationships are consistent with dengue's immunopathological foundation, which shows that an antibody-dependent improvement in secondary infection leads to enhanced destruction of WBCs and lymphocytes as well as stronger inhibition of hematopoiesis (Halstead, 2007; Martina et al., 2009). The study's conclusions are consistent with those of regional and international research. Leukopenia and thrombocytopenia were described by Ahmad et al. (2018) and Rasheed et al. (2021) as mutual hematological abnormalities in dengue patients, with more severe decreases in subsequent infections. The ADE theory outlined by Halstead (2007) is supported by the negative connection between IgG and hematological markers. Additionally, the lack of a significant correlation between serology and RBC counts supports the finding that dengue usually has little effect on RBCs until bleeding is problematic (Martina et al., 2009).

Conclusion:

NS1 positive patients with dengue fever thrombocytopenia, leukopenia, and lymphocytopenia are some of the most severe hematological disorders are being studied. In the case of later dengue infections, the changes appear to be more substantial as the

disease correlates with stronger IgG changes. These results underpin the concept of immune complex mediation of the disease being severe in some forms due to antibodies. The research adds local educational epidemiological information. In contrast to the clinical value of worldwide literature, local educational value is in the epidemiological research of severe dengue and the need to correlate hematological data in its due serological data to construct its confirmed warning.

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