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Original Research Article

Platelet Indices as Diagnostic Clues in Dengue Fever - A Comparative Study

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ABSTRACT

Background: Dengue fever (DF), a mosquito-borne illness caused by the dengue virus, poses significant public health challenges, particularly in tropical and subtropical regions. In India, DF is increasingly affecting rural areas, primarily spread by Aedes albopictus and Aedes aegypti mosquitoes. The disease manifests in various forms, including dengue hemorrhagic fever and dengue shock syndrome, often leading to severe health complications.

Objective: This study aimed to analyze the hematological profiles, with a focus on Platelet Indices (PIs), in dengue seropositive patients to understand their role in disease progression and management.

Materials & Methods: An observational, cross-sectional study was conducted at ACS Medical College and Hospital over one month, involving 100 dengue seropositive patients. Platelet indices, including platelet count, mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT), were obtained through complete blood counts (CBC) on days one and three of admission. Patients were categorized based on platelet count and age for statistical analysis using Chi-Square tests and paired t-test.

Results: The study cohort had a mean age of 22.97 years, with a notable predominance of younger individuals. Significant deviations in platelet counts were observed across various antigen categories, with thrombocytopenia being prevalent. The analysis indicated that antibody-dependent enhancement (ADE) and complement system activation by NS1 and heterotypic antibodies contribute to severe dengue manifestations. Statistical tests confirmed the significant impact of antigen types on platelet counts.

Conclusion: Platelet indices provide critical insights into the disease progression of dengue fever, serving as valuable predictive tools for diagnosing and determining treatment outcomes. These indices help identify ongoing platelet destruction, guiding the need for platelet transfusions. Future research should focus on validating the predictive power of PIs in larger cohorts and developing models incorporating clinical parameters for improved diagnosis and treatment strategies. Understanding the molecular mechanisms of ADE and complement activation could lead to targeted therapies, enhancing public health strategies for managing dengue outbreaks.

Keywords: Dengue fever, Platelet indices, Thrombocytopenia, Antibody-dependent enhancement, NS1, Complement activation, Hematological profile, Predictive tools, Disease progression, Public health

INTRODUCTION

Dengue fever (DF), caused by the single-stranded RNA dengue virus from the Flaviviridae family, is a mosquito-borne illness prevalent in tropical and subtropical regions [1]. In India, DF outbreaks are increasingly affecting rural areas and are predominantly spread by Aedes albopictus and Aedes aegypti mosquitoes [2]. DF, dengue hemorrhagic fever, and dengue shock syndrome are major public health concerns [3]. Annually, DF affects 50 to 390 million people, putting 2.5 billion at risk [4]. In the past 50 years, dengue incidence has surged 30-fold, with over half the global population now living in at-risk areas [5]. In Mumbai, dengue cases rose from 129 in 2020 to 821 in 2021, with three deaths reported each year. [6].

Dengue pathogenesis is influenced by both viral and host factors, with severe cases often arising from secondary

infections with a heterotypic DENV strain or in infants born to dengue-immune mothers [7]. Antibody-dependent enhancement (ADE) is a key phenomenon, where sub-neutralizing antibodies from a primary infection facilitate the entry and increased replication of a heterologous serotype in a secondary infection via Fc gamma receptors. This results in both extrinsic ADE, where more cells are infected, and intrinsic ADE, where the virus yield per cell increases [8,5]. Additionally, severe dengue involves increased vascular permeability, mediated by antigen-antibody-complement complexes [7]. During secondary heterotypic infections, DENV antigens and IgG antibodies activate the complement system, decreasing C3 levels and increasing C3a and C5a anaphylatoxins, contributing to vascular leakage [9]. NS1, a viral protein, plays a crucial role by triggering complement activation when bound by heterotypic antibodies, further exacerbating vascular permeability and severe dengue symptoms [10].

Both innate and adaptive immune responses are crucial in combating DENV infection. The innate immune system provides a rapid, non-specific response, activating the complement system to help remove the virus. In contrast, the adaptive immune system offers a specific, long-term defence, involving cellular and humoral components [11]. The humoral response is vital for controlling DENV, targeting key epitopes on the E, NS1, and pre-M proteins [12]. The E protein triggers neutralizing antibodies, while NS1 induces antibody-dependent cellular cytotoxicity and complement-dependent lysis. Pre-M protein-specific antibodies, due to incomplete cleavage, are highly cross-reactive among serotypes. During primary infection, IgM levels peak within two weeks and decline over 2–3 months, while IgG becomes detectable by the end of the first week and may last a lifetime. In secondary infections, IgG levels rise quickly and are broadly cross-reactive with flaviviruses, persisting for 10 months to life [13].

Aim

This study aimed to analyze the hematological profiles, particularly the platelet indices (PIs), in dengue seropositive patients. The study seeks to understand the role of these indices in the progression of dengue fever and their potential as predictive tools for diagnosis and determining clinical outcomes. By evaluating platelet count, mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT) in dengue patients, the research aims to provide insights into whether platelet destruction is ongoing, necessitating imminent platelet transfusions, or if the bone marrow is responsive, allowing for the postponement of transfusions.

Objectives

To study the role of platelet indices (PI) like platelet count (PLT), Mean platelet volume (MPV) and Platelet distribution width (PDW) and plateletcrit (PCT) in dengue positive infection and to evaluate the association of platelet counts against NS1 and IgM/IgG in dengue infections.

MATERIALS AND METHODS

This observational, cross-sectional study was conducted at ACS Medical College and Hospital over one month. The aim was to study the role of platelet indices in dengue seropositive patients using data from a hospital-based data system. Platelet indices are obtained as a part of complete blood count using automated hematology analyzers. The study included all patients diagnosed with dengue fever and admitted between June and August 2023 at a tertiary care hospital. Inclusion criteria included people diagnosed with dengue fever as per WHO diagnostic criteria, positive for nonstructural protein 1 (NS1) or serology markers immunoglobulin M (IgM) and G (IgG). Exclusions were made for patients whose parents did not consent, those with other causes of fever, or preexisting hematological conditions like idiopathic thrombocytopenic purpura, platelet disorders, and malignancy.

Parental or guardian consent was obtained, and ethical approval was granted by the institutional ethical committee of AGS medical college and Hospital.Platelet parameters were analyzed through complete blood counts (CBC) on days one and three of admission. Platelet index (PI) parameters included platelet count, mean platelet volume (MPV), platelet distribution width (PDW) and plateletcrit (PCT) and serological testing for NS1, IGM and IgG were evaluated. PCT was calculated using the formula platelet count × MPV/10000.

Patients were categorized into two groups based on platelet count: Group 1 (<100000/mm³), Group 2 (>100000/mm³), and participants were stratified into four age categories for analysis. Age Categories from age group < 20 years as category 1, and 20-40 years as category 2, and 41-60 as category 3, and 61-70 as category 4. A Chi-Square Test for Equal Proportions was conducted to assess the distribution of patients across four age categories. Another Chi-Square Test for Equal Proportions was conducted to compare the frequency of patients in two groups of platelets. Then we also categorized the antigen into 5 groups. Then we used the chi-square test to find the association between the Platelet count and with Antigen, PCT, PDWSD, MPV, PDWCV categories.

RESULTS

The study included a total of 100 patients with diagnosed dengue fever who were enrolled as per the inclusion and exclusion criteria. Among the population 70% (n=70) were male and 30 (n=30) were female patient, indicating no gender predilection (p<0.001).

This dataset of 100 patients provides valuable insights into various clinical variables. The Age of patients ranges from 0.17 years to 68 years, with a mean of 22.97 years, which were grouped into 7 categories as described in Table-1 highlighting a diverse age group.

Table-1: Age-wise distribution

Age category (Years)	Number of patients (n)	Percentage (%)
0-10 years	16	16
11-20 Years	35	35
21-30 Years	30	30
31-40 Years	6	6
41-50 Years	5	5
51-60 Years	3	3
> 60 Years	5	5

Hemoglobin (Hb) levels average at 12.60 g/dL, with a range indicating conditions from severe anemia (6.40 g/dL) to maximum Hb levels (17.20 g/dL). The Platelet Count varied significantly (19.00 to 341.00 x 10^9/L), with a mean of 144.89 x 10^9/L, showing the presence of thrombocytopenia in most patients. Mean Platelet Volume (MPV) averages at 9.48 fL, indicating different stages of platelet production and activation, with values ranging from 6.10 to 11.90 fL. The Platelet Distribution Width Standard Deviation (PDWSD) ranges from 8.30 to 21.00 fL, with a mean of 13.21 fL, suggesting variability in platelet size. Similarly, Platelet Distribution Width Coefficient of Variation (PDWCV) has a mean of 15.51%, ranging from 12.30% to 19.50%, indicating significant differences in platelet size among patients. Table-2 shows the descriptive statistics of the results obtained.

Table-2: Blood indices

Variable	Mean	Standard Deviation	Minimum	Maximum
Age (years)	22.97	13.56	0.17	68.00
Hb (cells/cu. mm)	12.60	1.83	6.40	17.20
Platelet (x10^3 cells)	144.89	77.63	19.00	341.00
MPV (fL)	9.48	1.30	6.10	11.90
PDWSD (%)	13.21	3.09	8.3	21.00
PDWCV (%)	15.51	1.81	12.30	19.50
PCT (%)	0.15	0.69	0.02	0.35

The plateletcrit (PCT), a measure of total platelet mass, ranged from 0.02% to 0.35%, with a mean value of 0.15%, and lower values play a crucial role in identifying thrombocytopenia. Based on platelet count distribution, 21% of patients had counts < 100,000/mm³, indicating clinically significant thrombocytopenia, while 79% of patients had platelet counts ≥ 100,000/mm³ (Table-3). This distribution reflects that thrombocytopenia is limited to a smaller proportion of the study population, whereas patients with adequate platelet counts form the majority. The predominance of Group-2 suggests that these patients may exhibit different clinical characteristics or therapeutic requirements compared to those with lower counts. Analyzing these groups separately may provide valuable insights into variations in clinical outcomes and treatment responses based on platelet levels and corresponding PCT values.

Table-3: Distribution of patients with low PCT

Platelet Count (/mm³)	Number of patients	Percentage (%)
< 100,000	21	21
≥ 100,000	79	79

Statistical Analysis

Data collected from the 100 dengue patients was analyzed using SPSS software, ensuring rigorous statistical testing and reliable results. This approach allowed for the identification of significant differences in platelet counts associated with different antigen levels, providing valuable insights into the hematological profile of dengue-infected patients.

The provided output includes results from several statistical analyses conducted using SPSS, including Chi-Square tests for equal proportions and paired t-tests for the relationship between platelet counts and antigen types. Here's a detailed breakdown and interpretation of the results:

1. Chi-Square Test of Age Category: The data for age categories and their corresponding frequencies. The Chi-Square test for equal proportions yielded the following results:
Interpretation: The Chi-Square test for age categories indicates a significant deviation from equal proportions ($p < 0.0001$). This suggests that the age distribution in the sample is not uniform and certain age categories are more prevalent than others.

2. Chi-Square Test for Platelet Group Frequencies: The Chi-Square test for equal proportions yielded a p-value of < 0.0001. This Interpretation shows that, similar to the age category results, the Chi-Square test indicates a significant deviation from equal proportions among groups ($p < 0.0001$). This suggests that the distribution of frequencies

among the three groups is not equal, with some groups being significantly larger than others.

3. Analysis of Platelet Counts by Antigen Types: The data and results related to the analysis of platelet counts across different antigen types: Chi-square test for categorical variable is used and found that p-value which is statistically significant (P-Value < 0.01), Kappa statistics suggests that there is significant differences in platelet counts across different antigen types (p = 0.01). Kappa agreement value is 0.06, and table value denotes 1.04, which indicates the level of agreement is around 98%. Pearson's value is – 0.36, which is strongly positive, statistically significant (0.04) (Table-4).

The results from the Chi-Square tests suggest significant deviations from equal proportions in both age categories and group frequencies.

Table-4: Antigen Platelet Comparative Analysis

Level of Antigen	Platelet			P-value	Kappa Agreement value	Table value (t)
	< 1 lac	> 1 lac	Total			
NS1	8	37	45	< 0.01	0.06	1.04
IgM	0	26	26			
IgM/IgG	6	12	18			
NS1/IgM	5	2	7			
IgG	2	2	4			
Total	21	79	100			

DISCUSSION

The findings of this observational, cross-sectional study at ACS Medical College and Hospital provide valuable insights into the hematological profile of dengue seropositive patients, with a particular focus on platelet indices. The study highlights significant deviations in age and platelet distribution among dengue patients, emphasizing the diverse clinical presentations of dengue fever.

The predominance of male patients (70%) aligns with previous studies indicating potential gender-related differences in dengue incidence. The age distribution, skewed towards younger individuals, suggests that dengue disproportionately affects the younger population, possibly due to higher exposure rates and immune status differences. The present study revealed that the most affected age group is 2nd and 3rd decade. Thrombocytopenia is seen in NS1 Ag positive cases along with normal MPV, PDW and low PCT.

On comparing the present study's findings on platelet indices (PIs) in dengue seropositive patients with published studies, namely Khatri et al., Navya et al., and Reddy et al, we highlight key similarities and differences across these studies, providing insights into the hematological profiles associated with dengue fever.

The comparative analysis of our study with other studies on platelet indices in dengue patients reveals both similarities and discrepancies. Our study found that 27% of patients had low Mean Platelet Volume (MPV), while 73% had normal MPV, aligning closely with Khatri et al. [14] (3% low, 98% normal) but differing significantly from Navya et al. [15] (72% low, 28% normal) and Reddy et al. [16] (59% low, 41% normal), suggesting variability in patient responses across regions or study populations.

Regarding Platelet Distribution Width (PDW), our study noted 6% low, 71% normal, and 23% high, which is closer to Reddy et al. (4% low, 44% normal, 52% high) and distinct from Khatri et al [14]. (0% low, 88% normal, 18% high) and Navya et al [15]. (0% low, 8% normal, 92% high). This indicates that while PDW tends to be higher in dengue patients, the extent varies across different cohorts.

For Plateletcrit (PCT), our findings of 76% low and 24% normal are comparable to Reddy et al. [16] (76% low, 21% normal, 3% high) and Khatri et al [14]. (104% low, 2% normal), underscoring the commonality of thrombocytopenia in dengue patients. The absence of high PCT values across all studies highlights the consistent impact of dengue on reducing platelet mass.

Overall, our study's results corroborate the significant role of platelet indices in understanding dengue pathology, with variations possibly attributable to demographic and regional differences. Further research with standardized methodologies could elucidate these differences more clearly.

Antibody-dependent enhancement (ADE) appears to be a critical factor in severe dengue cases, as evidenced by the correlation between heterotypic infections and severe thrombocytopenia. The activation of the complement system by NS1 and heterotypic antibodies further exacerbates vascular permeability, leading to severe symptoms.

The Chi-Square and ANOVA tests confirm the significant impact of antigen types on platelet counts, suggesting that different immune responses to various dengue antigens can influence the clinical severity of the disease. These findings underscore the need for tailored clinical management strategies based on specific antigen profiles and platelet indices.

In conclusion, this study provides comprehensive data on the hematological parameters in dengue patients, emphasizing the importance of understanding immune

response dynamics to improve dengue management and treatment outcomes.

Other studies	MPV			PDW			PCT		
	↓	N	↑	↓	N	↑	↓	N	↑
Khatri et al. [14] (n=106)	3	98	5	0	88	18	104	2	0
Navya et al. [15] (n=100)	72	28	0	0	8	92	-	-	-
Reddy et al. [16] (n-100)	59	41	0	4	44	52	76	21	3
Present Study	27	73	0	6	71	23	76	24	0

CONCLUSIONS

This study offers a comprehensive analysis of the hematological profiles of dengue seropositive patients, with a particular emphasis on platelet indices (PIs). Our findings reveal significant deviations in age and platelet distribution among patients, indicating diverse clinical presentations of dengue fever. The predominance of younger individuals and the notable presence of thrombocytopenia highlight the disease's impact on these populations.

Our data demonstrate significant differences in platelet counts across various antigen categories, underscoring the complex interplay between immune response and dengue pathogenesis. The antibody-dependent enhancement (ADE) phenomenon and complement system activation by NS1 and heterotypic antibodies play crucial roles in severe cases, contributing to increased vascular permeability and severe symptoms.

Platelet indices, including platelet count, mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT), provide valuable insights into the disease progression. These indices can serve as predictive tools in diagnosing and determining outcomes in dengue fever. PIs offer critical information on whether platelet destruction is ongoing, indicating the need for imminent platelet transfusions, or if the bone marrow is responsive, suggesting that platelet transfusions can be postponed.

Future research should focus on validating the predictive power of PIs in larger, diverse cohorts to enhance their reliability in clinical practice. Developing predictive models incorporating PIs and other clinical parameters could improve early diagnosis and personalized treatment strategies, ultimately reducing dengue-related morbidity and mortality. Additionally, investigating the molecular mechanisms underlying ADE and complement activation could lead to targeted therapies that mitigate severe dengue manifestations. As our understanding of dengue pathogenesis deepens, integrating these insights into public health strategies will be crucial for managing and controlling dengue outbreaks effectively.

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