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ORIGINAL ARTICLE

Bleeding frequency among dengue patients with thrombocytopenia across various serotypes

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ABSTRACT

Background: Thrombocytopenia in dengue fever leads to bleeding of varying severity. Identifying predictors of bleeding can improve management, while the roles of demographic factors and dengue serotypes remain unclear. This study aimed to determine the frequency of various dengue serotypes and to compare the frequency of bleeding with thrombocytopenia in dengue fever with different serotypes of the dengue virus.

Materials and Methods: This prospective cross-sectional study was conducted at Sharif Medical City Hospital, Lahore, Pakistan, from January 2025 to July 2025 following approval from the ethical committee. A total of 53 patients aged 15 years or older, diagnosed with dengue fever and confirmed by Dengue virus RNA PCR, were enrolled. Thrombocytopenia was classified into very mild, mild, moderate, and severe categories. Bleeding manifestations were categorized into minor and major types. Data were collected through medical records, physical exams, and laboratory tests, and analyzed using IBM SPSS version 25.

Results: The median age of patients was 38 (28-51.5) years, with 41 (77.4%) males. DENV-4 was the most common serotype, followed by DENV-2, DENV-1, and DENV-3. Bleeding was observed in 17 (32.1%) of patients, with bleeding frequency significantly associated with thrombocytopenia severity ($p < 0.001$) and age ($p = 0.037$), but not with gender ($p = 0.077$) or serotype ($p = 0.153$).

Conclusion: Thrombocytopenia severity is a key determinant of bleeding frequency in dengue patients, with moderate and severe thrombocytopenia being strongly associated with higher bleeding risk.

Keywords: Bleeding, Demographics, Dengue fever, Dengue serotype, Thrombocytopenia

BACKGROUND

Dengue fever is an infectious disease caused by the dengue virus (DENV) transmitted primarily through the bite of an infected Aedes aegypti.[1] The disease is caused by the Flaviviridae family of viruses.[1] Following infection through a mosquito bite, the virus reaches the bloodstream and disseminates to the various tissues and produces symptoms including fever, severe headache, retrobulbar pain, musculoskeletal pain, and bleeding.[2] Life-threatening complications, defined as dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS) are the result of the acute and virulent phases of dengue.[2]

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There are four different serotypes of DENV, which are labeled as DENV-1, DENV-2, DENV-3, and DENV-4.[3] Each of these is genetically different but shares some characteristics. Infection with one serotype protects against that particular type but not the others.[3] A person can become infected with dengue many times during his or her lifetime, and such subsequent infections tend to become exacerbated, particularly when the second infection is with a different serotype.[4] The immunity against one serotype can increase the severity of the disease when the other type is encountered, through what is called antibody-dependent enhancement (ADE).[5]

Severe dengue infection is also characterized by thrombocytopenia, as is the case with DHF,[6] predisposing to bleeding.[7] Thrombocytopenia is observed during the critical phase of the disease, which is day 3 to day 7 of the disease.[6] The bone marrow dysfunction and shortening of the life span of the platelets lead to the lysis of the platelets.[8] The increased capillary permeability, another characteristic feature of the dengue hemorrhagic form, leads to leakage of the plasma and a drop in the number of platelets.

The interaction between DENV's vascular permeability and thrombocytopenia makes the patient susceptible to bleeding, which is the main cause of morbidity and death resulting from severe disease.[8] Bleeding in dengue is manifested mostly by petechiae, ecchymosis, and nose or gum bleeding. In seriously affected individuals, there is gastrointestinal bleeding, hematuria, or spontaneous skin and organ bleeding.[9] Risk of bleeding is extremely high once the counts drop below 20×10⁹/L. Besides, coexistence with coagulopathies, yet another common complication in severe dengue, poses an additive risk to the occurrence of bleeding.

A cross-sectional study conducted in Burkina Faso found that 25% of all dengue patients experienced bleeding.[10] Similarly, a local comparative study revealed that 14% of patients had bleeding at a single site, while 43% experienced bleeding at multiple sites.[11] An observational study at a tertiary care hospital in Northwestern India showed that DENV 2 and DENV 4 were associated with the highest percentage of severe dengue cases, at 20.6% and 20%, respectively. In contrast, DENV 1 was present in 14.3% of severe cases, and DENV 3 had the lowest percentage at 3%.[12]

There is a distinct lack of information on the association of DENV serotypes with bleeding tendency in patients with thrombocytopenia. It is necessary to examine the frequency of bleeding in dengue thrombocytopenic patients for different serotypes in Pakistan in order to get a better understanding of the disease variability. Examining the variation in the bleeding tendency in different serotypes may aid in informing us about which serotypes are more prone to developing bleeding complications.

This study aimed to find out the frequency of various dengue serotypes and to compare the frequency of bleeding with thrombocytopenia in dengue fever with different serotypes of the dengue virus.

MATERIAL AND METHODS

This prospective cross-sectional study was conducted from January 2025 to July 2025 at Sharif Medical City Hospital in Lahore, following the approval of the study synopsis. The sample size was determined using the Raosoft sample size calculation formula, resulting in a total of 53 patients. This was based on a 95% confidence level and a 5% margin of error, using 43% prevalence of bleeding in a previous local study.[11]

The inclusion criteria consisted of individuals aged 15 years or older, of both genders, diagnosed with dengue fever confirmed by Dengue virus RNA PCR, and exhibiting thrombocytopenia (platelet count less than 150 ×10⁹/L). Very mild thrombocytopenia was defined as a platelet count between 100 and 149 ×10⁹/L, mild thrombocytopenia as platelet counts between 75 and 99 ×10⁹/L, moderate thrombocytopenia as platelet counts ranging from 50 to 74 ×10⁹/L, and severe thrombocytopenia as a platelet count below 50 ×10⁹/L. Exclusion criteria included individuals younger than 15 years, those with co-morbid conditions such as chronic liver disease (CLD), systemic lupus erythematosus (SLE), idiopathic thrombocytopenic purpura (ITP), thrombotic thrombocytopenic purpura (TTP), leukemia, or vitamin B12 deficiency, and individuals already undergoing antiplatelet therapy, including Clopidogrel and Aspirin.

Data collection commenced once approval from the hospital's ethics committee was obtained. Informed consent was acquired from all participants who met the inclusion criteria, ensuring confidentiality and privacy throughout the study. Data were gathered from patients admitted between the 3rd and 7th days of their dengue fever hospitalization. Information was recorded through medical record reviews, physical examinations, and symptom tracking conducted by a trained researcher. Bleeding was categorized based on visual presentations, distinguishing between minor bleeding (such as gum bleeding, epistaxis, or petechiae) and major bleeding (such as hematuria, gastrointestinal bleeding, or intracranial bleeding). Laboratory tests, including complete blood count (CBC) for dengue on the 3rd, 5th, and 7th days, and qualitative Dengue RNA PCR for serotype identification, were conducted. For PCR, RNA extraction was done by QIAmp® viral RNA minikit 250 (QIAGEN), and complementary deoxyribonucleic acid (cDNA) was synthesized using reverse transcriptase and specific primers. These samples were run on the ABI 7500 real-time PCR machine. Patients were not administered drugs, platelets, or blood transfusions that could influence platelet counts, and those requiring transfusions were excluded from the study.

Data analysis was performed using the Statistical Package for Social Sciences (SPSS) version 25. Quantitative variables, such as age, were expressed as median with interquartile range (IQR), while qualitative variables, such as gender, platelet count, and dengue

virus serotype, were presented as frequencies and percentages. Age was the only continuous variable, and its distribution was non-normal based on the Shapiro-Wilk test (p=0.04). Stratification by age and gender was carried out to control for potential effect modifiers. Post-stratification, a chi-square test was applied to determine the statistical significance of bleeding differences between groups, with a p-value ≤ 0.05 considered significant.

RESULTS

In the study, a total of 53 dengue-confirmed patients were analyzed, with a median age of 38 (28-51.5) years. Of these, 41 (77.4%) were male and 12 (22.6%) were female. Thrombocytopenia was categorized as very mild in 9 patients (17.0%), mild in 17 (32.1%), moderate in 18 (34.0%), and severe in 9 (17.0%) (as shown in Table I).

The distribution of dengue virus serotypes revealed DENV-4 as the most prevalent at 37.7% (20 cases), followed by DENV-2 at 34.0% (18), DENV-1 at 24.5% (13), and DENV-3 at 3.8% (2) (Table II).

Table III examined the distribution of dengue serotypes across demographic and clinical factors. Among patients aged ≤40 years (28 patients), DENV-1, DENV-2, and DENV-4 were each found in 9 cases (32.1%), while DENV-3 was present in 1 case (3.6%). In patients >40 years (25 patients), DENV-1 was found in 4 (16.0%), DENV-2 in 9 (36.0%), DENV-3 in 1 (4.0%), and DENV-4 in 11 (44.0%) patients. The association between age and dengue serotype was not statistically significant (p = 0.695). In male patients, 11 (26.8%) had DENV-1, 14 (34.1%) had DENV-2, 2 (4.9%) had DENV-3, and 14 (34.1%) had DENV-4. Among females, 2 (16.7%) had DENV-1, 4 (33.3%) had DENV-2, none had DENV-3, and 6 (50.0%) had DENV-4; the gender-based distribution also lacked statistical significance (p = 0.672). For patients with very mild thrombocytopenia (n=9), DENV-1 occurred in 5 (55.6%), DENV-2 in 1 (11.1%), and DENV-4 in 3 (33.3%). Among mild thrombocytopenia cases (n=17), DENV-1 occurred in 3 (17.6%), DENV-2 in 4 (23.5%), DENV-3 in 2 (11.8%), and DENV-4 in 8 (47.1%). In moderate thrombocytopenia (n=18), DENV-1 was 3 (16.7%), DENV-2 was 8 (44.4%), and DENV-4 was 7 (38.9%). Severe thrombocytopenia (n=9) included 2 patients with DENV-1 (22.2%), 5 with DENV-2 (55.6%), and 2 with DENV-4 (22.2%). No cases of DENV-3 were found in moderate or severe thrombocytopenia groups.

Table IV evaluated associations between bleeding status and various demographic and clinical factors. Bleeding was significantly more common among patients older than 40 years, with 12 out of 25 (48.0%) affected compared to 5 out of 28 (17.9%) in the younger group (p = 0.037). Gender-based differences showed that 16 out of 41 males (39.0%) and only 1 out of 12 females (8.3%) experienced bleeding, though this difference did not reach statistical significance (p = 0.077). Bleeding frequency was strongly associated with thrombocytopenia severity (p < 0.001). None of the patients with very mild (n=9) or mild thrombocytopenia (n=17) experienced bleeding. In contrast, 8 out of 18 patients (44.4%) with moderate thrombocytopenia and all 9 patients (100%) with severe thrombocytopenia showed bleeding. Regarding dengue serotypes, bleeding was reported in 2 out of 13 patients with DENV-1 (15.4%), 9 out of 18 with DENV-2 (50.0%), 0 out of 2 with DENV-3 (0%), and 6 out of 20 with DENV-4 (30.0%). However, the differences in bleeding frequency across serotypes were not statistically significant (p = 0.153).

Table-I: Patient demographics and platelet counts.

Parameters	Results	
Age (years) Median (IQR)	38 (28-51.5)	
Gender	Male n (%)	41 (77.4%)
	Female n (%)	12 (22.6%)
Thrombocytopenia	Very mild n (%)	9 (17.0%)
	Mild n (%)	17 (32.1%)
	Moderate n (%)	18 (34.0%)
	Severe n (%)	9 (17.0%)

Table-II: Frequency of Dengue Serotypes and Bleeding Status

Dengue Serotype	n (%)
DENV-1	13 (24.50%)
DENV-2	18 (34.00%)

DENV-3	2 (3.80%)
DENV-4	20 (37.70%)
Bleeding Status	
Yes	17 (32.10%)
No	36 (67.90%)

Table-III: Association of Dengue Serotype with Demographic Factors

Demographic Factors	Groups	Dengue Serotype				p-value
		DENV-1 (n=13)	DENV-2 (n=18)	DENV-3 (n=2)	DENV-4 (n=20)	
Age (years)	≤40 n (%)	9 (32.1%)	9 (32.1%)	1 (3.6%)	9 (32.1%)	0.695*
	>40 n (%)	4 (16.0%)	9 (36.0%)	1 (4.0%)	11 (44.0%)	
Gender	Male n (%)	11 (26.8%)	14 (34.1%)	2 (4.9%)	14 (34.1%)	0.672*
	Female n (%)	2 (16.7%)	4 (33.3%)	0 (0.0%)	6 (50.0%)	
Thrombocytopenia	Very mild n (%)	5 (55.6%)	1 (11.1%)	0 (0.0%)	3 (33.3%)	0.143*
	Mild n (%)	3 (17.6%)	4 (23.5%)	2 (11.8%)	8 (47.1%)	
	Moderate n (%)	3 (16.7%)	8 (44.4%)	0 (0.0%)	7 (38.9%)	
	Severe n (%)	2 (22.2%)	5 (55.6%)	0 (0.0%)	2 (22.2%)	

*Fischer's Exact Test

Table-IV: Association of Bleeding with Demographic and Clinical Factors

Demographic and Clinical Factors	Groups	Bleeding		p-value
		Yes (17) n (%)	No (36) n (%)	
Age (years)	≤40	5 (17.9%)	23 (82.1%)	0.037*
	>40	12 (48.0%)	13 (52.0%)	
Gender	Male	16 (39.0%)	25 (61.0%)	0.077*
	Female	1 (8.3%)	11 (91.7%)	
Thrombocytopenia	Very mild	0 (0.0%)	9 (100.0%)	<0.001*
	Mild	0 (0.0%)	17 (100.0%)	
	Moderate	8 (44.4%)	10 (55.6%)	
	Severe	9 (100.0%)	0 (0.0%)	
Dengue Serotype	DENV-1	2 (15.4%)	11 (84.6%)	0.153*
	DENV-2	9 (50.0%)	9 (50.0%)	
	DENV-3	0 (0.0%)	2 (100.0%)	
	DENV-4	6 (30.0%)	14 (70.0%)	

*Fischer Exact Test

DISCUSSION

Based on the results, bleeding was significantly associated with thrombocytopenia severity and patient age, but not with dengue serotype or gender. This finding aligns with established hematological mechanisms—severe thrombocytopenia reduces platelet-mediated clot formation, directly predisposing patients to hemorrhagic manifestations. The increased bleeding frequency in older patients may be attributed to age-related vascular fragility and comorbid conditions that exacerbate hemorrhagic risk. Although DENV-2 showed a relatively higher bleeding proportion, no statistically significant association was found between serotype and bleeding. This suggests that host immune response and platelet dynamics may play a more critical role than viral serotype alone in determining bleeding outcomes. These insights emphasize the clinical importance of platelet count monitoring and age-based risk assessment in managing dengue patients.[13-16]

Bleeding manifestations were seen in one-third of patients and were significantly associated with both age and thrombocytopenia severity, but not with gender or dengue serotype. DENV-4 was the most prevalent serotype, followed by DENV-2, DENV-1, and DENV-3. Notably, bleeding was most frequent among DENV-2 patients (50.0%), though not statistically significant.

Similar to our findings, Gupta reported a 33.33% bleeding rate in a cohort of 120 hospitalized dengue patients.[13] Severe thrombocytopenia was observed in 29.17%, moderate in 45.83%, and mild or normal counts in 25%, with rash/petechiae being the most common bleeding symptom (95%). Like our study, this research found that bleeding events were primarily associated with lower platelet levels rather than demographic factors, emphasizing the central role of thrombocytopenia in hemorrhagic manifestations.

Khan *et al*. found 32.8% of dengue patients had normal platelet counts and 42.4% had moderate thrombocytopenia.[14] Bleeding incidence was significantly associated with lower platelet levels ($p < 0.001$), but not with age or gender, mirroring our findings where thrombocytopenia severity (but not gender or serotype) was significantly linked to bleeding frequency.

In contrast, the study by Giri *et al*. involving 263 patients found that while 86.31% had thrombocytopenia, bleeding was not always proportionate to platelet counts.[15] Petechiae (27.4%) and mucosal bleeding (31.93%) were frequent, and moderate thrombocytopenia was common among bleeders, suggesting that platelet dysfunction or immune-mediated mechanisms may contribute beyond mere counts. This partially aligns with our data, where bleeding occurred most frequently in moderate and severe thrombocytopenia, but not in mild or very mild cases.

Logia *et al*. offered a more advanced perspective by identifying independent predictors of clinically significant bleeding in ICU-admitted patients with dengue.[16] Their retrospective analysis of 120 thrombocytopenic patients revealed that a SOFA score (aOR: 1.52), fever >38.3°C (aOR: 2.71), and aPTT >40s (aOR: 4.66) were the strongest predictors. The developed predictive score (AUC = 0.81) showed strong discriminatory power. The study concluded that beyond platelet count, clinical indicators like SOFA, aPTT, and fever provide a more accurate bleeding risk stratification tool in ICU settings.

Interestingly, the study by Giri *et al*. and this study both showed that petechiae were the predominant manifestation, though the specific frequencies varied. [15] While our study did not find a significant correlation between bleeding and dengue serotypes, Iqbal *et al*. noted that patients with blood Group B were more frequent and AB was least commonly affected by the DENV infections. However, no association was found between a particular blood group and disease severity. [17]

Our findings that DENV-2 and DENV-4 were more common in moderate and severe thrombocytopenia cases, and that DENV-2 had the highest proportion of bleeders (50%), is consistent with some earlier reports but did not reach statistical significance. This is in line with Khan *et al*., who also observed serotype differences in platelet trends but did not attribute statistical significance to these patterns.[14]

In light of the findings, it is evident that thrombocytopenia severity plays a central role in predicting bleeding outcomes in dengue patients, as emphasized by our study and supported by the existing literature. However, variations across studies suggest that while platelet count remains an important factor, additional clinical parameters, such as SOFA score, fever, and coagulation status, may offer further precision in bleeding risk stratification.[18-21] Our study contributes to the growing understanding of dengue pathophysiology and underscores the importance of close monitoring for bleeding, especially in patients with severe thrombocytopenia.

There are some limitations to the study. First, this is a single-center study, which may limit the generalizability of the findings. The sample size, although adequate for the analysis, may still be insufficient and unbalanced to detect smaller effects or trends. Multivariate analysis was also not done due to small numbers of patients in some subgroups. Additionally, the retrospective design restricts the ability to establish causal relationships between thrombocytopenia severity and bleeding risk. Further multi-center studies with larger sample sizes and prospective design are needed to confirm these findings and provide more comprehensive guidelines for managing bleeding in dengue patients across different regions and healthcare settings

CONCLUSION

The severity of thrombocytopenia is a significant predictor of bleeding in dengue patients, with moderate and severe thrombocytopenia being strongly associated with increased bleeding frequency. While demographic factors like age and gender showed some correlation, they did not have the same predictive value as platelet count. Additionally, dengue serotype alone does not significantly influence bleeding outcomes.

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CONFLICT OF INTEREST

None

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Declared none

AUTHOR CONTRIBUTION

Naila Ghouri: Conceptualizing the study, drafting the manuscript, and data collection, final approval, accountable for all aspects of publication.

Ayub Latif Khawaja: Contributed significantly to the development of the article, study design, analysis and interpretation of the data, final approval, accountable for all aspects of publication.

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