

SPECTRUM, PREDICTORS, AND OUTCOMES OF HEMORRHAGIC MANIFESTATIONS IN DENGUE FEVER: A PROSPECTIVE OBSERVATIONAL STUDY FROM A TERTIARY CARE HOSPITAL IN PAKISTAN

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ABSTRACT

Background: Dengue fever is a viral infection and in severe cases it can lead to hemorrhagic symptoms which can be fatal. Secondary dengue infection and co-morbidities have been found to be risk factors for severe dengue and hemorrhagic symptoms.

Aim: The aim of this study was to determine the Spectrum, Predictors, and Outcomes of Hemorrhagic Manifestations in Dengue Fever in patients with confirmed dengue fever admitted to a tertiary care hospital in Nowshera, Pakistan.

Materials and method: The present observational cohort study was conducted in the Department of Medicine at Nowshera Medical College, Qazi Hussain Ahmad Medical Complex Nowshera over a period of 12 months, from January 2025 to January 2026 after taking approval from the ethical committee of the hospital. Individuals of both gender and different age groups admitted to the hospital throughout the research period with Laboratory-confirmed dengue fever (positive NS1 antigen and/or dengue IgM antibodies) were included. A standardized proforma was used to record demographics, clinical data, and laboratory results. Hemorrhagic symptoms were testified and categorized. The statistical analysis was carried out using IBM SPSS version 26. Chi-square testing and multivariate logistic regression were used to investigate variables related to hemorrhagic symptoms. A p-value of <0.05 was considered statistically significant.

Results: In the current study a total of 400 individuals with laboratory-confirmed dengue fever were participated out of which 162 (40.5%) were females and 238 (59.5%) were male. The mean age of the study population was 33.9 ± 12.3 years (range: 6–78 years). Among the study participants 116 (29.0%) individuals had hemorrhagic symptoms. Participants with platelet counts below $50 \times 10^9/L$ exhibited a considerably greater prevalence of hemorrhagic symptoms compared to those no bleeding which was statistically significant ($p < 0.001$). Individuals with a hematocrit level of $\geq 45\%$ had a significantly higher risk of hemorrhagic symptoms compared to those absent bleeding ($p < 0.001$). Elevated ALT levels above 100 U/L were also substantially related with bleeding symptoms. Diabetes mellitus was substantially related with hemorrhagic symptoms ($p = 0.001$). Similarly, hypertension was significantly associated with bleeding problems ($p = 0.013$). Patients who presented with hemorrhagic symptoms had considerably poorer clinical outcomes.

Conclusion: The current study concluded that hemorrhagic manifestations were seen in 29% of the individuals with dengue fever. The independent predictors of bleeding were thrombocytopenia, severe dengue, coagulation problems and hemoconcentration. Early identification of these risk factors may allow for more effective therapy and better clinical results.

KEYWORDS: Dengue fever, hemorrhagic manifestations, thrombocytopenia, coagulation problems

INTRODUCTION

Dengue fever is a viral infection transmitted by mosquitoes that poses a serious public health risk throughout the world especially in tropical and subtropical regions. Recently the global prevalence of dengue has grown considerably, with an estimated 390 million infections occurring each year, of which around 96 million exhibit clinically. ¹ Dengue

outbreaks have frequently occurred in Pakistan; the Khyber Pakhtunkhwa province, which includes the Nowshera district, is especially vulnerable because of the region's ideal climate, fast urbanization, and insufficient vector control efforts.² Dengue may cause symptoms in a variety of ways, from mild infection to serious illness. Dengue is classified by the World Health Organization into three clinical phases: febrile, critical (plasma leakage phase), and recovery.³ While the majority of patients cure with supportive treatment, a small percentage develop severe dengue, which can be fatal and is characterized by organ failure, hemorrhagic symptoms, and plasma leakage.⁴ One especially worrying consequence of dengue infection is hemorrhagic symptoms. Epistaxis, gum bleeding, hematuria, hematemesis, melena, petechiae, and vaginal bleeding are just a few of the bleeding occurrences that fall under this category. Dengue-associated bleeding has a complicated and multifaceted pathogenesis that includes endothelial damage, thrombocytopenia, platelet dysfunction, and aberrant coagulation.⁵ Although thrombocytopenia is always seen in cases of severe dengue, there is no consistent relationship between platelet count nadir and the severity of bleeding, indicating that endothelial integrity and platelet function are equally significant.⁶ Advanced age, female sex, the existence of comorbid conditions including diabetes mellitus and hypertension, secondary dengue infection, and particular virus serotypes have all been found to be risk factors for severe dengue and hemorrhagic symptoms.⁷ However, there is still a lack of comprehensive characterization about the predictive usefulness of these characteristics in the Pakistani population, especially in the Khyber Pakhtunkhwa area. Furthermore, it has not been thoroughly assessed in local cohorts how serial laboratory parameters—more especially, the trajectory of platelet count, hematocrit, and white cell count—predict the onset and severity of hemorrhagic symptoms. Hemorrhagic symptoms have significant clinical consequences. Patients who are bleeding need to be closely watched, frequently need transfusions of blood products, and are more likely to be admitted to the critical care unit and die.⁸ Knowing the bleeding predictors might help with risk classification and the targeted distribution of resources to high-risk patients in Pakistan, where healthcare resources are few. There is a noticeable lack of prospective observational data on hemorrhagic symptoms in dengue from Pakistan, despite the clinical relevance. Therefore the present study was conducted to determine the frequency and spectrum of hemorrhagic manifestations in patients with confirmed dengue fever admitted to a tertiary care hospital in Nowshera, Pakistan.

MATERIALS AND METHOD

The present observational cohort study was conducted in the Department of Medicine at Nowshera Medical College, Qazi Hussain Ahmad Medical Complex Nowshera over a period of 12 months, from January 2025 to January 2026 after taking approval from the ethical committee of the hospital. This hospital is a major tertiary care referral center that serves Nowshera District and neighboring areas where dengue fever is endemic. Patients were included sequentially at the time of admission in order to ensure a representative sample and avoid selection bias. During the study duration, all consecutive individuals hospitalized with laboratory-confirmed dengue fever were enrolled. NS1 antigen and/or dengue IgM serology was used for the confirmation of Dengue infection. Non-probability consecutive sampling technique was used for data collection. A total of 400 individuals were enrolled in the study. Written consent was taken from each participant. Individuals of both gender and different age groups admitted to the hospital throughout the research period with Laboratory-confirmed dengue fever (positive NS1 antigen and/or dengue IgM antibodies) were included. Individuals with incomplete clinical or laboratory records, an alternative confirmed diagnosis during hospitalization and were not willing to participate were excluded from the study. Data were collected prospectively by the principal investigator and trained research assistants using a pre-designed, structured case report form. All data were collected at the bedside during the patient's hospital stay, ensuring real-time accuracy and completeness. Demographic variables including name, age, sex, and residential address were recorded. Clinical variables at admission and during stay were encompassed symptoms such as fever, rigors and chills, generalized body ache, headache, nausea, vomiting, abdominal pain, cough, sore throat, retro-orbital pain, and back pain; duration of illness from symptom onset to presentation; clinical stage documented as febrile phase, critical phase, or recovery phase as determined by the treating physician; presence of co-morbidities including diabetes mellitus, hypertension, ischemic heart disease, asthma, epilepsy, and chronic kidney disease; and vital signs including blood pressure, pulse rate, respiratory rate, and temperature. Laboratory variables were measured serially throughout the hospital stay. Dengue serology including NS1 antigen, IgM antibody, and IgG antibody were assessed at admission. Platelet count, hemoglobin, hematocrit, white blood cell count, and ALT were measured at admission and repeated daily or as clinically indicated until discharge or death. Other laboratory findings including urine routine, ultrasound findings, and malaria parasite testing were documented when performed. Hemorrhagic manifestations were systematically assessed daily and categorized as mucocutaneous including epistaxis, gum bleeding, petechiae, ecchymosis, and patchial rash; gastrointestinal including hematemesis, melena, hematochezia, and per rectal bleeding; genitourinary including hematuria and per vaginal bleeding; respiratory including hemoptysis; and multi-site hemorrhage defined as bleeding at two or more distinct sites. For each patient, we documented the presence or absence of each hemorrhagic manifestation, the day of illness when bleeding occurred, severity based on clinical assessment, and the need for specific interventions including nasal packing, tranexamic acid, vitamin K, and blood products. Treatment variables included intravenous fluids type, volume, and duration; antipyretics; antibiotics with type and indication; anti-emetics; antimalarial in cases of co-infection; antihypertensive for patients with hypertension; insulin or antidiabetics for

diabetic patients; transfusion details including type of product, number of units, and any transfusion reaction; and other medications including tranexamic acid, vitamin K, steroids, Hepamerz, and proton pump inhibitors. The study outcomes were evaluated. The major outcomes recorded were the development of any hemorrhagic manifestation during hospitalization, requirement for blood product transfusion, admission to the intensive care unit, length of hospital stay, mortality, and referral to another healthcare facility and Stable discharge from hospital. To ensure data quality and minimize measurement error, the principal investigator trained all research assistants on standardized data collection procedures. The case report form was pilot-tested on ten patients and refined accordingly. All clinical assessments and laboratory measurements followed hospital protocols. Daily supervision and data verification were performed by the principal investigator. A random ten percent of records were independently verified by a second reviewer for accuracy. Data were entered in duplicate in a secure database with range and logic checks. SPSS Statistics version 26 was used for data analysis. Categorical variables were expressed as frequencies and percentages. Continuous variables were presented as mean $\pm$ standard deviation. For the comparison of hemorrhagic manifestations among the study population independent-samples t-test was applied. Chi-square test or Fisher's exact test was used for categorical and variables Mann–Whitney U test for continuous variables. Univariate logistic regression was initially performed to identify potential predictors of hemorrhagic manifestations. Variables with a p-value <0.10 in the univariate analysis were entered into a multivariable logistic regression model. Results were reported as adjusted odds ratios (AORs) with 95% confidence intervals (CIs). Statistical significance was defined as a two-tailed p-value <0.05 . Subgroup analyses were planned according to age group, sex, comorbidity status, dengue serological profile (primary versus secondary infection), and clinical phase of illness. Serial laboratory trends were evaluated using repeated-measures analyses, while time to discharge was assessed using Kaplan–Meier survival analysis and compared using the log-rank test.

RESULTS

In the current study a total of 400 individuals with laboratory-confirmed dengue fever were participated out of which 162 (40.5%) were females and 238 (59.5%) were male. The mean age of the study population was 33.9 ± 12.3 years (range: 6–78 years). Majority of the individuals were from urban areas 266(56.5%). The most prevalent age group was 18–50-year 254(63.5%) followed by age group above 50 years 94(23.5%) and age group less than 18 years 52(13.0%) respectively. All participants had fever 400(100%). The most common clinical feature was headache 326(81.5%) followed by body aches 318(79.5%), nausea and vomiting 169 (42.3%), abdominal pain 141(35.3%), retro-orbital pain 124(31.0%), skin rash 101(25%), cough 88(22.0%) and sore throat 76(19%) respectively as presented in **table 1**. Overall, 262 (65.5%) patients had no reported underlying disease. Among those with comorbidities, hypertension was the top most frequent disorder, affecting 71 (17.8%) individuals, subsequent to diabetes mellitus, which was seen in 58 (14.5%). Ischemic heart disease was diagnosed in 18 (4.5%) participants, whereas asthma and chronic renal disease were found in 14 (3.5%) & 9 (2.3%) individuals, respectively as presented in **figure 1**. Laboratory results revealed significant thrombocytopenia, with a mean platelet count of $58 \times 10^9/L$. Mild leukopenia and high levels of ALT were also detected. During hospitalization, 116 (29.0%) individuals had hemorrhagic symptoms, whereas 284 (71.0%) did not. various forms of hemorrhagic symptoms were seen among these 116 individuals. the most prevalent hemorrhagic symptom was Petechiae 46(39.7%) followed by gum bleeding 24(20.7%) and epistaxis (nose bleeding) 18 (15.5%) respectively. Severe bleeding signs including hemoptysis & multi-site hemorrhage were rare as presented in **table 2**. Each patient received supportive care, including intravenous fluids & antipyretics. 7.3% of patients had platelet transfusions, while 7.8% were given tranexamic acid. Participants with platelet counts below $50 \times 10^9/L$ exhibited a considerably greater prevalence of hemorrhagic symptoms (76 patients) compared to those no bleeding (58 individuals), with a very significant correlation ($p < 0.001$). Individuals with a hematocrit level of $\geq 45\%$ had a significantly higher risk of hemorrhagic symptoms (61 participants) compared to those absent bleeding (76 individuals) ($p < 0.001$). Elevated ALT levels above 100 U/L were also substantially related with bleeding symptoms. Among individuals with high ALT, 49 experienced hemorrhagic problems, while 69 were not (p corresponds to 0.002). Diabetes mellitus was substantially related with hemorrhagic symptoms (26 participants vs. 32 no bleeding; $p = 0.001$). Similarly, hypertension was significantly associated with bleeding problems (28 individuals with bleeding versus 43 with no bleeding; $p = 0.013$). Patients who presented with hemorrhagic symptoms had considerably poorer clinical outcomes. ICU hospitalization was necessary for 24 (20.7%) individuals with hemorrhagic symptoms versus 12 (4.2%) participants without bleeding ($p < 0.001$). Similarly, 27 (23.3%) patients with hemorrhagic symptoms had blood transfusion, in contrast to only 2 (0.7%) individuals without bleeding needed it ($p < 0.001$). death rate was also considerably greater in the hemorrhagic group, with 7 (6.0%) mortality rate compared to 1 (0.4%) death rate among individuals with no hemorrhagic manifestations ($p = 0.001$) as presented in **table 3**. Independent predictors of hemorrhagic symptoms were platelet count $< 50 \times 10^9/L$, hematocrit above 45%, increased ALT, diabetes mellitus, plus critical-phase dengue, according to multivariable analysis. The best predictor was severe thrombocytopenia, which increased the risks of bleeding more than fivefold as shown in **table 4**.

Table 1. Demographic features and clinical parameters of the study population n=400

Variable	Category	Frequency (n)	Percentage (%)
Mean age	33.9 ± 12.3 years (range: 6–78 years)		
Age in years	Less than 18	52	13.0
	18–50	254	63.5
	>50	94	23.5
Gender	Male	238	59.5
	Female	162	40.5
Residence	Urban	226	56.5
	Rural	174	43.5
Clinical Features	Fever	400	100.0
	Headache	326	81.5
	Generalized body aches (Myalgia)	318	79.5
	Nausea/Vomiting	169	42.3
	Abdominal pain	141	35.3
	Retro-orbital pain	124	31.0
	Skin rash	101	25.3
	Cough	88	22.0
	Sore throat	76	19.0

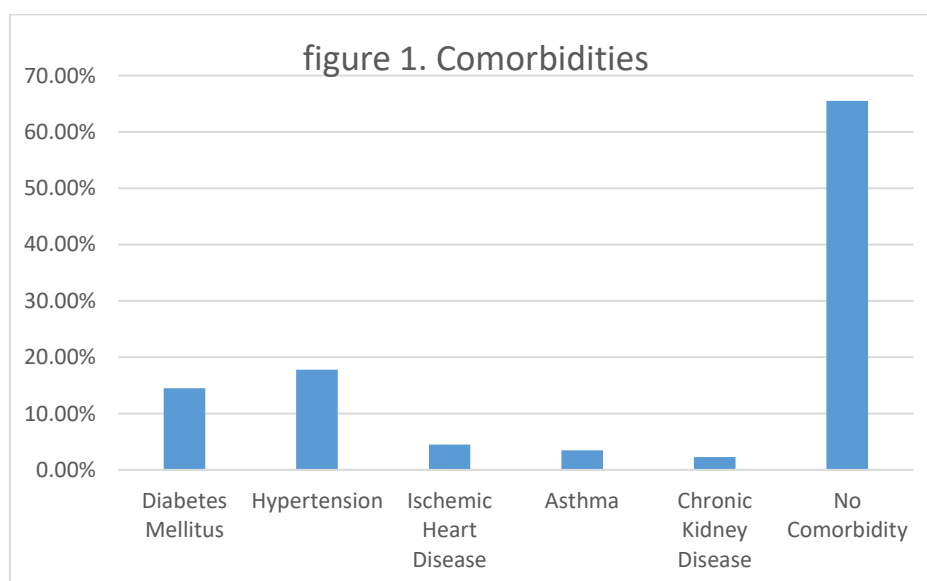


Table 2. Lab findings	
Factors	Mean ± SD
Hemoglobin (g/dL)	13.8 ± 1.9
Hematocrit (%)	42.6 ± 5.4
Platelet Count (×10 ⁹ /L)	58 ± 34
White Blood Cell Count (×10 ⁹ /L)	4.3 ± 1.8
ALT (U/L)	86 ± 51

Spectrum of hemorrhagic manifestations n=116		
Manifestation	Frequency	Percentage (%)
Petechiae	46	39.7
Gum bleeding	24	20.7
Epistaxis	18	15.5
Hematemesis	12	10.3
Melena	8	6.9
Hematuria	5	4.3
Hemoptysis	2	1.7
Multi-site bleeding	1	0.9

Table 3. Clinical outcomes and predictors of hemorrhagic manifestations among the population with dengue fever

Variable	Category	Hemorrhagic Manifestations Present (n=116)	Hemorrhagic Manifestations Absent (n=284)	Total (n=400)	p-value
Platelet Count ($\times 10^9/L$)	<50	76	58	134	<0.001
	≥ 50	40	226	266	
Hematocrit (%)	≥ 45	61	76	137	<0.001
	<45	55	208	263	
ALT (U/L)	>100	49	69	118	0.002
	≤ 100	67	215	282	
Diabetes Mellitus	Yes	26	32	58	0.001
	No	90	252	342	
Hypertension	Yes	28	43	71	0.013
	No	88	241	329	
ICU Admission	Yes	24	12	36	<0.001
	No	92	272	364	
Blood Transfusion	Yes	27	2	29	<0.001
	No	89	282	371	
Clinical Outcome	Recovered	109	277	386	0.001
	Died	7	1	8	

Table 4. Multivariable Logistic Regression			
Predictor	Adjusted OR	95% CI	p-value
Platelets $<50 \times 10^9/L$	5.11	3.02–8.65	<0.001
Hematocrit $>45\%$	2.81	1.68–4.69	<0.001
ALT >100 U/L	2.26	1.29–3.95	0.004
Diabetes Mellitus	2.14	1.10–4.13	0.025
Critical Phase Dengue	4.53	2.56–8.02	<0.001

DISCUSSION

Dengue fever is a common mosquito-borne viral illness that significantly impacts public health in tropical and subtropical regions. Its global incidence has increased rapidly in recent decades, putting nearly half of the world's population at danger. Dengue fever is a recurring epidemic in Pakistan, especially during monsoon rains and urban floods, which create ideal hatching circumstances for *Aedes aegypti* mosquitos.⁹ Dengue infection can cause a mild febrile illness or serious consequences such hemorrhagic fever & dengue shock syndrome (. Early diagnosis is crucial for commencing supportive treatment and minimizing illness progression, but can be challenging due to clinical presentation variability. Although hematological disorders such as thrombocytopenia and leukopenia are common, their impact on prognosis differs by community.¹⁰ The present study was conducted to determine the frequency and spectrum of hemorrhagic manifestations in patients with confirmed dengue fever admitted to a tertiary care hospital in Nowshera, Pakistan. In the current study a total of 400 individuals with laboratory-confirmed dengue fever were participated out of which 162 (40.5%) were females and 238 (59.5%) were male. Majority of the individuals were from urban areas (56.5%). The study found that dengue primarily affects urban populations and has slightly male preponderance. These findings similar with local studies showing that males living in the urban areas are at risk to mosquito bites due to increased outside exposure.¹¹ Males are more susceptible in endemic places, according to international data. However, research from Southeast Asia show more balanced gender distributions based on vector ecology & local immunity patterns.¹² All participants had fever 400(100%) which is a universal feature of dengue infection .The other most common clinical feature was headache (81.5%) followed by body aches (79.5%), nausea and vomiting (42.3%), abdominal pain 141(35.3%), retro-orbital pain 124(31.0%), skin rash 101(25%), cough (22.0%) and sore throat (19%) respectively. Although this pattern roughly matches worldwide dengue symptomatology, there is regional diversity. Research from Sri Lanka and Thailand found increased incidence of rash and gastrointestinal symptoms, probably due to variations in virus serotypes.¹³ In our study during hospitalization, 116 (29.0%) individuals had hemorrhagic symptoms, whereas 284 (71.0%) did not. These findings are similar to the study conducted by Khan et al in which 1/3 of the population infected by dengue virus had hemorrhagic manifestation which support our study.¹⁴ Our results explored that bleeding as a common clinical consequence that needs to be identified and managed as soon as possible. In the current study frequency of hemorrhagic manifestations were most prevalent in individuals who had platelet counts below $50 \times 10^9/L$. Similarly, higher ALT levels raised hematocrit, diabetes mellitus, and hypertension

were significantly associated with bleeding complications. These results imply that hepatic dysfunction, hemoconcentration, severe thrombocytopenia, especially pre-existing comorbidities are significant predictors of hemorrhagic dengue fever symptoms. Similar types of predictors were reported in the previous study which support our results.¹⁵ Patients who presented with hemorrhagic manifestation had considerably poorer clinical outcomes. ICU hospitalization was necessary for 24 (20.7%) individuals with hemorrhagic symptoms versus 12 (4.2%) participants without bleeding. Similarly, 27 (23.3%) individuals with hemorrhagic symptoms had blood transfusion, in contrast to only 2 (0.7%) individuals without bleeding needed it. Death rate was also considerably greater in the hemorrhagic group, with 7 (6.0%) mortality rate compared to 1 (0.4%) death rate among individuals with no hemorrhagic manifestations. According to these results, hemorrhagic symptoms are closely linked to worse outcomes and a more severe illness. Our study findings are comparable to the study conducted by Khan et al¹⁴ in which individuals with hemorrhagic manifestation had considerably poorer clinical outcomes which favor our results. Our results are also comparable to data from Latin America.¹⁶ Our study explored that hemorrhagic manifestations are significantly predicted by severe thrombocytopenia, elevated hematocrit, elevated ALT, diabetes mellitus, and hypertension, while hemorrhagic complications are linked to higher rates of ICU admission, increased blood transfusion requirements, and higher mortality. These findings highlight how crucial it is to identify and closely monitor individuals who are at high risk of bleeding.

Limitations of the study

The results of this single-center, hospital-based prospective observational research might not apply to all dengue fever patients in Pakistan, especially those treated in basic or secondary healthcare institutions or as outpatients. Because it is an observational research, it finds correlations between predictors and hemorrhagic symptoms rather than proving causation. Due to a lack of laboratory resources, dengue virus serotyping, viral load calculation, and sophisticated immunological and coagulation biomarkers—which may have offered more information about the severity of the illness and the risk of bleeding—were not evaluated.

CONCLUSION

The current study concluded that hemorrhagic manifestations were seen in 29% of the individuals with dengue fever. The independent predictors of bleeding were thrombocytopenia, severe dengue, coagulation problems and hemoconcentration. Early identification of these risk factors may allow for more effective therapy and better clinical results.

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