

Predictors, Risk Factors and Clinical Features Associated with Severe Dengue Fever

Amir Rashid, Amer Fakhr*, Abdul Rehman Azeem, Abdul Rehman Arshad**, Waqas Ahmed, Yastoor Ahmed Baig

Department of General Medicine, Pak Emirates Military Hospital/National University of Medical Sciences (NUMS), Rawalpindi Pakistan, *Department of Rheumatology, Pak Emirates Military Hospital/National University of Medical Sciences (NUMS), Rawalpindi Pakistan, **Department of Nephrology, Pak Emirates Military Hospital/National University of Medical Sciences (NUMS), Rawalpindi Pakistan

ABSTRACT

Objective: To study predictors, risk factors and clinical features associated with severe Dengue fever on basis of initial symptom onset, laboratory investigations and physical findings.

Study Design: Cross-Sectional Analytical Study.

Place and Duration of Study: Dengue Ward, Pak Emirates Military Hospital Rawalpindi, Pakistan from Dec 2021 to Mar 2022.

Methodology: Study included 198 hospitalized, serologically proven cases of dengue fever. Patient demographics, symptoms, laboratory parameters and disease complications including bleeding, pleural effusion, ascites were recorded. Parametric tests were done for normally distributed continuous variables. Comparison of means was done for categorical variables. Pearson coefficient was used for quantitative variables. A p value of <0.05 was taken as significant.

Results: Out of total 198 patients, 136(68%) were male and 62(31%) were female. Commonly reported symptoms were fever 76(38%), chills 57(29%), rigors 72(36%), headache 66(33%) and body aches 56(28%). Among disease complications bleeding occurred in 30(15%), pleural effusions in 49(24%), ascites in 44(22%) of patients.

Conclusion: The elderly individuals, male gender, patients with thrombocytopenia, leucopenia, and abnormal liver function test showed higher severity and complication rates.

Keywords: Bleeding, Dengue Fever, Serology.

How to Cite This Article: Rashid A, Fakhr A, Azeem AR, Arshad AR, Ahmed W, Ahmed Baig Y. Predictors, Risk Factors and Clinical Features Associated with Severe Dengue Fever. *Pak Armed Forces Med J* 2026; 76(4): 459-463. DOI: <https://doi.org/10.51253/pafmj.v76i4.10254>

This is an Open Access article distributed under the terms of the Creative Commons Attribution License (<https://creativecommons.org/licenses/by-nc/4.0/>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

INTRODUCTION

According to the data of World Health Organization, dengue fever is one of the leading top ten global health problems – it's also spreading rapidly. There has been a 30-fold increase in global incidence over the past few years. Its incidence in South Asian Subcontinent is also on the rise over recent decades.¹

Each year, millions of people are getting infected with dengue fever (approximately 390 million) around the world, resulting in many mortalities around 36,000 deaths/year.²

More than half of the population around the globe is at risk of dengue infection and people of approximately 141 countries are affected with dengue fever.³

Dengue is caused by a viral disease and spread by bite of *Aedes aegypti* mosquitoes. There are 4 serotypes of dengue virus (DENV 1-4), all of which can cause disease, among which the most common serotype in Pakistan is DENV 2. Previous infection with one dengue serotype is a risk factor for

developing severe infection.⁴

Presence of mosquitoes in fresh water around the homes and around plantation makes it a dreadful vector in disease transmission. It can breed in stagnant water in tyres, pots and water along the pot holes. Major outbreaks have been reported in summer and autumn season, at times extending well into winters.⁵

Most common symptoms of dengue are fever, rash, nausea, vomiting, body aches, headache especially retro orbital pain seen during first week of dengue fever. Some patients with dengue fever develop complications like pleural/pericardial effusion, ascites, profuse bleeding, shock and even death. The patient with severe dengue requires careful observation and management in hospital. Most crucial is the convalescent stage of dengue fever during which chances of dengue shock syndrome and dengue hemorrhagic fever are the greatest.⁶

There is no definitive treatment for dengue fever. Most of its management is supportive. Patients are monitored closely for signs of bleeding and shock, especially during the convalescent stage. Regular blood pressure monitoring, screening for signs of respiratory distress in form of pleuro-pericardial effusions and ascites is undertaken. Most sensitive

Correspondence: Dr Amir Rashid, Department of General Medicine, Pak Emirates Military Hospital Rawalpindi Pakistan

Received: 16 Apr 2023; revision received: 22 Jun 2023; accepted: 26 Jun 2023

marker for dengue shock syndrome was found to be narrow pulse pressure.⁷

Best way to avoid dengue is its prevention, using insecticides, mosquito nets, wearing full sleeves during dawn/dusk hours while outdoors. Measures should also be taken to reduce stagnation of fresh water in pots, containers and along plantations. Mosquito sprays on community level is also an effective way to reduce its spread.⁸

The objective of this study was to study predictors, risk factors and clinical features associated with severe Dengue fever on basis of their initial symptom onset, laboratory investigations and their relation to disease progression.

METHODOLOGY

This study was a prospective cross-sectional study conducted at a major tertiary care hospital managing epidemic of Dengue fever and receiving referrals from all over the country. Data was collected over the period of 4 months from December 2021 till March 2022. The sample size was calculated by using the WHO sample size calculator, considering 5% margin of error and a 95% confidence interval.⁹ The estimated sample size was n=198. Purposive sampling was done to recruit participants. The study started after obtaining approval from institutional Ethical Board Committee (vide letter no A/28/166(2)/EC/498/2023).

Inclusion Criteria: All individuals with positive NS-1 antigen that were admitted in the hospital during the duration of study were included in the study.

Exclusion Criteria: NS-1 negative patients with similar presenting symptoms and patients with past history of dengue fever were also excluded.

Informed consent for inclusion in the study was taken from all participants. Patient demographics including age, gender and day of illness were recorded. Presence of individual symptoms and clinical findings were recorded by interviewing and examining the patients at bed side. Patient's Complete Blood Counts, Renal and Liver Function test, reports of ultrasound chest/abdomen were also collected. Ultrasound chest and abdomen were performed by consultant radiologists with 15 years of experience. Ultrasound was done at patient's bedside to confirm the presence of pleural effusion and ascites

Data was entered into Statistical Package for Social Sciences version 23 (SPSS 23) for analysis. Parametric tests were done for normally distributed

continuous variables. Comparison of clinical parameters among males and females patients by chi square test. p-value of ≤ 0.05 was taken as statistically significant.

RESULTS

Out of total 198 patients, 136(68.3%) were male and 62(31.2%) were female. Mean age of sample population was 39.8 ± 12.8 years. Average day of illness was 5.9 ± 2.1 . Mean platelet counts were $82.0 \pm 55.4 \times 10^9$ while mean value of hemoglobin was 13.4 ± 4.6 g/dl. Mean value of leukocytes, urea, alanine aminotransferase and serum creatinine levels were $3.6 \pm 11.7 \times 10^6$, 4.6 ± 1.1 mg/dL, 87.9 ± 52.1 umol/L and 97.0 ± 17.1 umol/L respectively as shown in Table-I.

Table-I: Demographic and Laboratory Parameters of Patients with Dengue Fever (n=198)

Parameter(s)	Values
Age (years)	39.8 ± 12.8
Day of Illness	5.9 ± 2.1
Total Leucocytes count (TLC)	$3.6 \pm 11.7 \times 10^6$
Hemoglobin (Hb) g/dl	13.4 ± 4.6
Platelets count (billion per liter)	$82.0 \pm 55.4 \times 10^9$
Aminotransferase (AST) umol/L	87.9 ± 52.1
Serum Creatinine umol/L	97.0 ± 17.1
Urea mg/dL	4.6 ± 1.1

Commonly reported symptoms were fever 76(38.3%), chills 57(28.7%), rigors 72(36.3%), headache 66(33.3%) and body aches 56(28.2%). Among disease complications, 30(15.1%) patients developed bleeding while pleural effusions occurred in 49(24.7%) and ascites in 44(22.2%) of patients as shown in Figure.

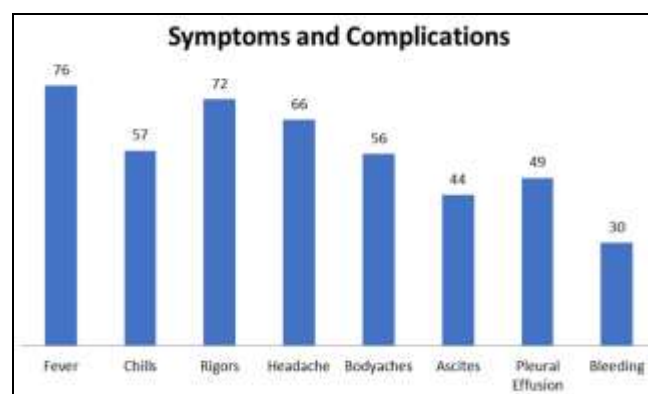


Figure: Commonly Reported Symptoms And Complications Among Patients with Dengue Fever (n=198)

Significant differences between genders were noted in symptoms and complications, fever was reported in 50(36.7%) of the male patients and in 26(41.9%) of the female patients. Similarly, body aches

were reported in 42(30.8%) males and 14(22.5%) females. Rate of complications were higher among male population, like 23(16.9%) of males developed bleeding and only 7(11.2%) females underwent a bleeding episode. Similarly, ascites was present in 35(25.7%) of males and 9(14.5%) females. Pleural effusion was seen in 40(29.4%) male patients and 9(14.5%) female patients as shown in Table-II.

Table-II: Comparison of Clinical Parameters Among Males and Females Patients (n=198)

Parameter(s)	Males (n=136)	Females (n=62)	p-value
Fever	50 (36.7%)	26(41.9%)	0.001
Body aches	42(30.8%)	14(22.5%)	0.015
Pleural Effusion	40(29.4%)	9(14.5%)	0.020
Ascites	35(25.7%)	9(14.5%)	0.001
Bleeding	23(16.9%)	7(11.2%)	0.001

DISCUSSION

The results of our study revealed that advancing age, male gender and patients with thrombocytopenia, leucopenia and abnormal liver function are more prone to complications of dengue fever. Bashir et al in a study done in Sudan found that most common bleeding manifestations were hematuria, hematemesis and hemoptysis. Bleeding rates were higher in patients with lower platelets and higher platelets distribution width.¹⁰ Similar results were found in our study in which higher rates of bleeding were related to lower platelet counts.

The center where study was conducted was getting referrals from all over the country so our results include adults with different age groups belonging to different cities of country. Both males and females were included and the risk for disease severity was greater in males as compared to females. Therefore, as per our study male gender is at higher risk of developing severe dengue.

Our results showed higher male to female ratio, the results are similar to study by Momin *et al*, in which significantly higher number of male population was infected with dengue fever as compared to the female population¹¹. These findings were in contrast to studies conducted in Latin America showing the similar rates of dengue fever in males and female population and even higher in female.¹² One of the reasons behind the higher prevalence of dengue in males could be the cultural one as males and female clothing in our part of world is different as compared to Americas. Males here work outside, take off their

shirts while working in fields in summer while females stay at home and fully cover their body even at home. Second reason could be that male patients seek medical attention and visit hospitals much more conveniently as compared to females in our part of the world, who try home remedies for any illness first due to social issues and lack of education/awareness.

A study conducted in university hospital Thailand, as per the study the severity of dengue was compared between adults and children, adults were at higher risk of developing severe dengue and its complications as compared to younger age group¹³.

In early stages of dengue, the sign and symptoms in patients are difficult to differentiate from other viral illnesses. Other viral hemorrhagic fever presents in early stages in similar fashion like Q fever, rickettsia infections, malaria and Congo fever. Tewari *et al*. in their study at a tertiary care hospital found dengue fever with warning signs to be present in 11% of their patients, out of which severe bleeding occurred in only 2% of patients, although initially 67% of patients were found to have thrombocytopenia¹⁴. It may be inferred that initial complete blood counts along with clinical features and manifestations in patients with dengue, help with early diagnosis and risk stratification. Patients with low total leucocytes (<4000/ μ L) and low platelet counts can be predicted to develop severe dengue infection.

The cases included in our study were (NS1) nonstructural protein positive. Antibodies test including IgM and IgG also helps in diagnosis if patient presents late in disease course or is NS1 negative. A study conducted by Azeredo *et al*. in Burma determined antibodies against dengue fever to be also a marker for severity of disease. Patients with positive antibodies showed higher disease progression and severity as compared to patients with negative antibodies. Patients infected with DENV 2 serotype showed higher progression to development of Dengue Shock Syndrome (DSS)¹⁵.

Basurko *et al*. in his systematic review and meta-analysis, found that the main predictors for severe dengue were child age group, repeated dengue infection from different serotypes, pre-existing co-morbidities [i.e., diabetes and renal disease(s)]¹⁶. These findings were different from our study because patients with different co morbidities including diabetes and hypertension did not show significant severity. In our part of the world, we need more studies especially including children to better

understand the factors responsible for severity in this age group.

Our study found low platelets count, leukopenia and transaminitis to be related with higher severity rates and development of complications like pleural effusion, ascites and gall bladder wall thickness. This is similar to a study conducted by Quinn *et al*, in which leukopenia and low platelets counts were reported to be related with higher rates of bleeding¹⁷.

In our study fever was present in 79% of patients, 58% had body aches, 66% reported headache, 57% had rigors, 72% had Chills and retro orbital pain was present in 25% of patients as initial symptoms at presentation. A study conducted by Haroon *et al*. in one of the major hospitals of Pakistan¹⁸, showed fever in 100% of patients, headache in 97% and body aches in 93% off patients. Abdominal pain was reported in 84% while bleeding occurred in only 8% of patients. Bleeding rate was higher in our study as compared to the study done by Haroon *et al*. the symptoms in both studies are similar. According to Khan *et al*. severity was higher in patients with kidney and lungs disease, secondary infections and diabetes, this shows the patients with co-morbidities should be given attention timely to prevent the complications of dengue.¹⁹

Akinsolu *et al*. researched the pathogenesis of dengue virus infection and development of novel treatments²⁰. Chan *et al*. showed reverse transcriptase polymerase chain reaction (RRT-PCR) to be a very reliable investigation for detection of dengue virus in difficult to diagnose cases²¹. Afridi *et al*. also showed RT-PCR to be a reliable investigation for early diagnosis of dengue fever during first week of illness. They showed that immunoglobulin IgM levels are useful after first week of dengue infection²². Hassan *et al*. studied relationship of bleeding in dengue patients with the coagulation time and platelet counts. They also found a significant relationship between bleeding and platelet count although no relationship was found between bleeding time and coagulation parameters²³. These findings are in concordance with findings of our study in which lower platelet counts were associated with higher bleeding rates.

CONCLUSION

According to our study elderly patients, male gender, patients with thrombocytopenia, leucopenia, and abnormal liver function test were related with higher severity as they developed higher number of complications including bleeding, ascites and pleural effusion. However, no co relation of co morbidities like diabetes mellitus, ischemic

heart disease, chronic kidney disease and hypertension was noticed.

LIMITATION OF STUDY

The current study is a single hospital based study with fewer number of admitted cases. For better results we need multi-centered studies at different hospitals in different parts of country. Patients with mild symptoms were not included in this study as they did not undergo extensive laboratory work up nor were offered hospital admission. More studies are required to be done on populations with mild symptoms which shall help in better understanding of the disease.

ACKNOWLEDGEMENT

We acknowledge contributions made by our colleagues Dr. Bilal Ahmed Kayani, and our mentor Prof. Dr. Shazia Nisar for their support.

Conflict of Interest: None.

Discolure:

Funding Source: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

AR & AF: Data acquisition, data analysis, critical review, approval of the final version to be published.

ARA & ARA: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

WA & YAB: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

REFERENCES

1. Khan T, Nisar S, Qureshi M, Samiullah M, Israr M. Dengue Fever Outbreak in Twin Cities; A Tertiary Care Center Experience. *Pak Armed Forces Med J* 2021; 71(5): 1524-1528. <https://doi.org/10.51253/pafmj.v71i5.4165>
2. Shabir M, Nisar S, Urooj Z, Sohail M, Khan MS, Khan DH. Thrombocytopenia and its Relationship with Bleeding Manifestations in Dengue Patients-A Tertiary Care Hospital Experience. *Pak Armed Forces Med J* 2022; 72(6): 2021-2024. <https://doi.org/10.51253/pafmj.v72i6.4553>
3. Department of Disease Control, Ministry of Public Health. Dengue Report; Department of Disease Control, Ministry of Public Health: Nonthaburi, Thailand, 2022.
4. Irshad Z, Jaffar N, Zehra T, Zeeshan F, Tashfeen S, Sheikh A. Association of Abnormal Coagulation Tests in Dengue Fever with Clinical Outcomes of The Patients. *Pak Armed Forces Med J* 2022; 72(1): 159-163. <https://doi.org/10.51253/pafmj.v72i1.4255>
5. Ur Rehman MM, Zakaria M, Mustafvi SA. Clinical And Laboratory Profile Of Dengue Fever Patients Admitted In Combined Military Hospital Rawalpindi In Year 2015. *Pak Armed Forces Med J* 2017; 67(4): 496-501.

6. World Health Organization. Dengue fever – Pakistan [Internet]. Geneva: World Health Organization; 2019 Nov 19 [cited 2023 Jan 3].
7. Irshad Z, Shabbir A, Shaikh A, Hasan SM, Abid M. Association of thrombocytopenia and prolonged bleeding time in dengue with the clinical outcome of the patient. *Pak Armed Forces Med J* 2019; 69(5): 1029-1034.
8. Ahmad S, Aziz MA, Aftab A, Ullah Z, Ahmad MI, Mustan A. Epidemiology of dengue in Pakistan, present prevalence and guidelines for future control. *Int J Mosq Res* 2017; 4(6): 25-32.
9. Srisuphanunt M, Puttaruk P, Kooltheat N, Katzenmeier G, Wilairatana P. Prognostic Indicators for the Early Prediction of Severe Dengue Infection: A Retrospective Study in a University Hospital in Thailand. *Trop Med Infect Dis* 2022; 7(8): 162.
10. Bashir AB, Mohammed BA, Saeed OK, Ageep AK. Thrombocytopenia and bleeding manifestations among patients with dengue virus infection in Port Sudan, Red Sea State of Sudan. *J Infect Dis Immun* 2015; 7(2): 7-13. <https://doi.org/10.5897/IJDI2014.0143>
11. Momin A, Anwar A, Imtiaz M, Mustafa N. Gender and age based evaluation of clinical signs and symptoms of dengue: A secondary data analysis. *SOJ Microbiol Infect Dis* 2019; 6(1): 1-4.
12. Lopez-Gatell H, Hernandez-Avila M, Hernández Avila JE, Alpuche-Aranda CM. Dengue in Latin America: a persistent and growing public health challenge. In: *Neglected Tropical Diseases: Latin America and the Caribbean*. Vienna: Springer; 2015 p 203-224. https://doi.org/10.1007/978-3-7091-1422-3_11
13. Khare RK, Raj P. Dengue fever with thrombocytopenia and its complications: a hospital based study. *J Adv Med Dent Scie Res* 2017; 5(3): 72.
14. Tewari K, Tewari VV, Mehta R. Clinical and hematological profile of patients with dengue fever at a tertiary care hospital—an observational study. *Mediterr J Hemat Infect Dis* 2018; 10(1): 1-7. <https://doi.org/10.4084/MJHID.2018.021>
15. Azeredo EL, Monteiro RQ, de-Oliveira Pinto LM. Thrombocytopenia in dengue: interrelationship between virus and the imbalance between coagulation and fibrinolysis and inflammatory mediators. *Mediators Inflamm* 2015; 2015: 313842. <https://doi.org/10.1155/2015/313842>
16. Basurko C, Everhard S, Matheus S, Restrepo M, Hildéral H, Lambert V, et al. A prospective matched study on symptomatic dengue in pregnancy. *PLoS One* 2018; 13(10): e0202005. <https://doi.org/10.1371/journal.pone.0202005>
17. Quinn EJ, Cheong AH, Calvert JK, Higgins G, Haesey T, Gordon DL, et al. Clinical features and laboratory findings of travelers returning to south australia with dengue virus infection. *Trop Med Infect Dis* 2018; 3(1): 6-10. <https://doi.org/10.3390/tropicalmed3010006>
18. Haroon M, Jan H, Faisal S, ALi N, Kamran M, Ullah F. Dengue outbreak in peshawar: clinical features and laboratory markers of dengue virus infection. *J Infect Public Health* 2019; 12(2): 258-262. <https://doi.org/10.1016/j.jiph.2018.10.138>
19. Khan MM, Khan H. DENGUE FEVER IN PAKISTAN: WHAT TO DO NOW? *Gomal J Med Sci* 2015; 13(4): 197-198.
20. Akinsolu FT, de Paiva VN, Souza SS, Varga O. Patent landscape of neglected tropical diseases: an analysis of worldwide patent families. *Global Health* 2017; 14-13(1): 82. <https://doi.org/10.1186/s12992-017-0306-9>
21. Chan HBY, How CH, Ng CW. Definitive tests for dengue fever: when and which should I use?. *Singapore Med J* 2017; 58(11): 632-635. <https://doi.org/10.11622/smedj.2017100>
22. Afridi N, Ahmed S, Khan S, Ali N, Rauf S. early diagnosis of dengue virus infection in clinically suspected cases. *Pak Armed Forces Med J* 2016; 66(6): 837-840.
23. Hassan J, Borhany M, Abid M, Zaidi U, Fatima N, Shamsi T. Coagulation abnormalities in dengue and dengue haemorrhagic fever patients. *Transfus Med* 2019; 30(1): 1-5. <https://doi.org/10.1111/tme.12658>