

Research Article

Dengue Hemorrhagic Fever: Risk Factors in Pakistani Cohort

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Abstract

Background: Dengue fever is a mosquito-borne infectious disease with potential complications such as dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) and has fatality risk of greater than 20% if left untreated. There is lot of heterogeneity in factors predicting development of DHF in different populations.

Objective: To determine clinical, biochemical and radiological parameters associated with risk of developing DHF in Pakistani population.

Methods: This prospective observational study was conducted in Jinnah Hospital Lahore from October 2022 to December 2022. 180 patients with confirmed Dengue fever were included. Detailed history, clinical examination and laboratory/radiological investigations were performed. Patients were followed for development of DHF. Univariate analysis followed by logistic regression analysis was used to determine independent predictors for DHF.

Results: Among 180 patients with Dengue fever with mean age of 33.04 (± 14.12) and male to female ratio of 1.53/1 (109/71), we identified presence of mucosal bleeding {OR 4.7 (95% CI 2.05-10.78) p value <0.000}, abdominal pain {OR 2.73 (95% CI 1.17-4.38) p value 0.013}, persistent vomiting {OR 3.09 (95% CI 1.51-6.34) p value 0.002}, tender right hypochondrium {OR 3.98 (95% CI 1.94-8.16) p value <0.000} and presence of peri-cholecystic fluid {OR 7.78 (95% CI 3.25-18.63) p value < 0.000} to be significantly associated with risk of developing DHF with 83.6% accuracy on logistic regression analysis.

Conclusion: Mucosal bleeding, right hypochondrium pain, persistent vomiting and presence of peri-cholecystic fluid in a patient of dengue fever predict risk of developing dengue hemorrhagic fever.

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Introduction

The burden of dengue fever, an infectious disease with high prevalence in tropical regions, is growing quickly. Any one of the four dengue virus serotypes can

be the cause: DENVs 1-4.¹ Since it is a mosquito-borne illness, the female Aedes mosquito is the main vector for human transmission.² Dengue virus infection causes a range of clinical states, from mild asymptomatic dengue fever (DF) to severe dengue hemorrhagic fever (DHF) and potentially fatal dengue shock syndrome (DSS).³ Rapid urbanization, an increase in international travel, a lack of efficient mosquito control techniques, and globalization have



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all contributed to the Dengue virus remarkable global spread.⁴

Each year, the dengue virus infects humans in over 100 nations, putting an estimated 3.6 billion people at risk. The incidence of dengue has grown 30-fold over the previous 50 years (CDC 2014).⁵ Numerous dengue fever epidemics that affected thousands of people and resulted in hundreds of fatalities occurred in Pakistan over last 2 decades. Comparing data from these epidemics reveals a change from a mild to a more severe illness patterns, which could be seen as the country's epidemiological transition pattern.⁶ Numerous deaths are reported every year in Pakistan related to dengue fever due to evolving severity of illness in our region. It has grown to be a significant health issue in Pakistan and is predicted to get worse over the next few years.⁷

Dengue fever, like other viral infections, is otherwise a self-limiting disease in majority of cases. It is feared because of its potential complications like Dengue Hemorrhagic Fever And Dengue Shock Syndrome that have a mortality rate of more than 20% when untreated.⁸ The range of disease severity is very broad varying from classical break bone fever to DHF and DSS manifested by warning signs like abdominal pain, intractable vomiting, mucosal bleeding, lethargy, decreasing platelets and rising hematocrit.⁹

There have been many studies correlating risk factors that can increase mortality in dengue patients. A study in 2013 predicting the prognostic factors for dengue severity revealed that risk factors for DHF were age more than 6 years, bleeding episodes, white cell count $> 5,000/\mu\text{L}$, platelet $\leq 100,000/\mu\text{L}$ and the factors that precipitate the risk of DSS included hepatomegaly, bleeding episodes, pulse pressure ≤ 20 mmHg, SBP < 90 mmHg, hematocrit $> 40\%$ white cell count $> 5,000/\mu\text{L}$, and platelet $\leq 100,000/\mu\text{L}$.¹⁰ A study conducted between 2009 and 2013 in Taiwan identified GIT bleeding < 72 hours, thrombocytopenia, AKI, leukocytosis as risk factors that increase mortality in hospitalized patients within 3 days of presentation and within 7 days of dengue onset.¹¹ Another study in 2017 showed that raised ALT, AST and bilirubin levels with low albumin levels were reliable prognostic indicators from day 4-6.¹² A study in Brazil showed older age (> 55 years), gastrointestinal bleeding, hematuria, and thrombocytopenia as predictors of mortality in severe dengue cases.¹³ Other

factors include being a child, secondary infection, diabetes and renal disease.¹⁴

There is lot of heterogeneity in factors predicting development of DHF in different populations and these parameters also lack specificity and sensitivity as number of other diseases can effect these variables as well. Since dengue arrives as epidemic in Pakistan every year and disease has shown evolution over the years, we planned a study to determine clinical, biochemical and radiological parameters associated with risk of developing dengue hemorrhagic fever.

Methods

The study, after approval from Institutional Ethical Board (ERB 144/5/09-06-2023/S1 ERB), was conducted In Jinnah Hospital Lahore from October 2022 to December 2022. Sample size calculated for study using CliniCalc® online calculator, was 126 keeping margin of error $< 5\%$, 90% confidence level and 30% patients expected to develop dengue hemorrhagic fever. Due to possible dropouts, we include 180 patients in our study. All the suspected or confirmed cases of dengue fever admitted in the Medical units of Jinnah Hospital were enrolled in the study. Inclusion criteria was patients having fever of 2-7 days duration with two of the associated symptoms such as arthralgia/myalgia, abdominal pain, hemorrhagic manifestations, retro orbital pain, headache, rash and decreased urine output. Only patients with confirmed Dengue fever as diagnosed by positive NS1 Ag during first 5 days of fever, positive IgM, PCR or 4 fold rise in titer of IgG serology for dengue fever were included and admitted for follow up.⁽¹⁵⁾ Patients with fever of less than 2 days or more than 10 days were excluded from study. Patients with chronic liver disease, chronic kidney disease or those with concomitant infections like pneumonia, urinary tract infection, meningitis suspected clinically and confirmed with relevant tests etc were excluded.

Patients were followed up from the day of admission till the day of discharge from hospital or death. Detailed history and clinical examination was performed with prime focus on tender hepatomegaly, Maculopapular rash and signs of plasma leakage. All the laboratory/radiological investigations like Complete blood count, liver function tests, renal function tests, Abdominal Ultrasound and X ray chest were also followed during

the study. Patients were monitored 4 hourly for vitals, pulse pressure, fluid intake/output and signs of hemodynamic instability. Monitoring was done every 15 minutes for patients in dengue shock syndrome. Dengue hemorrhagic fever was diagnosed in patients of dengue fever who were confirmed to have plasma leakage with pleural effusion and/or ascites on ultrasound examination. Patients who had drop in pulse pressure to < 20 mm of Hg or had systolic blood pressure < 90 mm of Hg were diagnosed as patients of Dengue Shock Syndrome (DSS).⁽¹⁵⁾ Convalescent or recovery phase was diagnosed once patient is afebrile, had hemodynamic stability with pulse pressure above 30mm of Hg, systolic blood pressure > 90 mm of Hg, stable hematocrit, and rise of platelet count above 50,000/mm.³

Data was analyzed using SPSS 22® (Armonk NY:IBM corp). Numerical variables were analyzed as mean± standard deviation (SD) while percentage was used for nominal or categorical variables. Median± interquartile range (IQR) was used to express variables with non-parametric distribution.

Clinical, laboratory and radiological variables of patients were independent variable while presence of DHF was considered as dependent variable. Mann Whitney U test was used for non-parametric variables while unpaired student's t test and chi square χ^2 were used for numerical and nominal variables with normal distribution respectively to determine association with DHF. P value of <0.05 was considered significant. Once variables with significant association with DHF were identified, binary logistic regression analysis was used to evaluate combined association of these variables with dengue hemorrhagic fever.

Results

Total of 180 patients with confirmed Dengue fever were included in study with mean age of 33.04 (±14.12) and male to female ratio of 109/71. Mean duration of illness in included patients was 8.31(±1.8) days and mean span of fever in these patients was 5.61(±1.69) days. Apart from fever, 138(76.7%) patients had headache, 104(57.8%) reported retro-orbital pain, 102(56.7%) developed abdominal pain, 58(32.2%) complained of sore throat, 67(37.2%) complained of mucosal bleeding, gastrointestinal bleeding was reported by 29(16.1%), menorrhagia was noted by

13(7.2%) and 155 (86.1%) patients developed significant fatigue with dengue fever. Diabetes mellitus was present in 20(11.1%) patients, 15(8.3%) were suffering from hypertension and 18(10%) had suffered from dengue fever previously as well.

At hospital admission, 27(15%) patients had tachycardia while systolic blood pressure was < 90 mm of Hg in 26(14.4%) patients. Pulse pressure was <20mm of Hg in 20 (11.1%) patients at admission in hospital while 14(7.8%) were jaundiced and 86(47.8%) had tender right hypochondrium. During admission 57(31.7%) patients were diagnosed to have ascites, 31(17.2%) developed pleural effusion while 30 (16.8%) had both pleural effusion and ascites on ultrasound examination. Peri-cholecystic fluid was reported in 78(43.3%) patients. Dengue hemorrhagic fever (DHF) was identified in 128 (71.1%) of study patients and 18(10%) of these patients also developed dengue shock syndrome (DSS).

Patients with DHF were managed in high dependency unit (HDU). Normal saline bolus were needed in 92 (51.1%) patients to maintain pulse pressure above 30 mm of Hg. Dextran 40 was used in 14 (7.8%) patients, 500ml in 9 (5%), 1000 ml in 3(1.7%) and 2(1.1%) patients needed 1.5 liters of Dextran 40 to maintain pressures. Whole blood transfusion was needed in 2 (1.1%) and platelet concentrates in 2 (1.1%) patients of gastrointestinal bleeding.

All patients recovered and got discharged after in-hospital management except 2(1.1%) patient who recovered after suffering viral encephalitis. Mean duration of illness till rise of platelet count above 50,000/mm³ on serial testing 24 hours apart, indicative of start of disease resolution was 6.94(±2.48) days. We compared clinical, biochemical and imaging parameters between patients with and without dengue hemorrhagic fever (DHF) to identify factors associated with DHF as shown in table-I. We identified presence of mucosal bleeding {OR 4.7 (95% CI 2.05-10.78)p value <0.000}, abdominal pain {OR 2.73 (95% CI 1.17-4.38)p value 0.013}, persistent vomiting {OR 3.09 (95% CI 1.51-6.34)p value 0.002}, tender right hypochondrium {OR 3.98 (95% CI 1.94-8.16) p value <0.000} and presence of peri-cholecystic fluid {OR 7.78 (95% CI 3.25-18.63)p value < 0.000} to be significantly associated with risk of developing DHF.

Model comprising of these 5 variables with significant association had 2 log likelihood of 151.93 for predicting dengue hemorrhagic fever with 83.6% accuracy in logistic regression analysis. (Table-II)

Table 1: Clinical, Biochemical and Imaging Parameters between Patients with and without Dengue Hemorrhagic Fever (DHF)

Variables	Patients with DHF N-128	Patients with no DHF N- 52	P value
Headache	96	42	0.18
Retro-orbital pain	70	34	0.18
Pharyngitis	44	14	0.33
Body rash	16	4	0.35
Mucosal bleeding	65	13	<0.00
Abdominal pain	80	22	0.013
Persistent vomiting	65	13	0.002
Tender Right hypochondrium	73	13	0.000
HTN/DM	10/16	5/4	0.10
Hepatomegaly	13	3	0.39
Splenomegaly	15	6	0.97
Peri cholecystic fluid	71	7	0.000
	Mean(±SD)	Mean(±SD)	
Age	33.1(14.75)	32.8(12.5)	0.89
Duration of fever	5.64(1.64)	5.54(1.85)	0.71
Bilirubin	1.12(1.2)	1.7(2.5)	0.11
Albumin	3.03(1.05)	2.8(0.92)	0.83

Table 2: Classification table for predicting Dengue Hemorrhagic fever

			Predicted		
			Dengue haemorrhagic fever		Percentage Correct
			Yes	No	
Step 1	Dengue haemorrhagic fever	Yes	117	10	92.1
		No	19	31	62.0
	Overall Percentage				83.6
a. The cut value is .500					

a. The cut value is .500

Model Summary			
Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	151.938 ^a	.283	.406

a. Estimation terminated at iteration number 6 because parameter estimates changed by less than .001.

Discussion

Every other year Pakistan faces a Dengue epidemic with increasing severity and mortality.¹⁶ In the year 2021 alone, 48,906 cases with 186 deaths were reported,

despite having developed a robust community-based program for dengue surveillance and control. In our study, clinical, laboratory and radiological parameters were analyzed for their association with DHF. Dengue haemorrhagic fever was diagnosed in 71% patients out of which 10% develop DSS as well. Amongst the parameters studied, abdominal pain, tender Right Hypo-chondrium, peri-cholecystic fluid, mucosal bleed and persistent vomiting were significant predictive factors for DHF.

We noted presence of peri-cholecystic fluid as risk factor for developing DHF. A main cardinal feature of DHF is increased capillary permeability which leads to loss of albumin and fluid in the extra vascular place. Pericholecystic fluid is one manifestation of this process, along with gall bladder wall edema while pleural and pericardial effusion, ascites, raised haematocrit and hypoalbuminemia are other manifestations of same disease process.^{17,18} This suggests that pericholecystic fluid is one of the earliest predictors for DHF and can be used as a significant feature to predict future course of disease.

Our study also identified mucosal bleeding as a strong predictive factor for DHF. Hemorrhagic manifestations mostly occurred around the time of defervescence^{19,20} and these Hemorrhagic manifestations might be due to increased capillary fragility as a result of thrombocytopenia or platelet dysfunction.²¹ Out of 180 total patients, mucosal bleeding occurred in 67(37.2%), gastrointestinal bleeding was reported by 29(16.1%), menorrhagia was noted by 13(7.2%) and these patients had higher frequency of DHF. In a study by Medagama A et al comparing features of patients dying due to dengue fever and those with full recovery, identified active bleeding as a significant ($p < 0.0001$) mortality related factor.²² Studies conducted in Karachi have also noted higher risk of complicated disease in patients of our community with mucosal bleeding.^{23,24}

Vomiting is the most frequent clinical symptom in dengue fever and presence of persistent vomiting is a warning sign of severe illness in dengue infection²⁵. Our data showed persistent vomiting {OR 3.09 (95% CI 1.51-6.34) p value 0.002} to be significantly associated with risk of developing DHF. Yuan K et al concluded that those with persistent vomiting have 5.6 time more risk of severe disease in dengue fever.²⁶ This correlation

of persistent vomiting with DHF is also consistent with other studies conducted in Japan and Thailand.^{27,28}

We included patients only from one tertiary care setup which may limit generalizability of our study. More than 70% of study patients had DHF which is too high as compared to actual risk of developing DHF for a patient suffering from dengue fever in community. As we included patients being admitted in hospital with dengue fever, higher proportion of DHF is understandable and it enabled us to have meaningful data for risk factors of DHF.

In conclusion, Abdominal pain, peri-cholecystic fluid, tender Right Hypochondrium, persistent vomiting and mucosal bleeding were the predictive factors that were found to have significant association with the development of DHF. In a resource poor country like Pakistan, early identification of predictors of severe disease can help in triage and deciding management Stratification of patients accordingly. After triage, strict vital monitoring and early resuscitation can help in reducing the overall mortality from DHF and DSS.

Conclusion

Mucosal bleeding, pain right hypochondrium, persistent vomiting and presence of peri-cholecystic fluid in a patient of dengue fever predicts risk of developing dengue hemorrhagic fever. Presence of these warning signs should guide us in early triage of patient to high dependency unit for strict monitoring which can save lives.

Ethical Approval: The Ethical Review Board, Allama Iqbal Medical College/ Jinnah Hospital, Lahore approved the study vide letter No. ERB144/5/09-06-2023/S1 ERB.

Conflict of Interest: The authors declare no conflict of interest.

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Authors' Contribution:

AA: Acquisition of data, Conception & design, drafting of article, final approval

AAA: Acquisition of data, drafting of article

AS: Acquisition of data, drafting of article

AM: Acquisition of data, drafting of article

SS: Conception & design, analysis & interpretation of data, drafting of article, critical revision for important intellectual content, final approval

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