Original Article

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Leucocytosis and early organ involvement as risk factors of mortality in adults with dengue fever

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SUMMARY The clinical profile and risk factors for mortality in dengue fever have evolved over the years. The all-cause mortality in admitted dengue patients is around 6%. We aimed to evaluate the recent change in trends of the clinical characteristics and risk factors for in-hospital mortality in adults with dengue fever. This is a retrospective study on adults with confirmed dengue fever admitted in a medical unit of a tertiary care center in North India. Medical records of confirmed dengue fever patients admitted between January 2011, and December 2016 were reviewed. Chi-squared tests with Bonferroni correction for multiple testing were used to identify risk factors for mortality. 232 records were included, of which 66.8% were males. The mean age was 31.6 ± 14 years. There were 17 deaths with an all-cause mortality rate of 7.3% with 76.5% being classified as severe dengue at admission. Among the 17 mortality cases, dyspnea (47%), tachypnea (86.7%), leucocytosis (58.8%), raised urea (80%), and elevated serum creatinine (52.9%) at presentation were significantly associated with mortality ($p < 0.001$). Shock at any time during the hospital stay (58.8%) was also found to be significantly associated with mortality ($p < 0.001$). We found that dyspnea, tachypnea, acute kidney injury, and leucocytosis at presentation was significantly associated with in-hospital mortality. Based on our results, we recommend aggressive management of patients with severe dengue and those with mild/moderate disease with the above risk factors.

Keywords Dengue, clinical presentation, mortality, India, retrospective

1. Introduction

Dengue fever is rapidly re-emerging as an epidemic in the Indian subcontinent and spreading to newer areas across the globe (*1*). It continues to be a significant cause of morbidity and mortality, particularly in resource-limited settings in the countries of South-East Asia. A 2018 meta-analysis reported a pooled case fatality rate of 2.6% in India (*2*). The national statistics, however, puts the case fatality rate for 2019 to be about 0.09%. It is a matter of urgent public health priority for endemic countries like India (*3*).

Dengue can have a myriad of manifestations ranging from being asymptomatic to mild fever to having fatal complications. The in-hospital all-cause mortality for dengue fever is reported to be 5.9% as a result of referral bias (*4*). It is crucial to identify clinical and laboratory features which portend severe illness and are risk factors for poor outcomes. In the initial research around the risk factors for mortality, bleeding, and thrombocytopenia were given much importance (*5,6*). It was later discovered that bleeding is a marker for severity and thrombocytopenia did not portend poor outcomes. The focus later shifted to systemic and other organ involvement. The knowledge of mortality risk factors will help in better triage of patients and the efficient utilization of limited healthcare resources. The available evidence is, however, scarce and difficult to interpret.

We aimed to perform a retrospective analysis of the clinical characteristics of adult patients admitted with confirmed dengue fever. We further analyzed the admission characteristics that are risk factors for mortality in these patients.

2. Materials and Methods

This is a retrospective observational study on confirmed cases of dengue fever in adults. Ethical clearance was obtained from the institutional ethics committee. Medical records of confirmed cases of dengue fever admitted under the medical unit between January 2011 and December 2016 were reviewed. These records were classified under the codes A90 and A91 of the 10th Revision of the International Classification of Diseases (ICD)-10.

Inclusion criteria included admitted patients with either a positive Enzyme-Linked Immunosorbent Assay (ELISA) based NS-1 antigen test or a positive anti-dengue IgM antibody capture ELISA (MAC-ELISA) test. Any patient aged less than 14 years was excluded from the study. The cases were classified as mild, moderate, and severe dengue based on the national guidelines for the clinical management of dengue fever (*3*).

Mild dengue is fever without complications, signs of capillary leak, and organ involvement. Any patient with warning signs like recurrent vomiting, abdominal pain, lethargy, hepatomegaly, or signs of a capillary leak is classified as moderate dengue. Patient with extremes of age, pregnancy, diabetes, hypertension, coronary artery disease (CAD), hemoglobinopathy, immunosuppression, are at high risk and classified as moderate dengue. Dengue fever with significant bleeding, severe metabolic abnormalities, shock, or multiple organ involvement is classified as severe dengue.

Data were extracted to a predesigned proforma containing demographic details, presentation, investigations, and outcomes of the patients. This was analyzed using Stata 12 software (Stata Corp [2011], College Station, TX). Categorical variables are represented as frequency (percentage), while continuous variables are presented as mean (standard deviation) or median (interquartile range). Demographic details, presentation, and investigations were categorized into clinically meaningful subgroups. These were then analyzed using a Chi-square test or Fisher's exact test to identify differences based on the outcome of the patient (death *vs*. survival). Significance was considered at an alpha of 0.05 and a 95% confidence interval. The analysis was subjected to a Bonferonni correction to account for multiple tests. Following this, the *p*-value for significance was considered at a value < 0.002.

Table 1. Demographic characteristics of the study population.

Characteristics	Frequency (%)
Age	
14-30 years	138 (59.5)
31-45 years	57 (24.6)
46-60 years	26 (11.2)
> 60 years	11 (4.7)
Sex	
Male	155 (66.8)
Female	77 (33.2)
Hospital stay	
Less than 5 days	113 (48.7)
5-10 days	100 (43.1)
> 10 days	19 (8.2)
Comorbidities	
Hypertension	12 (5.2)
Diabetes Mellitus	07 (3.0)
Chronic kidney disease	04 (1.7)
Chronic liver disease	02 (0.9)
Others	19 (8.2)

3. Results

3.1. Demographic data and clinical profile at presentation

A total of 232 cases of confirmed dengue fever were included in the study after satisfying the inclusion criteria. The mean age was 31.6 ± 14 years, and 66.8 % were males. The demographic details are presented in Table 1. The median number of comorbidities in our cases was 0 (0, 0) with the maximum being three. 94.4% of the patients were from Delhi and the neighboring states of Haryana and Uttar Pradesh. The number of cases distributed by year is depicted in Figure 1.

Of the 232 patients, 42.7% of patients were classified as mild, 39.6% of patients were classified as moderate, and 17.7% had severe dengue. 47.8% presented between the 4th and 6th day of onset of fever (critical phase) with the mean duration of illness at a presentation being 5.7 ± 4.8 days. 15.1% of the patients were admitted beyond the 6th day of fever (recovery phase).

The clinical presentation of the patients is depicted in Table 2. Patients presenting with bleeding manifestations had a significantly lower platelet count at admission (32,000 cells/mm^3) when compared to those who did not present with bleeding manifestations (48,000 cells/mm^3). The most common sites of bleeding included mucosal bleed (21%) followed by bleeding from venipuncture site (21%). Menorrhagia in females (16% of females) was a common presenting complaint. Severe bleeding in the form of massive hematemesis or retroperitoneal hematoma was seen in 3% of the patients.

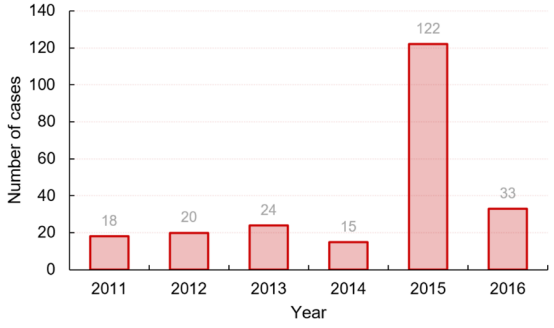

Figure 1. Year-wise distribution of cases in the study population (*n* = 232).

Table 2. Clinical profile of the study population (n = 232).

Clinical characteristic	Number of patients [n (%)]
Symptoms	
Fever	232 (100)
Myalgia	129 (55.6)
Recurrent vomiting	116 (50.0)
Headache	110 (47.4)
Abdominal pain	087 (37.5)
Bleeding	081 (34.9)
Oral	17 (21.0)
Venipuncture site	17 (21.0)
Malena	10 (12.3)
Hematemesis	08 (9.9)
Epistaxis	06 (7.4)
Hematuria	06 (7.4)
Hematochezia	04 (4.9)
Others	14 (17.3)
Rash	052 (22.4)
Arthralgia	039 (16.8)
Examination findings	
Pulse rate (mean ± SD)	88.7 ± 15.3
Systolic blood pressure (mmHg); (mean ± SD)	114.9 ± 20.44
Diastolic blood pressure (mmHg); (mean ± SD)	74.13 ± 15.17
Respiratory rate (mean ± SD)	19 ± 4.7
Hepatomegaly	20 (8.6)
Serositis (Ascites/pleural effusion)	47 (20.2)

Table 3. Risk factors for in-hospital mortality

Characteristic	Mortality [n (N)]	Survivor [n (N)]	p value
Demographic			
Age > 45 years	8 (17)	38 (215)	0.003
Male sex	13 (17)	142 (215)	0.380
Symptoms			
Rash	3 (17)	49 (214)	0.618
Bleeding manifestation	9 (17)	72 (212)	0.115
Headache	4 (17)	106 (213)	0.037
Abdominal pain	10 (17)	77 (213)	0.064
Dyspnea*	8 (17)	19 (213)	< 0.001
Arthralgia	1 (17)	38 (213)	0.21
Vomiting	9 (17)	107 (213)	0.83
Myalgia	6 (17)	123 (213)	0.073
Examination			
Pulse Rate > 100 bpm	6 (17)	11 (212)	0.060
Respiratory Rate > 20/min*	13 (15)	83 (209)	< 0.001
Shock*	10 (17)	10 (202)	< 0.001
Investigations			
Hemoglobin < 10 g/dL*	10 (17)	188 (207)	< 0.001
Corrected hematocrit > 20%	5 (15)	32 (208)	0.071
TLC < 4000 cells/mm^3	0 (17)	70 (205)	0.004
TLC > 11000 cells/mm^{3*}	10 (17)	20 (205)	< 0.001
Platelet < 50000 cells/mm^3	12 (17)	118 (213)	0.224
Urea > 20 mg/dL*	12 (15)	61 (185)	< 0.001
Serum creatinine > 1.2 mg/dL*	9 (17)	18 (186)	< 0.001
Transaminitis	8 (12)	92 (156)	0.60
Albumin < 3.5 g/dL	9 (12)	64 (147)	0.035

*Significance considered at $p < 0.002$ after Bonferroni correction

3.2. Organ system involvement

Acute kidney injury (AKI) was defined as serum creatinine greater than 1.2 mg/dL without a previous history or imaging evidence of chronic kidney disease. This was seen in 14.6% of our study population at presentation. A Fisher's exact test showed a significant association between hypotension at any point in the hospital stay and the presence of AKI ($\chi^2 = 26.45$, df = 1, $p = 0.002$).

Transaminitis was defined as an elevation of alanine transaminase (ALT) or aspartate transaminase (AST) beyond three times the upper limit of normal (> 120 IU/L). This was seen in a total of 51.6% of 172 patients with available liver enzyme data. When transaminitis was present, the median AST/ALT ratio was 1.8 (1.3, 2.6), and the median total bilirubin level was 0.7 (0.4, 1.4). Hepatomegaly was seen in 20 patients. A Fisher's exact test showed no significant difference in the presence of hepatomegaly between those with and those without transaminitis ($\chi^2 = 0.006$, df = 1, $p = 0.9$). There was also no significant difference in the presence of vomiting or pain abdomen at admission between those with and those without transaminitis ($\chi^2 = 0.21$, df = 1, $p = 0.64$).

Complications involving the central nervous system (CNS) in the form of altered sensorium, drowsiness, seizures, or any features of encephalopathy or encephalitis were seen in 11.6% of the patients. One patient was diagnosed with dengue encephalitis with an initial presentation of fever, seizures, and headaches. Blood and CSF IgM antibodies for dengue were positive. Other causes of viral encephalitis (Herpes, Japanese encephalitis) were ruled out in this patient.

Twenty-five patients required invasive mechanical ventilation during their hospital stay. Respiratory failure (defined as a pf ratio < 300) was the indication in 48% of the patients.

3.3. Mortality and its risk factors

Seventeen patients died, leading to an all-cause mortality rate of 7.3%. Among the mortality cases, 13 were classified as severe dengue at admission. 11 out of the 17 patients did not have any comorbidities. A Mann Whitney U test did not show any significant differences in the number of comorbidities between the mortality and the survival cases. 15 out of the 17 mortality cases required invasive mechanical ventilation with eight being intubated for respiratory failure.

The demographic characteristics, symptoms, and laboratory investigations were categorized. Chi-square tests and Fisher's exact tests were done with Bonferroni corrections for multiple testing to identify differences between mortality cases and those that survived. This is depicted in Table 3. Dyspnea ($\chi^2 = 22.1$, df = 1, $p < 0.001$), respiratory rate > 20/min ($\chi^2 = 12.6$, df = 1, $p < 0.001$), total leucocyte count > 11,000 cells/mm^3 ($\chi^2 = 32.3$, df = 1, $p < 0.001$), urea > 20 mg/dL ($\chi^2 = 13.2$, df = 1, $p < 0.001$), and serum creatinine > 1.2 mg/dL ($\chi^2 = 25.3$, df = 1, $p < 0.001$) at presentation were significantly associated with mortality. Shock at anytime during the hospital

Table 4. Clinical spectrum during hospital stay and outcome of cases categorized by severity of Dengue fever

Characteristic	Mild Dengue (*N* = 99)	Moderate Dengue (*N* = 92)	Severe Dengue (*N* = 41)
Day of illness at admission (Median (IQR))	4 (6, 7)	4.75 (6, 8)	4 (5, 9)
Number of patients with 1 or more risk factors (*N* (%))	0 (0)	26 (28.3)	14 (34.1)
Organ Involvement (*N* (%))			
Hepatic (Bilirubin > 2 mg/dL)	3 (3.0)	5 (5.4)	11 (26.8)
Renal (Creatinine > 1.2 mg/dL)	4 (4.0)	11 (11.9)	16 (39.0)
Neurologic (GCS < 15)	5 (5.1)	8 (8.7)	14 (34.1)
Respiratory (p/f ratio < 300)	1 (1.0)	7 (7.6)	12 (29.3)
Cardiovascular (MAP < 65 mmHg)	1 (1.0)	6 (6.5)	13 (31.7)
Mortality (*N* (%))	0 (0)	4 (4.3)	13 (31.7)

stay was also found to be significantly associated with mortality ($\chi^2 = 57.8$, df = 1, $p < 0.001$).

Among organ failures, we found that hepatic, renal, neurologic, respiratory, cardiovascular, and acute kidney injury were higher in patients with severe dengue (Table 4).

3.4. Co-infections

Twelve patients (~5%) were identified to have co-infections with other tropical fevers. Seven patients tested positive for malaria where all patients were infected with vivax malaria and one infected with mixed species of Plasmodium. Five patients were positive for IgM Chikungunya. All of these patients had an uneventful recovery.

4. Discussion

Our study analyzed dengue cases spanning over six years. In our analysis, we found that dyspnea, tachypnea, leucocytosis, and acute kidney injury at presentation were significantly associated with in-hospital mortality. The year 2015 contributed to the bulk of the cases in our study. This is in keeping with the national statistics as India experienced its worst outbreak in 2015 with a total of 99,913 recorded cases (*7*).

The initial assessment and triage of patients as mild, moderate, or severe can be useful during admission and management decision making. 13 out of the 17 deaths were classified as severe dengue at admission. This further emphasizes the need to classify and manage severe cases aggressively. Untreated severe dengue has a mortality as high as 20%. With treatment, this number can be as low as 1-2% (*8*). The mortality rate in our study is 7.3% reflecting a berksonian bias as our hospital is a tertiary care referral center.

We found that 100% of our cases presented with a history of fever. Asymptomatic disease is known in dengue and is thought to be a reservoir of infection during epidemics (*1*). However, in symptomatic dengue, fever is the most common symptom as described in our study. Special attention and close monitoring are recommended in pregnancy as they are prone to have a rapid downhill course. Among our study population, two women were admitted in the second trimester of pregnancy, and both were discharged without any feto-maternal complications. A study by Agarwal *et al.* who retrospectively analyzed 62 dengue cases in pregnancy concluded that dengue hemorrhagic fever (DHF)/dengue Shock Syndrome (DSS) was associated with significant maternal morbidity and mortality (*9*). Pregnancy-related management of dengue fever does not differ from the usual empirical treatment. However, monitoring of the patient and the fetus is required with interdepartmental coordination with Obstetrics and Gynecology.

AKI was present in 14.6% of our patients which is in keeping with existing quotes between 13 and 16% (*10,11*). Our study shows a 11.6% prevalence of neurologic manifestations. The quoted prevalence of neurologic manifestations (both central and peripheral) ranges between 0.5-20% (*12*). We did not note the presence of any peripheral nervous manifestations of dengue. Transaminitis was seen in nearly half the patients with available enzyme data. Our results suggest that dengue hepatitis consists of anicteric hepatitis wherein the bilirubin levels are normal/marginally elevated when compared to transaminases. The AST/ALT ratio is also greater than 1 in our study, which is classical of dengue hepatitis. It has been proposed that liver involvement in dengue is heralded by abdominal pain and vomiting, with some cases showing hepatomegaly (*13*). We, however, found that transaminitis is not significantly associated with abdominal pain, vomiting, or hepatomegaly. We would like to propose that this may be the case because abdominal pain and vomiting may also hint at an intestinal manifestation of dengue (dengue enteritis). Bowel wall oedema in the critical phase also manifests similarly, which may out shadow hepatitis which is usually seen late in the clinical course.

We found that shortness of breath and tachypnea at presentation was the only clinical features significantly associated with mortality. Tachypnea in dengue patients can be attributed to direct lung involvement, Acute Respiratory Distress Syndrome (ARDS), fluid overload, renal involvement, myocarditis,

or improper fluid management. It is important to note that neither thrombocytopenia nor bleeding manifestations at presentation were predictors of mortality. Thrombocytopenia, as a risk factor for mortality, was considered initially (*5,6*). Recent studies, however, show that thrombocytopenia is not a predictor for mortality. Some studies show that bleeding manifestations do predict mortality (*5,14*). We state that bleeding manifestations are a presentation of severe dengue and do not directly predict mortality. We found anemia (Hemoglobin < 10 g/dL) to be in much higher proportion in the survivor group. The explanation for the same is beyond us. However, we believe it hints at the presence of hemoconcentration at presentation and the need for appropriate fluid resuscitation. This, however, needs to be decided on a case-by-case basis.

Among organ failures, we found that acute kidney injury was associated with morality as supported by existing literature (*15*). While severe hepatitis (transaminitis > 1,000 IU/L) has been proposed as a predictor of mortality, we did not find such an association with transaminitis or severe hepatitis (*6,15*). Leucopenia is a known manifestation of dengue fever. It is interesting to note that we found a significant association between leucocytosis at presentation and mortality. This has been scarcely reported so far (*4*). We believe that these markers are an indication of close monitoring and aggressive management.

Seven patients in this study tested positive for malaria (all *Plasmodium vivax* and one mixed malaria), and five patients had IgM Chikungunya ELISA positive. This is an important observation as co-infections require a prompt diagnosis. Identification of one cause of the febrile illness may mask and delay the diagnosis of others. This may affect clinical outcomes and prognosis. Previous studies have also reported cases of co-infection (*16*). This finding highlights the importance of awareness of the possibility of concurrent infections. In countries like India, with the presence of seasonal epidemics of acute febrile illness, it becomes crucial to test broadly and rule out causes that have specific treatment modalities.

Atypical cases of dengue fever in our cohort included one case of CSF confirmed dengue encephalitis and one case of dengue with hemophagocytic lymphohistiocytosis (HLH). Dengue encephalitis is a rare manifestation attributed to the direct neurotropic effect of the virus (*12*). In highly endemic settings, dengue should also be suspected as an etiological agent in the evaluation of acute encephalitis syndrome. HLH is a hyper-inflammatory condition that may occur secondary to dengue infection, possibly due to the dysregulated immune system triggered by the virus. This patient had persistent fever, organomegaly, high ferritin, pancytopenia, low fibrinogen, and evidence of haemophagocytosis on bone marrow. He required steroids for management and was discharged in stable condition. This has been previously described only in case reports (*17,18*).

In conclusion, early diagnosis and close dynamic monitoring remain the key to the management of dengue fever. We found that shortness of breath and tachypnea at presentation was the only clinical features significantly associated with mortality. Acute kidney injury and leucocytosis at presentation were other markers that were significantly associated with in-hospital mortality. Based on our results, we recommend aggressive management of patients with severe dengue and those with mild/moderate disease with the above risk factors.

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