Original Research Article

Association of clinical features, comorbidities and laboratory profile with outcomes among dengue patients admitted in a tertiary care hospital, Delhi NCR

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ABSTRACT

Background: Dengue fever is an endemic disease across multiple countries. Dengue infection results in a wide spectrum of non-specific clinical manifestations with unpredictable clinical course and outcome. Objective of the study was to understand the association of different clinical features, comorbidities and laboratory profile with outcomes (ICU use, ventilation use and blood transfusion) among dengue patients admitted in a tertiary care hospital in Delhi, National Capital Region.
Methods This cross-sectional study included 75 dengue patients with fever <1 week confirmed based on NS-1 antigen and/or IgM antibody positivity. Descriptive analysis was used.
Results: Gender was not significantly associated with the outcomes. The duration of fever was significantly higher among those with ICU use (median: 6 versus 4 days; p=0.005), ventilator use (median: 5.5 versus 4.0 days; p=0.049] and blood transfusion (median: 6 versus 4 days; p=0.013). Dengue patients with co-morbidities (diabetes, hypertension, or chronic obstructive pulmonary disease) or co-infection had a significantly higher odds of the outcomes. The platelet level was significantly lower while liver enzymes were significantly higher among those with the outcomes.
Conclusions: The clinical features, comorbidities and laboratory profile can help in identifying critical patients for ICU admission and timely intervention to improve outcome.

Keywords: Dengue, Clinical features, Laboratory, Outcomes, Delhi

INTRODUCTION

Dengue caused by a dengue virus (DENV) is regarded as one of the most rapidly spreading vector-borne disease.[1] It has been considered as a major global health problem by the World Health Organization (WHO), due to its impact on the healthcare system worldwide.[2] It is endemic across multiple countries around the globe including India.[3] Dengue infection results in a wide spectrum of non-specific clinical manifestations with unpredictable clinical course and outcome. In majority of patients, dengue is manifested as a mild self-limiting disease, however, some of the patients may also require critical clinical management in intensive care unit (ICU) and the progression to severe clinical manifestations is usually unpredictable.[4] Approximately 0.3-14.9% develop severe manifestations that result in ICU admission, and 1-5% die without early recognition and proper treatment.[4-8] Timely access to proper treatment for dengue patients by primary healthcare professionals not only reduces the number of unnecessary hospital admissions but also lowers fatality rates below 1%.[9]

The group progressing from non-severe to severe disease is difficult to define, but this is an important concern since appropriate treatment may prevent these patients from developing more severe clinical conditions. Healthcare resources such as ICU beds and close monitoring may be limited during a large epidemic, making effective triage of patients who may require ICU requirement more crucial. A very limited data is available in the literature about the association of demographic profile, clinical features and comorbidities with the prognosis/complications of dengue. The association will help in identifying the high risk dengue patients. Also, since the available resources are usually limited, there is a need to identify critical patients who require clinical attention on priority and possibly ICU stay. Moreover, for overall dengue patients, the mortality is usually very low but in case of secondary dengue and dengue with co-morbidities, the mortality is reported to be higher, so there is a need to identify critical patients by identifying trigger signs for ICU admission and timely intervention to improve outcome.

According to the 2009 WHO classification system, patients can be clinically classified as 'probable dengue', 'dengue with warning signs' or 'severe dengue'.[4] In the literature, few case series have been reported focusing on clinical and laboratory risk factors at first presentation in hospital that are predictive of clinical severity, as defined by the requirement for ICU, instead of the WHO classification criteria.[10-12] Moreover, with the recommendation of close monitoring of patients with warning signs in hospital, there is a greater need to identify these high risk dengue patients 24 hours prior to ICU requirement during hospitalization, which is currently lacking.[4] The different warning signs can be used for early detection of potentially severe cases for timely treatment, to avoid unnecessary hospitalizations, and to decrease the case-fatality of this disease. However, various clinical and epidemiological aspects have still not been completely elucidated, especially in the Indian population. Henceforth, this study aims to understand the association of different clinical features, comorbidities and laboratory profile with ICU use, ventilation use and blood transfusion among dengue patients.

METHODS

The cross-sectional study was carried out over 15 months (1st August 2017 to 31st October 2018) in Max Super Speciality, a tertiary care hospital in Vaishali, Delhi NCR, India. All the prerequisite approval was obtained from the ethics committee and institutional review board of the hospital. The study population included dengue confirmed patients admitted in the inpatient department of the hospital after obtaining their informed consent. The inclusion criteria were patients aged ≥18 years having fever <1 week duration with proven cases of dengue fever previously diagnosed or diagnosed [with serology non-structural protein 1 (NS1) antigen or Immunoglobulin M (IgM) antibody by enzyme-linked immunosorbent assay (ELISA)] during hospitalisation. The exclusion criteria

were patients aged <18 years, those without a recent evidence of dengue infection [immunoglobulin G (IgG) positive but IgM negative] and those not giving the consent.

For each of the included patients, the following information was captured using a predefined study pro-forma. Age (in years); gender (male/female); clinical features; existing co-morbidities; laboratory tests [complete blood count, liver function test, malaria antigen and peripheral smear for malaria parasite, chikungunya polymerase chain reaction (PCR) and/or serology], radiological procedures [chest x-ray (CXR), ultrasound whole-abdomen]. The outcomes of dengue fever are reported as need of ICU care, ventilator support, blood transfusion [packed red blood cells (PRBC)/single donor platelets (SDP)/random donor platelets (RDP); given in patients with clinical bleeding or platelets count <10,000 per mm^3] and mortality during the hospital stay.

The number of the patients considered in the study depended on the patient flow in the hospital during the study time-period. No formal sample size was calculated. Every alternate dengue patient admitted in the inpatient department was considered.

All the variables were entered into a Microsoft excel and analysed using SPSS version 17.0 software. The variables were tested for normality using a Kolmogorov-Smirnov test. The continuous variables are presented as median (interquartile range) and categorical variables are expressed as frequencies and percentages. The association of categorical variables with the outcomes of interest was assessed using chi-square test or Fischer exact test, while that of continuous variables using Mann-Whitney U test. The correlation between two continuous variables was evaluated using Spearman's correlation coefficient. A two tailed p value <0.05 was considered as statistically significant.

RESULTS

A total of 75 patients with dengue fever [dengue NS-1 antigen positive: 58 (77.3%) patients, IgM antibody positive: 10 (13.3%) patients, and both positive: 7 (9.3%) patients]. Of these, 51 (68.0%) patients were males and 24 (32.0%) patients were females. A total of 25 (33.3%) patients were in the age group of 21-30 years, followed by 21 (28%) in 31-40 years, 8 (10.7%) in 18-20 years, 8 (10.7%) in >60 years, 7 (9.3%) in 50-60 years and 6 (8%) in 41-50 years. Type-2 diabetes mellitus was the most observed comorbidities among the patients [16 (21.3%)], followed by chronic obstructive pulmonary disease [COPD; 13 (17.3%)], coronary artery disease [CAD; 5 (6.7%)], hypertension [4 (5.3%)], chronic kidney disease [3 (4%)].

Also, a total of 14 (18.7%) patients also had co-infection, with 10 (13.3%) patients having malaria and 4 (5.3%) having chikungunya.

Association of demographic factors with the outcomes

Gender was not significantly associated with intensive care use (ICU; p=0.917), ventilator use (p=0.884) and blood transfusion (p=0.716) (Table 1). However, dengue patients with ICU use (median: 25 versus 35 years; p=0.035), ventilator use (24 versus 34 years; p=0.024) but not blood transfusion (median: 25 versus 34 years; p=0.267) were observed to be younger as compared to those without.

Association of clinical features with the outcomes

The duration of fever was significantly higher among those with ICU use (median: 6 versus 4 days; p=0.005), ventilator use (median: 5.5 versus 4.0 days; p=0.049) and blood transfusion (median: 6 versus 4 days; p=0.013). ICU usage was observed to be significantly higher among those with haematuria (100% versus 16.2%; p=0.028), however, it was significantly lower among those with retro orbital pain/headache (9.6% versus 34.8%; p=0.008) and generalized weakness (10.7% versus 36.8%; p=0.009). The ventilator use was found to be significantly lower among those with retro orbital pain / headache (9.6% versus 21.7%; p=0.004). The blood transfusion was observed to be significantly higher among those with haematuria (100% versus 13.5%; p=0.028), however, it was significantly lower among those with retro orbital pain / headache (7.7% versus 30.4%; p=0.01) (Table 2).

Association of comorbidities with the outcomes

Dengue patients with co-morbidities had a significantly higher odds of ICU use, ventilator use and blood transfusion. Those with diabetes had a significantly higher odds of ICU use [OR: 174 (17.8-1697.3)], ventilator use [74.6 (8.2-679.7)] and blood transfusion [96.7 (10.5-890.8)]; with hypertension had a significantly higher odds of ICU use [OR: 18.3 (1.7-193.8)], ventilator use [7.9 (1.0-63.9)] and blood transfusion [23.6 (2.2-255.2)]; with CAD had a significantly higher odds of ICU use [OR: 9 (1.3-60.8)], blood transfusion [36 (3.5-368.6)]; with COPD had a significantly higher odds of ICU use [10.9 (2.7-43.2)], ventilator use [12.4 (2.8-55.1)] and blood transfusion [5.8 (1.4-23.6)]; with co-infection had a significantly higher odds of ICU use [48.3 (9.4-249.3)], ventilator use [39.3 (6.8-229.2)] and blood transfusion [53.1 (8.9-316.0)] (Table 3).

Association of laboratory parameters with the outcomes

Haemoglobin (Hb) and white blood cells (WBC) levels were not significantly different among those with and without outcomes. However, platelet level was significantly lower among those with ICU use (median: 16,000 versus 60,000 per mm^3; p<0.001), ventilator use median: 18,000 versus 60,000 per mm^3; p=0.001) and blood transfusion (median: 14,500 versus 60,000 per mm^3; p<0.001). SGOT was significantly higher among those with ICU use (median: 278 versus 79 U/l; p<0.001), ventilator use (median: 320 versus 81 U/l; p=0.001) and blood transfusion (median: 278 versus 81 U/l; p=0.001). SPGT was significantly higher among those with ICU use (median: 180 versus 56 U/l; p=0.01), ventilator use (median: 160 versus 57 U/l; p=0.03) and blood transfusion (median: 180 versus 57 U/l; p=0.04) (Table 4). Also, duration of fever was mild to moderately correlated with SGOT (rho=0.483; p<0.001) and SGPT (rho=0.360; p=0.002) values.

Table 1: Association of gender with outcomes among dengue patients.

Outcomes	Male (%)	Female (%)	OR (95% CI)	P value
ICU				
Yes	9 (69.2)	4 (30.8)	1.071 (0.294-3.902)	0.917
No	42 (67.7)	20 (32.3)	Reference	
Ventilator				
Yes	7 (70)	3 (30)	1.114 (0.261-4.743)	0.884
No	44 (67.7)	21 (32.3)	Reference	
Blood transfusion				
Yes	8 (72.7)	3 (27.3)	1.302 (0.313-5.419)	0.716
No	43 (67.2)	21 (32.8)	Reference	

Table 2: Association of clinical features with outcomes among dengue patients.

Clinical features	ICU (%)	Ventilator (%)	Blood transfusion (%)
Vomiting			
Yes	8 (23.5)	6 (17.6)	6 (17.6)
No	5 (12.2)	4 (9.8)	5 (12.2)
Pain in abdomen			
Yes	3 (25)	3 (25)	1 (8.3)

Continued.

Clinical features	ICU (%)	Ventilator (%)	Blood transfusion (%)
No	10 (15.9)	7 (11.1)	10 (15.9)
Oliguria			
Yes	0 (0)	0 (0)	0 (0)
No	13 (18.1)	10 (13.9)	11 (15.3)
Black stool			
Yes	0 (0)	0 (0)	0 (0)
No	13 (17.6)	10 (13.5)	11 (14.9)
Haematuria			
Yes	1 (100)*	1 (100)	1 (100)
No	12 (16.2)	9 (12.2)	10 (13.5)*
Joint pain			
Yes	2 (14.3)	2 (14.3)	2 (14.3)
No	11 (18)	8 (13.1)	9 (14.8)
Retro orbital pain/headache			
Yes	5 (9.6)	5 (9.6)	4 (7.7)
No	8 (34.8)*	5 (21.7)*	7 (30.4)*
Bleeding sites			
Yes	4 (33.3)	4 (33.3)	3 (25)
No	9 (14.3)	6 (9.5)	8 (12.7)
Rashes			
Yes	3 (25)	3 (25)	2 (16.7)
No	10 (15.9)	7 (11.1)	9 (14.3)
Itching			
Yes	0 (0)	0 (0)	0 (0)
No	13 (18.6)	10 (14.3)	11 (15.7)
Generalized weakness			
Yes	6 (10.7)	6 (10.7)	6 (10.7)
No	7 (36.8)*	4 (21.1)	5 (26.3)
Cough			
Yes	4 (25)	4 (25)	2 (12.5)
No	9 (15.3)	6 (10.2)	9 (15.3)
Shortness of breath			
Yes	4 (33.3)	4 (33.3)	2 (16.7)
No	9 (14.3)	6 (9.5)	9 (14.3)

*p<0.05

Table 3: Comparison of different parameters with outcomes among dengue patients.

Variables	Yes Median (IQR)	No Median (IQR)	P value
ICU (yes: 13; no: 62)			
Age (years)	25 (19-35.5)	34.5 (27-46)	0.035
Duration fever (days)	6 (4.5-6)	4 (3-5)	0.005
Hb (g/dl)	16 (12-16.5)	14 (12-16)	0.154
Platelet ($x10^3/mm^3$)	16 (10-22.5)	60 (24.8-90.8)	<0.001
Leucocyte ($x10^3/mm^3$)	4 (3.5-7)	3 (3-4.25)	0.053
SGOT (U/l)	278 (131.5-5.725.5)	78.5 (52.3-141)	<0.001
SGPT (U/l)	180 (50.5-2.070)	56 (40-94)	0.01
Ventilator (yes: 10; no: 65)			
Age (years)	24 (19.5-33.5)	34 (27-47)	0.024
Duration fever (days)	5.5 (3.8-6)	4 (3-5)	0.049
Hb (g/dl)	15.5 (11.5-16.5)	14 (12-16)	0.233
Platelet ($x10^3/mm^3$)	18 (9-23.8)	60 (22-90)	0.001
Leucocyte ($x10^3/mm^3$)	5 (3.5-6.5)	3 (3-4.5)	0.087
SGOT (U/l)	319.5 (148.5-6.963)	81 (53.5-147)	0.001

Continued.

Variables	Yes Median (IQR)	No Median (IQR)	P value
SGPT (U/l)	160 (53.3-2.352.2)	56.5 (40.5-97)	0.03
Blood transfusion (yes: 11; no: 64)			
Age (years)	25 (20-55)	34 (27-43)	0.267
Duration fever (days)	6 (5-6)	4 (3-5)	0.013
Hb (g/dl)	16 (11.9-16.6)	14 (12-16)	0.213
Platelet (x10^3/mm^3)	14.5 (10-25)	60 (21-90)	<0.001
Leucocyte (x10^3/mm^3)	4 (3-6)	4 (3-5)	0.567
SGOT (U/l)	278 (97-2.098)	80.5 (53.3-147)	0.001
SGPT (U/l)	180 (44-1.823)	57 (40-95)	0.04

Table 4: Association of comorbidities with outcomes among dengue patients.

Outcome comorbidity	Yes (%)	No (%)	P value	OR (95% CI)
ICU (n=13)				
Diabetes	12 (75)	1 (1.7)	<0.001	174 (17.8-1697.3)
Hypertension	3 (75)	10 (14.1)	0.002	18.3 (1.7-193.8)
CAD	3 (60)	10 (14.3)	0.009	9 (1.3-60.8)
CKD	1 (33.3)	12 (16.7)	0.455	2.5 (0.2-29.8)
COPD	7 (53.8)	6 (9.7)	<0.001	10.9 (2.7-43.2)
Co-infection	10 (71.4)	3 (4.9)	<0.001	48.3 (9.4-249.3)
Ventilator (n=10)				
Diabetes	9 (56.3)	1 (1.7)	<0.001	74.6 (8.2-679.6)
Hypertension	2 (50)	8 (11.3)	0.027	7.9 (1.0-63.9)
CAD	1 (20)	9 (12.9)	0.65	1.694 (0.2-16.9)
CKD	0 (0)	10 (13.9)	0.488	NA
COPD	6 (46.2)	4 (6.5)	<0.001	12.4 (2.8-55.1)
Co-infection	8 (57.1)	2 (3.3)	<0.001	39.3 (6.8-229.2)
Blood transfusion (n=11)				
Diabetes	10 (62.5)	1 (1.7)	<0.001	96.7 (10.5-890.8)
Hypertension	3 (75)	8 (11.3)	<0.001	23.6 (2.2-255.2)
CAD	4 (80)	7 (10)	<0.001	36 (3.5-368.6)
CKD	2 (66.7)	9 (12.5)	0.009	14 (1.1-170.6)
COPD	5 (38.5)	6 (9.7)	0.008	5.8 (1.4-23.6)
Co-infection	9 (64.3)	2 (3.3)	<0.001	53.1 (8.9-316.0)

CAD: coronary artery disease; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease

DISCUSSION

Our study was on dengue, a major health problem in India. There were a higher proportion of males and younger age group patients in our study. With respect to the co-morbidities, type-2 diabetes mellitus (21.3%) and COPD (17.3%) were the most common co-morbidities. Also, approximately 20% of patients had co-infection suggesting that dengue fever can co-exist with other arboviral or vector-borne parasitic disease.

In our study, dengue patients with ICU use and ventilator use were observed to be younger as compared to those without. This finding might be due to relatively higher proportion of younger patients (almost 70% aged <40 years) in our study. Dengue patients aged >55 years had 5 times higher risk of death in a multiple logistic regression model and those aged ≥60 years had 3 times higher risk of severe organ involvement than age group between 12–29 years of age.[13,14]

As expected, dengue patients having any pre-existing co-morbidity had a significantly higher odds of ICU use, ventilator use and blood transfusion. Similarly, it was observed that those with diabetes, hypertension, coronary arterial disease (CAD), COPD, or co-infection had a significantly higher odds of one or more outcomes (ICU use, ventilator use and blood transfusion). In consistent with our findings, dengue patients who presented with (versus without) any pre-existing co-morbidity [adjusted odds ratio (AOR): 1.6; 95% CI: 1.1–2.5] and ≥2 existing co-morbidities (2.9; 95% CI: 1.7–5.1) had a significantly higher risk of severe organ involvement. Also, those with (versus without) pre-existing diabetes (AOR: 2.2; 95% CI: 1.1–5.0); with (versus without) pre-existing cardiac disorder (AOR: 4.3; 95% CI: 1.5–12.8); with pre-existing asthma (AOR: 2.1; 95% CI: 1.0–4.4) had a significantly

higher risk of severe organ involvement.[13] Likewise, another study reported that patients with diabetes mellitus had a significantly higher risk (11.6; 95% CI: 1.3-1077) of ICU requirement compared with patients with no diabetes by Pang et al. Additionally, patients who died had a significantly higher prevalence of diabetes along with hypertension and other comorbidities as compared to those who survived.[15]

The duration of fever was significantly higher among those with ICU use, ventilator use and blood transfusion. Only some of the clinical features were significantly associated with the outcomes. For instance, ICU usage and blood transfusion were observed to be significantly higher among those with haematuria. However, ICU usage, ventilator usage and blood transfusion were significantly lower among those with retro orbital pain / headache and ICU usage was lower among those generalized weakness. In similar line, cough, fever, rashes, and headache were observed to be significantly less in fatal patients as compared with survivors.[15] Likewise, other signs and symptoms such as haemorrhagic manifestation, rash, leucopoenia, nausea/vomiting, ache, and pains and tardycardia were not observed to be significantly associated with ICU requirement.[13] Similarly, in a multiple logistic regression model, hematuria (OR 5.07) was observed to be significantly associated with death (OR 2.55).[14]

With respect to the laboratory parameters, only platelet level and liver enzymes were significantly associated with the outcomes such that platelet level was significantly lower while liver enzymes (SGOT and SPGT) were significantly higher among those with the outcomes. ICU mortality was significantly positively associated with lower platelet count in a multiple logistic regression model.[6] Only thrombocytopenia, hepatic dysfunction in the form of raised bilirubin were associated with significantly higher risk of mortality.[16] Liver enzymes (alanine and aspartate aminotransferases) were observed to be significantly higher at presentation among dengue patients who progressed with severe organ involvement; elevated hepatic transaminase >500 IU/l was observed to be an independent predictor of mortality in multivariate logistic regression; and the AST and ALT level at first presentation were positively correlated with ICU requirement.[13,17]

There are some limitations in our study that should be taken into consideration when interpreting the results. First, this is a single centre study with a relatively small number of patients with ICU requirement which might result in low statistical power to detect true association. Second, no dengue serotype data were available for individual study subjects. Also, the clinical manifestations, laboratory tests reported here were that observed at the time of presentation and not during hospitalization. Therefore, our findings may not be generalizable to all populations at risk as well as in different clinical setting and healthcare system.

CONCLUSION

In India, dengue is a notifiable disease. Fever is the most common clinical presentation in dengue patients and the duration of fever is observed to be higher among those with the outcomes. Also, patients with co-morbidities (such as diabetes, hypertension, CAD, COPD) and co-infections had a significantly higher risks of the outcomes. Moreover, platelet level was significantly lower while liver enzymes were significantly higher among those with the outcomes. No specific treatment exists for dengue/severe dengue. There is a potential of lowering fatality rates with early detection and access to proper medical care. These clinical features, comorbidities and laboratory profile can help in identifying critical patients for ICU admission and timely intervention to improve outcome.

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