Original Article

A prospective 3 year study of clinical spectrum and outcome of dengue fever in ICU from a tertiary care hospital in North India

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ABSTRACT

Background and Aims: The incidence of specific complications and adverse outcomes in dengue patients needing admission to intensive care units (ICU) may be quite variable in different regions of India presumably because of different strains of dengue virus or due to re infection. **Methods:** Patients admitted with acute febrile illness (AFI) with either positive IgM antibody or NS1 antigen for dengue were enrolled. Data were collected for 3 years (2015-2017). A total of 313 patients with acute febrile illness were admitted in the study period (2252 total ICU admissions). A total of 137 (43.76%) cases were serologically proven as dengue fever. **Results:** Median age (IQR) of study population was 36.0 (26.0–52.0) years. Liver (65.7%) was the main organ involved followed by acute kidney Injury (AKI) (18.6%). Dengue Shock Syndrome (DSS) was found in 18.6% of cases. Fifty-two patients died and the crude mortality was 38.0%. On multivariate analysis APACHE Score >10, thrombocytopenia, hepatic dysfunction, AKI and dengue shock syndrome (DSS) were associated with the risk of mortality. **Conclusion:** This study in ICU patients showed high mortality in relatively younger patients. Liver (in the form of raised Bilirubin) was the most common organ dysfunction. The need to recognise early warning signs for ICU admission is highlighted.

Key words: Acute Physiology and Chronic Health Evaluation, dengue fever, IgM, intensive care unit, NS1, shock, sequential organ failure assessment

INTRODUCTION

Dengue fever is an acute febrile illness (AFI) caused by one or more dengue viruses belonging to genus Flavivirus and transmitted by Aedes aegypti mosquito. According to World Health Organization (WHO), two-fifth of the world's population is at risk from dengue disease. India is one of the seven identified countries in South-East region regularly reporting dengue fever (DF) outbreaks, and all four serotypes are known to be circulating either singly or in combination.[1] Although the majority of infections are self-limiting, a small subset of patients develop severe complications, needing intensive care. These complications including organ failure, occur relatively late in the disease, potentially providing a window of opportunity to identify the group of patients likely to progress to these complications. However, due to non-specific presentation it is difficult to identify patients, who will require intensive care.

The purpose of our study was to describe the clinical profile of dengue patients needing admission to intensive care unit (ICU) and to evaluate the risk factors associated with poor outcome in serologically confirmed cases during the period 2015, 2016 and 2017.

METHODS

It is a prospective observational study. All patients admitted with acute febrile illness (AFI) admitted to the ICU and positive for either IgM antibody or NS1

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antigen for dengue were enrolled after taking informed consent from the next of kin. 313 adult patients with AFI (defined as fever of less than 7 days duration), were admitted to a 46 bed ICU of a tertiary care centre in North India. Patients with other concomitant infectious diseases like malaria, leptospirosis, viral hepatitis or bacterial sepsis were excluded. The ethical clearance for the study was taken from the Institutional ethical committee (EC/10/13/599) on 30/10/2013 and data of the enrolled patients was kept anonymous. This study was conducted as per the Helsinki declaration.

IgM dengue antibody was estimated using PANBIO dengue IgM capture ELISA. NS1 Ag assay was performed using new PLATELIA TM Dengue NS1 Ag assay (BIORAD, Marnes-la-coquette, France). ICU charts, laboratory investigation and medical case records were used to collect patient data. Demographic data included gender, age, Acute Physiology and Chronic Health Evaluation (APACHE) II score and sequential organ failure assessment (SOFA) scores of patients were also collected. The scores were calculated after the first 24 hours of ICU admission. Outcome details including organ dysfunction and survival to hospital discharge or mortality were recorded. Other parameters such as duration of ICU stay, vasopressor therapy, renal replacement therapy and ventilation support were also recorded.

Central Nervous System (CNS) dysfunction was defined clinically by assessing the level of consciousness. The Glasgow Coma Score or presence of cerebral oedema from Computed Tomography (CT) scan of the head were recorded only as additional confirmation because of their poor sensitivity in diagnosing cerebral oedema. Cardiovascular (CVS) dysfunction was defined by hypotension needing vasopressors to keep the mean arterial pressure above 65 mm of Hg. Presence of third space compartment volume accumulation such as ascites, pleural effusion, gall bladder oedema was done by bedside ultrasonography. Hepatic dysfunction was defined as raised Bilirubin >2 mg/dl and Alanine aminotransferase (ALT) >3 times the upper limit of normal (ULN). Acute Kidney Injury (AKI) was defined by increase in creatinine >1.5 time the baseline levels or the need for renal replacement therapy. Thrombocytopenia was defined as platelet count of less than 100×10^9/L. Coagulopathy was described as International normalised ratio (INR) of more than 1.5. ARDS was defined as per the recent Berlin definition.[2]

Multiple organ dysfunction syndrome (MODS) was defined as the presence of 2 or more organ failure. Complications of Dengue in the form of unusual plasma leakage syndrome resulting in hypovolaemic shock – was labelled as dengue shock syndrome (DSS). Evidence of plasma leakage due to increased vascular permeability consists of at least one of the following:

(a) An elevated haematocrit ≥20% above the population mean haematocrit for age and sex
(b) A decline in haematocrit after volume-replacement treatment of ≥20% of the baseline haematocrit
(c) Presence of pleural effusion or ascites detected by radiography or other imaging method
(d) Hypoproteinaemia or hypoalbuminaemia as determined by laboratory test.

Continuous variables were presented as means ± standard deviations (SD) or median (25%–75% interquartile range [IQR]) and were compared using student's independent *t*-tests. Categorical variables were presented as numbers (*n*) or proportions (%) where appropriate and were compared using the Chi square test with Yates correction. Wilcoxon's ranked sum test was used for between group comparisons of non-normally distributed data. Multivariate logistic regression model was used to determine predictors of mortality and presented with odds ratio and 95% confidence interval. Two-sided $P < 0.05$ was considered as statistically significant. Data were analysed using Statistical Package for the Social Sciences (SPSS, IBM) version 23.0TM software for windows.

RESULTS

A total of the 313 adult patients were admitted with AFI during the study period, out of which 137 were serologically proven Dengue fever (prevalence of 43.76%). Of the total of 2252 ICU admissions during this period dengue fever was the cause in 6% cases. The median age of dengue patients admitted to ICU was 36 years and 55% were males. Only 14 out of 137 patients (0.7%) patients were more than 65 years of age [Table 1]. Pre-existing medical conditions were present in 24% of patients. 14 patients had diabetes, 13 patients had hypertension, and 6 patients had Chronic Kidney disease. The predominant presenting symptoms were fever (58.39%), abdominal pain (50.36%), loss of appetite (45.25%), vomiting (30.7%) and spontaneous bleeding from nose and oral cavity (31.3%) [Table 2]. These are included as warning signs as per WHO 2009 criteria. The laboratory parameters on admission are shown in [Table 3].

Table 1: Demographic characteristics

Demographics	Total, (*n*=137)	Non-survivor (*n*=53)	Survivor (*n*=84)	*P*
Median Age (IQR: 25-75%)	37 (30 - 57.5) years	35 (25 - 48.5)	0.160	0.160
Age >65	8 (15.1) years	6 (7.1)	0.135	0.135
Gender, Male	38 (71.7)	37 (44.0)	0.002	0.002
APACHE-II	12 (8-16)	17 (14-22)	9 (7-12)	<0.0001
SOFA	6 (4-10)	10 (8-12)	4 (3-7)	<0.0001
Duration ICU Stay (days)	4 (3-6.2)	3 (2-7.2)	4 (3-6)	0.247

APACHE – Acute Physiology and Chronic Health Evaluation; SOFA – Sequential Organ Failure Assessment

Table 2: Presenting Symptoms with frequency (%)

Presenting Symptoms	Frequency	Percentage (%)
Fever	80	58.39
Abdominal Pain	69	50.36
Loss of appetite	62	45.25
Oral/nasal bleed	30	31.30
Vomiting	40	30.65
Headache	39	28.47
Jaundice	30	21.89
Loose stools	20	14.59
Altered sensorium	21	15.32

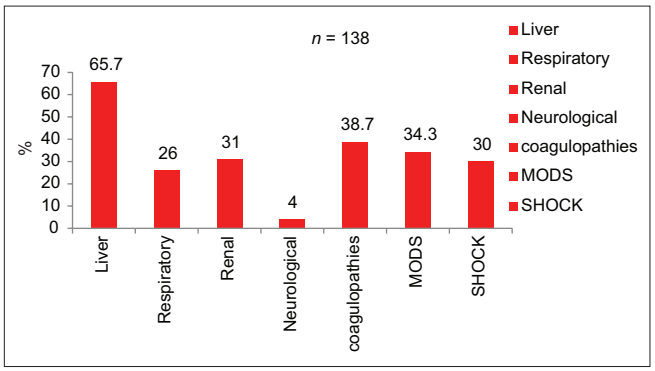

Figure 1: Clinical Presentation organ involvement (%). (MODS: Multiple organ dysfunction syndrome)

A significant number of patients with dengue presented with organ dysfunction to ICU. The Median SOFA Score at 24 hours was 4 (IQR 3–7) in survivors and 10 (IQR 6–14) in non-survivors (OR 1.25 IQR 1.13–1.39). Liver was the most common organ involved in 90 patients (65.7%). Elevation of bilirubin >2 mg/dl, and median ALT level was 811 IU/L (range 74–3422) in non-survivors. [Table 4] 30% of patients had hypotension needing vasopressor therapy, 26% had respiratory failure needing mechanical ventilation, 31% with renal failure needed renal replacement therapy and 37% had coagulopathy. A small proportion (4%) of patients had neurological impairment in the form of encephalopathy or seizure. A total of 32 (23.4%) patients had dengue shock syndrome (DSS) out of which 24 (75%) died. Multiple organ dysfunction was present in 27 (19.7%) patients out of which 12 (44.44%) died [Figure 1]. 15 (10.94%) of patient presented with severe rhabdomyolysis with a peak creatinine phosphokinase (CK) level of 11,210 U/l complicated by renal failure.

There were 85 (61.32%) patients who survived to discharge, and the overall mortality was 38.68%. Most deaths occurred within 3 days of admission to the ICU. Median duration of stay for survivors was 4 days (IQR 3-6) and that for non survivors was 3 days (IQR 2–7.25). The median APACHE score was 12 (9 in survivors and 17 in non-survivors) [Table 1].

The parameters which were found to be significant in the univariate analysis were subjected to multiple logistic regression to find out association with mortality. Only thrombocytopenia (platelets $<100 \times 10^9$/L) OR 1.01 (1.002-1.027), Dengue Shock Syndrome OR 11.036 (1.99–61.23), hepatic dysfunction in the form of raised Bilirubin OR 7.002 (1.52–32.23), and Creatinine >1.5 times baseline OR 1.416 (1.03–1.94) were associated with significantly higher risk of mortality. The APACHE Scores on admission was associated with mortality OR 0.60 (0.47–0.77) [Table 5].

DISCUSSION

The natural history of dengue fever has three phases: febrile phase (3–7 days), a defervescense phase when complications are seen, and the spontaneous recovery phase. As per the WHO dengue classification, patients are now classified as having either dengue or severe dengue. Patients having any of the following conditions are designated as having severe dengue: plasma leakage resulting in shock, accumulation of serosal fluid to cause pulmonary oedema, severe bleeding; and severe organ impairment.[1,3,4] The new classification includes some warning signs which may help clinicians to identify patients likely to develop complications.

There are only a few Indian studies focussed on mortality predictors in severe dengue patients needing intensive care. The mortality reported in our

Table 3: Laboratory parameters at the time of admission in survivors and non survivors

Lab parameters	Total, (*n*=137)	Non-survivor (*n*=53)	Survivor (*n*=84)	*P*
Haemoglobin (gm/dl)	11.6±2.8	11.3±2.9	11.8±2.7	0.257
Platelet (<100×10^9/L)	91 (66.4)	48 (90.6)	43 (51.2)	<0.0001
INR	1.20 (1.0-1.6)	1.56 (1.26-2.3)	1.10 (1.0-1.2)	<0.0001
Total bilirubin (mg/dl)	1.10 (0.7-3.1)	2.3 (1.4-5.5)	0.84 (0.7-1.5)	<0.0001
AST (U)	223 (104-2375.5)	1211 (204.5-9937.5)	157.5 (82.3-462)	<0.0001
ALT (U)	149 (56-1102.5)	811 (77-3422)	98.5 (45.75-232.0)	<0.0001
ALT >3×ULN	64 (46.7)	36 (67.9)	28 (33.3)	<0.0001
creatinine (mg/dl)	1.23 (0.79-2.84)	2.8 (1.68-4.10)	0.81 (0.67-1.29)	<0.0001
BUN (mg/dl)	27.3±27.8	39.5±25.3	19.6±26.6	<0.0001

INR – International normalised ratio; AST – Aspartate Aminotransferase; ALT – Alanine Aminotransferase; BUN – Blood Urea Nitrogen

Table 4: Complications

	Total, (*n*=137)	Non-survivor (*n*=53) (%)	Survivor (*n*=84) (%)	*P*
ARDS	11 (8.0)	5 (9.4)	6 (7.1)	0.631
DSS	32 (23.4)	24 (45.3)	8 (9.5)	<0.0001
Hepatic Injury	90 (65.7)	46 (86.8)	44 (52.4)	<0.0001
MODS	27 (19.7)	20 (37.7)	7 (8.3)	<0.0001
AKI	53 (38.6)	16 (30.1)	37 (44.0)	0.04

ARDS – Acute Respiratory Distress Syndrome; DSS – Dengue Shock Syndrome; MODS – Multiple organ dysfunction syndrome; AKI – Acute Kidney Injury

Table 5: Multivariate analysis of survivors and non survivors among dengue patients (Continuous data which are significant in univariate analysis were included)

	Odds Ratio (95%CI)	*P*
APACHE II score (>10)	0.6016 (0.47-0.77)	**0.011**
Creatinine (>1.5 mg/dl)	1.4160 (1.03-1.94)	**0.030**
Bilirubin (Total) (>2.0/dl)	7.0027 (1.52-32.23)	**0.012**
ALT (IU/L)	1.00 (1.00-1.00)	0.519
Coagulopathy	3.32 (0.01-10.95)	0.058
Platelet (<100×10^9/L)	1.015 (1.002-1.027)	**0.021**
DSS	11.03 (1.98-61.23)	**0.006**

Survivors vs Non survivors (Model=AUC 97.5%, accuracy 89.6%, R2=0.689, *P*<0.001). APACHE – Acute Physiology and Chronic Health Evaluation; ALT – Alanine Aminotransferase; DSS – Dengue Shock Syndrome

study (38%) is higher than that reported previously in studies done in ICU patients.[5,6,7] This may be explained by selection bias because we generally get patients from other hospitals where they are treated for a few days and when complications develop are transferred to us. The lead time bias was not factored in the protocol of the study.

Indian studies have reported variable mortality. Two studies done in the last decade reported mortalities of 11.1% (8 deaths among 72 patients) and 6.1% (12 deaths among 198 patients), in similar studies conducted in Indian ICUs.[6,7] Although the first study did not report severity score data, the latter reported a mean APACHE II score of 7.5 The median APACHE II score on admission in our study cohort was 12, which indicates more severe disease in the patients included in our study. More recent studies with similar severity indices have shown an increasing trend in mortality.[8,9] A study in Taiwan published in 2016 with 143 critically ill patients and mean APACHE Score of 17.9 reported a mortality of 23.1%. However, the mean age of patients in this study was 69.7 years.[10] A recent Indian study published in 2019 with 96 dengue patients had an overall mortality of 21.1%. The APACHE Scores in this study was 6.0 in survivors and 17.5 in non-survivors.[11] The critical phase starts when the defervescence sets in, and signs of capillary leak such as haemoconcentration and hypoproteinaemia with pleural effusions and ascites. Dengue shock syndrome is recognised by narrow pulse pressure, severe hypotension, cold clammy skin and organ dysfunction (such as hepatitis, encephalitis, myocarditis), and disseminated intravascular coagulation. Our finding that the median duration for non survivors was 3 days (IQR 2–7.25) can be explained that we received our patients in the critical phase of the illness.

The use of NS1 antigen may have led us to include more cases as this test was not done routinely in most centres until recently. NS1 antigen, is detectable from day 1 of fever and has been shown to be a reliable parameter for the early diagnosis of dengue fever.[12] However Dengue PCR was not available in our hospital and IgG was not routinely done. This precluded us from estimating the burden of re infection in this cohort.

In our study we could not show the association of pre-existing disease like diabetes mellitus, hypertension or chronic kidney disease with mortality in dengue patients probably because our cohort is much younger (median age 36 years). Previous studies have shown that chronic kidney disease significantly increased risk of death. The severity of renal impairment was associated with dengue haemorrhagic

fever (DHF)/DSS.[13] Diabetes mellitus has been reported to be a risk factor for dengue severity.[14]

Prompt restoration of the circulating plasma volume is the cornerstone of therapy for dengue shock syndrome which is also highlighted in the WHO management guidelines. Although the recommendations were successful in focusing attention on the need for volume replacement, they need to be updated. WHO and the Indian guidelines recommend colloids in the form of dextran and gelatines which are not routinely used presently, due increased concerns of coagulopathy and risk of renal failure. Moreover, these guidelines have not been widely disseminated and most hospitals have their own protocols. Fluid resuscitation is not without risk and has been associated with laryngeal oedema especially in the initial capillary leak phase as mentioned in some case reports.[15] We broadly followed the guidelines of the Surviving Sepsis Campaign and used crystalloids with Albumin boluses.[16]

In our study Liver was the most common organ involved. Hepatic involvement is common in dengue, and liver enzymes are frequently elevated in infections of all severity grades as shown by several studies.[17,18] Elevation of liver enzymes especially ALT levels more than 1000 IU/L was found in 35% cases, the median value being 811 IU/L (range 74–3422) in non survivors. Raised ALT levels has been shown to be associated with worse outcomes in several studies.[19] However, in our study Bilirubin (>2.0 mg/dl) was associated with the risk of mortality in the multivariate analysis, but elevated ALT (>3 × ULN) failed to reach statistical significance suggesting that both hepatocyte necrosis as well as biliary obstruction due to oedema contribute to hepatic dysfunction.

Severe rhabdomyolysis and its complications are not mentioned as a potential manifestation of dengue. The medical literature contains only a few reports of rhabdomyolysis in dengue fever.[19] In our studies CK levels were not done in all cases, so we did not include it in the logistic regression. CK levels in a larger cohort of patients with dengue virus infection would be necessary to confirm that dengue virus can cause rhabdomyolysis. However, if renal failure develops despite aggressive volume resuscitation, we opt for early dialysis rather than use mannitol, bicarbonate or free radical scavengers which are not supported by robust evidence.[20,21] It would be interesting to do further studies on association of rhabdomyolysis and neurological complications in severe dengue cases.

The study is not without limitations. Ours being a tertiary centre selection bias is expected as usually severe cases are being referred to such centres. The study population may not be representative of the total dengue population during the time period studied. Furthermore, there is a lack of information regarding treatment received prior to transfer and we did not factor in lead time bias. IgG estimation was not done which did not allow us to know how many of the proven dengue patients were due to re infection which in itself presents a higher risk of mortality.

CONCLUSION

This study showed high mortality in relatively younger patients with severe dengue infection.

Hepatic dysfunction, AKI, thrombocytopenia and DSS were associated with significantly higher risk of mortality. Although our study confirmed the risk factors already known, this study indicated that younger patients in the productive age group had a high mortality raising public health concerns. There is a need for interventions to be more evidence-based. Severe Dengue continues to be a challenge, no vaccine is yet available and the vector control measures are inadequate.

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Conflicts of interest

There are no conflicts of interest.

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