FACTORS ASSOCIATED WITH SEVERITY OF ILLNESS IN PATIENTS WITH DENGUE FEVER IN A TERTIARY CARE HOSPITAL IN SOUTHERN INDIA

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ABSTRACT

Objective: Denguefeveris one of the important tropical disease of public health significance caused by flavivirus. It is a major cause of morbidity and mortality worldwide. Identification of factors associated with severity of dengue can improve the prognosis of the disease.This study tried toassess the factors associated with severity of dengue.

Methods: A record based study was conducted in a tertiary care hospital setting in southern India. A total of 550 case files were reviewed to ascertain demographic, clinical and laboratory parameters among confirmed cases of dengue. The severity of dengue was categorized using WHO 2009 classification.

Results: Of 550 records reviewed, 449 (81.6%) were classified as non-severe dengue and 101 (18.4%) as severe dengue. Factors associated with severe dengue on univariate analysis were: gender, backache, skin rash, nausea and vomiting, abdominal distension, haemorrhage, breathlessness, oliguria, hepatomegaly, splenomegaly, ascites, leukopenia, hypoproteinemia, and elevated serum alanine transaminase (ALT) >63 IU/L.On multivariate analysis,haemorrhage (OR=11.75, 95%; CI=6.38-21.62), oliguria (OR=4.01, 95%; CI=1.32-12.15), ascites (OR=2.68, 95%; CI=1.19-6.01), ALT>63 IU/L (OR=1.77, 95%; CI=1.01-3.1) and hypoproteinemia (OR=5.57, 95%; CI=2.82-10.98) were found to have significant association with the development of severe dengue.

Conclusion: This study indicates thatwhen dengue patients present with bleeding episodes, ascites, oliguria,raised ALT and low serum protein levels, clinicians should be alert to the appearance of severe complications. Early identification of these factors will help clinicians to recognise the severity of dengue illness and enable them to implement appropriate interventions.

Keywords: Dengue infection, Flavivirus, Plasma leakage,Severe dengue.

INTRODUCTION

Dengue is a debilitating vector-borne disease with a 30-fold rise in disease incidence over the past five decades.According to the World Health Organization (WHO), dengue is a major global threat [1]. More than 70% of the dengue disease burden is in South-East Asia and the Western Pacific. Urbanization, rapid movement of people and goods, favourable climatic conditions and lack of trained staff have all contributed to the global increase of dengue. An estimated 500000 people with severe dengue require hospitalization each year, and about 2.5% of those affected die [2]. In 2015, India has reported about 6280 deaths due to dengue fever [3].

Dengue infection can present with a wide spectrum of clinical manifestations, from a simple febrile illnessto severe features of plasma leakage leading to shock [1].The factors associated with severe dengue such as age >40 years, male gender, secondary infection, presence of abdominal pain, persistent vomiting, bleeding, raised haematocrit, lymphopenia, high AST or ALT levels by more than 3 times the upper limit of normal and hypoproteinemia by using either the 1997 or 2009 WHO definition has been well described but with varying results [4-7]. Based on this background, this study was designed to identify thefactors associatedwith the dengue severity by using the WHO 2009 definition. Additionally, this study will provide an overview on the demographics as well as clinical and laboratory profile of the individuals affected with dengue.

METHODS

A total of 550patient's medical records diagnosed as dengue feverwere reviewed ata tertiary care teaching hospital in south India.Both male and female subjects, ≥18 years admitted to medical wards with positive serology for dengue infection confirmedby either dengue IgM ELISA or non-structural protein 1 (NS1) antigen test were included in the study. Presence of concomitant febrile illnesses along with dengue such as malaria, scrub typhus, typhoid and leptospirosis were excluded.The following information related todemography,clinical characteristics, laboratory results; complications associated with dengue fever andadministered treatment was documented in a structured questionnaire.

The World Health Organization (WHO) 2009 classification of dengue [1] was used to group the patients into non-severe dengue (NSD)and severe dengue (SD).AKI was defined as increased serum creatinine >1.5 times from the baselineor a decreased urine output of<0.5 ml/kg/hour for 6 hours.The study protocol was approved by the Institutional Ethical Committee (IEC) and since the study was retrospective, written informed consent was not required.

Statistical analyses were carried out using SPSS 16.0. Frequency and percentage was used to summarize categorical variables while mean±SD or median (IQR) was used to summarize continuous variables. Chi square test was used to find association between categorical

exposure variables (clinical, demographic and laboratory) with severe dengue. Independent sample t-test (Mann-Whitney U test) was used to compare mean (median) of continuous exposure variables (clinical, demographic and laboratory) with severe dengue. Logistic regression analysis was used to find factors associated withsevere dengue. All variables with p<0.2 on univariate analysis were considered for logistic regression analysis. Backward Wald elimination procedure was used to select significant variables. A p value of <0.05 was considered as statistically significant.

RESULTS

A total of 550 patient's medical records were reviewed. Out of which 405 (73.6%) were males and 145 (26.4%) were females. The male to female ratio was 2.8:1. The most affected age group was 21- 30 years followed by 31- 40 years. The mean age of the patients was 32.41 (SD=11.64) years. There was no statistically significant difference observed in mean age between the two groups. Majority of the patients were working in agriculture setting (114/550) 20.7%.

Clinical characteristics in patients with dengue fever are described in Table 1. Fever was the most consistent complaint 547 (99.5%) followed by headache 263 (47.8%), myalgia 241 (43.8%), vomiting 227 (41.3%) and pain abdomen 165 (30%).Haemorrhagemanifested in 79 (14.4%) cases in the form of: petechiae 35 (6.4%);melena 18 (3.3%); hematemesis 8 (1.5%); gum bleed13 (2.4%); epistaxis 4 (0.7%); haematuria 9 (1.6%); and menorrhagia 7 (4.8%). Some patients presented with more than one haemorrhagic manifestation.

Twenty-nine (5.3%) patients had shock as the predominant complication followed by AKI (4.2%).Acute hepatitis with aminotransferase levels increased to at least 10 times their normal values was observed in 16 (2.9%) cases.All patients with acute respiratory distress syndrome (ARDS)required ventilator support. Of these, eight patients improved and were successfully weaned off the ventilator.

Rapid decline in WBC and platelet counts were frequently noted in the early phase of the disease.Large number of patients had a platelet count of less than 50,000/mm^3 (Table 2). Further, the prevalence of bleeding episodes among patients with platelet count <50,000/mm^3 was significantly higher (p=0.001) among SD group (22/60) as compared to NSD group (29/225). Therise in transaminase levels was commonly observed and in most cases, there was a greater elevation in AST than ALT levels. The salient laboratory findings are summarized in Table 3.

Antipyretics (oral paracetamol) were used along with intravenous fluids when required. Platelet transfusion was done in 103 (18.7%) patients with low platelet counts and bleeding during hospitalization. Packed red blood cells were transfused in 12 caseswith anaemiaand bleeding episodes. The median duration of hospitalization was 5 days (IQR, 4-6 days) in mostcases. Fifty-four (9.8%) patients required admission to intensive care units (ICU).The mortality was observed in 7 (1.3%) and all fatal cases were due to shock, ARDS and multi-organ failure.

The results of multivariate logistic regression analysis for factors associated with severe dengue are presented in Table 4. From univariate analysis of clinical, demographic and laboratory parameters, we found that gender, backache, skin rash, nausea and vomiting, abdominal distension, haemorrhage, breathlessness, oliguria, hepatomegaly, splenomegaly, ascites, leukopenia, hypoproteinemia and high ALTshowed significant association with severe dengue. The corresponding unadjusted Odd's ratio ranges from 0.4 to 7.93. After taking into consideration all these variables for binary logistic regression analysis, skin rash, haemorrhagic episodes, oliguria, low serum protein, high ALT and ascites were found to be associated with severe disease. The corresponding adjusted Odd's ratio ranges from 0.42 to 11.75. The risk of severe dengue was more among patients who had haemorrhage (OR=11.75, 95%; CI=6.38-21.62), oliguria(OR=4.01,95%;CI=1.32-12.15),ascites(OR=2.68, 95%; CI=1.19-6.01),hypoproteinemia (OR=5.57, 95%; CI=2.82-10.98) and high ALT (OR=1.77, 95%; CI=1.01-3.1).

DISCUSSION

The existing global distribution of the risk of dengue virus infection and its complications are now becoming prevalent and severe. Additionally, the changing epidemiology and rapid urbanization in developing countries such as India has enormously increased the prevalence of life threatening diseases like dengue [8].Frequent outbreaks of dengue fever havebeen reported over the last few decades with large number of patients presenting with atypical features such as pancreatitis, myositis, serositis, myocarditis, hepatitis, acalculous cholecystitis, central nervous system involvement, and even death [9,10]. Given the wide range of clinical manifestations of dengue fever, one of the challenges to the treating clinician is to be able to identify which patients are likely to develop severe dengue. Early recognition of factors associated with the severity of dengue will help identify the patients with severe infection.

Table 1: Demographic and clinical profile of dengue infection

Patient characteristics	Total (n=550)	Dengue with or without warning signs (n=449)	SD (n=101)	p
Male	405 (73.6)	342 (76.2)	63 (62.4)	0.004*
Female	145 (26.4)	107 (23.8)	38 (37.6)	
Age (years)#	32.41±11.64	31.96±11.51	34.39±12.04	0.058
Fever	547 (99.5)	447 (99.6)	100 (99.0)	0.502
Headache	263 (47.8)	223 (49.7)	40 (39.6)	0.067
Myalgia	241 (43.8)	198 (44.1)	43 (42.6)	0.780
Arthralgia	98 (17.8)	81 (18.0)	17 (16.8)	0.774
Backache	35 (6.4)	32 (7.1)	3 (3.0)	0.122
Pain abdomen	165 (30.0)	133 (29.6)	32 (31.7)	0.683
Abdominal distension	30 (5.5)	18 (4.0)	12 (11.9)	0.002*
Nausea and vomiting	227 (41.3)	177 (39.4)	50 (49.5)	0.063
Hemorrhage	79 (14.4)	37 (8.2)	42 (41.6)	<0.001*
Breathlessness	13 (2.4)	6 (1.3)	7 (6.9)	0.001*
Oliguria	19 (3.5)	8 (1.8)	11 (10.9)	<0.001*
Conjunctival congestion	94 (17.1)	79 (17.6)	15 (14.9)	0.508
Skin rash	170 (30.9)	145 (32.3)	25 (24.8)	0.138
Hepatomegaly	62 (11.3)	42 (9.4)	20 (19.8)	0.003*
Splenomegaly	32 (5.8)	23 (5.1)	9 (8.9)	0.142
Pleural effusion	13 (2.4)	8 (1.8)	5 (5.3)	0.038*
Ascites	44 (8)	27 (6.0)	17 (16.8)	<0.001*
SBP (mmHg)#	119±14	120±12	115±19	0.001*
DBP (mmHg)#	77±12	78±9	72±21	<0.001*

#Data are expressed as mean±SD, SD: Standard deviation, SBP: Systolic blood pressure, DBP: Diastolic blood pressure. *p<0.05. SD: Severe dengue

Table 2: Platelet counts in patients with dengue fever

	Total (n=550)	Dengue with or without warning signs (n=449)	SD (n=101)	p value
<20,000	133 (24.2)	97 (21.6)	36 (35.6)	0.004*
<50,000	285 (51.8)	225 (50.1)	60 (59.4)	0.118
50,000–100,000	154 (28.0)	132 (29.4)	22 (21.8)	0.107
100,000–150,000	54 (9.8)	45 (10.0)	9 (8.9)	0.705

*p<0.05. SD: Severe dengue

Table 3: Clinical investigations among dengue fever patients

Investigations	Dengue with or without warning signs (n=449) mean±SD	SD (n=101) mean±SD	p
Hemoglobin (g/dL)	14.7±1.9	14.3±2.6	0.001*
Hematocrit (%)	44.2±5.7	42.7±7.8	0.097
White cell count (/μL)#	5200 (3500–8100)	6200 (4200–9450)	0.120
Leukopenia (n, %)	144 (32.1)	22 (21.8)	0.042*
Lymphocytes (%)	36.6±16.3	30.4±15.2	0.632
Platelets (/μL)#	47,000 (21,000–87,000)	37,000 (15,000–83,000)	0.797
Total bilirubin (mg/dL)#	0.5 (0.4–0.8)	0.7 (0.4–1.3)	<0.001*
Direct bilirubin (mg/dL)#	0.2 (0.1–0.3)	0.3 (0.2–0.8)	<0.001*
Total protein (g/dL)	6.8±0.7	6.4±0.8	0.002*
Hypoproteinemia (n, %) (<6 g/dL)	37 (8.2)	31 (30.7)	<0.001*
Serum albumin (g/dL)	3.8±0.5	3.5±0.6	<0.001*
Hypoalbuminemia (n, %) (<3.5 g/dL)	78 (17.4)	43 (42.6)	<0.001*
AST (>40 IU/L) (n, %)	412 (91.8)	94 (93.1)	0.620
ALT (>63 IU/L) (n, %)	259 (57.7)	70 (69.3)	0.026*

#Data are expressed as median, IQR: interquartile range, SD: Standard deviation, AST: Aspartate transaminase, ALT: Alanine transaminase, *p<0.05. SD: Severe dengue

Table 4: Multivariable analysis of factors for acquiring SD

Variables	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	p value for adjusted OR
Sex (female)	1.93 (1.22–3.05)		
Backache	0.4 (0.12–1.33)		
Skin rash	0.69 (0.42–1.13)	0.42 (0.23–0.78)	0.005*
Nausea and vomiting	2.01 (1.09–3.72)		
Abdominal distension	3.23 (1.5–6.94)		
Hemorrhage	7.93 (4.72–13.32)	11.75 (6.38–21.62)	0.014*
Breathlessness	5.5 (1.81–16.73)		
Oliguria	6.74 (2.64–17.22)	4.01 (1.32–12.15)	0.001*
Leukopenia	0.59 (0.35–0.99)		
Hypoproteinemia	4.93 (2.87–8.47)	5.57 (2.82–10.98)	0.001*
High ALT	1.69 (1.06–2.7)	1.77 (1.01–3.1)	0.048*
Hepatomegaly	2.39 (1.34–4.29)		
Splenomegaly	1.81 (0.81–4.04)		
Ascites	3.16 (1.65–6.06)	2.68 (1.19–6.01)	0.017*

*p<0.05. SD: Severe dengue, ALT: Alanine transaminase, CI: Confidence interval, OR: Odd's ratio

Although no difference in the gender distribution of dengue cases exist, several studies have reported varying results.In the majority of reports of dengue outbreaks in India, males outnumbered females [11,12].This gender difference in dengue cases may be due to increased mobility of male population in the society and better access to health-care [13]. However, our study did not find gender as a risk of dengue infection severity.Dengue virus infections affect human populations of all age groups worldwide. In some parts of the world, dengue is mainly a paediatric health problem[1]. In this study, majority of cases were seen in the 21-30 years' age group which supports the observations made by some authors who reported that dengue infection in India is predominantly a disease of young adults [14,15].

The classical symptoms of dengue infectionsuch asfever,headache,and pain abdomen with vomiting were observed in majority of cases. Althoughbleedingin the form of petechiae and melena was seen in many patients, none of our patients had severe haemorrhage.Bleeding in severe dengue infection may be related to impaired platelet function with moderate to severe thrombocytopenia and coagulopathy, with activation of the coagulation system and fibrinolysis [16]. Fluid accumulation due to plasma leakage including ascites and pleural effusion was noted in 8% and 2.4% of patients on ultrasound scan of abdomen while acalculous cholecystitis was noted in only 5 cases.Presence of ascites and/or pleural effusion and its correlation with disease severity is well documented in the previous studies, but the association of acalculous cholecystitis with severe dengue is yet to be understood [17,18].In this study, ascites wasfound to be associated with severity.

Clinical evidence includes hepatomegaly, with liver involvement being more frequentin the severe form of disease [19]. Hepatomegalywas found to be a strong risk factor for severe dengue in many studies in the past [20,21], however, our study did not find hepatomegaly as a risk for dengue infection severity. Though splenomegaly is not a common feature in dengue fever itwas noted in 5.8% of patients. In the current study, we did not find statistically significant association of splenomegaly with severe illness. In a recently published report from Pakistan, it was observed that significant number of patients with severe dengue had splenomegaly [22]. The reason for spleen enlargement in severe dengue infection may be due to replication of dengue virus in spleen, resulting in splenomegaly [23]. These clinical findings emphasize the fact that presence of hepatomegaly and ascites in addition to with or without splenomegaly in a patient with dengue infection should prompt a clinician to suspect severe illness and manage severity early in the course of the illness.

Asignificant number of patients (5.3%) had shock in the present series. Leo *et al.*, conducted a 5-year retrospective study in Singapore on confirmed adult dengue fatalities and found that deaths among dengue cases were due to shock (100%) and organ failure (85.7%) [24]. Prolonged shock in severe dengue is most often complicated by metabolic acidosis, multi-organ impairment and severe bleeding which carries a poor prognosis [16].

Hepatic dysfunction is a well-recognized feature of dengue infection, often demonstrated by hepatomegaly and mild-to-moderate increases in transaminase levels although jaundice and acute hepatitis are uncommon.The liver dysfunction in dengue infection can be a result of the direct effect of the virus on liver cells or the dysregulated host immune response against the virus [19,25].The present study showed AST>ALT which is consistent with the observations made by Kuo *et al.* in an evaluation of 270 dengue patients, observed abnormal levels of AST and ALT in 93.3% and 82.2% respectively. They reported that elevation of AST levels was usually greater than ALT [26]. This may be due to the release of AST during myocyte damage in dengue infection.However, on regression analysis, we noticed that raised ALT was independently associated with severe disease. ALT is primarily associated with hepatocytes, with minimal activity in kidney and skeletal muscle. It is possible that raised ALT in severe dengue may reflect both liver and renal dysfunction.

The sinister symptom that points to renal dysfunction such as oliguria was observed in 19 (3.5%) cases with AKI (n=23, 4.2%). It was noted to be associated with severe illness and in majority it was self-limited.The proposed mechanisms include increased plasma leakage and loss of fluid from the intravascular compartment leading to shock which may lead to reduced renal perfusion and acute tubular necrosis [27].

We observed that serum protein levels were associated with severe dengue, whereas haematocrit,platelet count, leukocyte count and serum albumin were not. In addition to hypoproteinemia, we found that raised ALT levels were associated with severe form ofdisease. This is in contrast to observations made by Jayaratne *et al.*,stated that raised AST levels were associated with severe dengue and have better predictive value in predicting severe disease [28]. Ours findings indicate that in addition to evaluating hemoconcentration and decreased platelet counts, the presence of low serum protein and raised ALT levels may be taken as a marker for predicting severe disease.

Our study had some limitations such as only hospitalized patients with dengue fever were included in this study and secondly, few studies are available pertaining to factors associated with severe dengue based on the 2009 WHO classification. In the 1997 WHO classification, DHF and DSS comprise the severe form of the disease. Due to differences in the variables included in each classification, comparing the results of the present study with the WHO 1997 classification may not be much justifiable.

CONCLUSION

Based on the results, we conclude that bleeding episodes, ascites, oliguria, raised ALT and low serum protein levels were associated with severe illness. When dengue patients present with these features, the clinician should be aware of the possibility of severe complications. Early identification of factors associated with dengue severity is important for the clinicians in order to implement appropriate interventions for better prognosis.

AUTHOR CONTRIBUTIONS

MSP, CUK, SN and GT planned the study. MSP and CUK designed the study protocol. MSP compiled the data. MSP, CUK, VK and VG analysed and interpreted the relevant data. CUK and MSP drafted the manuscript. CUK, SN and GT critically revised the manuscript for intellectual content.All authors read and approved the final manuscript. MSP, CUK, SD and VG are guarantors of the paper.

CONFLICT OF INTEREST:

None declared.

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