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Original Research Article

Clinico-laboratory spectrum of dengue fever and predictors of severe dengue infection: a study from a tertiary care hospital in Mumbai

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ABSTRACT

Background: Dengue is a rapidly spreading arboviral infection that can progress from flu-like illness to life-threatening severe forms. Since early prediction of severity is difficult, identifying clinical and laboratory predictors is essential for proper management.
Methods: A total 200 patients of either gender and of age ≥18 years with confirmatory diagnosis of dengue fever by dengue NS1 ELISA and/or RT-PCR were enrolled in this study from August 2017 to November 2018. Detailed clinical history was documented.
Results: Of 200 patients, 89% had non-severe (group A) and 11% had severe (group B). Common age group affected in both the groups were 18-30 years. In non-severe dengue, 7.3% patients presented with signs of bleeding as compared to 63.6% in severe dengue. Signs of plasma leakage were only seen in severe dengue (68.2%). Hepatomegaly was predominantly associated with severe dengue (90.9%) as compared to non-severe dengue (10.1%). Splenomegaly was noted from 31.8% patients with severe dengue as compared to only 1.7% patients with non-severe dengue. Secondary dengue infection was present in 2.2% of non-severe cases and 18.2% of severe cases. All patients with severe dengue had significantly higher viral load (≥1000 copies/ml) as compared to 78.7% patients with non-severe dengue.
Conclusions: The possible predictors of severe dengue may include young age with symptoms like rash, vomiting, lethargy and dyspnoea having signs of bleeding, plasma leakage and organomegaly. In addition, laboratory findings supporting severity are secondary infection, high viral load, thrombocytopenia, high haematocrit, raised liver enzymes and increased serum creatinine.

Keywords: Dengue, Severe dengue, Predictors of severity, Dengue criteria

INTRODUCTION

Dengue is the most common acute febrile illness, which is a rapidly spreading mosquito borne arboviral infection in the world.[1,2] Presently about 40% of the world's population are at risk and 50-100 million dengue cases occur annually worldwide with approximately 22,000 deaths each year.[3,4]

Dengue is known to be endemic in India and has myriad manifestations with increasing frequency of severe forms in current times.[2,5] Since last few decades dengue has dramatically expanded in rural areas, apart from outbreaks in urban areas.[1,6]

In humans, the dengue infection is caused by four genetically similar but antigenically distinct serotypes i.e. DENV1, DENV2, DENV3 and DENV4, belonging to

family Flaviviridae and genus Flavivirus.[7] The infection is transmitted by the bite of infected *Aedes aegypti* as well as *Aedes albopictus* mosquito.[1,2] Though most infections are asymptomatic, dengue has a potential to cause a spectrum of illness ranging from flu-like non-severe dengue fever (DF) to a life threatening severe dengue which can lead to fatal complications such as dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS).[1,7,8]

In the early stages of infection, it is practically impossible to differentiate non-severe dengue from severe dengue.[9] Multiple factors have been suggested that contributes to severity such as secondary infections, viral load as well as infecting serotype and genotype.[10] Along with other valuable insights, the viral hypothesis proposes that some viruses may have evolved to replicate faster and to higher levels, thus causing more severe diseases.[11] Therefore, the present study was undertaken to evaluate the possible clinical and laboratory predictors of severe dengue enabling appropriate management and instituting prevention and control measures.

METHODS

The prospective study was conducted in Department of Microbiology, at TNMC and BYL Nair Ch. Hospital and molecular diagnostic reference laboratory, Kasturba hospital, Mumbai, Maharashtra (India), from August 2017 to November 2018. Informed consent was taken from all patients enrolled in the study.

A total of 200 admitted patients belonging to either gender and age ≥18 years with confirmatory diagnosis of dengue fever by Dengue NS1 ELISA and/or RT-PCR were enrolled in this study. Patients without confirmed diagnosis of dengue fever, age <18 years, with history of significant systemic diseases like autoimmune disorders, chronic liver disease, renal disease and other co-infections like malaria, typhoid, leptospirosis and chikungunya were excluded from the study.

Detailed clinical history and laboratory investigation data of enrolled patient was recorded. Confirmed dengue fever cases were then classified into non-severe (group A) and severe dengue (group B) based on WHO (2009) criteria. Results of rapid and/or ELISA for dengue IgM and IgG were recorded to distinguish primary dengue infection from secondary dengue infection. Blood sample of 5ml from enrolled patient was collected aseptically in EDTA vacutainer and subjected to plasma separation by centrifugation.

Separated plasma was transferred in a cryogenic vial and transported under cold chain to molecular diagnostic reference laboratory, Kasturba hospital, Mumbai for viral load estimation by real-time RT-PCR. Viral load was estimated by comparing Ct value with a standard curve. Standard curve was obtained by testing standard from PCR kit.

RESULTS

In the present study, out of 200 patients, 89% were non-severe dengue (group A) and 11% were severe dengue (group B).

Age and gender

Common age group affected in group A (71.9%) as well as group B (81.8%) were 18-30 years of age. Group A showed female preponderance (51.1%) while in group B, predominantly male were (59.1%) affected (Figure 1).

Symptoms

Fever was the most common presenting symptom in both groups. In group A, other common associated symptoms were headache (91%) followed by chills (86%), bodyache (79.8%), nausea (51.1%), vomiting (39.9%), retro-orbital pain (37.1%), lethargy (27%), abdominal pain (21.9%), and myalgia (15.2%). While in Group B, headache (95.5%) was followed by bodyache (86.4%), chills (77.3%), vomiting (68.2%), nausea (59.1%), lethargy (54.5%), retro-orbital pain (54.5%), and abdominal pain (40.9%). A notable feature in group B was the presence of maculopapular rash in 36.4% patients. Also, dyspnoea was more frequently associated with group B (27.3%) than group A (2.3%) (Table 1).

Signs

Hepatomegaly (90.9%) and splenomegaly (31.8%) were commonly associated with patients in group B compared to patients in group A (10.1% and 1.7% respectively). Signs of bleeding (such as petechiae and mucosal bleed) were also a consistent finding in group B (63.6%) patients compared to group A (7.3%) patients. Whereas signs of plasma leakage (like oedema, ascites, pleural effusion) was only associated with group B patients (68.2%) (Table 1). Among haemodynamic and cardiovascular indices, hypotension and narrow pulse pressure were also consistently linked to group B (40.9% and 59.1% respectively) patients compared to group A (6.7% and 5.1% respectively) patients while tachycardia was observed in 18.2% of group B compared to 11.2% of group A patients (Table 2).

Investigations

Haematological investigations showed leukopenia in 37.6% patients from group A and 40.9% patients from group B. Overall (n=200) only 1% patients had leukocytosis (one patient each from both group). In group A, 50% patients presented with anaemia as compared to 45.5% patients in group B. All the patients (100%) of group B had thrombocytopenia as compared to 77% patients of group A. while among these thrombocytopenic patients, 81.2% patients of group B had severe thrombocytopenia while only 13.87% patients of group A had the same. High haematocrit value was observed in

72.7% patients in group B compared to 11.2% patient in group A (Table 3).

Among biochemical tests more than 90% patients of group B as compared to less than 50% patients of group A showed elevated liver enzymes (AST and ALT) while high serum creatinine level was observed in 13.6% patients of group B as compared to 2.3% patients of group A (Table 3).

Further microbiological investigation reported that 97.8% patients of group A and 81.8% patients of group B had primary infection whereas remaining patients from both groups (2.2% and 18.2% respectively) had secondary infection.

All patients of group B while only 78.7% of group A had dengue RNA viral load of $>10^3$ copies/ml (Table 3).

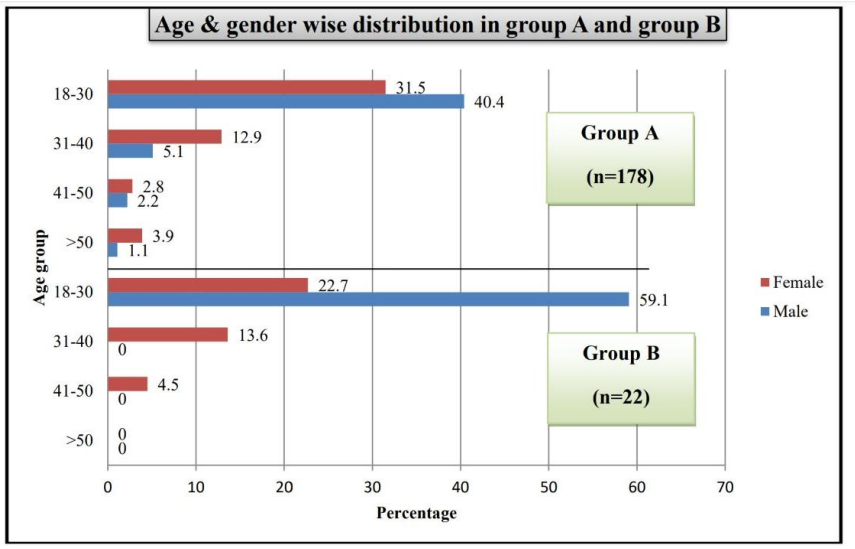

Figure 1: Age and gender distribution among group A and group B dengue patients.

Table 1: Clinical manifestations of dengue cases among group A and group B at presentation.

Parameters	Group A (%)	Group B (%)	P value
Symptoms			
Fever	100	100	0.999
Headache	91	95.5	0.700
Chills	86	77.3	0.338
Bodyache	79.8	86.4	0.578
Myalgia	15.2	13.6	0.999
Retro-orbital pain	37.1	54.5	0.163
Rash	11.8	36.4	0.006
Nausea	51.1	59.1	0.507
Vomiting	39.9	68.2	0.001
Lethargy	27	54.5	0.012
Abdominal pain	21.9	40.9	0.063
Dyspnoea	2.3	27.3	0.001
Arthralgia	7.3	4.5	0.999
Convulsions	3.9	13.6	0.083
Clinical signs			
Jaundice	1.7	9.1	0.094
Hepatomegaly	10.1	90.9	0.001
Splenomegaly	1.7	31.8	0.001
Petechiae	3.4	13.6	0.063
Mucosal bleed	3.9	50	0.001
Oedema	0	4.6	0.110
Ascites	0	31.8	0.001
Pleural effusion	0	31.8	0.001

Table 2: Distribution of hemodynamic and cardiovascular indices among group A and group B.

Parameters	Group A (%)	Group B (%)	P value
Pulse rate			
Bradycardia	0.6	0	0.606
Normal	88.2	81.8	
Tachycardia	11.2	18.2	
Pulse pressure			
Narrow	5.1	59.1	0.001
Normal	82.6	40.9	
Wide	12.4	0	
Blood pressure			
Hypotension	6.7	40.9	0.001
Normal	88.2	54.6	
Hypertension	5.1	4.5	

Table 3: Laboratory investigations among group A and group B.

Parameters	Group A (%)	Group B (%)	P value
Leukocyte count (per µl)			
Leukopenia (<4000)	37.6	40.9	0.189
Normal (4000–11000)	61.8	54.6	
Leukocytosis (>11000)	0.6	4.5	
Haemoglobin (g/dl)			
Severe anaemia (≤5)	0	0	0.31
Moderate anaemia (5-8)	1.1	9.1	
Mild anaemia (8-12)	48.9	36.4	
Normal (≥12)	50	54.6	
Platelet count (per µl)			
Severe thrombocytopenia (<50000)	10.7	81.8	0.001
Moderate thrombocytopenia (50000–100000)	32.6	18.2	
Mild thrombocytopenia (100000–150000)	33.7	0	
Normal (150000–450000)	23	0	
Haematocrit (%)			
Normal	88.8	27.3	0.001
High	11.2	72.7	
Biochemical tests			
SGOT (AST) (U/l)			
Normal (≤40)	51.1	4.5	0.001
High (>40)	48.9	95.5	
SGPT (ALT) (U/l)			
Normal (≤40)	70.2	9.1	0.001
High (>40)	29.8	90.9	
Serum creatinine (mg%)			
Low (≤0.5)	3.9	0	0.016
Normal (0.6–1.2)	93.8	86.4	
High (≥1.3)	2.3	13.6	
Type of infection			
Primary	97.8	81.8	0.006
Secondary	2.2	18.2	
Viral load (copies/ml)			
$\leq 10^3$	21.3	0	0.05
$>10^3$	78.7	100	

DISCUSSION

In recent times, dengue has become a major public health problem in developing countries, creating a large financial burden on society. In India, focal outbreaks have reported a case fatality rate of 3-5% with the largest outbreak reported in 2015, accounting 99913 cases and 220 deaths.[1,12]

Dengue has a wide spectrum of clinical presentations, often with uncertain pathogenesis and outcomes. While majority of patients recover following a self-limiting non-severe clinical course, a small proportion progress to severe disease.[13] Dengue with or without warning signs are subgroups of non-severe dengue.[1]

In the absence of any biomarkers for progression of disease, early recognition of severity is challenging hence there is an urgent need to have composite reference standards (CRS) for dengue as predictors of progression of infection.

The present study is a comprehensive evaluation of dengue virus infections from a tertiary care hospital in Western India and findings of this study have confirmed that, there is a clear difference between patients with severe dengue and non-severe dengue using a set of clinical and laboratory parameters.

Trend of severe and non-severe dengue in India

In our study, 89% were non-severe dengue whereas 11% were severe dengue, conforming with studies by Mallhi et al from Malaysia and Bhushan et al from eastern India respectively.[4,14]

Table 4: Trend of severe and non-severe dengue.

Authors	Place	Non-severe dengue (%)	Severe dengue (%)
Mallhi et al[4]	Malaysia	88.2	11.8
Bhushan et al[14]	Eastern India	89.1	10.9
Tewari et al[15]	New Delhi	96.8	3.2
Subbalaxmi et al[16]	South India	40.5	59.5
Wijeratne et al[17]	Sri Lanka	39.2	60.8

Development of severe disease in dengue virus infection is not fully understood, as the pathogenesis remains complex, involving viral characteristics (serotype, strain, virulence) and host variables (age, genetics, ethnicity, immunity, and chronic illness).[17,18]

Age

In our study, the majority of dengue cases (73%) occurred in the 18–30 age group, comprising 71.9% of non-severe and 81.8% of severe cases. These findings align with several regional studies includes Laul et al reported 61.7% of cases in the same age from Northern India, while Tewari et al and Kumar et al found 56% and 50% of cases in the 19–45 and 20–40 age groups, respectively.[15,19,20] In contrast, Mallhi et al observed a higher incidence of both dengue fever (23.3%) and severe dengue (38%) in individuals over 40.[4] Notably, Wijeratne et al found no significant statistical difference in age between non-severe and severe cases.[17]

Ultimately, the high adult prevalence in our study may be attributed to the increased vector exposure among the mobile, working-age population, better healthcare access, and more frequent reporting to physicians.[4,21]

Gender

In present study, among total dengue cases gender equality was observed, however, male preponderance (59.1%) was observed in severe dengue while slightly a greater number of females (51.1%) were found to be affected by non-severe dengue than males (48.9%). Muruganathan et al from Sri Lanka have also reported approximately an equal gender distribution among dengue patients with 49.3% males and 50.7% females.[22] Jain et al have reported male preponderance in severe dengue cases [DHF (66.4%) and DSS (56.5%)].[12] Wijeratne et al from Sri Lanka have reported male preponderance both in non-severe (62.1%) as well as severe (68.9%) dengue cases.[17] Males are more involved in outdoor activities, hence are more exposed to mosquitoes.[16] Thus, male preponderance was seen in various studies, but in recent times, the increasing, equitable participation of both male and female personnel in outdoor occupational sectors has resulted in uniform, gender-independent exposure risks to vector at the workplace.

Presenting symptoms

In the present study, all patients presented with fever from both the group, whereas headache was the second most common presenting symptoms in both the group (91% and 95.5% respectively). Compared to non-severe dengue (group A) significantly higher proportions of patients in severe dengue (group B) experienced vomiting (39.9% and 68.2% respectively; p value <0.001), lethargy (27% and 54.5% respectively; p value <0.05), maculopapular rash (11.8% and 36.4% respectively; p value <0.01), dyspnoea (2.3% and 27.3% respectively; p value <0.001) and convulsions (3.9% and 13.6% respectively; p value <0.001).

Jain et al also reported fever and headache as the most common symptoms across dengue fever (DF), dengue haemorrhagic fever (DHF), and dengue shock syndrome (DSS). Vomiting (DF:47%, DHF:54.4%, DSS:65.2%) and dyspnoea (DF:2%, DHF:3.2%, DSS:45.6%) increased with severity.[12]

Subbalaxmi et al observed that all cases of severe and non-severe dengue presented with fever. This was followed by vomiting (30%), rash (28.3%), headache (18.3%), bodyache (17.7%) and abdominal pain (16.7%) in non-severe cases whereas severe cases had vomiting (40.9%), rash (34.1%), bodyache (24.4%), headache (22.7%) and abdominal pain (22.7%).[16]

Mallhi et al showed fever as the leading symptom in 94.7% patients of non-severe and 93.7% patients of severe dengue. Dyspnea, rash and vomiting were significant presentation in severe dengue (17.7%, 56.9% and 63.3% respectively) compared to non-severe cases (10%, 41.8% and 54.1% respectively).[4]

Because non-severe dengue can progress rapidly, identifying early clinical markers/presentation is critical. Vigilant monitoring of initial symptoms provides the earliest prediction tool to prevent disease progression.[4] Hence, presence of vomiting, rash, dyspnea, lethargy and convulsions at presentation can be identified as a predictor of disease severity.

Clinical signs

Hepatic manifestations

In the current study, jaundice was observed in 1.7% of patients with non-severe dengue (group A) and 9.1% of patients with severe dengue (group B). This trend aligns with data from Subbalaxmi et al who reported jaundice rates of 1.6% and 6.8% in non-severe and severe dengue respectively.[16] Conversely, Mallhi et al documented jaundice in 12.6% of non-severe and 16.5% of severe dengue cases.[4] Clinical jaundice serves as a critical marker for secondary hepatic impairment or acute liver failure, functioning as an independent indicator of poor clinical prognosis.[15]

Haemorrhagic manifestations

Haemorrhagic manifestations, primarily petechiae and mucosal bleeding, were identified in 7.3% of the non-severe (group A) and 63.6% of the severe dengue (group B), demonstrating a highly significant statistical association ($p<0.001$).

Comparatively, Karoli et al noted haemorrhagic symptoms in 14% of non-severe and 100% of severe cases, while Subbalaxmi et al reported rates of 21.7% and 55.7%, respectively.[16,23] In contrast, Wijeratne et al observed bleeding complications in only 2.2% of severe dengue patients.[17]

Bleeding is an established complication of dengue, driven by severe thrombocytopenia, functional platelet abnormalities, and vascular endothelial leakage. The underlying pathophysiology often involves consumptive coagulopathy, exacerbated by prolonged prothrombin time and rapid fibrinogen consumption.[16,19,24]

Plasma leakage and capillary permeability

Signs of plasma leakage including generalized ascites (31.8%), pleural effusion (31.8%), and oedema (4.6%) were present in 68.2% of severe dengue cases. Notably, no patients in the non-severe group exhibited evidence of plasma leakage, establishing a statistically significant difference ($p<0.05$). Similarly, Karoli et al reported evidence of fluid extravasation exclusively in severe cases (100%).[23] Other literature presents a varied distribution of fluid accumulation in dengue cases. Regarding ascites, Subbalaxmi et al noted it in 15% of non-severe and 22.7% of severe cases.[16] Mallhi et al reported rates of 2.6% and 5.1% respectively, while Wijeratne et al documented ascites in 100% of severe cases.[4,17] For pleural effusion, Jain et al observed it in 46.2% of non-severe and 52% of severe cases, whereas Mallhi et al noted lower rates of 2.6% and 10.1% respectively, and Wijeratne et al reported an incidence of 22.22% in severe cases.[4,12,17] Finally, looking at edema, Mallhi et al observed mild variations in peripheral edema between their non-severe (2%) and severe (2.5%) dengue cases.[4]

It is an established fact that unmodulated cytokine storm drives the pathogenesis of DHF and DSS.[12] In severe dengue, there is an acute increase in vascular permeability that leads to leakage of plasma to extravascular compartment which leads to haemoconcentration, hypotension, hypoproteinaemia and collection of fluid in serous cavities.[25]

Organomegaly

In this study, hepatomegaly and splenomegaly were significantly associated with disease severity. In group B (severe), hepatomegaly occurred in 90.9% of cases and splenomegaly in 31.8%. In group A (non-severe), these rates were substantially lower at 10.1% and 1.7%, respectively. Similarly, Karoli et al and Wijeratne et al also mentioned higher rates of hepatomegaly in severe dengue (60% and 22.22% respectively) compared non-severe dengue (49% and 6.9% respectively) but Jain et al found mild variation with 9.9% severe compared to 9.1% non-severe cases having hepatomegaly.[12,17,23] Regarding splenomegaly, comparative literature reveals varying baseline rates. Subbalaxmi et al observed splenomegaly in 17.1% of severe dengue as compared to 16.7% in non-severe dengue, while Mallhi et al and Jain et al reported lower rates in severe (3.8% and 4.7% respectively) and as well as non-severe cases (1% and 3.5% respectively).[4,12,16]

Presence of hepatomegaly and splenomegaly during the early phases of non-severe dengue is a crucial diagnostic clue indicating the need for close monitoring of patient to anticipate progression towards severity.[15]

Hemodynamic and cardiovascular indices

In our study, tachycardia was observed in 18.2% of severe patients compared to 11.2% of non-severe patients.

Conversely, sinus bradycardia was a rare finding, isolated to a single non-severe patient (0.9%) and entirely absent in severe cases. Mallhi et al reported comparatively lower rates of tachycardia across both non-severe (0.5%) and severe (1.3%) groups.[4]

Our study observed that 59.1% patients of severe dengue and 5.1% patients of non-severe dengue had narrow pulse pressure which was statistically significant (p value <0.001). Wide pulse pressure was seen only in non-severe dengue patients (12.4%).

Hypotension was observed in 40% cases of severe dengue as compared to 6.7% cases of non-severe dengue which was statistically significant (p value <0.001). While hypertension was noted transiently in 4.5% of non-severe and 5.1% of severe patients.

Persistent systemic hypotension alongside a narrow pulse pressure can serve as strong indicators of clinical deterioration.

Haematological profile

Leukocyte kinetics

In the present study, leukopenia (<4,000/µl) was observed in 37.6% of patients with non-severe dengue and 40.9% of those with severe dengue. Conversely, leukocytosis (>11,000/µl) was rare, occurring in only one patient from each group. This trend aligns with Subbalaxmi et al who observed 33.3% non-severe compared to 35.2% severe dengue cases with leukopenia.[16] Conversely, Jain et al showed 38% non-severe compared to 29.2% severe dengue cases with leukopenia, while Mallhi et al reported 54.6% leucopenia in non-severe dengue and 53.2%patients of severe dengue.[4,12] Gajera et al reported an overall leucopenia rate of 39%.[25]

Regarding leukocytosis, our findings were notably lower than literature counterparts; for instance, Subbalaxmi et al and Jain et al noted leukocytosis rates of 6.7% and 4.6% patients with non-severe compared to 20.5% and 14.6% patients with severe dengue, respectively.[12,16] Gajera et al reported an overall leukocytosis rate of 12%.[25]

Leukopenia during dengue virus (DENV) infection typically stems from virus-induced bone marrow suppression targeting myeloid progenitor cells, or accelerated peripheral destruction.[19] The marked degeneration of mature cells paired with a reactive "shift to left" during the acute febrile phase further precipitates this decline.[20] In contrast, emerging leukocytosis during the course of the disease strongly indicates a secondary bacterial co-infection.[16]

Haemoglobin and haematocrit dynamics

Anaemia was detected in 50% of non-severe cases and 45.5% of severe cases; however, no patient presented with severe anaemia (Hb <5 g/dl). The mean haemoglobin level was 12.18 g/dl in the non-severe and 11.65 g/dl in the severe cases. This marginal drop in severe cases mirrors the trends reported by Jain et al and Subbalaxmi et al with mean haemoglobin level of 13.3 g/dl and 13.2 g/dl respectively in non-severe versus 12.7 g/dl and 12.0 g/dl respectively in severe dengue.[12,16]

A critical divergence was noted in haematocrit values as only 11.2% of patients with non-severe dengue exhibited elevated haematocrit compared to 72.7% in the severe group, a difference that was highly statistically significant (p<0.001). Mallhi et al have also reported 9.5% haematocrit rise in non-severe compared to 21.5% in severe dengue.[4] Whereas, Gajera et al reported overall high haematocrit rate of 28% in dengue cases.[25]

The depression of haemoglobin in severe dengue is primarily driven by acute bleeding manifestations superimposed on pre-existing nutritional anaemia.[16] Conversely, the abrupt rise in haematocrit is a hallmark of severe dengue, caused by a systemic increase in vascular permeability. This leads to plasma leakage into extravascular spaces, causing haemoconcentration.[25]

Platelet kinetics and thrombocytopenia

In the present study, 79.5% had thrombocytopenia while 20.5% had normal platelet counts; all patients with normal platelet counts belongs to non-severe group. Whereas severe dengue (group B) was uniformly associated with thrombocytopenia (100%). Conversely, non-severe (group A) patients primarily exhibited normal (23%), mildly decreased (100,000–150,000 cells/cmm: 33.7%), or moderately decreased (50,000–100,000 cells/cmm: 32.6%) counts. Overall, severe thrombocytopenia (platelet count <50,000 cells/cmm) was significantly more frequent in severe dengue (81.8%) than in non-severe dengue (10.7%, p<0.001).

These findings align with existing literature establishing a direct correlation between the degree of thrombocytopenia and clinical severity. Koroli et al have reported thrombocytopenia in 100% of severe cases and 84% patients of non-severe cases.[23] Similarly, Wijeratne et al have reported very low platelet counts in 55.56% of severe dengue compared to only 3.4% patients of non-severe dengue.[17] He also observed that 20.69% patients of non-severe dengue had platelet counts of >100000 cells/cmm as compared to 2.22% in severe dengue. Mallhi et al have also reported 70.8% patients of severe dengue and 58.3% patients of non-severe dengue with thrombocytopenia, stating thrombocytopenia was more common among severe dengue patients.[4]

Broader distribution profiles by Gajera et al have reported platelet counts of 50000-100000 cells/cmm in 34% patients, 20000-50000 cells/cmm in 37% and <20000 cells/cmm in 10% of patients.[25] Only 19% patients had platelet counts of >100000 cells/cmm in overall dengue

cases. Similarly, Srinivas et al have also reported 53.6% patients had platelet counts of 20000-60000 cells/cmm, 21.7% had <20000 cells/cmm and only 5.8% had 80000-100000 cells/cmm in overall dengue patients.[26]

Thrombocytopenia in dengue infection may be due to spontaneous aggregation of platelets to virus infected endothelium, bone marrow suppression or immune mediated clearance.[19] Other possibility includes impaired megakaryocytes production earlier in the disease, platelet specific antibodies, immune complexes or DIC.[25]

Biochemical profile

Hepatic transaminases (AST/ALT)

Hepatic impairment was significantly more pronounced in the severe cases ($p<0.001$). Elevated aspartate aminotransferase (AST/SGOT) was seen in 95.5% of severe cases compared to 48.9% of non-severe cases. Similarly, alanine aminotransferase (ALT/SGPT) was elevated in 90.9% of severe patients versus 29.8% of non-severe patients.

This high prevalence of transaminitis in severe dengue matches the findings of Mallhi et al who reported 84.8% patients with elevated SGOT/AST and 59.5% patients with elevated SGPT/ALT among severe cases compared to 64.6% patients with elevated SGOT/AST and 53.6% patients with elevated SGPT/ALT among non-severe group.[4] Jain et al also reported 72.6% patients of severe dengue and 63.1% patient of non-severe dengue had elevated SGOT/AST, whereas 61.6% patients of severe dengue and 44.9% patients of non-severe dengue had elevated SGPT/ALT.[12]

Liver enzyme elevation is a common feature of dengue infection. Hepatic injury results from either direct viral cytopathy or an unregulated, storm-like host immune response. In severe instances, acute hepatitis can progress to massive hepatic necrosis, fulminant hepatic failure, hepatic encephalopathy, and death.[24] Grossly elevated transaminases serve as a reliable biomarker for severe clinical phenotypes.[4]

Renal function and serum creatinine

Elevated serum creatinine was significantly associated with severe dengue, presenting in 13.6% of severe cases compared to just 2.3% of non-severe cases ($p<0.05$). The mean serum creatinine in our study was 0.89±0.17 mg/dl in non-severe cases and 0.97±0.25 mg/dl in severe cases. This slight but clear distinction matches the mean values reported by Jain et al (0.7 mg/dl non-severe versus 0.8 mg/dl severe).[12] Notably, Mallhi et al observed a much higher burden of renal impairment, reporting elevated creatinine in 65.8% of severe patients compared to 9.9% of non-severe patients.[4]

Acute kidney injury (AKI) is a severe complication of dengue infection.[27] The spectrum of dengue-induced nephropathies ranges from transient proteinuria to severe AKI. The underlying mechanisms include direct viral-mediated glomerular damage, immune-complex deposition within the glomeruli, and systemic hemodynamic instability leading to renal hypoperfusion.[4]

Primary versus secondary

In the present study, primary dengue infection was identified in 97.8% of patients with non-severe dengue and 81.8% of those with severe dengue. Secondary dengue infection was present in 2.2% of non-severe cases and 18.2% of severe cases, demonstrating a statistically significant association with disease severity ($p<0.05$). This finding aligns with Mallhi et al who similarly reported a significantly higher rate of secondary infection in severe dengue (22.8%) compared to non-severe dengue (9.9%, $p<0.05$).[4] Furthermore, Vaughn et al reported that over 90% of severe dengue cases were linked to secondary infections.[28]

In endemic regions, adults frequently experience prior subclinical exposure, elevating their risk for subsequent secondary infections and clinical severity.[4] It has been suggested that the severity of disease associated with dengue infection is determined by the number of cells infected with the virus. During secondary heterologous infections, this is driven by antibody-dependent enhancement (ADE), which accelerates the infection of peripheral blood leukocytes.[29] Additionally, cross-reactive memory T cells generated during the primary infection often exhibit sub-optimal clearance of the secondary serotype. This aberrant immune response triggers an excessive inflammatory cascade, ultimately predisposing patients to severe clinical manifestations.[17]

Viral load

The primary site of human DENV replication resides within mononuclear phagocytes, and the pathogenesis of severe dengue is strongly associated with the total burden of infected cells. Consequently, patients exhibiting severe clinical manifestations are hypothesized to possess a higher burden of infected mononuclear cells and, by extension, elevated viral replication. Provided viral release remains uninhibited, this model dictates that disease severity positively correlates with viremia levels.[30] Supporting this hypothesis, the present study demonstrated that 100% of patients with severe dengue exhibited a DENV RNA viral load exceeding 1000 copies/ml, compared to 78.7% of patients with non-severe dengue, establishing a statistically significant difference ($p<0.05$).

This positive correlation between viral burden and clinical severity is consistent with findings by Murgue et al who reported significantly higher magnitudes of viremia in severe cases relative to non-severe cases.[31] Similarly, Wang et al have also observed that most non-severe

dengue patients had undetectable plasma dengue RNA when the fever subsided whereas all severe dengue patients continued to have high levels.[11]

Conversely, early work by Gubler et al detected no significant differences in circulating viral titres between mild and severe manifestations, postulating that the peripheral blood of severe patients could render virologically sterile due to widespread antigen-antibody complexing.[30] However, these historical discrepancies must be contextualized alongside recent advancements in high-sensitivity molecular viral load detection technologies.

On the basis of our study, we proposed the "composite reference standard" which may be known as "SAVE criteria" to predict progression of dengue towards severity as follows.

Table 5: "SAVE" criteria to predict progression towards severity of dengue.

1.	Host factor	Young adult
2.	Symptoms – any one	Vomiting
		Lethargy
		Dyspnoea
		Rash
3.	Clinical signs – any one	Hypotension
		Haemorrhagic manifestations
		Evidence of plasma leakage
		Hepatomegaly and/or splenomegaly
4.	Laboratory findings– any one	Evidence of secondary dengue
		Moderate thrombocytopenia (<100000 cells/cmm)
		High haematocrit (>44%)
		Elevated liver enzymes (>200 U/l)
		High serum creatinine (>1.3 mg/dl)
		Viral load (>1000 copies/ml)

Patients fulfilling these criteria should be considered at higher risk for severe dengue and warrant close monitoring and timely intervention.

Limitation of the study is low numbers of patients with severe dengue.

CONCLUSION

Identifying validated predictors of dengue severity allows clinicians to risk-stratify high-risk individuals early and intervene timely to reduce morbidity. To achieve this, our study introduces a composite reference standard called as "SAVE criteria" that facilitates the identification of patients prone to adverse outcomes, drastically reducing fatalities. Ultimately, these findings will help policy makers to improve prevention and treatment strategies.

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