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# Clinical correlates of severe dengue fever in children admitted at a tertiary care hospital

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## Abstract

It is the most common and widespread arboviral infection in the world today caused by Dengue virus. Dengue viruses (DV) belong to the family Flaviviridae and there are four serotypes of the virus referred to as DV-1, DV-2, DV-3 and DV-4.The course of the disease has changed in the recent years from milder form to severe form like dengue hemorrhagic fever & severe dengue fever and with increasing outbreaks frequency.Data was collected by face to face interview from the parents of the children admitted in pediatric emergency ward with diagnosis of dengue fever and severe dengue fever in Department of pediatrics. The presence of bleeding manifestations like melena, epistaxis, hematemesis, petechiae, hematurias more in DF with warning signs(37.5%) and Severe dengue fever(55.6%). There is significant association between bleeding manifestations and severity of dengue fever($p<0.001$). Thrombocytopenia was found in 83.8% in dengue fever, 93.8% in DF with warningsignsand81.5%inseveredenguefeveranditisnotstatisticallysignificant($p=0.308$).

**Keyword:** clinical correlates, severe dengue fever, children

## Introduction

Dengue is an essential mosquito-transmitted viral infection having significant mortality andmorbidity. It is a significant public health concern with its geographical distribution becoming worldwide, involving nearly all the tropical and subtropical regions of the world[1]. It is the most common and widespread arboviral infection in the world today caused by Dengue virus. Dengue viruses (DV) belong to the family Flaviviridae, and there are four serotypes of the virus referred to as DV-1, DV-2, DV-3 and DV-4[2].The course of the disease has changed in the recent years from milder form to severe form like dengue hemorrhagic fever & severe dengue fever and with increasing outbreaks frequency[3]. Approximately 1.8 billion (more than 70%) of the population at risk for dengue worldwide live in Member States of the WHO South-East Asia Region (SEAR) and Western Pacific Region, which bear nearly 75% of the current global disease burden due to dengue[4]. During the 1780s, the dengue epidemics were first recognized to occur almost simultaneously in Asia, Africa and North America, shortly after the identification and naming of the disease in 1779. Benjamin Rush confirmed the first case report in 1789 and he coinedDengue as "Breakbone Fever" because of the symptoms of myalgia and arthralgia[5]. Nearly 10,000 deaths are attributed to dengue infection yearly, which is secondary to rapid urbanizationandovercrowding. Temporal trends suggest that the incidence of dengue nearly doubled in every

decade since 1990[6]. Dengue is the primary cause of childhood death in many countries in Southeast Asia.
According to WHO 2012 guidelines, the clinical spectrum of disease includes[8]

- Dengue fever.
- Dengue with warning signs.
- Severe dengue fever (DF).

Severe dengue is defined as a suspected dengue patient associated with severe bleeding, severe organ dysfunction or severe plasma leakage leading to shock.
In addition to the distinction between severe and non-severe dengue, the WHO recognizes three phases in the clinical course of a dengue infection, i.e. the febrile, critical and recovery phase.
This study is aimed to find out the prognostic indicators in severe dengue fever in children which will help us in turn to identify severe dengue fever at the earliest and to assess the prognosis.

## Methodology

Data was collected by face to face interview from the parents of the children admitted in pediatric emergency ward with diagnosis of dengue fever and severe dengue fever in Department of pediatrics.
This was a case control study design in which 201 cases of dengue fever admitted in the pediatric emergency ward, were enrolled. After taking written informed consent, data were collected in a predesigned semi structured questionnaire regarding Socio-Demographic profile, medical history, clinical and hematological profile and outcome. Investigations such as Complete blood count, Blood test(Serology) for Dengue fever, urine routine, serum electrolytes, random blood sugar, WIDAL/Blood culture, Liver enzymes, Chest x ray, Ultrasound abdomen, PT, aPTT, INR were done based on the clinical scenario and if necessary, blood urea, serum creatinine, CSF analysis, 2D echo, CT scan brain/MRI was also done. Non randomized purposive sampling technique will be adopted to select both cases and controls.
Since this study is a time bound study, where a series of dengue cases (as per inclusion criteria) were enrolled during a study period of one year i.e., from November 2017 to October 2018. During this study period, we were able to enroll a total of 201 cases, out of which 142 were only dengue fever, 32 were dengue fever with warning signs and 27 were severe dengue fever.

## Inclusion criteria

I) **For cases:** Any child, between age 1 month to 12 years, having tested positive for dengue NS1 antigen in serum or tested positive for antibodies (IgM) in serum against dengue fever virus along with complications such as shock or fluid accumulation with respiratory distress or severe bleeding or severe organ involvement such as liver, CNS, heart and other organs.
II) **For controls:** Any child, between age 1 month to 12 years, having tested positive for dengue NS1 antigen in serum or tested positive for antibodies (IgM) in serum against dengue fever virus without any complications.

## Exclusion criteria

1) Children having other co-infections like malaria, typhoid or infective hepatitis, interfering with interpretation of the laboratory data.

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2) Immunocompromised subjects
3) Children less than 1 month.
4) Patients discharged against medical advice.

## Results

**Table 1:** Age group versus clinical type of dengue diagnosis

| Age group | Dengue fever | | DF with warning signs | | Severe DF | | |
|---|---|---|---|---|---|---|---|
| | Frequency | Percent | Frequency | Percent | Frequency | P value | Percent |
| < 1 yr | 15 | 10.6 | 1 | 3.1 | 3 | 11.1 | 0.71 |
| 1-5 yrs | 46 | 32.4 | 10 | 31.3 | 9 | 33.3 | |
| 10-15 yrs | 20 | 14.1 | 8 | 25.0 | 4 | 14.8 | |
| 5-10 yrs | 61 | 43.0 | 13 | 40.6 | 11 | 40.7 | |
| Total | 142 | 100.0 | 32 | 100.0 | 27 | 100.0 | |
| Mean ± SD | 6.39 ± 3.96 | | 7.38 ± 4.07 | | 6.67 ± 3.87 | | 0.449 |

Mean age group of dengue fever were 6.39+3.93 yrs, DF with warning signs were 7.38+4.07 yrs, severe dengue fever were 6.67+3.87 yrs(p=0.449).

**Table 2:** Sex versus clinical type of dengue diagnosis

| Sex | Dengue fever | | DF with warning signs | | Severe DF | | P value |
|---|---|---|---|---|---|---|---|
| | Frequency | Percent | Frequency | Percent | Frequency | Percent | |
| Female | 59 | 41.5 | 10 | 31.3 | 9 | 33.3 | 0.458 |
| Male | 83 | 58.5 | 22 | 68.8 | 18 | 66.7 | |
| Total | 142 | 100.0 | 32 | 100.0 | 27 | 100.0 | |

Although in the present study, the incidence of dengue fever, DF warning signs and Severe dengue fever was more in males, there is no significant association with the severity of dengue fever(p=0.458).

**Table 3:** Bleeding manifestations versus clinical type of Dengue diagnosis

| Bleeding MF | Dengue fever | | DF with warning signs | | Severe DF | | P value |
|---|---|---|---|---|---|---|---|
| | Frequency | Percent | Frequency | Percent | Frequency | Percent | |
| No | 138 | 97.2 | 20 | 62.5 | 12 | 44.4 | <0.001 |
| Yes | 4 | 2.8 | 12 | 37.5 | 15 | 55.6 | |
| Total | 142 | 100.0 | 32 | 100.0 | 27 | 100.0 | |

The presence of bleeding manifestations like melena, epistaxis, hematemesis, petechiae, hematuria s more in DF with warning signs(37.5%) and Severe dengue fever(55.6%). There is significant association between bleeding manifestations and severity of dengue fever(p<0.001).

**Table 4:** Pulse pressure versus clinical type of Dengue diagnosis

| Pulse pressure | Dengue fever | | DF with warning signs | | Severe DF | | P value |
|---|---|---|---|---|---|---|---|
| | Frequency | Percent | Frequency | Percent | Frequency | Percent | |
| ≥ 20 mmHg | 117 | 82.4 | 28 | 87.5 | 15 | 55.6 | <0.001 |
| < 20 mmHg | 12 | 8.5 | 3 | 9.4 | 12 | 44.4 | |
| NR | 13 | 9.2 | 1 | 3.1 | 0 | 0.0 | |
| Total | 142 | 100.0 | 32 | 100.0 | 27 | 100.0 | |

Narrow pulse pressure(<20 mmhg) was found in 8.5% in dengue fever, 9.4% in DF with warning signs, 44.4% in severe dengue fever and it is statistically signific(p<0.001).

**Table 5:** CRT versus clinical type of Dengue diagnosis

| CRT | Dengue fever | | DF with warning signs | | Severe DF | | P value |
|---|---|---|---|---|---|---|---|
| | Frequency | Percent | Frequency | Percent | Frequency | Percent | |
| ≤ 3 seconds | 141 | 99.3 | 32 | 100.0 | 12 | 44.4 | <0.001 |
| > 3 seconds | 1 | 0.7 | 0 | 0.0 | 15 | 55.6 | |
| Total | 142 | 100.0 | 32 | 100.0 | 27 | 100.0 | |

Prolonged Capillary refill time of > 3 seconds was found in 55.6% in severe dengue fever which is statistically significant($p<0.001$).

**Table 6:** $SpO_2$ levels versus clinical type of Dengue diagnosis

| $SpO_2$ | Dengue fever | | DF with warning signs | | Severe DF | | P value |
|---|---|---|---|---|---|---|---|
| | Frequency | Percent | Frequency | Percent | Frequency | Percent | |
| Low | 8 | 5.6 | 6 | 18.8 | 16 | 59.3 | <0.001 |
| Normal | 134 | 94.4 | 26 | 81.3 | 11 | 40.7 | |
| Total | 142 | 100.0 | 32 | 100.0 | 27 | 100.0 | |

Low $spO_2$ were identified in 5.6% in dengue fever, 18.8% in DF with warning signs and 59.3% in severe dengue fever and this has significant association with severity of dengue fever($p<0.001$).

**Table 7:** Anaemia versus clinical type of Dengue diagnosis

| Anaemia | Dengue fever | | DF with warning signs | | Severe DF | | P value |
|---|---|---|---|---|---|---|---|
| | Frequency | Percent | Frequency | Percent | Frequency | Percent | |
| Yes | 47 | 33.1 | 11 | 34.4 | 8 | 29.6 | 0.921 |
| No | 95 | 66.9 | 21 | 65.6 | 19 | 70.4 | |
| Total | 142 | 100.0 | 32 | 100.0 | 27 | 100.0 | |

Anaemia was found in 33.1% in dengue fever, 34.4% in DF with warning signs and 29.6% in severe dengue fever and it is not statistically significant($p=0.921$).

**Table 8:** Progressive leucopenia versus clinical type of Dengue diagnosis

| Leucopenia | Dengue fever | | DF with warning signs | | Severe DF | | P value |
|---|---|---|---|---|---|---|---|
| | Frequency | Percent | Frequency | Percent | Frequency | Percent | |
| Yes | 93 | 65.5 | 14 | 43.8 | 11 | 40.7 | 0.01 |
| No | 49 | 34.5 | 18 | 56.3 | 16 | 59.3 | |
| Total | 142 | 100.0 | 32 | 100.0 | 27 | 100.0 | |

Progressive leukopenia was found in 65.5% of dengue fever, 43.8% in DF with warning signs and 40.7% in severe dengue fever and it is not statistically significant in our present study($p=0.01$). Leukocytosis was identified more in severe dengue who presented with/developed bleeding manifestations which was significantly associated with severity of dengue fever.

**Table 9:** Lymphocytopenia versus clinical type of Dengue diagnosis

| Lymphocytopenia | Dengue fever | | DF with warning signs | | Severe DF | | P value |
|---|---|---|---|---|---|---|---|
| | Frequency | Percent | Frequency | Percent | Frequency | Percent | |
| Yes | 50 | 35.2 | 13 | 40.6 | 6 | 22.2 | 0.306 |
| No | 92 | 64.8 | 19 | 59.4 | 21 | 77.8 | |
| Total | 142 | 100.0 | 32 | 100.0 | 27 | 100.0 | |

Lymphocytopenia was found in 35.2% in dengue fever, 0.6% in DF with warning signs and 22.2% in severe dengue fever which is not statistically significant.

**Table 10:** Raising hematocrit versus clinical type of Dengue diagnosis

| Hematocrit | Dengue fever | | DF with warning signs | | Severe DF | | P value |
|---|---|---|---|---|---|---|---|
| | Frequency | Percent | Frequency | Percent | Frequency | Percent | |
| Yes | 70 | 49.3 | 17 | 53.1 | 13 | 48.1 | 0.912 |
| No | 72 | 50.7 | 15 | 46.9 | 14 | 51.9 | |
| Total | 142 | 100.0 | 32 | 100.0 | 27 | 100.0 | |

Raising hematocrit was identified in 49.3% in dengue fever, 53.1% in DF with warning signs and 48.1% in severe dengue fever and it is statistically not significant in our present study(p=0.912).

**Table 11:** Thrombocytopenia versus clinical type of Dengue diagnosis

| Thrombocytopenia | Dengue fever | | DF with warning signs | | Severe DF | | P value |
|---|---|---|---|---|---|---|---|
| | Frequency | Percent | Frequency | Percent | Frequency | Percent | |
| Yes | 119 | 83.8 | 30 | 93.8 | 22 | 81.5 | 0.308 |
| No | 23 | 16.2 | 2 | 6.3 | 5 | 18.5 | |
| Total | 142 | 100.0 | 32 | 100.0 | 27 | 100.0 | |

Thrombocytopenia was found in 83.8% in dengue fever, 93.8% in DF with warning signs and 81.5% in severe dengue fever and it is not statistically significant(p=0.308).

**Table 12:** Outcome versus clinical type of Dengue diagnosis

| Outcome | Dengue fever | | DF with warning signs | | Severe DF | | P value |
|---|---|---|---|---|---|---|---|
| | Frequency | Percent | Frequency | Percent | Frequency | Percent | |
| Expired | 0 | 0.0 | 0 | 0.0 | 4 | 14.8 | <0.001 |
| Improved | 142 | 100.0 | 32 | 100.0 | 23 | 85.2 | |
| Total | 142 | 100.0 | 32 | 100.0 | 27 | 100.0 | |

The mortality from dengue fever was seen in 14.8% from severe dengue fever.

## Discussion

Narrow pulse pressure(< 20 mmhg) and prolonged Capillary refill time(>3 secs)and altered mental state i.e. irritability was found to have significant association with severity of dengue fever as showed in the study done by Rajapakses *et al*.[7]

Low oxygen saturation was found in 59.3 % of severe dengue fever cases in our study, which is showing statistically significant association with the dengue fever severity.Progressive leukopenia, hyponatraemia, elevated SGOT/SGPT levels, prolonged PT/APTT/INR levels, presence of pleural effusion, LRTI, tender hepatomegaly and ascites was significant association with the severity of dengue fever as shown by many of the studies. But this study did not find the association of anemia, lymphocytopenia, raising hematocrit, thrombocytopenia with severity of dengue fever. This could be because of early identification, diagnosis and intervention with IV fluids resulting in masking of results.

However many studies proposed hemoconcentration as a prognostic factor for the severity of dengue infection[8,9].

Vasculopathy in dengue causes increased vascular permeability, leading to hemo-concentration and shock. Some studies concluded that white cell count > 5,000/μL is a prognostic factor for dengue severity[10] while others found leucopenia. Normal leukocytes or

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mild leukocytosis may be found in early dengue infection. When body temperature declines, most patients experienced leucopenia from bone marrow suppression. Stress in accompanied with shock may somehow cause leukocytosis.

Thrombocytopenia was found to have association with the severity of dengue fever in the studies conducted by Jayashree K *et al.*, Mogra G *et al.* and Mourao *et al.*, but this was not established in our present study[11].

Low platelets are explained by bone marrow suppression and immune response induced platelet destruction by the liver and spleen.

Hyponatraemia was found to have significant association with severity of dengue fever.Studies done by Adisorn Lumpaopong *et al.* showed mild hyponatremia is a common electrolyte disturbance and renal involvement is mild in patients with DF and DHF[12].

Studies done by Dayal A *et al.* and Sahana *et al.*[10] found the association of pleural effusion, ascitis and tender hepatomegaly with the severity of dengue fever, which was again proved in our study. Although moderate liver enlargement is a normal response to dengue infection, it is more associated with severe dengue fever compared to DF.

The mortality among the severe dengue fever in our study was 14.8% which was more than those reported by Sahana *et al.* where it was 2%. The overall mortality of dengue fever in our study was 0.02%. Various measures for early diagnosis and prompt intervention with emphasis on the warning signs and good supportive care could help decrease the fatality and morbidity associated with dengue.

## Conclusion

The severity of dengue infection is significantly associated with some routine clinical parameters like presence of bleeding manifestations, pulse pressue<20 mmhg, prolonged CRT, low $O_2$ saturation, Hyponatraemia, elevated SGOP/SGPT levels, Prolonged PT/APTT/INR levels, respiratory and abdominal involvement. These parameters may be used to predict, to forecast disease severity in patients suspected of dengue infection and to manage it early in the course of the illness. Various measures for early diagnosis and prompt intervention with emphasis on the warning signs and good supportive care would help decrease the fatality and morbidity associated with Dengue.

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