

# Clinical and Laboratory Predictors of Outcome in Children Hospitalized with Dengue

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## Abstract

**Objectives:** To evaluate the utility of clinical features and laboratory markers to predict the severity of illness and mortality in dengue infection.

**Methods:** This prospective observational study included children between 2 months to 12 years, admitted with dengue NS1 and/or IgM positive excluding those with other concurrent infections. Clinical features and laboratory parameters were assessed for their association with progression to severe dengue (SD) and mortality.

**Results:** Out of a total of 150 children, hospitalized with dengue, 21 (14%) cases were classified as SD, 7 of which (33%) died. On multivariate logistic regression analysis, decreased urine output and serum albumin levels on admission were the significant predictors for severe dengue while high serum lactate levels at admission was an independent predictor of dengue mortality.

**Conclusion:** Children who presented with decreased urine output and low serum albumin levels were at high risk of severe dengue, and those with high lactate levels on admission were at risk of mortality. Thus, these children need careful monitoring.

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**Key Words:** Dengue, Predictors, Severity, Mortality, Children

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## Introduction

Dengue is a rapidly spreading vector borne infection owing to massive urbanization, life style shifts, poor management of water storage [1,2]. About 40% of the global population is affected by dengue [3]. A non-structural 1 (NS1) antigen ELISA, particularly when used in combination with the IgM capture ELISA, confirms diagnosis of dengue infection in an endemic area [4]. Most of the common clinical symptoms of dengue last for 2 to 7 days and include petechiae, rashes, retro-orbital discomfort, headache, bone pain as well as myalgia and arthralgia. Children suffering from dengue are mostly asymptomatic or present with minimal symptoms. A small percentage of cases progress to dengue hemorrhagic fever, which causes hemorrhage, thrombocytopenia and leakage of plasma, or dengue shock syndrome [5-8]. The objectives of this study were to evaluate the utility of clinical features and laboratory parameters to predict the severity of illness and mortality in dengue infection.

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## Materials and Methods

This prospective observational study conducted in the Department of Pediatrics of a tertiary care hospital of north India, from August 2017 to May 2019 including children from 2 months to 12 years of age admitted with dengue NS1 and/or IgM positive. The children suffering from dengue with warning signs and SD were admitted, and children suffering from dengue without warning signs were also admitted, if they have a poor oral intake. Those with other concurrent infections or dengue like illness but not tested positive for NS1Ag or IgM, who refused to give consent, patients with other chronic diseases and who were discharged against medical advice (DAMA) were excluded from the study.

Previously researchers have performed different studies to evaluate the utility of clinical features to predict the severity and mortality of dengue infection. The prevalence of SD found in these articles ranges between 5 - 30% [13,20]. Therefore, assuming  $p = 10$  with 5% margin of error, the minimum required sample size at 5% level of significance was 138 patients.

Details including age, gender, fever duration, vomiting, cough, abdominal pain/tenderness, decreased urine output, clinical fluid accumulation (CFA), mucosal bleed, positive

tourniquet test, hepatomegaly and hypotension were recorded on admission or during hospitalization. Other parameters recorded included duration of hospital stay, need of boluses, total fluid required in first 24 hour and need of blood and blood products. CFA was assessed by clinical features like facial puffiness, reduced air entry in chest and ascites. Laboratory parameters were sent after 24 hours or before as and when required.

Patients were classified as per WHO Dengue guidelines into non severe dengue (NSD) and SD, the latter being shifted to PICU as per need. The patient was categorized under SD group, if he/she was experiencing fever for 2-7 days, with CFA or shock due to plasma leakage and/or severe bleeding and/or severe organ impairment assessed by levels of liver enzymes. Patients were treated as per WHO 2009 Dengue guidelines. Clinical and laboratory parameters were analyzed for their association with severity of dengue infection and mortality

### Statistical Analysis

The Statistical Package for Social Sciences (SPSS) version 18.1 was used to conduct the statistical analysis (SPSS, Inc., Chicago, IL). Quantitative variables were compared between the two groups using an unpaired t-test/Mann-Whitney Test. The Chi-Square test/exact Fisher's test was used to compare dichotomous variables, with calculation of relative risk. Statistical significance was taken at p value of < 0.05. A univariate and multivariate analysis was used to evaluate possible factors associated with SD.

### Results

Of the 172 children hospitalized with dengue fever 22 cases were excluded. Thus, among the enrolled 150 patients, 21 (14%) cases were classified as SD and 129 (86%) cases as NSD. Seven patients out of 21 cases (33%) with SD died (Figure 1).

Abdominal pain, oliguria, hypotension and hepatomegaly, are found more often among patients with SD than patients with NSD. Elevated liver enzymes on admission [SGOT and SGPT], deranged coagulation profile, a positive tourniquet test, thrombocytopenia on admission, high serum lactate levels and lower serum albumin levels were significantly more in SD than in NSD patients. The age, gender, vomiting, cough, duration of hospital stays, TLC and hematocrit, were comparable. The comparison of parameters between children with SD and NSD is shown in Table 1.

Oliguria, hypotension, hepatomegaly and shock were seen more common among non survivors, compared to the survivors. Elevated liver enzymes on admission, deranged coagulation profile, positive tourniquet test, thrombocytopenia on admission, high serum lactate levels

and lower serum albumin levels were significantly associated with the mortality. Comparison of parameters between survivors and non-survivors are shown in Table 2.

On analyzing the predictors of SD and mortality by multivariate logistic regression, it was found that the decreased urine output and low serum albumin levels on admission were the significant predictors (OR=0.054, 95% CI=0.006 to 0.464, p=0.008 and OR=0.10, 95% CI=0.014 to 0.717, p=0.022 respectively) for SD, Higher serum lactate levels were found to be independently associated with mortality. (OR=1.203; 95% CI: 1.040–1.391; p = 0.013).

### Discussion

In this study, the clinical and laboratory parameters at admission and during hospital stay of 150 children hospitalized with dengue were assessed for their association with progression to severe dengue and mortality. Decreased urine output and hypoalbuminemia were found to be independent predictors of SD and high serum lactate level was a predictor of mortality.

In the current study, the mean age of children was slightly higher in SD compared to NSD but no significant association was found (p= 0.071). However, Pongpan et al conducted a study and described children > 6 years of age were at risk of SD [9]. In our study, male population predominated in both groups with no significance which was in contrast to a previous study [10,11].

Similar to the study done by Sreenivasan et al, and Khan MAS et al, oliguria and CFA was observed more in SD compared to NSD [11,13]. In our study, hepatomegaly was observed more often in SD as compared to NSD, corroborating with earlier studies [8].

We observed that children presenting with secondary dengue infection developed more SD compared to NSD, similar to earlier studies [14]. As expected, hypotension on admission and during hospitalization was observed more often in SD compared to NSD. A study done by Pongpan et al has reported that systolic blood pressure (SBP) <90 mm-Hg and pulse pressure  $\leq$  20 mm-Hg are prognostic factors for dengue shock syndrome (DSS) [9]. All patients with SD were managed in PICU in our study. A study done by Juneja et al has found that patient with SD may require ICU admission for organ failure and outcome can be improved with appropriate aggressive care and organ support in ICU [15]. We observed in our study that blood products (Fresh Frozen Plasma, Packed Red Blood Cells and platelet rich plasma) were needed more often in SD compared to NSD, similar to that found in a study done by Vazhayil et al. where they observed that in 78 dengue positive patients, 23.7% developed SD and blood products

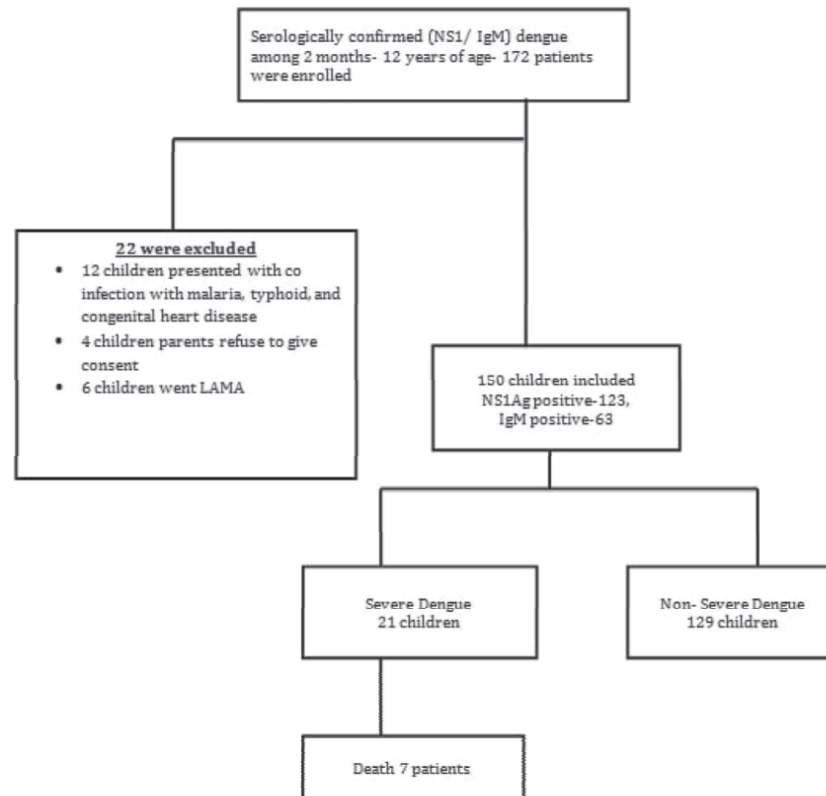


Figure 1 : Flowchart showing enrolment of children in to the study

Table 1: Comparison of the parameters between children with severe dengue and non-severe dengue

Characteristics	Non-severe dengue	Severe dengue	RR/OR of SD [95% CI]	P value
Age, Months, Mean (SD)	70.8±44.7	88.5±38.2	1.01 [0.99-1.02]	0.071
Male gender, n (%)	80(62)	15(71.4)	1.44 [0.59 -3.51]	0.406
Abdominal Pain, n (%)	50(38)	15(71.4)	3.27 [1.34-7.96]	0.008*
Vomiting, n (%)	84 (65.1)	15(71.4)	1.28 [0.53-3.12]	0.571
Cough, n (%)	42(32.6)	4(19)	0.53 [0.18-1.49]	0.308
Decreased Urine Output, n (%)	16(12.4)	18(85.7)	20.47 [6.41-65.36]	<0.001*
Hepatomegaly n (%)	27(20.9)	18(85.7)	14.0 [4.34-45.17]	<0.001*
Hypotension n (%)	4(3.1)	8(38.1)	7.08 [3.68-13.61]	<0.001*
Tourniquet test n (%)	31(24)	20(95.2)	38.82 [5.36-281.11]	<0.001*
Mortality, n (%)	0(0)	7(33)	10.21 [6.21- 16.8]	-
TLC (cells per cumm), Mean (SD)	7747.6±5118.9	9280.95±8000.2	1.0 [1.0-1.0]	0.292
Platelet counts (lac per mm <sup>3</sup> ), Median (IQR)	2.0(1.72-2.58)	0.80(0.38-1.40)	0.7 [0.02-0.19]	<0.001*
Hematocrit, Mean (SD)	35.0±4.62	38.1±7.52	1.12 [1.02-1.22]	0.102
SGOT (IU/L), Mean (SD)	114±134	1830±1891.7	1.005 [1.002-1.008]	<0.001*
SGPT (IU/L), Mean (SD)	74.0±137.4	1743.6±3291	1.005 [1.002-1.008]	<0.001*
Serum Lactate (mmol/L), Mean (SD)	1.8±0.9	5.24±3.7	1.18 [1.13-1.27]	<0.001*
Serum Albumin (g/dl), Mean (SD)	4.0±0.5	2.8±0.5	0.027 [0.007-0.099]	<0.001*
PT (seconds), Mean (SD)	13.4±1.6	24.0±11.3	1.04 [0.98-1.11]	<0.001*
INR, Mean (SD)	1.09±0.2	2.3±1.5	112.48 [4.68-2701.51]	<0.001*
Duration of hospital stay, days, mean (SD)	4.4±1.4	5.6± 2.8	1.43 [1.11-1.84]	0.052

**Table 2: Comparison of the parameters between survivors and non-survivors among children with dengue**

Characteristics	Non-Survivors	Survivors	RR/OR of mortality [95% CI]	P value
Age, Months, Mean (SD)	97.57±16.65	72.05±44.79	1.015 [0.99-1.03]	0.14
Male gender, n (%)	2(28.6)	93(65)	0.23 [0.04-1.15]	0.1
Abdominal Pain, n (%)	5(71.4)	60(42)	3.26 [0.65-16.31]	0.24
Vomiting, n (%)	7(100)	92(64.3)	-	0.096
Cough, n (%)	0(0)	46(32.2)	-	0.101
Decreased Urine Output, n (%)	6(85.7)	28(19.6)	20.47 [2.55-164.21]	0.001*
Hepatomegaly n (%)	7(100)	38(26.6)	-	<0.001*
Hypotension n (%)	3(42.9)	9(6.3)	8.62 [2.17-34.14]	0.012*
Tourniquet test n (%)	7(100)	44(30.8)	-	<0.001*
Shock	3(42.9)	6(4.2)	11.750 [3.08-44.72]	0.005*
TLC (cells/cumm), Mean (SD)	13842.86±12681.46	7674.41±4934.6	1.0 [1.0-1.0]	0.095
Platelet counts (per cumm), Median (IQR)	.63±0.49	2.40±3.2	0.05 [0.01-0.24]	<0.001*
Hematocrit, Mean (SD)	37.87±7.73	35.3±5.07	1.09 [0.95-1.24]	0.159
SGOT (IU/L), Mean(SD)	3154.29±1510.09	217.15±626.85	1.001 [1.001-1.002]	<0.001*
SGPT (IU/L), Mean (SD)	3708.57±5066.21	141.31±463.1	1.002 [1.001-1.003]	<0.001*
Lactate (mmol/L), Mean (SD)	79.20±30.41	15.95±8.34	1.22 [1.05-1.42]	<0.001*
Albumin (g/dl), Mean (SD)	2.60±0.40	3.87±0.59	0.42 [0.007-0.265]	<0.001*
PT (seconds), Mean (SD)	32.33±12.47	15.39±12.95	1.040 [0.99-1.08]	<0.001*
INR, Mean (SD)	3.22±1.88	1.13±0.32	68.45 [7.2-650.37]	<0.001*
Duration of hospital stay, days, mean (SD)	3.00±1.29	4.69±1.67	0.32 [0.13-0.75]	0.008*

were needed in 15.38 % cases. [16] In our study, seven children needed PRBCs transfusion and out of these seven five died similar to other studies.[17]

We observed that hypoalbuminemia was more in SD compared to NSD, in line with the study conducted by Alikunju et al and Pone SM et al [18,19]. Elevated liver enzymes on admission were observed more in SD as compared to NSD, which has been established by the meta-analysis by Zhang et al [20]. In our study, a positive tourniquet test on admission was found more commonly in SD as compared to NSD, which corroborates with earlier study [21]. We observed that deranged coagulation profile was found more in SD as compared to NSD. Chacko et al observed INR >1.5 to be associated with SD [12]. We evaluated all the enrolled dengue positive children and it was observed that thrombocytopenia on admission occurred more in SD as compared to NSD, similar the study results of Pongpan et al [9]. In our study, high serum lactate levels (mmol/L) were observed to be more in SD as compared to NSD at the time of admission, consistent with the results of previous study [22].

As in our study, Gupta et al observed capillary leakage signs like pleural effusion and ascites, to be significantly associated with SD [23-27]. High serum lactates at admission was more in non-survivors compared to survivors. Another retrospective cohort study conducted

by Sani et al, on 199 patients with SD found serum lactate to be statistically significant predictor of mortality.[26] Liver enzymes at admission were raised more in non-survivors as compared to survivors, in congruence with study results conducted by Sachdev et al [24].

In the current study, it was observed that the mortality in children with SD was high (33.3%). Furthermore, this study observed that increased mortality was seen in patients who had presented with shock on admission. In another study conducted on 72 patients of northern India, who were critically ill with dengue, mortality of 11.1% (8 patient) was observed [28]. We observed that admission serum lactate levels were a significant predictor of mortality, while the study conducted by Thanachartwet et al, reported that serum lactate can be used as a biomarker in the diagnosis of SD [29].

There were some limitations of the study such as small sample size. Severity in dengue fever also depends on the phase of illness which was not considered in the current study. Virological studies were not performed due to non-availability of these investigations in our hospital.

## Conclusion

Decreased urine output and hypoalbuminemia are independent predictors of SD and high serum lactate level on admission is an independent predictor of dengue

mortality. Thus, such children need more careful monitoring. Larger studies are required to establish the role of these markers to predict dengue severity and mortality at an early stage.

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<b>Ethics:</b>	There is no ethical violation as it is based on voluntary anonymous interviews
<b>Funding:</b>	No external funding
<b>Guarantor:</b>	Dr. Dinesh Raj will act as guarantor of this article on behalf of all co-authors.

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