Scholars Journal of Applied Medical Sciences
Abbreviated Key Title: Sch J App Med Sci
ISSN 2347-954X (Print) | ISSN 2320-6691 (Online)
Journal homepage: https://saspublishers.com

OPEN ACCESS

Pediatrics

Mortality Predictors in Children with Severe Dengue at Dhaka Shishu (Children) Hospital

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DOI: https://doi.org/10.36347/sjams.2024.v12i12.009 | **Received:** 29.10.2024 | **Accepted:** 03.12.2024 | **Published:** 07.12.2024

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Abstract **Original Research Article**

Background: There are many tropical areas where dengue is a significant mosquito borne disease and causes substantial global mortality. Despite the high burden of dengue virus (DENV) infections, severe dengue remains fatal in Bangladesh. Nevertheless, few risk factors are known for death in cases of severe dengue. Being aware of these predictors are crucial to advance patient management and provide counseling for clinical decisions. ***Methods:*** This cross sectional analytical study was conducted at Dhaka Shishu (Children) Hospital from May 2019 to February 2020. Using convenient sampling the study enrolled a total of 350 children with severe dengue. Of these 16 died, and 334 survived. Comparisons of physiologic, clinical and laboratory parameters between survival and mortality groups were performed to identify predictors of death. ***Results:*** The majority (81%) of incidents were in children aged 5 to 10 years who attended. There was no significant differences in gender of the patients. The clinical predictors of mortality were major bleeding, plasma leakage (P >20% rise in hematocrit, ascites, pleural effusion), hepatomegaly, and refractory shock ($p<0.05$). Laboratory findings in the group with high mortality were thrombocytopenia (<15,000/mm³), elevated liver enzymes (ALT, AST), prolonged PT/INR, hypoalbuminemia and high ferritin values ($p<0.001$). ***Conclusion:*** In children with severe dengue, major bleeding, plasma leakage, refractory shock, severe thrombocytopenia, and raised ferritin were significant predictors of mortality. Knowing early the presence of these risk factors will enable timely and judicious management in at risk children to improve outcomes.

Keywords: Predictors, mortality, Severe dengue, children.

INTRODUCTION

Dengue is the most rapidly spreading mosquito borne viral disease globally, a significant public health challenge especially where vector and viral conditions are tropical or subtropical. Estimates for current incidence range roughly to nearly 390 million infections per year for the total and a projected 96 million for clinical illness with a consequent 20,000 deaths per year worldwide [1]. However large in number, a large amount of these deaths take according to developing countries having limited health resources. Dengue infection is estimated to affect 3.9 billion people in more than 128 countries, but numbers and cases increase annually due to urbanization, climate change, and increased global travel [2,3].

The first epidemic of dengue hemorrhagic fever (DHF) occurred in Bangladesh in 2000, with 5,551 reported cases and 93 fatalities, giving a case fatality rate (CFR) of 1.7% [4]. DENGUE VIREMIA OUTBREAK, 2011: The most prevalent viral types were DENV-1, 2, and 3; secondary infections increased the risk for severe manifestations [5]. The dengue virus (DENV-1 to DENV-4) is the principal cause of dengue infection of the Flaviviridae family and is transmitted by Ae. Aegyptus and Ae. albopictus mosquitoes [6]. Primary infection typically results in self-limiting febrile illness whereas secondary infection in which the non-neutralizing antibodies from primary infection stimulates viral replication and immune response is pathogenic due to antibody dependent enhancement [7,8].

Dengue is a clinical spectrum from asymptomatic cases and mild febrile illness to severe complications such as DHF and dengue shock syndrome. Plasma leakage, pronounced bleeding tendencies and/or organ involvement characterize severe dengue and

normally require careful monitoring and prompt intervention to avoid fatal outcomes [9]. The 2009 revised WHO classification of dengue subdivides dengue cases into dengue without warning signs, dengue with warning signs and severe dengue, which aids diagnostic and management strategy [10].

Important clinical and laboratory parameters for predicting severe denguel and mortality. An important biomarker of immune dysregulation, coagulation disturbances, and severe disease outcome has been hyperferritinemia [11]. Additional predictors in this model include hepatic dysfunction, thrombocytopenia, gallbladder wall thickening, and elevated transaminase levels [12,13]. In endemic regions, children comprise 90% of cases of DHF [14]. Timely management of children with severe dengue depend on identifying risk factors and early predictors in this demographic, as children with severe disease often progress rapidly to shock or multiorgan failure [15].

The prevention of dengue continues to rely on vector control. Nevertheless, it is often hampered by difficulties supporting long term interventions. Early diagnosis and supportive care are emphasized due to no available universally available vaccine and absence of an effective antiviral treatment [16]. CFRs in many regions have been lowered by advances in case management to less than 1% from 10–20% [17]. Overall, however, localized studies examining predictors of outcome severity and mortality are needed to enhance disease outcomes in certain populations during resource limited settings such as Bangladesh [18].

Although the incidence of dengue has been rising in Bangladesh, there are insufficient studies to identify mortality predictors in children. With an ultimate aim of better management of children with dengue, this study seeks to identify factors associated with mortality in children with dengue and thus a framework for early risk stratification.

Objective

The objective of this study were to assess the predictors of mortality in Severe Dengue.

METHODOLOGY & MATERIALS

This cross sectional analytical study was conducted at Department of pediatrics, Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh, from January 2019 to December 2020. A total of 350 children admitted in inpatient department of Dhaka Shishu (Children) hospital with the diagnosis of Severe Dengue are included in this study. Convenient sampling method was applied for this study.

Inclusion Criteria:

I. Children up to 15 years of age irrespective of gender.
II. Serologically confirmed (NS1 antigen positive, NS1 and Dengue IgM both positive or both IgM and IgG positive) with clinical features of Severe Dengue.

Exclusion Criteria:

I. NS1 antigen negative dengue like illness.
II. Children with only IgG positive.
III. Severe Dengue children with pre-existing liver, renal and lung diseases.

Data Collection

After proper approval from the ethical review committee of BICH suspected patients of dengue fever (n=633) were screened. Patients were evaluated after proper informed written consent from the parents or local guardians. A standard questionnaire was designed with a view to collect data from the respondents. Initial evaluation of each patient by baseline characteristics, and common clinical and laboratory parameters were also done. Findings were recorded in the predesigned questionnaire by the researcher herself. After inclusion and exclusion, 350 patients were included in this study. Patients were monitored daily during their hospital stay and findings were noted. The clinical and laboratory findings of fatal cases and severe dengue survivors were extensively compared.

Ethical consideration

Permission was taken from the ethical committee of Bangladesh Institute of Child Health (BICH). Written informed consent was obtained from all the parents/guardians after they were thoroughly briefed about the nature, interest, and purpose of the study. Reassurance was given to all the parents as there was no harmful effect for babies or any economic loss. Photographs were taken with due permission of the parents. If any risk or adverse condition developed during study period, adequate facilities were ensured to manage such situations.

Statistical Analysis of Data

Data was collected and checked for completeness, correctness. After proper edition and cleaning, data were analyzed thoroughly and processed using frequency, tabulation, means, and standard deviation in computer aided statistical software SPSS (Statistical Package for Social Sciences) version 22.0. Presentation was done by table and diagram. Level of significance was defined as P value <0.05 and highly significant by p value < 0.001.

RESULT

Table-1: Demographic characteristics of the study patients in two group (N=350)

Characteristics		Survived(n=334)		Death (n=16)		p-value
		No.	%	No.	%	
Age(years)	<5	90	26.95	5	31.25	0.840
	5-10	192	57.49	7	43.75	
	10-15	52	15.57	4	25.00	
Mean±SD		7.02±3.13		7.18±2.70		
Gender	Male	199	59.58	8	50.00	0.467
	Female	135	40.42	8	50.00	

Table- 1 shows that 350 children with Severe Dengue were included in the study. Of which 334 children were survived and 16 patients were died. Mean age of survived group was 7.02±3.13 years and mean age of death group was 7.18±2.70 years. Majorities of survived belonged to age group 5-10 years (57. 49%). In death group majority belonged to age group 5-10 years also (43.75%). Age distribution between survived group and death group was not significant (p= 0.840).

Majorities were male in survived group 199(59.58%) and female 135(40.42%). In death group male and female patients were in equal distribution. Sex difference between two groups were not significant (p=0.467).

Table-2: Symptoms of severe dengue patients between survived and death (N=350)

Symptoms	Survived (n=334)		Death(n=16)		p-value
	No.	%	No.	%	
Fever	334	100.0	16	100.0	-
Headache	197	58.98	12	75.00	0.2025
Retro	158	47.31	10	62.50	0.2355
Myalgia	80	23.95	7	43.75	0.0778
Arthralgia	65	19.46	1	6.25	0.1876
Cough	253	75.75	16	100.00	<0.005
Breathlessness	88	26.35	12	75.00	<0.005
Vomiting	300	89.82	12	75.00	0.0631
Abdominal Pain	193	57.78	15	93.75	<0.005
Diarrhea	92	27.54	2	12.50	0.1855
Convulsion	28	8.38	1	6.25	0.763
Rash	267	79.94	14	87.50	0.4584
Major Bleeding	85	25.45	11	68.75	<0.005
Minor Bleeding	171	51.20	5	31.25	0.1195
No Bleeding	78	23.35	0	0.00	0.0286

Table-2 shows association of clinical symptoms between survived and death group of Severe Dengue patients. Cough and abdominal pain, breathlessness and major bleeding were highly associated with mortality (p <0.05).

Table- 3: Physical examination and findings of severe dengue patients between survived and death (N=350)

Signs	Survived(n=334)		Death(n=16)		p-value
	No.	%	No.	%	
>20% rise of HCT	167	50.00	15	93.75	<0.005
Signs of pleural effusion	233	69.76	16	100.00	0.0092
Signs of ascites	161	48.20	16	100.00	<0.005
Hepatomegaly	224	67.07	15	93.75	0.0253
Refractory shock	63	18.86	12	75.00	<0.005

Table-3 shows association of clinical signs between survived and death group of severe dengue patients. Signs of plasma leakage (>20% rise of HcT, signs of pleural effusion, signs of ascites), refractory shock, hepatomegaly were significantly associated with mortality (p<0.05).

Table 4: Hematological profile of severe dengue patients between survived and death (N=350)

Hematological profile	Survived(n=334)		Death(n=16)		p-value
	No.	%	No.	%	
Leukocytosis	55	16.47	1	6.25	0.627
Leucopenia	56	16.77	4	25.00	
Normal total count	223	66.77	11	68.75	
Total platelet count at admission (mean±SD)	99624.1±85401.6		58571.4±32133.6		0.0564
Lowest platelet count (mean±SD)	45220.3±28846.4		11342.8±3778.0		<0.005

Table- 4 shows the relationship of hematological parameters between survived and death group of Severe Dengue patients. No significant difference of platelet count at admission, during treatment there is highly significant mean of lowest platelet count in death group compare to survived group ($p<0.001$).

Table-5: Biochemical profile of severe dengue patients between survived and death (N=350)

Biochemical profile		Survived (n=334)		Death (n=16)		p-value
		No.	%	No.	%	
S. ferritin (microgram/L)	≤500	115	34.43	4	25	<0.001
	>500	83	24.85	12	75	
	Not done	136	40.72	0	0	
PT (sec)	Normal	82	24.55	7	43.75	0.001
	Raised	28	8.38	7	43.75	
	Not done	224	67.07	2	12.5	
INR	>1.5	84	25.15	10	62.5	0.001
	<1.5	250	74.85	6	37.5	
Others	ALT (U/L)	102.1±102.8		220.1±142.8		<0.001
	AST (U/L)	215.9±186.3		486.0±307.4		<0.001
	S albumin (mmol/l)	26.1±6.57		14.4±3.0		<0.001
	S sodium (mmol/l)	138.2±6.3		136.0±3.7		0.206
	S HCO3 (mEq/L)	103.4±5.7		102.7±3.2		0.654

Table-5 shows the relationship of biochemical parameters between survived and death group of severe dengue patients. Mean of ALT, AST were increased and S. albumin decreased in death group and they were statistically highly significant ($p<0.001$). There were highly significant ($p<0.001$) raised Serum ferritin (≥500µ/L) and raised prothrombin time and INR (>1.5) present in death group in comparison to survived group.

DISCUSSION

During this study period, 360 severe Dengue patients were selected from 633 suspected Dengue fever patients. From the selected patients, 7 patients having severe Dengue with renal diseases and 3 patients went out to ICU due to lack of bed in ICU, DSH.

Among 350 Severe Dengue patients 16 were died. Case Fatality Rate (CFR) were 5.33% which is high. A study done by Lora *et al.*, (2014) in Dominican Pediatric population and found CFR 5.1% in their study period [19]. In the study, mean age of children was 7.02± 3.13 years in survived group and 7.18±2.70 in death group and common age group affected was between 5-10 years in both group. Lora., (2014), Ahmed *et al.*, (2001); Gupta *et al.*, (2011) reported that maximum number of cases were below 10 years in their work which is similar to this study finding. [4,9,19]

Male (59.58%) were more in this study than female (40.42%) in survived group but no difference in death group which is consistent with the study of Lora *et al.*, (2014) and Gupta *et al.*, (2011) but in the study of Pinto *et al.*, (2016) female (3.9%) were more in death cases where male was 3.7% [4,9,20].

In this study, fever was present 100% in both the group and among other clinical symptoms cough (100%), breathlessness (75%), abdominal pain (93.75%) were present which were the symptoms for plasma leakage.

Major bleeding was observed in 68.75% in death cases which were similar to the study of Pinto *et al.*, (2016), who showed presence of bleeding manifestations was significantly predictive of Severe Dengue [20].

This study showed association of clinical signs between survived and death group of severe dengue patients. Sings of plasma leakage, shock, refractory shock, hepatomegaly were significantly associated with mortality ($p<0.05$).

Mortality is usually due to a delay in the recognition and treatment of plasma leakage and usually occur around the time of defervescence. In our study

plasma leakage was seen by 20% rise of HCT in 93.75% and both pleural effusion and ascites were 100%, so sign of plasma leakage were highly significant in this study. In the study of Pongpan *et al.,* (2013), Raju *et al.,* (2019) Phakhounthong *et al.,* (2018) found rise in hematocrit significantly [8,21,22]. But in Pinto *et al.,* (2016) showed plasma leakage in death group only 4% but in non-death group 96% which is dissimilar with this study [20].

In patients with Severe Dengue, there is increase in capillary permeability with leakage of fluid, electrolytes and sometimes RBC. The patients also tend not to eat or vomit thereby getting dehydrated. As a result, the patients are hemoconcentrated, hypovolumic, with increase in cardiac work, tissue hypoxia, metabolic acidosis and hyponatraemia.

In this study signs of pleural effusion and signs of ascites showed significant association with mortality.

In the study by shrishu and suchitra., (2006) they have analyzed on 109 cases of severe dengue. There among 9 death cases of their study 6 patients died with refractory shock. It was found that complications such as DIC, diastolic dysfunction, abdominal compartment syndrome, ARDS and hepatic dysfunction were more frequent in severe established shock [23].

In this study refractory shock was 18.86% in survived group and 75% in death group which is significantly associated with mortality. Early recognition in conjunction with meticulous monitoring and targeted supportive care is the comerstone of a successful outcome. However, particularly in children that present late with refractory shock, it is important to be aware of entities such as diastolic dysfunction and ACS which, unless recognized and appropriately managed, may contribute a higher CFR.

This study showed no significant difference of platelet at admission but mean of lowest platelet count (<15000/mm3) significantly decreased in death group compare to survived group ($p<0.001$) which showed similar results that thrombocytopenia associated with mortality with different studies.

Immune related platelet damage and inhibition of platelet aggregation contribute to the thrombopathy apart from decreased platelet number and function, DHF patients can have abnormal hemostasis (vasculopathy, coagulopathy and DIC).

In the studies of Srishu and Shuchitra, (2006) showed Platelet count less than 50,000/mm3 was noted in 62.3%. DHF patients with a platelet count < 50,000/mm3 have been reported to have a six-fold higher mortality than those with platelet counts > 50,000/mm3. In the study of John *et al.,* (2019) found that thrombocytopenia did not predict mortality [24].

This study showed relationship of biochemical parameters between survived and death group of severe dengue patients. Deranged liver function test (Mean of SGPT, SGOT, raised prothrombin time, INR (>1.5), reduced S. albumin) and Serum ferritin (> 500µg/L) were significantly associated with mortality which is similar to the results of Raju *et al.,* (2019), *et al.,* (2015), Ho *et al.,* (2013) who found serum albumin, SGOT, SGPT, ALP, PT and INR were 3.8g/dl, 233.18U/L, 118.15U/L, 200.65 U/L, 12.9s and 1.09 respectively [13, 22]. The mean SGOT was significantly higher than SGPT which were associated with poor prognosis and outcome in Severe Dengue. Through knowledge about these hepatic manifestations in Severe Dengue will certainly help in arriving at an early diagnosis and help avoid mortality.

Limitations and Recommendations

The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community. Meticulous evaluation of patient with regular monitoring and laboratory parameters should be done so that early judicial management can be performed to prevent mortality in children with Severe Dengue.

CONCLUSION

This research suggests that several factors may serve as potential indicators of mortality in children with Severe Dengue. These include indications of significant hemorrhage, evidence of plasma leakage (such as a 20% increase in hematocrit, accumulation of fluid in the abdominal cavity, and fluid around the lungs), shock that does not respond to treatment, severely low platelet count (below 15,000/mm3), and elevated ferritin levels (exceeding 500 microgram/L).

Financial support and sponsorship: No funding sources.

Conflicts of interest: There are no conflicts of interest.

Ethical approval: The study was approved by the Institutional Ethics Committee.

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