Original article

Clinical and Laboratory Predictors of Mortality in Pediatric Patients with Severe Dengue at Dhaka Shishu Hospital

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Abstract

Background:
Dengue fever, particularly in its severe form, poses a significant health challenge in tropical regions like Bangladesh. Understanding the clinical and laboratory predictors of mortality in pediatric patients with severe dengue is crucial for improving management strategies and patient outcomes.

Methods:
This cross-sectional analytical study was conducted at the Department of Pediatrics, Dhaka Shishu (Children) Hospital, Dhaka, Bangladesh, from January 2019 to December 2020. It included 300 pediatric patients diagnosed with severe dengue.

Results:
Of the 300 participants, 286 (95.33%) survived, while 14 (4.67%) succumbed to the disease. Major bleeding, refractory shock, a significant rise in hematocrit, signs of pleural effusion, and ascites were significantly associated with mortality. Hematologically, a low platelet count (<15000/mm3) was a strong predictor of mortality. Elevated serum ferritin levels (>500 micrograms/L) were also significantly associated with increased mortality risk.

Conclusions:
The study highlights major bleeding, refractory shock, significant hemoconcentration, pleural effusion, ascites, low platelet count, and high serum ferritin levels as key predictors of mortality in pediatric patients with severe dengue. These findings underscore the need for comprehensive clinical monitoring and targeted management strategies to improve outcomes in pediatric dengue patients.

Keywords: Dengue fever, Pediatrics, Mortality predictors, Hematological profile, Biochemical markers

Introduction:

Dengue represents a serious public health problem in tropical and subtropical regions worldwide. Estimates indicate 390 million dengue infections occur annually, resulting in over 96 million symptomatic cases.[1] Pediatric populations are disproportionately impacted, accounting for an estimated 34% of apparent cases globally despite only representing 25% of the at-risk population.[2] In Bangladesh, dengue incidence has increased 30-fold over the past five decades, with cyclical epidemics occurring every 2–5 years.[3] Dengue fever is an acute febrile illness caused by four distinct dengue virus serotypes, primarily transmitted by Aedes aegypti mosquitoes, causing mild to severe symptoms, while a subset of patients progresses to severe disease manifestations such as dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS).[4] These are characterized by plasma leakage, hemorrhage, and organ impairment. Case fatality rates for severe dengue average around 2-5% in Asia, but

have exceeded 6% in some outbreaks.[5,6] Compared to adults, dengue infection in children frequently presents atypically or with nonspecific features adding diagnostic challenges.[7,8] Pediatric populations face higher DENV infection risks, leading to severe disease, adverse outcomes, and mortality. Identifying these children can optimize treatment interventions, with higher viral burden, persistent viremia, and secondary infection being independent risk factors.[9,10] Thrombocytopenia and liver transaminases are linked to mortality in Vietnamese children, but simple clinical signs like lethargy, abdominal pain, bleeding, and fluid accumulation have similar prognostic value.[11-13] The current study aims to identify key clinical and laboratory predictors of mortality in pediatric patients which could help identify children at high risk, provide affordable substitute indicators, and guide healthcare capacity growth and preparedness efforts in Bangladesh.

Methods:

This cross-sectional analytical study was conducted at the Department of Pediatrics, Dhaka Shishu Hospital in Bangladesh from January 2019 to December 2020 with 300 pediatric severe dengue cases admitted to the inpatient department, selected through purposive sampling. Inclusion criteria encompassed children up to 15 years old with serologically-confirmed severe dengue, while exclusion criteria eliminated IgG inly positive cases and children with chronic illness. Dengue with indications of severe plasma leakage leading to shock or fluid accumulation with respiratory distress, severe bleeding, or severe organ impairment (e.g., elevated liver enzymes, heart problems) was termed as Severe Dengue Fever.[6] Minor bleeding defined as petechiae, easy bruising, epistaxis lasting less than 10 minutes, gingival bleeding without oozing, or menometrorrhagia lasting less than 7 days. Overt bleeding requiring medical or surgical intervention (e.g., transfusion), prolonged or recurrent bleeding from any site, hematemesis, melena, gross hematuria, or intracranial, intraocular, or retroperitoneal bleeding defined as major bleeding.[14]

The study was approved by the Institutional Ethics Committee. Data on clinical and laboratory parameters were collected at admission using predefined sheets and analyzed using SPSS version 22.0. Ethical approval was obtained, and written informed consent was obtained from parents or guardians.

Results:

Among the total 300 participants, 286 patients (95.33%) survived, while 14 patients (4.67%) succumbed to the disease. (Figure-1)

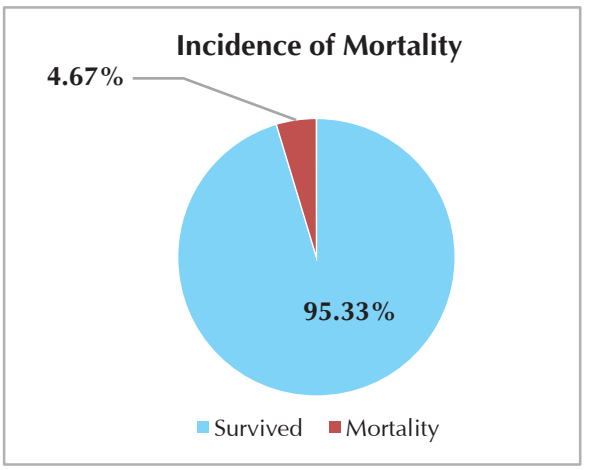

Figure-1: Distribution of participants by incidence of mortality (n=300)

In both survivors (n=286) and deceased patients (n=14), fever was universally present. While headache, retro orbital pain, myalgia, and arthralgia showed no significant differences between the groups, cough, breathlessness, and abdominal pain were significantly higher among the deceased patients ($p<0.05$, $p<0.001$, and $p<0.01$ respectively). (Table-I)

Table-I: Comparison of symptoms among participants by survival (n=300)

Symptoms	Recovery (n=286)	Mortality (n=14)	p-value
	no.(%)	no.(%)	
Fever	286(100)	14(100)	>0.05
Headache	169(59.09)	11(78.57)	>0.05
Retro orbital pain	136(47.55)	9(64.29)	>0.05
Myalgia	69(24.13)	6(42.86)	>0.05
Arthralgia	56(19.58)	1(7.14)	>0.05
Cough	217(75.87)	14(100)	<0.05
Breathlessness	75(26.22)	11(78.57)	<0.001
Vomiting	257(89.86	11(78.57)	>0.05
Abdominal pain	166(58.04)	13(92.86)	<0.01
Diarrhea	79(27.62)	2(14.29)	>0.05
Convulsion	24(8.39)	1(7.14)	>0.05
Rash	229(80.07)	12(85.71)	>0.05

There was a significant difference in major bleeding between survivors (25.17%) and deceased patients (71.43%), with a p-value of <0.001. However, no significant difference was observed in minor bleeding (51.05% in survivors, 28.57% in deceased; p>0.05) or the absence of bleeding (23.78% in survivors, 0.00% in deceased; p>0.05). (Table-II)

Table-II: Comparison of bleeding type among participants by survival (n=300)

Bleeding Severity	Recovery (n=286)	Mortality (n=14)	p-value
	no.(%)	no.(%)	
Major Bleeding	72(25.17)	10(71.43)	<0.001
Minor Bleeding	146(51.05)	4(28.57)	>0.05
No Bleeding	68(23.78)	0(0.00)	>0.05

A>20% rise of hematocrit (HCT) was noted in 50.00% of survivors compared to 92.86% of deceased (p<0.05). Signs of pleural effusion were present in 69.93% of survivors and 100.00% of deceased (p<0.05), while signs of ascites were observed in 48.25% of survivors and 100.00% of deceased (p<0.001). Additionally, hepatomegaly was detected in 67.13% of survivors and 92.86% of deceased (p<0.05), and refractory shock was identified in 18.88% of survivors and 78.57% of deceased (p<0.001). (Table-III)

Table-III: Comparison of physical examination findings among participants by survival (n=300)

Physical findings	Recovery (n=286) no.(%)	Mortality (n=14) no.(%)	p-value
>20% rise of HCT	143(50)	13(92.86)	<0.05
Signs of pleural effusion	200(69.93)	14(100)	<0.05
Signs of ascites	138(48.25)	14(100)	<0.001
Hepatomegaly	192(67.13)	13(92.86)	<0.05
Refractory shock	54(18.88)	11(78.57)	<0.001

There was no significant difference in leukocytosis (16.43% in survivors, 7.14% in deceased; p>0.05) or leucopenia (16.78% in survivors, 21.43% in deceased; p>0.05). Most participants had a normal total leukocyte count (66.78% in survivors, 71.43% in deceased; p>0.05). The mean platelet count at admission did not significantly differ between survivors (99624.1±85401.6) and deceased (58571.4±32133.6; p>0.05). However, the mean lowest platelet count was significantly lower in deceased patients (11342.8±3778.0) compared to survivors (45220.3±28846.4; p<0.001).(Table-IV)

Table-IV: Distribution of Hematological findings among participants by survival (n=300)

Hematological Profile	Recovery (n=286)	Mortality (n=14)	p-value
	no.(%)	no.(%)	
Leukocytosis	47(16.43)	1(7.14)	
Leucopenia	48(16.78)	3(21.43)	>0.05
Normal Total Count	191(66.78)	10(71.43)	
Mean±SD Platelet count at admission	99624.1±85401.6	58571.4±32133.6	>0.05
Mean±SD Lowest platelet count	45220.3±28846.4	11342.8±3778.0	<0.001

Significant differences were found in serum ferritin levels, with 34.27% of survivors having ≤500 micrograms/L compared to 21.43% of deceased patients (p<0.001). Prothrombin time and international normalized ratio of prothrombin time also showed significant differences between survivors and deceased patients (p<0.001). Additionally, biochemical markers including ALT, AST, and S albumin exhibited significant variations between the two groups (p<0.001). Conversely, no significant differences were observed in serum sodium (S sodium) and bicarbonate (S HCO3) levels.(Table-V)

Table-V: Distribution of Biochemical profile among participants by survival (n=300)

Biochemical Profile	Recovery (n=286)	Mortality (n=14)	p-value
	no.(%)	no.(%)	
Serum Ferritin (microgram/L)			
500	98(34.27)	3(21.43)	
>500	71(24.83)	11(78.57)	<0.001
Not done	117(40.91)	0(0.00)	
Prothrombin Time			
Normal	70(24.48)	642.86)	
Raised	24(8.39)	6(42.86)	<0.001
Not done	192(67.13)	2(14.29)	
International Normalized Ratio of Prothrombin time			
>1.5	72(25.17)	9(64.29)	<0.001
1.5	214(74.83)	5(35.71)	
Other Biochemical Findings (Mean±SD)			
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 (m^3q/L)	103.4±5.7	102.7±3.2	0.654

Clinical factors including major bleeding (β =0.214, p=0.017), refractory shock (β=0.649, p=0.021), and a >20% rise of hematocrit (β =1.242, p=0.014) were statistically significant predictors of mortality. Similarly, signs of pleural effusion (β=0.565, p=0.0451) and ascites (β =1.193, p=0.037) exhibited significant associations with mortality. In terms of biochemical factors, a mean lowest platelet count (<15000/mm3) (β=2.558, p=0.018) and elevated serum ferritin (>500microgram/L) (β=1.082, p=0.016) were found to be statistically significant predictors of mortality. (Table-VI)

Table-VI: Multivariate logistic regression for mortality predictors of severe dengue patients (n=300)

Predictors	β	p-value	OR	95% CI Lower–Upper
Clinical factors				
Major bleeding	0.214	0.017	4.12	1.104 –7.328
Refractory shock	0.649	0.021	2.93	1.507–8.127
20% rise of HCT	1.242	0.014	2.15	2.015-9.534
Signs of pleural effusion	0.565	0.0451	1.759	1.126-11.612
Signs of ascites	1.193	0.037	3.295	2.580-18.416
Hepatomegaly	0.71	0.422	0.492	.087–2.781
Biochemical factors				
Mean of Lowest platelet count (<15000/mm3)	2.558	0.018	33.16	1.842–52.31
SGPT	0.02	0.072	0.98	.959–1.002
SGOT	0.009	0.065	1.009	.999–1.019
S ferritin (>500 microgram/L)	1.082	0.016	1.339	1.052–3.215
PT	0.516	0.674	1.676	.151–18.539
INR (>1.5)	0.127	0.908	1.136	.130–9.928
S. albumin	0.087	0.432	1.091	.878–1.354

Discussion:

The survival rate of 95.33% among the study participants is consistent with other studies conducted in similar settings, indicating effective management and treatment protocols for severe dengue in pediatric populations,[15] The study found significant differences in cough, breathlessness, and abdominal pain between survivors and non-survivors, indicating the severity of dengue and potential predictors of poor outcomes.[10,16,17] Major bleeding was linked to mortality in dengue patients, as evidenced by high prevalence and significant p-value, consistent with previous studies identifying hemorrhagic manifestations as a key risk factor.[18] The study reveals that the severity of bleeding, rather than its presence, significantly influences dengue patient outcomes, with a high incidence of major bleeding among deceased patients.[18-20] The significant increase in hematocrit (HCT) in deceased patients observed in our study aligns with Halstead's (2007) findings on hemoconcentration and thrombocytopenia in severe dengue cases.[21] Elevated levels of serum ferritin, ALT, and AST in deceased patients also support previous observations, indicating liver involvement and severity in dengue.[22,23] The significant association of major bleeding with mortality is consistent with the findings of previous studies that have highlighted hemorrhagic manifestations as a key risk factor in dengue mortality.[18,24] Similarly, the identification of refractory shock as a significant predictor of mortalityaligns with the literature emphasizing the critical nature of shock in the progression of severe dengue.[21] The study's finding that a >20% rise in hematocrit is significantly associated with mortality resonates with the understanding that hemoconcentration is a hallmark of plasma leakage, a severe complication in dengue.[24] The ORs for signs of pleural effusion and ascites further reinforce their role as important clinical indicators of severe disease and potential mortality, as noted in previous research.[25] In terms of biochemical factors, the strong predictive value of a low platelet count (<15000/mm3) for mortalityis a critical finding. This is in line with studies that have identified thrombocytopenia as a marker of severe dengue.[26] The significant association of high serum ferritin levels with mortality, indicated by an OR of 1.339, suggests the potential role of ferritin as a biomarker for severe disease, as supported by other studies.[15] However, the lack of significant

associations for other biochemical factors such as SGPT, SGOT, PT, INR, and serum albumin with mortality highlights the complexity of the disease and the need for a multifaceted approach in predicting outcomes in severe dengue.

Limitations:
The study was conducted in a single hospital with a small sample size. So, the results may not represent the whole community.

Conclusion:
The 95.33% survival rate in severe dengue cases is due to effective treatment protocols. Non-survivors show higher symptoms, emphasizing early intervention. Major bleeding, refractory shock, and hematocrit rise are key indicators of disease progression. Low platelet count and elevated ferritin levels predict outcomes. Further research is needed to improve prognosis in high-risk regions like Bangladesh.

References:

1. Bhatt S, Gething PW, Brady OJ, Messina JP, Farlow AW, Moyes CL,et al. The global distribution and burden of dengue. Nature. 2013 Apr 25;496(7446):504-7. doi: 10.1038/nature12060.
2. Undurraga EA, Halasa YA, Shepard DS. Use of expansion factors to estimate the burden of dengue in Southeast Asia: a systematic analysis. PLoS Negl Trop Dis. 2013;7(2):e2056. doi: 10.1371/journal.pntd.0002056.
3. Hossain MS, Noman AA, Mamun SMAA, Mosabbir AA. Twenty-two years of dengue outbreaks in Bangladesh: epidemiology, clinical spectrum, serotypes, and future disease risks. Trop Med Health. 2023 Jul 11;51(1):37. doi: 10.1186/s 41182-023-00528-6.
4. Simmons CP, Farrar JJ, Nguyen vV, Wills B. Dengue. N Engl J Med. 2012 Apr 12;366(15):1423-32. doi: 10.1056/NEJMra1110265.
5. Ong A, Sandar M, Chen MI, Sin LY. Fatal dengue hemorrhagic fever in adults during a dengue epidemic in Singapore. Int J Infect Dis. 2007 May;11(3):263-7. doi: 10.1016/j.ijid.2006.02.012.
6. Ranjit S, Kissoon N. Dengue hemorrhagic fever and shock syndromes. Pediatr Crit Care Med. 2011 Jan;12(1):90-100. doi: 10.1097/PCC.0b013e3181e911a7.
7. Peeling RW, Artsob H, Pelegrino JL, Buchy P, Cardosa MJ, Devi S, et al. Evaluation of diagnostic tests: dengue. Nat Rev Microbiol. 2010 Dec;8(12 Suppl):S30-8. doi: 10.1038/nrmicro2459.
8. Pothapregada S, Kamalakannan B, Thulasingam M. Clinical Profile of Atypical Manifestations of Dengue Fever. Indian J Pediatr. 2016 Jun;83(6):493-9. doi: 10.1007/s12098-015-1942-9.
9. Vaughn DW, Green S, Kalayanarooj S, Innis BL, Nimmannitya S, Suntayakorn S, et al. Dengue viremia titer, antibody response pattern, and virus serotype correlate with disease severity. J Infect Dis. 2000 Jan;181(1):2-9. doi: 10.1086/315215
10. Kalayanarooj S, Vaughn DW, Nimmannitya S, Green S, Suntayakorn S, Kunentrasai N, et al. Early clinical and laboratory indicators of acute dengue illness. J Infect Dis. 1997 Aug;176(2):313-21. doi: 10.1086/514047.
11. Islam MA, Ahmed MU, Begum N, Chowdhury NA, Khan AH, Parquet Mdel C, et al. Molecular characterization and clinical evaluation of dengue outbreak in 2002 in Bangladesh. Jpn J Infect Dis. 2006 Apr; 59(2):85-91.
12. Banu S, Hu W, Guo Y, Hurst C, Tong S. Projecting the impact of climate change on dengue transmission in Dhaka, Bangladesh. Environ Int. 2014 Feb;63:137-42. doi: 10.1016/j.envint.2013.11.002.
13. Huy NT, Van Giang T, Thuy DH, Kikuchi M, Hien TT, Zamora J, et al. Factors associated with dengue shock syndrome: a systematic review and meta-analysis. PLoS Negl Trop Dis. 2013 Sep 26;7(9):e2412. doi: 10.1371/journal.pntd.0002412.
14. Arnold DM, Donahoe L, Clarke FJ, Tkaczyk AJ, Heels-Ansdell D, Zytaruk N, et al. Bleeding during critical illness: a prospective cohort study using a new measurement tool. Clin Invest Med. 2007;30(2):E93-102. doi: 10.25011/cim.v30i2.985
15. Guzman MG, Halstead SB, Artsob H, Buchy P, Farrar J, Gubler DJ, et al. Dengue: a continuing global threat. Nat Rev Microbiol. 2010 Dec;8(12 Suppl):S7-16. doi: 10.1038/ nrmicro2460.
16. Zhang H, Zhou YP, Peng HJ, Zhang XH, Zhou FY, Liu ZH, et al. Predictive symptoms and signs of severe dengue disease for patients

with dengue fever: a meta-analysis. Biomed Res Int. 2014;2014:359308. doi: 10.1155/2014/359308.
17. Tsheten T, Clements ACA, Gray DJ, Adhikary RK, Furuya-Kanamori L, Wangdi K. Clinical predictors of severe dengue: a systematic review and meta-analysis. Infect Dis Poverty. 2021 Oct 9;10(1):123. doi: 10.1186/s40249-021-00908-2.
18. Srikiatkhachorn A, Krautrachue A, Ratanaprakarn W, Wongtapradit L, Nithipanya N, Kalayanarooj S,et al. Natural history of plasma leakage in dengue hemorrhagic fever: a serial ultrasonographic study. Pediatr Infect Dis J. 2007 Apr;26(4):283-90; discussion 291-2. doi: 10.1097/01.inf.0000258612.26743.10.
19. Sachdev A, Pathak D, Gupta N, Simalti A, Gupta D, Gupta S,et al. Early Predictors of Mortality in Children with Severe Dengue Fever: A Prospective Study. Pediatr Infect Dis J. 2021 Sep 1;40(9):797-801. doi: 10.1097/INF.0000000000003179.
20. Suwarto S, Nainggolan L, Sinto R, Effendi B, Ibrahim E, Suryamin M, et al. Dengue score: a proposed diagnostic predictor for pleural effusion and/or ascites in adults with dengue infection. BMC Infect Dis. 2016 Jul 8;16:322. doi: 10.1186/s12879-016-1671-3.
21. Halstead SB. Dengue. Lancet. 2007 Nov 10;370(9599):1644-52. doi: 10.1016/S 0140-6736(07)61687-0.
22. Selvamuthukumaran S. Severity of Dengue Fever and Serum Ferritin Levels- A Correlative Study in a Rural Tertiary Care Medical College and Hospital in Tamil Nadu (South India). AIMDR [Internet]. 2018 May [cited 2024 Jan 16];4(3). Available from: http://www.aimdrjournal.com/pdf/vol4Issue3/ME13_OA_V4N3.pdf
23. Nguyen RN, Lam HT, Phan HV. Liver Impairment and Elevated Aminotransferase Levels Predict Severe Dengue in Vietnamese Children. Cureus. 2023 Oct 24;15(10):e47606. doi: 10.7759/cureus.47606.
24. Srikiatkhachorn A. Plasma leakage in dengue haemorrhagic fever. ThrombHaemost. 2009 Dec;102(6):1042-9. doi: 10.1160/TH 09-03-0208.
25. Htun TP, Xiong Z, Pang J. Clinical signs and symptoms associated with WHO severe dengue classification: a systematic review and meta-analysis. Emerg Microbes Infect. 2021 Dec;10(1):1116-1128. doi: 10.1080/22221751.2021.1935327.
26. Das S, Abreu C, Harris M, Shrader J, Sarvepalli S. Severe Thrombocytopenia Associated with Dengue Fever: An Evidence-Based Approach to Management of Thrombocytopenia. Case Rep Hematol. 2022 Aug 12;2022:3358325. doi: 10.1155/2022/3358325.