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ORIGINAL ARTICLE

Determinants of Mortality in Patients with Dengue Fever in a Tertiary Care Hospital of Dhaka City

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ABSTRACT

Background & objective: Dengue fever, an endemic mosquito-borne viral disease, poses a significant health challenge globally, especially in tropical regions like Bangladesh. The country has witnessed an alarming rise in dengue-related mortality, particularly since 2021, culminating in a record high in 2023, necessitating an investigation into the determinants of dengue mortality to improve patient outcomes. This study aims to identify demographic, clinical, and biochemical factors associated with mortality in patients diagnosed with dengue fever in a tertiary care hospital in Dhaka City.

Methods: This case-control study was conducted at Aalok Hospital in Mirpur, Dhaka, focusing on patients aged 18 years and older who were admitted during the dengue outbreak of 2024. The study included 123 participants, comprising 7 cases (patients who died from dengue) and 116 controls (patients who survived) of the disease. Inclusion criteria required a confirmed diagnosis of dengue fever or dengue hemorrhagic fever based on clinical and laboratory findings, including positive dengue NS1 antigen or IgM antibodies. Patients with severe comorbidities and those with a recent history of dengue infection were excluded to avoid bias. Data were collected on demographic, socioeconomic, clinical, and biochemical factors, suspected to be associated with the death (the outcome variable) of dengue patients. All the suspected exposure variables were then compared between case and control groups to see whether they were associated with the outcome fo interest.

Result: The study found that the mean age of the cases was significantly higher than that of the controls. A notable proportion of both groups belonged to middle- and upper-middle-class families, with no significant difference in socioeconomic status. However, service-holders carried a higher mortality risk compared to other occupants. Clinical symptoms such as hypotension, retro-orbital pain, and restlessness were significantly more common among the case group. Furthermore, the cases demonstrated a higher incidence of altered sensorium, ascites, and electrolyte imbalances. Notably, 57% of the cases exhibited acute liver injury (ALT > 200 U/L), compared to only 11.2% of the controls. Thrombocytopenia and gastrointestinal bleeding manifestations were more prevalent in the case group. Additionally, complications like shock syndrome and disseminated intravascular coagulation (DIC) were significantly associated with mortality.

Conclusion: Addressing the multifaceted determinants of dengue mortality is crucial for improving patient outcomes and reducing the burden of this disease in Bangladesh. A comprehensive, concerted clinical management, is essential to combat the rising dengue incidence and the mortality caused by it.

Keywords: Determinants, mortality, dengue fever, Tertiary Care Hospital etc.

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INTRODUCTION:

Dengue, caused by the dengue virus (DENV), is a potentially fatal mosquito-borne viral disease endemic in over 100 countries, particularly in South and Southeast Asia, and presents a significant global health concern.[1] The single-strand ribonucleic acid (RNA) virus has four serotypes (DEN1 to DEN4) and is primarily transmitted by female Aedes aegypti and Aedes albopictus mosquitoes.[2] Frequent epidemics during the rainy season characterize dengue's prevalence in tropical and subtropical regions.[3] Due to increased travel, it has become a leading cause of acute febrile illness for individuals in endemic areas. Symptoms range from asymptomatic seroconversion to severe conditions like dengue hemorrhagic fever and dengue shock syndrome. Common abnormalities in affected individuals include cytopenias, altered liver function tests, and elevated inflammatory markers such as serum C-reactive protein (CRP) and serum ferritin.[4]

In Bangladesh, dengue-related deaths have significantly increased since 2021, culminating in a record high in 2023. That year, 1,705 deaths were reported, surpassing total deaths from the previous 23 years, with only 853 deaths recorded from 2000 to 2022. Over the past three years, Bangladesh has consistently recorded higher case fatality rates (CFR).[5] Alarmingly, majorities of these infections (96.1%) and deaths (95.2%) occurred between July and September.[6] While dengue mortality is preventable,[7] limited success with primary prevention strategies necessitates a focus on reducing mortality through identifying risk factors and effective patient management. In a case-control study conducted by Karunakaran et al.[8] at the Medical College Hospital in Thiruvananthapuram, researchers found that patients over 40 years were 9.3 times more likely to die from dengue than younger patients. Notable clinical features associated with increased mortality included altered sensorium, abnormal reflexes, edema, diabetes mellitus, and hypertension. After adjustments, altered sensorium and hypertension emerged as independent mortality predictors. However, these risk factors may vary by geographical location and population characteristics, suggesting that dengue management should be tailored to local findings.

The unprecedented global increase in dengue cases in 2023, exceeding 6.5 million cases and over 7,000 deaths, underscores the urgency of this issue.[1] This surge highlighted the spread of outbreaks into previously unaffected regions. Among the most affected countries, Brazil reported 3,088,223 dengue cases in 2023, followed by Bangladesh (321,179), Mexico (277,963), Peru (274,227), and the Philippines (195,603). Bangladesh had the highest global dengue-related deaths that year, totaling 1,705, with a CFR of 0.53%, in contrast to Brazil (1,163 deaths, 0.03%) and the Philippines (657 deaths, 0.34%).[5] This alarming trend necessitates a thorough investigation into factors contributing to increasing mortality rates associated with dengue in Bangladesh. Data reveal that Bangladesh has recorded higher CFRs consistently over the last three years (2021-2023). The significant rise in dengue mortality began in 2021, with each subsequent year surpassing the previous year's death toll. The alarming fatality rate in 2023, reaching 1,705 deaths, raises concerns for 2024, particularly given a higher CFR of 1.11% recorded during the non-seasonal period from January to April when only 2,204 dengue patients were hospitalized.[5] This increased incidence of deaths due to dengue in recent times could be due to shift in demographic factors or inadequate address of clinical and biochemical variables at the time of admission to the hospital or during hospital stay. Addressing these factors through early treatment and targeted interventions is, therefore, essential for reducing mortality.

METHODS

This single-center study was conducted employing a case-control study design to capture a comprehensive assessment of the determinants of death in dengue fever patients. The study was conducted in Aalok Hospital, Mirpur, Dhaka, Bangladesh, particularly focusing on areas with high incidences of dengue fever. While patients who died of dengue fever constituted cases, those who survived the disease were considered as controls. A

case was defined as a patient who was admitted with a probable diagnosis of dengue, confirmed by a positive test for the dengue-specific NS-1 antigen during the course of illness or becoming positive for dengue IgM, and died during the hospital stay following complications related to dengue illness including dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS). The controls were serologically confirmed dengue patients who developed dengue, DHF or DSS but completely recovered from the illness. Thus, this design allowed for the examination of the association of demographic, clinical, management, and environmental factors with mortality rates.

The inclusion was limited to patients (aged 18 years and above) admitted to the index hospital during the outbreak period of 2024 with the established diagnosis of dengue fever or dengue hemorrhagic fever based on clinical and laboratory criteria (e.g., positive dengue NS1 antigen or IgM antibodies). However, patients with co-existing severe comorbidities (e.g., cancer, severe cardiac conditions) that could independently influence mortality and those with a previous history of dengue fever in the past 6 months to avoid bias from repeat infections were excluded. Having obtained the ethical clearance from the Ethical Review Committee of the study hospital and using the following formula for hypothesis testing for the difference between two proportions, a total of 123 patients from the study population (defined earlier) were included in the study (7 cases + 116 controls). While exposure variables of interest in this study were demographic factors (age, gender, socio-economic status), clinical factors (symptom severity, laboratory findings), environmental factors (temperature, rainfall, residential status), access to healthcare (timeliness of treatment, type of facility), and management loopholes/weaknesses, the outcome variable was only the mortality.

A semi-structured questionnaire was used to collect demographic, clinical, and socio-economic data from patients at the time of admission. Patients' medical records were reviewed to extract relevant clinical details (e.g., laboratory results, treatment regimen). Data were entered into statistical software, SPSS (Statistical Package for Social Sciences), version 25.0 for analysis. Descriptive statistics (mean, median, percentage) summarized the characteristics of the study population. Inferential statistics were used to assess the association between key exposure variables and mortality. The level of statistical significance was set at 5% and a p-value < 0.05 was considered significant.

RESULTS:

The mean age of the cases was significantly higher than their control counterparts ($p = 0.017$). A significant proportion of patients both in the case and control groups belonged to middle- and upper-middle-class families with no significant difference between the groups in terms of socioeconomic status ($p = 0.755$). Service-holders were more likely to die of dengue than the other occupants ($p = 0.033$). Educational status and body mass index (BMI) did not have any association with the death of dengue patients ($p=0.210$ and $p=0.206$ respectively). Dengue patients who died of the disease had significantly longer stays in the hospital than those who survived the disease ($p = 0.001$) (Table I).

Presenting symptoms, like hypotension, retro-orbital pain, and headache restlessness demonstrated their significant presence among the cases than those among the controls ($p = 0.004$, $p = 0.048$, and $p = 0.016$ respectively). Decreased urine output was considerably higher in the former group than in the latter group, though the difference did not reach the level of significance ($p = 0.127$) (Table II). Examination of the presence of clinical signs revealed that altered sensorium, ascites, electrolytes imbalance, and oedema were staggeringly higher in the case group than those in their control peers ($p < 0.001$, $p=0.009$, $p < 0.001$, and $p < 0.001$ respectively) (Table III).

Over half (57.1%) of the cases had an acute liver injury (ALT > 200 U/L) as opposed to 11.2% of the controls ($p = 0.001$). Acute kidney injury was invariably present in the case group as compared to only 6% in the control group ($p < 0.001$). A significant presence of thrombocytopenia was

evident in the case group compared to that in the control group ($p < 0.001$). The gastrointestinal haemorrhage was more significantly present in the former group than in the latter group ($p < 0.001$). Other bleeding manifestations were invariably found in the case group only ($p < 0.001$). Shock syndrome and DIC were the predominant complications in the case group than those in the control group ($p < 0.001$ and $p < 0.001$ respectively). Encephalitis/meningitis and cholecystitis were inappreciably higher in the former group than those in the latter group (< 0.001 and $p < 0.001$ respectively) (Table IV).

Table I. Comparison of Socio-demographic status between case and control groups

Socio-demographic status*	Group		#p-value
	Case (n = 07)	Control (n = 116)	
Age (years)	56.7 ± 14.7	42.2 ± 15.6	0.017
Socioeconomic status			
Poor	0(0.0)	4(3.4)	
Lower middle class	2(28.6)	19(16.4)	
Middle class	3(42.9)	39(33.6)	0.755
Upper middle class	2(28.6)	40(34.5)	
Rich	0(0.0)	14(12.1)	
Occupation			
Housewife	1(14.3)	30(25.9)	
Business	1(14.3)	26(22.4)	
Farmer	0(0.0)	8(6.9)	0.033
Service	5(71.4)	23(19.8)	
Others	0(0.0)	29(25.0)	
Education			
Illiterate	1(14.3)	2(1.7)	
Primary	1(14.3)	16(13.8)	
Secondary	2(28.6)	19(16.4)	0.210
Higher secondary	2(28.6)	35(30.2)	
Graduate plus	1(14.3)	44(37.9)	
Hospital stay (days)	6.6 ± 2.8	4.0 ± 1.8	0.001
BMI (kg/m2)*			
Normal	6(85.7)	52(44.8)	
Obese	0(0.0)	16(13.8)	0.206
Overweight	1(14.3)	42(36.2)	
Underweight	0(0.0)	6(5.2)	

Figures in the parentheses indicate corresponding. ***Chi-squared Test** (χ^2) was done to analyze the data. #Data were analyze using **Unpaired t-Test** and were presented as **mean ± SD.** **Fisher's Exact Test was done to analyze the data.

Table II. Comparison of symptoms between case and control groups

Symptoms	Group		#p-value
	Case (n = 07)	Control (n = 116	
Hypotension	7(100.0)	50(43.1)	0.004**
Pallor	0(0.0)	22(19.0)	0.204*
Chills	1(14.3)	44(37.9)	0.200**
Arthralgia	2(28.6)	73(62.9)	0.081**
Myalgia	5(71.4)	79(68.1)	0.609**
Retro-orbital pain	6(85.7)	60(51.7)	0.048**
Cough	1(14.3)	50(43.1)	0.133**
Anorexia	0(0.0)	70(60.3)	0.002**
Constipation	0(0.0)	31(26.7)	0.114*
Loose stools	2(28.6)	40(34.5)	0.551**
Abdominal pain	1(14.3)	63(54.3)	0.045**
Sore throat	0(0.0)	20(17.2)	0.230*
Rash	4(57.1)	48(41.4)	0.331**
Vomiting	4(57.1)	56(48.3)	0.473**
Decreased urine output	3(42.9)	22(19.0)	0.127*
Headache and Restlessness	4(57.1)	22(19.0)	0.016*
Hypertension	0(0.0)	13(11.2)	0.349*

Figures in the parentheses indicate corresponding. ***Chi-squared Test** (χ^2) was done to analyze the data. **Fisher's Exact Test was done to analyze the data.

Table III. Comparison of signs between case and control groups

Signs	Group		#p-value
	Case (n = 07)	Control (n = 116	
Abnormal reflex	1(14.3)	2(1.7)	0.162**
Altered sensorium	5(71.4)	7(6.0)	< 0.001*
Ascites	5(71.4)	30(25.9)	0.009*
Thrombocytopenia	5(71.4)	15(14.2)	< 0.001*
Leucopenia	2(28.6)	23(19.8)	0.577*
Elevated ESR	0(0.0)	71(61.2)	0.002**
C-reactive protein 5 > mg/dl	0(0.0)	56(48.3)	0.012**
Anemia	3(42.9)	20(17.2)	0.091*
Diabetes mellitus	2(28.6)	27(23.3)	0.749*
Electrolyte imbalance	5(71.4)	18(15.5)	< 0.001*
Abnormal LFT	3(42.9)	33(28.4)	0.334**
Edema	6(85.7)	5(4.3)	< 0.001*

Figures in the parentheses indicate corresponding. ***Chi-squared Test** (χ^2) was done to analyze the data. **Fisher's Exact Test was done to analyze the data.

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Table IV. Comparison of complications between case and control groups

Complications	Group		#p-value
	Case (n = 07)	Control (n = 116	
Acute liver injury (ALT > 200 U/L)	4(57.1)	13(11.2)	0.001*
AKI (S. creatinine > 1.5 mg/dl)	7(100.0)	7(6.0)	< 0.001*
Gastrointestinal hemorrhage	4(57.1)	5(4.3)	< 0.001*
Brain hemorrhage	0(0.0)	1(0.9)	0.943**
Other bleeding manifestations	7(100.0)	7(6.0)	< 0.001*
Shock syndrome	6(85.7)	11(9.5)	< 0.001*
Encephalitis / Meningitis	4(57.1)	2(1.7)	< 0.001*
DIC	5(71.4)	0(0.0)	< 0.001**
Cholecystitis	5(71.4)	6(5.2)	< 0.001*

Figures in the parentheses indicate corresponding. ***Chi-squared Test*** (χ^2) was done to analyze the data. **Fisher's Exact Test was done to analyze the data.

DISCUSSION:

The findings of this study shed light on the determinants of mortality among dengue fever patients in Dhaka City, Bangladesh, highlighting critical clinical, and demographic factors that contribute to increased mortality rates. The alarming rise in dengue-related deaths in recent years, particularly the record high of 1,705 fatalities in 2023, underscores the urgent need for targeted interventions and improved management strategies in the face of this escalating public health crisis.

The analysis revealed several significant clinical factors associated with increased mortality in dengue patients. Notably, altered sensorium, hypotension, and gastrointestinal bleeding were prevalent in the case group, aligning with findings from previous studies that emphasize the importance of these symptoms as warning signs of severe dengue. The presence of acute liver and kidney injuries and thrombocytopenia further corroborates the critical nature of these clinical manifestations, as they are commonly linked to severe dengue and poor outcomes. The significant association between electrolyte imbalance and mortality also indicates that electrolyte imbalance may exacerbate the shock syndrome and disease's severity, leading to higher fatality rates. Mahmood and associates[9] in an attempt to determine the clinical and biochemical predictors of mortality in patients with dengue fever demonstrated that leukocytosis and acute kidney injury (serum creatinine > 1.5 mg/dl) were the significant independent predictors of mortality. Medagama and colleagues[10] identified a number of clinical characteristics (postural dizziness, bleeding, presence of plasma leakage, abdominal tenderness, and signs of cardiorespiratory instability) at admission and laboratory parameters (elevated CRP, AST, or ALT > 500 IU/L, and AKI) during hospital stay to increase the risk of dying from dengue. However, multivariate logistic regression revealed bleeding at admission, AKI, and elevated hepatic transaminase >500 IU/L to be independent predictors of mortality.[10] Mortality was also observed to be increased in those patients with co-morbidities such as diabetes mellitus, and hypertension. However, only altered sensorium and hypertension emerged as independent predictors of mortality after multivariate regression analysis.[8] A systematic review of 18 eligible papers, with a total of 25,851 patients, and a meta-analysis of 12 high-quality observational studies of patients with dengue reported that severe hepatitis, dengue shock syndrome, altered mental status, diabetes mellitus, and higher pulse rate are associated with mortality in patients with dengue.[11]

The identification of shock syndrome & disseminated intravascular coagulation (DIC) as predominant complications in the mortality group is particularly concerning. These conditions are known to be associated with severe dengue and highlight the need for early recognition and aggressive management of severe cases. The presence of these complications suggests that a concerted approach in monitoring and managing patients with severe manifestations could potentially reduce mortality rates.

While the study did not find a significant association between socioeconomic status and mortality, the higher mortality rates among older patients suggest that advanced age may influence the immunity status of the dengue patients predisposing them to death. This finding is consistent with a record-based case-control study conducted in the Medical College Hospital in Thiruvananthapuram, where dengue patients over 40 years of age were found to be 9.3

(95% CI; 1.9 - 44.4) times more likely to die compared with younger patients.[8] In the present study, mortality was also significantly higher among service-holders than in other occupants. This finding indicates that certain demographic groups may be at higher risk of death, for unknown reasons.

The findings of this study underscore the necessity for integrated public health strategies that focus on early detection, timely treatment, and effective management of dengue fever. Enhanced community awareness programs targeting high-risk populations, particularly service-holders, could improve early recognition of severe dengue symptoms and encourage timely healthcare-seeking behavior. Moreover, the results highlight the importance of ongoing surveillance and research to further elucidate the complex interactions between demographic, clinical, and biochemical determinants of dengue mortality. Future studies should explore the impact of healthcare access and quality on outcomes, as well as the effectiveness of intervention strategies in reducing mortality rates.

CONCLUSION:

This study underscores the importance of recognizing demographic, clinical, and biochemical factors in managing dengue fever. Effective strategies must be implemented to enhance early detection and treatment of severe cases, particularly among high-risk groups. Public health initiatives addressing awareness, and timely healthcare access are vital to reducing dengue mortality in Bangladesh. Future research should explore longitudinal trends in dengue mortality and the effectiveness of intervention strategies to better inform healthcare practices.

REFERENCES:

1. World Health Organization, Dengue and severe dengue; 2024, https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue [accessed 25 April 2024]
2. Shah MM, Shah N, Iftikhar M, Abbas S, Rahim F, Jamal A. Frequency of pruritic rash in patients with dengue fever presenting to a tertiary care hospital. *KJMS [Internet]*. 2021;14(1):4-7. Available from: https://kjms.com.pk/index.php/kjms/article/view/58
3. Jahan F: Dengue Fever (DF) in Pakistan. *Asia Pac Fam Med*, 2011;10:1. https://doi.org/10.1186/1447-056X-10-1
4. Rahim F, Amin S, Noor M, Ali B, Wahab A. Dengue Fever, Crimean-Congo Hemorrhagic Fever, and COVID-19 Triple Co-infection: Out of the Frying Pan Into the Fire. *Cureus*, 2022;14(9):e29028. doi: 10.7759/cureus.29028.
5. Khan S, Akbar SMF, Mahtab MA, Yahiro T, Hashimoto T, Kimitsuki K, et. al. Bangladesh records persistently increased number of dengue deaths in recent years: Dissecting the shortcomings and means to resolve. *IJID Reg*, 2024;12:100395. doi: 10.1016/j.ijregi.2024.100395.
6. Ali N. The recent burden of dengue infection in Bangladesh: A serious public health issue. *Infect Public Health*,2024; 17(2):226-228. doi: 10.1016/j.jiph.2023.12.003.
7. Giselle HM, Eliane de FD, Elisabeth C. Mortality from severe dengue in Brazil: a population based case-control study. *Am J Trop Med Hyg*, 2013;88(4):670-676.
8. Karunakaran A, Ilyas WM, Sheen SF, Jose NK, Nujum ZT. Risk factors of mortality among dengue patients admitted to a tertiary care setting in Kerala, India. *Journal of Infection and Public Health JIPH*, 2014;7(2):114-120. https://doi.org/10.1016/j.jiph.2013.09.006.
9. Mahmood A, Haq AU, Amin S, Rahim F, Noor M, Gul H, et. al. Predictors of Mortality in Patients With Dengue Fever: Insights From a Comparative Analysis. *Cureus*, 2023; 15(3):e36040. doi: 10.7759/cureus.36040.
10. Medagama A, Dalugama C, Meiyalakan G, Lakmali D. Risk Factors Associated with Fatal Dengue Hemorrhagic Fever in Adults: A Case Control Study. *Can J Infect Dis Med Microbiol*, 2020;2020:1042976. doi: 10.1155/2020/ 1042976.
11. Chagas GCL, Rangel AR, Noronha LM, Veloso FCS, Kassar SB, Oliveira MJC, et. al. Risk factors for mortality in patients with dengue: A systematic review and meta-analysis. *Trop Med Int Health*, 2022;27(8):656-668. doi: 10.1111/tmi.13797.