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Classical and Hemorrhagic Dengue among Bangladeshi Adults: A Single Center Cohort Study

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Abstract

Background: Dengue is a mosquito-borne viral disease worldwide. The number of new cases and mortality in Bangladesh increased in recent years. This study aims to observe the difference between demo-graphic data, warning signs, high-risk comorbidity, treatment pattern, and laboratory investigations in two different types of dengue fever during the pick tropical season.

Method: This retrospective observational study was done in Holy Family Red Crescent Medical College from May to October 2019 from hospital records of a total of 102 dengue NS1 positive patients. The classical dengue fever (CDF) group consists of 72 patients and the dengue hemorrhagic fever (DHF) group consists of 30 patients. Demographic data, high-risk co-morbidity (pregnancy, old age, DM, HTN), 'warning sign' (abdominal tenderness, mucosal bleeding, lethargy, restlessness, persistent vomiting, clinical fluid accumulation, liver enlargement > 2cm, increase HCT, decrease Platelet), treatment pattern, and laboratory findings were compiled, analyzed and compared between two varieties.

Result: Out of 102 patients, the majority were male 63 (61.76%). The mean age was 34 years in both groups of patients. 'Warning signs' were observed in a higher percentage in the dengue hemorrhagic fever group, which were statistically significant ($p < 0.01$ and $p < 0.05$). Most of the patients (80.55%, 93.33%) received 1000 ml infusion/day in both groups. Where only 15 patients received fresh frozen plasma. Use of cephalosporin (30%), steroid (43.33%), and tranexamic acid (23.33%) were higher percentages in dengue hemorrhagic fever than classical dengue fever (12.5%, 26.39%, 18.05%). Among hematological tests, changes observed in platelet and total WBC count in between two groups were statistically significant. Radiological and other lab findings also revealed a higher percentage of patients affected in the dengue hemorrhagic fever group.

Conclusion: The incidence rate of classical dengue was higher than the hemorrhagic type, but the 'warning sign' and significant thrombocytopenia and leucopenia in hemorrhagic dengue fever can be considered for the progression towards dengue shock syndrome. Monitoring hematocrit concentration and plasma therapy is not much of benefit in hemorrhagic type because of fluid accumulation.

Key words: Dengue, warning sign, antibiotics, corticosteroid, hematological changes.

1 | INTRODUCTION

Dengue fever is a common mosquito-borne disease, mostly occurring in tropical and sub-tropical countries. The global prevalence rate of dengue fever has increased in recent years (1) . This fever changes its epidemiological pattern and spread to new areas (2) . Dengue fever and dengue hemorrhagic fever are common in Southeast Asia, Thailand, Vietnam, Singapore, and Malaysia, and recently in Bangladesh (3).

Dengue fever is a viral infection started with the sudden onset of high fever (4) . Dengue infection may be symptomatic and asymptomatic also. Symptomatic dengue infection is grouped into classical dengue fever (CDF), dengue hemorrhagic fever (DHF), and expanded dengue syndrome (DSS). CDF is known as saddleback or biphasic, break-bone fever, associated with muscle pain, headache, retro-orbital pain, and a rash (5) , (6) . The disease proceeds to a critical phase as fever resolves (7). In this stage, due to plasma leakage from the blood vessels, fluid accumulates in the chest and abdominal cavity. The fluid deple-tion that occurs from the circulation leads to organ dysfunction and severe bleeding (7) . This detri-tion reflects on haemogram especially platelet and hematocrit level, and other biomarkers like SGPT, serum creatinine, serum electrolyte level. Most of the patients with ultrasound findings of ascites, pleural effusion, and gall bladder edema in this period.

Next, the recovery phase occurs with the resorption of the leaked fluid into the bloodstream. A 'fluid overload' condition may happen in this stage. This overload act on the brain, causes a decreased level of consciousness or seizures (8), lowers blood pressure level, vital organs did not get enough blood supply, thus increases the possibility of bleeding and the other major complication of dengue fever. Within 3 to 4 days, the fluid shifts back into the vascular system (9).

The first reported epidemics of dengue fever occurred in 1779-1780 in Asia, Africa, and North America. In Bangladesh, the first upsurge of dengue fever was documented in 1964 in Dhaka and the first epidemic of DHF occurred in middle of 2000, total of 5,551 dengue infected cases were reported in Dhaka, Chittagong, and Khulna cities, most of them were adults. The case fatality rate was documented by 1.7% with 93 deaths reported (10). Directorate General of Health Service (DGHS) of Bangladesh reported that 1,01,354 confirmed the case. and 164 deaths in the year 2019 (11).

No specific antiviral drugs are available to treat dengue fever. Treatment depends on the clinical presentations of the individual patient and proper fluid balance is the key component of the treatment (12). National guideline of Bangladesh suggested that pa-tients have no "warning signs" managed at home with daily follow-up and oral rehydration therapy. Patients who have high risk co-morbidities, have "warning signs", or cannot manage regular follow-up should be admitted to the hospital. After admis-sion, the amount of fluid administration is titrated to stable vital signs and normalization of hematocrit level (13). Other than acetaminophen, NSAIDs like ibuprofen and aspirin are avoided to decrease the risk of bleeding. Packed red blood cells or whole blood are recommended, rather than platelets and fresh frozen plasma12. Corticosteroids also have a controversial effect on dengue fever (14).

Despite this management, dengue fever has become a grave condition nowadays. Many people die and many are in danger, especially in Dhaka city. The current study is aimed to observe the variation in comorbidities, warning signs, treatment pattern, and change in their biomarker in CDF and DHF affected patients in recent years.

2 | METHOD:

This retro-prospective observational study was held in a 720-bed non-government Holy Family Red Crescent Medical College Hospital (HFRCMCH),

Supplementary information The online version of this article (https://doi.org/10.15520/jmrhs.v4i4.339) contains supplementary material, which is available to authorized users.

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Dhaka, Bangladesh from May to October 2019. The study was approved by the designated hospital authority and the institutional ethics board.

All dengue NS1 positive patients of 16 to 70 years of age range, admitted with a 'warning sign' (clinical observations need hospitalization for close monitoring) / high-risk condition (host factors donates to more severe condition of the disease and its complications) in hospital in the study period were included. Patients diagnosed with other fever and unavailability of all data were excluded from the study. 102 cases were conveniently selected as the study population. 102 patients were divided into two groups, 72 patients in the classical dengue fever (CDF) group, and 30 patients in the dengue hemorrhagic fever (DHF) group.

Demographic data (age, gender, length of hospital stay), 'warning signs based on clinical sign (abdominal tenderness, mucosal bleeding, lethargy, restlessness, persistent vomiting) and clinical examination and lab investigation (clinical fluid accumulation, liver enlargement > 2cm, increase HCT, decrease platelet), high-risk co-morbidity (pregnancy, old age, DM, HTN), treatment pattern, and lab investigation report attached with patient personal record file were collected from hospital record room. All data are written in customized proforma. Statistical analysis was done using SPSS version 21.0 and all p values were two-tailed, with $p < 0.05$ considered statistically significant.

3 | RESULT:

A total of 63 (61.76%) patients were male, with the mean age of 34 years in both groups. A higher percentage of high-risk co-morbidities was hypertension (12.67%, 16.67%), along with diabetic mellitus, old age, and pregnancy. In the case of 'warning signs,' the dengue hemorrhagic fever (DHF) group has a higher percentage than the classical dengue fever (CDF) group except for vomiting, which was statistically significant (Table 1).

TABLE 1: Demographic data

Characteristics		Classical Dengue Fever (n= 72)	Dengue Hemorrhagic fever (n= 30)	Statistical significant test
Age - mean± SD		34.39± 15.01	34.33± 14.11	
Gender- Male/ Female		41/ 31	22/ 08	
Length of hospital stay (Days)- mean± SD		05.42± 01.59	05.53± 01.48	
High risk co-morbid conditions				
pregnancy		01/ 72 (01.39%)	01/ 30 (03.33%)	Chi-square= 1.1145. p =.773568. Result is not significant
Old age		03/ 72 (04.67%)	02/ 30 (06.67%)	
DM		11/ 72 (15.28%)	03/ 30 (10%)	
HTN		12/ 72 (16.67%)	05/ 30 (16.67%)	
Presence of 'warning sign'- no./total no. (%)				
By clinical sign	Abdominal Tenderness	07/ 72 (09.72%)	04/ 30 (13.33%)	Chi-square = 24.5622. p = .000062. Result is significant
	Mucosal bleeding	07/ 72 (09.72%)	15/ 30 (50%)	
	Lethargy	14/ 72 (19.44%)	09/ 30 (30%)	
	Restlessness	03/ 72 (04.67%)	03/ 30 (10%)	
	Persistent vomiting	51/ 72 (70.83%)	18/ 30 (60%)	
By clinical examination and lab investigations.	Clinical fluid accumulation	04/ 72 (05.55%)	05/ 30 (16.67%)	Chi- square= 8.0398. p = .045196. Result is significant.
	Liver enlargement > 2cm	01/ 72 (01.39%)	03/ 30 (10%)	
	Increase HCT	04/ 72 (05.55%)	16/ 30 (53.33%)	
	Decrease Platelet	15/ 72 (20.83%)	16/ 30 (53.33%)	

TABLE 2: Treatment given in Dengue patients

Drugs	Classical Dengue Fever (n= 72)	Dengue Hemorrhagic fever(n=30)
Fresh frozen Plasma transfusion	08/ 72 (11.11%)	07/ 30 (27.33%)
Antibiotic		
Cephalosporin	09/ 72 (12.50%)	09/ 30 (30%)
Amoxicillin	01/ 72 (01.39%)	01/ 30 (03.33%)
Meropenem	-	01/ 30 (03.33%)
Azithromycin	06/ 72 (08.33%)	01/ 30 (03.33%)
Ciprofloxacin	03/ 72 (04.17%)	-
Metronidazole	02/ 72 (02.78%)	-
Nidazoxanide	03/ 72 (04.17%)	02/ 30 (06.06%)
Steroid	29/ 72 (26.39%)	13/ 30 (43.33%)
Plasma+ Steroid	05/ 72 (06.94%)	05/ 30 (16.67%)
Tranexamic acid	13/ 72 (18.05%)	07/ 30 (23.33%)

Most of the patients received intravenous infusion during their hospital stay. Among them (80.55%, 93.33%) received 1000 ml/day in both groups. Four patients did not receive any intravenous infusion in the CDF group. Total 15 patients out of 102, received fresh frozen plasma. DHF patients (27.33%) had a higher percentage than another group (11.11%) who received fresh frozen plasma.

Among antibiotics, cephalosporin was the most common (12.50%, 30%) in both groups. Corticosteroid used in higher percentage (43.33%) in DHF group. Among 42 patients who received steroids, 10 patients received fresh frozen plasma. Tranexamic acid was used mostly (23.33%) in the DHF group, who were at risk of complication.

Hematological tests were done on admission, and after 24, 48, 72 hours for each individual. Changes in Hb% ranges from 12 to 13 gm/dl in both CDF and DHF groups. Changes in the level of hematocrit range from 40.29 to 41.83 in both groups which were not statistically significant at $p < .05$ in the two-tailed t-test.

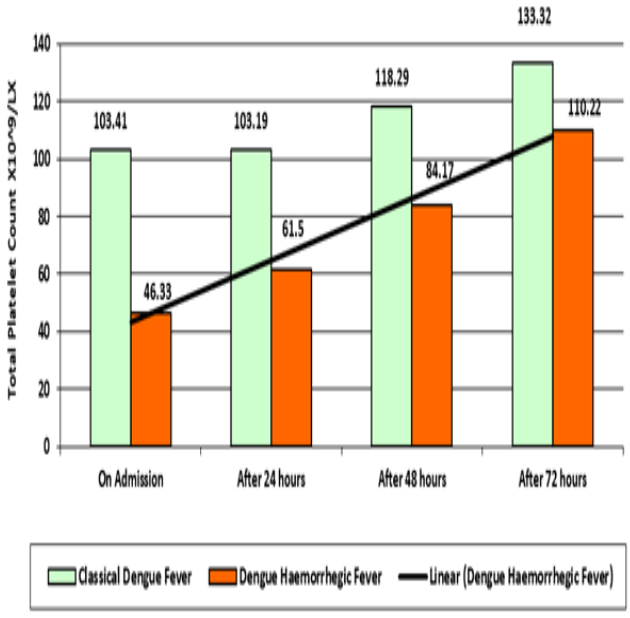

FIGURE 1: Changes in Total platelet count in Classicaldengue fever and Dengue hemorrhagic fever patients over period of time.

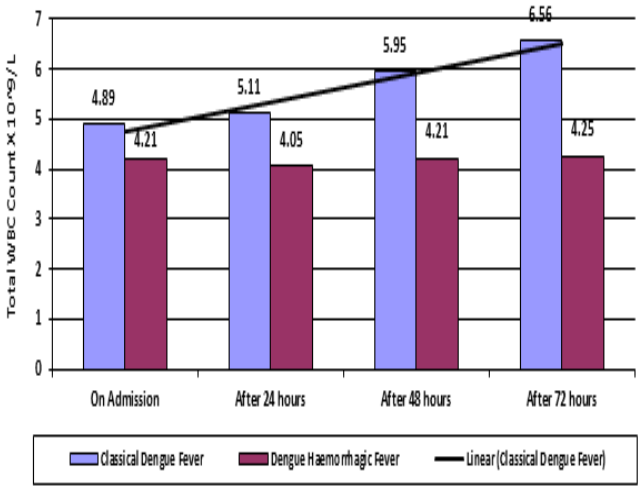

FIGURE 2: Changes in Total WBC count in Classical denguefever and Dengue hemorrhagic fever patients over period of time.

Changes are also seen in total platelet count and total WBC count level on admission, after 24 hours, after 48 hours, and after 72 hours (Figure 2 & Figure 3). Levels were statistically significant in both CDF and DHF groups. The result was statistically significant (p=.047258 and p=.009757) at $p < .05$ in a two-tailed *t*-test.

TABLE 3: Change in the other laboratory findings

	Classical Dengue Fever (n= 72)	Dengue Hemorrhagic fever (n=30)
SGPT	78.89± 54.21	86.61± 54.24
RBS	07.81± 01.77	08.40± 02.94
Serum Creatinine	01.05± 0.21	0.97± 0.24
Serum Electrolyte		
Na	138.44± 07.13	140± 05.81
K	03.85± 0.55	04.06± 0.59
Cl	100.53± 06.25	101.57± 3.59
X ray		
Plural effusion	06/ 72 (08.33%)	08/ 30 (26.67%)
USG		
Echogenic sludge	01/ 72 (01.39%)	-
Thick GB wall	03/ 72 (04.17%)	02/ 30 (06.67%)
Fatty liver	02/ 72 (02.78%)	01/ 30 (03.33%)
Mild Hepatomegaly	02/ 72 (02.78%)	04/ 30 (13.33%)
Mild ascites	-	05/ 30 (16.67%)

Other supportive investigations like SGPT, RBS, serum creatinine, serum electrolyte level were also done. Radiological findings in x-ray and USG shows a higher percentage of fluid accumulation and other findings in the body in the DHF group (26.67%,16.67%).

4 | DISCUSSION:

Dengue is an important flavivirus infection that affects millions of people worldwide, particularly in urban and semi-urban areas of the tropical and sub-tropical regions. Management of dengue fever is symptomatic and supportive. This study focuses on the difference between, 'warning sign', co-morbidities, treatment pattern, and lab investigation on classical dengue fever (CDF) and dengue hemorrhagic fever (DHF).

Our observational study shows a mean age of 34 years in both CDF and DHF groups. Rahman et al show a indistinguishable age range (18-33 years) was most affected in their study like ours (15) . Several previous studies revealed their paints in the 20-40 age group (16),(17). The number of male patients (63) was higher in two groups than female (39). Some previous studies also observed the male predominant condition (16) , (18) . The duration of hospital stay was 5 to 6 days in both groups of patients. Here in this study, we show high-risk co-morbid conditions like DM (15.28%,10%) and HTN (12.67%, 16.67%). In the recently upgraded national guideline, patients with two or more, 'warning signs' got priority in hospital admission. A higher percentage of 'warning signs' present in the DHF group, which were statis-tically significant.

In this study, both CDF and DHF patients received symptomatic and supportive treatment. Intravenous infusion gave not at all in four patients and 1000ml/day in case of rest of the population more cautiously to avoid 'fluid overload'(12),(13) Fresh frozen plasma was also giving with great care by only 15 patients for the same reason. But in 2008, an RCT held in Srilanka shows the effects of fresh frozen plasma on platelet counts in dengue (19). In this study, several groups of antibiotics were used along with symptomatic treatment among them cephalosporin (12.50%, 30%) used in a higher percentage in two groups of patients. Hafeez et al, Adrizein et al show the same group of antibiotics in their dengue pa-tients (20) , (21) .

Here in this observational study, 44 patients received corticosteroid, most of the cases (29) were in the CDF group. Zhang et al showed in their review that the use of corticosteroids at an early stage of dengue, prevent dengue-related shock syndromes (14). But the quality of evidence is low, inconclusive, and needs a randomized controlled trial. In our study, tranexamic acid was received in 20 cases. Though tranexamic acid was used to minimize menstrual bleeding and gastrointestinal bleeding, there are no controlled studies on its use in dengue (22) .

In our study, hematological changes were observed at admission day to after 24, 48, 72 hours' interval. Among all hematological markers, statistically significant changes were observed in leucopenia and thrombocytopenia. These changes in the hematological marker were almost the same in previous studies (15) , (16) , (17).

Our study also focuses on some other lab Investigations especially radiological and ultrasonographical findings. Plural effusion (26.67%), ascites (16.67%), and thick gall bladder wall (06.67%), which were in higher percentage in the DHF group. Ahmed et al, show 17.55% pleural effusion, 16.25% ascites, 16.25% thickened gall bladder wall, and less percentage of organomegaly in their study, which were close to our result17. But Manam et al found 65.08% thickened gall bladder wall and 49.21% pleural effusion in their patients (23).

5 | CONCLUSION:

Dengue causes more illness and death than any other viral infection in Bangladesh in recent years. In this study, we found the incidence rate of classical dengue was higher than the hemorrhagic type, but 'warning sign' and significant thrombocytopenia and leucopenia was observed in hemorrhagic dengue fever. Monitoring hematocrit concentration and plasma therapy is not much of benefit in hemorrhagic type because of fluid accumulation.

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