## ORIGINAL ARTICLE

# LIVER FUNCTION DERANGEMENT AND BLEEDING MORBIDITY IN DENGUE FEVER AND DENGUE HAEMORRHAGIC FEVER IN A TERTIARY HOSPITAL IN BANGLADESH

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**Abstract:**

**Background:** Dengue is a major international health concern that is prevalent in tropical and sub tropical countries. Study of dengue infection and its Liver complications are scarce from countries like India. This study was done to assess the frequency and spectrum of liver dysfunction and bleeding morbidity in Dengue infection patients. **Methods:** A Cross sectional prospective observational study was performed in the of Department of Medicine Sir Salimullah Medical College Mitford Hospital. All the inpatients who were diagnosed with dengue infection between July 2015 to July 2016 were included in this study. A total of 70 patients were included in the study. **Results:** Patients were classified as classical dengue fever (DF) 61.5.% dengue haemorrhagic fever (DHF) 38.5%. The mean age was 28.607±10.45 years in DF group and 26.78±11.78 years in DHF group and male: female ratio was 3:1. Deranged serum glutamic-oxaloacetic transaminase (SGOT) and/or Serum glutamic pyruvic transaminase (SGPT) was present in most of the patients. Elevation of ALT level occured more in DHF group patient (81%) than DF group (46%). Out of 70 patient 28(40%) patient were within normal value. 42 (60%) patient had elevated ALT level which is statistically significant (p value-<0.05)..The degree of rise of SGOT, SGPT,and Bilirubin was significantly more in DHF and DSS, as compared to DF. About bleeding morbidity, purpura was a mentionable finding 29(41%) but gum bleeding 15(21%), echymosis 14(20%), are less in both DF and DHF group. Major bleeding like hematomesis 5 (7%), melaena 4 (5%) and haematuria 1 (1%) also occured in both group of patients. **Conclusion:** Liver dysfunction in the form of raised SGPT was seen in almost all patients. Preferentially high SGOT may serve as an early indicator of dengue infection while high values of bilirubin, SGOT, SGPT,may be an indicator of severe disease and poor prognosis.

**Keywords:** dengue infection, liver, bilirubin, heart failure, acute viral hepatitis

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## Introduction:

Dengue is the most widely distributed mosquito-borne viral infection of humans, affecting up to 100 million persons each year across the tropical world.[1,2] Dengue prevalence in Bangladesh was 2.7 per 1000 in 2019, which is gradually increasing. Infection with any of the four dengue viral serotypes may result in asymptomatic infection or may cause a range of disease manifestations from non-specific fever to a syndrome characterized by increased vascular permeability, thrombocytopenia, and deranged haemostasis. In severe cases, the increased vascular permeability results in circulatory compromise and the patient may develop potentially life-threatening dengue shock syndrome (DSS).[2–4] No specific antiviral therapy is available but the physiologic derangements are transient, and most patients recover fully if supported with parenteral fluid therapy during the period of maximal vascular leakage. Current mortality rates for DSS are less than 1% in experienced hands.[5–7]

Dengue shock syndrome is an important cause of hospitalization among children living in dengue-endemic areas. However, in general, severe bleeding is not a major problem in this group, despite often profound thrombocytopenia and clear evidence of a coagulopathy.[8–10] In recent years, there has been a notable increase in the number of adults with dengue requiring hospitalization in Asia and South America.[6,11,12] Dengue shock syndrome appears to be less frequent in adults than children, possibly reflecting age-dependent differences in intrinsic vascular permeability, but there is anecdotal evidence to suggest that bleeding manifestations and hepatic dysfunction are both more common in older age groups.[6,11,13] There have been few prospective studies focused on disease manifestations in adults, and there is little systematic data describing the clinical profile of disease in older patients or those with co-morbidities, or detailing the evolution of clinical and laboratory parameters through the various stages of the infection.

Hepatic dysfunction is a well recognized feature of dengue infections, often demonstrated by hepatomegaly and mild-to-moderate increases in transaminase levels although jaundice and acute liver failure are generally uncommon.[14–17] Biopsy specimens obtained from a small number of patients with DSS who died have shown a variety of patterns including microvesicularsteatosis, hepatocellular necrosis with associated councilman bodies, Kupffer cell destruction, and inflammatory infiltrates at the hepatic portal tracts.[18,19] Dengue antigens and viral RNA have been demonstrated in some of these fatal cases, and dengue viruses have been isolated occasionally from hepatic tissue.[19–22] However, biopsy specimens are rarely obtained from less severe cases and the relevance of these findings to the broad spectrum of dengue infections remains uncertain. Debate continues as to whether dengue associated hepatic dysfunction indicates a direct viral effect, arises secondary to an aggressive host immune response to the virus, or reflects a complex interaction of these two mechanisms.

One factor that may influence the pattern of disease seen in adults is the greater likelihood of underlying chronic diseases, potentially compounding the effects of the acute infection. Chronic viral hepatitis is common among adults in many tropical and sub-tropical countries where dengue is endemic, and it has been postulated that dengue infection occurring on a background of chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) may result in more severe liver dysfunction and/or haemorrhage than is usual in non-infected persons. However, the evidence to date is conflicting; two small studies indicated no effect,[14,15] and one study suggested that concomitant HBV infection may result in greater hepatic dysfunction.

## Methods:

A hospital based cross sectional prospective observational study was performed in the of Department of Medicine Sir Salimullah Medical College Mitford Hospital. All the in patients (>13 years) who were diagnosed with dengue infection between July 2015 to July 2016 were included in this study. History, clinical features, Investigation and treatment given was collected from the records. Patients with pre existing or concurrent liver disease due to any other etiology were excluded from the study (e.g. diagnosed Chronic Liver Disease co- existing or recent history of infectious disease like acute viral hepatitis, malaria, typhoid, leptospirosis, history of intake of any hepatotoxic drugs, history of alcoholic liver disease, history of Non-alcoholic Fatty Liver Disease (NAFLD) Wilson's disease, autoimmune hepatitis and heart failure etc.). A total of 70 patients were included in the study. Patients were categorized in to classical dengue fever (DF), Dengue hemorrhagic fever, Dengue shock syndrome as per WHO criteria.16 Dengue infection was detected using Rapid test (Immunochromatography) for Dengue NS1 Antigen/IgM Dengue. Few were confirmed using ELISA for IgM Dengue.

## Statistical analysis

Results for continuous variables were expressed as means and standard deviation. Categorical variables were expressed as percentages. Student's t-test for

continuous variables and Chi square test for discrete variables were used to test significance. The p value of less than 0.05 was considered statistically significant. The SPSS 22 software was used for statistical analysis.

## Results:

A total number of 70 serologically confirmed patients were selected for this study. The cases of dengue patients mentioned throughout the study were divided into Dengue Fever (DF) and Dengue Hemorrhagic Fever (DHF). Dengue shock Syndrome cases were also identified but did not mention separately here.

While interpreting the results from the study, the demographic factors and general characteristics of the patients were analyzed. Bleeding manifestations of the DF and DHF were analyzed as well. Serum bilirubin level between respondents was identified. The analysis also comprises aminotransferase (ALT and AST) levels of patient's groups. The correlation and comparisons were done between different variables. All the results were presented in both tabular and diagram form.

Before the result analysis, the baseline information was analyzed and general characteristics were compiled.

The mean age of the respondents was 28.607±10.45 years in DF group and 26.78±11.78 years in DHF group. However, out of 70 patients, 43 patients were from the DF group and rest of the 27 patients was from DHF group. Most of the patients (34 patients) were from the age group of 21-30 years. The age group of 13-20 years, 9 patients suffered from DF and 5 patients suffered from DHF. Only 1 patient was found from DF group, whose age was in between 51-60 years. In DF group, 34(49%) patients were male and 9(12%) were female. In DHF group, 6 patients were female and 21 patients were male. In total, 55(78%) patients were male and 15(21%) patients were female. In both DF and DHF group male were more in number than female

In this study, occupational status of the respondents represents that, most of the patients with DF were engaged in service (14) and business (10). In DHF group, it was found that 6 patients were businessman, 7 were service holders and 2 were housewives. In total, it was found that most of the patients were service holders (21).

Pattern of fever among patients are shown in figure 1
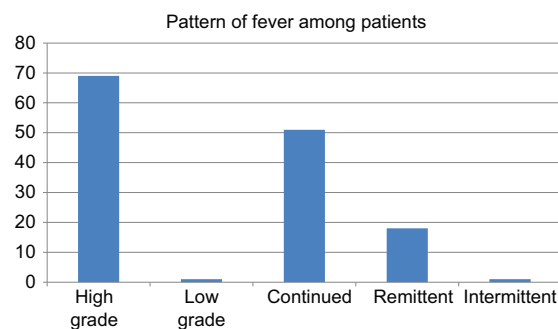


**Fig.-1:** *Pattern of fever among patients*

**Table-I**
*Bleeding profile of the patient*

|  | Type of patient | Total | DF | DHF |  |
| --- | --- | --- | --- | --- | --- |
| Purpura | Yes | 0 | 19 | 29 |  |
|  | No | 33 | 8 | 41 | <0.05 |
| Total |  | 43 | 27 | 70 |  |
| Echymosis | Yes | 4 | 10 | 14 |  |
|  | No | 39 | 17 | 56 | <0.01 |
| Total |  | 43 | 27 | 70 |  |
| Gum bleeding | Yes | 3 | 12 | 15 |  |
|  | No | 40 | 15 | 55 | <0.01 |
| Total |  | 43 | 27 | 70 |  |
| Nasal bleeding | Yes | 0 | 6 | 6 |  |
|  | No | 43 | 21 | 64 | <0.01 |
| Total |  | 43 | 27 | 70 |  |
| Blood vomiting | Yes | 0 | 5 | 5 |  |
|  | No | 43 | 22 | 65 | <0.01 |
|  | Total | 43 | 27 | 70 |  |

*p value calculated on basis of z-Test

In this table, purpura was present among 19 DHF patients and 10(23%) DF patients. Ten patients had echymosis from DHF group and 4 patients from DF group. Nasal bleeding were found only 6 patients among DHF group. Gum bleeding had 12 patient from DHF and 3 from DF group. Besides, blood vomiting was found only 5 from DHF.

**Table-II**

*Other bleeding profile of the patient*

| | | Type of patient | | Total | |
| --- | --- | --- | --- | --- | --- |
| | | DF | DHF | | |
| Haematuria | Yes | 0 | 1 | 1 | <0.01 |
| | No | 43 | 26 | 69 | |
| Total | | 43 | 27 | 70 | |
| Black tarry stool | Yes | 0 | 4 | 4 | |
| | No | 43 | 23 | 66 | <0.01 |
| Total | | 43 | 27 | 70 | |
| Blood mixed sputum | Yes | 0 | 1 | 1 | |
| | No | 43 | 26 | 69 | <0.01 |
| Total | | 43 | 27 | 70 | |

• P value calculated on basis of z-Test

This table showshaematuria was only 1 patient from DHF group. Black tarry stool was found among 4 patients from group DHF and not in DF. Blood mixed sputum was found only 1 patient in DHF but not in DF.
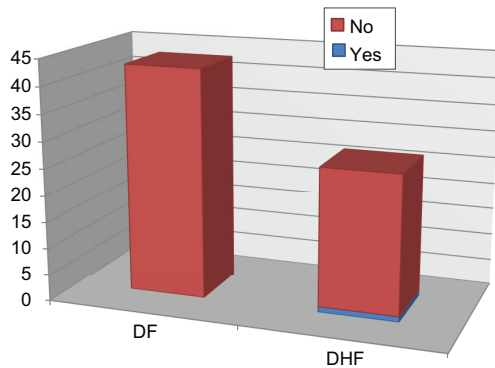


**Fig.-2:** *Past history of Dengue among the patient*

In this figure out of 43 patients of DF none had past history of dengue. In DHF group, out of 27 patients only one had past history of dengue.

**Table-III**

*Value of Aminotransferase (AST) in study population n=70*

| | Frequency | | P* |
| --- | --- | --- | --- |
| AST(SGOT) | DF | DHF | value |
| Group 1 (≤46u/L) | 24 | 2 | <0.05 |
| Group 2 (47-120u/L) | 18 | 17 | >0.05 |
| Group 3 (121-400 u/L) | 1 | 7 | <0.05 |
| Group 4 (≥400u/L) | 0 | 1 | >0.05 |
| Total | 43 | 27 | |

* P value calculated on basis of z-Test

In table-V, the value of AST is presented in 4(four) groups. Maximum patient's AST values was in group-2, 35(50%) and in group-1, 26(37%). In group-3, 8(11%) patients had AST level was more than 3 to 8 times the upper normal limit. Only 1 patient was in group-4. here only the value shows significant between DF and DHF in group-3.

**Table-IV**

*Value of Aminotransferase (ALT) in study population n=70*

| | Frequency | | P* |
| --- | --- | --- | --- |
| AST(SGOT) | DF | DHF | value |
| Group 1 (≤50u/L) | 23 | 5 | <0.05 |
| Group 2 (51-120u/L) | 18 | 8 | >0.05 |
| Group 3 (121-400 u/L) | 2 | 10 | <0.05 |
| Group 4 (≥400u/L) | 0 | 4 | >0.05 |
| Total | 43 | 27 | |

* P value calculated on basis of z-Test

In this table, the measured ALT level is divided into 4 group. Most of the patient was in Group-1 and the number of patients was 28 (40%). In group-2, total number of patients was 26 (37%). Group-4 shows 4 patients had altered ALT, about 8 times more the above normal limit, in DHF group. In this table serum aminotransferase changes is statistically significant between DF and DHF group.

**Table V**

*Anti Dengue antibody (IgG) profile in study population n=70*

|       |          | Type of patient | | Total | P*value |
|-------|----------|-----|-----|-------|---------|
|       |          | DF | DHF | | |
| **IgG** | Positive | 25 | 19 | 44(62.8%) | <0.05 |
|       | Negative | 18 | 8 | 26(37%) | |
|       | Total    | 43 | 27 | 70 | |

* P value calculated on basis of z-Test

In this table it is shown that out of total 70 patients, 44 (62.8%) patients were IgG positive and 26 (37%) patients were IgG negative. The difference in IgG positivity and negativity in DF and DHF patients were significant (P<0.05).
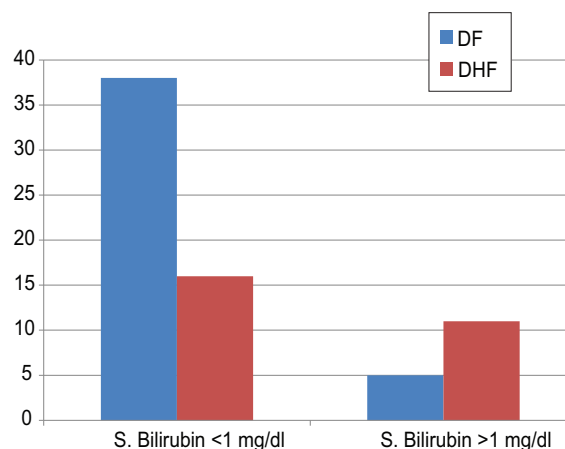
**Table-VI**

*Relationship between past history of dengue in DF or DHF*

**ANOVA test**

|  | Sum of Squares | df | Mean square =Sum of Squares df | F |
|--|----------------|-----|-------------------------------|---|
| Between Groups | .649 | 1 | .649 | 4.185 |
| Within groups | 10.551 | 68 | .155 | |
| Total | 11.200 | 69 | | |

a. Predictors: (Constant), past history of dengue

b. dependent Variable: Type of patient

In this study the association between different variables across the study, patient's past history of dengue and its association with Dengue morbidity was also tested with a one way ANOVA test (Analysis of Variance). Hereby, experimental factor of past history of Dengue was to be distinguished by experimental groups of DF and DHF. And we may take a null ($H_0$) hypothesis that, past history of Dengue has no significance with DF and DHF. In this test, the using the regression model, the sum of square value between the groups was.649 at 1 degree of freedom. Besides, sum of squares value within groups was counted at 155. However, the F value was counted as F=.649/.155= 4.185 F value at df 1 and 68 at 5% level of significance =4.035 (From the F-distribution table) which is lower than the calculated value of F and thus the value of p<0.05. Thus, null (H0) hypothesis may be counted as rejected and it has been found that past history is significant in DF and DHF.



**Fig.-3:** *Comparison of serum bilirubin between DF and DHF patients.*

Above figure showed the comparison between S. bilirubin among DF and DHF patients and found that the variance were relatively higher.

**Table-VII**

*AST and bleeding morbidity  n=70*

| AST | Bleeding morbidity | | P-value |
| | Yes | NO | |
|---|---|---|---|
| AST normal | 16 | 10 | <0.05 |
| AST raised | 37 | 07 | |
| Total | 53 | 17 | |

*P value calculated on the basis of $X^2$- test

In this table, the total number of patients of bleeding manifestations were 53in both DF and DHF. In raised AST level, the number of patients was 37. The ("p") value was <0.05. So there is significant relationship between raised AST and bleeding morbidity.

**Table-VIII**

*ALT and bleeding morbidity n=70*

| AST | Bleeding morbidity | | P-value |
| | Yes | NO | |
|---|---|---|---|
| AST normal | 16 | 12 | <0.05 |
| AST raised | 37 | 05 | |
| Total | 53 | 17 | |

*P value calculated on the basis of $X^2$- test

In this table there is also significant between raised serum ALT level and bleeding morbidity in DF and DHF.

**Discussion:**

In Bangladesh, the magnitude of Dengue fever was largely unknown until an epidemic of DF and DHF broke out in June, 2000. Since then, it has become endemic here.Dengue prevalence in Bangladesh was 2.7 per 1000 in 2019, which is gradually increasing

A total number of 70 serologically confirmed (IgM +ve) Patients were selected for the study. The cases of dengue patients in this study were divided into Dengue Fever (DF) and Dengue Hemorrhagic fever (DHF).

Out of total 70 patient maximum patients were from the age group of 21 to 30 years and is 34 (49%). The mean age of DF patient was 28.6±10.45years and DHF patient was 26.78±11.78 years. In the study of Farizshafhan et al, (2008) the mean age was 31±12 years and Luiz Jose de Souza et al, (2004) the mean age was 35.5±16.3 years that are nearer to this study.

In this study, 21% (15) patient was female, 78% (55) patient was male (figure-7). Male patients were almost

3 times than female in both DF and DHF group. In SrivenuItha et al, (2005) study out of 55 patient 29 were male and 16 were female where male is about 2 times more than female. In our society male are empowered and they are the main earning source. So they are privileged for medical treatment.

In occupation, out of 70 patient, maximum (21) were service holder followed by 16 were business man. This is due to the fact that most of the patient came from urban and peri-urban area. In Buke T (1968) and Wichmann O (2007) study maximum patients were service holder and businessman.

According to patient statement, no past history of Dengue was found in 56 patients from DF group, bit only 1 patient from DHF group who had a past history of Dengue. But in table 7, out of 70 patient 44(63%) had IgG +ve. This indicates that in majority cases past history of dengue remains unidentified.

Most of the patients serum bilirubin level was below the normal range in both DF and DHF group. only 16 (22%) had above 1mg/dl. Statistically it is significant in DF and DHF group (pvalue<0.01).

About bleeding morbidity, purpura was a mentionable finding 29(41%) but gum bleeding 15(21%), echymosis 14(20%), are less in both DF and DHF group. Major bleeding like hematomesis 5 (7%), melaena 4 (5%) and haematuria 1 (1%) also occured in both group. As a whole the bleeding profile of dengue patient in both group is statistically significant. In study of FarizSafhan et al, shows major bleeding -14.6%, minor bleeding 36.8%. So this study showed significant association existed between bleeding outcome and dengue patient. In majority, bleeding is not severe and improve spontaneously. However, we should be cautious about bleeding and not to use aspirin or antiplatelet drug in dengue.

**Conclusion:**

Liver damage is a common complication of dengue infection and aminotransferase levels are a valuable marker for monitoring these cases. These changes are not life threatening and the level of serum aminotransferase will become normal spontaneously.

**Limitation of the Study:**

The study was a hospital based and only a small number of respondents were taken. Patients from all socioeconomic status and all parts of the country did not come to seek medical attention in the study place.. Due to financial constrain much of the tests was not possible to cross check the results of serological findings for acute precision and accuracy. It will be more authentic if this study can be done on

a large population group in more institutions with longer duration of study.

**Ethical consideration:**

The study was conducted after approval from the ethical review committee. The confidentiality and anonymity of the study participants were maintained.

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