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Laboratory Investigations as Predictors of Severe Dengue Viral Infection

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Abstract:
Background: *Dengue is the most rapidly spreading mosquito-borne disease caused by flavivirus. Approximately 50% of world's population is at risk of dengue virus (DENV) infection. Fatal aspects of DENV infection are dengue hemorrhagic fever (DHF), dengue shock syndrome (DSS) and expanded dengue syndrome (EDS) and are frequently diagnosed later due to less availability of molecular and serological diagnostic tools especially in rural areas. Some cheap and time saving laboratory tests could be used as evidence of severe dengue infection before getting worse.*
Aim of study: *To correlate the serum alanine transaminase (ALT), aspartate transaminase (AST) level, platelet, neutrophil and lymphocyte count with severity of DENV infection.*
Materials and Methods: *This observational study was done in Faridpur medical college hospital (tertiary care government hospital), Faridpur, Bangladesh from 1 July 2019 to 31 December 2019. 106 admitted diagnosed dengue fever cases with NS1 antigen positive test aged over 18 years, both male and female were included in this study with informed written consent from individual. All the collected data were compiled, analyzed and interpreted statistically using SPSS (Statistical Package for Social Sciences) Version 21.0 statistical Analysis Software. The values were represented in Number (%) and Mean ± SD.*
Result: *Mean ALT was found 108.7±34.5 IUL in severe dengue and 43.2±18.6 IUL in non-severe dengue. Mean AST was found 132.7±38.7 IUL in severe dengue and 71.9±20.1 IUL in non-severe dengue. The mean platelet counts were found 29389.1±7298.4 /µL in severe dengue and 69728.0±18747.1 /µL in non-severe dengue. Lymphocytes counts was 899.6±156.0/µL in severe dengue and 1016.2±168.3/µL in non-severe dengue. Neutrophil counts were 1255.8±298.7/µL in severe dengue and 1278.9±287.4/µL in non-severe dengue. All findings were statistically significant except neutrophil count.*
Conclusion: *Increased level of ALT and AST, Thrombocytopenia and lymphopenia signify the severe dengue viral infection.*
Key words: *Severe Dengue, ALT, AST, Platelet, Neutrophil, Lymphocytes.*

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I. Introduction

Dengue is the most rapidly spreading mosquito-borne disease caused by flavivirus. Approximately 50% of world's population is at risk of dengue virus (DENV) infection with increasing geographic expansion to new countries and in the present decade, from urban to rural settings. Major challenge in dengue management in resource limited settings is the confirmation of diagnosis. Molecular diagnostic tools are not readily accessible to clinicians [1]. Moreover due to overlapping of the clinical features with other prevalent infections such as flu, chikungunya, leptospirosis and other exanthematous febrile illnesses, the confirmation of diagnosis become more difficult [2]. Although primary dengue patients present with acute febrile illness and may be undiagnosed, patients with secondary infection by different serotype may be rapidly deteriorated, progressing to hemorrhage and vascular leakage. In Expanded Dengue syndrome (EDS) involving liver, brain and heart the patients rapidly develop fatal condition with worse prognosis due to difficulties in early diagnosis. During these difficult periods, patients can experience bleeding, thrombocytopenia, ascites, pleural effusion, increased hematocrit, severe abdominal pain, vomiting, restlessness and sudden reduction in temperature with profuse perspiration and adynamia [3]. Laboratory diagnosis of dengue infection is similar to any other viral infection; it includes viral isolation, detection of viral nucleic acid, antigens, or antibodies. In the initial stage of infection, (first 4-5 days), dengue virus can be isolated from the plasma, serum, and circulating blood cells [4] but the procedure is least

available and costly. The commonly used NS1 (Non-Structural protein 1) viral antigen testing (either by rapid testing or ELISA) is most sensitive (55–66%) in the first 3 days of the illness with specificity varying between 89 and 92% [5]. Virus detection and serological assessment have been the main tools of diagnosis for many years.[6] Although RT-PCR is not easily available, NS1 antigen testing is commonly done. Raised hematocrit in dengue indicates hemoconcentration due to plasma leakage but other laboratory testing as well as clinical parameters which are helpful to predict the prognosis of the patient are very much important. In this study we have identified the important laboratory parameters to identify the severe dengue patients from non-severe.

II. Methods and materials

This observational study was conducted in Faridpur medical college hospital (tertiary care hospital), Faridpur, Bangladesh from 1 July 2019 to 31 December 2019. 106 admitted dengue fever cases diagnosed with NS1 antigen positive test were included in this study with informed written consent from individual.

Inclusion criteria:

1. Dengue fever cases diagnosed with positive NS1 antigen test
2. Age- 18 years and above
3. Sex- both male and female

Exclusion criteria:

1. Those who had other associated infections like pneumonia, urinary tract infection, enteric fever, malaria and diarrhea.
2. Those who had comorbidity such as diabetes mellitus (DM), chronic liver disease (CLD) and chronic kidney disease (CKD).

Severe dengue was mentioned as,

(a) Dengue fever with plasma leakage which was evidenced by raised hematocrit (>20% rise from baseline) and by ascites or pleural effusion and

(b) Dengue fever with features of shock evidenced by narrow pulse pressure (< 20mm Hg), rapid weak pulse, cold clammy skin and unconsciousness.

Clinical features such as fever, rash, body ache, headache, bleeding manifestations, body temperature, heart rate, blood pressure (BP) including pulse pressure and presence of pleural effusion and ascites were noted in every patient on admission. Laboratory investigations- complete blood count (CBC) with differential, total platelet count, serum ALT and AST level was measured daily in every patient from admission to discharge from hospital. X-ray chest and ultrasonography of abdomen was done on selected patients on day of admission and discharge. The data from individual patient were noted down and the demographic details were categorized and calculated to obtain mean ± standard deviation (SD). All these details are represented in each of the tables. Statistical analyses of the results were obtained by using window based computer software devised with Statistical Packages for Social Sciences (SPSS-26). The results were presented in tables, figures, diagrams. Comparison of means made by using Student t-test and categorical data.

III. Results

Among 106 cases, 52 (49.1%) were severe dengue cases and 54 (50.9%) were non-severe. Male were predominant over female. Among 52 severe dengue cases male were 31(59.6%) with mean hematocrit 53±14.2% and female were 21 (40.4%) with mean hematocrit 50±34.2%. The mean age was 31.4(±14.2) in severe dengue group and 32.8 (±13.9) in non-severe dengue group. Age, sex and hospital stay were not statistically significant ($p>0.05$) between two groups (Table -1). The mean ALT was found 108.7±34.5 IUL in severe dengue and 43.2±18.6 IUL in non-severe dengue. Mean AST was found 132.7±38.7 IUL in severe dengue and 71.9±20.1 IUL in non-severe dengue. The mean platelet counts were found 29389.1±7298.4 /µL in severe dengue and 69728.0±18747.1 /µL in non-severe dengue. The mean lymphocytes counts were found 899.6±156.0 /µL in severe dengue and 1016.2±168.3 /µL in non-severe dengue. Neutrophil counts were 1255.8±298.7/µL in severe dengue and 1278.9±287.4/µL in non-severe dengue. All above mentioned laboratory parameters were statistically significant ($p<0.05$) except neutrophil count. Pleural effusions were found in 2 (3.8%) among severe dengue cases and 0 (0.0%) in non-severe cases ($p= 0.234$). Ascites was found in 1(1.9%) cases of severe cases and 0 (0.0%) in non-severe cases ($p=0.491$). Both these findings were statistically non-significant (Table-2). Significant negative correlation ($r= -0.726$; $p=0.001$) was noted between ALT and severe dengue (Fig-1), similarly significant negative correlation ($r= -0.716$; $p=0.001$) was found between AST and severe dengue (Fig-2) Significant positive correlation ($r= 0.866$; $p=0.001$) between platelet counts and severe dengue (Fig-3) and also significant positive correlation ($r= 0.340$; $p=0.001$) between lymphocytes counts and

severe dengue (Fig-4) was found. Not significant negative correlation (r= -0.037; p=0.704) was found between neutrophil counts and severe dengue. (Fig-5)

Table 1: Demographic characteristics of the study patients

	Severe dengue (n=52)	Non-severe dengue (n=54)	P value
Sex			
Male	31 (59.6%)	34 (63.0%)	[a]0.723[ns]
Female	21 (40.4%)	20 (37.0%)	
Age (years)	31.4±14.2	32.8±13.9	[b]0.609[ns]
Hospital stay (days)	5.3±1.2	5.0±1.0	[b]0.164[ns]

ns= not significant
[a] = P value reached from chi square test
[b] = P value reached from unpaired t-test
Male were predominant, the mean age 31.4(±14.2) was in severe dengue group and 32.8 (±13.9) in non-severe group. Age, sex and days of hospital stay were not statistically significant (p>0.05) between two groups.

Table 2: Clinical and laboratory features of the study patients

	Severe dengue (n=52)	Non-severe dengue (n=54)	P value
Pleural effusions	2 (3.8%)	0 (0.0%)	[a]0.234[ns]
Ascites	1 (1.9%)	0 (0.0%)	[a]0.491[ns]
Bleeding manifestations	3 (5.8%)	0 (0.0%)	[a]0.115[ns]
Pulse pressure ≤20 mmHg	4 (7.7%)	0 (0.0%)	[a]0.054[ns]
AST (IU/L)	132.7±38.7	71.9±20.1	[b]0.001[s]
ALT (IU/L)	108.7±34.5	43.2±18.6	[b]0.001[s]
Platelet counts (/µL)	29389.1±7298.4	69728.0±18747.1	[b]0.001[s]
Lymphocytes counts (/µL)	899.6±156.0	1016.2±168.3	[b]0.001[s]
Neutrophil counts (/µL)	1255.8±298.7	1278.9±287.4	[b]0.686[ns]

s= significant, ns= not significant
[a] = P value reached from chi square test
[b] = P value reached from unpaired t-test
The mean ALT was found 108.7±34.5 IUL in severe dengue and 43.2±18.6 IUL in non-severe dengue. Mean AST was found 132.7±38.7 IUL in severe dengue and 71.9±20.1 IUL in non-severe dengue. The mean platelet counts were found 29389.1±7298.4 /µL in severe dengue and 69728.0±18747.1 /µL in non-severe dengue. The mean lymphocytes counts were found 899.6±156.0 /µL in severe dengue and 1016.2±168.3 /µL in non-severe dengue. Neutrophil counts were 1255.8±298.7/µL in severe dengue and 1278.9±287.4/µL in non-severe dengue.

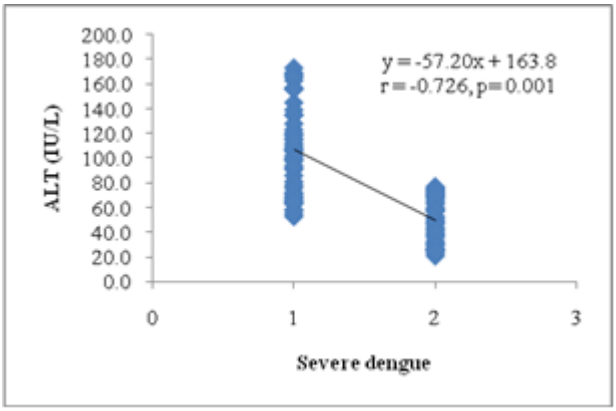

Fig-1. Significant negative correlation (r= -0.726; p=0.001) between ALT and severe dengue

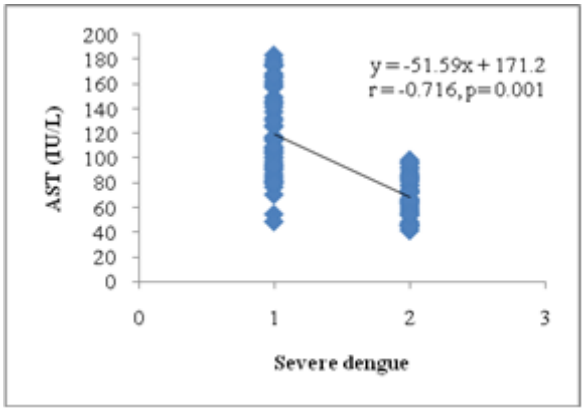

Fig-2. Significant negative correlation (r= -0.716; p=0.001) between AST and severe dengue

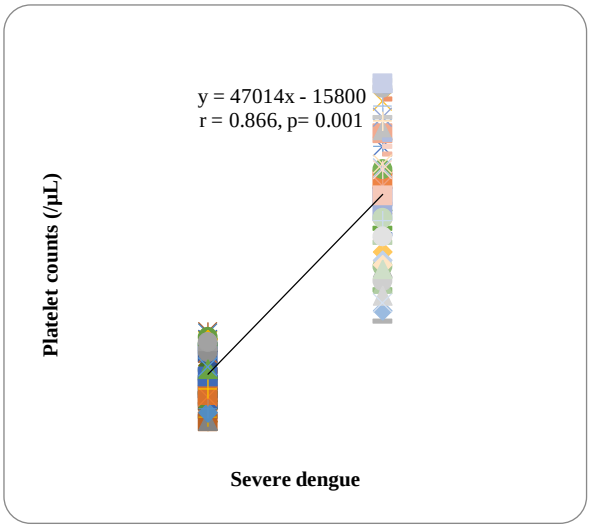

Fig-3 Significant positive correlation (r= 0.866; p=0.001) between platelet counts and severe dengue

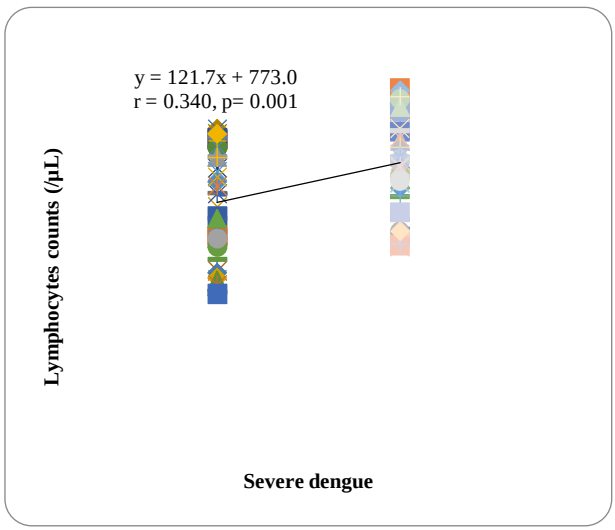

Fig-4 Significant positive correlation (r= 0.340; p=0.001) between lymphocytes counts and severe dengue

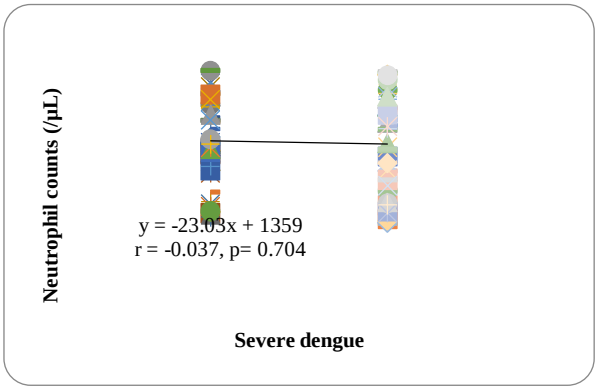

Fig-5 Not significant negative correlation (r= -0.037; p=0.704) between neutrophil counts and severe dengue

IV. Discussion

In this study we observed that male was predominant over female. The mean age was 31.4(±14.2) in severe dengue group and 32.8 (±13.9) in non-severe group. Mean hospital stay was 5.3(±1.2) days in severe group and 5.0(±1.0) in non-severe group. Age, sex and duration of hospital stay were not statistically significant (p>0.05) between two groups. Similar observation was found in Paranavitane et al7 study. They reported patients with severe dengue presented to hospital on an average of day 5.04 (SD ± 1.12) of illness and those with non-severe dengue presented on an average of day 5.01(± 1.11) of illness.

In the present study we observed that the mean AST was 132.7±38.7 IUL in severe dengue and 71.9±20.1 IUL in non-severe dengue. The mean ALT was found 108.7±34.5 IUL in severe dengue and 43.2±18.6 IUL in non-severe dengue. The mean platelet counts were found 29389.1±7298.4 /µL in severe dengue and 69728.0±18747.1 /µL in non-severe dengue. The mean lymphocytes counts were found 899.6±156.0 /µL in severe dengue and 1016.2±168.3 /µL in non-severe dengue. Liao et al.8 reported that the mean AST was 101.97±55.51 IUL in severe dengue and 32.95±15.88 IUL in non-severe dengue and mean ALT was 162.97±55.51 IUL in severe dengue and 44.36±18.63 IUL in non-severe dengue and the mean platelet counts were found 63.7±28.3 109/L in severe dengue and 111.7±33.3 109/L in non-severe dengue. Which were statistically significant (p<0.05) between two groups. In the study by Jakribettu et al.9 Hb, TC, neutrophils, lymphocytes, eosinophils, monocytes and platelets were statistically significant (p<0.05). Many investigations about the usefulness of liver transaminase levels, platelet counts and other clinical and laboratory parameters in predicting severe dengue, shown that none of these parameters can be used alone to predict severe dengue.10-13 Two other studies it was observed that the dengue patients had a mean total leucocyte count of 4,984 ± 3,082 as compared to 7,926 ± 2,760 of dengue negative cases where neutrophils counts were 49 ± 19, as compared to 63 ± 15 of dengue negative cases.14-15

In present study we observed the non-significant negative correlation (r= -0.037; p=0.704) between neutrophil counts and severe dengue. Paranavitane et al.7 reported progressive leucopenia and rapid decline in platelet counts is known to precede plasma leakage16 and others have shown that leucopenia and especially lymphopenia was associated with severe dengue.17-19 Our study found that the more the rise of ALT and AST, the more worsening the condition of dengue patients and the same observation was found with declining counts of platelets and lymphocytes.

V. Conclusion

To assess the severity of dengue patients both ALT and AST level, especially two and half times the normal can be considered as marker of severe dengue infection. Similarly, thrombocytopenia especially platelet count less than 30000/ µL and lymphopenia bears the same significance. Presence of multiple positive parameters are more significant than single one. Still there is a need to study these parameters in the context of assessment of severity of dengue viral infection.

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