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Correlation of D-dimer levels with Severity of Dengue Infection

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ABSTRACT
Background: Dengue is disease of worldwide importance and more so in the tropical and subtropical regions. The natural history of the disease is variable with a spectrum encompassing a range from an acute febrile illness to the dreaded refractory shock and massive bleeding which carry a high mortality. Mechanisms of bleeding in dengue infection are vasculopathy, thrombocytopenia, coagulopathy and dissiminated intravascular coagulopathy (DIC).
Objective: To correlate D-dimer (DD) levels and the clinical outcomes in dengue virus infection.
Method: Patients admitted with suspected dengue infection at Hitech Medical College and Hospital were
included. D-dimer (DD) was measured in asequential manner during the course of hospital admission using whole blood rapid semiquantitative test (SimpliRed). Diagnosis of dengue infection was confirmed by serological investigation. Dengue severity was classified using WHO criteria.
Results: 41 dengue patients, 22 females and 19 males were recruited in the study. The mean age was 39.68 years. There were 12 (29.3 %) cases of dengue fever (DF) and 29 (70.7 %) cases of dengue hemorrhagic fever (DHF). DD was more significantly present in the DHF group (87 %) than in the DF group (13%) (P<0.03). The sensitivity and specificity of DD in predicting severe dengue infection (DHF) were 90% and 67 %, respectively. Higher levels of DD in all stages of dengue infection was demonstrated. It correlated with the disease severity.
Conclusion: This study finds significant correlation between levels of DD as measured by semiquantitative assay and the severity of disease in all stages in patients of dengue virus infection.

I. INTRODUCTION

In recent decades, Dengue has emerged as a major infectious disease in the tropics and subtropical regions of the world. It is reported that 2.5 billion people are at risk for dengue with up to 100 million dengue virus infections each year and more than 25,000 deaths reported annually. The natural history of the disease is variable with a spectrum encompassing a range from an acute febrile illness to the dreaded refractory shock and massive bleeding, which carry a high mortality rate . In dengue virus infections, the pathogenesis of hemorrhage is not yet fully understood. Mechanisms of bleeding in dengue infection are vasculopathy, thrombocytopenia, coagulopathy and dissiminated intravascular coagulopathy (DIC). Decreased fibrinogen, increased fibrinogen degradation products (FDP), prolonged partial thromboplastin time, low levels of coagulation factors VIII and XII, plasminogen, prothrombin, and antiplasmin maybe seen signifying abnormality in the coagulation and fibrinolysis pathways during infection [1, 2]. The presence of the D-dimer (DD) indicated activation of the coagulation system resulting from the destruction of cross-linked fibrin and reflects clot formation and lysis [3, 4]. Therefore the D-dimer, being a specific marker for cross-linked fibrin, can be assayed as a marker for DIC [5-8].

It was hypothesized that DD status would correlate with dengue severity. Therefore, a prospective descriptive study was undertaken to determine the relationship between D-dimer and the clinical outcome in dengue infection.

II. MATERIALS AND METHODS

This study was performed with the approval of the Ethics Committee of Hitech Medical College and Hospital, Bhubaneswar and with consent of the participating patients. The study group consisted of 41 patients (19-65 years of age) with suspected dengue infection admitted to Hitech Medical College and Hospital, Bhubaneswar during October 2023 to November 2023.

Sample collection

D-dimer was measured during the course of illness in a sequential manner using whole blood as sample in a rapid semiquantitation system

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(SimpliRed; AGEN Biomedical Limited; Brisbane, Australia). The SimpliRed D-dimer Test was a rapid quantitative invitro test for the detection of cross-linked fibrin degradation products in whole blood. A fingerstick sample was suitable for testing. In the presence of DD, this assay leads to RBC agglutination. For each sample, at least 10 ml of blood was placed in a test well and mixed with reagent for 2 minutes. Absence of DD was confirmed by a negative control if there was no agglutination. Incase of agglutination, its intensity was graded as either weak (1+) or strong (2+) according to the manufacturer specifications. Intensity of reaction was directly proportional to the levels of DD. The lower limit of detection was 120 ng/ml, which is the upper limit of normal for DD.

Diagnosis of dengue infection

The diagnosis was confirmed using an enzyme linked immunosorbent assay (ELISA) for IgM and IgG antibodies to dengue virus. Serum anti dengue IgM above 40 units or 2-fold increase of serum anti IgG with absolute level above 100 units confirmed the diagnosis. Dengue severity was classified according to the WHO criteria.

Statistical analysis

Continuous data were reported as means. Categorical variables were compared using chisquare test except for when the value was small. In those instances we used the Fisher's Exact Test. Analyses were performed using SPSS for Windows. All reported P values are two-tailed, and value <0.05 were considered statistically significant.

III. RESULTS

Forty-one patients with serological confirmed dengue infection were studied. The age of patients ranged between 19-65 years with a mean age of 39.68 years. Twenty-two patients (54 %) were females and 19 patients (46 %) were males. There were 12 (29.3 %) cases of dengue fever (DF) and 29 (70.7 %) cases of dengue hemorrhagic fever (DHF) with one case each of grades III and IV, and, rest of grades I and II.

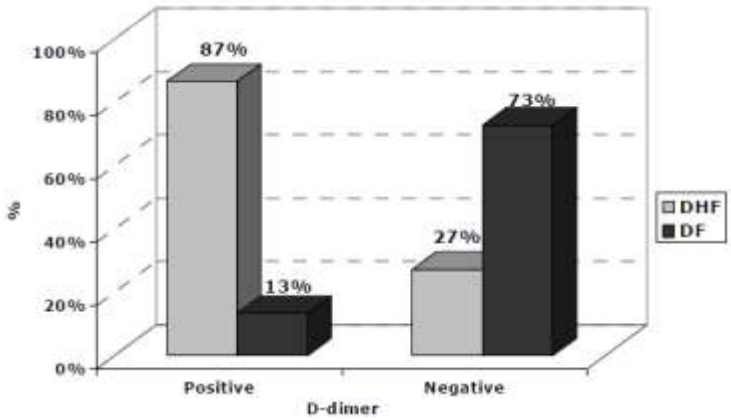

Fig. 1 D-dimer results in DHF in comparison to DF (P-value <0.001)

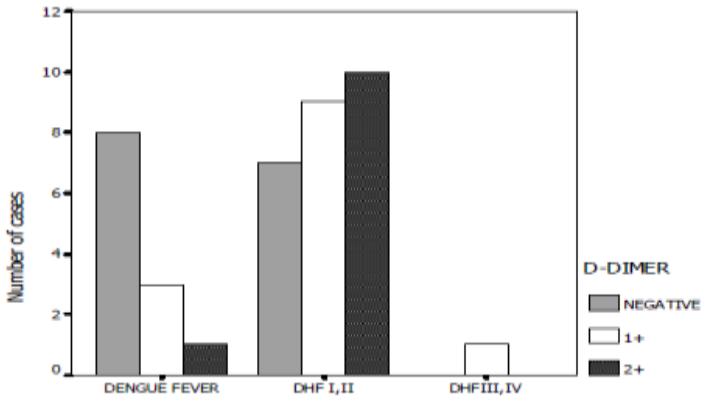

Fig. 2 D-dimer results in DF in comparison to DHF grade I, II and DHF grade III, IV (febrile stage) (P-value: 0.023)

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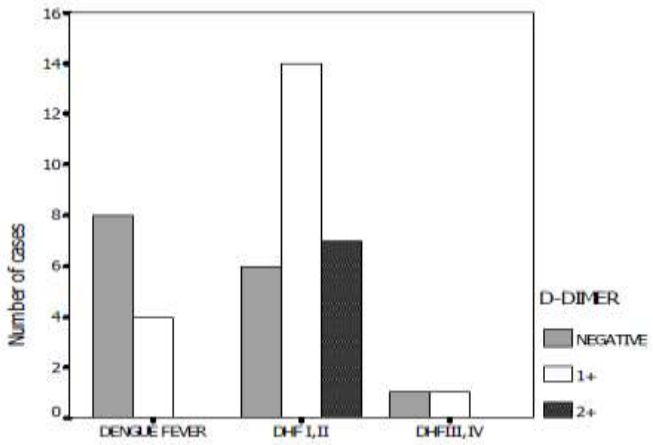

Fig. 3 D-dimer results in DF in comparison to DHF grade I, II and DHF grade III, IV (toxic stage) (P-value: 0.038)

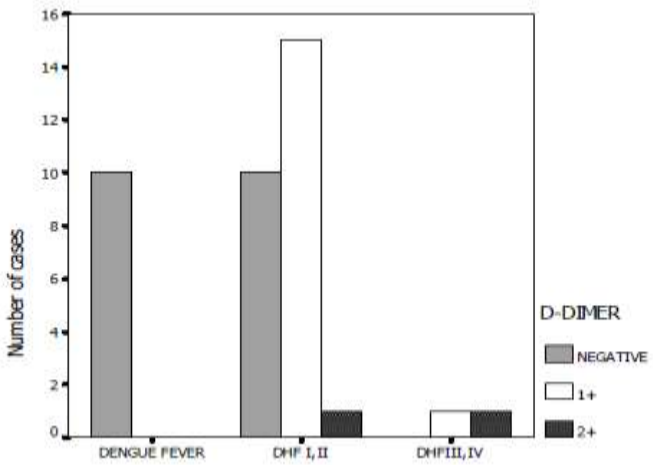

Fig. 4 D-dimer results in DF in comparison to DHF grade I, II and grade III, IV (covalescent stage) (P-value < 0.01)

Figure 1 shows a comparion of the DD levels in DF and DHF. DD was found to be positive in 26 (87 %) DHF and 4 (13 %) DF patients. This showed that DD was more significantly present in the DHF group (87 %) than DF group (13 %) (P-value <0.01). For prediction of DHF, the specificity and sensitivity of DD was found to be 67 % and 90 %, respectively. The positive and negative predictive values of DD were 87 % and 72 %, respectively. Correlation of DD levels with dengue severity in all stages of the disease is presented in **Figs. 2-4**. Weak (1+) and strong (2+) intensity of DD was mostly found in DHF grade I and II. Dengue severity was found to be positively correlated with DD levels in all stages of disease namely febrile, toxic and convalescent stages (P-value <0.05). **Fig. 2** D-dimer results in DF in comparison to DHF grade I, II and DHF grade III, IV (febrile stage) (P-value: 0.023).

IV. DISCUSSION

The pathogenesis of hemorrhage in dengue virus infection is not fully understood, several studies showed abnormal hemostasis including DIC in DHF [9, 10]. The presence of the D-dimer (DD) indicated activation of the coagulation system resulting from the destruction of cross-linked fibrin and reflects clot formation and lysis [3, 4]; and therefore the DD assay being a specific marker of cross-linked fibrin is used as a marker for DIC [5-8]. This study showed that the D-dimer levels in DHF were significantly higher as compared to DF patients. Sensitivity of DD in predicting DHF was 90%. DD was also found to be positively correlated with dengue severity in all stages of disease namely febrile, toxic and convalescent (P-value <0.05). The presence of increased levels of DD in the febrile stage may be used as a predictor for the possible progression to severity. It will help the clinician in prognostication

and prediction of severity even before the toxic stage has set in and thus proper monitoring and expectant management can be instituted. It is also quite easy to perform the semiquatitative DD assay at the bedside because of it's simplicity and non-invasiveness. If DD is detected in the acute febrile stage, it suggests that there is early DIC with activation of fibrinolytic system which may even occur before the onset of severe hemorrhagic manifestations in patients with dengue virus infection. Future studies on this basis maybe considered inorder to qualify any need of early intervention. The shortcoming of this study is the limited number of patients and the absence of DHF grade III and IV patients. A larger study may further substantiate the results of the present study.

V. CONCLUSION

To conclude, this study finds significant correlation between levels of DD as measured by semiquantitative assay and the severity of disease in all stages in patients of dengue virus infection.

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