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TO FIND OUT THE CORRELATION OF THROMBOCYTOPENIA WITH D-DIMER AN INDICATOR OF SEVERITY OF DENGUE HEMORRHAGIC FEVER

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ABSTRACT
Dengue is a mosquito-borne infectious disease, rising health problem worldwide and there is a need to find out a marker associated with severity of disease. Study was therefore designed to find out the correlation of thrombocytopenia with D-Dimer an Indicator of severity of dengue hemorrhagic fever. The study included 81 confirmed patients of dengue hemorrhagic fever, more than 18 years old who agreed to participate in study and fulfill inclusion criteria i.e. blood culture negative and IgM or NS-1 positive. The DHF patients divided in four grades according to WHO criteria. These were 55 males and 26 females. Values of platelet counts and D-Dimer were estimated. There were 53 (65.4%) cases belong to DHF-I, 20 (24.6%) cases belong to DHF-II, and 8 (9.88%) cases belong to DHF-III, and DHF-IV. 55 (67.9%) were male and 26(32.1%) were female. It is observed that 42% patients have an age of ≤ 30, 28.4% with age range 31-45 years, 29.6% with age range 46-60 years. Majority of patients (29.6%) had their platelet counts below 25000, 23.5% between 25000 and 50000. A dominant majority (72.8%) had their D dimer levels in between 201–700. Positive significant correlation (P<0.001) was observed between platelet count and D-dimer with r value 0.53. The DHF-I group had D dimer levels for all of the cases below 700. Study concluded that increased level of D-Dimer Levels along with thrombocytopenia may be an indicator of severity of dengue hemorrhagic fever.

KEYWORDS: Dengue hemorrhagic fever, thrombocytopenia, D-dimer.

INTRODUCTION
Dengue is a mosquito-borne infectious disease, rising health problem worldwide. Dengue virus (DENV) is a single positive-stranded RNA virus belong to the family Flaviviridae transmitted by Aedes mosquito. DENV is consists of four genetically different serotypes: DENV serotype 1 to DENV serotype 4. Each serotype is capable of inducing dengue haemorrhagic fever (DHF) as well as dengue shock syndrome (DSS).[1] The virus exist as co-infections both in vector and host and use its cellular parts for its replication.[2] Infection by DENV is either shows no symptoms of or may cause symptoms that vary from mild dengue fever to serious illness including dengue haemorrhagic fever and dengue shock syndrome.[3]

It has taken an endemic form in more than 100 countries of South East Asia, Africa, America, Eastern Mediterranean regions and Western Pacific.[4] Pakistan is in the middle of dengue renaissance; more than 15,000 cases were recorded in Lahore alone, which is potentially disastrous for the country's health-care system and showing a higher mortality as a result of massive internal bleeding or irreversible dengue shock syndrome.[5]

D-Dimer is used as a primary screening test to identify patients who have symptoms indicate venous thromboembolism as it is a indicator of fibrinolysis.[6] Level of D-dimer is raised in number of conditions. Physiologic reason of increased level of D-dimer is old age, pregnancy, postoperative period, trauma and cigarette smoking.[7] Pathologic causes for D-dimer were mainly thrombosis which may be venous or arterial thrombosis.[8] There are few cases where deep vein thrombosis is directly related with dengue fever.[9,10] Thrombotic problems associated with deep vein thrombosis (DVT), mesenteric vein thrombosis and pulmonary thromboembolism are reported in dengue patients.[11]

DHF is related with increased permeability of vessels and plasma leakage results in thrombocytopenia and loss of clotting factors. This may lead to bleeding at first due to thrombocytopenia and afterward due to disseminated intravascular coagulation (DIC), often as incurable event.

D-dimer of blood is a sensitive indicator for early DIC. The mechanisms underlying the bleeding in DHF are numerous. These are thrombopathy, vasculopathy and DIC. Thrombopathy is associated with thrombocytopenia and platelet dysfunction.[12,13]

Study was designed to find out the corelation between the severity of thrombocytopenia and D-dimer as an indicator of dengue hemorrhagic Fever.

MATERIAL AND METHODS

This was a cross sectional analytical study. The study was carried out in the Department of Pathology and Medicine at Shaikh Zayed Postgraduate Medical Institute, Lahore. The study included 81 confirmed patients of dengue hemorrhagic fever, more than 18 years old who agreed to participate in study and fulfill inclusion criteria i.e. blood culture negative and IgM or NS-1 positive. The DHF patients divided in four grades according to WHO criteria. These were 55 males and 26 females. Platelet counts were estimated using Hematological Analyzer (Sysmex model No 1800). D-Dimer was estimated by Latex Agglutination Slide Test.[14]

Statistical Analysis

All the collected data were entered in to the computer and analyzed through a SPSS computer software version 20. Numerical data was presented as mean and standard deviation like age, platelet count and D-dimer. The Chi-square test was applied to compare the respective plasma levels of different perimeters like platelet count and D-dimer among different grades of DHF. P-value <0.05 was taken as significant.

RESULTS

81 patients of dengue hemorrhagic fever were included in the study. There were 53 (65.4%) cases belong to DHF-I, 20 (24.6%) cases belong to DHF-II, and 8 (9.88%) cases belong to DHF-III, and DHF-IV. 55 (67.9%) were male and 26(32.1%) were female (data not shown).

Age distribution of cases suffering dengue hemorrhagic fever was tabulated as table 1. It is observed that 42% patietns have an age of ≤ 30, 28.4% with age range 31-45 years, 29.6% with age range 46-60 years.

Majority (29.6%) had their platelet counts below 25000, 23.5% between 25000 and 50000. There were only 17 (2.0%) of patients who had platelet counts above 75000 yet below normal levels (Table 2). A dominant majority (72.8%) had their D dimer levels between 201–700, only 2.5% had below 200 and 3.7% had levels above 1200 (Table 3). A positive significant correlation (P<0.001) was observed between platelet count and D-dimer with r value 0.53 (Fig).

The DHF-I group had D dimer levels for all of the cases below 700, in DHF-II 40.0% had between 200 and 700, and 60% had between 700 and 1200. In DHF-III 62.5% had between 700 and 1200 and remaining 37.5% had above 1200. The difference was highly significant between three groups with p-value <0.001 (Table 4).

Table 1: Age distribution of cases suffering dengue hemorrhagic fever (n=81).

Age (years)	No. of patients	Percentage
≤ 30	34	42.0
31 – 45	23	28.4
46 – 60	24	29.6
Total	**81**	**100.0**

Table 2: Distribution of platelet counts for cases suffering dengue hemorrhagic fever (n=81).

Platelet counts	No. of patients	Percentage
≤ 25000	24	29.6
25001 - 50000	19	23.5
50001 - 75000	21	25.9
75001+	17	21.0
Total	81	100.0

Table 3: Distribution of D Dimer level for cases suffering dengue hemorrhagic fever (n=81).

D Dimer	No. of patients	Percentage
≤ 200	2	2.5
201 – 700	59	72.8
701 - 1200	17	21.0
1201+	3	3.7
Total	81	100.0

Table 4: Comparison of D dimer status among three grades of dengue fever (n=81).

D Dimer	DHF							
	DHF-I		DHF-II		DHF-III & IV		Total	
	N	%	n	%	n	%	n	%
≤ 200	2	3.8	0	0.0	0	0.0	2	2.5
201 - 700	51	96.2	8	40.0	0	0.0	59	72.8
701 - 1200	0	0.0	12	60.0	5	62.5	17	21.0
1201+	0	0.0	0	0.0	3	37.5	3	3.7
Total	53	100.0	20	100.0	8	100.0	81	100.0

Chi-square = 70.52, p-value <0.001.

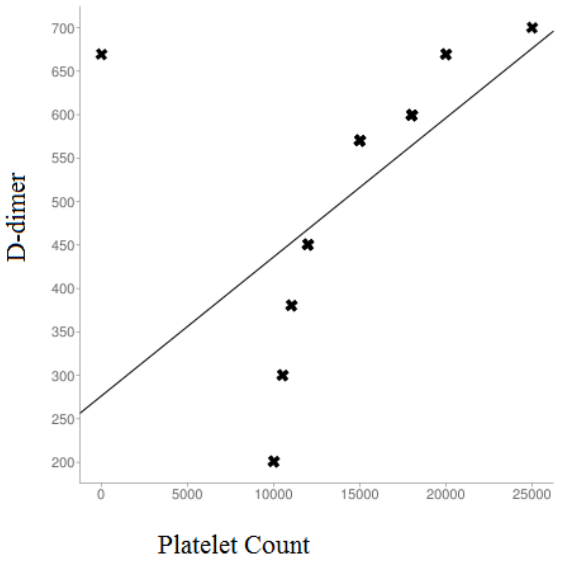

Fig: Positive significant correlation between D-dimer and Platelet count (r = 0.53).

DISCUSSION

Dengue infection is a febrile illness with thrombocytopenia, dengue haemorrhagic fever and dengue shock syndrome. The main problem of dengue Fever is associated with DHF and DSS. Thrombocytosis is related with high risk of thrombotic complications[15] (Agarwal 2016).

Present study observed that 42% of dengue patients with in the age of <30 years. Our study is in line with a study who reported that 33% of dengue cases were in the age group of 21-30 years.[16] It is reported that high prevalence of Dengue infection in children relative to adults is due to the increase vascular permeability. This may increase the overall incidence of dengue.[17]

In our study the platelet counts distribution of dengue patients showed that in majority of patients the range of platelet count was <25,000 to 75,000. It is proposed that after infected endothelial cell dengue virus combine with platelets and damage these platelets. It may be a main reason of thrombocytopenia in dengue fever.[18]

According to our study, 65.4% (53 cases) patients belong to class DHF1, 24.6% (20 cases) belong to DHF11 and 9.88% (08 cases) belong to DHF 111 and DHF 1V. Our study is in accord with a study who also observed that most cases of DHF were DHF grade I and II, and small number of DHF patients grade III,IV.[19] However, our study is in contrast from a study who found the 40.9% of dengue patients belong to grade1 DHF, 43% of dengue patients belong to grade 11 and 10.8% of dengue patients belong to grade 111 & 1V.[20] It is reported that variations in dengue genotypes, dengue virus strains as well as structural differences of dengue viruses may correlate with pathogenesis and have an important role in disease severity.[21,22]

Several mechanisms may be involved in the pathogenesis of bleeding as a result of dengue infection which may include vasculopathy, thrombocytopenia, coagulopathy and dissiminated intravascular coagulopathy. A group of workers found that detection of D-dimer in the febrile stage of dengue infection may be helpful in predicting the clinical course of the disease and in predicting dengue severity before the patients enter into toxic stage.[19]

An increased level of plasma D-dimer with severe thrombocytopenia in patients with DHF suggests that activation of fibrinolytic system and thrombocytopenia may be related with pathogenesis of DHF. Studies found that D-dimer indicated the activation of the coagulation system resulting from the destruction of cross-linked fibrin and reflects clot formation and lysis and it may relate with dengue severity.[23,24] It is suggested by Marchi that dengue virus infection alters the balance of coagulation-fibrinolysis toward hyperfibrinolysis as polymerization of fibrinogen into fibrin may results the release of D-dimer.[25,26]

CONCLUSION

A positive correlation between thrombocytopenia and increased level of D-Dimer Levels may be an indicator of severity of dengue hemorrhagic fever.

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