

Association of Abnormal Coagulation Tests in Dengue Fever with Clinical Outcomes of The Patients

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ABSTRACT

Objective: To assess the coagulation test abnormalities (prothrombin time, activated partial thromboplastin time and fibrin degradation products) in dengue fever patients and its impact on clinical outcomes of the patient.

Study Design: Cross-sectional study.

Place and Duration of Study: Hematology Department, Pakistan Naval Ship Shifa Hospital, Karachi Pakistan, from Aug 2016 to Feb 2017.

Methodology: A total of 135, serologically proven positive dengue-infected IgM cases, based on enzyme-linked immunosorbent assay, were included in the study. Prothrombin time, activated partial thromboplastin time, and fibrin degradation products levels were measured on STA Compact Max® (STAGO) and SysmexCA-1500. Clinical Outcomes of the patient were noted.

Results: At the time of admission, elevated prothrombin time was observed in 8(5.6%) cases and remained high at the time of discharge (p -value 0.008). Elevated activated partial thromboplastin time was observed in 57 (42.2%) cases at admission whereas, at discharge, it was observed in 56 (41.5%) cases. Increased level (>5) of fibrin degradation products was seen in 30 (22.2%) cases while at the time of discharge increased level of fibrin degradation products was observed in 25 (18.5%) cases (p -value 0.007). Out of 135 patients, mortality was observed in two cases and the remaining 133 (98.52%) survived and were discharged.

Conclusion: In conclusion, prothrombin time, activated partial thromboplastin time, and fibrin degradation products can be labeled as early predictors of disease severity and their derangements are associated with clinical outcome in dengue infection.

Keywords: Activated partial thromboplastin time, Dengue, Fibrin degradation products, Prothrombin time.

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INTRODUCTION

Dengue fever also known as break-bone fever or bone crusher disease, was named by Dr. Benjamin Rush Philadelphia in 1789. Dengue is one of the most common mosquito-borne infections in tropical and subtropical regions around the world. Approximately 2.5 billion population is at risk.¹ Overall, 100 million dengue cases are reported globally each year and overall 2.5% of those affected may die.² The attack rate is 40-90% among susceptible individuals as observed during epidemics.³ During the 20th century, the disease was considered sporadic. However, a dramatic change in the pattern has occurred and currently, it ranks as the most common cause of mosquito-borne disease.⁴ Over the last 50 years, increasing geographic expansion to new countries has caused raised prevalence of dengue fever to more than 30 fold and in the present decade, from urban to a rural setting.⁵ Dengue

fever is now endemic in Southeast Asia, Western Pacific, Africa, the Americas, and the Eastern Mediterranean regions.⁶ The most seriously affected regions are South-east Asia and the Western Pacific.⁶

The haematological system is one of the main targets of dengue fever. Common symptoms are fever, bone pain, vomiting, bleeding tendencies and erythematous rash. Many factors play part in the pathogenesis of haematological manifestations including thrombocytopenia and coagulopathy that result in derangement of activated partial thromboplastin time (APTT) and prothrombin time (PT). The coagulation cascade is composed of intrinsic and extrinsic pathways that lead to the activation of different coagulation factors. There is mild to moderately prolonged partial thromboplastin time and prothrombin time.⁷ Coagulopathy is found in most of the dengue haemorrhagic fever cases and activated partial thromboplastin time is more frequently abnormal than prothrombin time.^{8,9} Coagulopathy usually lasts a few days in most cases during the course of the disease. There is also a decreased fibrinogen level and increased fibrinogen degradation

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products.

It was reported that non-structural protein (NS1) binds to prothrombin and thrombin. It then inhibits its activation that may contribute to APTT prolongation within the first week of presentation of symptoms when antibodies are not yet developed.¹⁰

Studies have been done in Asian countries to find predictors of clinical outcome in dengue virus infection but our study was unique as we conducted serial changes in the coagulation profile and its effect on clinical outcome.⁹ Pakistan is an under resource country and the majority of people have financial constraints. Early detection of predictors of disease severity will help in the early prompt treatment and reduces the long hospital stays. Unnecessary use of blood components transfusion can be avoided with regular monitoring of these parameters as these parameters become normalize gradually. This study gave recent trends of dengue in our population. This study highlighted the role of coagulation and fibrinolysis in the genesis of complications in dengue infection.

METHODOLOGY

This cross-sectional study was conducted at the Hematology Department, Pakistan Naval Ship Shifa Hospital, Karachi, from August 2016 to February 2017. The sample size was calculated by using the WHO sample size calculator with 95% confidence level and 7% absolute precision. By taking proportion of prothrombin time 9 (22%), the estimated sample size was 135. The non-probability consecutive sampling technique was used. Verbal informed consent was taken from all the patients or their guardian before enrolment in the study. Ethical clearance for the study was obtained from the Ethical Review Board of PNS Shifa Hospital. The diagnosis was based on enzyme-linked immunosorbent assay (ELISA).

Inclusion Criteria: All the serologically proven positive dengue-infected IgM cases, of either gender (age 2-65 years) were included in the study.

Exclusion Criteria: Patients with the history of bleeding disorders, chronic liver disease, acute febrile illnesses with negative dengue IgM serology and those on anti-coagulation medications were excluded from the study.

Blood sample of patients was collected into the sodium citrate (blue-top) tube on the admission day and on the day of discharge (in survivors). If the patient expired during a hospital stay, the latest reports were considered and proforma were filled accordingly.

Citrated blood samples were centrifuged at 3,500 rpm for 10 minutes within 4 hours of blood collection. PT, APTT, and FDP levels were measured by STA Compact Max® (STAGO) and Sysmex CA-1500 with commercially available reagents. Abnormal results were repeated manually.

The normal ranges for PT and APTT were 11-16 seconds and 28-36 seconds respectively, whereas FDPs normal value was <5 µg/ml. For this study, the value above these ranges was considered abnormal. Patients were followed up during their stay in the hospital for clinical progression. Clinical Outcomes of the patients included patient survival after illness, the complete recovery, trend towards normalization of prothrombin time, activated partial thromboplastin time, fibrin degradation products without any intervention i.e blood component (red cell, platelet, fresh frozen plasma) transfusion, or patient expiry.

Statistical Package for Social Science (SPSS-23) was used to analyze the data. Frequency and percentages were computed for categorical observations like gender, PT, APTT, FDPs, and clinical outcome. Mean and standard deviation were computed for age, PT, APTT, and FDPs (at the time of admission). Pearson chi-square test was used to check the association of studied parameters with clinical outcome. The *p*-value of ≤0.05 was considered statistically significant.

RESULTS

A total of 135 serological proven dengue-infected cases were included. The age of patients' ranged from 2-63 years with the mean of 29.12 ± 13.11 years.

At the time of admission, elevated prothrombin time (PT) was observed in 8 (5.6%) cases and remain elevated at the time of discharge. Elevated APTT was observed in fifty seven (42.2%) cases at the admission whereas, at discharge, it was observed in 56 (41.5%) cases. Increased level of fibrin degradation products was in thirty (22.2%) cases while at the time of discharge increased level was observed in 25 (18.5%) cases as shown in Table-I. There was a significant association between raised PT and FDPs level with clinical outcome (*p*-value 0.008 and 0.007 respectively) as shown in Table-II.

Out of 135 patients, mortality was observed in two (1.48%) cases and the remaining one hundred and thirty three (98.52%) survived and were discharged. The average hospital stay of the patients was 5.55 ± 2.97 days (95% CI: 5.04 to 6.05).

Table-I: Coagulation abnormality in dengue patients (n=135).

Haemostatic Manifestations		At the time of Admission n (%)	On Discharge n (%)
Prothrombin Time			
11-16 second	Normal	127 (94.1%)	127 (94.1%)
>16 second	Abnormal	8 (5.9%)	8 (5.9%)
Activated partial thromboplastin time			
28-36 second	Normal	78 (57.8%)	79 (58.5%)
>36 second	Abnormal	57 (42.2%)	56 (41.5%)
Fibrin Degradation Products			
<5	Normal	105 (77.8%)	110 (81.5%)
≥ 5	Abnormal	30 (22.2%)	25 (18.5%)

Table-II: Association of coagulation abnormality in dengue patients with clinical outcome (n=135).

Haemostatic Manifestations in Dengue		On Discharge		p-value
		Survive	Expired	
Prothrombin Time				
11-16 second	Normal	127 (100%)	-	0.008
>16 second	Abnormal	6 (75%)	2 (25%)	
Activated partial thromboplastin time				
28-36 second	Normal	79 (100%)	-	0.097
>36 second	Abnormal	54 (96.4%)	2 (3.6%)	
Fibrin Degradation Products				
<5	Normal	110 (100%)	-	0.007
≥ 5	Abnormal	23 (92%)	2 (8%)	

Both expired patients were males and their age was above 30 years (40 years and 58 years). They expired within 3-5 days of their hospital stay. Both the patients had raised PT, APTT, FDPs levels. This showed a significant association of raised PT and FDPs with the clinical outcome of the patient.

DISCUSSION

In the past, studies have been conducted on a comparatively small number of patients who had a severe form of the disease, sometimes with complications and secondary involvement of multiple organ systems, that confound the results.^{8,11} There have been scarce data focusing on the changes in coagulation parameters during the period of hospital stay as the haemostatic changes develop gradually.

It has been reported that there is molecular mimicry between dengue virus (DENV) proteins with coagulation and fibrinolysis factors that may generate autoantibody production and can inhibit hemostasis.¹² Generally, antibodies are produced a week after getting the infection and there are direct pathogenic roles of DENV or its products, especially in the early stage of DENV infection.¹³ These autoantibodies can cross-react to prothrombin, thrombin, plasmin, and factors VII, VIII, IX, X.¹⁴

In our study, there was male predominance and the mean age of patients was 29.12 ± 13.11 years. Findings were consistent with previous studies by Yashaswini *et al*, and Sharif *et al*, which showed that adults were more affected.^{15,16} We observed that young males were more vulnerable to get the infection, as there are greater chances of exposure to mosquito bites because of their outdoor activities (occupational and recreational). This finding was similar to an earlier study conducted by Jain *et al*, in North India, who reported majority (67.5%) were males.¹⁷ It was also observed by Gajera *et al*, that there was male predominance and male: female ratio was 2:118.

Deranged coagulation profile, in particular, raised APTT was the most significant finding. In most of the patients, it remained raised at the time of discharge. As consistent with previous studies, raised APTT was observed in 57.8% of the patients. Studies conducted by Yashaswini *et al*, Balakrishnan *et al*, and Bashir *et al*, showed there were raised APTT in 38%, 33.3%, and 72.7% of patients respectively.^{15,19,20} APTT prolongation in dengue fever is possibly due to impaired coagulation factors synthesis that are involved in intrinsic pathway.²¹

In contrast to APTT, the PT was found to be raised (moderately) in 5.9% of the cases, as we also observed in a study conducted by Nagaram *et al*, that 12.64% of cases have raised PT level.²² It remained elevated at the time of discharge. In other words, we can say the extrinsic pathway is less commonly affected in dengue infection but has a greater impact on clinical outcome. It was found that the p-value was 0.008 indicating that there was a significant association between raised PT and poor clinical outcome. Laoprasopwattana also suggested PT has the most significant role as a predictor of severe bleeding.²³ It can be justified as factor VII has the shortest half-life and in turn, it affects the extrinsic pathway easily and cause severe disease.

We also noticed fibrin degradation products level (>5) was raised in 22.2% of the cases. Our study found that there was a significant relation between FDPs and poor clinical outcome (p-value=0.007). In 2015, Bashir *et al*, highlighted the fibrinolysis in dengue infection and found that 86.4% of the cases have raised FDPs level.²⁴ There are several possibilities in the derangement of APTT and FDPs. This may be due to consumptive coagulopathy or secondary to acute derangement of liver function that affects coagulation factors synthesis.⁵ The study conducted by Jain *et al*, observed

that clinical outcome in severe disease/dengue haemorrhagic fever is devastating, the patients who died with laboratory proven disseminated intravascular coagulation (increased levels of FDPs) and complications of shock have 100% mortality.¹⁷

In our study, the majority of the patients' normalization of coagulopathy occurred gradually over a few weeks. Patients who had more deranged coagulopathy were those with a longer hospital stay. Most of the patients had a hospital stay of 2-5 days.

Fortunately, the mortality rate was around 1.48% that was much less than published in earlier studies (by Riaz *et al*, and Bandaru *et al*) with a mortality rate of 4.6% and 3.8% respectively.^{9,25} The low mortality rate in our study might be because of the early detection and management of dengue fever in these patients. Both the patients had secondary disseminated intravascular coagulation and expired due to cardiopulmonary arrest despite ample supportive care and proper hydration. The worth noting finding in our study was that the expired patients had normal platelet count and bleeding time but PT, APTT and FDPs levels were raised. These blood tests can be marked as predictors in dengue fever with poor prognosis. Early detection and timely management can prevent mortality in dengue infection.

These simple and cheaper coagulation tests should be routinely done in every patient with dengue fever for timely management and prevention of complications. In the future, these parameters may be useful in the development of scoring systems and guidelines regarding dengue infection severity and to predict outcome early in the course of the disease. This study strongly emphasizes the significance of the blood coagulation profile testing of the patient, which includes PT, APTT, FDPs levels and if markedly abnormal then follow up of the cases, as they would be manifested as serious complications and even death. This study will be helpful to clinicians for detecting the disease severity earlier as these markers are correlated with clinical outcome.

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RECOMMENDATIONS

Future studies on this subject should be done on other parameters such as on protein C and S, fibrinogen levels. In addition, serial changes in haemostatic parameters during

illness and follow up of these patients should be done in the future studies.

CONCLUSION

In conclusion, PT, APTT, and FDPs can be labeled as early predictors of disease severity and their derangements are associated with clinical outcome in dengue infection.

Conflict of Interest: None.

Authors' Contribution

ZI: Conception design data collection, NJ: Data analysis, interpretation, TZ: Drafting the article, FZ: Final Approval of write, ST: Manuscript review, AS: Data interpretation.

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