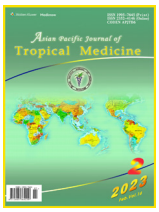

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Coagulation abnormalities and their relationship with bleeding manifestations in patients with dengue-A single center observational study

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ABSTRACT

Objective: To evaluate coagulation abnormalities and their relationship with bleeding manifestations among patients with dengue.

Methods: This observational study was conducted on 292 adult dengue patients who were admitted to a tertiary care hospital of Western India from July 2021 to June 2022. Coagulation tests including prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (*a*PTT), fibrinogen, and *D*-dimer were performed. Patients were monitored for bleeding manifestations.

Results: Coagulation abnormalities were reported in 42.8% of the patients. Overall, prolonged *a*PTT was the most common coagulation abnormality (40.8%), followed by low fibrinogen (38.7%), raised *D*-dimer (31.2%), raised INR (26.0%) and prolonged PT (19.2%). Bleeding manifestations were present in 19.9% patients. PT, INR, *a*PTT and *D*-dimer levels were significantly higher ($P<0.01$) and fibrinogen level was significantly lower ($P<0.001$) in patients with bleeding compared to patients without bleeding. Patients with bleeding had a significantly higher rate of all coagulation abnormalities than patients without bleeding ($P<0.01$).

Conclusions: Patients with bleeding showed a significantly higher frequency of coagulation abnormalities compared to patients without bleeding. Patients with dengue should be assessed for coagulation abnormalities.

KEYWORDS: Dengue; Coagulation abnormalities; Coagulation parameters; Prothrombin time; Activated partial thromboplastin time; Bleeding manifestations

1. Introduction

Dengue is currently the most important mosquito-borne viral disease in the tropical and sub-tropical areas of the world[1]. It is caused by one of the four antigenically and genetically distinct, but closely related, dengue virus (DENV) serotypes (DENV-1 to DENV-4)[2], and *Aedes aegypti* is the primary vector of transmission[3]. According to estimates of the World Health Organization (WHO), the incidence of DENV infection has increased dramatically around the world in recent years, with the number of reported cases increased over 2-fold within a decade from 2.4 million in 2010 to 5.2 million in 2019[3].

Significance

Coagulation abnormalities and their relationship with bleeding manifestations in patients with dengue were evaluated. This study demonstrated a significantly higher frequency of coagulation abnormalities among dengue patients with bleeding compared to patients without bleeding. Hence, patients with dengue, particularly dengue with warning signs and severe dengue, should be assessed for coagulation abnormalities. Early detection and correction of coagulation abnormalities even before the patient develops significant bleeding after carefully considering risk and benefit of blood components replacement therapy can reduce the rate of morbidity and mortality associated with dengue.

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Dengue is usually a self-limiting febrile illness. However, in some cases, patients may develop the life-threatening severe dengue characterized by the presence of abnormal hemostatic activities demonstrated by bleeding manifestations, increased capillary permeability that leads to plasma leakage into interstitial space resulting into circulatory failure known as dengue shock syndrome (DSS)[4–7]. DSS is associated with a high mortality rate[8].

The underlying mechanisms responsible for bleeding in dengue infection remain poorly understood. Present evidence suggests that hemorrhage in dengue may be a consequence of multiple mechanisms that include endothelium defect, platelet dysfunction, thrombocytopenia, coagulopathy and hyperfibrinolysis. The severity depends upon the clinical manifestations of the patients, such as circulatory disturbance[9–11].

Various studies have reported significant abnormalities in the coagulation system in dengue. Prolonged activated partial thromboplastin time (*a*PTT) and prothrombin time (PT), raised international normalized ratio (INR), and decreased fibrinogen level have been observed in several studies[12–14], but fibrin degradation products (FDPs) and *D*-dimer levels are not elevated to a degree consistent with classical disseminated intravascular coagulation[10,15,16]. Increased morbidity and mortality in dengue patients is associated with deranged coagulation profile resulting into hemorrhagic manifestations[17]. Early detection and correction of coagulation abnormalities after carefully considering risk and benefit of blood components replacement therapy may be helpful to reduce further complications in dengue patients.

Although coagulation abnormalities in patients with dengue have been investigated in many parts of the world, limited studies were conducted across the globe including India that evaluated the relationship between deranged coagulation profile and bleeding manifestations in dengue. Moreover, results of previous studies are inconsistent in some of the coagulation parameters such as fibrinogen and FDPs level[16]. Therefore, this study was carried out to evaluate the coagulation abnormalities and their relationship with bleeding manifestations among adult dengue patients who were admitted at a large tertiary care hospital of the Western India. This study will provide great help to guide appropriate management, thereby reducing the rate of morbidity and mortality associated with dengue.

2. Materials and methods

2.1. Study design and study population

This prospective observational study was conducted in the Department of Medicine at Mathura Das Mathur Hospital, Jodhpur, Rajasthan, India over a period of 1 year from July 2021 to June 2022. A total of 292 adult patients (age range of 18-70 years) of either sex admitted with fever and thrombocytopenia (platelet count $<150 \times 10^9$/L) who were diagnosed with dengue (seropositive for dengue NS1 antigen and/or IgM antibody) were included in this study. Patients with history of pre-existing bleeding diathesis or hemostatic disease, on anticoagulant or antiplatelet therapy, alcoholics, with chronic liver disorders, pregnant and menstruating women, on hormonal contraceptives, and with other underlying medical condition known to cause coagulation abnormalities such as chronic renal disease, malignancies, autoimmune diseases, and other systemic diseases were excluded from the study (Figure 1).

2.2. Study procedure

Ethical approval (SNMC/IEC/IIP/2021/049) for this study was obtained from the Institutional Ethics Committee. A written informed consent was taken from all patients prior to their enrolment in the study. All patients enrolled in the study were subjected to detailed clinical history including bleeding manifestations and thorough clinical examination with special emphasis on bleeding sites. All patients were monitored daily during stay in the hospital for bleeding manifestations. Laboratory investigations including complete blood count (CBC), PT with INR, *a*PTT, fibrinogen,

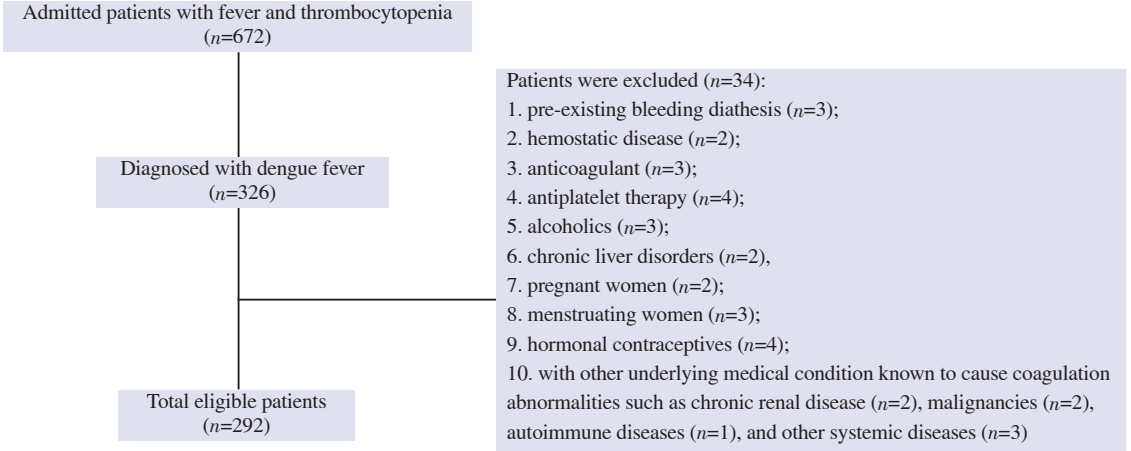

Figure 1. Flowchart of the study samples selection process.

D-dimer, liver function tests including serum bilirubin, serum alanine transaminase (ALT), serum aspartate transaminase (AST), serum albumin and globulin, and renal function tests including blood urea and serum creatinine were performed in each study subject on every alternate day from the day of admission till the patient entered into the convalescence phase. CBC was performed from ethylene diamine tetra acetic acid-anticoagulated peripheral venous blood samples using an identical fully automated hematology analyzer (Sysmex 5-part fully automated analyzer xs-800i) within 4 hours of venipuncture. Coagulation parameters (PT, INR, *a*PTT, fibrinogen and *D*-dimer) measurement was performed from citrate-anticoagulated blood using automated coagulation analyzer (Stago). Biochemistry tests were done from serum samples using auto analyzer. Only the worst value of all the parameters among all values obtained right from the day of admission till the patient entered into the convalescence phase, irrespective of transfusion status, was selected and analyzed.

2.3. Operational definitions

For this study, *a*PTT was considered prolonged if it was >40 seconds, PT was considered prolonged if it was >14 seconds, INR was considered raised if it was >1.2, *D*-dimer was considered raised if it was >0.5 μg/mL, and fibrinogen was defined as low if it was 200 mg/dL. Coagulation abnormalities were considered when any one or more of these parameters were deranged. Severe thrombocytopenia was defined as platelet count ≤20 × 10^9/L.

Based on the WHO dengue guidelines 2009, patients were classified as dengue without warning signs, dengue with warning signs and severe dengue[18]. Dengue with warning signs was defined when one of the following symptoms or signs were present during the critical phase: severe abdominal pain, persistent vomiting, rapid breathing, bleeding gums or nose, fatigue, restlessness, liver enlargement and blood in vomit or stool. They were also grouped into dengue with bleeding and dengue without bleeding manifestations to compare the laboratory parameters and coagulation abnormalities.

2.4. Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) software version 21.0 for Windows (Version 21.0 for Windows; SPSS Inc., Chicago, Illinois, USA). The distribution of the data was checked using the Kolmogorov-Smirnov test and found to be normally distributed. Continuous variables were expressed as mean ± standard deviation (SD). Categorical variables were indicated as frequency (*n*) and percentage (%). The significance of difference between patients with bleeding and without bleeding was analyzed using Student's *t*-test for continuous variables and Pearson's *Chi*-squared (χ^2) test or Fisher's exact test for categorical values as appropriate. A *P*-value <0.05 was considered statistically significant.

3. Results

A total of 292 patients were included in this study. Among these, 256 patients were seropositive for either dengue NS1 antigen alone or for both dengue NS1 antigen and IgM antibody, whereas the remaining 36 patients were seropositive for dengue IgM antibody alone. Of these, 189 (64.7%) patients were of dengue without

Table 1. Hematological, biochemical and coagulation parameters in patients with dengue.

Parameters (mean ± SD)	Normal reference values	All cases (*n*=292)	Without bleeding (*n*=234)	With bleeding (*n*=58)	*P*-value
Hematological parameters					
Hemoglobin (g/dL)	12.0-16.0	13.44 ± 1.74	13.46 ± 1.81	13.23 ± 1.63	0.378
Hematocrit (%)	36.0-50.0	40.41 ± 5.96	40.69 ± 6.78	39.73 ± 5.51	0.318
TLC (×10^9/L)	4.00-11.00	4.85 ± 2.54	4.78 ± 2.65	5.32 ± 2.09	0.149
Neutrophils (%)	38.0-70.0	44.58 ± 15.45	43.17 ± 17.84	46.79 ± 15.17	0.156
Lymphocytes (%)	20.0-45.0	44.91 ± 17.31	45.35 ± 17.42	43.49 ± 15.16	0.456
Platelet count (×10^9/L)	150-450	27.90 ± 22.14	29.80 ± 12.54	24.30 ± 13.24	0.003
Biochemical parameters					
Blood urea (mg/dL)	17-43	20.16 ± 5.44	20.05 ± 5.25	21.48 ± 8.41	0.106
Serum creatinine (mg/dL)	0.6-1.2	0.63 ± 0.19	0.62 ± 0.17	0.70 ± 0.59	0.073
Total bilirubin (mg/dL)	0-1.0	1.07 ± 5.58	1.03 ± 5.47	2.06 ± 10.10	0.291
AST (IU/L)	0-37	134.58 ± 60.76	129.59 ± 47.54	155.56 ± 93.19	0.003
ALT (IU/L)	0-40	112.31 ± 120.09	109.52 ± 114.25	161.57 ± 123.02	0.002
Total protein (g/dL)	6.2-8.0	6.55 ± 0.74	6.57 ± 0.66	6.31 ± 1.34	0.035
Albumin (g/dL)	3.5-5.0	3.68 ± 0.39	3.72 ± 0.34	3.54 ± 0.63	0.003
Coagulation parameters					
PT (sec)	≤14	13.91 ± 1.31	13.88 ± 1.27	14.58 ± 2.11	0.001
INR	≤1.2	1.14 ± 0.18	1.10 ± 0.17	1.20 ± 0.25	<0.001
*a*PTT (sec)	≤40	39.07 ± 4.39	38.90 ± 3.47	40.79 ± 5.24	0.001
Fibrinogen (mg/dL)	>200	219.78 ± 54.43	221.75 ± 51.84	198.98 ± 47.88	0.003
D-dimer (μg/mL)	≤0.5	0.719 ± 2.226	0.456 ± 1.638	1.667 ± 5.721	0.005

TLC: total leucocyte count, AST: aspartate transaminase, ALT: alanine transaminase, PT: prothrombin time, INR: international normalized ratio, *a*PTT: activated partial thromboplastin time.

warning signs, 71 (24.3%) of dengue with warning signs, and 32 (11.0%) of severe dengue. The age of patients ranged from 18 to 70 years with a mean age ± SD of (29.6 ± 14.82) years.

The mean values of hematological, biochemical and coagulation parameters among dengue patients are shown in Table 1. The mean platelet count showed a statistically significant difference (P=0.003) between patients with bleeding and without bleeding. However, there was no statistically significant difference in the mean value of hemoglobin (P=0.378), hematocrit (P=0.318), total leukocyte count (P=0.149), neutrophils (P=0.156), and lymphocytes (P=0.456) between patients with bleeding and without bleeding. The result also showed a significantly higher mean value of AST (P=0.003) and ALT (P=0.002) in patients with bleeding compared to patients without bleeding. There was a statistically significant difference between patients with bleeding and without bleeding with regard to the mean value of PT (P=0.001), INR (P<0.001), *a*PTT (P=0.001), fibrinogen (P=0.003), and *D*-dimer (P=0.005).

Distribution of different types of coagulation abnormalities among dengue patients is shown in Table 2. Coagulation abnormalities were reported in 125 (42.8%) patients. Fifty (17.1%) patients reported both prolonged *a*PTT and prolonged PT, while 69 (23.6%) patients reported the isolated prolonged *a*PTT and 6 (2.1%) patients reported the isolated prolonged PT. Patients with bleeding had a significantly higher proportion of all abnormal coagulation test results compared to patients without bleeding.

Table 2. Distribution of different coagulation abnormalities among dengue patients (n=292).

Coagulation abnormalities	All cases (n=292)	Without bleeding (n=234)	With bleeding (n=58)	P-value
PT (sec)				
≤14	236 (80.8)	199 (85.0)	37 (63.8)	0.001
>14	56 (19.2)	35 (15.0)	21 (36.2)	
INR				
≤1.2	216 (74)	182 (77.8)	34 (58.6)	0.004
>1.2	76 (26)	52 (22.2)	24 (41.4)	
*a*PTT (sec)				
≤40	173 (59.2)	151 (64.5)	22 (37.9)	0.0003
>40	119 (40.8)	83 (35.5)	36 (62.1)	
Fibrinogen (mg/dL)				
≤200	113 (38.7)	78 (33.3)	35 (60.3)	0.0003
>200	179 (61.3)	156 (66.7)	23 (39.7)	
D-dimer (μg/mL)				
≤0.5	201 (68.8)	170 (72.6)	31 (53.4)	0.007
>0.5	91 (31.2)	64 (27.4)	27 (46.6)	
Platelet count ($\times10^9$/L)				
≤20	152 (52.1)	114 (48.7)	38 (65.5)	0.0273
>20	140 (47.9)	120 (51.3)	20 (34.5)	

PT: prothrombin time, INR: international normalized ratio, *a*PTT: activated partial thromboplastin time.

Distribution of different types of bleeding manifestations among dengue patients is depicted in Table 3. Bleeding manifestations were present in 58 (19.9%) patients, and 24 (8.2%) had more than one bleeding manifestations. Of these, 8 (13.8%) patients were of dengue without warning signs, 26 (44.8%) of dengue with warning signs, and 24 (41.4%) of severe dengue. Among patients with bleeding manifestations, 38 (65.5%) required transfusion of blood products (platelets, fresh frozen plasma or both), whereas 20 (34.5%) patients did not require transfusion. Overall, platelets were transfused to 97 (33.2%) patients based on departmental protocol (who had bleeding manifestations and/or platelet count <10 $\times10^9$/L) as well as due to family concerns. Among these 76 (78.4%) patients had deranged coagulation parameters, whereas 21 (21.6%) had normal coagulation parameters. In patients with normal coagulation parameters, platelets were transfused owing to bleeding manifestations and/or severe thrombocytopenia (platelet count <10 $\times10^9$/L). Fresh frozen plasma transfusion was done in 24 (8.2%) patients, all of them had coagulation abnormalities.

Table 3. Distribution of bleeding manifestations in patients with dengue (n=292).

Bleeding manifestations	n (%)
Epistaxis	14 (4.8)
Hematemesis	8 (2.7)
Hemoptysis	3 (1.0)
Gum bleeding	23 (7.9)
Hematuria	6 (2.1)
Melena	12 (4.1)
Purpura/petechiae/eccymoses	47 (16.1)
Palatal hemorrhage*	21 (7.2)
Conjunctival hemorrhage	13 (4.5)
Total	58 (19.9)

*Petechial or purpuric lesions over the palatal mucosal surface.

4. Discussion

Our study reported coagulation abnormalities in 42.8% of patients. Prolonged *a*PTT was the most common coagulation abnormality present in 40.8% of patients. There is a wide variation of reported prevalence of prolonged *a*PTT (12.0%-89.7%) among various previous studies conducted in different countries[9,16,19–30]. The prevalence of prolonged PT in our study was 19.2%. The reported prevalence of prolonged PT also varies widely (1.5%-49.0%) among different studies across the globe[9,16,19–21,23,24,26–31]. No abnormality of extrinsic pathway was found as indicated by normal PT in a study by Kannan *et al*[25]. These differences could reflect the variations in sample size, age group of study participants, cut-off criteria of *a*PTT and PT used for their prolongation, and stage and severity of the disease during sample collection.

The precise mechanism for dengue-associated coagulation abnormalities is not known. Various pathogenetic mechanisms have been suggested. The *a*PTT and PT are indicators of the intrinsic and extrinsic pathways of the coagulation system, respectively.

Prolongation of PT and *a*PTT might be caused either by the downregulation of synthesis of specific factors or by an increase in consumption of specific factors. The non-structural protein 1 of the dengue virus can bind both to thrombin and prothrombin. Binding to thrombin does not make any changes, whereas prothrombin activation is inhibited. This can explain changes in *a*PTT occur early before antibodies are formed[13]. APTT prolongation in the dengue patients is caused by a lack of intrinsic pathway probably due to impaired synthesis of coagulation factor[4]. Reductions in the levels of specific coagulation factors such as Ⅱ, Ⅴ, Ⅶ, Ⅷ, Ⅸ, Ⅹ, antithrombin, and alpha-2 antiplasmin have been reported in dengue hemorrhagic fever (DHF) patients[16]. IL-6 plays its role in down-regulating the synthesis of factor Ⅻ, the first factor to initiate the intrinsic pathway of coagulation[25].

The prevalence of low fibrinogen in our study was 38.7%, consistent with finding of a study by Kumari *et al*. which showed low fibrinogen in 39% of all dengue patients[27]. Similarly, increased rates of consumption of fibrinogen were demonstrated in patients who had DHF both with and without shock or hemostatic abnormalities in a study that used 125 I-fibrinogen[12]. The various pathophysiological mechanisms implicated in low fibrinogen in dengue patients are poorly understood. However, a possible mechanism is that dengue infection primarily activates fibrinolysis in the absence of a thrombotic stimulus, degrading fibrinogen directly and prompting secondary activation of various procoagulant homeostatic mechanisms[32].

The other coagulation parameter assessed in this study was *D*-dimer. The frequency of raised *D*-dimer in our study was 31.2%, in agreement with a previous study done by Kumari *et al*. which showed raised *D*-dimer in 31% of all dengue patients[27]. Another study by Setrkraising *et al.* also showed similar results[33]. The exact cause for the rise of *D*-dimer has not been determined, but some studies suggested that disseminated intravascular coagulation play a role in the pathogenesis of coagulopathy in dengue.

Bleeding manifestations are among the important clinical features of dengue. In the current study, the prevalence of bleeding manifestations among dengue patients was 19.9%, comparable to the findings of other studies[9,16]. Kulasinghe *et al*. observed a lower prevalence (8.2%) of bleeding manifestations[10], whereas a higher prevalence (26.0%-28.1%) was found in other studies[22,25,31]. This variation could be due to inclusion of patients with different grades of severity of dengue and varying age in these studies which could have an effect on bleeding manifestations. Children experience more prolonged *a*PTT than other age groups[34]. A study conducted by Hamond *et al*. showed that infants and children from 4 to 6 years of age were significantly more likely than adults to develop DHF/DSS or manifestations of severe clinical illness[35]. The presence of shock and hemorrhagic manifestations during infancy can be attributed to passively transferred circulating antibodies from the mother[36].

Given the reported coagulation abnormalities in 42.8% of participants and bleeding in only 19.9% of participants, our study showed a discrepancy between coagulation abnormalities and bleeding manifestations in dengue. Study showed that bleeding manifestations occurred only in 30.4% of patients with coagulation abnormalities, whereas 69.6% of patients did not have bleeding. Natural anticoagulants such as protein C, protein S, and antithrombin Ⅲ are significantly reduced during the early disease stages due to leakage of these proteins through the vascular endothelium[15]. Tissue factor, thrombomodulin, and plasminogen activator inhibitor-1 (PAI-1) levels are elevated due to endothelial, platelet, and/or monocyte activation and may be a secondary response to direct activation of fibrinolysis by the dengue virus. In most patients with dengue, these combined effects do not result in derangements severe enough to cause clinically significant bleeding[15,16].

Our study compared the coagulation parameters between patients with bleeding and without bleeding. We showed that patients with bleeding had a significantly higher proportion of all abnormal coagulation test results compared to patients without bleeding. Very few studies have been carried out previously which demonstrated this relationship. Prolonged *a*PTT values and its correlation with bleeding manifestations in dengue is supported by Kulasinghe S *et al*, Kannan *et al*. and Budastra *et al*[10,25,31]. PT was a less reliable predictor of bleeding in previous studies. However, Kulasinghe *et al.* also showed that a raised INR was significantly associated ($P<0.01$) with bleeding[10]. In contrast to our findings, Hassan *et al*. did not show any statistically significant association with the risk of bleeding manifestations even though almost all the coagulation parameters were deranged to an extent[16].

In the current study, 76 (60.8%) patients with coagulation abnormalities received platelet transfusion; however, bleeding manifestations were seen in only 38 (30.4%) patients. This implies that half of the patients received platelet transfusion despite the absence of bleeding manifestation in view of severe thrombocytopenia and suspecting impending severe bleeding manifestations as well as due to family concerns. Twenty-one (12.6%) patients with normal coagulation parameters also received platelet transfusion in view of bleeding manifestation due to causes other than coagulopathy such as severe thrombocytopenia.

Thus, this study emphasized on the significance of coagulation abnormalities in dengue patients. As various studies have shown that bleeding manifestations in dengue indicate severe dengue which is associated with a high morbidity and mortality rate, patients with dengue, particularly dengue with warning signs and severe dengue, should be assessed for various coagulation abnormalities. Early detection and correction of coagulation abnormalities even before onset of significant bleeding after carefully considering risk and

benefit of blood components replacement therapy will prevent the serious and life-threatening complications among dengue patients. This will help in reducing morbidity and mortality in these patients.

The present study had some important limitations to be considered. The major limitation of this study was that only the worst value of all the coagulation parameters were selected and analyzed. Only using the worst value of all parameters is indeed not helpful. Coagulation parameters were not analyzed separately in febrile phase, critical phase and convalescent phase. Therefore, the exact pattern of coagulation abnormalities prevalent in patients with dengue at different stages may not have been observed in the study. Another limitation of this study was that owing to the relatively small sample size, we could not able to compare various coagulation abnormalities among three categories of dengue patients i.e. patients without bleeding manifestations, patients with bleeding manifestations that did not require transfusion of blood products, and patients with bleeding manifestations requiring transfusion of blood products. Finally, although menorrhagia or hypermenorrhea is a one of the bleeding manifestations of dengue, we excluded patients with this manifestation as it could occur due to causes other than dengue and it was difficult to distinguish other etiologies of hypermenorrhea from dengue.

In conclusion, our study demonstrated that there was a high prevalence of coagulation abnormalities among dengue patients. Prolonged *a*PTT was the most common coagulation abnormality, others being prolonged PT, raised INR, low fibrinogen, and raised *D*-dimer. In addition, patients with bleeding showed a significantly more deranged all coagulation parameters compared with patients without bleeding. Moreover, frequency of all coagulation abnormalities observed were significantly higher in patients with bleeding compared to patients without bleeding.

We recommend that patients with dengue, particularly dengue with warning signs and severe dengue, should be assessed for various coagulation abnormalities. Early detection and correction of coagulation abnormalities even before the patient develops significant bleeding after carefully considering risk and benefit of blood components replacement therapy can reduce the rate of morbidity and mortality associated with dengue. Further large scale studies are needed to substantiate our findings as well to correlate coagulation abnormalities with clinical outcomes in dengue patients.

Conflict of interest statement

The authors declare that there is no conflict of interest.

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Authors' contributions

GRP, IT and MN substantially contributed to the research design; MN and RK performed the study acquisition; GRP and IT analyzed the data and wrote the paper; GRP, IT, MN and RK revised it critically, and approved the final manuscript.

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