

Predictors of Clinically Significant Bleeding in Thrombocytopenic Dengue Patients Admitted to Intensive Care Unit: A Retrospective Study

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ABSTRACT

Background: Recognition of clinically significant bleeding (CSB) is vital for effective management of dengue patients. The primary objective was to identify the predictors of CSB among dengue patients and to formulate a simple scoring system. The secondary objective was to compare the grades of bleeding and severity of thrombocytopenia.

Materials and methods: We conducted a retrospective study of adults aged above 18 years with dengue, admitted to the intensive care unit (ICU) of a tertiary care hospital in South India from 2015 to 2021. Demographic, clinical, and laboratory variables on admission were collected. The association of clinically significant bleeding with the above parameters was assessed by univariate and multivariate analysis.

Results: A total of 9,817 dengue cases were hospitalized during the study period. A total of 120 patients with thrombocytopenia (<100000 cells/mm³) were admitted to the ICU and of them 38 (31.6%) had CSB. On univariate analysis fever, sequential organ function assessment (SOFA) score, elevated activated partial thromboplastin time (aPTT), and altered sensorium were significantly associated with CSB. The multivariate model identified SOFA score [adjusted odds ratio (aOR): 1.52; 95% confidence interval (CI): 1.11–2.08], temperature $>38.3^{\circ}\text{C}$ (aOR: 2.71; 95% CI: 1.1–6.47) and elevated aPTT >40 seconds (aOR: 4.66; 95% CI: 1.42–15.3) as independent risk factors. A clinical predictive score was developed incorporating these three parameters. The performance of the score identified by the receiver operating characteristic (ROC) curve [area under the curve (AUC): 0.81; 95% CI: 0.73–0.91] demonstrated a sensitivity of 81% and specificity of 77%.

Conclusion: This study revealed that temperature above 38.3°C , elevated aPTT, and an increase in SOFA score were identified as independent risk factors for CSB. A clinical predictive score derived from these variables can identify patients likely to develop CSB.

Keywords: Clinically significant bleeding, Dengue, India, Intensive care unit, Predictors.

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HIGHLIGHTS

Patients with dengue and thrombocytopenia are often admitted to the intensive care unit (ICU) due to fear of bleeding. This study unveiled elevated activated partial thromboplastin time (aPTT), increase in sequential organ function assessment (SOFA) score, and fever as independent predictors of clinically significant bleeding (CSB). A scoring system of three variables aids in risk stratification and efficient use of valuable medical resources.

INTRODUCTION

Acute dengue infection remains a significant global health burden, characterized by periodic epidemic outbreaks that result in substantial mortality and morbidity. The incidence of dengue has increased with about half of the world's population now at risk.¹ Over 80% are generally mild and asymptomatic presentation.¹ In India, dengue remains endemic with multiple outbreaks involving all four serotypes of the dengue viruses over the years.² The case fatality rate among laboratory-confirmed patients is 2.6% [95% confidence interval (CI): 2–3.4].³ Although dengue shock syndrome is a major contributor to mortality, bleeding in thrombocytopenic dengue patients is a serious concern.⁴ The frequency of major bleeding in dengue patients is around 32%.⁵ Thrombocytopenia is commonly observed in many cases, but literature shows that platelet transfusion in adult dengue patients with a platelet count below $20000/\text{mm}^3$ without bleeding manifestations did not reduce

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bleeding or expedite platelet recovery.² However, this practice causes potential harm by slowing the recovery of platelet count to $>50000/\text{mm}^3$ and increasing the length of hospitalization.⁶ Factors causing severe bleeding in thrombocytopenic dengue patients are not fully understood.

Early identification of dengue patients with thrombocytopenia who could develop severe bleeding can form a crucial group for close observation and timely intervention, potentially reducing mortality rates. While many studies have focused on risk factors

associated with the progression of general dengue severity^{7–11} or factors linked to death,^{12,13} only a few studies have investigated risk factors for bleeding in adults. Furthermore, clinical studies show substantial variability in terms of predictors of severe bleeding.^{14–17} Understanding the predictors of severe bleeding in this specific patient population not only enhances our comprehension of the disease pathophysiology but also aids in risk stratification, clinical decision-making, and targeted therapeutic interventions. This retrospective study aims to bridge existing knowledge gaps by systematically examining the potential predictors associated with CSB in thrombocytopenic dengue patients who required ICU admission.

OBJECTIVES

The study was designed to identify the frequency of CSB, the associated risk factors (predictors) in thrombocytopenic dengue patients admitted to ICU and to develop a scoring system with the risk factors. The secondary objective was to compare severity of thrombocytopenia and the grades of bleeding among the study participants.

MATERIALS AND METHODS

Study Design and Brief Procedure

This retrospective study was conducted in the department of critical care medicine of a tertiary care university hospital Southern India. Data were extracted from the case records of thrombocytopenic dengue patients, admitted to the adult ICU from 2015 to 2021.

After obtaining Institutional Ethics Committee's (IEC) clearance, detailed information of dengue cases, encompassing both clinical and laboratory parameters was retrieved from the case files and laboratory system, utilizing their unique identity number. Comprehensive data from hospital's system and case reports were assessed to compile information of all variables relevant to the study. Based on the inclusion and exclusion criteria, the eligible patients were finally identified.

Throughout the study period, admission to ICU was based on several criteria including serum hematocrit (HCT), $\geq 50\%$; blood pressure, $\leq 90/60$ mm Hg; postural drop in systolic blood pressure, >20 mm Hg; pulse, ≥ 100 /minute; clinical bleeding, patients with early warning signs (such as severe abdominal pain and persistent vomiting), elderly patient with underlying conditions (e.g., diabetes, hypertension, heart failure, stroke, cancer), and thrombocytopenia. A standardized dengue care path was used to manage patients.¹⁸

Study Participants and Duration

All clinically identified dengue patients who were above 18 years of age were included in the study after laboratory confirmation. Laboratory confirmed dengue infection was determined by a positive test for non-structural protein 1 (NS1) antigen-based enzyme-linked immunosorbent assay (ELISA) test (indicating primary dengue) and/or immunoglobulin G/immunoglobulin M (IgG/IgM) ratio ≥ 1.1 (ELISA) with IgG cut-off above 3 (indicating secondary dengue), accompanied by a platelet count of less than 100000 cells/mm³. Patients having coinfections with other pathogens and thrombocytopenia due to other causes (such as those with idiopathic thrombocytopenic purpura, chronic liver

disease, and hematological malignancies) were excluded from the study. Data were retrieved for a period of 7 years from 2015 to 2021.

Study Variables

The study focused on the outcome variable of CSB. Clinically significant bleeding was defined as the presence of any of the following events during the hospital stay: Hematemesis, melena, fresh rectal bleeding, menorrhagia, hemoptysis, macroscopic hematuria, intracranial bleeding or a clinical drop in hemoglobin that necessitated whole blood or packed red cell transfusion.¹⁹ These events were recorded and categorized as either present or absent.

Demographic, clinical, and laboratory variables on admission such as applied physiology and chronic health evaluation (APACHE), sequential organ failure assessment (SOFA) score, heart rate (HR), cumulative fluid balance, HCT, serum bicarbonate, WBC (white blood cells), platelet count, aPTT, blood urea nitrogen (BUN), absolute neutrophil count (ANC), absolute lymphocyte count (ALC), aspartate transaminase (AST), and alanine transferase (ALT) were collected from patients' case files (Table 1). In cases where bleeding was present, it was categorized into four grades as follows:²⁰

Grade I: Includes petechiae, purpura, ecchymosis, and subconjunctival hemorrhage.

Grade II: Mild mucosal bleed—gum, vagina, epistaxis, hematoma in deep tissue, joint bleed, melena, hematochezia, hematemesis, and no drop in hemoglobin or hypotension.

Grade III: Any bleeding necessitating transfusion, hemodynamic instability (>30 mm Hg) or 30% decrease in systolic blood pressure.

Grade IV: Involves fatal bleeding from any source, intracranial bleed, retinal bleed causing visual impairment, hypotension >50 mm/Hg fall or $>50\%$ decrease in systolic blood pressure requiring packed red blood cell (PRBC) transfusion.

Statistical Analysis

The data were entered in Microsoft Office Excel and analyzed using Statistical Package for the Social Sciences (SPSS) software, version 24.0. Univariate associations of the collected parameters with CSB were identified by appropriate parametric and non-parametric tests. Independent sample *t*-test was used for normally distributed variables (mean). Chi-square test was used for categorical variables (median) those were not normal distributed. Mann–Whitney *U* test was used for comparison of median of discrete variables without normal distribution. A step wise multivariate logistic regression was used to identify independent predictors of CSB. Furthermore, a predictive score was developed from the variables and the performance of the score was assessed using receiver operating characteristic (ROC) curve. The cut-off was estimated, the sensitivity and specificity was determined to evaluate the predictive accuracy of the model.

RESULTS

During the study period, overall, 9,817 patients were admitted with the diagnosis of dengue and of them 160 patients had dengue with thrombocytopenia (<100000 cells/mm³). Of these 160 patients, 40 were excluded from the study either due to the

Table 1: Demographic, clinical, and bleeding characteristics of study participants (N = 120)

S. No.	Characteristics	CSB		p-value
		Yes (N = 38)	No (N = 82)	
1	Age in years (mean ± SD)	34.4 ± 15.3	31.9 ± 14.3	0.41
2	Gender n (%)			
	Male	21 (29.6)	50 (70.4)	0.55
	Female	17 (34.7)	32 (65.3)	
3	APACHE (median, IQR)	3 (1–3)	3 (1–7)	0.21
4	SOFA (mean ± SD)	4.26 ± 1.1	3.38 ± 1.7	0.005*
5	Symptoms n (%)			
	Temperature >38.3°C/101°F	18 (47.4)	20 (52.6)	0.01*
	Myalgia	4 (40)	6 (60)	0.55
	Headache	4 (57.1)	3 (42.9)	0.13
	Backpain	8 (32)	17 (68)	0.96
	Eye pain	11 (34.4)	21 (65.6)	0.70
	Nausea/vomiting	10 (25.6)	29 (74.4)	0.32
	Abdominal pain/tenderness	16 (26.2)	45 (73.8)	0.19
	Rash	4 (100)	0	0.003*
6	Secondary dengue n (%)			
	Yes	14 (31.1)	31 (68.9)	0.91
	No	24 (32)	51 (68)	
7	Vasopressor n (%)	1 (16.7)	5 (83.3)	0.42
8	Altered mental status n (%)	2 (100)	0	0.04*
9	Cardiac involvement n (%)	2 (66.7)	1 (33.3)	0.19
10	Length of hospital stay in days (mean ± SD)	5.4 ± 2.7	5.7 ± 2.8	0.66
11	Length of ICU stay in days (mean ± SD)	3.4 ± 1.8	3.5 ± 1.8	0.75
12	Duration of platelet recovery in days (mean ± SD)	3.8 ± 1.5	3.7 ± 1.8	0.78

*Statistically significant (p < 0.05); SD, standard deviation

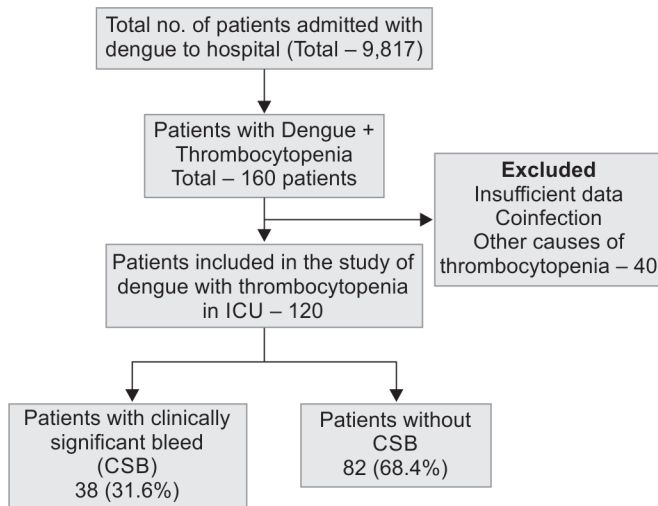


Fig. 1: Flow diagram showing the selection of patients into the study

presence of coinfection, other reasons of thrombocytopenia (28 patients) or had insufficient study variables (12 patients) captured or combination of these. Finally, 120 eligible patients were included in the study and of them 38 (31.6%) had CSB (Fig. 1).

A comparative analysis of the demographic, clinical and laboratory characteristics of the included patients was conducted to assess the difference between those who experienced CSB and those who did not (Tables 1 and 2). Univariate Chi-square analysis revealed that several parameters, including SOFA score, presentation with a temperature exceeding 38.3°C, altered sensorium and elevated aPTT (>40 seconds) were associated with higher risk of developing CSB (p = 0.005). Only two patients had altered sensorium. Even though there was a statistical significance, it was not considered clinically significant. Since altered sensorium was attributed to intracranial bleed and dengue encephalitis in these two patients. It was observed that patients across various platelet count categories at presentation and the lowest platelet count category had no association with the grades of bleeding (Figs 2 and 3).

To identify independent predictors, multivariate logistic regression model was employed in a step-wise manner incorporating study variables that were significant on univariate analysis. Ultimately, three predictors—SOFA score, temperature >38.3°C and elevated aPTT—were found to be statistically associated with CSB. The multivariate analysis demonstrated that the odds of bleeding increases by 1.52 times for every unit increase in SOFA score (95% CI: 1.11–2.08, p = 0.009), by 2.71 times for presence of temperature >38.3°C (95% CI: 1.13–6.47; p = 0.03) and 4.66 times for elevated aPTT (95% CI: 1.42, 15.3; p = 0.01) (Table 3). The predictive ability

Table 2: Laboratory parameters and CSB of study participants (N = 120)

S. No.	Laboratory parameters	CSB		p-value
		Yes (N = 38)	No (N = 82)	
1	HCT (mean ± SD)	41.7 ± 6.4	41.1 ± 6.7	0.76
2	Bicarbonate (mean ± SD)	20.6 ± 3.3	20.9 ± 3.8	0.68
3	WBC cells/mm ³ (median, IQR)	6250 (4410–9700)	7945 (5400–10500)	0.09
4	BUN mg/dL (median, IQR)	10 (6–12)	9 (6–13)	0.61
5	ANC cells/mm ³ (median, IQR)	4036 (1881–6199)	4213 (2472–6936)	0.55
6	ALC cells/mm ³ (median, IQR)	2384 (1850–3264)	2701 (1657–3990)	0.32
7	AST IU/L (median, IQR)	182 (114–318)	167 (107–301)	0.53
	AST n (%)			
	35–70 IU/L	2 (18.2)	9 (81.8)	0.40
	71–102 IU/L	17 (37.8)	28 (62.2)	
	>103 IU/L	19 (29.7)	45 (70.3)	
8	ALT IU/L (median, IQR)	111 (64 – 221)	103 (59–158)	0.54
	ALT n (%)			
	41–80 IU/L	7 (29.2)	17 (70.8)	0.85
	81–120 IU/L	18 (30.5)	41 (69.5)	
	>121 IU/L	13 (35.1)	24 (64.9)	
9	Albumin mg/dL (mean ± SD)	3.1 ± 0.7	3.1 ± 0.6	0.96
10	aPTT n (%)			
	Normal	4 (12.1)	29 (87.9)	0.005*
	Elevated	34 (39.1)	53 (60.9)	
11	Platelet at presentation cells/mm ³ n (%)			
	<10000	32 (36.4)	56 (63.6)	0.16
	10001–20000	5 (20)	20 (80)	
	20001–50000	0	5 (100)	
	50001–100000	1 (50)	1 (50)	
12	Platelet lowest cells/mm ³ n (%)			
	<10000	34 (32.7)	70 (67.3)	0.47
	10001–20000	4 (36.4)	7 (63.6)	
	20001–50000	0	4 (100)	
	50001–100000	0	1 (100)	

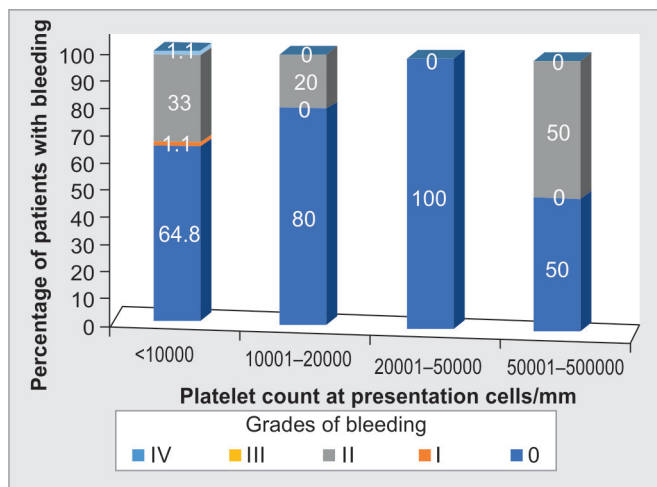


Fig. 2: Association between grades of bleeding and platelet count at presentation (N = 120)

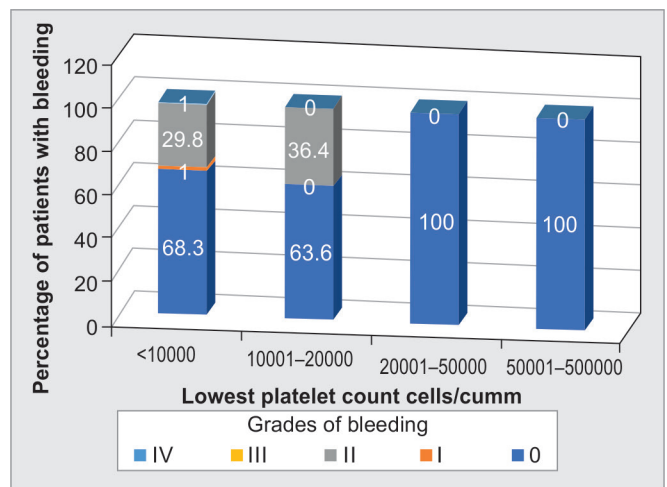


Fig. 3: Association between grades of bleeding and lowest platelet count (N = 120)

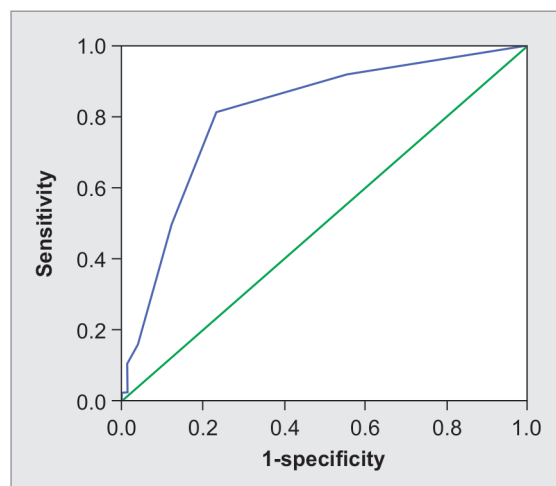
Table 3: Multivariate binary logistic analysis of factors that predict CSB among dengue patients (N = 120)

Predictors	Beta coefficient	Adjusted odd's ratio	95% CI		p-value
			Lower	Upper	
SOFA	0.417	1.52	1.11	2.08	0.009*
Fever (Presence of body temperature >38.4°C/101°F)	0.998	2.71	1.13	6.47	0.03*
Elevated aPTT	1.541	4.66	1.42	15.3	0.01*

*Statistically significant ($p < 0.05$). The p -value based on multivariate binary logistic regression

Table 4: Allotment of scores for different variables: Total maximum score 12

APTT value score	Temperature score	SOFA score
<35-0	<95°F: 1	0-3: 0
36-45: 1	95.1-99°F: 0	4-7: 1
46-55: 2	99.1-100.9°F: 1	8-11: 2
56-65: 3	>101°F: 2	>11: 3
66-75: 4		
76-85: 5		
86-95: 6		
>96: 7		

**Fig. 4:** Combined predictive ability of the variables (by giving scores to different variables)

of aPTT (aPTT > 40 seconds) alone, demonstrated by area under the ROC curve 0.734 (95% CI: 0.64–0.82) had sensitivity of 60% and specificity of 68%.

A predictive score was derived utilizing the three variables. The variables were assigned specific weightage based on their severity (Table 4). The cumulative maximum score of 12 was established. The predictive ability of this score was evaluated using area under the ROC curve 0.81 (95% CI: 0.73–0.89) and the ideal cut-off score >4 had sensitivity of 81% and specificity of 77% was demonstrated (Fig. 4).

DISCUSSION

The current study identified predictors of CSB in thrombocytopenic dengue patients admitted to the ICU through a retrospective

analysis. The results revealed that an elevated SOFA score, temperature above 38.3°C at presentation and elevated aPTT (>40 seconds) are independent predictors of CSB on multivariate analysis. The findings of the study offer valuable insight into the complex interplay of factors contributing to bleeding complications in dengue patients.

As CSB was observed in only a third of the thrombocytopenic patients and no correlation existed between the severity of thrombocytopenia and extent of bleed, identifying factors associated with CSB in thrombocytopenic patients will lead to a better understanding, thereby avoiding unnecessary platelet transfusion based on only platelet count thresholds. Prior studies demonstrated platelet transfusion can actually impede platelet recovery and increase in the length of hospital stay.⁶ Also platelet function in dengue is not associated with platelet count.²¹ Recognizing potential predictors of CSB will play a pivotal role in determining the individuals who will benefit most from transfusion.

The most significant finding in the study was the association between elevated aPTT and risk of developing CSB. Bleeding manifestations in dengue are multifactorial due to vasculopathy, coagulopathy, and thrombocytopenia. Endothelial cell activation, inflammatory response, autoantibodies to coagulation factors disrupt the balance between procoagulant and anticoagulant factors, leading to abnormalities in the intrinsic pathway of the coagulation cascade.²²⁻²⁴ Most studies that have demonstrated a connection between elevated aPTT and CSB have primarily focused on pediatric population.^{22,25} This study confirms the validity of aPTT as a predictor even in adult population.

Similarly, increase in the SOFA score, a measure of severity of organ system dysfunction was associated with increased risk of bleeding.⁵ This aligns with the concept that greater the organ dysfunction increases the likelihood of bleeding due to impaired clotting mechanisms.

The third significant predictor of CSB identified in the study was the presence of an elevated temperature exceeding 38.3°C.⁵ Fever is a common symptom in dengue cases, and its association with increased bleeding risk highlights the intricate relationship between systemic inflammation and coagulation. These findings emphasize the need to monitor temperature as a potential indicator of bleeding risk.

In contrast to earlier literature, the current study was not able to establish an association between liver enzymes such as AST, ALT, and CSB.^{5,14,16,19,26} There were no discernible differences in the occurrence of CSB even after analyzing patients with AST and ALT levels that were 2–3 times higher than normal. This lack of significance could be attributed to the study's exclusive focus on adult ICU patients wherein almost all patients had elevated liver enzymes, unlike previous studies that included a broader range of hospitalized patients.^{16,19} Similarly, a study by Lee LK et al. yielded findings consistent with our study, indicating liver enzymes were not associated with hemorrhagic manifestations.²⁶

Although prior studies claimed the association of multiple parameters like age, gender, prolonged prothrombin time, increased D-dimer levels, abdominal pain, hepatomegaly, pleural effusion, secondary dengue infection, and severe dengue with CSB, most of the studies have evaluated the association by univariate analysis.^{5,16,27–29} Adjusted risk assessment using multivariate regression analysis has not been reported. Discrepancies in previous literature might be due to differences in sample size and analytical methods.

Considering the platelet count was not a correlate of CSB, a predictive score was derived using three identified predictors (SOFA score, elevated aPTT and fever). The area under the ROC curve was 0.81 (95% CI: 0.73–0.89) indicating a clear discrimination of individuals who are likely to bleed. The ideal cut-off score above 4 had a sensitivity of 81% and specificity of 77%. This scoring system enables a more nuanced evaluation of each patient's bleeding risk profile, moving beyond a simple platelet count threshold and allows the clinician to allocate resources more efficiently.

The current study has several strengths. The findings are derived from a selective subset of ICU patients drawn from an extensive cohort of patients who were admitted to a tertiary care hospital over a 7-years span with diverse dengue viral infections due to multiple outbreaks. The association between predictive factors and CSB was analyzed using multivariate logistic regression analysis which adjusted for the confounding variables in a robust fashion. However, the predictive model is derived from a retrospectively evaluated derivation cohort and it needs to be tested prospectively in validation cohort in multiple other institutions before extrapolating to the routine care of patients.

We recognize that the utilization of retrospective data introduces inherent biases and constraints. Additionally, findings in this study are limited to a specific population of ICU-admitted thrombocytopenic adult dengue patients, potentially limiting the generalizability to other patient groups. Few patients ($n = 2$) had no fever at presentation and developed fever subsequently and they were not included in analysis.

CONCLUSION

Identifying patients with dengue infection who are at risk of bleeding is crucial for patient management. The presence of independent predictors (fever, increased SOFA score, and increased aPTT) indicates bleeding tendency. A predictive score above 4 generated by including three variables can be utilized for risk stratification. These findings, complemented with clinical judgement in reviewing daily clinical and laboratory data, can identify low-risk patients who are safe not to admit to the ICU.

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