



Factors Associated with Platelet Recovery in Dengue Patients on Fever Day 7

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Article information

Submitted
21-12-2025

Accepted
01-07-2026

Published
30-08-2026

Abstract

Background: Thrombocytopenia is a common hematological feature of dengue infection, and platelet recovery is a reliable prognostic indicator. The seventh day of fever typically marks the beginning of the recovery phase, but some patients show delayed platelet recovery. This study aimed to identify the factors affecting platelet recovery in adult dengue patients on fever day 7.

Methods: This cross-sectional study was conducted from April 2024 to April 2025 at Universitas Andalas Hospital and involved 35 adult dengue patients selected through total sampling. Retrospective data on clinical and laboratory characteristics were collected. Platelet recovery was defined as an increase in platelet count of more than 20,000/mm³ within 48 hours between fever days 5 and 7. Patients who received platelet transfusion or corticosteroid therapy were excluded. Associations between variables were analyzed using the Chi-square test and Fisher's Exact Test.

Results: A significant association was found between platelet recovery and thrombocytopenia status at admission ($p = 0.037$). Age, sex, comorbidity, hematocrit level, leukocyte count, and day of fever at admission were not significantly associated with platelet recovery ($p > 0.05$). Only 10 of the 35 patients (28.6%) showed platelet recovery on fever day 7. Most patients were male (57.1%) and aged ≤ 40 years (80.0%), while 22.9% had comorbidities.

Conclusion: Thrombocytopenia status at hospital admission was significantly associated with platelet recovery in dengue patients. Early recognition of this factor may help identify clinically at-risk patients and enable more effective clinical management.

Keywords: thrombocytopenia, clinical predictor, fever day of admission

Introduction

Dengue remains one of the major public health problems in Indonesia and other tropical countries. It is transmitted through the bites of *Aedes aegypti* and *Aedes albopictus* mosquitoes that carry the dengue virus. Dengue has a broad clinical spectrum, ranging from asymptomatic infection to severe disease that can lead to dengue shock and death. It also remains one of the leading causes of hospitalization and mortality in several hospitals, particularly during the dry season, when the mosquito population increases significantly.¹⁻³

The World Health Organization (WHO) reported that dengue accounted for approximately 70% of the global disease burden, with the highest number of cases reaching 6.5 million and 7,300 deaths recorded in 2023. Surveillance data from the Directorate General of Disease Prevention and Control, Ministry of Health of the Republic of Indonesia, showed a rise in dengue cases to 53,131 cases with 404 deaths from dengue hemorrhagic

fever by March 2024, increasing further to 60,296 cases with 455 deaths in the following week. This increase was largely driven by environmental factors such as changing weather patterns, erratic rainfall, and inadequate community awareness of environmental hygiene.^{4,5}

A common clinical finding and warning sign in dengue patients is thrombocytopenia, defined as a platelet count below the normal range ($<150,000/\text{mm}^3$). Thrombocytopenia is also one of the WHO criteria used as a potential indicator of clinical severity in dengue. It can result from several mechanisms, including impaired platelet production in the bone marrow, increased platelet destruction due to immune activation, and platelet aggregate formation resulting from plasma leakage and intravascular coagulation. Some dengue patients with thrombocytopenia may develop spontaneous bleeding, which carries a risk of dengue shock and increased morbidity and mortality.^{6–8}

Platelet counts generally remain within normal limits or decrease only slightly during the early febrile phase of dengue, from day 1 to day 3. A marked decline occurs during the critical phase, from day 4 to day 6, coinciding with a rising hematocrit due to plasma leakage. Patients with severe bleeding or dengue shock require close monitoring and optimal fluid therapy to prevent more serious complications. Patients enter the convalescent phase from day 7 to day 10 as the critical phase resolves, and the platelet count begins to rise. This increase is termed platelet recovery, defined as an increase in platelet count of more than $20,000/\text{mm}^3$ within 48 hours between fever days 5 and 7. Plasma leakage also subsides as the patient's clinical condition improves during this phase.^{6,9}

A case study by Rajapakse reported that platelet counts progressively improved by day 7 and returned to normal by day 10 in dengue patients. Another study reported that platelet counts declined from fever day 3 through day 7 and reached normal levels by day 8 or 9. Not all patients achieve good platelet recovery during the recovery phase; some remain thrombocytopenic or show poor platelet recovery and require prolonged hospitalization.^{10–12}

The variability in platelet recovery among dengue patients on fever day 7 is influenced by multiple factors related to patient characteristics, immune response, and disease severity. Archuleta et al. showed that older age was an independent predictor of poor platelet recovery; each one-year increase in age raised the odds of poor recovery by 3%. This finding is supported by a systematic review by Tule et al., which reported that the greatest decline in platelet count occurred in the 46–65-year age group, with a mean decrease of $58,000 \text{ cells}/\text{mm}^3$.^{12,13}

Pribadi et al. found that good platelet recovery was more common among males, although the association between platelet recovery and sex was not statistically significant. A systematic review by Tule et al. reported that dengue occurred more frequently in males (56%) than in females (44%), a susceptibility attributed to less efficient antibody production against infection in males compared with females.^{13,14}

Comorbidity has also been identified as a factor influencing platelet recovery. A comparative study by Ashraf et al. found that comorbid conditions such as diabetes and hypertension were strongly associated with the risk of developing severe dengue. Sangkaew et al. reported that hypertension, diabetes, kidney disease, and cardiovascular disease were positively associated with progression to severe dengue and poor platelet recovery, whereas Latt et al. found no strong association between diabetes and severe dengue or poor platelet recovery.^{15–17}

Hematocrit level has also been considered a factor influencing platelet recovery. Handayani et al. reported a significant association between hematocrit level and dengue severity, with a hematocrit value of 46.8% associated with grade IV dengue hemorrhagic fever, suggesting an influence on disease severity and thrombocytopenia status.^{18,19}

Thrombocytopenia status at admission was identified by Archuleta et al. as one cause of poor platelet recovery; 43.9% of patients with poor recovery had markedly low platelet counts ($<20,000 \text{ cells}/\text{mm}^3$) at admission. Low leukocyte counts at admission were also associated with poor recovery. The timing of hospital admission was likewise related to the ongoing phase of illness: patients admitted earlier in the febrile course tended to show

slower platelet recovery, which was attributable to ongoing platelet destruction and bone marrow suppression from viral activity.¹²

Current research continues to seek biomarkers and clinical factors that predict dengue severity early in the illness, yet studies specifically focused on the factors affecting platelet recovery on fever day 7 remain limited. No prior study at Universitas Andalas Hospital has specifically evaluated the factors affecting platelet recovery on fever day 7. The researchers were therefore motivated to investigate this topic, aiming to contribute to the understanding of platelet recovery and to inform potential targeted therapeutic interventions.

Methods

Study Design

This study used an observational analytic design with a cross-sectional approach. It was conducted at Universitas Andalas Hospital from January to July 2025.

Participants and Eligibility Criteria

The study population consisted of adult patients diagnosed with dengue and treated in the inpatient ward of Universitas Andalas Hospital, based on medical record data from April 2024 to April 2025. Total sampling was used, in which the entire population meeting the inclusion criteria was enrolled as the study sample.

The inclusion criteria were adult patients diagnosed with dengue and treated in the inpatient ward between April 2024 and March 2025, whose medical records contained complete data on the study variables, and who started hospital treatment no later than fever day 5 and could be monitored through fever day 7. The exclusion criteria were patients with a history of other hematological disorders, such as leukemia and thrombotic thrombocytopenic purpura (TTP), or immune disorders affecting platelet count, such as lupus and idiopathic thrombocytopenic purpura (ITP), and patients who received platelet transfusion or corticosteroid therapy during hospitalization.

Data Collection and Variables

Platelet recovery was defined as an increase in platelet count of more than 20,000/mm³ over 48 hours, from fever day 5 to fever day 7. Age was categorized as ≤40 years or >40 years, while comorbidities included hypertension, diabetes, cardiovascular disease, chronic liver disease, and obesity. An elevated hematocrit level at admission was defined as >43% for females and >48% for males, leukopenia as ≤5,000 cells/mm³, and thrombocytopenia as mild (100,000–150,000 cells/mm³) or moderate to severe (<100,000 cells/mm³). The day of fever at admission was categorized as early (days 1–3, febrile phase) or late (days 4–6, critical phase).

Data Analysis

This study used bivariate analysis to examine the effect of the independent variables—age, sex, comorbidity, hematocrit level, leukocyte count, thrombocytopenia status at admission, and day of fever at admission—on platelet recovery in dengue patients. Data were analyzed using the Chi-square test, followed by Fisher's Exact Test when the expected-count assumption was not met, and results were considered significant at $p < 0.05$.

Ethical Considerations

This study received ethical approval from the Research Ethics Committee of the Faculty of Medicine, Universitas Andalas (No. 414/UN.16.2/KEP-FK/2025).

Results

This study used medical record data from Universitas Andalas Hospital for a population of 63 adult dengue patients treated from April 2024 to April 2025. Sampling was performed using the total sampling technique, and 35 patients met the inclusion criteria.

Table 1. Frequency distribution of the study variables

Study variable	n (%)
Platelet recovery	
Recovery	10 (28.6)
Non-recovery	25 (71.4)
Age	
>40 years	7 (20.0)
≤40 years	28 (80.0)
Sex	
Female	15 (42.9)
Male	20 (57.1)
Comorbidity	
Present	8 (22.9)
Absent	27 (77.1)
Day of fever at admission	
Day 1–3	15 (42.9)
Day 4–6	20 (57.1)
Hematocrit level at admission	
Increased	17 (48.6)
Not increased	18 (51.4)
Leukocyte count at admission	
Decreased	30 (85.7)
Not decreased	5 (14.3)
Thrombocytopenia status at admission	
Mild	17 (48.6)
Moderate–severe	18 (51.4)

As shown in Table 1, most of the 35 dengue patients did not achieve platelet recovery on fever day 7 (71.4%), while 28.6% did. Patient age ranged from 18 to 85 years, with the highest frequency in the 20–21-year age group. The sex distribution was fairly balanced, comprising 20 males (57.1%) and 15 females (42.9%). The comorbidities identified included cardiovascular disorders, electrolyte disturbances, and other chronic conditions. Most patients presented on fever days 4–6. On average, patients were admitted with a normal hematocrit, a low leukocyte count, and moderate-to-severe thrombocytopenia.

Table 2. Effect of age, sex, comorbidity, and day of fever at admission on platelet recovery in dengue patients on fever day 7

Variable	Platelet recovery, n (%)		n	p-value	
	Recovery	Non-recovery			
Age					
>40	2 (28.6)	5 (71.4)	7	1.000 ^a	0.690 ^b
≤40	8 (28.6)	20 (71.4)	28		
Sex					
Female	2 (13.3)	13 (86.7)	15	0.084 ^a	0.087 ^b
Male	8 (40.0)	12 (60.0)	20		
Comorbidity					
Present	2 (25.0)	6 (75.0)	8	0.799 ^a	0.589 ^b
Absent	8 (29.6)	19 (70.4)	27		
Day of fever at admission					
Day 1–3	6 (40.0)	9 (60.0)	15	0.195 ^a	0.179 ^b

Variable	Platelet recovery, n (%)		n	p-value
	Recovery	Non-recovery		
Day 4–6	4 (20.0)	16 (80.0)	20	
Total	10 (28.6)	25 (71.4)	35	

a. Chi-square test; b. Fisher's Exact Test; Day 1–3 = fever days 1–3; Day 4–6 = fever days 4–6.

As shown in Table 2, the proportion of platelet recovery was similar between the ≤ 40 -year and > 40 -year age groups, with the distribution dominated by younger patients. Fisher's Exact Test showed no significant association between age and platelet recovery ($p = 0.690$). Sex was also not significantly associated with platelet recovery, although a greater proportion of males experienced recovery ($p = 0.087$). The comorbidities identified among patients with recovery included hyponatremia and hepatic dysfunction, whereas patients without recovery had co-infections (typhoid fever, hemochezia) and cardiovascular disorders (hypotension, hypertension); comorbidity, however, showed no significant association with platelet recovery ($p = 0.589$). The day of fever at admission was also not significantly associated with platelet recovery ($p = 0.179$).

Table 3. Effect of hematocrit level, leukocyte count, and thrombocytopenia status at admission on platelet recovery in dengue patients on fever day 7

Variable	Platelet recovery, n (%)		n	p-value	
	Recovery	Non-recovery			
Hematocrit at admission					
Increased	6 (35.3)	11 (64.7)	17	0.392 ^a	0.315 ^b
Not increased	4 (22.2)	14 (77.8)	18		
Leukocyte count at admission					
Decreased	9 (30.0)	21 (70.0)	30	0.647 ^a	0.553 ^b
Not decreased	1 (20.0)	4 (80.0)	5		
Thrombocytopenia status at admission					
Mild	2 (11.8)	15 (88.2)	17	0.032 ^a	0.037 ^b
Moderate–severe	8 (44.4)	10 (55.6)	18		
Total	10 (28.6)	25 (71.4)	35		

a. Chi-square test; b. Fisher's Exact Test; increased hematocrit = $> 43\%$ for females and $> 48\%$ for males; not increased = $\leq 43\%$ for females and $\leq 48\%$ for males; decreased leukocyte count = $\leq 5,000$ cells/mm³; not decreased = $> 5,000$ cells/mm³; mild thrombocytopenia = 100,000–150,000 cells/mm³; moderate–severe thrombocytopenia = $< 100,000$ cells/mm³.

As shown in Table 3, the hematocrit level at admission showed no significant association with platelet recovery; the mean hematocrit was slightly higher among patients with recovery, but both the Chi-square test and Fisher's Exact Test were non-significant ($p = 0.315$). The leukocyte count at admission was likewise not significantly associated with platelet recovery, regardless of the presence of leukopenia ($p = 0.553$). In contrast, thrombocytopenia status at admission showed a significant association: patients with moderate-to-severe thrombocytopenia had lower mean platelet counts at admission, and Fisher's Exact Test showed a significant association between thrombocytopenia status at admission and platelet recovery on fever day 7 ($p = 0.037$).

Discussion

The majority of patients in this study had not achieved platelet recovery by fever day 7, indicating that recovery in this population occurred later than the expected physiological timeline. This high proportion of non-recovery may relate to the characteristics of the study population, which was dominated by moderate-to-severe cases, as is common at referral hospitals. This finding was consistent with Afgriyuspita et al., who reported that platelet increases on day 7 were generally still suboptimal; it differed, however, from Sari et al., who found that more than 50% of patients achieved a meaningful platelet increase by day 7. This discrepancy may be explained by variation in disease severity, immune response, comorbidity, and the clinical phase of the patients at admission;

most patients in this study were likely still in the critical phase or showed slower improvement than other study populations.^{18,20–22}

This study found that dengue predominantly affected younger individuals, which was consistent with the well-recognized epidemiological profile of dengue in endemic regions, where the highest incidence occurs among the productive age group. This finding was consistent with Tule et al., who reported that most dengue cases occurred in patients aged <46 years (61%) and were rare among the elderly (1.2%). A study at Sanglah General Hospital, Denpasar, showed a similar pattern, with the 17–25-year group representing the largest proportion (31.8%) and the 56–65-year group only 2.4%. This predominance of younger patients may reflect higher social activity and mobility, which increase exposure to *Aedes aegypti*. Nevertheless, elderly patients remain a group requiring particular attention, as declining immunity and mobility make them more vulnerable to severe dengue.^{13,23}

In terms of sex distribution, male patients predominated in this study, suggesting that dengue disproportionately affected males in this population. This finding was consistent with Tule et al. (56% male; 44% female), who attributed it to less efficient antibody production in males and the enhancing effect of estrogen on the immune response in females. However, Ahmad et al. reported the opposite pattern, with more females affected (65.3%) than males (34.7%), which they explained by greater indoor activity among females—indoor spaces being the primary habitat of *Aedes aegypti*. These conflicting findings suggest that the effect of sex on dengue incidence is complex and shaped by immunological, hormonal, and behavioral factors that may vary across populations and regions.^{13,24}

Most patients in this study presented without comorbidities, indicating that dengue was the primary driver of hospitalization, with pre-existing chronic conditions playing a minimal contributory role in most cases. This finding was consistent with Lien et al., who reported a higher proportion of patients without comorbidities (67.6% vs. 32.4%), but differed from Ashraf et al., who found a higher proportion of patients with comorbidities (50.3%). This difference reflects epidemiological variation across populations and settings and underscores that comorbidity remains an important risk factor in the clinical management of dengue.^{16,25}

The comparable proportions of elevated and normal hematocrit values observed at admission suggested that the study population was not confined to a single disease phase but rather encompassed patients presenting during both the early febrile period and the later critical phase of dengue. This pattern was consistent with Syuhada et al. and Nandwani et al. It differed from Saputra et al., who reported a higher proportion of hemoconcentration (52.8%), possibly due to variation in the timing of presentation and the disease phase at examination. The high prevalence of leukopenia at admission in this study was consistent with the well-recognized hematological profile that accompanies the critical phase of dengue. This finding was consistent with Firdaus et al., although Kakumani et al. reported a higher proportion of normal leukocyte counts, possibly reflecting differences in disease phase and population characteristics. Leukopenia occurs more often during the critical phase because of bone marrow suppression and leukocyte migration into tissue, so its high prevalence here suggests that many patients presented during the critical phase.^{26–30}

Thrombocytopenia severity at admission was nearly equally divided between the mild and moderate-to-severe categories, although more severe cases were slightly more common. This suggests that many patients had reached the critical phase, as moderate-to-severe thrombocytopenia is a hallmark of this stage. This pattern was consistent with Retnowati et al., who also reported a predominance of moderate-to-severe thrombocytopenia—again suggesting that many patients presented during the critical phase. It differed from Vallurupalli et al., who found that most patients did not have thrombocytopenia, suggesting earlier presentation in the febrile phase before the platelet decline began. Most patients in this study presented on fever days 4–6 (57.1%), which was consistent with Lestari et al. and Rizky et al. This pattern suggests that many patients had not received early treatment during the initial phase, increasing the risk of complications and reinforcing the importance of community education on the early detection and management of dengue.^{31–34}

No significant association was found between age and platelet recovery on fever day 7, suggesting that age was not a determining factor for recovery within the expected timeframe in this study population. The recovery rates were similar across the younger and older age groups, implying that other variables may have had a greater

influence on recovery outcomes than age itself. This differed from Archuleta et al., who reported age as a predictor of poor platelet recovery (OR 1.03), and from Tule et al., who found a greater platelet decline in the 46–65-year group attributable to immunosenescence. This discrepancy may reflect the small sample size, particularly in the >40-year group ($n = 7$), and an uneven age distribution. Age was therefore not shown to affect recovery in this population, and a larger sample will be needed for confirmation.^{12,13}

Bivariate analysis showed no significant association between sex and platelet recovery on fever day 7, indicating that male and female patients had similar likelihoods of achieving recovery within the observed timeframe. Although a descriptive difference was noted, with a higher proportion of males achieving recovery than females, this difference did not reach statistical significance. This finding was consistent with Pribadi et al. and Faridah et al. The descriptive difference may relate to biological mechanisms such as testosterone-enhanced platelet aggregation and a lower antibody response in males, which allows faster recovery, whereas females mount a stronger adaptive immune response due to estrogen, which may prolong inflammation and delay platelet recovery.^{14,35,36}

Comorbidity was not significantly associated with platelet recovery by fever day 7, suggesting that underlying chronic conditions did not independently influence recovery outcomes. Although patients with comorbidities descriptively showed a somewhat lower recovery rate, the difference was not statistically significant. This finding was consistent with Nabila et al., who also reported no significant association, although comorbidities such as hypertension and diabetes descriptively tended to prolong illness duration. In contrast, Archuleta et al. and Faridah et al. found that comorbidities—including hypertension, diabetes, kidney disorders, multi-organ dysfunction, and impaired liver function—can worsen systemic inflammation and inhibit bone marrow regeneration, making them predictors of poor platelet recovery. Although comorbidity showed no significant effect in this study, it remains clinically important and may still delay recovery, together with other possible contributing factors such as dengue serotype and variation in immune response.^{12,35}

Bivariate analysis showed no significant relationship between the day of fever at admission and platelet recovery on fever day 7, implying that the timing of presentation alone was not a key determinant of recovery in this study. A descriptive pattern suggested that earlier presenters had a higher recovery rate, but this observation lacked statistical confirmation. This finding remains physiologically consistent with Archuleta et al., who reported that very early presentation predicted poor platelet recovery when evaluated on hospital day 2, while patients were still febrile and recovery had not yet occurred. Clinically, patients admitted earlier were likely still febrile and received treatment before entering the critical phase, which lowered the risk of plasma leakage and bone marrow suppression, whereas patients presenting on days 4–6 generally entered the critical phase, marked by endothelial damage and cytokine activation that may inhibit platelet regeneration.^{7,12}

An elevated hematocrit at admission did not significantly affect platelet recovery by fever day 7, indicating that hemoconcentration was not an independent predictor of recovery. Although patients with an increased hematocrit descriptively showed a higher recovery rate, the difference was not statistically significant. This finding was consistent with Simangunsong et al., who reported no significant association between hematocrit and platelet count. In contrast, Sagar et al. found that a high hematocrit was associated with bleeding and severe thrombocytopenia, which may delay platelet recovery ($p < 0.001$). This discrepancy may reflect variation in the disease phase at presentation and heterogeneity in the inflammatory response between individuals; the hematocrit at admission therefore does not consistently predict platelet recovery on fever day 7.^{37,38}

Bivariate analysis showed that the leukocyte count at admission was not significantly associated with platelet recovery by fever day 7, implying that the presence of leukopenia alone did not determine recovery outcomes. A descriptive trend toward slightly better recovery in patients with leukopenia was noted, yet this finding lacked statistical significance. This finding was consistent with Jayanthi et al., who reported that leukopenia at admission was not significantly associated with complications or clinical recovery in dengue patients.^{14,39} Leukopenia more likely reflects transient bone marrow suppression rather than a direct effect on megakaryocyte regeneration, which determines platelet recovery. In contrast, Archuleta et al. found that leukopenia was associated with poor platelet recovery (adjusted OR = 0.79; $p = 0.0002$),¹² a difference that may relate to the timing of assessment: this study evaluated recovery on fever day 7, whereas Archuleta et al. assessed patients

on hospital day 2, generally still within the critical phase. The relationship between leukocyte count and platelet recovery therefore appears to be strongly influenced by the disease phase and inflammatory dynamics at the time of evaluation.

Bivariate analysis showed a significant association between thrombocytopenia status at admission and platelet recovery on fever day 7, indicating that the severity of thrombocytopenia at presentation was a notable predictor of recovery outcomes. This result differed from Archuleta et al., who reported that severe thrombocytopenia was instead associated with poor platelet recovery (adjusted OR = 0.78; $p = 0.004$), reflecting greater bone marrow suppression and a higher bleeding risk.¹² This discrepancy may be explained by differences in the timing of evaluation: Archuleta et al. assessed patients on hospital day 2, when most were still in the critical phase, whereas this study assessed patients on fever day 7, which represents the recovery phase. From a pathophysiological perspective, this finding can be understood through the mechanism of regenerative rebound. During the critical phase, thrombocytopenia results from bone marrow suppression, peripheral platelet destruction via NS1-mediated complement activation, and increased platelet consumption through aggregation. As patients transition into the convalescent phase, typically around fever day 7, viral clearance reduces immune-mediated destruction and the bone marrow begins to recover its function. In patients who experienced more profound thrombocytopenia, the thrombopoietin-driven stimulus for megakaryocyte regeneration may be more potent, resulting in a rapid increase in platelet production, a phenomenon consistent with rebound thrombocytosis.

Conclusions

Thrombocytopenia status at hospital admission was significantly associated with platelet recovery in dengue patients on fever day 7. Patients with moderate-to-severe thrombocytopenia who were admitted on fever days 4–6 tended to show good platelet recovery. Age, sex, comorbidity, hematocrit level, leukocyte count, and day of fever at admission were not significantly associated with platelet recovery in dengue patients on fever day 7.

Acknowledgements

The authors thank all parties involved in this study for their support in its completion.

Declaration concerning generative AI and AI-augmented technologies in the compositional process

In the course of preparing this paper, the authors utilized ChatGPT to enhance readability and linguistic quality. Subsequent to utilizing this tool/service, the writers assessed and amended the information as necessary and assume complete accountability for the publication's content.

Declarations of competing interest

No potential competing interest was reported by the authors.

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