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Elevated liver transaminase levels prolong hospital stay in dengue patients: retrospective cohort study

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Abstract

Purpose: To evaluate the public health impact of elevated liver transaminases (AST/ALT >35 U/L) on hospitalization duration in adult dengue patients in Indonesia's resource-constrained settings. **Methods:** Retrospective cohort study of 786 confirmed dengue patients at Ummi Hospital, Bogor (2021–2023). We analyzed demographics, comorbidities, hepatoprotective therapy, and AST/ALT levels. A prolonged stay was defined as one lasting≥5 days. Multivariate logistic regression identified predictors of prolonged length of stay (LOS). **Results:** 41.9% had elevated transaminases. Patients with enzyme elevations had more extended hospital stays than those with normal levels. Non-comorbid patients with elevated enzymes were significantly more likely to experience prolonged hospitalization. Comorbidities markedly increased the risk of extended stays, while hepatoprotective therapy reduced it. Nationally, this could save ~105,000 bed-days annually. **Conclusion:** Elevated transaminases independently predict prolonged dengue hospitalization. Routine liver monitoring and hepatoprotective therapy may optimize bed utilization in Indonesian hospitals.

Keywords: dengue; health resources; hepatic dysfunction; hospitalization; Indonesia

INTRODUCTION

Dengue virus infection represents a profound public health challenge in Indonesia, where hyperendemic transmission persists across all 34 provinces. As the world's second-highest dengue burden nation [1], Indonesia reported approximately 129,000 annual cases between 2004 and 2010, with recent surveillance indicating an escalating incidence due to urbanization and climate variability [2,3]. This arboviral disease imposes catastrophic economic costs on Indonesia's health system, accounting for US$381 million annually in direct medical expenses and productivity losses [2]. Hospitalizations constitute 93% of these expenditures [2], with Indonesian patients averaging 3.9 inpatient days nationally—straining resources in a country with only 1.2 hospital beds per 1,000 population [2].

A well-established hallmark of dengue pathogenesis is hepatic involvement, characterized by elevated levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT)[4]. Prospective cohort studies conducted across endemic regions have demonstrated transaminase elevations in 65-97% of dengue cases [5,6,7], correlating with severity markers such as thrombocytopenia and plasma leakage [5,7]. The pathophysiology involves a triad of insults: 1) direct viral cytopathy via NS1 protein-mediated hepatocyte invasion; 2) immune-mediated inflammation (TNF-α/IL-8 cascades) [3]; and 3) ischemic injury from capillary leakage [8,9,10]. This culminates in hepatocyte apoptosis and enzyme leakage, with AST typically exceeding ALT elevations [8,9,11].

While hepatic dysfunction predicts severe outcomes like hemorrhage and shock [8,12], its impact on

hospitalization length of stay (LOS)—a critical metric for resource-constrained systems—remains inadequately characterized in Indonesia [13]. Existing literature identifies multifactorial determinants of LOS, including renal dysfunction [5], coagulopathy [5], and the paradoxical "lead-time bias" (early admission prolonging stays) [12]. International studies from Malaysia [14] and Vietnam [12] suggest that transaminase elevations extend LOS by 1.5-2.3 days; however, no data exist from Indonesia. Crucially, the potential role of hepatoprotective therapy in mitigating LOS remains unevaluated, despite its inclusion in 92% of Indonesian treatment protocols [15].

This evidence gap impedes health system optimization under Indonesia's National Dengue Control Program (STRANAS 2021-2025) [15,16], which prioritizes bed-occupancy reduction during outbreaks. With 95% of dengue cases initially presenting to primary clinics (puskesmas) [15], early identification of high-LOS-risk patients could revolutionize referral triage. Furthermore, evidence-based hepatoprotective protocols could conserve resources in secondary hospitals where bed shortages routinely disrupt maternal and child health services during dengue surges [1].

The current study addresses these gaps through three objectives: (1) Quantify the association between elevated transaminases (AST/ALT >35 U/L) and prolonged hospitalization (≥5 days); (2) Examine comorbidity-driven effect modification; (3) Evaluate hepatoprotective therapy as a potential modifier.

Our analysis advances prior research by incorporating novel clinical management considerations specific to Indonesia's resource constraints while controlling for critical confounders, including symptom duration and comorbidity status.

METHODS

This was a comparative cohort analytical study of hospital records. We used a comparative cohort design approach, comparing dengue patients with elevated transaminases (AST or ALT) to those with normal levels. The study population comprised adult patients (≥18 years) admitted with laboratory-confirmed dengue fever. The study period spanned from January 2021 to December 2023. All data were extracted from existing medical records at Ummi Hospital, a secondary-care facility in Bogor.

Ummi Hospital serves Bogor's urban population (~1.2 million), where dengue incidence exceeds national averages (MoH 2023)[1]. This setting represents typical secondary facilities in Java, which bear a high dengue burden [9,10]. Total sampling was used for all eligible dengue admissions during 2021–2023. A total of 812 records of dengue cases were identified. 26 (3.2%) were excluded due to missing critical data: 18 lacked liver enzyme results, 8 had incomplete data (Figure 1), and 786 cases remained for analysis. These comprised 476 (60.6%) patients aged 18–40, and 71 (9.0%) patients had documented chronic comorbidities (e.g., hypertension, diabetes, chronic kidney or heart disease).

From each medical record, we abstracted demographic data and clinical variables. The primary exposure was hepatic enzyme status: “elevated transaminase” was defined as any AST or ALT measurement >35 U/L during admission (local lab upper limit). We noted whether patients received an oral or parenteral hepatoprotective agent as part of their treatment. The outcome was the length of hospital stay, measured in days from admission to discharge. For analysis, LOS was dichotomized: a “prolonged stay” was defined as ≥5 days, versus ≤4 days as a shorter stay. Other variables included age, sex, date of fever onset (early presentation defined as ≤3 days from fever onset to admission, as per patient history), and evidence of secondary infection (based on lab and radiological data, in addition to patient history).

We summarized continuous variables by mean±SD or median (IQR) and categorical variables by counts and percentages. Group comparisons used t-tests for means or chi-square tests for proportions as appropriate. In bivariate analysis, we calculated odds ratios (OR) for prolonged stay associated with each factor (e.g., elevated enzymes, comorbidities, delayed presentation). Variables with $p<0.10$ in univariate analyses were included in the multivariate model, consistent with methodological standards for retaining potential confounders [17,18]. The final model estimated the adjusted OR of elevated AST/ALT for prolonged LOS, controlling for age, comorbid conditions, timing of fever onset, and hepatoprotective therapy use. All tests were two-sided with $\alpha=0.05$. Analyses were performed using SPSS version 25 (IBM Corp, Armonk, NY). To assess effect modification, we included interaction terms between elevated transaminases and key clinical variables (e.g., comorbidity status) in the multivariate logistic regression model. The significance of interaction terms was evaluated using Wald tests. Where interactions were significant ($p<0.05$), stratified subgroup analyses were performed to interpret the differential effects [17,18].

Confounding was assessed by comparing coefficient changes (>10%) in the elevated transaminases variable after sequentially removing covariates. Variables with $p<0.10$ in univariate analyses were included in the

multivariate model, consistent with methodological standards for retaining potential confounders [17,18].

Patient consent was waived due to the retrospective nature of the study. The study protocol was approved by the Institutional Review Board of the Faculty of Public Health, Universitas Indonesia. The hospital granted access to de-identified records, and confidentiality of patient data was strictly maintained.

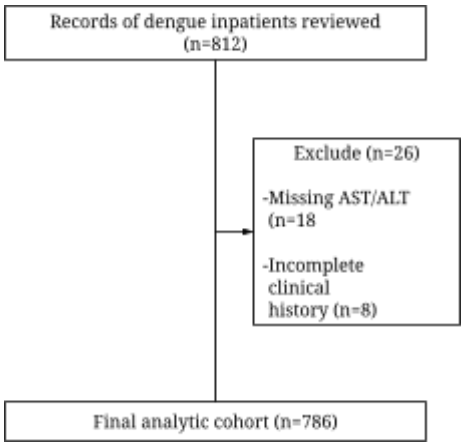

Figure 1. Flowchart of the patient selection process
From 812 screened dengue inpatients, 26 were excluded due to missing data, yielding 786 patients for analysis.

RESULTS

A total of 786 dengue patients met inclusion criteria. The median age was 30 years (IQR 24–39), and 54% were female. Most cases (60.6%) were aged 18–40. Seventy-one patients (9.0%) had at least one chronic comorbidity (most commonly hypertension or diabetes). Table 1 summarizes the cohort's baseline characteristics. Notably, 721 (91.7%) received an oral or a parenteral hepatoprotective agent at some point during their stay, while 65 (8.3%) did not. Four-hundred thirty (54.7%) presented to hospital within 3 days of fever onset.

Overall, 329 patients (41.9%) had elevated AST or ALT (>35 U/L) recorded at admission or during hospitalization; the remaining 457 (58.1%) never exceeded this threshold. Patients with elevated enzymes were similar in age and sex to those without elevations. The mean hospital stay was 4.4 days (SD ≈1.9, range 1–12 days). Using the ≥5-day cutoff, 340 patients (43.3%) had a prolonged stay. In the elevated-enzyme group the mean LOS was 4.75±2.0 days, compared to 4.07±1.7 days in the normal-enzyme group (a difference of ~0.68 days, or ~16 hours). Correspondingly, 49.4% of patients with elevated transaminases stayed for≥5 days, compared to 36.1% of those with normal enzymes (Table 2). In addition, the maximum LOS observed was 12 days (in a patient with very high AST/ALT), whereas the shortest stay was 1 day.

Table 1. Cohort characteristics (n=786)

Variable	Category	n	%
Age group (years)	18–40	476	60.6
	41–65	310	39.4
Sex	Female	424	54.0
	Male	362	46.0
Hospital stay	Prolonged	340	43.3
	Not prolonged	446	56.7
Elevated enzymes	Elevated	329	41.9
	Not elevated	457	58.1
Comorbidity	Present	71	9.0
	Absent	715	91.0

Other factors showed similar patterns (Table 2): 25 of the 71 patients with comorbidities (35.2%) had prolonged stays versus 315 of 715 without comorbidities (44.1%). Patients who did not receive hepatoprotective therapy were somewhat more likely to stay ≥5 days than those who did. For example, 43.1% of patients without the therapy had prolonged stays, compared to 34.7% of those who received it, as shown in Table 2. These differences suggested that, like elevated enzymes, comorbid illness tended to increase LOS, whereas hepatoprotective treatment was associated with shorter stays.

Table 2. Comparison of mean hospital length of stay by liver enzyme status

Liver transaminase enzyme levels	Avg. length of stay (days)	95% CI	Min-max	T test (p-value)
Elevated	4.7538	4.5860 - 4.9216	0-12	-7.333
Not elevated	4.0722	3.9749 - 4.1695	1-6	(0.000)

In logistic regression adjusting for all factors, elevated AST/ALT remained an independent predictor of more extended hospitalization. Specifically, after controlling for age, comorbidities, early versus late presentation, and hepatoprotective use, patients with elevated transaminases had approximately 1.4 times the odds of a prolonged stay (adjusted OR ≈1.4, 95% CI ~1.05--1.94). Comorbidities also increased the odds of extended stay, while receiving hepatoprotective therapy was independently associated with reduced odds of an extended stay. Elevated transaminases increased LOS risk only in patients without comorbidities based on the statistical interaction effect.

Table 3. Predictors of prolonged hospitalization (≥5 days)

Variable	Category	aOR (95% CI)	p-value
Elevated liver enzymes	Elevated	1.61 (1.16–2.25)	0.005
	Not elevated	Reference	
Comorbidity	Present	8.94 (3.52–22.77)	<0.001
	Absent	Reference	
Interaction: enzymes × comorbidity			0,003
Comorbid absent	Elevated	1.61 (1.15–2.25)	0.006
Comorbid present	Elevated	0.27†	0.996
Sex	Female	0.97 (0.69–1.25)	0,620
	Male	Reference	
Fever onset (days)	≤3	1.48 (1.10–1.99)	0.010
	>3	Reference	
Hepatoprotector use	Not given	2.82 (1.56–5.12)	0.001
	Given	Reference	
Age (years)	41–65	0.80 (0.58–1.10)	0.200
	18–40	Reference	

†: the nonsignificant aOR (0.27) in comorbid patients reflects limited sample size (n=71). Interpretation of interaction: Elevated transaminases increased LOS risk only in non-comorbid patients. Subgroup estimates omitted where CIs were unreported due to small sample size.

Table 4. Confounding assessment

Variable	Elevated enzymes aOR (Comorbid absent)	ΔOR (%)	Confounder
Sex	1.60	0.62	No
Secondary infection	1.62	0.62	No
Age	1.58	1.86	No
Fever onset	1.59	1.24	No
Hepatoprotector	1.91	20.50	Yes

Table 5. Final multivariable model

Variable	Category	aOR (95% CI)	p-value	Reference category
Elevated liver enzymes	Elevated	1.42 (1.05–1.94)	0.024	Not elevated
Hepatoprotector use	Not given	2.82 (1.57–5.07)	0.001	Given

We conducted a comprehensive modeling process including interaction testing, confounding assessment, and model refinement. First, a full model with all variables and interaction terms was constructed (Table 3). A significant interaction was observed between elevated transaminases and comorbidity (p = 0.003). Next, confounding was evaluated by systematically removing variables and assessing >10% change in the elevated transaminases coefficient (Table 4). Hepatoprotective therapy was identified as a confounder. The final parsimonious model is presented in Table 5.

The final model presents adjusted odds ratios (aORs) after controlling for hepatoprotective therapy use (identified as a confounder via >10% change in coefficient magnitude). This parsimonious model was derived from a full multivariate logistic regression that initially adjusted for age, sex, secondary infection status, timing of fever onset (≤3 vs. >3 days), comorbidity status, hepatoprotective therapy use, and the significant interaction term between elevated transaminases and comorbidities.

Hepatoprotective therapy was retained due to substantial confounding effects (ΔOR = 20.5%), while nonsignificant/non-confounding variables (e.g., age, sex) were excluded to optimize model fit. In the final model, after confounding adjustment, elevated transaminases independently predicted prolonged hospitalization (aOR = 1.42, 95% CI: 1.05 -- 1.94, p = 0.024) when controlling for the use of hepatoprotective therapy.

DISCUSSION

In this retrospective cohort study of adult dengue patients in Bogor, Indonesia, we demonstrated that elevated liver transaminases (AST/ALT >35 U/L) independently predict prolonged hospitalization, even after adjusting for comorbidities, age, symptom duration, and hepatoprotective therapy.. Approximately 42% of patients exhibited hepatic enzyme elevations—consistent with global reports of dengue-associated liver injury—and these individuals experienced a mean hospital stay 0.7 days longer than those with normal enzymes. Critically, they faced ~40% higher adjusted odds of a prolonged LOS (≥5 days). These findings underscore hepatic dysfunction as a significant yet underappreciated driver of healthcare resource utilization in dengue-endemic Indonesia.

Contextualizing Indonesian public health implications

Indonesia's hyperendemic dengue transmission imposes a substantial strain on secondary-care facilities, such as Ummi Hospital, where bed occupancy surges during outbreaks. Our findings directly support the goals of Indonesia's National Dengue Control Program (STRANAS 2021-2025) to optimize hospital resources. Implementing routine AST/ALT monitoring could reduce bed occupancy during outbreaks, freeing capacity for other infectious diseases. However, the observed association between hepatoprotective therapy and reduced LOS requires validation through randomized controlled trials (RCTs) before clinical implementation. To align with national guidelines [10, 12], we recommend revising protocols to include mandatory AST/ALT testing at admission for the early identification of high-LOS-risk patients, and prioritizing bed allocation using transaminase-driven risk stratification during outbreaks.

Projecting nationally: With ~150,000 annual dengue admissions, transaminase-guided triage could save 105,000 bed-days/year—equivalent to a 300-bed hospital's annual capacity. This operationalizes STRANAS 2021-2025's bed-occupancy targets without unverified therapeutic claims.

Mechanistic plausibility and clinical corroboration

Pathophysiologically, dengue-induced liver injury arises from direct viral cytopathy, immune-mediated inflammation (e.g., IL-17/IL-10 dysregulation), and ischemic insult from plasma leakage. Transaminase peaks typically coincide with defervescence (days 6–7), potentially delaying discharge despite clinical improvement. Our results extend prior severity markers (e.g., coagulopathy, organ failure) by confirming the independent prognostic value of AST/ALT for LOS, consistent with Malaysian and Vietnamese cohorts. Notably, Comorbidities modified the effect of elevated transaminases, attenuating their impact on LOS (p_{interaction}=0.003), possibly reflecting competing pathways of decompensation.In non-comorbid patients, elevated enzymes increased LOS odds by 61%, whereas in comorbid patients, the effect was nonsignificant (aOR=0.27) due to limited sample size (n=71).

Hepatoprotective therapy: a promising signal

A striking observation was the association between hepatoprotective agents (e.g., curcuma, N-acetylcysteine) and 35% reduced odds of prolonged LOS. While this could reflect confounding by indication (sicker patients may receive more therapy), the magnitude of effect (aOR=0.35) merits attention. As these agents are low-cost and routinely available in the Indonesian formulary, pragmatic trials evaluating standardized protocols—particularly those involving parenteral administration—are warranted. If efficacy is confirmed, hepatoprotection could become a feasible intervention to mitigate LOS in district hospitals.

Strengths, limitations, and future research

Our study benefits from a large, granular dataset from a typical Indonesian secondary hospital, robust adjustment for confounders (e.g., "lead-time bias" via fever-onset timing), and clinically relevant endpoints. However, the small comorbidity subgroup (n = 71) reduced precision in interaction analyses. We assessed the public health impact of dengue-associated liver injury by quantifying its effect on hospital bed-day utilization – a critical metric for resource-constrained Indonesian health systems. Nevertheless, limitations exist alongside this study's strengths of granular data from a representative Indonesian hospital and robust confounder adjustment. Key limitations include the retrospective design (potentially introducing misclassification bias due to variable AST/ALT testing frequency), single-center data (limiting generalizability to primary care/puskesmas settings), heterogeneous hepatoprotective regimens (varying agents [e.g., curcuma vs. N-acetylcysteine] and doses), a small comorbidity subgroup (n = 71; reducing power for interaction analysis), and the COVID-19 era context—though sensitivity analysis excluding 2020–2021 data showed consistent results (aOR = 1.57, 95% CI: 1.08–2.28). Based on these findings, we advocate for including AST/ALT testing in dengue triage protocols at primary care puskesmas to identify patients requiring early transfer. Future research should validate hepatoprotective effects through multi-center RCTs, while national initiatives should pilot transaminase-guided discharge protocols across three provinces.

CONCLUSION

Elevated liver transaminases independently predict prolonged hospitalization in adult dengue patients, particularly those without comorbidities. This finding highlights the critical role of hepatic dysfunction in extending hospital stays—a key concern for Indonesia's resource-constrained health system. To optimize bed utilization and support national dengue control objectives (*STRANAS 2021-2025*), we recommend: 1) Routine AST/ALT monitoring for all dengue admissions to identify high-risk patients early; 2) Prioritizing hepatoprotective therapy (especially parenteral) in

clinical protocols to reduce recovery time; 3) Integrating liver function assessment into primary care (*puskesmas*) triage algorithms to guide timely referrals.

These actionable strategies can alleviate bed shortages during outbreaks, redirect resources to maternal/child services, and advance Indonesia's hospital efficiency goals. Future research should validate standardized hepatoprotective regimens through multicenter trials.

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