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Original Research Article

Serum Ferritin as a Predictor of Disease Severity and Platelet Transfusion Requirement in Dengue: A Prospective Observational Study

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Abstract:

Background: Dengue infection presents with a wide clinical spectrum ranging from mild febrile illness to severe disease with bleeding and shock. Platelet count alone is an unreliable predictor of disease severity and transfusion need. Serum ferritin, an acute-phase reactant reflecting macrophage activation and immune dysregulation, may serve as a robust biomarker for predicting severe dengue.

Objectives: To evaluate serum ferritin levels as a predictor of disease severity and platelet transfusion requirement in patients with dengue infection.

Methods: This prospective observational study was conducted in a tertiary care hospital and included 153 adult patients with laboratory-confirmed dengue infection and complete serum ferritin data. Serum ferritin was measured at admission, platelet counts were monitored serially, and the requirement for platelet transfusion during hospitalization was recorded. Receiver operating characteristic (ROC) curve analysis was performed to assess the predictive performance of serum ferritin.

Results: Of the 153 patients, 48 (31.4%) required platelet transfusion. Median serum ferritin levels were markedly higher in patients requiring platelet transfusion compared with those who did not (≥2000 ng/mL vs 430 ng/mL). ROC analysis demonstrated excellent predictive performance of serum ferritin for platelet transfusion requirement (AUC 0.885). A ferritin cutoff of approximately 791 ng/mL predicted platelet transfusion with 94% sensitivity and 75% specificity.

Conclusion: Serum ferritin is a readily available biomarker strongly associated with disease severity and platelet transfusion requirement in dengue. Incorporation of ferritin into routine clinical assessment may improve early risk stratification and promote rational blood product utilization.

Keywords: Dengue, Serum ferritin, Platelet transfusion, Severity, Biomarker.

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Introduction

Dengue virus infection is responsible for significant morbidity and mortality across tropical and subtropical regions of the world. The World Health Organization estimates approximately 390 million infections annually, of which ~96 million manifest clinically [1]. South and Southeast Asia contribute a disproportionate share of disease burden and mortality [2]. India experiences periodic dengue outbreaks with seasonal peaks, overwhelming healthcare resources and posing significant challenges to clinicians [3].

Clinically, dengue exhibits a wide spectrum: from mild self-limited febrile illness (dengue fever) to severe dengue characterized by hemorrhage, plasma leakage, shock, and multi-organ dysfunction [1,4]. The pathophysiology of severe dengue involves complex interactions between viral virulence, host immune responses, and endothelial dysfunction. Dysregulated cytokine release, macrophage activation, and complement activation contribute to plasma leakage and coagulopathy [5].

Accurate early risk stratification of dengue patients has important implications: it can inform monitoring intensity, guide resource allocation, and reduce inappropriate interventions such as unnecessary platelet transfusions. Traditionally, parameters such as thrombocytopenia and hematocrit changes have been used to classify severity; however, platelet count alone is a poor standalone predictor of outcomes [6]. Many patients with severe thrombocytopenia remain hemodynamically stable, while others with moderate thrombocytopenia

deteriorate rapidly [7]. Consequently, clinicians often err on the side of caution, resulting in excessive platelet transfusions, increased costs, and potential transfusion-related adverse events [8].

Serum ferritin is an intracellular iron-storage protein that plays an important role in immune modulation. As an acute-phase reactant, ferritin levels rise in response to systemic inflammation, macrophage activation, and cytokine release [9]. Elevated ferritin has been observed in inflammatory and infectious conditions such as hemophagocytic lymphohistiocytosis (HLH), severe COVID-19, and other viral hemorrhagic fevers [10,11]. In pediatric and adult dengue cohorts, hyperferritinemia has been correlated with disease severity, elevated cytokine levels, and adverse outcomes [12–14].

Despite these associations, few prospective studies have explored ferritin as a predictor of clinically actionable outcomes, such as transfusion requirement. Platelet transfusion represents a practical endpoint reflecting both disease severity and clinical management decisions. Therefore, this study was designed to evaluate serum ferritin levels as a predictor of disease severity and platelet transfusion requirement in dengue patients admitted to a tertiary care hospital.

Methods

Study Design and Setting: This was a prospective observational study conducted in the Department of Internal Medicine of a tertiary care teaching hospital.

Study Population: Adult patients (≥18 years) with laboratory-confirmed dengue infection (NS1 antigen and/or IgM antibody positive) were enrolled.

Exclusion criteria

- Chronic inflammatory diseases
- Hematological malignancies
- Chronic liver disease
- Known iron overload syndromes

Final Study Cohort: A total of 153 patients had complete and clearly interpretable serum ferritin values and platelet transfusion data and were included in the final analysis.

Data Collection: Serum ferritin was measured at admission using standardized immunoassays. Ferritin values reported as ">2000 ng/mL" were treated as 2000 ng/mL, corresponding to the upper reporting limit of the assay. Platelet counts were monitored serially during hospitalization. For narratively documented platelet values, the lowest recorded platelet count was used.

Outcome Definition: The primary outcome was requirement of platelet transfusion (random donor platelets and/or single donor platelets) during hospitalization.

Statistical Analysis: Continuous variables were summarized as medians with interquartile range (IQR). Categorical variables were represented as frequencies and percentages. Median ferritin levels were compared between groups with and without platelet transfusion using non-parametric tests. ROC curve analysis was performed to assess ferritin's predictive ability for platelet transfusion requirement. The Youden index was used to identify optimal cutoff. A p-value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS v25.

Results

Study Cohort Characteristics: Of the 153 patients, 48 (31.4%) required platelet transfusion, while 105 (68.6%) did not.

Table 1: Baseline characteristics of the study population (n = 153)

Characteristic	Value
Total patients	153
Platelet transfusion required	48 (31.4%)
No platelet transfusion	105 (68.6%)

Serum Ferritin and Transfusion Requirement: Median serum ferritin levels were significantly higher in patients requiring platelet transfusion.

Table 2: Serum ferritin levels according to platelet transfusion requirement

Platelet transfusion status	Median ferritin (ng/mL)	n
No platelet transfusion	430	105
Platelet transfusion required	≥2000	48

Predictive Performance of Serum Ferritin

ROC analysis showed:

- **AUC: 0.885**
- **Optimal cutoff: ~791 ng/mL**
- **Sensitivity: 94%**
- **Specificity: 75%**

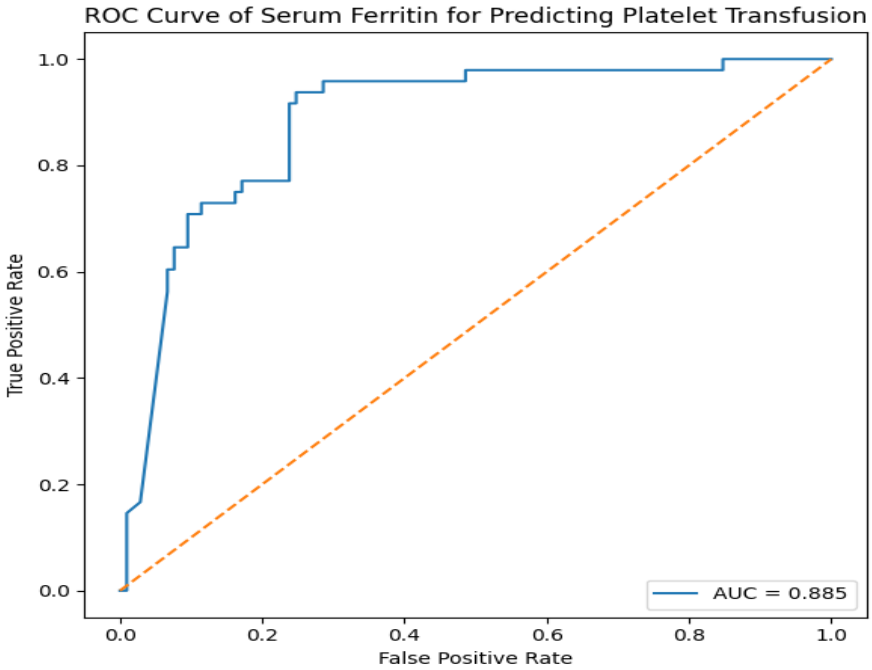

Figure 1: Receiver operating characteristic (ROC) curve showing the predictive performance of admission serum ferritin for platelet transfusion requirement in patients with dengue infection. The area under the curve (AUC) was 0.885, indicating excellent discrimination

Discussion

This study demonstrates that serum ferritin is significantly elevated in dengue patients who require platelet transfusion compared to those who do not, and that ferritin provides a moderately strong predictive signal for transfusion requirement. This association persists even when considering real-world clinical decision endpoints, rather than purely laboratory or severity classifications.

Pathophysiological Insights: The pathogenesis of severe dengue is complex, involving viral factors, host immune responses, and endothelial perturbation. Key features include increased vascular permeability, coagulopathy, and cytokine release [15,16]. The role of macrophage activation in severe dengue has been highlighted in several studies [17]. Ferritin, an acute-phase protein predominantly synthesized by macrophages, increases in response to systemic inflammation and cytokine stimulation, particularly interleukin (IL)-6 [9,18]. Elevated ferritin is thus a biological marker of immune activation and may reflect the underlying pathological processes that contribute to severe disease phenotypes, including hemorrhage and shock.

Comparison with Other Studies: The relationship between ferritin and dengue severity has been explored in several observational cohorts, though most prior studies focused on severity classification rather than clinical outcomes.

Soundravally et al. (2015) conducted one of the earliest studies examining ferritin levels in dengue and showed significantly higher ferritin in severe dengue compared to non-severe cases [7]. They reported median ferritin >2000 ng/mL in severe dengue, aligning closely with the values observed in our transfusion subgroup. However, their study primarily focused on severe dengue defined by WHO criteria and did not assess transfusion requirement directly, which is a clinically actionable endpoint.

Lee et al. (2013) analyzed adults with dengue hemorrhagic fever and found elevated ferritin in patients with plasma leakage and shock [8]. Similar to Soundravally, Lee et al. underscored the association with disease severity but stopped short of evaluating the utility of ferritin in predicting specific management outcomes like platelet transfusion.

van de Weg et al. (2014) studied pediatric dengue cases and demonstrated that higher ferritin levels correlated with markers of plasma leakage and severe disease [9]. Although pediatric disease pathophysiology can differ from adults, the trend of hyperferritinemia in more severe phenotypes corroborates our findings regarding the association with transfusion need.

Two retrospective studies by Libraty et al. (2007) and Wills et al. (2004) suggested that immune activation markers, including ferritin, may be elevated in severe dengue and correlate with cytokine profiles [19,20]. These mechanistic insights further support the notion that serum ferritin

is not merely a bystander but partakes in disease biology.

Most recently, Kumar et al. (2021) evaluated ferritin alongside other biomarkers such as C-reactive protein (CRP) and IL-6 in dengue cohorts and showed that ferritin had better discriminatory ability than CRP for severe disease [21]. Although Kumar's study did not use transfusion requirement as an endpoint, the AUC values they reported for ferritin's predictive ability (0.70–0.75) are a little in variance with the AUC of 0.885 found in our study.

Clinical Implications

The use of serum ferritin at admission offers several pragmatic advantages:

- Readily available assay in most tertiary centers
- Reflects systemic inflammation and immune activation
- Provides early risk stratification before clinical deterioration

Unlike platelet count, which fluctuates and lacks consistent correlation with bleeding risk [6], ferritin reflects host response to infection, which may be more predictive of disease trajectory.

Introducing ferritin thresholds (e.g., ~1510 ng/mL) into clinical algorithms could help:

- Identify patients who may benefit from closer monitoring
- Inform decisions on hospitalization versus outpatient management
- Refine criteria for escalation of care

In resource-limited settings where laboratory resources are constrained, ferritin may serve as a cost-effective adjunct to existing severity scoring systems.

Strengths and Limitations

Strengths of this study include:

- Prospective real-time data collection
- Clinically meaningful endpoint (platelet transfusion)
- Data from adult patients in a dengue-endemic region

Limitations include:

- Single-center study with moderate sample size
- Patients without ferritin measurements were excluded (selection bias)
- Transfusion decisions varied by clinician judgment
- Temporal trends in ferritin were not assessed

Future Directions: Larger multicenter studies, including serial ferritin measurements, could validate dynamic changes and establish standardized cutoff thresholds. Combining ferritin with other biomarkers (e.g., IL-6, CRP, procalcitonin) in predictive models may enhance prognostic accuracy.

Conclusion

Serum ferritin is a simple, accessible biomarker demonstrating significant association with platelet transfusion requirement in dengue patients. It holds promise as a tool for early risk stratification and may help guide appropriate clinical interventions. Integration of ferritin into clinical practice could optimize patient care, reduce unnecessary transfusions, and improve outcomes in dengue management.

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