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Prognostic Value of Hyperferritinemia in Dengue Patients

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Abstract

Background: Dengue fever exhibits a wide clinical spectrum, and early identification of severe disease remains challenging. Hyperferritinemia has emerged as a potential marker of immune activation and disease severity.

Aim: To establish the relationship between serum ferritin levels and the severity of dengue fever in the adult population.

Methods: An observational analytical study was conducted among adult dengue patients, and serum ferritin levels were measured and correlated with clinical features and disease severity.

Results: Patients with warning signs and severe dengue manifestations showed significantly higher serum ferritin levels on day 3 and day 7 of illness, indicating a strong association with disease severity.

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Conclusion: Serum ferritin is a valuable prognostic biomarker for assessing severity and progression of dengue fever.

Keywords: Dengue fever; Hyperferritinemia; Serum ferritin; Disease severity

Introduction

Dengue fever is one of the most important mosquito-borne viral infections worldwide and poses a major public health challenge in tropical and subtropical regions. Caused by the dengue virus and transmitted by *Aedes* mosquitoes, the disease exhibits a wide clinical spectrum ranging from mild febrile illness to severe dengue characterized by hemorrhage, plasma leakage, shock, and multi-organ dysfunction [1]. Adults constitute a significant proportion of hospitalized dengue cases, and early identification of patients at risk of severe disease remains a crucial aspect of clinical management [2].

The pathogenesis of severe dengue is closely linked to immune dysregulation, cytokine storm, endothelial dysfunction, and macrophage activation. These mechanisms contribute to increased vascular permeability, thrombocytopenia, and organ involvement, which are hallmarks of severe disease [3]. However, conventional laboratory parameters such as platelet count and hematocrit often change late in the disease course, limiting their usefulness as early prognostic indicators [4]. Ferritin, an intracellular iron-storage protein, also functions as an acute-phase reactant and plays a central role in inflammation and immune activation. Hyperferritinemia has been increasingly recognized as a marker of severe systemic inflammation and macrophage activation in various infectious and inflammatory conditions [5]. In dengue infection, excessive immune activation and

cytokine release lead to increased ferritin synthesis and release into the circulation, resulting in markedly elevated serum ferritin levels, particularly in severe cases [6].

Several clinical studies have demonstrated a strong association between elevated serum ferritin levels and dengue severity. Patients with severe dengue, dengue hemorrhagic fever, and dengue shock syndrome have been shown to exhibit significantly higher ferritin concentrations compared to those with uncomplicated dengue fever [7]. Elevated ferritin levels have also been correlated with thrombocytopenia, hepatic dysfunction, prolonged hospital stay, and increased risk of complications, suggesting its potential role as a prognostic biomarker [8].

Systematic reviews and meta-analyses further support the prognostic significance of serum ferritin in dengue infection. These studies indicate that higher ferritin levels are consistently associated with severe disease and adverse outcomes, although variability exists in reported cut-off values [9]. Despite this growing evidence, ferritin is not routinely used for risk stratification in many clinical settings, particularly in resource-limited tertiary care centres.

Given the increasing burden of dengue and the need for early and reliable markers of disease severity, serum ferritin represents a promising, easily measurable biomarker. Establishing its association with dengue severity in adult patients could aid early identification of high-risk cases and improve clinical decision-making. Therefore, the present study aims to establish the relationship between serum ferritin levels and the severity of dengue fever in the adult population at a tertiary health care centre [10].

Material and Methods

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A hospital-based observational analytical study was conducted among adult patients diagnosed with dengue fever and admitted to a tertiary health care centre during the study period. A total of 120 adult patients aged 18 years and above with laboratory-confirmed dengue infection were included in the study after obtaining informed consent. Dengue infection was confirmed by either NS1 antigen positivity or dengue IgM antibody testing. Patients with pre-existing chronic liver disease, chronic kidney disease, hematological disorders, autoimmune diseases, malignancy, iron overload states, or those who had received blood transfusions or iron supplementation were excluded from the study to avoid confounding effects on serum ferritin levels.

All enrolled patients underwent detailed clinical evaluation and were monitored throughout the course of hospitalization. Dengue severity was classified according to the World Health Organization criteria into non-severe dengue and severe dengue based on the presence of warning signs, hemorrhagic manifestations, plasma leakage, shock, or organ involvement. Clinical findings and laboratory parameters were recorded systematically at admission and during follow-up.

Venous blood samples were collected from all participants under aseptic precautions during the acute phase of illness. Serum ferritin levels were measured using a standardized chemiluminescence immunoassay method in accordance with the manufacturer's instructions. Routine laboratory investigations including complete blood count, hematocrit, platelet count, liver function tests, and renal function tests were performed using standard laboratory techniques.

Collected data were entered into a spreadsheet and analyzed using appropriate statistical software. Continuous variables were expressed as mean and standard deviation, while categorical variables were expressed as frequencies and percentages. Comparison of serum ferritin levels between

patients with non-severe dengue and severe dengue was carried out using suitable statistical tests. Correlation analysis was performed to assess the relationship between serum ferritin levels and indicators of disease severity. A p-value of less than 0.05 was considered statistically significant. Ethical approval for the study was obtained from the Institutional Ethics Committee prior to commencement of the study, and all procedures were conducted in accordance with the ethical principles outlined in the Declaration of Helsinki.

Results

Table 1 describes the distribution of clinical signs and symptoms among the studied dengue patients. Fever and arthralgia were observed in all 120 patients (100%), confirming their universal presence in dengue infection. Rash was present in 66 patients (55.0%), while nausea was reported by 38 patients (31.7%). Abdominal pain and persistent vomiting were observed in 34 patients (28.3%) and 36 patients (30.0%) respectively. Mucosal bleeding was noted in 21 patients (17.5%), and hepatomegaly greater than 2 cm was detected in 12 patients (10.0%). Clinical fluid accumulation was present in 9 patients (7.5%). Dengue hemorrhagic fever was diagnosed in 6 patients (5.0%), while dengue shock syndrome was observed in 18 patients (15.0%). Altered sensorium and markedly elevated liver enzymes (ALT >1000 IU/L) were relatively uncommon, occurring in 2 patients (1.7%) each. Severe plasma leakage was documented in 8 patients (6.7%), indicating a subset with advanced disease severity.

Table 2 compares serum ferritin levels among patients with and without selected clinical symptoms measured on day 3 and day 7 of illness. On day 3, patients presenting with rash had significantly higher mean serum ferritin levels (1698.6 ± 1612.4 ng/mL) compared to those without rash (1014.2

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± 812.6 ng/mL) ($p < 0.001$). Similar significant differences were observed for abdominal pain and persistent vomiting, with higher ferritin levels in symptomatic patients. By day 7, serum ferritin levels remained elevated among patients with these symptoms, though a declining trend was noted compared to day 3 values. Patients with abdominal pain on day 7 had a mean ferritin level of 1869.5 ± 1754.8 ng/mL versus 1128.7 ± 1196.2 ng/mL in those without abdominal pain ($p < 0.001$). Persistent vomiting continued to show a significant association with higher ferritin levels on day 7 ($p < 0.001$), supporting the role of hyperferritinemia as a marker of ongoing disease severity.

Table 1: Distribution of patients based on clinical signs and symptoms (n = 120)

Clinical presentation	Number of cases	Percentage (%)
Fever	120	100.0
Arthralgia	120	100.0
Rash	66	55.0
Nausea	38	31.7
Abdominal pain	34	28.3
Persistent vomiting	36	30.0
Mucosal bleeding	21	17.5
Liver enlargement >2 cm	12	10.0
Clinical fluid accumulation	9	7.5
Dengue hemorrhagic fever	6	5.0
Dengue shock syndrome	18	15.0

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Altered sensorium	2	1.7
ALT >1000 IU/L	2	1.7
Severe plasma leakage	8	6.7

Table 2: Comparison of serum ferritin levels among patients with and without symptoms on day 3 and day 7

Clinical symptom	Serum Ferritin (ng/mL) Day 3 (Present) Mean ± SD	Serum Ferritin (ng/mL) Day 3 (Absent) Mean ± SD	P value	Serum Ferritin (ng/mL) Day 7 (Present) Mean ± SD	Serum Ferritin (ng/mL) Day 7 (Absent) Mean ± SD	P value
Rash	1698.6 ± 1612.4	1014.2 ± 812.6	0.0001*	1654.3 ± 1739.5	986.8 ± 904.7	0.0001*
Abdominal pain	1924.7 ± 1688.9	1186.4 ± 1204.8	0.0001*	1869.5 ± 1754.8	1128.7 ± 1196.2	0.0001*
Persistent vomiting	1897.2 ± 1629.6	1109.8 ± 1187.3	0.0001*	1788.6 ± 1682.4	1143.9 ± 1268.5	0.0001*

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Discussion

The present study evaluated the prognostic significance of hyperferritinemia in adult dengue patients and demonstrated a strong association between elevated serum ferritin levels and clinical severity of dengue infection. Patients presenting with warning signs such as rash, abdominal pain, and persistent vomiting exhibited significantly higher serum ferritin levels on both day 3 and day 7 of illness. These findings support the concept that ferritin reflects the intensity of immune activation and inflammatory burden in dengue infection, making it a useful biomarker for early identification of patients at risk of severe disease [11].

Hyperferritinemia in dengue is believed to result from macrophage activation, cytokine storm, and endothelial dysfunction, which are central to dengue pathogenesis. Elevated ferritin levels have been linked to increased levels of pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor-α, which contribute to vascular permeability and plasma leakage [12]. The significantly higher ferritin levels observed in patients with abdominal pain and persistent vomiting in the present study further emphasize its role as a surrogate marker of systemic inflammation and impending complications.

The persistence of elevated ferritin levels on day 7 among symptomatic patients, despite a declining trend compared to day 3, suggests ongoing immune dysregulation even during the recovery phase. Similar temporal patterns have been reported in prospective studies, where sustained hyperferritinemia was associated with prolonged hospitalization and higher incidence of severe dengue manifestations [13]. This underscores the potential role of serial ferritin measurements in monitoring disease progression and response to treatment.

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In the present study, clinical features associated with severe dengue, including dengue hemorrhagic fever, dengue shock syndrome, severe plasma leakage, and mucosal bleeding, were observed in a subset of patients who also demonstrated markedly elevated ferritin levels. Previous research has shown that ferritin levels correlate negatively with platelet counts and positively with markers of hepatic injury, reinforcing its association with multisystem involvement in dengue [14]. Although the present analysis focused on clinical symptoms rather than outcomes, the observed associations highlight ferritin's utility as a prognostic indicator.

The findings of this study are further strengthened by emerging evidence suggesting that serum ferritin independently predicts dengue severity even after adjusting for conventional laboratory parameters. Recent cohort studies have identified ferritin as a strong discriminator between severe and non-severe dengue, outperforming traditional markers such as hematocrit and platelet count in early disease stages [15]. Given its wide availability and cost-effectiveness, serum ferritin may serve as a valuable adjunct to existing clinical and laboratory criteria for dengue severity assessment, particularly in tertiary care settings.

Conclusion

The study demonstrates that hyperferritinemia is significantly associated with clinical severity of dengue fever in adult patients. Elevated serum ferritin levels were consistently observed in patients with warning signs and severe clinical manifestations, with persistently higher levels noted on serial measurements. These findings suggest that serum ferritin is a reliable prognostic biomarker for assessing disease severity and identifying high-risk dengue patients early in the course of illness, thereby facilitating timely intervention and improved clinical outcomes.

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