ORIGINAL RESEARCH PAPER

Medicine

KEY WORDS:

SERUM FERRITIN AS A PROGNOSTIC MARKER IN ADULT DENGUE PATIENTS

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ABSTRACT

Background: Dengue is a major public health problem in tropical countries like India, with an unpredictable clinical course ranging from mild febrile illness to severe dengue associated with plasma leakage, bleeding, shock, and organ dysfunction. Early identification of patients at risk of developing severe dengue remains a challenge, as conventional laboratory markers often appear late in the disease course. Serum ferritin, an acute-phase reactant and marker of macrophage activation, has emerged as a potential early prognostic biomarker. **Objectives:** To evaluate the role of serum ferritin as a prognostic marker in adult dengue patients and to assess its correlation with disease severity, laboratory parameters, and clinical outcomes. **Methods:** This cross-sectional analytical study was conducted over 18 months at a tertiary care center in Rajasthan, India. A total of 135 adult patients with confirmed dengue infection were enrolled and classified according to WHO 2009 criteria into dengue without warning signs (Group A), dengue with warning signs (Group B), and severe dengue (Group C). Serum ferritin levels were measured on Day 1 and Day 4 of admission using a sandwich immuno-luminometric assay. Clinical features, hematological parameters, inflammatory markers, liver enzymes, and outcomes were analyzed and correlated with disease severity. **Results:** Serum ferritin levels showed a significant stepwise increase with increasing dengue severity. Mean ferritin levels on Day 1 were 520 ± 130 ng/mL in Group A, 1120 ± 240 ng/mL in Group B, and 2980 ± 550 ng/mL in Group C, with a further significant rise on Day 4. Serum ferritin demonstrated a strong inverse correlation with platelet count and a strong positive correlation with hematocrit, liver enzymes, plasma leakage, shock, and bleeding manifestations. Patients with severe dengue and secondary dengue infection showed markedly elevated ferritin levels. No mortality was observed in the study population. **Conclusion:** Serum ferritin is a reliable and early prognostic marker for assessing disease severity in adult dengue patients. Its routine use may aid in early risk stratification, timely intervention, and improved clinical outcomes, particularly in resource-limited settings.

INTRODUCTION

Dengue fever is a rapidly emerging arthropod-borne viral disease and a major public health concern in tropical and subtropical regions. It is caused by the dengue virus (DENV), a single-stranded RNA virus of the Flaviviridae family, with an estimated 390 million infections annually worldwide[1]. The virus has four antigenically distinct serotypes (DENV-1 to DENV-4). Infection with one serotype provides lifelong immunity to that serotype but increases the risk of severe disease during secondary infections due to antibody-dependent enhancement[2]. India bears a significant dengue burden, with outbreaks commonly occurring during the monsoon season[3]. Dengue presents with a wide clinical spectrum ranging from asymptomatic infection to severe dengue characterized by plasma leakage, bleeding, and organ dysfunction. The World Health Organization (WHO) classification (2009) categorizes dengue into dengue without warning signs, dengue with warning signs, and severe dengue[4]. However, early prediction of disease severity remains difficult as conventional laboratory markers often appear late in the disease course. Severe dengue is associated with a hyperinflammatory state resulting from immune dysregulation and cytokine storm, leading to endothelial dysfunction and multiorgan involvement[5]. Macrophage activation syndrome (MAS), a similar hyperinflammatory condition, has been increasingly linked with dengue infection[6]. Biomarkers such as serum ferritin reflect macrophage activation and systemic inflammation[7]. Ferritin, an acute-phase reactant, is significantly elevated in inflammatory conditions. In dengue, hyperferritinemia correlates with disease severity and may serve as an early prognostic marker, with levels above 1000–2000 ng/mL associated with severe disease[8,9]. Early identification of severe dengue is essential for improving outcomes, especially in resource-limited settings where management is primarily supportive. Ferritin estimation is simple, cost-effective, and widely available, making it a useful tool for early risk stratification[10]. Given the increasing burden of dengue and limited Indian data, this study aims to evaluate serum ferritin as an early predictor of disease severity in adult dengue patients.

AIM:

To evaluate serum ferritin as an early prognostic marker in adult dengue patients.

OBJECTIVE:

1. To measure serum ferritin levels in adult dengue patients.
2. To correlate serum ferritin levels with severity of dengue as per WHO 2009 classification.
3. To assess the association between serum ferritin levels and clinical outcomes such as shock, complications, and need for intensive care.

MATERIALS AND METHODS

Study Design: This is Cross sectional analytical study.

Study Place: Patients coming to the Out Patient Department as well as those admitted to the ward at Pacific Institute of Medical Sciences, Udaipur, Rajasthan.

Study Duration: 18 Months

Number of Cases: 135

Sampling Technique: All Dengue positive patients coming to the OPD as well as those getting admitted to the ward at Pacific Institute of Medical Sciences, Udaipur will be examined and studied after proper informed consent.

Sample Size Calculation:

Statistical Formula:

$n = 4pq/l^2$

P = Prevalence of sensitivity of serum ferritin was 94.1% [13]

q=(100-p)= 5.9%

l= Relatively error = 5% of prevalence=4.07

$n = 4*94.1*5.9/(4.07)^2 = 134.06$

Sample Size: 135

Inclusion Criteria:

- All fever cases which are dengue NS1 antigen positive or which show classical signs and symptoms of dengue.

- All patient who will give consent for participation.
- All patient of age 18 and above.

Exclusion Criteria

- Patients who do not have serological evidence of NS1 positivity or IgM antibody.
- Patient with anaemia (Hb <11g/dl) and transfusion dependent chronic disease

Method

All the dengue-positive cases were examined, and their clinical history was assessed. The dengue patients were classified according to severity as per the WHO 2009 guidelines, and their serum ferritin levels were estimated on day 1 (D1). The patients were monitored daily to assess the progression of the disease. A second sample was drawn on day 4 (D4) to estimate the serum ferritin levels. The ferritin levels on D1 and D4 of admission were compared with the severity of dengue. Day 1 corresponds to 3– 7 days of illness, whereas D4 corresponds to 7–11 days of illness. For purpose of our study, we categorized dengue without warning signs or probable dengue (according to the WHO definitions) as grade A, dengue with warning signs as grade B, and severe dengue as grade C.

Grouping of Dengue Patients According To levels of severity

- **Group A - Dengue Without Warning Signs**
- **Group B - Dengue with Warning Signs**

Warning Signs

- Abdominal pain or tenderness.
- Persistent vomiting.
- Clinical fluid accumulation.
- Mucosal bleed.
- Lethargy or restlessness.
- Liver enlargement > 2 cm.
- Laboratory finding of increasing HCT concurrent with rapid decrease in platelet count.

- **Group C - Severe Dengue**

- Severe Plasma leakage
- Severe bleeding
- Dengue hemorrhagic fever
- Dengue shock syndrome

Data Collection

Informed consent will be obtained from all patients to be enrolled for the study. In all the patient's relevant information will be collected in a predesigned and semi- structured Proforma. This will be conducted on Dengue positive patients coming to the OPD as well as those being admitted to the ward at Pacific Institute of Medical Sciences. A detailed history of most common presenting complaints like fever with rash, oedema, weakness or any other symptoms will be noted. Later, detailed history of other co- morbidities will be noted. Relevant blood investigations like CBC, C-Reactive Proteins, ESR, S. ferritin levels, will be performed.

There is significant role of serum ferritin as a prognostic indicator among adult dengue patients. Hence, there could be a need for early diagnosis and effective treatment of Dengue to avoid mortality, so serum ferritin plays a vital role as a prognostic indicator in diagnosis.

Statistical Analysis

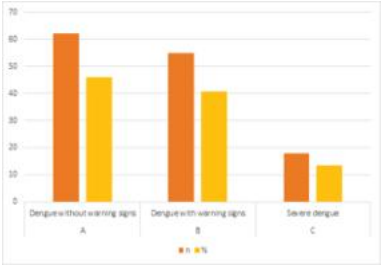
This data will be entered in MS Excel software and analysed using Statistical Packages for Social Sciences (SPSS). The data will be presented as number and percentages for the qualitative data, and mean, standard deviations and ranges for the quantitative data. Chi-square test will be used in the comparison of qualitative data and Fisher exact test will be used instead of the Chi-square test when the expected count in any cell found less than 5. The comparison between more than two groups with quantitative data and parametric distribution will be done by using One Way Analysis of Variance (ANOVA) test and Z test will be used. All tests were two sided. p-value < 0.05 was considered statistically significant.

Result

Table 1. Case Distribution According to Distribution of Dengue Patients According to Severity

Group	Description	n	%
A	Dengue without warning signs	62	45.9
B	Dengue with warning signs	55	40.7
C	Severe dengue	18	13.3
Total	—	135	100

As per the WHO 2009 classification, a total of 135 dengue patients were included in the study. Among them, 62 patients (45.9%) were classified as dengue without warning signs (Group A), 55 patients (40.7%) were classified as dengue with warning signs (Group B), and 18 patients (13.3%) were categorized as severe dengue (Group C). The findings indicate that the majority of patients belonged to the dengue without warning signs group, while severe dengue constituted the smallest proportion of the study population.



Graph 1. Case Distribution According to Distribution of Dengue Patients According to Severity

Basic Demographic Characteristics

A total of 135 patients with dengue infection were included in the study. The age distribution showed that the majority of patients belonged to the 31–45 years age group (38.5%), followed by 18–30 years (35.6%). Patients aged 46–60 years constituted 18.5% of the study population, while those aged above 60 years accounted for only 7.4%, indicating that dengue predominantly affected young and middle-aged adults.

There was a clear male predominance, with 82 patients (60.7%) being male and 53 patients (39.3%) being female. This trend was consistent across all severity groups, suggesting a higher exposure risk or healthcare-seeking behavior among males.

Table: Baseline Demographic Characteristics of Study Population (N = 135)

Variable	Category	Number (n)	Percentage (%)
Age (years)	18–30	48	35.6
	31–45	52	38.5
	46–60	25	18.5
	>60	10	7.4
Gender	Male	82	60.7
	Female	53	39.3

Clinical Features Across Severity Groups

Clinical features varied significantly with increasing severity of dengue. Fever was the most common symptom across all groups (>95%). Warning signs such as abdominal pain, vomiting, and mucosal bleeding were markedly higher in severe dengue. Shock was observed exclusively in severe dengue patients (44.4%), indicating disease progression.

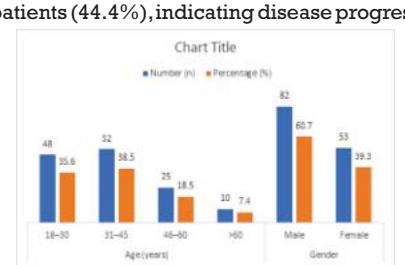


Table 3: Clinical Features Across Severity Groups

Feature	Group A	Group	Group C
Fever	60 (96.8%)	54 (98.1%)	18 (100%)
Abdominal pain	6 (9.6%)	30 (54.5%)	15 (83.3%)
Vomiting	12 (19.3%)	28 (50.9%)	16 (88.9%)
Mucosal bleed	0	10 (18.1%)	12 (66.7%)
Hepatomegaly	4 (6.4%)	14 (25.4%)	10 (55.6%)
Shock	0	0	8 (44.4%)

4. Hematological Parameters

Significant hematological alterations were observed with increasing disease severity. Platelet count showed a marked decline, while hematocrit increased significantly, indicating hemoconcentration. Total leukocyte count also decreased with severity.

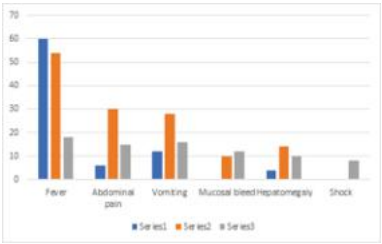


Table 4: Comparison of Hematological Parameters

Parameter	Group A	Group B	Group C	p-value
Hemoglobin (g/dL)	12.8 ± 1.1	12.4 ± 1.3	11.9 ± 1.4	0.04
WBC (/mm³)	4800 ± 1300	4200 ± 1200	3700 ± 1050	0.02
Platelets (/mm³)	135,000 ± 28,000	98,000 ± 24,000	54,000 ± 18,000	<0.001
Hematocrit (%)	38.4 ± 3.5	41.2 ± 4.1	46.3 ± 5.2	<0.001

5. Serum Ferritin Levels (Primary Outcome)

Serum ferritin levels showed a significant increase with both disease severity and progression over time. The highest values were observed in severe dengue patients, demonstrating a clear severity gradient (Group A < Group B < Group C).

Table 5: Serum Ferritin Levels (Day 1 vs Day 4)

Group	Day 1 (ng/mL)	Day 4 (ng/mL)	p-value
Group A	520 ± 130	610 ± 140	0.04
Group B	1120 ± 240	1560 ± 310	<0.001
Group C	2980 ± 550	4280 ± 720	<0.001

6. Correlation of Ferritin with Severity Indicators

Serum ferritin demonstrated strong correlations with key indicators of disease severity. It showed a significant negative correlation with platelet count and positive correlations with hematocrit, liver enzymes, plasma leakage, and shock.

Table 6: Correlation Analysis of Ferritin

Variable	Correlation (r)	p-value
Platelet count	–0.68	<0.001
Hematocrit	+0.61	<0.001
AST	+0.53	<0.001
ALT	+0.48	0.002
Plasma leakage	+0.72	<0.001
Shock	+0.79	<0.001

7. Clinical Outcome

The majority of patients recovered with standard ward-based management. A small proportion required ICU admission, mainly from severe dengue cases. No mortality was observed.

Table 7: Outcome Distribution

Outcome	Group A	Group B	Group C	Total
Recovered (ward)	62	50	10	122
ICU admission (recovered)	0	5	8	13
Mortality	0	0	0	0

Parameter	Group A	Group B	Group C	p-value
AST (IU/L)	48 ± 18	82 ± 26	148 ± 45	<0.001
ALT (IU/L)	42 ± 15	74 ± 22	132 ± 38	<0.001

Liver Function Parameters

The comparison of liver enzyme levels among the three dengue severity groups demonstrated a significant increase with increasing disease severity. The mean aspartate aminotransferase (AST) levels showed a progressive rise from 48 ± 18 IU/L in Group A (dengue without warning signs) to 82 ± 26 IU/L in Group B (dengue with warning signs), and further to 148 ± 45 IU/L in Group C (severe dengue). Similarly, alanine aminotransferase (ALT) levels increased from 42 ± 15 IU/L in Group A to 74 ± 22 IU/L in Group B and 132 ± 38 IU/L in Group C.

Both AST and ALT showed a statistically highly significant association with disease severity ($p < 0.001$), indicating increasing hepatic involvement with progression of dengue. These findings suggest that elevated liver enzymes are strongly correlated with severe dengue and may serve as important markers of disease severity.

DISCUSSION

In the present study, dengue patients were categorized according to WHO 2009 classification, with 45.9% having dengue without warning signs, 40.7% with warning signs, and 13.3% classified as severe dengue. This distribution indicates that the majority of patients presented with non-severe disease, while a smaller proportion progressed to severe dengue. Similar trends have been reported by Guzman MG et al. [16] and Lee IK et al.,[17] who observed that only a minority of dengue cases evolve into severe forms, emphasizing the importance of early identification of high-risk patients.

Dengue infection in the present study predominantly affected young and middle-aged adults, with a peak incidence in the 31–45 years age group, along with a clear male predominance. These findings are consistent with studies by Gupta E et al.[18] and Dash PK et al., [19] which also reported higher disease occurrence in males and working-age populations, likely due to increased outdoor exposure and vector contact.

Clinical features in this study demonstrated a strong association with disease severity. Fever was the most consistent symptom across all groups, while warning signs such as abdominal pain, vomiting, and mucosal bleeding increased significantly with severity. Notably, shock was observed exclusively in severe dengue cases, indicating advanced disease. These findings are in agreement with studies by Lee IK et al.[17] and Kalayanarooj S et al.,[20] which identified gastrointestinal symptoms, bleeding manifestations, and shock as key predictors of severe dengue. The progressive increase in hepatomegaly with severity further supports systemic involvement in advanced disease.

Hematological parameters showed significant alterations with increasing severity. A progressive decline in platelet count and leukocyte count, along with a rise in hematocrit, was observed. These findings are consistent with WHO guidelines and studies by Srikiatkhachorn A et al.,[21] which highlight thrombocytopenia and hemoconcentration as hallmark features of severe dengue. The inverse relationship between platelet count and disease severity underscores its importance in clinical monitoring.

A key finding of the present study was the significant elevation of serum ferritin levels with increasing disease severity and progression over time. Patients with severe dengue demonstrated markedly higher ferritin levels compared to non-severe groups. These findings are comparable to studies by Soundravally R et al.[11] and Van de Weg CA et al.,[12] which reported hyperferritinemia as a strong predictor of severe dengue and systemic inflammatory response. Ferritin, being an acute-phase reactant, reflects macrophage activation and

cytokine-mediated inflammation, both of which play a central role in dengue pathogenesis. The progressive rise in ferritin from Day 1 to Day 4 further supports its role as an early prognostic biomarker.

Liver enzyme levels (AST and ALT) were significantly elevated with increasing severity of dengue in the present study. These findings are in agreement with studies by Kuo CH et al. [22] which demonstrated that hepatic involvement is common in severe dengue and is associated with worse clinical outcomes. The higher elevation of AST compared to ALT observed in this study is also consistent with previous reports and may reflect systemic inflammation and muscle involvement in addition to hepatic injury.

Correlation analysis revealed that serum ferritin had a strong negative correlation with platelet count and positive correlations with hematocrit, liver enzymes, plasma leakage, and shock. These findings are consistent with previous studies, particularly by Van de Weg CA et al.,[12] which demonstrated that elevated ferritin levels are closely associated with disease severity and complications. The strong association with shock and plasma leakage highlights the potential of ferritin as a marker of severe systemic involvement.

In terms of clinical outcomes, the majority of patients recovered with supportive management, and no mortality was observed. A small proportion required ICU admission, primarily among severe dengue cases. These findings are comparable to those reported by Lee IK et al.[17] emphasizing that early diagnosis and appropriate management significantly improve outcomes in dengue patients.

CONCLUSION

The present study demonstrates that dengue severity is significantly associated with clinical warning signs, hematological alterations, and elevated inflammatory markers. Serum ferritin levels showed a strong correlation with disease severity and increased progressively with worsening clinical status.

These findings suggest that serum ferritin is a reliable and early prognostic biomarker for identifying patients at risk of severe dengue. Incorporation of ferritin estimation into routine clinical assessment may aid in early risk stratification, timely intervention, and improved patient outcomes.

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