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SERUM FERRITIN AS A SEVERITY PREDICTIVE INDICATOR IN CHILDREN WITH DENGUE A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Introduction*: Dengue fever, a mosquito-borne viral illness caused by four dengue virus serotypes, poses a significant health burden globally, particularly among children who are vulnerable to severe forms. Early prediction of severe dengue remains challenging. Serum ferritin, an acute-phase reactant, has emerged as a potential biomarker for severity. This study aims to evaluate serum ferritin as an early predictor of severity in pediatric dengue cases.*

Methodology*: A prospective observational study was conducted involving 42 children aged 1–18 years with confirmed dengue infection (NS1 antigen and/or IgM positive) admitted to RL Jalappa Hospital. Clinical data and laboratory investigations, including serum ferritin measured at admission by enhanced chemiluminescence, were collected. Statistical analysis using SPSS v22 included Chi-square, independent t-test, and ROC curve analysis, with significance set at $p < 0.05$.*

Results*: The study population had a mean age of 10.38 years with a female predominance (59.5%). Initial diagnosis at admission was classified as dengue without warning signs (57.1%), dengue with warning signs (9.5%), and severe dengue (33.3%) based on clinical features. Severe dengue was significantly associated with lower white blood cell counts ($p = 0.044$) and markedly reduced platelet counts (mean ~35,435 cells/mm³; $p = 0.001$). Serum ferritin levels showed a strong positive correlation with disease severity: dengue without warning signs (mean ~480 ng/mL), dengue with warning signs (~836 ng/mL), and severe dengue (~1349 ng/mL) ($p < 0.001$). Hemoglobin and packed cell volume did not differ significantly across severity groups.*

Conclusion*: Serum ferritin is a significant and reliable biomarker for predicting severity in pediatric dengue. Elevated ferritin levels correlate strongly with severe clinical manifestations, reflecting immune activation and plasma leakage. Incorporating serum ferritin measurement into clinical protocols may enhance early identification and management of high-risk pediatric dengue cases. Further standardization of ferritin cutoffs and timing is recommended to optimize clinical utility.*

Keywords*: Paediatric dengue, Serum ferritin, Dengue severity prediction, Thrombocytopenia, Hyperferritinemia*

INTRODUCTION

Dengue fever is a mosquito-borne viral illness caused by the dengue virus (DENV), which comprises four distinct serotypes (DENV-1 to DENV-4). In 2024, the global transmission of dengue reached unprecedented levels. The WHO documented 14,434,584 cases, with 7,718,585 confirmed through laboratory tests, 52,738 classified as severe, and 11,201 resulting in fatalities across all six regions. The spread of the virus intensified between February and May and remained elevated in several locations during the last quarter, highlighting the virus's increasing climate sensitivity and the growing urban presence of Aedes mosquitoes.[1] Children are particularly vulnerable to severe forms of the disease, including dengue with warning signs and severe dengue, which contribute significantly to morbidity and mortality in endemic regions.[2] Early prediction of severe dengue remains a clinical challenge. While the World Health Organization (WHO) criteria provide a framework for disease classification and management, the need for reliable laboratory markers to predict severity—especially in the early febrile phase—is increasingly recognized.[3] Serum ferritin, a well-known acute-phase reactant and iron storage protein, has

emerged as a potential biomarker in various inflammatory and infectious diseases, including dengue.[4] Elevated ferritin levels in dengue patients have been associated with increased disease severity, potentially reflecting the underlying hyperinflammatory state, cytokine storm, and immune dysregulation.[5,6] Some studies have demonstrated significantly higher ferritin levels in patients with severe dengue compared to those with non-severe manifestations, suggesting its utility as a prognostic marker.[7] In children, who may exhibit atypical presentations and more rapid clinical deterioration, timely identification of severe disease is critical. Therefore, evaluating serum ferritin as an early predictor of severity could aid in triaging, monitoring, and optimizing the management of paediatric dengue cases. This study aims to assess the role of serum ferritin as a predictive indicator of severity in children diagnosed with dengue fever.

AIMS AND OBJECTIVES

AIM: To assess the role of serum ferritin as a predictive indicator of severity in children diagnosed with dengue fever.

OBJECTIVES OF THE STUDY:

1. To estimate the serum ferritin levels in children between 1 to 18 years of age with dengue admitted in RLJH.
2. To study the correlation between serum ferritin levels and severity of clinical manifestations

MATERIALS AND METHODS

The study included all children aged 1–18 years with confirmed dengue infection (NS1 antigen positive and/or IgM positive) admitted to RL Jalappa Hospital and was conducted as a prospective observational study over one year after obtaining ethical clearance or until the required sample size was achieved. Inclusion criteria comprised all admitted children within the specified age range with dengue NS1 antigen or IgM positivity who provided informed consent, while exclusion criteria ruled out children with hematopoietic disorders such as thalassemia requiring regular blood transfusions, iron deficiency anemia, and patients with immunosuppression due to chemotherapy or radiotherapy. The sample size was calculated based on the sensitivity of serum ferritin levels (94.1%) for predicting severe dengue, as reported in a previous study, using the formula $n = (Z\alpha/2)^2 \times P \times (1 - P) / d^2$, where $P = 0.941$, $d = 0.075$, and $Z\alpha/2 = 1.96$ at a 95% confidence level, resulting in 38 subjects; accounting for a 10% non-response rate, the final sample size was 42 participants. Detailed clinical histories were obtained, and necessary investigations were performed for all participants, who were followed throughout the clinical course of the disease. After informed consent, 2 mL of venous blood was collected from each participant for serum ferritin assay at admission. Dengue infection was confirmed by NS1 antigen positivity during days 2–8 of illness and/or IgM positivity during days 6–10 of illness. Dengue IgM antibodies were estimated using a micro-ELISA kit autoanalyzer, NS1 antigen positivity detected using an ELISA kit, and serum ferritin levels measured by enhanced chemiluminescence using the Vitros 5600 analyzer. Data were entered into Microsoft Excel and analyzed with SPSS version 22 software; categorical variables were expressed as frequencies and proportions, continuous variables as mean and standard deviation. The Chi-square test assessed associations between qualitative variables, and the independent t-test compared means of quantitative variables. Receiver Operating Characteristic (ROC) curves evaluated the predictive value of serum ferritin for severe dengue, with sensitivity, specificity, positive predictive value, and negative predictive value calculated using optimal cut-off points from the ROC curve. A p-value of <0.05 was considered statistically significant. Graphical representations, including bar diagrams and pie charts, were prepared using MS Excel and MS Word.

RESULTS The mean age of the study participants was 10.38 ± 4.75 years, while the median age was 11.00 years. Fever was present in all participants (42, 100%), making it the most common clinical feature.

Table 1: Demographic and Clinical Characteristics of Study Participants

Parameter	Frequency (n)	Percentage (%)

Total participants	42	100
Age Distribution		
<5 years	9	21.4
6–10 years	10	23.8
11–15 years	17	40.5
>15 years	6	14.3
Mean age (years)	10.38 ± 4.75	—
Gender Distribution		
Male	17	40.5
Female	25	59.5
Common Clinical Features		
Fever	42	100
Nausea and vomiting	21	50.0
Abdominal pain	20	47.6
Myalgia	16	38.1
Lethargy/Restlessness	14	33.3
Clinical fluid accumulation	13	31.0
Mucosal bleeding	7	16.7
Persistent vomiting	4	9.5

Out of the 42 study participants, 24 (57.1%) were diagnosed with dengue without warning signs, making it the most common category. Severe dengue was observed in 14 participants (33.3%), while dengue with warning signs was reported in 4 participants (9.5%).

Table 2: Diagnosis and Vital Parameters

Parameter	Frequency (n)	Percentage (%)
Diagnosis		
Dengue without warning signs	24	57.1
Dengue with warning signs	4	9.5
Severe dengue	14	33.3
Vital Parameters (Mean ± SD)		
Pulse rate (bpm)	94.10 ± 13.2	—
Respiratory rate (bpm)	24.93 ± 6.31	—
Systolic BP (mmHg)	105.88 ± 8.82	—
Diastolic BP (mmHg)	65.66 ± 5.57	—
Temperature (°C)	38.75 ± 0.55	—
C-reactive protein (CRP) (mg/dL)	32.70 ± 27.78	—

Hematological analysis revealed no significant difference in hemoglobin or packed cell volume across severity groups. However, severe dengue was significantly associated with leukopenia (mean WBC ~4713 cells/mm³, p=0.044) and marked thrombocytopenia (mean platelet count ~35,435 cells/mm³, p=0.001). Packed cell volume showed a non-significant trend toward elevation in severe cases.

Table 3: Hematological Parameters by Dengue Severity

Parameter	Dengue without warning signs (Mean ± SD)	Dengue with warning signs (Mean ± SD)	Severe dengue (Mean ± SD)	p-value
Hemoglobin (g/dL)	12.87 ± 1.93	12.43 ± 0.70	13.60 ± 2.42	0.466
White blood cell count (cells/mm³)	6233.58 ± 2015.81	6838.50 ± 2372.28	4713.14 ± 1646.07	0.044*
Platelet count (cells/mm³)	108,696.63 ± 83,052.64	164,433.00 ± 58,738.59	35,434.57 ± 26,437.50	0.001*
Packed cell volume (%)	38.27 ± 4.98	34.33 ± 8.09	40.08 ± 7.38	0.259

*Statistically significant ($p < 0.05$)

Serum ferritin levels demonstrated a strong positive correlation with disease severity, rising from approximately 480 ng/mL in dengue without warning signs to over 1300 ng/mL in severe dengue ($p < 0.001$). This indicates hyperferritinemia as a reliable biomarker for early prediction of severe pediatric dengue.

Table 4: Serum Ferritin Levels by Dengue Severity

Severity Category	Mean Serum Ferritin (ng/mL) ± SD	Range (ng/mL)	p-value
Dengue without warning signs	479.81 ± 274.54	91.0 – 1184.1	<0.001*
Dengue with warning signs	836.00 ± 255.46	462.0 – 1000.0	
Severe dengue	1348.89 ± 700.89	1000.0 – 2930.4	

*Highly statistically significant ($p < 0.001$)

DISCUSSION

Hematological parameters demonstrated both consistencies and divergences across studies. The current study reported a mean hemoglobin (Hb) of 13.07 ± 2.03 g/dL with no statistically significant difference across severity groups, though a trend toward higher Hb in severe dengue was noted. This contrasts with Sekhar et al. and Prabhavathi et al., who observed lower Hb in severe dengue, suggesting possible hemolysis or bleeding effects.[8,9] Packed cell volume (PCV) showed a non-significant increase with severity in the current study (mean 40.08% in severe dengue), aligning with the hemoconcentration phenomenon described in Sekhar et al., Prabhavathi et al., and Valero et al., where elevated hematocrit

reflects plasma leakage.[8–10] White blood cell (WBC) counts in the current study averaged 5784 ± 2041 cells/mm³, with a significant leukopenia in severe dengue (4713 ± 1646) compared to less severe forms, consistent with Sekhar et al. and Golhar et al., who also linked leukopenia to severity.[8,11] Prabhavathi et al., however, reported elevated WBC in severe dengue (8429 cells/mm³), potentially reflecting secondary infections or inflammatory responses, highlighting variability in WBC dynamics across populations and disease phases.[9]

Platelet counts were markedly reduced in severe dengue across all studies. The current study found a mean platelet count of 35,435 ± 26,438 cells/mm³ in severe cases, closely mirroring Sekhar et al. and Prabhavathi et al., who documented progressive thrombocytopenia with severity and emphasized its clinical importance as a bleeding risk factor.[8,9] Golhar et al. similarly reported thrombocytopenia as a common and significant severity marker. [11] This consistency underscores thrombocytopenia's critical role in dengue pathophysiology and clinical monitoring.Serum ferritin emerged as a robust and consistent biomarker across the current and comparative studies. The current study demonstrated significantly elevated ferritin levels in severe dengue (1348.89 ± 700.89 ng/mL), paralleling Sekhar et al.'s identification of a 1200 ng/mL cut-off predictive of severe disease with high sensitivity during days 5 to 7 of illness.[8] Golhar et al. corroborated these findings, linking elevated ferritin with both severity and in-hospital mortality, with mean ferritin levels significantly higher in severe and non-survivor groups at admission and defervescence.[11] Valero et al. expanded on this by demonstrating concurrent elevation of ferritin and interleukin-18 (IL-18) in children with severe dengue, implicating immune activation and cytokine storm in pathogenesis.[10] Their study also revealed differential expression patterns of ferritin and IL-18 according to dengue virus serotypes, notably DENV-2 infection associated with higher IL-18 but lower ferritin levels, suggesting complex host-virus interactions influencing disease severity. This nuanced insight into cytokine and acute phase reactant dynamics enhances understanding of dengue immunopathology and supports ferritin's role as a prognostic biomarker. Integrating these findings, clinical indicators such as fever, nausea, abdominal pain, bleeding, fluid accumulation, and shock consistently correlate with laboratory markers including hematological indices, liver function tests, coagulation profiles, and particularly serum ferritin levels. The convergence of data from diverse geographic and demographic settings reinforces the utility of this integrated approach for early identification and management of severe dengue in pediatric populations. The consistent association of hyperferritinemia with severe disease and mortality underscores its potential value in clinical triage and monitoring, demanding further research to standardize ferritin cut-offs and elucidate its mechanistic role in dengue pathophysiology. Moreover, observed variations in WBC responses and the interplay of cytokines like IL-18 highlight the complexity of host immune responses, suggesting that personalized assessment incorporating viral serotype and immune profiling may enhance prognostic accuracy. The consistent patterns of thrombocytopenia, hemoconcentration, leukopenia, liver dysfunction, coagulation abnormalities, and hyperferritinemia across studies provide a robust framework for severity assessment. The emerging role of ferritin and related immunological markers as prognostic tools represents a promising avenue for improving dengue management and outcomes in children, especially in resource limited settings like India.

STRENGTHS AND LIMITATIONS

Strengths of the study include its prospective design, focused pediatric population, and use of standardized assays (enhanced chemiluminescence) for serum ferritin measurement, enabling reliable correlation with dengue severity. The study also employed robust statistical methods, including ROC curve analysis, to validate ferritin as a predictive biomarker.

Limitations involve the relatively small sample size (42 participants), which may affect generalizability. The single-center setting limits broader applicability across different regions or populations. Additionally, the study did not standardize the timing of ferritin measurement relative to disease onset, which could influence levels and predictive accuracy.

CONCLUSION

This study demonstrated a clear, statistically significant increase in ferritin levels with worsening disease severity, outperforming traditional markers such as hemoglobin and packed cell volume. Incorporating serum ferritin measurement into clinical protocols can enhance early identification and risk stratification of high-risk pediatric dengue cases, thereby improving triage and management decisions. To maximize clinical utility, further research is recommended to standardize ferritin cutoff values and optimal timing of measurement, especially for application in resource-limited settings.

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