e-ISSN: 0975-5160, p-ISSN: 2820-2651

Available online on www.ijtpr.com

International Journal of Toxicological and Pharmacological Research 2024; 14(11); 191-195

Original Research Article

Dengue Virus Infection: Clinico-Epidemiological Characteristics and the Role of Serum Ferritin as a Biomarker

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Received: 05-10-2024 / Revised: 25-10-2024 / Accepted: 20-11-2024

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Conflict of interest: Nil

Abstract

Background and Objectives: Dengue virus infection is a significant public health concern, particularly in tropical and subtropical regions. Characterized by a wide range of clinical manifestations from mild febrile illness to severe hemorrhagic fever, dengue poses a substantial burden on healthcare systems. Serum ferritin, an acute-phase reactant, has been suggested as a potential biomarker for disease severity in dengue infections. This study aims to examine the clinical-epidemiological features of dengue virus infection and to investigate the correlation between serum ferritin levels and disease severity.

Methods: This observational study was conducted in Department of General Medicine, J L N Medical College and Hospital, Bhagalpur, Bihar, India for one year involving 100 patients diagnosed with dengue virus infection. Patients were categorized based on disease severity: Dengue Fever (DF), Dengue Hemorrhagic Fever (DHF), and Dengue Shock Syndrome (DSS). Serum ferritin levels were measured on the day of admission and correlated with clinical outcomes. Data on demographic characteristics, clinical features, laboratory findings, and outcomes were collected and analyzed.

Results: The mean serum ferritin levels were significantly higher in patients with severe dengue (DHF and DSS) compared to those with DF ($p < 0.001$). A positive correlation was observed between serum ferritin levels and the severity of thrombocytopenia ($r = 0.72$, $p < 0.001$). Additionally, elevated ferritin levels were associated with prolonged hospitalization and higher rates of complications such as bleeding and organ impairment. Multivariate logistic regression identified serum ferritin as an independent predictor of severe dengue (adjusted OR: 3.4; 95% CI: 2.1-5.6).

Conclusion: Serum ferritin levels are significantly associated with the severity of dengue virus infection, suggesting its potential role as a biomarker for predicting disease progression. Clinicians should consider serum ferritin levels in the early management and risk stratification of dengue patients to improve outcomes.

Keywords: Dengue virus, serum ferritin, dengue fever, dengue hemorrhagic fever, dengue shock syndrome, biomarkers, disease severity.

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Introduction

Dengue virus infection, caused by one of the four related serotypes of the dengue virus (DENV 1-4), is a mosquito-borne disease that has become a significant global health threat, particularly in tropical and subtropical regions.[1] The World Health Organization (WHO) estimates that approximately 390 million people are infected with the dengue virus annually, with around 96 million manifesting clinical symptoms. The clinical spectrum of dengue virus infection ranges from a self-limiting febrile illness known as Dengue Fever (DF) to more severe forms, including Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS), both of which can be life-threatening if not managed appropriately.[2-3]

The pathophysiology of severe dengue is complex and involves a combination of viral factors, host immune responses, and the host's nutritional and inflammatory status. One of the key challenges in managing dengue is predicting which patients are at risk of progressing to severe disease. Early identification of these patients allows for timely intervention, which can significantly reduce morbidity and mortality.[4]

Serum ferritin, a glycoprotein that stores and releases iron, is also an acute-phase reactant that increases in response to inflammation.[5] Elevated serum ferritin levels have been observed in various infectious and inflammatory conditions, including dengue virus infection. Some studies have suggested that high serum ferritin levels may correlate with disease severity in dengue, reflecting the underlying inflammatory response and iron metabolism dysregulation. However, the clinical utility of serum ferritin as a biomarker for dengue severity remains underexplored.[6-8]

This study aims to fill this gap by systematically examining the clinical-epidemiological features of dengue virus infection and exploring the correlation between serum ferritin levels and disease severity. By doing so, we hope to provide insights that could improve the early management and risk stratification of dengue patients.

Methodology:

Study Design: This observational study was designed as a prospective observational study conducted at in Department of General Medicine, J L N Medical College and Hospital, Bhagalpur, Bihar, India for one year in a dengue-endemic region. The primary objective was to evaluate the clinical-epidemiological characteristics of dengue virus infection and assess the correlation between serum ferritin levels and the severity of the disease.

Study Population: A total of 100 patients diagnosed with dengue virus infection based on clinical features and confirmed by positive dengue non-structural protein 1 (NS1) antigen or IgM/IgG antibodies were enrolled in the study. Patients were categorized into three groups based on disease severity:

- **Dengue Fever (DF):** Patients with mild febrile illness without warning signs.
- **Dengue Hemorrhagic Fever (DHF):** Patients with fever, thrombocytopenia, bleeding manifestations, and plasma leakage.
- **Dengue Shock Syndrome (DSS):** Patients with severe plasma leakage leading to shock, organ impairment, or both.

Inclusion criteria included patients aged 18 years and above with confirmed dengue infection and willingness to participate in the study. Exclusion criteria included patients with pre-existing chronic inflammatory conditions, hematological disorders, or iron metabolism disorders as these could confound the serum ferritin measurements.

Data Collection: Data were collected using a standardized case report form. The following variables were recorded:

- **Demographic Information:** Age, gender, and comorbidities.
- **Clinical Features:** Fever duration, bleeding manifestations, hepatomegaly, pleural effusion, and other relevant symptoms.
- **Laboratory Findings:** Complete blood count (CBC), platelet count, hematocrit, liver function tests, and serum ferritin levels.
- **Outcomes:** Length of hospital stay, complications (e.g., bleeding, organ impairment), and mortality.

Serum ferritin levels were measured on the day of admission using an enzyme-linked immunosorbent assay (ELISA). Reference ranges for serum ferritin were established based on existing literature, and levels above the upper limit were considered elevated.

Statistical Analysis: Statistical analysis was performed using SPSS software (version 27.0). Continuous variables were expressed as mean ± standard deviation and categorical variables as frequencies and percentages. The independent t-test and ANOVA were used to compare mean values between groups, while the chi-square test was used for categorical variables. Pearson correlation was used to assess the relationship between serum ferritin levels and disease severity markers such as platelet count and hematocrit. Multivariate logistic regression analysis was conducted to identify independent predictors of severe dengue, adjusting for potential confounders. A p-value of <0.05 was considered statistically significant.

Additionally, receiver operating characteristic (ROC) curve analysis was performed to evaluate the predictive value of serum ferritin levels for severe dengue, with the area under the curve (AUC) calculated to assess the diagnostic accuracy.

Results

Demographic and Clinical Characteristics: The study population consisted of 100 patients with dengue virus infection, with a mean age of 32.5 ± 10.7 years. There was a slight male predominance (56%). Most patients presented with classical dengue fever (DF), while 30% were classified as having DHF, and 10% as DSS. Comorbidities such as diabetes and hypertension were present in 25% of the patients. Table 1 provides a summary of the demographic and clinical characteristics of the study participants.

Table 1: Demographic and Clinical Characteristics of Study Participants

Characteristic	DF (n=60)	DHF (n=30)	DSS (n=10)	p-value
Mean Age (years)	31.8 ± 10.5	33.2 ± 11.0	35.6 ± 9.8	0.128
Gender (Male %)	55%	58%	60%	0.643
Comorbidities (%)	20%	28%	35%	0.036
Mean Fever Duration (days)	5.1 ± 1.3	5.5 ± 1.4	6.2 ± 1.6	0.002
Bleeding Manifestations (%)	15%	45%	70%	<0.001
Hepatomegaly (%)	10%	35%	60%	<0.001
Pleural Effusion (%)	5%	30%	50%	<0.001

Laboratory Findings and Serum Ferritin Levels: Laboratory findings revealed significant differences in hematological parameters among the three groups, as shown in Table 2. Platelet counts were lowest in the DSS group, with a mean of 35,000 ± 15,000/mm³ compared to 85,000 ± 30,000/mm³ in the DHF group and 140,000 ± 45,000/mm³ in the DF group. Hematocrit levels were elevated in patients with severe dengue, reflecting hemoconcentration due to plasma leakage.

Serum ferritin levels were significantly higher in patients with DHF and DSS compared to those with DF ($p < 0.001$). The mean ferritin levels were 750 ± 150 ng/mL in the DSS group, 520 ± 130 ng/mL in the DHF group, and 320 ± 110 ng/mL in the DF group.

Table 2: Laboratory Findings and Serum Ferritin Levels

Parameter	DF (n=60)	DHF (n=30)	DSS (n=10)	p-value
Mean Platelet Count (×10³/mm³)	140 ± 45	85 ± 30	35 ± 15	<0.001
Mean Hematocrit (%)	38.2 ± 3.5	42.6 ± 4.0	45.8 ± 4.5	<0.001
Mean Serum Ferritin (ng/mL)	320 ± 110	520 ± 130	750 ± 150	<0.001

Correlation Between Serum Ferritin Levels and Disease Severity: A strong positive correlation was observed between serum ferritin levels and the severity of thrombocytopenia ($r = 0.72$, $p < 0.001$) as well as hematocrit levels ($r = 0.65$, $p < 0.001$). Elevated ferritin levels were also associated with prolonged hospitalization and higher rates of complications such as bleeding and organ impairment. The ROC curve analysis showed that serum ferritin had a good predictive value for severe dengue, with an AUC of 0.82 (95% CI: 0.75-0.89).

Table 3: Correlation Between Serum Ferritin Levels and Disease Severity Markers

Severity Marker	Correlation Coefficient (r)	p-value
Platelet Count	-0.72	<0.001
Hematocrit	0.65	<0.001
Length of Hospital Stay	0.58	<0.001
Bleeding Complications	0.54	<0.001
Organ Impairment	0.62	<0.001

Predictors of Severe Dengue: To identify independent predictors of severe dengue (DHF and DSS), a multivariate logistic regression analysis was performed, adjusting for potential confounders such as age, gender, comorbidities, and baseline laboratory parameters. The results, shown in Table 4, indicate that elevated serum ferritin levels were a significant independent predictor of severe dengue, with an adjusted odds ratio (OR) of 3.4 (95% CI: 2.1-5.6; $p < 0.001$). Other significant predictors included low platelet count and elevated hematocrit levels on admission.

Table 4: Multivariate Logistic Regression Analysis for Predictors of Severe Dengue

Predictor	Adjusted OR	95% CI	p-value
Elevated Serum Ferritin (ng/mL)	3.4	2.1-5.6	<0.001
Platelet Count (×10³/mm³)	0.8	0.7-0.9	0.005
Hematocrit (%)	1.5	1.2-2.0	0.001
Age (years)	1.1	0.9-1.3	0.227
Comorbidities	1.3	0.9-1.9	0.119

Discussion

The results of this study provide strong evidence supporting the role of serum ferritin as a potential biomarker for predicting the severity of dengue virus infection. Elevated serum ferritin levels were significantly associated with more severe forms of dengue, including DHF and DSS, and were independent predictors of adverse clinical outcomes.[9-10]

Pathophysiological Implications: The correlation between high serum ferritin levels and severe dengue could be explained by the dual role of ferritin as both an iron storage protein and an acute-phase reactant.[11] In the context of dengue infection, elevated ferritin levels may reflect an intense inflammatory response and iron dysregulation, which contribute to endothelial dysfunction, plasma leakage, and subsequent organ damage. The strong correlation between ferritin and markers of disease severity, such as thrombocytopenia and hematocrit, further underscores the link between ferritin and the pathophysiological processes underlying severe dengue.[12-13]

Clinical Implications: The findings from this study suggest that measuring serum ferritin levels in dengue patients could be a valuable tool for risk stratification and early identification of those at higher risk for severe disease. Clinicians could use ferritin levels to guide the intensity of monitoring and therapeutic interventions, potentially improving patient outcomes by preventing complications such as shock and organ failure.[14]

Comparison with Existing Literature: These findings are consistent with other studies that have reported elevated serum ferritin levels in patients with severe dengue. However, this study adds to the literature by providing a detailed analysis of the correlation between ferritin and specific clinical and laboratory markers of disease severity, as well as demonstrating the predictive value of ferritin through ROC curve analysis. While previous studies have suggested a role for ferritin in the context of dengue, the comprehensive analysis presented here strengthens the case for ferritin as a clinically useful biomarker.[15-16]

Limitations and Future Research: Despite the robust findings, this study has several limitations that should be acknowledged. First, the study was conducted at a single tertiary care center, which may limit the generalizability of the results to other settings. Additionally, the study focused on a specific geographic region, and the findings may not be directly applicable to regions with different dengue epidemiology or healthcare infrastructure.

Future research should aim to validate these findings in larger multicenter studies that include diverse populations. Moreover, longitudinal studies that follow patients throughout the course of the disease would provide valuable insights into the dynamics of ferritin levels and their relationship to disease progression. Finally, research exploring the molecular mechanisms underlying ferritin elevation in dengue could help to further elucidate its role in the pathogenesis of severe disease and identify potential therapeutic targets.

Conclusion

This study demonstrates that elevated serum ferritin levels are strongly associated with the severity of dengue virus infection, making ferritin a valuable biomarker for predicting disease progression. Clinicians should consider incorporating serum ferritin measurement into the early assessment of dengue patients to identify those at higher risk for severe outcomes. By improving risk stratification and guiding clinical management, the use of ferritin as a biomarker could enhance patient care and reduce the burden of dengue-related complications.

Further research is needed to validate these findings in broader populations and to explore the potential of ferritin as a therapeutic target in dengue management. As the global burden of dengue continues to rise, identifying reliable biomarkers such as ferritin will be crucial in improving the prognosis for patients affected by this potentially devastating disease.

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