Dengue Diagnosis Demystified: The Significance of Serum Ferritin

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ABSTRACT

Dengue fever, a globally prevalent viral hemorrhagic disease caused by the Flavivirus genus, poses a substantial public health threat. The disease, transmitted by Aedes mosquitoes, affects millions globally, with diverse clinical manifestations. Diagnosis relies on detecting NS1 antigen and IgM antibodies but recent studies propose serum ferritin as a potential diagnostic marker with prognostic implications. To assess serum ferritin's diagnostic efficacy in dengue and explore its correlation with disease severity and patient outcomes. A hospital-based prospective study involving 49 Dengue-positive cases was conducted, focusing on NS1-positive or IgM-positive patients. Serum ferritin levels were measured on admission (Day 1) and Day 5. Statistical analysis employed Jamovi software, with a $p<0.05$ considered significant. Among 49 Dengue-positive cases the average age was 47.4 ± 20.9 for females and 29.4 ± 13.0 for males. Day 1 Ferritin levels ranged predominantly from 1500->1650 ng mL^{-1}, while Day 5 Ferritin consistently fell below 500 ng mL^{-1}. A 12.2% mortality rate was observed having a trend of higher values of ferritin levels on Day 5, emphasizing the severity of the disease. The study reveals significant age disparities and a concerning mortality rate, emphasizing the need for nuanced interventions. Day 1 and Day 5 Ferritin dynamics offer insights into the inflammatory response, potentially aiding in predicting disease severity and guiding clinical decisions. Tailored interventions and ongoing research are essential for Dengue management, emphasizing age-specific vulnerabilities and the integration of Ferritin monitoring in routine assessments for timely adjustments. Continuous surveillance is recommended for early outbreak detection.

INTRODUCTION

Dengue fever, a globally significant viral hemorrhagic disease, is caused by the Flavivirus genus's Arbovirus, with four distinct serotypes. It affects approximately 3.97 billion people in 128 endemic countries, including India, and is transmitted by Aedes aegypti and Aedes albopictus mosquitoes. The illness manifests in four spectrums asymptomatic, acute febrile, classic dengue fever (with or without hemorrhagic manifestation) and dengue hemorrhagic fever (including Dengue Shock Syndrome and expanded dengue syndrome). Clinical suspicion arises when an acute febrile illness of 2-7 days presents with two or more of the following headache, retroorbital pain, myalgia, arthralgia, rash and hemorrhagic manifestations[1].

Dengue diagnosis involves NS1 antigen detection via ELISA within the initial 5 days, followed by IgM detection through MAC-ELISA, detectable within 5-7 days but possibly up to 12 days. NS1 is highly sensitive (>90%) in the first 2-3 days, decreasing after day 5. Dengue-specific IgM, with a slow response (50% at 3-5 days, 80% >5 days, 99% at day 10), is delayed in secondary infections. In secondary DVI, IgM response is delayed, and IgG appears earlier than IgM. Elevated serum ferritin, a diagnostic surrogate post-NS1 cessation, correlates with an increased risk of complications. Studies suggest a strong correlation between serum ferritin levels and the severity of dengue infection, with serum ferritin on the 4th or 5th day providing an indicative measure for dengue infection[2].

A study from the Caribbean island Aruba concluded that ferritin can be used as a clinical marker to discriminate between dengue and other febrile illnesses. The occurrence of hyperferritinemia in dengue virus infected patients is indicative for highly active disease resulting in immune activation and coagulation disturbances. Therefore, patients with hyperferritinemia are recommended to be monitored carefully. The same study concluded that high serum ferritin level with a cut-off p>1500 in confirmed DENV infection is associated with increased severity of dengue related illness in adults. Ferritin levels measured at Day 4-5 may be a good predictor in outcome in dengue[3].

Aims and objectives:

- To evaluate the diagnostic efficacy of serum ferritin in dengue fever
- To find out the correlation between serum ferritin levels with dengue severity and patient outcomes

MATERIALS AND METHODS

This hospital-based prospective study employs a cross-sectional design and is conducted in the Department of General Medicine, KPC Medical College and Hospital in Kolkata, West Bengal, during the period from August 2023, to September, 2023 (a period when dengue incidence was on the high). The study focuses on patients with NS1 positivity (Days 2-8) and/or positive IgM for dengue (Days 6-10) prior to discharge were considered to be dengue cases. Inclusion criteria encompass patients aged 15 years and above and exclusion criteria apply to all those patients that involved anemia, chronic inflammatory disease, chronic comorbid conditions and a recent blood transfusion. The sample size for this study is 49 which was determined employing complete enumeration sampling technique fulfilling the inclusion criteria. All the dengue-positive cases were examined, and their clinical history was assessed. The dengue patients' 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 5 (D5) to estimate the serum ferritin levels. The ferritin levels on D1 and D5 of admission were compared with the prognosis of dengue and patient's outcome. Day 1 corresponds to 3-7 days of illness, whereas D5 corresponds to 7-11 days of illness.

Statistical methods: Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on mean±SD and results on categorical measurements are presented in numbers (%). A p<0.05 was considered statistically significant. The following assumptions on data are made. Normality of data was tested by Shapiro-Wilk test and Kolmogorov-Smirnoff test and visually by Q-Q plot. Histogram and Box-Plots were shown to compare multiple groups of data. The statistical software, namely, Jamovi version 2.4.11 for Windows were used for the analysis of the data. Microsoft Word 2010 and Microsoft Excel 2010 have been used to generate Tables.

RESULTS

Over a span of 2 months, our hospital admitted 49 patients with confirmed Dengue infections to either General wards or Intensive Care Units (ICU). Comprehensive data, derived from a variety of blood reports, was meticulously gathered and subsequently subjected to thorough analysis. The average age of the study cohort stood at 47.4±20.9 for females and 29.4±13.0 for males, encompassing individuals aged between 15 and 88 years. Among the 49 patients diagnosed with Dengue, a regrettable 12.2% specifically, 6 individuals-succumbed to mortality Fig 1-6 and Table 1.

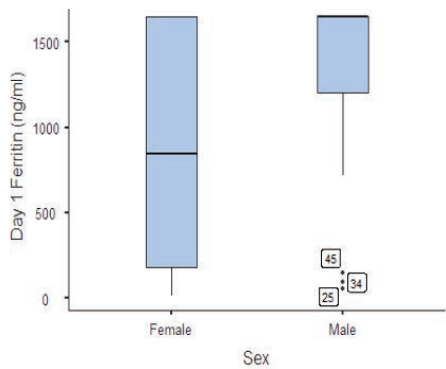Examination of Day 1 Ferritin (ng mL^{-1}) revealed mean values of 1324±544 for males and 850±633 for

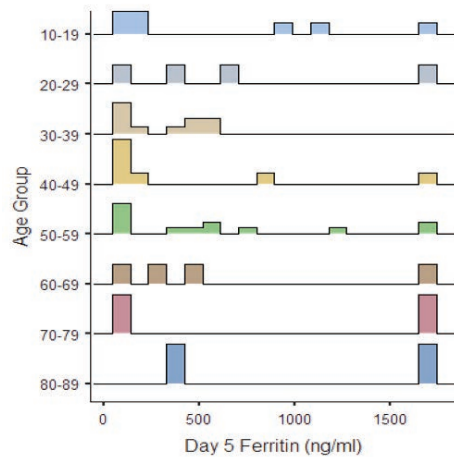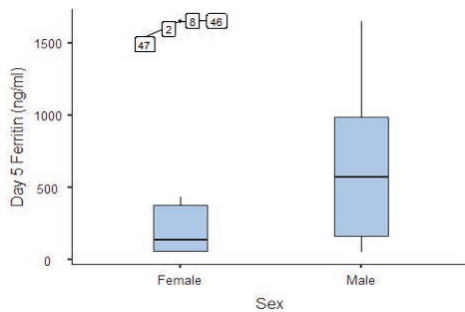Fig. 1: The average duration of hospitalization was 6.79±1.56 for males

Fig. 2: The average duration of hospitalization was 6.36±1.55 for females

Fig. 3: The average duration of hospitalization was 6.79±1.56 for male age group

females, while Day 5 Ferritin (ng mL^{-1}) exhibited mean values of 685±551 for males and 408±568 for females. The average duration of hospitalization was 6.79±1.56 for males and 6.36±1.55 for females. An analysis of the histogram underscores that, on Day 1, Ferritin levels across all age groups were predominantly concentrated within the range of 1500 to >1650 ng mL^{-1}.

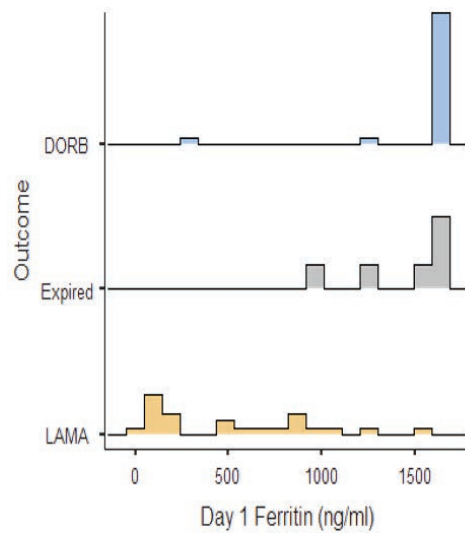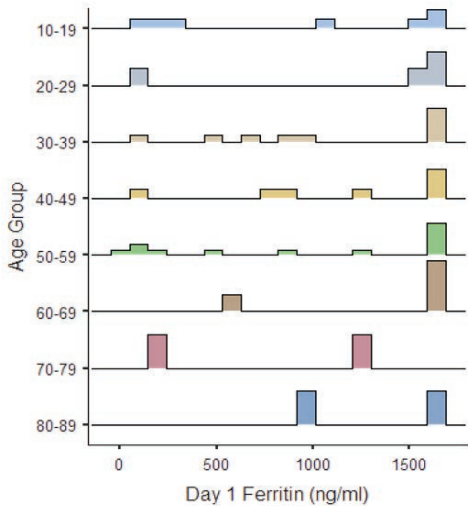Fig. 4: The average duration of hospitalization was felame age group

Fig. 5: The average duration of hospitalization was 6.79±1.56 for males outcome

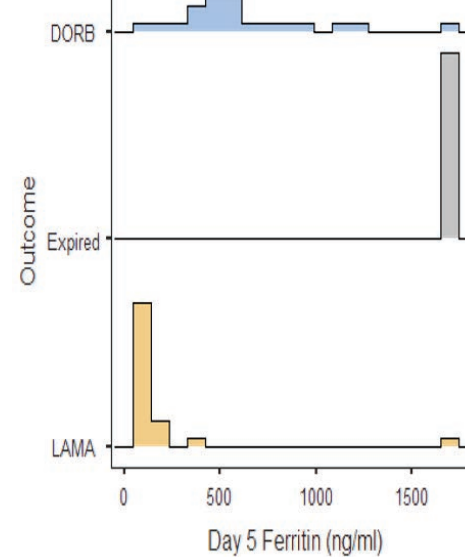Fig. 6: The average duration of hospitalization was 6.36±1.55 for females outcome

Table 1: Dengue infections

Descriptives					
	Sex	Age	Day 1 Ferritin (ng/ml)	Day 5 Ferritin (ng/ml)	Duration of Hospital Stay
N	Female	25	25	25	25
	Male	24	24	24	24
Mean	Female	47.4	850	408	6.36
	Male	29.4	1324	685	6.79
Median	Female	44	843	138	6
	Male	24.5	1650	571	7.00
Standard deviation	Female	20.9	633	568	1.55
	Male	13.0	544	551	1.56

Conversely, the trend for Day 5 Ferritin in each age group consistently fell below the threshold of 500 ng mL^{-1}. Importantly, this histogram signifies that patients who succumbed to the infection exhibited a higher mean value (1500->1650) in Day 5 Ferritin, whereas those who chose DORB (Do Not Resuscitate/Do Not Opt for Resuscitation) and LAMA (Leave Against Medical Advice) demonstrated a mean value of Day 5 Ferritin ranging from 0-500 ng mL^{-1}.

DISCUSSIONS

The findings of our prospective study on Dengue-positive patients present a compelling snapshot of the disease's impact within our hospital over a two-month period. The mean age disparity between male and female patients, with females averaging 47.4±20.9 years and males 29.4±13.0 years, underscores potential gender-specific susceptibility or reporting patterns. Alarming is the 12.2% mortality rate observed among the 49 Dengue-positive patients, highlighting the severity of the disease. This rate calls for a nuanced exploration of factors contributing to mortality, addressing the urgent need for targeted interventions to reduce fatalities. The examination of Ferritin dynamics reveals intriguing patterns, particularly on Day 1 and Day 5. The concentration of Day 1 Ferritin, with a major attribution in the range of 1500->1650 ng mL^{-1} across all age groups, prompts questions about its predictive value and association with disease severity[4].

Contrastingly, the trend in Day 5 Ferritin consistently falls below the range of 500 ng mL^{-1}, indicating a potential shift in the inflammatory response during the course of the illness. Noteworthy is the association between Day 5 Ferritin levels and patient outcomes. Patients who succumbed to the disease exhibited higher mean Day 5 Ferritin values (1500->1650 ng mL^{-1}), whereas those opting for discharge against medical advice or leaving against medical advice (DORB and LAMA) showed lower mean values (0-500 ng mL^{-1}). This suggests a potential prognostic significance of Day 5 Ferritin in predicting outcomes and could guide clinical decision-making[5].

CONCLUSION

In conclusion, our two-month prospective study on Dengue-positive patients revealed significant age disparities and a concerning 12.2% mortality rate. The dynamic patterns of Day 1 and Day 5 Ferritin levels offer insights into the inflammatory response, with potential implications for predicting disease severity and guiding clinical decisions. These findings underscore the complexity of Dengue management and highlight the need for targeted interventions, emphasizing the importance of on-going research to enhance our understanding of the disease and improve patient outcomes. Tailored interventions based on age-specific vulnerabilities, implement a mortality risk assessment tool considering age and Ferritin dynamics, integrate routine Ferritin monitoring for timely adjustments and engage in collaborative research for validation and contribute to standardized protocols, alongside continuous surveillance for early outbreak detection in Dengue management are highly recommended[6].

REFERENCES

1. Chaudhuri, S.R., S. Bhattacharya, M. Chakraborty and K. Bhattacharjee, 2017. Serum ferritin: A backstage weapon in diagnosis of dengue fever. Interdiscip. Perspect. Infect. Dis., 2017: 1-6.
2. Suresh, S.C., R. Hanumanthaiha, C. Ramakrishna, R. Sandeep and P.S. Narasimhasetty et al., 2020. Serum ferritin as a prognostic indicator in adult dengue patients. The Am. J. Trop. Med. Hyg., 104: 1072-1078.
3. Weg, C.A.M.V., R.M.H.G. Huits, C.S. Pannuti, R.M. Brouns and R.W.A.V. Berg et al., 2014. Hyperferritinaemia in dengue virus infected patients is associated with immune activation and coagulation disturbances. PLoS. Neglected. Trop. Dis., Vol. 8 .10.1371/journal.pntd.0003214

4. WHO, 2022. Guidelines for the Clinical Diagnosis and Treatment of Dengue, Chikungunya, and Zika. Pan American Health Organization,, Washington, D.C., ISBN-17: 978-92-75-12488-8, Pages: 83.

5. Mustafa, M., A. Bansal and V. Rastogi, 2011. Flightless aedes mosquitoes in dengue control. Med. J. Armed. Forces. India, 67: 192-193.

6. Chong, Z.L., S.D. Sekaran, H.J. Soe, D. Peramalah, S. Rampal and C.W. Ng, 2020. Diagnostic accuracy and utility of three dengue diagnostic tests for the diagnosis of acute dengue infection in Malaysia. BMC. Infect. Dis., 20: 1-210.