ORIGINAL ARTICLE

Serum Ferritin Level in Children with Severe Dengue Infection and Its Association with Outcome: A Single-center Prospective Cohort Study

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Abstract

Background and aims: Dengue viral infection (DENVI) can vary from a simple fever to severe dengue infection (SDI) and death. The study aims to identify the utility of serum ferritin (SF) and its association with intensive care unit (ICU) mortality in children with SDI.

Patients and methods: This is a prospective cohort study of 144 children aged 1 month to 18 years admitted to the pediatric intensive care unit (PICU) with SDI. The association between peak SF level with disease severity and outcome variables were assessed. A receiver-operating characteristic curve and a logistic regression analysis were conducted to evaluate the association of peak SF levels with ICU mortality.

Results: Our study included 144 children; 83 (57.6%) were males and 61 (42.36%) were females. Among these, 131 (90.97%) recovered, 9 (6.25%) died, 3 (2.08%) underwent liver transplant, and 1 (0.69%) left against medical advice. Median peak SF level was 6732 ng/mL (range 2813–17890 ng/mL). Majority of our patients recovered with standard supportive management alone. In our study, a peak SF level of 15691 ng/mL observed during the PICU stay was a "good" predictor of mortality among patients with SDI, with an area under curve of 0.826. Peak SF level greater than 10000 ng/mL ($n = 51/144$) was significantly associated with the development of disease-related complications ($p < 0.05$).

Conclusion: Hyperferritinemia is common among children with SDI. A peak SF level > 10000 ng/mL is associated with a higher risk of mortality and disease related complications.

Keywords: Hyperferritinemia, Severe dengue infection, Serum ferritin.

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Introduction

Dengue viral infection (DENVI) is a common arboviral disease with potentially fatal complications. It ranges from asymptomatic infection to severe dengue (SD) with complications.[1] Diagnosis of DENVI is based upon specific clinical signs and symptoms along with positive serology or NS1 antigen. Over the last three decades, the number of reported cases per year has increased, resulting in serious public health problems worldwide.[2]

Despite the large disease burden, there is still no specific treatment for DENVI. The focus of treatment is titrating fluid therapy, preventing and managing shock/organ dysfunction. The pathogenesis of dengue involves a complex interplay between viral factors and host response. It is hypothesized that an excess immune response through inflammatory mediators may lead to observed complications like bleeding, shock, and organ dysfunction among children with SDI. Therefore, an effective marker that can indicate the progression of complications will help in better management.[3]

Various biomarkers have been studied to assess complications in critical dengue illness, including serum ferritin (SF), serum ceruloplasmin, platelet count (thrombocytopenia), interleukin assays, and rising hematocrit levels.[4,5] Of all the severity biomarkers studied, SF levels have shown the greatest promise.[4,6]

Measurement of SF is easy, cheap, and readily available in most intensive care units (ICUs).[7] A prognostic indicator could provide a proactive approach in managing severe dengue infection (SDI), anticipate potential complications, and aid in early referral to a tertiary care pediatric intensive care unit (PICU). Therefore, we suggest that SF could potentially serve as a biomarker, indicating an association with dengue-related mortality. This finding could aid in decision-making processes.

The primary objective of the study was to evaluate observed peak SF level during the PICU stay among children with SDI and its association with mortality.

The secondary objective aimed to study various DENVI-related complications like acute kidney injury (AKI), fluid overload (FO) at 24 hours of PICU admission, the occurrence of pediatric acute liver failure (PALF), requirement of high-flow nasal oxygen (HFNO), noninvasive ventilation (NIV) or invasive mechanical ventilation (IMV), and requirement of immunomodulatory therapy (IMT) in relation to the observed peak SF level in these children.

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Table 1: Patient distribution, demographic details, laboratory parameters, and clinical presentations among the recruited cohort

Cohort details and lab parameters	*Numbers (%) and clinical variables, median (IQR) (n = 144)*
Male	83 (57.6%)
Age distribution (months)	71 (34–93)[a]
Peak SF (ng/mL)	6732 ng/mL (1673–17890)[a]
Nutritional status	Overweight: 16 (11.1%)
	Underweight: 5 (3.4%)
Length of PICU stay (days)	4 (2–6)[a]
Survived	131 (90.97%)
Lowest platelet count (cells/μL)	32000 (16000–63000)[a]
Peak AST (U/L)	222 (100–1,402)[a]
Peak INR	1.2 (0.95–2.4)[a]
Peak serum lactate (mmol/L)	2.16 (1.2–4.4)[a]
Fluid overload within 24 hours of admission (%)	3 (2–6.1)[a]
Pediatric risk of mortality-III scores	8 (5–15)[a]
Pediatric logistic organ dysfunction-II scores	5 (3–10)[a]

AST, aspartate aminotransferase, INR, international normalized ratio; [a]Median (interquartile range)

Patients and Methods

We undertook a prospective cohort study over a 26-month period (January 2021 to February 2023) at a tertiary care PICU of a children's hospital in southern India. The study was approved by our institutional ethics committee (Registration number ECR/676/Inst/TN/2014/RR-20). Children aged 1 month to 18 years with clinical and laboratory-confirmed dengue illness (NS1 antigen ± IgM antibody) requiring ICU admission were included in the study.

As per study protocol, SF level was measured on day-1 of PICU admission. A repeat SF measurement was performed on day 3 of PICU admission or earlier as deemed necessary by the treating physician based on the child's clinical condition. Given that patients with SDI were frequently referred from other hospitals or arrived from the community on oral antipyretics, the precise date of their illness could not be reliably ascertained. As a result, the first day of PICU admission was designated as the reference point for measuring the "admission SF level." Children who recovered and were transferred from the PICU to a ward before the completion of 3 days of PICU stay were not required to undergo a repeat SF assay unless clinically indicated. Patient demographics, clinical, and laboratory parameters, and treatment details were collected and entered on a Microsoft Excel data sheet (Table 1). Patients with known chronic inflammatory disease, chronic kidney disease, multisystem inflammatory syndrome in children related to COVID-19 (MIS-C), and patients with coinfection with other febrile illnesses (*Salmonella typhi* infection, malaria, scrub typhus, leptospirosis, and protozoal infection) were excluded from the study. Serum ferritin was measured by two-site sandwich immunoassay using standardized direct chemiluminometric technology (ADVIA Centaur, Siemens, Germany).

Classification of dengue severity into dengue fever, dengue with warning signs, or SD was based on the World Health Organization (WHO) 2009 criteria.[1,2] All patients included in the study were treated as per WHO 2009 treatment guidelines. Organ support like oxygen for increased work of breathing and hypoxia, drain insertion (pleural or peritoneal) for significant fluid leak and third spacing, escalation to NIV or IMV, and initiation of renal replacement therapy (RRT) were done whenever indicated clinically. Fluid overload was calculated by using daily intake and output from ICU admission:[8]

$$\text{Percent FO} = \frac{\sum \text{Daily [fluid in (liters)} - \text{Fluid out (liters)}]*100}{\text{ICU admission weight (kg).}}$$

We used hemophagocytic lymphohistiocytosis (HLH) 2004 criteria to identify dengue-associated hemophagocytic lymphohistiocytosis (DA-HLH). A decision for instituting IMT was made based on clinical features like high-grade fever, underlying multiorgan dysfunction (MOD), and the extent of hyperinflammation beyond critical phase of dengue illness.

For study purpose, we classified our cohort into two groups based on peak SF level above and at or below 10000 ng/mL.[4,9] Peak SF level was the highest observed SF value during the PICU stay. The overall illness severity of patients requiring ICU admission was assessed using Pediatric Risk of Mortality-III and Pediatric Logistic Organ Dysfunction-II scores within 24 hours of PICU admission. Nutritional status was assessed using Z-scores: Weight-for-age and height-for-age for children up to 5 years old (underweight ± stunting or overweight) and body mass index-for age for children over 5 years old with SDI.[10] Acute kidney injury was defined using Kidney Disease Improving Global Outcomes definition.[11]

Data were analyzed using STATA 11.0 software version 25.0. Categorical variables and continuous variables were summarized as frequency (percentage) and mean [standard deviation (SD)] or median interquartile range (IQR), respectively. For comparative analysis of unpaired categorical data, Chi-square test was performed. A p-value < 0.05 was considered significant. Receiver-operating characteristic (ROC) curve analysis was done to find out the value of peak SF along with cut off for sensitivity and specificity to estimate mortality. A logistic regression analysis using Wald statistic was done to assess the association between peak ferritin level and ICU mortality.

Based upon the study conducted by Mishra et al.[12] which showed that 13% of children with dengue fever had SDI, and considering precision of 5% with a confidence interval of 95%, we determined the required sample size to be 174 patients. However, due to the ongoing COVID-19 pandemic, it was not possible to achieve the desired sample size within the specified timeframe. Therefore, we opted to capture a sample size of convenience, from January 2021 to February 2023. This resulted in the inclusion of a total of 144 patients in the study.

Results

We enrolled 144 patients with SDI in our study. There were 83 (57.6%) boys and 61 (42.36%) girls. Most patients belonged to the age-group 5–10 years (44.5%). Our study had 97 (67.3%) patients from the emergency room and 47 (32.6%) patients as in-house transfers (from the ward).

With respect to clinical presentation, a majority [94 (65.2%)] presented as dengue shock syndrome (DSS). Among those children with DSS, 46 (48.9%) presented with only shock, 23 (24.9%) had symptoms of DSS along with PALF, 20 (21.3%) had signs of clinically significant FO at 24 hours exceeding 5%. Five (5.3%) children had mixed features of shock, organ dysfunction (AKI, PALF, left ventricular dysfunction), significant bleeding, and FO.

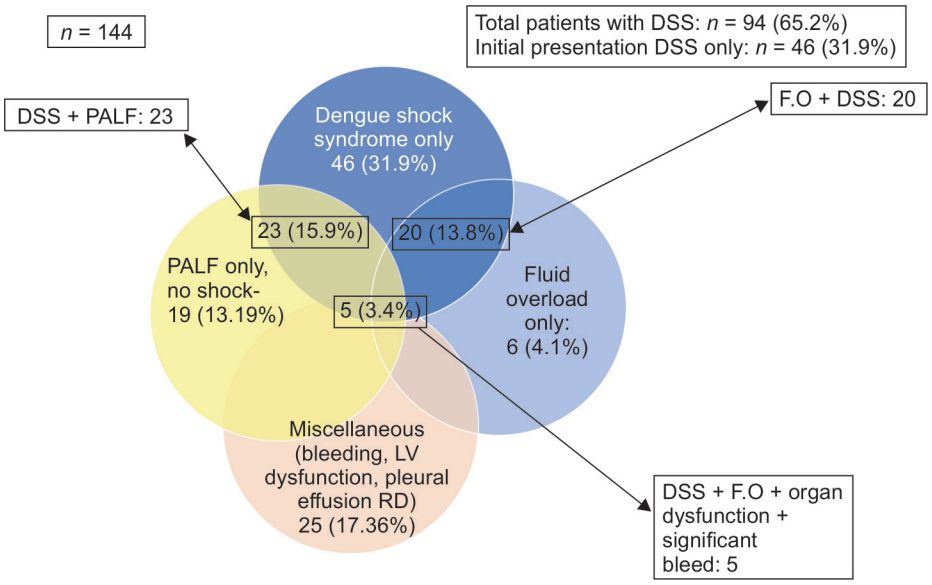

Fig. 1: Presenting symptoms in PICU

DSS, dengue shock syndrome; FO, fluid overload; LV, left ventricular; PALF, pediatric acute liver failure; RD, respiratory distress

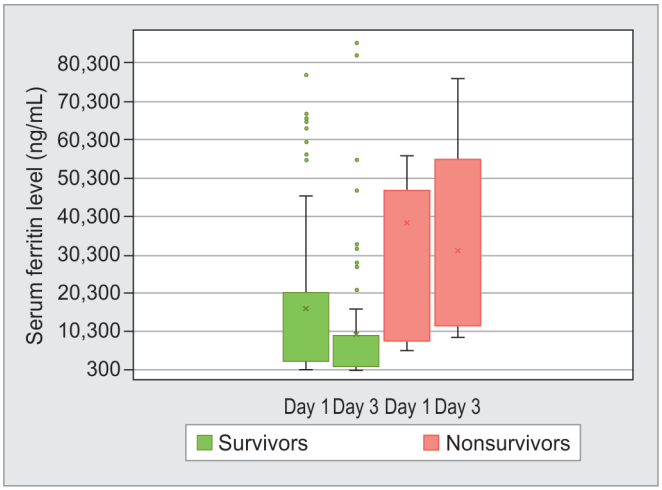

Fig. 2: Serum ferritin level trend among survivors (n = 135) and nonsurvivors (n = 9)

Among the 47 (32.6%) children with PALF, 19 (40.5%) presented with features of PALF only without significant plasma leak or shock, whereas 28 (59.5 %) had shock with PALF.[13] Three children with PALF were referred to a liver transplant center due to fulminant liver failure not responsive to supportive medical therapy. All three underwent liver transplantation, and two (66.7%) survived. Six children (4.1%) had only clinically significant FO and no other organ dysfunction (Fig. 1).

In our study cohort of 144 children with SDI, 139 (96.5%) had SF level > 500 ng/mL. Median admission SF levels was 5170 ng/mL (IQR 1775–12340), whereas median peak SF recorded was 6732 ng/mL (2813–17890). The lowest and the highest peak SF level recorded were 203 ng/mL and 166250 ng/mL, respectively. Six (4.1%) patients had multiorgan dysfunction syndrome (MODS) with SF levels above 100000 ng/mL on admission, of whom two died. During the study, a gradual decrease in SF levels was observed as patients' symptoms improved (Fig. 2). Likewise, despite being small in number (n = 9), there was an upward trend observed in SF levels among nonsurvivors (Fig. 2).

In our study, nine children died, of whom seven died due to SDI with MODS. Two children presented with brainstem dysfunction secondary to acute necrotizing encephalopathy of childhood without any shock or organ dysfunction. Peak SF >10000 ng/mL had a significant association with ICU mortality (p = 0.017; Chi-square test) (Table 2). A univariate logistic regression analysis revealed a statistically significant association between peak SF and ICU mortality, as evidenced by the Wald statistic (Wald = 9.051, p = 0.003 (95% CI: 1.513–12.414). The wide variation within the confidence interval was attributed to the limited number of deaths observed in the study. A multivariable binary logistic regression analysis incorporating all factors associated with clinical outcomes in SDI, such as AKI and ALF, as presented in Table 2, revealed that AKI (Wald = 6.500, p = 0.011, 95% CI: 2.012–210.022) and the requirement for continuous RRT (Wald = 4.538, p = 0.033, 95% CI: 1.164–38.177) were independently associated with an unfavorable outcome in patients with SDI. Using ROC curve analysis, it was observed that a peak SF level of 15691 ng/mL was 73% sensitive and 77% specific in estimating mortality risk with an area under the curve of 0.82 (95% CI: 0.78–0.92; p < 0.05) (Fig. 3).

Peak SF levels were above 10000 ng/mL in 51 (35.4%) children, out of which 44 (86.2%) recovered with standard ICU and supportive management alone and 7 (13.8%) received IMT. Peak SF levels >10000 ng/mL had a statistically significant association with FO of >5% at 24 hours of PICU admission, PALF, drain requirements, and need for RRT.

Out of the seven patients who received immunomodulation, two died. Immunomodulatory agents used were methylprednisolone (n = 3), intravenous immunoglobulin (IVIG) (n = 2) and anakinra (n = 1) and one patient received both IVIG and methylprednisolone.

Discussion

Dengue fever contributes significantly to morbidity and mortality in South East Asian endemic regions.[14] Clinical phenotypes of dengue in children and adults differ, with children experiencing

Table 2: Peak SF level > 10000 ng/mL, and their clinical outcome

Clinical outcome	*Serum ferritin ≤10000 ng/mL, n (%) (n = 93)*	*Serum ferritin >10000 ng/mL, n (%) (n =51)*	*p-value*	*OR (univariate)*	*95% CI: (lower–upper)*	*p-value (OR)*
AKI	7 (7.5%)	22 (43.1%)	0.0001#	48.381	5.725–406.92	0.00
CRRT	3 (3.2%)	12 (23.5%)	0.0041#	30.889	6.614–144.252	0.00
Drain insertion (pleural/peritoneal)	7 (7.5%)	20 (39.2%)	0.0001#	12.095	2.80–52.12	0.001
Fluid overload > 5% at 24 hours	11 (11.8%)	20 (39.2%)	0.0003#	6.46	1.61–25.18	0.008
HFNO/NIV	23 (24.7%)	30 (58.8%)	0.0005#	45.64	2.60–801.62	0.009
Overweight	12 (12.9%)	9 (17.6%)	0.644#	1.067	0.125–9126	0.953
ALF	15 (16.1%)	32 (62.7%)	0.0001#	9.45	1.88–47.40	0.006
Immunomodulation	1 (1%)	6 (11.7%)	0.004#	7.22	1.51–26.81	0.006
ICU mortality	2 (2.1%)	7 (13.7%)	0.017#	9.05	1.51–12.41	0.003

AKI, acute kidney injury, CRRT, continuous renal replacement therapy, PALF, pediatric acute liver failure, HFNO, high-flow nasal oxygen, NIV, noninvasive ventilation, OR, odds ratio; #Chi-square test

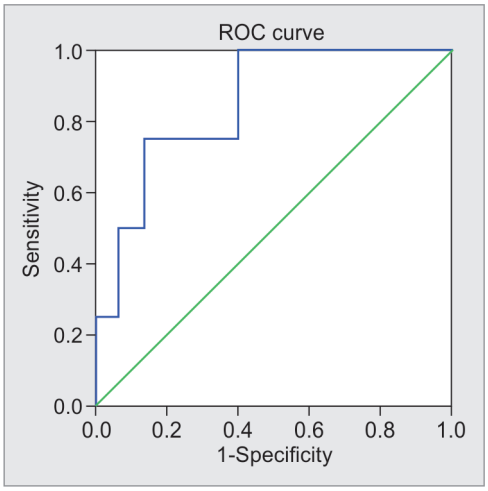

Fig. 3: Receiver-operating characteristic curve analysis of peak SF level and mortality. Area under the curve 0.826 at 95% CI: 0.515–0.954 with standard error 0.0653, $p < 0.05$. Peak ferritin 15691 ng/mL is 72.5% sensitive and 76.5% specific in predicting mortality

higher incidences of shock compared with adults.[15] Additionally, mortality due to SDI is 15.9 times higher in children under 14 years of age.[4,16] The mortality rate observed in our cohort was 6.25%. In a similar study conducted by Sachdev et al., involving 78 pediatric patients with SDI the mortality rate was 35.6%. In another study conducted by Lakshmanan et al. with 55 dengue patients requiring admission to PICU, the reported mortality was 5.45%.[16,17] Among studies involving adult patient with SDI, the reported mortality are lower than children at 2 and 2.6%, respectively.[18]

Among survivors, peak SF levels showed decreasing trends with clinical recovery (Fig. 2). A similar study conducted by Lakshmanan et al. showed a decreasing trend in SF level among SDI children as clinical symptoms improved.[16]

With regard to SDI and associated complications, our study was in agreement with studies conducted by Soundravally et al. and Channapatna et al., where SF level increases with increase in dengue severity.[3,18] An Increasing trend in SF level in a child with dengue illness can, therefore, alert a treating clinician to anticipate complications, facilitate in early recognition, and support timely intervention or referral to higher-level ICU. Hyperferritinemia observed in SDI may reflect underlying viremia and a degree of dysregulated immune response triggered by the release of proinflammatory cytokines. As the disease improves with timely intervention of organ support, hyperferritinemia also decreases, further emphasizing SF's role in understanding treatment outcomes.[4,16]

Contrary to a common belief that overnutrition or appropriate for age-related growth might be a risk factor for SDI, our study had no significant association between being overweight and severity of dengue illness ($p = 0.644$). Eleven other studies examined the relationship between SD and nutritional status but were inconclusive.[10]

Fluid overload (FO) has been strongly implicated in morbidity and mortality among children in the PICU.[19] Studies have identified FO ≥ 5% as clinically significant in children.[8] Our study demonstrated that SF > 10000 ng/mL was associated with higher instances of clinically significant FO (Table 2).

Dengue-associated-HLH is a life-threatening complication of DI, categorized under expanded dengue syndrome in the revised classification.[1] A study done by Ramachandran et al. suggested DENVI as an important cause of secondary HLH observed at a tertiary care ICU.[20] In our study, only 7 (4 %) children received IMT and, therefore, we could not make any meaningful comparison between SF levels and the need for immunomodulation. A study done by Jamaludin et al. suggested that one should strongly suspect DA-HLH in SDI with unremitting fever and hyperferritinemia (level >20000 ng/mL) and early immunomodulation may benefit.[21] In our study, 34 patients (23.6%) had SF levels exceeding 20000 ng/mL, of whom five received immunomodulation. All patients who received immunomodulation had multiorgan dysfunction, and required vasopressors/inotropic support. Therefore, immunomodulation should be individualized based on the patient's clinical condition. In a recent study done by Lakshmanan et al. of 55 children with SDI in PICU, the decision to use IMT was made on case-to-case basis guided by SF level, clinical manifestations, and degree of organ dysfunction.[16] However, currently, even in the absence of established DA-HLH, there is emerging evidence for the initiation of IMT earlier in the critical phase to halt the inflammatory progression and the disease process, but relevant data to support this approach remains limited.[4]

Although our study offers valuable insights into the relationship between SF levels and dengue severity, it is essential to acknowledge certain limitations that warrant consideration.

Our study was conducted at a single center, which may limit the generalizability of our findings. We did not evaluate other markers of inflammation like tumor necrosis factor-α, interleukin-10, interferon-γ, etc., which could provide a more comprehensive understanding of underlying immune response in SDI patients, as these tests are expensive and not readily available. Our study did not clarify the type, timing, and dose of immunomodulation needed to avert immunological activation and cytokine storm. As the current study is observational, we cannot infer causality. The oldest patient in our cohort was 16 years old; so the results cannot be directly extrapolated to adults. Lastly, we could not get expected sample size due to the COVID-19 pandemic, which could have provided a better understanding of the role of IMT among SDI cohorts.

Conclusion

Serum ferritin levels (>10000 ng/mL) are associated with dengue-related complications and mortality. Acute kidney injury and the need for RRT are associated with poor outcomes in SDI patients. Trends of SF is a good marker of disease progression/recovery. Decreasing SF may indicate early recovery, while increasing levels can suggest worsening complications.

CTRI Registration

CTRI: REF/2024/05084028.

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