RESEARCH PAPER

# Serum Ferritin as a Diagnostic Biomarker for Severity of Childhood Sepsis

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**Objective**: To explore association between serum ferritin and severity of sepsis among children, and relate levels to the final outcome. **Methods**: This observational study was conducted in a tertiary care hospital between I February and 30 July, 2019. Serum ferritin level was estimated in children (age 6 months to 12 years) suffering from sepsis, irrespective of the probable etiology. Children with hemoglobinopathies, autoimmune diseases, previous blood transfusion, severe acute malnutrition, hemophagocytic lymphohistiocytosis and chronic hepatitis were excluded. The ferritin level was measured sequentially at pre-defined stages of illness viz., sepsis, severe sepsis, septic shock and multiorgan dysfunction syndrome (MODS). Association between serum ferritin and severity of sepsis was analyzed, and ferritin level was related to the final outcome of death or recovery by receiver operating characteristic (ROC) curve analysis. **Results**: The study group included 47 children with sepsis who progressed to a state of MODS; 32 recovered from MODS. Significant differences in serum ferritin level were observed with severity of sepsis. There was clear demarcation of ferritin levels between sepsis severity stages. The proportion of death among the 47 MODS cases was 31.9% (95% CI 18.6 – 45.2%). ROC analysis in the MODS group indicated that serum ferritin >1994.3 ng/mL predicts mortality (AUC 0.73 [95% CI 0.58-0.85]) with sensitivity 66.7% [95% CI 38.4-88%] and specificity 100.0% [95% CI 89.1-100%]. **Conclusions**: There is clear demarcation of serum ferritin levels that can help differentiation of sepsis severity stages in children with sepsis. There is no such demarcation between survivors and non-survivors in MODS cases.

**Keywords:** *Mortality*, *Multiorgan dysfunction syndrome, Outcome, Septic shock*.

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Sepsis in pediatric age group contributes approximately 10-15% to childhood mortality worldwide, with the risk being higher among those admitted to pediatric emergency in state of septic shock [1]. In the natural course of sepsis, development of septic shock and multiorgan dysfunction syndrome (MODS) have several determinants [2,3]. Categorizing the patients into sepsis stages has a role in administering appropriate management and it is done largely on the basis of clinical features and laboratory investigations [4,5]. Hence, attempts have been made to identify biomarkers in blood samples that can reliably indicate severity stage transitions in the absence of florid signs and symptoms [6,7]. However, serum ferritin has not been adequately studied in sepsis in children as a marker of severity of sepsis [8]. We have tried to address this lacuna through a prospective observational study in a tertiary care setting.

## METHODS

The study was conducted between February and July, 2019 after approval from the institutional ethics committee. Children of either sex, between 6 months to 12 years of age, admitted with proven sepsis, were screened. These children were included through purposive sampling. Children with significant comorbidities like hemoglobinopathies, autoimmune diseases, previous blood transfusion, severe acute malnutrition, hemophagocytic lymphohistiocytosis and chronic hepatic illness were excluded. While the subjects were managed conservatively in intensive care, few amongst them deteriorated further to MODS and some eventually succumbed to multiorgan failure. Those who recovered were followed-up for their clinical condition till one week after being discharged or shifted from intensive care. Definitions adopted by International pediatric sepsis consensus were followed to define the different stages of sepsis [9].

The predetermined phases evaluated for serum ferritin level were the stages of sepsis, severe sepsis or septic shock and MODS. The stage of severe sepsis and septic shock were clubbed together into one stage to avoid bias in categorizing them as small margin of discrimination allowed in their differentiation criteria. Another blood sample for ferritin level assay was obtained at 7th day post-recovery in subjects who recovered from MODS. The ferritin level was measured by electrochemilumine scence immunoassay (ECLIA) using COBAS E411 analyzer (Roche Diagnostics). The lower and upper limits of quantification were 0.1 ng/mL and 2000 ng/mL, respectively.

*Statistical analysis*: Comparison between subgroups was done using Mann-Whiney U test, with $P< 0.05$ as the cut-off for statistical significance in such comparisons. Receiver operating characteristics (ROC) analysis was done to identify cut-offs of serum ferritin for predicting poor outcome.

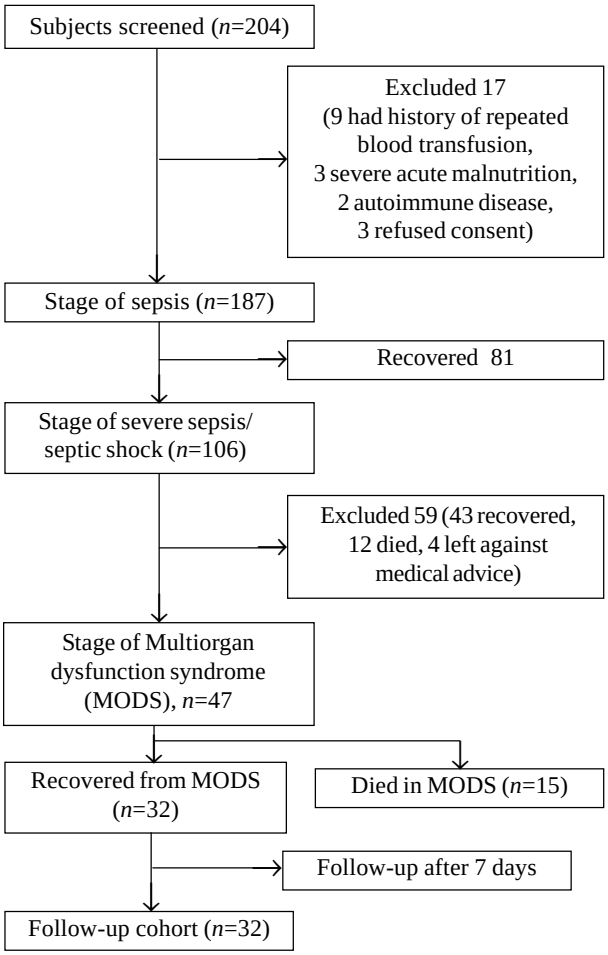


**Fig. 1** Study flow chart.

## RESULTS

We screened 204 children and finally 187 children with sepsis were recruited; of these 47 (25.13%) advanced from the stage of severe sepsis or septic shock to the stage of MODS (**Fig. 1)**. Within the MODS group, 15 children died (31.9%, 95% CI 18.6-45.2%) and 32 recovered, who were followed-up for one-week post-discharge or transfer-out from the intensive care unit.

The median (IQR) serum ferritin amongst MODS subjects were 371.5 ng/mL (265.1-442.33), 892.2 ng/mL (764.5-1029.4), and 1784.9 ng/mL (1657.5-1916.4) in the stage of sepsis, stage of severe sepsis or shock, and stage of MODS, respectively. The change of serum ferritin level during transition from one phase to another was found to be significant ($P<0.001$). There was statistically significant difference between the ferritin level in severe sepsis versus MODS ($P<0.001$). The ferritin level median (IQR) observed in the recovery cohort was 808.85 ng/mL (672.5-929.8) at one-week post-discharge or transfer-out from ICU. The trend of ferritin levels found at different stages along the course of illness among the children who recovered from sepsis induced MODS are depicted graphically in **Fig. 2**.

Correlation analysis in the MODS cohort indicated weak to moderate correlation between the ferritin levels across the spectrum of illness (Spearman's rank correla-tion coefficient 0.454 between sepsis and severe sepsis; 0.367 between severe sepsis and MODS). This indicates that although there is elevation of ferritin as a whole, the pattern in individual subjects is variable. **Table I** presents the descriptive summary of serum ferritin levels in survivors and non-survivors in the MODS cohort, along their spectrum of illness. The data indicate that there is

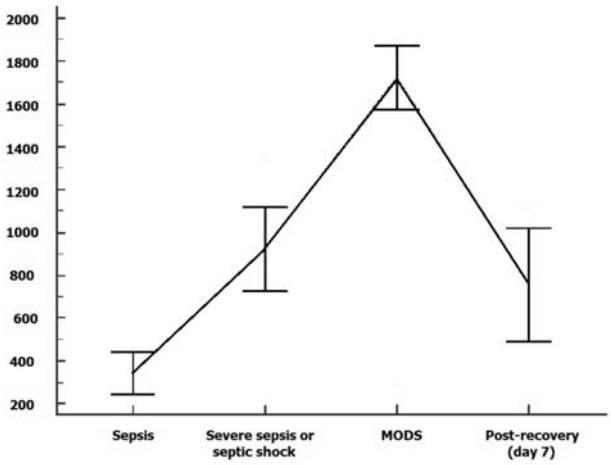


**Fig. 2** Ferritin level (ng/mL) at successive stages of illness in children with sepsis who recovered. Error bars indicate median (IQR).

**WHAT THIS STUDY ADDS?**

- Serum ferritin levels can help in demarcation of sepsis severity stages in children.

**Table I Serum Ferritin in Children With Sepsis-Induced Multiorgan Dysfunction Syndrome (MODS) (*N* = 47)**

| *Severity of illness* | *Death cohort (n=15)* | *Recovered cohort (n=32)* | *P value* |
|---|---|---|---|
| Stage of sepsis | 378.6 (249.93-451.73) | 358.1 (280.55-433.35) | 0.715 |
| Stage of severe sepsis / shock | 879.2 (649.83-1032.23) | 895.2 (788.40-1012.75) | 0.615 |
| Stage of MODS | 2001.0 (1700.60-2001.00) | 1750.2 (1615.60-1837.30) | 0.011 |
| Stage of recovery | – | 808.8 (672.50-929.80) | – |

*Ferritin values are in median (IQR) ng/mL.*

statistically significant difference only in the MODS stage, the median value being higher in the non-survivors compared to survivors (*P*=0.011). Accordingly, ROC curve analysis of serum ferritin in these subjects to identify mortality cut-offs was successful only in the MODS stage – serum ferritin >1994.3 ng/mL predicted mortality (area under ROC curve 0.73 [95% CI 0.58-0.85]) with sensitivity 66.7% [95% CI 38.4-88%] and specificity 100% [95% CI 89.1-100%].

## DISCUSSION

Classically, ferritin biology focuses on its role in iron storage and homeostasis, with low ferritin levels indicative of deficiency and high levels suggesting primary or secondary hemochromatosis. However, iron, redox biology and inflammation are linked and serum ferritin has been established as an acute phase reactant [10]. Its rise can be observed with inflammatory response mediated through various pro-inflammatory cytokine stimulants like tumor necrosis factor, interleukin-1 and interleukin-6 [10,11].

In children, sepsis staging can be difficult because differentiating signs are often subtle [12-14]. Therefore, a single biomarker that can reliably differentiate stages in the spectrum of sepsis illness can be quite helpful in guiding management step-up and prognostication. In the present study, a significant rise of serum ferritin value could be observed among children who suffered from sepsis induced MODS. The study indicates that ferritin can fulfill the differentiating biomarker role in childhood sepsis and, although there is some overlap at extremes of range.

Earlier studies have reported that high serum ferritin value is associated with unfavorable outcomes in pediatric sepsis [15]. In our study the highest values occurred in the MODS stage and a cut-off value of serum ferritin of nearly 2000 ng/mL could be identified to predict mortality. However, no cut-off could be identified for the earlier stages. Garcia, et al. [8] studied ferritin levels in children with severe sepsis and septic shock and found that level >500 ng/mL was associated with 58% mortality. Our study had mortality of around 32% in the MODS stage.

Consistent with the fact that ferritin is an acute phase reactant, the levels declined with resolution of the sepsis and the 7-day post-recovery values were considerably lower than the peak levels attained in the MODS state. However, we did not follow-up these children till normalization of ferritin levels. Despite the limitations of our study, we can conclude that there is clear demarcation of serum ferritin levels which can help differentiation of sepsis severity stages in children with sepsis. There is no such demarcation between survivors and non-survivors in MODS cases, but serum ferritin >1994.3 ng/mL is associated with poor outcome in MODS cases.

*Ethics clearance*: Institutional ethics committee of NB Medical College; No. IEC/NBMC/2018-19/91, dated: February 01, 2019.
*Contributors*: AN: primary investigator, data collection, making draft; TM: making draft, literature search, interpretation, statistical help; DD: draft, patient management, literature search; SR: study review, Review draft and interpretation; NK: technical inputs, data Collection, data interpretation; IM: reviewing draft, study interpretation, literature search: AH: literature search, review draft, statistical analysis; RM: conception of study, reviewing draft, study design, and literature search.
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