RESEARCH PAPER

Serum Ferritin for Predicting Outcome in Children With Severe Sepsis in the Pediatric Intensive Care Unit

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Objectives: To evaluate the prognostic ability of serum ferritin when estimated within 5 days of onset of illness in children with severe sepsis admitted to a pediatric intensive care unit. **Methods:** This observational study enrolled children aged 1 month to 12 years with severe sepsis. Hemoglobin, serum ferritin and C-reactive protein levels were measured within five days of illness. Final outcomes were recorded in all enrolled children. **Results:** 70 children with median (IQR) age of 27 (8,108) months were enrolled during the study period (July, 2019 to August, 2021). 28 (40%) of these had poor outcome (non-survival). The median (IQR) level of serum ferritin was 1369 (558-5607) ng/mL in non-survivors and 282 (129-680) ng/mL in survivors (P<0.05). A significant correlation was seen between serum ferritin and Pediatric Risk of Mortality III (PRISM III) score (r=0.364 P=0.002) and pediatric Sequential Organ Failure Assessment (pSOFA) score (r=0.246 P=0.04) at 48 hours of admission. 54 (77.1%) children were anemic. Serum ferritin levels in children with anemia also had a good predictive ability for poor outcome [AUC: 0.764, 95% CI: 0.634, 0.894]. **Conclusions:** Serum ferritin levels, within five days of onset of illness, predicted poor outcome in critically ill children with severe sepsis and in children with microcytic anemia.

Keywords: *Anemia*, *C-reactive protein, Infection, Mortality*.

Sepsis is a major cause of morbidity and mortality in children worldwide [1], with high fatality rate. Biomarkers can diagnose, monitor, stratify, predict outcomes and aid in evaluating therapy response and recovery in sepsis [2]. C-reactive protein (CRP) and procalcitonin are the two extensively studied biomarkers [3]. Although CRP is widely available, its ability to accurately predict outcomes is yet to be established, while the use of procalcitonin is limited in developing countries. Elevated levels of serum ferritin in sepsis has been linked with poor outcome in children aged 28 days to 18 years [4,5]. Serum ferritin, when used as a biomarker to risk-stratify hospitalized children, would be helpful in clinical management [3]. The role of serum ferritin as a biomarker to prognosticate severe sepsis in children with concurrent iron deficiency; however, still needs to be studied.

The primary objective of this study was to predict the outcome in children with severe sepsis, using serum ferritin. The secondary objectives were to find the correlation between serum ferritin levels and Pediatric Risk of Mortality (PRISM) III score as well as pediatric Sequential Organ Failure Assessment (pSOFA) score. The predictive ability of serum ferritin and CRP for outcomes in children with severe sepsis were also compared.

METHODS

This was an observational study conducted at the pediatric intensive care unit (PICU) of our institution from July, 2019 to August, 2021, after approval from the institutional ethics committee.

Children aged 1 month to 12 years with severe sepsis were included. Severe sepsis was defined as sepsis plus one of the following: cardiovascular organ dysfunction or acute respiratory distress syndrome or two or more other organ dysfunctions [6]. Children with chronic organ dysfunction like chronic liver, kidney, lung or heart disease, beyond five days of onset of illness, family history or previous diagnosis of hemophagocytic lymphohistiocytic syndrome (HLH), recipient of a blood transfusion in the last four months, children with proven or suspected genetic malformation or inborn error of metabolism and children diagnosed/suspected with childhood malignancy and autoimmune disease were excluded. Definitions of the terms used in the study were as per standard definitions [6-10].

Enrolled children were treated according to standard PICU protocols. At admission to PICU, an additional 2 mL of venous sample was collected for serum ferritin, that was estimated using Beckman Coulter kit by chemiluminescence method. Serum CRP levels were estimated using immunoturbidimetry principle in Horiba Microsemi CRP LC-667G Hematology Analyzer. PRISM III score was calculated within 24 hours of admission. pSOFA score was calculated every 48 hours from admission till discharge of the patient from the PICU. Children enrolled in the study were followed up till discharge to record the outcome, which was classified as survival or non-survival.

Sample size was based on a previous study [4], where the predictive sensitivity was observed to be 64%. With an absolute precision of 10% and type 1 error of 5% (0.05), the estimated sample size was 96.

Statistical analysis: Data were analyzed using SSPS software version 23. Non-parametric continuous variables were compared using Mann-Whitney test while categorical variables were compared using Chi-square test or Fisher exact test. The receiver operating characteristic (ROC) curve for serum ferritin levels were plotted to derive the cut-off value and estimate the area under curve (AUC) to predict mortality in children with severe sepsis. Statistical significance was taken at *P* value of <0.05.

RESULT

During the study period, we could enroll only 70 children, whose baseline data is shown in **Table I**. Of these, 54 (77.1%) children had septic shock at admission, while 16 (22.9%) had multiple organ dysfunction syndrome (MODS) at the time of admission. An additional 41 children developed features of MODS during their PICU stay. Pneumonia was found to be the most common cause of severe sepsis, followed by acute meningoencephalitis.

The median (IQR) duration of PICU stay was 4 days (2,9) and pSOFA score at end of 96 hours of PICU stay was 9 (6.5,12). The median (IQR) vasoactive inotrope score was 30 (10,80). Ventilatory support was required in 54 (77%) children, and renal replacement therapy in 13 (19%) children in the form of peritoneal dialysis.

The median (IQR) duration for the development of poor outcome (non-survival) was 3 days (2,10) **Table II**. A cut-off value of serum ferritin of 558 ng/mL had a sensitivity of 74.1% and specificity of 67.7% to predict the development of poor outcome (non-survival) [*n*=70; AUC (95% CI): 0.731 (0.599,0.864)]. The best cutoff of CRP to predict non-survival was 3.08 mg/dL with a 63% sensitivity and 41.9% specificity [*n*=58; AUC (95% CI): 0.458 (0.308, 0.608)] **Fig. 1).**

Fifty four (77.1%) of children had microcytic anemia; however, their median levels of serum ferritin were higher than non-anemic children (**Table II**). Serum ferritin levels in anemic children with severe sepsis were found to have a good predictive ability to detect poor outcome [(AUC (95% CI): 0.764 (0.634, 0.894); **Fig.1b**] compared to non-anemics [AUC (95% CI): 0.450 (0.150, 0.750)]. The

Table I Baseline Characteristics of Children With Severe Sepsis Enrolled in the Study (*N*=70)

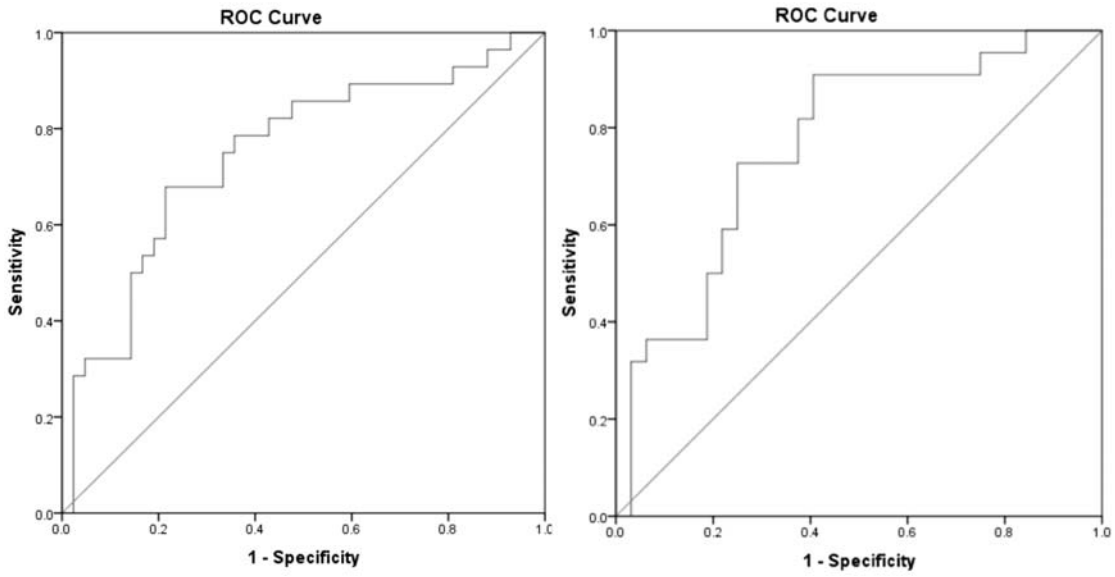
Characteristics	*Value*
Age (mo) [a]	27 (8,108)
Male gender	41 (59)
Day of illness	2 (1,4)
Stunting	16 (23)
Severe stunting (%)	10 (14.2)
Wasting	20 (53)
Severe wasting	11 (55)
Thinness [b]	6 (19)
Severe thinness	3 (50)
pSOFA score at admission [a]	9 (6.5,12)
Pediatric risk of mortality (PRISM III) score [a]	17 (10,20)
Pediatric intensive care unit stay (d) [a]	4 (2,9)
Ventilated	55 (78.6)
Renal replacement therapy	13 (18.6)

Data expressed as no. (%) or [a]median (IQR). [b]in children aged 5-12 years. pSOFA - Pediatric sequential organ failure assessment.

Table II Outcome Characteristics in Children With Severe Sepsis Enrolled in the Study (*N*=70)

Characteristics	*Value*
Serum ferritin (ng/mL) [a]	558 (192,1505)
C-Reactive protein (mg/dL) (*n*=58) [a]	5 (2,13)
Elevated CRP	36 (62)
Multiple organ dysfunction syndrome	57 (81) [b]
Septic shock	13 (19)
Outcome	
Survivors	42 (60)
Non-survivors	28 (40)
Multiple organ dysfunction syndrome [b]	57 (93)
Septic shock	2 (7)
Serum ferritin (ng/mL) [a]	
Anemic group (*n*=54)	627.7 (198.23, 1885.5)
Non-anemic group (*n*=16)	360.03 (219.08, 800.07)
Survival group (*n*=42)	282.2 (129, 680)
Non-survival group (*n*=28)	1369.15 (558,5607)

Values in no. (%) or [a]median (IQR). [b]16 children had features of MODS at the time of admission,41 more developed MODS during PICU stay.



(*a*) (*b*)

Fig. 1 Receiver operating characteristics (ROC) curves of serum ferritin levels for predicting non-survival in *a*) all children with severe sepsis, and *b*) anemic children with severe sepsis.

correlation between serum ferritin and PRISM III score (P=0.002) or pSOFA score (r=0.246, P=0.04) was statistically significant.

DISCUSSION

The present study concluded serum ferritin as a good predictor of poor outcome in children with severe sepsis. Hyper-ferritinemia, has been suggested to identify patients with sepsis-induced macrophage activation syndrome [11]. Management of hyper-ferritinemic sepsis is usually preferred with immunomodulation including IVIG [12].

Earlier, few studies from developing country settings have evaluated the serum ferritin levels and its predictive utility for outcome in children admitted with sepsis [12-16]. Two studies [4,14], had a similar study design, developing country setting and survival outcome as the present study. The median level of serum ferritin in this study was similar to an earlier study [14], where both studies had a high proportion of children with septic shock at admission. The median levels of CRP were higher [14] than the present study, for reasons that are not clear. The association between serum ferritin levels and outcome was statistically significant [4,15], as seen in this study. Serum ferritin was observed to be a better predictor of outcome than serum CRP in the present study, probably as there were lesser proportion of children with elevated CRP than those with elevated ferritin.

A high prevalence of anemia was earlier reported in a similar study [14]; however, the number of children with elevated ferritin was approximately 30% lower compared to our study. In hyperinflammatory state like severe sepsis, the interaction between serum ferritin levels and iron deficiency can be complex. Children with iron deficiency anemia are more immunosuppressed than non-deficient children. As a result, iron-deficient individuals are likely to progress to a hyperinflammatory state when challenged by infection, resulting in higher levels of serum ferritin than non-deficient children. Iron deficiency can be the cause of higher serum ferritin levels in anemic group [17]. Children who reach hyperinflammatory state either because of agent or immunological or treatment related factors can have significant activation of macrophage-monocyte system. CD163, a marker of macrophage activation and hemoglobin scavenger receptor, is elevated in these hyperinflammatory states. The rate and severity of hemo-globin scavenger function by macrophages-monocyte system by CD 163, is increased in these hyperinflammatory states, thereby resulting in anemia. Here, anemia is the end result of the hyperinflammatory state [18]. It is difficult to ascertain the likely pathology in our study group as other inflammatory markers and CD 163 levels were not performed. These could be responsible for better predictive function of serum ferritin and its higher levels in the anemic group.

Our study had several limitations. The initial targeted sample size of 96 could not be achieved due to slower recruitment amidst the COVID 19 pandemic. We were able to test CRP levels only in 58 children as the sample taken at admission was hemolyzed in the rest. We were unable to

WHAT THIS PAPER ADDS?

- Serum ferritin estimated before fifth day of illness is predictive of poor outcome in children with severe sepsis.

estimate the iron profile of anemic children in our study.

The present study adds further evidence to the predictive and prognostic ability of serum ferritin for poor outcome in pediatric sepsis. A large proportion of children in developing countries is anemic and has iron deficiency. In this context, it is noteworthy that serum ferritin was a predictor of poor outcome even in children with anemia.

Ethics clearance: Institutional ethics committee, JIPMER; No. JIP/IEC/2019/0136, dated June 24, 2019.
Contributors: GNS: collected and analyzed data, drafted the manuscript; JGR: concept and designed the study, analyzed the data and supervised the study; NP: managed the cases, analyzed the data and supervised the study; GPS: performed biochemical investigation, analyzed the data and supervised the study. JGR: guarantor of the paper. All authors approved the final version of manuscript and are accountable for all aspects related to the study.
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