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Serrum ferritin: A prognostic marker in patients with sepsis in Pediatric age group: A prospective cohort study

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Abstract
Objectives: To determine serum ferritin value, to study its correlation with PRISM/PELOD score and mortality in patients with sepsis.
Methods: This Analytical Observational prospective cohort study was done in12-bedded Pediatric intensive care unit (PICU) of Sir Ganga Ram Hospital, New Delhi. 149 patients with sepsis were included for the study with an inclusion criteria of age >28 days or <16 years and PICU stay >24 hours. Serum ferritin was collected at the time of diagnosis of sepsis. Patient demographics were noted and Pediatric risk of mortality (PRISM) score and Pediatric logistics dysfunction (PELOD) score were calculated. All patients were followed up throughout their hospital stay and outcome data (survival or mortality) was obtained.
Results: Of the 149 patients, 93 survived while 56 died in PICU. Non survivors had a significant higher median ferritin (1205.50 ng/ml) as compared to survivors ($p < 0.001$). At a cut off of 1100 ng/ml, serum ferritin was associated with a 2.3 (1.571-3.614) relative risk ($p < 0.0001$) for predicting mortality in patients with sepsis. PRISM and PELOD score were independently associated with mortality and also had a weak correlation with serum ferritin value. No significant difference was found in C- reactive protein (CRP) as well as procalcitonin value in survivors and non survivors group.
Conclusion: High serum ferritin level is associated with poor outcome in patients of sepsis and can be used as a predictive marker of mortality along with current prognostic scores.

Keywords: ferritin, biomarkers, sepsis, children, pediatric intensive care, prognostic scores

1. Introduction
Sepsis is a leading cause of death in critically ill patients despite the use of modern antibiotics and resuscitation therapies [1]. Diagnosis of sepsis in children is difficult in everyday practice for many reasons: the clinical signs and symptoms in children are very variable and nonspecific at the start of the infection; microbiological culture results are expected only after 48-72 hours and false negatives are common. In 2002, an International Sepsis Consensus Conference (ISCC) held in USA led to framing and adoption of specific clinical definitions for sepsis [2]. Early diagnosis and stratification of severity of sepsis is very important, increasing the possibilities of initiating timely and specific treatment [3, 4].
Biomarkers can indicate the presence or absence or severity of sepsis [5, 6]. They also have roles in prognostication, guiding antibiotic therapy, evaluating the response of therapy and recovery from sepsis predicting sepsis complications and the development of organ dysfunction [7]. During the last decade, measurement of C reactive protein (CRP), a good inflammatory marker, has been added to the set of hematological tests (total leukocyte count, neutrophils, band form counts) that have long been used in clinical practice. However, it does not have the specificity required to distinguish viral from bacterial infections. The calcitonin pro-hormone procalcitonin (PCT) has also been used clinically; its level is low in healthy individuals (< 0.5 ng/ml) [8, 10]. It has been proposed as a more specific and better prognostic marker than CRP, although its value has also been challenged [11, 13]. It remains difficult to differentiate sepsis from other non infectious causes of systemic inflammatory response syndrome (SIRS), and there is a continuous search for better biomarkers of sepsis.
New research and novel understanding of the molecular basis of the disease reveals an abundance of exciting new markers that may be of utility in clinical practice. One such marker is serum ferritin which is an iron storage protein that sequesters iron in the ferric (Fe3+) state. It is a complex of iso ferritins produced by the reticulo endothelial (RE) system. The RE system plays a critical role in iron metabolism by processing hemoglobin from senescent red blood cells. Acute inflammation and infection induce the blockade of iron release resulting in a decreased serum iron, a virulence factor for many microorganisms. Elevated levels of serum ferritin, an acute-phase reactant, reflect the clinical response to deprive microorganisms of serum iron [14, 16]. There have been studies in adults which describe association of ferritin and critical care outcome. Taking into account the new definition of sepsis in children and evaluating the need for effective and rapid laboratory (quantitative) indicator, we studied the co-relation of serum ferritin with the diagnosis and prognosis of sepsis in children.

Materials and Methods
This analytical observational prospective cohort study was conducted over a period of 16 months (May 2012-August 2013) in the pediatric intensive care unit (PICU) of Sir Ganga Ram Hospital, Rajinder Nagar, New Delhi which is a 650-

bedded tertiary care centre. Approval was taken from hospital ethics committee and written consent was obtained from parents.

Children were selected on the basis of sepsis definition defined by the International Pediatric Sepsis Consensus Conference [2]. 149 patients with sepsis were included for the study with an inclusion criteria of age >28 days to <16 years and PICU stay >24 hours. Exclusion criteria included (1) pediatric surgical, trauma and burn cases, (2) children dying within 24hours of PICU admission, (3) autoimmune diseases, (4) evidence of malaria, (5) diagnosis of hemophagocytic syndrome, (6) recipient of blood transfusion in the last 4 months, (7) cases of hepatitis, (8) children with other causes of shock, not due to sepsis itself, e.g., cardiogenic, anaphylactic, and dengue shock, (9) children with known malignancies and immunosuppressive treatment.

Following data was collected for the eligible enrolled patients: age, gender, primary organ involvement, duration of mechanical ventilation, vasoactive ionotropic score [17], length of stay in the PICU and hospital along with final outcome (survival/mortality). Pediatric risk of mortality score (PRISM) and pediatric logistic organ dysfunction score (PELODS) were used to assess the severity of illness and organ dysfunction. Patients with sepsis, severe sepsis and septic shock were identified using definitions provided by Goldstein *et al.* [18] In addition, the results of all the investigations necessary for routine management sent by PICU team at admission and in the next 24 hours were recorded.

Serum ferritin level was measured (at the time of diagnosis of sepsis) by immunochemiluminiscent assay which is a competitive immunometric assay involving liquid phase ligand-labelled protein binding.

Continuous variables were presented as mean ± standard deviation or medians (minimum-maximum) as per the distribution. Categorical variables were expressed as frequencies (%). Differences between groups were assessed with Chi-square or Fisher's exact test for categorical variables. Unpaired t test was used for comparison of continuous variables between the two groups. For non parametric data, Mann Whitney U test was used. The area under the receiver operator characterstic (ROC) was used to assess the ability to predict outcome. Multivariate logistic regression analysis was also done to predict an outcome from a set of predictor variables in univariate analysis. P<0.05 was considered statistically significant. Statistical analysis was performed with SPSS version 17.0 program for Windows (SPSS Inc., Chicago, IL, USA).

Results

149 children were enrolled in the study with a median age of 1.8 (0.5- 6) years with maximum cases (59.1 %) below 3 years of age (Figure 1). There were 104 (69.8%) boys. Respiratory system was involved in majority (34.9 %) of the cases followed by CNS (17.4%) and GIT (14.1%). Although, no significant difference was seen in serum ferritin value in relation to primary organ involved. The duration of PICU and total hospital stay was higher in survivors as compared to non survivors (p=0.001, p<0.001, respectively) but no correlation of either was seen with the serum ferritin levels (p=0.630, p=0.798) (Table 1). Furthermore, 114 (76.5%) patients required mechanical ventilation out of which 50 (33.5%) died. Total number of deaths was 56 (37.6%). We studied association between use of vasoactive drugs[17] and ferritin and found it to be positive (r = 0.362, p < 0.001). Such association has not been reported so far.

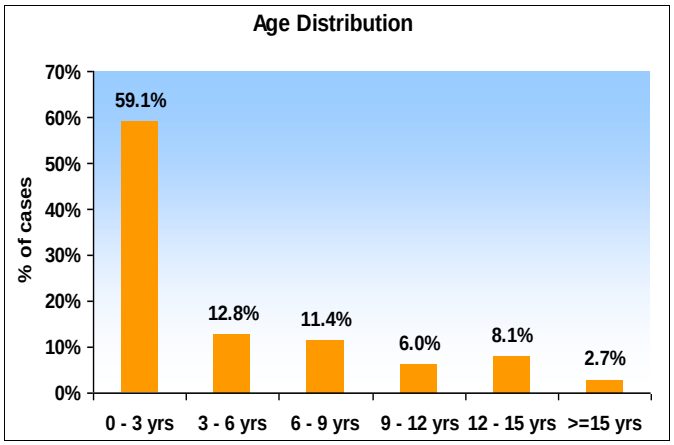

Fig 1: Age Distribution (n=149)

Table 1. Correlation between duration of PICU/hospital stay and serum ferritin level

		Ferritin
PICU Stay (in days)	Pearson Correlation coefficient(r) p-value	0.040 0.630
Hospital Stay (in days)	Pearson Correlation coefficient(r) p-value	-0.021 0.798

The median serum ferritin value was 761 (178-1886.50) ng/ml. Ferritin above 1100 ng/mL had 58.9% sensitivity and 75.3% specificity to predict death, and was associated with a 2.3 (1.571-3.614) relative risk of death (p < 0.0001) with 0.685 area under ROC curve (Figure 2).

The median values of PRISM score at 12 hours and at 24 hours were 11 (range: 5-17) and 10 (range: 5-16) respectively. Median values of PELOD score on day 1 and day 2 were 21 (range: 11-31) and 21 (range: 10.50-31) respectively. We also tested the correlation of PRISM/PELODS with ferritin values and found that ferritin had a direct (though weak) correlation with PRISM at 12 hours and 24 hours (r =0.349; p<0.001, r=0.311; p< 0.001 respectively) and with PELOD score on day 1 (r = 0.249; p =0.002) and day 2 (r=0.269; p=0.001). Higher PRISM (> 15 at 12 hours) and PELOD (> 21 on day 1) scores were independently associated with increased mortality (p< 0.001, p=0.001, respectively).

Known inflammatory biomarkers namely CRP and Procalcitonin (PCT) were also studied. While no association was seen between CRP and ferritin value (r=0.160, p=0.243), PCT had a weak direct correlation with serum ferritin values (0.230, p=0.005). Contrary to earlier studies done on biomarkers, CRP and procalcitonin were not significantly associated with increased mortality in our study cases (p=0.839, p=0.346, respectively).

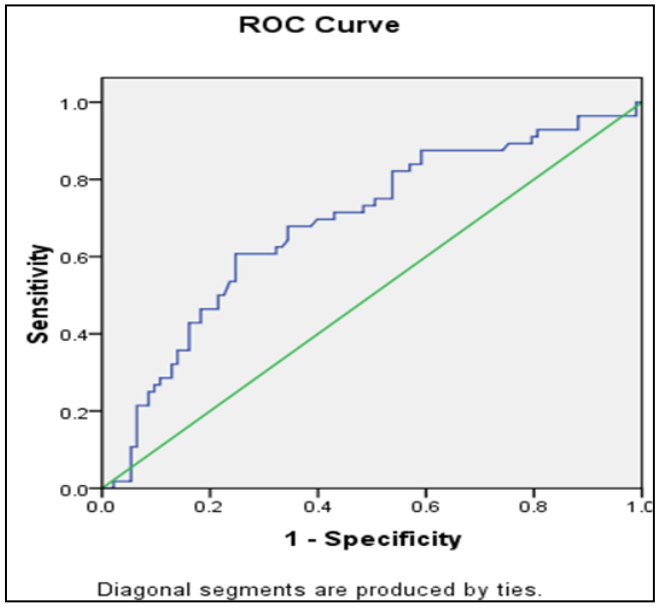

Fig 2: ROC curve for serum ferritin

Discussion

Sepsis caused by infection remains a major cause of mortality and morbidity among children. Several inflammatory markers have failed to meet the requirements for early diagnosis and prognostication of sepsis. This study evaluated the potential value of measuring ferritin in patients with clinically suspected and proven sepsis, correlated it with PRISM/PELODS and outcome of patients and compared it with established inflammatory markers like C- reactive protein (CRP) and procalcitonin (PCT).

Ferritin has been reported to be elevated in some previous reports from cases of sepsis in adults [19, 20]. Garcia *et al* have studied it in small number of patients (n=36) in pediatric age group[21]. We have found that ferritin value >1100ng/ml had a 58.9% sensitivity and 75.3 % specificity to predict mortality with a relative risk of 2.38 (95% CI :1.57-3.61) and an odds ratio of 4.36 (95% CI:2.14 -8.88).The area under ROC curve was 0.685. Our findings have been consisitent with earlier studies in adults. We also found out that ferritin has direct correlation with procalcitonin value but none with CRP. This association has not been reported before in children. It is evident from our study that high values of PRISM and PELODS score have a poor outcome. So, these prognostic scores can be used along with ferritin to predict mortality in sepsis.

There are some limitations of our study. First, we studied only the cases with clinical sepsis and no controls were included in our study. Second, we did not exclude cases who were admitted/treated elsewhere before being referred to our hospital. Third, other components of iron metabolism like lactoferrin, transferrin etc. which can affect iron availability, were not studied in our cases due to financial limitation.

Despite of these limitations, ferritin appears to be an important early prognostic marker for mortality in sepsis, hence, should be included as a part of routine sepsis work up. Its predictive performance can be increased with use of existing prognostic scores. More studies are needed to study effect of deranged iron profile on ferritin values.

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