Original Research Article

Study of role of serum ferritin in predicting outcome in children with severe sepsis at a tertiary hospital

Manjushree S Kulkarni[1], Deepak A Shukla[2*]

[1]Associate Professor, Department of Paediatrics, Prakash Institute of Medical Sciences and Research Centre, Urunislampur. INDIA.
[2]Assistant Professor, Department of Pediatrics, BKL Walawalakar Trust Rural Medical Collage, Sawarde, Ratnagiri, INDIA.
Email: manjushree1205@gmail.com, doeshuk23@gmail.com

Abstract

Background: Severe sepsis is defined as sepsis plus one of the following: Cardiovascular organ dysfunction OR acute respiratory distress syndrome OR two or more other organ dysfunctions (renal, neurologic, hematologic, or hepatic). The present observational study was aimed to evaluate serum ferritin as in predicting outcome in children, critically ill with sepsis and whether serum ferritin is associated with unfavorable outcomes. **Material and Methods:** Present prospective and observational study was conducted in children 1-5 years age group with severe sepsis. Serum ferritin level was considered raised if the result was >300 mg/L. **Results:** In present study 60 children satisfying study criteria were studied. Boys (63.3 %) were more than girls (36.7 %) and mean age was 36.46 ± 13.64 months. Mean duration of illness before admission and duration of fever before admission was 5.37 ± 1.26 days and 4.23 ± 3.48 days respectively. 58.3 % children received antibiotics before admission and 18.3 % children had malnutrition. Common suspected source of infection was pneumonia (35.0 %), Urinary tract infection (18.3 %), Meningitis (18.3 %), Intra-abdominal infection (6.7 %) and from other focus (21.7 %). Blood culture was positive in 23.3 %. Mean serum ferritin levels were 172.56 ± 118.3 ng/mL and ferritin ≥ 300 ng/mL was noted in 26.7 %. According to severe sepsis criteria cardiovascular organ dysfunction (65.0 %) was most common, followed by one or more Organ dysfunctions (40.0 %) and acute respiratory distress syndrome (36.7 %). We compared variables between cases with serum ferritin < 300 ng/ml (n=46) and cases with serum ferritin ≥ 300 ng/ml (n=14). We noted a statistically significant difference in cases of survivors, non-survivors, cases of multiorgan dysfunction syndrome (MODS), pediatric risk of mortality score (PRISM III) at 24 h and length of Pediatric intensive care unit (PICU) stay. While duration of mechanical ventilation and need of mechanical ventilation on day 1 were comparable in both groups and difference was not significant statistically. **Conclusion:** Serum Ferritin levels can be helpful predictive marker of mortality in severe sepsis and higher ferritin is associated with increasing organ dysfunction.

Keywords: serum ferritin, PICU, multiorgan dysfunction syndrome, severe sepsis,

[*]**Address for Correspondence:**
Dr Deepak A Shukla, Assistant Professor, Department of Pediatrics, BKL Walawalakar Trust Rural Medical Collage, Sawarde, Ratnagiri, INDIA.
Email: manjushree1205@gmail.com

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INTRODUCTION

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.[1] Severe sepsis is defined as sepsis plus one of the following: Cardiovascular organ dysfunction OR acute respiratory distress syndrome OR two or more other organ dysfunctions (renal, neurologic, hematologic, or hepatic). In 2017, almost half (20 million) of all estimated sepsis cases worldwide occurred in children under 5 years of age. The study estimated that 41.5% (20.3 million) of incident sepsis cases and 26.4% (2.9 million) deaths related to sepsis worldwide were among children younger than five

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years.[3] The three most common causes of sepsis-related deaths among children were infections related to neonatal disorders (for example, preterm birth, encephalopathy, hemolytic disease), lower respiratory infections and diarrheal diseases.[4] The increase in plasma ferritin concentration paralleled the increase in plasma CRP during acute pneumonia, tuberculosis, rheumatoid arthritis and neutropenic sepsis, suggesting that ferritin was acting as an acute phase protein.[9] The present observational study was aimed to evaluate serum ferritin as in predicting outcome in children, critically ill with sepsis and whether serum ferritin is associated with unfavorable outcomes.

MATERIAL AND METHODS

Present prospective and observational study was conducted in Department of Paediatrics, Prakash Institute of Medical Sciences and Research Centre, Urunislampur, India. Study duration was of 1 year (April 2020 to March 2021). Study was started after obtaining approval from institutional ethics committee

Inclusion Criteria

Children 1-5 years age group with severe sepsis. Severe sepsis[2] was defined as sepsis plus one of the following: Cardiovascular organ dysfunction OR acute respiratory distress syndrome OR two or more other organ dysfunctions (renal, neurologic, hematologic, or hepatic).

1. Cardiovascular organ dysfunction - Despite >40 ml/kg of isotonic intravenous fluid in 1 hour - Hypotension ≤5th percentile for age or systolic blood pressure <2 SD below normal for age;

OR Need for vasoactive drug to maintain blood pressure;
OR 2 of the following 5:

- Unexplained metabolic acidosis: Base deficit>5 meq/L
- Increased arterial lactate: >2 times upper limit of normal
- Oliguria: Urine output <0.5 ml/kg/hour
- Prolonged capillary refill: >5 sec
- Core to peripheral room temperature gap >3°C.

2. Acute respiratory distress syndrome (ARDS) was defined by - the presence of a PaO2/FiO2 ratio ≤300 OR PaCO2 65 torr or 20 mm Hg over baseline PaCO2 OR Need for non-elective invasive or noninvasive mechanical ventilation
3. Organ dysfunctions (neurological, renal, hepatic or hematologic) was defined as -

(i) Neurological: GCS score ≤ 11 or acute change in mental status with GCS of ≥ 3 points from abnormal baseline.
(ii) Renal: Serum creatinine >2 times upper limit of normal or 2 fold increase in baseline creatinine.
(iii) Hepatic: Total bilirubin ≥ 4 mg/dl or ALT level twice the upper limit of normal for age.
(iv) Hematological: Platelet count < 80,000 or a 50% decline in the platelet count from the highest value recorded over the last 3 days or INR >2.

Exclusion Criteria

Non-infective causes that alter the levels of inflammatory markers, such as chronic inflammatory conditions (including rheumatoid arthritis, inflammatory bowel disease, and Wilson's disease).
Conditions with iron overload whether primary, e.g., hereditary hemochromatosis or secondary, e.g., transfusion overload, porphyria cutanea tarda, and ineffective erythropoiesis (in sideroblastic anemia or thalassemia), and hematological malignancy. Study was explained to parents/relatives and written consent was taken. Detailed history regarding symptoms, past/medical history was collected from parents/relatives. All children underwent anthropometric measurements, detailed general/systemic examination. Relevant laboratory investigations were done at admission, such as total white blood cells count, differential count, erythrocyte sedimentation rate, platelet count and serum ferritin levels. Serum ferritin level was considered raised if the result was >300 mg/L. 5 ml of blood was collected with aseptic precautions and blood culture was performed by using agar based growth mediums and into bile broth using standard techniques. All children received antibiotics and ICU care as per standard operating procedures of department. Treatment details, clinical course were noted in proforma. Follow up was kept till 1 month of discharge. Data was collected and compiled using Microsoft Excel, analysed using SPSS 23.0 version. Difference of proportions between qualitative variables were tested using chi- square test or Fisher exact test as applicable. P value less than 0.5 was considered as statistically significant.

RESULTS

In present study 60 children satisfying study criteria were studied. Boys (63.3 %) were more than girls (36.7 %) and mean age was 36.46 ± 13.64 months. Mean duration of illness before admission and duration of fever before admission was 5.37 ± 1.26 days and 4.23 ± 3.48 days respectively. 58.3 % children received antibiotics before admission and 18.3 % children had malnutrition. Common suspected source of infection was pneumonia (35.0 %), Urinary tract infection (18.3 %), Meningitis (18.3 %), Intra-abdominal infection (6.7 %) and from other focus (21.7 %). Blood culture was positive in 23.3 %. Mean serum ferritin levels were 172.56 ± 118.3 ng/mL and ferritin ≥ 300 ng/mL was noted in 26.7 %.

Table 1: Overall characteristics

Patient characteristics	No. of cases / Mean ± SD	Percentage
Age (months)	36.46 ± 13.64	
Gender		
Boys	38	63.3
Girls	22	36.7
Duration of illness before admission (days)	5.37 ± 1.26	
Duration of fever (days)	4.23 ± 3.48	
Receipt of antibiotics before admission	35	58.3
Malnutrition ≤2SD of Z-score	11	18.3
Suspected source of infection		
Pneumonia	21	35.0
Meningitis	11	18.3
Intra-abdominal infection	4	6.7
Urinary tract infection	11	18.3
Other focus	13	21.7
Blood culture		0.0
Positive	14	23.3
Negative	46	76.7
Leukocytes/µL	16952 ± 6231	
CRP mg/dL	16.36 ± 11.27	
Ferritin ng/mL	172.56 ± 118.3	
Ferritin ≥300 ng/mL	16	26.7

According to severe sepsis criteria cardiovascular organ dysfunction (65.0 %) was most common, followed by one or more Organ dysfunctions (40.0 %) and acute respiratory distress syndrome (36.7 %).

Table 2: severe sepsis criteria

Criteria	No. of cases (n=60)	Percentage
Cardiovascular organ dysfunction	39	65.0
Hypotension	23	38.3
Need for vasoactive drug to maintain blood pressure;	12	20.0
Unexplained metabolic acidosis: Base deficit>5 meq/L	10	16.7
Increased arterial lactate: >2 times upper limit of normal	5	8.3
Oliguria: Urine output <0.5 ml/kg/hour	21	35.0
Prolonged capillary refill: >5 sec	15	25.0
Core to peripheral room temperature gap >3°C.	8	13.3
Acute respiratory distress syndrome (ARDS)	22	36.7
PaO2/FiO2 ratio ≤300	12	20.0
Need for non-elective invasive or noninvasive mechanical ventilation	22	36.7
Organ dysfunctions	24	40.0
Neurological ,	12	20.0
Renal,	18	30.0
Hepatic	14	23.3
Hematologic	8	13.3

We compared variables between cases with serum ferritin < 300 ng/ml (n=46) and cases with serum ferritin ≥ 300 ng/ml (n=14). We noted a statistically significant difference in cases of survivors, non-survivors, cases of multiorgan dysfunction syndrome (MODS), pediatric risk of mortality score (PRISM III) at 24 h and length of Pediatric intensive care unit (PICU) stay. While duration of mechanical ventilation and need of mechanical ventilation on day 1 were comparable in both groups and difference was not significant statistically.

Table 3: Serum ferritin levels

Variables	Serum ferritin < 300 ng/ml (n=46) No. of cases / mean ± SD	Serum ferritin ≥ 300 ng/ml (n=14) No. of cases/ mean ± SD	P value
Survivors	7 (15.2 %)	5 (35.7 %)	0.001
Non-survivors	39 (84.8 %)	9 (64.3 %)	0.001
Multiorgan dysfunction syndrome (MODS)	17 (37.0 %)	11 (78.6 %)	0.001
Need of Mechanical Ventilation on Day 1	21 (45.7 %)	6 (42.9 %)	0.53

Pediatric risk of mortality score (PRISM III) at 24 h	12.22 ± 3.47	18.1 ± 4.23	0.001
Duration of mechanical ventilation (days)	5.4 ± 2.1	6.7 ± 2.6	0.46
Length of Pediatric intensive care unit (PICU) stay (days)	12.13 ± 4.1	7.34 ± 3 12	0.08

DISCUSSION

Clinical experience and various studies have shown that the most important measure in reducing the mortality from sepsis is early identification of the condition and prompt initiation of therapy.[5,6] Among the biomarkers, commonly used are leukocyte count, C-reactive protein (CRP) and ferritin levels, the last two had limited studies in pediatrics correlating serum levels with unfavorable outcomes.[7,8] Assessment of severity of illness at admission is important for effective patient management, prognostication, and optimum utilization of resources. Simple interventions such as early rapid fluid administration, early antibiotics therapy, oxygen supplementation, and early use of inotropes through peripheral intravenous access have shown to improve the outcome of pediatric sepsis.[10] In a global study, the prevalence of severe sepsis was 8.2% among children in ICU (<18 years old) with the associated hospital mortality of 25%, which was not different by age and between developed and developing countries.[11] Ferritin is an iron-storing protein, in inflammatory processes, a great production of this protein occurs, inducing a decrease in serum iron, believed to minimize the availability of iron to microorganisms. For this reason, ferritin in critically ill pediatric patients may be elevated, and it is associated with severity in some diseases.[12,13] Elevate serum ferritin is associated with several inflammatory conditions, such as sepsis, multiorgan dysfunction syndrome (MODS), and Macrophage Activation Syndrome.[14] Pedro Celiny *et al.*,[15] studied 36 children aged 1 month–16 years with severe sepsis or septic shock requiring intensive care. Ferritin was <200 ng/mL in 13 children, 200–500 ng/mL in 11 children and >500 ng/mL in 12 children. The mortality associated with these groups was 23%, 9% and 58%, respectively. A ferritin >500 ng/mL was associated with a 3.2 (1.3–7.9) relative risk of death (p = 0.01). Ferritin Index of 1.7 was the best cutoff value for identifying those who died. Ferritin was raised in children with septic shock and high ferritin level was associated with poorer outcome. In study by Sarkar M *et al.*,[16] they studied 132 children of 1 month to 12 years with a diagnosis of septic shock or severe sepsis, mortality rate was 22.7%. PRISM III and PELODS-2 were significantly high in non-survivors (P ≤ 0.001 and 0.006, respectively). The cutoff value of ferritin at 2375 ng/dl had sensitivity 96.7% and specificity 88% to predict mortality. Serum ferritin values ≥2375 ng/mL in children with septic shock, and severe sepsis was significantly associated with mortality. Arnab Nandy *et al.*,[17] studied 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%. ROC analysis in the MODS group indicated that serum ferritin >1994.3 ng/mL predicts mortality with sensitivity 66.7% and specificity 100%. Major limitations of present study were single-center study, factors such as pre-existing anemia/ liver dysfunction were not considered and investigations to estimate body iron store were not done. Multicentric large sample studies are recommended.

CONCLUSION

Serum Ferritin levels can be helpful predictive marker of mortality in severe sepsis and higher ferritin is associated with increasing organ dysfunction. Serum ferritin levels > 300 ng/ml can be useful in predicting outcome in children with severe sepsis.

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