Original Research Article

Study of Serum Ferritin level in children with sepsis admitted in Pediatric Intensive Care Unit (PICU)

Utsav Anand[1*], Suhas G Kumbhar[2]

[1]Junior Resident III, [2]Professor and HOD, Department of Paediatrics, Bharati Vidyapeeth (Deemed to be University) Medical College and Hospital, Sangli, Maharashtra, INDIA.
Email: utsavanand7@gmail.com

Abstract

Background: Serum ferritin, in addition to representing body iron stores, is an acute-phase protein that increases in the presence of circulating inflammatory cytokines. When these mediators are stimulated, iron stored in the form of ferritin tends to increase while iron stored in the reticuloendothelial system tends to decrease. Ferritin is believed to be a serum marker of cellular damage and does not appear to produce deleterious effects. Elevated serum ferritin is associated with several inflammatory conditions, such as sepsis, multiorgan dysfunction syndrome (MODS), and Macrophage Activation Syndrome **Methodology:** This cross-sectional study was conducted in Pediatric Intensive Care Unit, at Bharati Vidyapeeth (Deemed to be University) Medical College and Hospital Sangli, Maharashtra. All children from 2 months to 18 years of age who fulfills criteria of sepsis were included in the study. Informed consent will be taken. The study protocol was approved by Institutional Ethical Committee. **Result:** In the present study, thirty patients were included, among them raised Serum Ferritin was observed in 22(73.3%) patients. Among the total number of cases, SIRS was seen in 4 cases, Sepsis in 12 cases, Severe Sepsis in 5 cases and Septic Shock in 9 cases with means serum ferritin level of 419, 769, 747 and 811 respectively. Total of 5(16.7%) cases had 3 or more organ involvement. In comparison to males, females have 4 times more chance of mortality, but it is non significant. Patients on ventilator had 28.385 times more chance of mortality than patients who did not require ventilator support, and it is significant (p=0.01).In comparison to patients having PRISM III score <15, patients having PRISM III score >15 have 23.4 times more chance of mortality, and it is significant (p=0.02). Patients with ferritin >500 have 28.385 times more chance of mortality, and it is significant (0.01). Patients who required Ionotropic Support had 28.385 times more chance of mortality, and it is significant (0.01). Mean ferritin level value in overall is 731.8(84-2982)ng/mL and it was significantly higher in non survivors (1556) as compared to survivors (605.04) (p=0.03). Sr. Ferritin >500 had: Sensitivity of 1.00 (95% Confidence Interval 0.40-1.00) and Specificity of 0.76 (95% Confidence Interval 0.56-0.91). Chi square test was done to compare between Sr ferritin level and survivors. It was found that all non survivors were having Sr ferritin level >500. Unpaired t test was done to compare PRISM III score, Duration of Mechanical Ventilator(days) and Length of PICU stay(days) and no significant difference in comparison to Sr ferritin level was found. **Conclusion:** This study shows that Sr Ferritin is raised in children with sepsis and high Ferritin level(>500ng/mL) is associated with poorer outcome. It is one of the useful biomarker of predictor of mortality. Serum Ferritin can be useful to predict poor outcome in children with sepsis.

Keyword: Serum Ferritin level, mortality, critically ill children, PRISM III score, Sepsis, MODS, Septic Shock.

[*]**Address for Correspondence:**
Dr Utsav Anand, Junior Resident III, Department of Paediatrics, Bharati Vidhyapeeth (Deemed to be University) Medical College and Hospital, Sangli, Maharashtra, INDIA.
Email: utsavanand7@gmail.com

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Serum ferritin, in addition to representing body iron stores, is an acute-phase protein that increases in the presence of circulating inflammatory cytokines. When these mediators are stimulated, iron stored in the form of ferritin tends to increase while iron stored in the reticuloendothelial system tends to decrease. Ferritin is believed to be a serum marker of cellular damage and does not appear to produce deleterious effects. Garcia *et al.*[1] described for the first time, the association of this biomarker with unfavorable

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outcomes in children with septic shock in 2007. Since then, interest in ferritin has grown in pediatric intensive care. Sepsis is a life-threatening condition that remains a leading cause of death in children worldwide. Prognostic markers in sepsis are useful for identifying patients at increased risk of death, selecting which therapies are most appropriate in certain situations and guiding the response to treatment over time. The use of ferritin in low- and middle-resource settings is facilitated by its low cost and wide availability in most centers. In critical illness due to sepsis, a systemic inflammatory response (SIR) is triggered and high levels of proinflammatory cytokines are present in early phases of illness. Because proinflammatory cytokines such as interleukin 6, interleukin 8, and tumor necrosis stimulate ferritin synthesis, ferritin level in these patients should be raised. Indeed, in critically ill adults, ferritin levels ranged from 340 to 830 ng/mL, which is much higher than the level expected in a 'normal' inflammatory response.

Septic shock is a complex syndrome displaying a tremendous degree of heterogeneity. Mortality in sepsis is mainly due from refractory shock and/or life-threatening organ dysfunction syndrome due to dysregulated host immune response to infection. Categorize sepsis subtypes through stratification of myriad biomarkers that are products of dysregulated inflammatory response may be fruitful endeavor with clinical implication.[3] Elevated serum ferritin is associated with several inflammatory conditions, such as sepsis, multiorgan dysfunction syndrome (MODS), and Macrophage Activation Syndrome. In addition to iron, ferritin synthesis is regulated by cytokines at various levels (transcriptional, posttranscriptional, and translational) during development, cellular differentiation, proliferation and inflammation. Ruddell *et al.* proposed extracellular ferritin can act as a pro-inflammatory signaling molecule in hepatic stellate cells which is entirely independent of its classic role as an iron-binding protein.[4] Hence, serum ferritin has emerged as an independent marker of the severity of the disease and help in predicting the outcome of the critically ill patients.[9]

Definition of sepsis: The diagnosis of severe sepsis and septic shock was based on the International pediatric sepsis consensus conference(2005): Definitions for sepsis and organ dysfunction in pediatrics.[2]

SIRS: Two of 4 criteria on core temperature, heart rate, respiratory rate, and leukocyte count. One of which must be abnormal temperature or abnormal leukocyte count.

Sepsis: SIRS in the presence of or as a result of suspected or proven infection.

Severe sepsis: Sepsis plus one of the following: cardiovascular organ dysfunction OR acute respiratory distress syndrome OR two or more other organ dysfunctions.

Septic shock: Sepsis plus cardiovascular dysfunction.

MODS: MODS is defined as a clinical syndrome characterized by the development of progressive and potentially reversible physiologic dysfunction in 2 or more organs or organ systems that is induced by a variety of acute insults

In this study we have examined ferritin levels in critically ill children with sepsis and assessed its association with outcome.

METHODOLOGY

This cross-sectional study was conducted in Pediatric Intensive Care Unit, at Bharati Vidyapeeth (Deemed to be University) Medical College and Hospital Sangli, Maharashtra. All children from 2 months to 18 years of age who fulfills criteria of sepsis were included in the study. Informed consent will be taken**. The study protocol was approved by Institutional Ethical Committee.**

The objectives of the study were-

1. To study the ferritin level in children with sepsis.
2. To study the outcome of sepsis in relation to raised ferritin level by corelating PRISM III score.

Inclusion Criteria:

1. All Patients aged 2 months to 18 years of age admitted to Pediatric Intensive Care Unit and admitted for atleast 24 hours, who fulfill the clinical criteria of sepsis.

Exclusion Criteria:

1. Transfusion dependent hemolytic anemia.
2. Autoimmune diseases which alters serum ferritin level.
3. Recipient of blood transfusion in past 4 months.
4. Children with known malignancies and immune-suppresive treatment.

The study subjects were evaluated in detail and data were filled on preformed structured proforma. The following data were collected for all patients and were included in the study: demographic characteristics- Age, Weight, Sex and BMI, Detailed history, general examination and systemic examination were done in each patient to find out the possible cause of sepsis. Necessary Investigations were carried out to find the cause and possible diagnosis and all data were recorded in a specially designed proforma for this study.

Pediatric risk of mortality score(PRISM III) was calculated to predict risk of death on 1st day of admission in all study patients.

Data on the initial blood tests CBC, SGOT, SGPT, ABG, RFT, Electrolyte, Lactate, PT, APTT, CRP, Blood Culture and Sr Ferritin of each patient with vital signs measured at arrival to the medical admission unit and primary complaint were entered in proforma. Other investigations like USG, Doppler, 2D ECHO etc were done as and when required on case to case basis.

Serum Ferritin level was measured at Bharati Hospital biochemistry lab at the time of diagnosis using CLIA (Chemiluminescence Immunoassay Analyser) technique. Machine model that was used was Maglumi 800(SNIBE). Time taken to run each sample was 45minutes.
The diagnosis of severe sepsis and septic shock was based on the International pediatric sepsis consensus conference. Serum ferritin, according to age was evaluated based on the following reference range.

Table

Age	Normal Sr Ferritin level(ng/mL)	Age
2months -5months	50-200	2months -5months
6 months -18 years	7-140	6 months -18 years

Clinical Course in the hospital in terms of length of hospital stay, use of inotropes and whether on mechanical ventilator were entered in proforma. Outcome in terms of death and discharge were documented.
The data was compiled and entered in SPSS version 23 for statical analysis. The analysis was done using Unpaired t test and Chi-square test, considering p value<0.05 as statically significant.
Ethical Approval: This study protocol was approved by The Chairman, Instutional Ethics Committee Bharati Vidyapeeth (Deemed to be University) Medical College and Hospital, Sangli, Maharashtra. BV(DU)MCandH/Sangli/IEC/498/22

RESULTS

In the present study, thirty patients were included, among them raised Serum Ferritin was observed in 22(73.3%) patients. Among the total number of cases, SIRS was seen in 4 cases, Sepsis in 12 cases, Severe Sepsis in 5 cases and Septic Shock in 9 cases with means serum ferritin level of 419, 769, 747 and 811 respectively. Total of 5(16.7%) cases had 3 or more organ involvement.
In comparison to males, females have 4 times more chance of mortality, but it is non-significant. -Patients on ventilator had 28.385 times more chance of mortality than patients who did not require ventilator support, and it is significant (p=0.01).- In comparison to patients having PRISM III score <15, patients having PRISM III score >15 have 23.4 times more chance of mortality, and it was significant (p=0.02).- Patients with ferritin >500 have 28.385 times more chance of mortality, and it is significant (0.01).
Patients who required Ionotropic Support had 28.385 times more chance of mortality, and it is significant (0.01).- Mean ferritin level value in overall is 731.8(84-2982)ng/mL and it was significantly higher in non survivors (1556) as compared to survivors (605.04) (p=0.03)
Sr. Ferritin >500 had: Sensitivity: 1.00 (95% Confidence Interval 0.40-1.00)
Specificity: 0.76 (95% Confidence Interval 0.56-0.91)
Chi square test was done to compare between Sr ferritin level and survivors. It was found that all non survivors were having
Sr ferritin level >500. Unpaired t test was done to compare PRISM III score, Duration of Mechanical Ventilator(days) and Length of PICU stay(days) and no significant difference in comparison to Sr ferritin level was found.

Table 1: Characteristics among survivors and non-survivors based on outcome.

	All Children (n=30)	Survivors(n=26)	Non Survivors(n=4)	Odd Ratio	p-value
Boys	16(53%)	15(58%)	1(25%)	4.091	0.50
Positive Blood culture	6(20%)	5(19%)	1(25%)	0.71	0.79
Mechanical ventilated	10(33%)	6(23%)	4(100%)	28.385	0.01*
PRISM III Score>15	11(37%)	7(27%)	4(100%)	14.143	0.02*
Ferritin <500	20(66%)	20(76%)	0(0%)	28.385	0.0136*
Ferritin >500	10(33%)	6(24%)	4(100%)	28.385	0.0136*
Ionotropic Support	10(33%)	6(23%)	4(100%)	28.385	0.0136*
Mean Ferritin	731.8	605.04	1556	Unpaired t statistic 2.26	0.03*

Table 2: Comparison of Outcomes based on Serum Ferritin level.

	Sr. Ferritin <500()ng/mL (n=20) No. of cases/mean+_SD	Sr Ferritin>500ng/mL (n=10) No. of cases/mean+_SD	p- value
Survivors	20(100%)	6(60%)	Chi square statistic= 6.09
Non-Survivors	0(0%)	4(40%)	P value= 0.01
PRISM III Score	13.65±3.75	15.4±6.84	Unpaired t statistic= 0.91 P value= 0.37
Duration of Mechanical Ventilator(days)	6±1	3.8±2.17	Unpaired t statistic= 2.06 P value= 0.07
Length of PICU stay(days)	6.3±4.54	4.5±3.03	Unpaired t statistic= 1.13 P value= 0.27

DISCUSSION

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. Sepsis and septic shock are major health-care problems, affecting millions of children around the world each year.[6] Globally, an estimated 22 cases of childhood sepsis diagnosed per 100,000 person-years translating into 1.2 million cases of childhood sepsis per year.[7] Mortality for children with sepsis ranges from 4% to as high as 50%, depending on illness severity, risk factors, and geographic location.[8] A raised serum ferritin concentration in critical illness is associated with a poor outcome. Serum Ferritin can be a marker of disease severity. It is can also be an independent predictor of mortality and can be associated with poor outcome in critically ill children. This study is designed to investigate whether serum ferritin can predict prognosis including mortality on pediatric patients in PICU. Among the biomarkers, commonly used are leukocyte count, C-reactive protein (CRP) and ferritin levels. 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. 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.[10,11] Elevate serum ferritin is associated with several inflammatory conditions, such as sepsis, multiorgan dysfunction syndrome (MODS), and Septic Shock. Pedro Celiny *et al.*,[1] studied 36 children aged 1 month–16 years with severe sepsis or septic shock requiring intensive care. Ferritin was 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 was raised in children with septic shock and high ferritin level was associated with poorer outcome. Arnab Nandy *et al.*,[13] 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. According to Bennett *et al.*, in the pediatric population, serum ferritin levels of >3000 ng/mL, was associated with increased risk for both receipt of critical care and subsequent death[13]: On the other hand, Garcia *et al.*[14] have studied it in a small number of patients (n = 36) and reported 58% mortality in children with high ferritin levels >500 ng/dl and severe sepsis. In another pediatric study from India by Sharma and Sharma found that ferritin value >1100 ng/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 0.68.[15] In an adult study done by Lachmann *et al.* found that in septic shock maximum ferritin level was 1545 ng/ml.[16]

CONCLUSION

This study shows that Sr Ferritin is raised in children with sepsis and high Ferritin level(>500ng/mL) is associated with poorer outcome.

It is one of the useful biomarker of predictor of mortality.

Serum Ferritin can be useful to predict poor outcome in children with sepsis.

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