Original Article
DOI: https://doi.org/10.70749/ijbr.v3i6.1717

INDUS JOURNAL OF BIOSCIENCE RESEARCH
https://induspublishers.com/IJBR
ISSN: 2960-2793/ 2960-2807

Assessment of Serum Ferritin Levels for Predicting the Outcome in Children Admitted with Severe Sepsis in Paediatric Intensive Care Unit in CMH Abbottabad

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ARTICLE INFO

Keywords: Serum Ferritin, Severe Sepsis, Pediatric ICU, Prognostic Marker, Diagnostic Accuracy.

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Declaration
Authors' Contribution
All authors equally contributed to the study and approved the final manuscript

Conflict of Interest: No conflict of interest.

Funding: No funding received by the authors.

Article History
Received: 09-03-2025 Revised: 24-05-2025
Accepted: 11-06-2025 Published: 30-06-2025

ABSTRACT

Background: Severe sepsis in pediatric patients remains a critical challenge in intensive care, with high morbidity and mortality rates. Identifying reliable, cost-effective prognostic markers is essential for timely risk stratification and intervention. Serum ferritin, an acute-phase reactant, has emerged as a potential predictor of adverse outcomes, though its diagnostic utility in children with sepsis requires further validation. **Objective:** To evaluate the diagnostic accuracy of serum ferritin in predicting adverse outcomes in pediatric patients with severe sepsis taking non survivors as gold standard. **Study Design:** Cross-sectional validation study. **Duration and Place of Study:** The study was conducted from May 2023 to December 2023 in the Paediatric Intensive Care Unit (PICU) at Combined Military Hospital, Abbottabad. **Methodology:** A total of 186 pediatric patients between the ages of 1 month and 12 years with confirmed severe sepsis were enrolled using consecutive non-probability sampling. Serum ferritin concentrations were assessed within the first 48 hours following admission to the pediatric intensive care unit (PICU) through a chemiluminescent immunoassay method. A threshold of 558 ng/mL or higher was applied to indicate a likelihood of adverse outcomes. **Results:** The average age of the participants was 5.66 ± 3.55 years, with a male-to-female ratio of 1.4:1. Out of the 186 cases, serum ferritin exhibited a sensitivity of 63.04%, specificity of 75%, positive predictive value (PPV) of 45.31%, negative predictive value (NPV) of 86.07%, and an overall diagnostic accuracy of 72.04%. Stratified analyses showed higher diagnostic performance in children ≤8 years and in those with illness duration ≤7 days. **Conclusion:** Serum ferritin is a moderately accurate, non-invasive prognostic biomarker for adverse outcomes in pediatric severe sepsis, particularly when integrated with clinical assessment.

INTRODUCTION

Sepsis in children is the body's dysregulated response to infection that results in functional organ dysfunction.[1] It is also still one of the significant reasons for morbidity and mortality in children in the world's pediatric intensive care units.[2] Early detection and immediate intervention are fundamental due to children having undeveloped immunity and different body reactions to complications compared to adult cases.[3] Clinical presentation of pediatric sepsis is very heterogeneous, ranging between subtle findings of systemic inflammation to sudden deterioration to septic shock, therefore causing particular challenges in diagnosis and treatment in reference to time.[4]

Patients admitted with severe sepsis are also at high risk for adverse outcomes, like prolonged inpatient stays, multi-organ dysfunction, and death.[5] Delay in the initiation of antibiotics, and the underlying comorbid diseases like malnutrition or immunodeficiency are among the relevant prognostic factors.[6] Despite modern supportive therapy, the mortality in severe pediatric sepsis is too high especially in centers of limited resources.[7] Accurate risk stratification tools and prognostic factors are required to guide clinical decision support and appropriate allocation of critical care resources.

The acute-phase reactant serum ferritin is also under consideration as an outcome predictor in children presenting with sepsis.[8] Raised ferritin is an indication of iron metabolism dysfunction superimposed on background systemic immunologic activation and inflammation.[9] Persistent raised or drastically raised ferritin in children presenting with severe sepsis are distinguished by elevated risk of adverse outcome, such as multi-organ dysfunction/failure, prolonged ventilator support, and death.[10] Hyperferritinemia is especially correlated with macrophage activation syndrome and the secondary hemophagocytic lymphohistiocytosis, the

complications of the course of sepsis.[11] Ferritin therefore serves to indicate excessive immunologic dysregulation central to the severity of the disease.[12] Inclusion of ferritin measurements in the initial work-up could thus allow for risk stratification, for the tailoring of the aggressively of supportive measures, and perhaps for the selection of potential candidates for immunomodulatory intervention.

Shaikh et al. reported that serum ferritin, with a cut-off value of 558 ng/mL, had a sensitivity of 74.1% and specificity of 67.7% in predicting adverse outcomes (non-survival) in children admitted with severe sepsis, with a non-survivor prevalence of 40%.[13]

There is a pressing requirement to conduct studies in Azad Kashmir on the prognostic value of serum ferritin in children admitted to the ICU for severe sepsis. The region is afflicted by certain healthcare issues, like limited access to advanced diagnostic facilities and the burden of infection in children. Provincial data on biomarkers of sepsis like serum ferritin are unavailable, and the former impedes the proper risk stratification and evidence-based approach. Conducting studies of the sort would yield us information particular to the region and would potentially optimize early prognostic ability and outcome in children in the ICU.

METHODOLOGY

This cross-sectional validation study was conducted in the Paediatric Intensive Care Unit (PICU) of Combined Military Hospital (CMH), Abbottabad, from May 2023 to December 2023. The study aimed to evaluate the diagnostic performance of serum ferritin levels in predicting outcomes in children admitted with severe sepsis. A total of 186 children aged between 1 month and 12 years were enrolled using non-probability consecutive sampling. The sample size was calculated with a 95% confidence level, assuming a sensitivity of 74.1%, specificity of 67.7%, and an estimated prevalence of non-survivors at 40%,[13] allowing a 10% margin of error.

Children were eligible if they fulfilled the clinical definition of severe sepsis, characterized by systemic infection accompanied by cardiovascular compromise, acute respiratory distress syndrome, or dysfunction of two or more organ systems. Patients were excluded if they had chronic organ dysfunction (e.g., hepatic, renal, cardiac, or pulmonary), received a blood transfusion in the preceding four months, or were known/suspected cases of malignancy, autoimmune disease, or metabolic disorders.

At admission, demographic and clinical information including age, gender, weight and duration of illness were recorded. A 2 mL venous blood sample was obtained within the first 48 hours of PICU admission and analyzed for serum ferritin using a chemiluminescence immunoassay method. A serum ferritin threshold of ≥558 ng/mL was used as the predictive cut-off for poor outcome. All patients were monitored until discharge or death, and outcomes were categorized as survival or non-survival.

Serum ferritin's ability to predict adverse outcomes was evaluated by analyzing its sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the area under the receiver operating characteristic (ROC) curve. Data were analyzed using SPSS version 27.0, with subgroup analyses performed to assess associations with age groups, gender, and duration of illness.

RESULTS

The demographic data of the children revealed a mean age of 5.655 years ± 3.552 SD and a mean weight of 14.466 kg ± 7.330 SD. The average duration of illness was 7.683 days ± 4.002 SD, and the mean serum ferritin level was 515.600 ng/mL ± 176.769 SD (as shown in Table-I).

Table I

Demographics of children with severe sepsis

Demographics	Mean ± SD / n (%)
Age (years)	5.655 ± 3.552
Weight (kg)	14.466 ± 7.330
Duration of Illness (days)	7.683 ± 4.002
Serum Ferritin (ng/mL)	515.600 ± 176.769
Gender	
Male	109 (58.6%)
Female	77 (41.4%)

Among the 186 children, 109 (58.6%) were male, and 77 (41.4%) were female. In terms of serum ferritin levels and survival outcomes, 64 (34.4%) children had positive serum ferritin levels, while 122 (65.6%) had negative levels. Among non-survivors, 46 (24.7%) had positive serum ferritin levels, and 140 (75.3%) had negative levels (as shown in Table-II).

Table II

Overall results of serum ferritin and non survivors

Variable	Serum Ferritin	Non survivors
Positive	64 (34.4%)	46 (24.7%)
Negative	122 (65.6%)	140 (75.3%)
Total	186 (100%)	186 (100%)

The diagnostic performance of serum ferritin in predicting adverse outcomes was assessed using a 2x2 contingency table. The chi-square test yielded a value of 22.20 with a p-value of 0.000, indicating a statistically significant association between serum ferritin levels and adverse outcomes (as shown in Table-III).

Table III

Comparison of serum ferritin versus non survivors in diagnosis of adverse outcomes

Serum ferritin	Non survivors		Total
	Positive	Negative	
Positive	29 (TP)	35 (FP)	64
Negative	17 (FN)	105 (TN)	122
Total	**46**	**140**	**186**

Chi square = 22.20
P value = 0.000

Key:
TP = True positive
FP = False positive
FN = False negative
TN = True negative

The sensitivity of serum ferritin in diagnosing adverse outcomes was 63.04%, specificity was 75%, diagnostic accuracy was 72.04%, positive predictive value (PPV) was 45.31%, and negative predictive value (NPV) was 86.07% (as shown in Table-IV).

Table IV

Sensitivity, Specificity, Diagnostic Accuracy, PPV and NPV of Serum ferritin in diagnosis of adverse outcomes

Diagnostic Parameter	Result
Sensitivity	63.04%
Specificity	75%
Diagnostic Accuracy	72.04%
PPV (Positive Predictive Value)	45.31%
NPV (Negative Predictive Value)	86.07%

Stratified analysis based on demographic variables revealed varied diagnostic performance of serum ferritin. Among children aged 8 years or younger, the sensitivity was 63.33%, specificity was 74.75%, diagnostic accuracy reached 72.10%, with a positive predictive value (PPV) of 43.18% and a negative predictive value (NPV) of 87.06%. In children older than 8 years, sensitivity was 62.50%, specificity 75.61%, diagnostic accuracy 71.93%, PPV 50%, and NPV 83.78%. For male patients, the sensitivity was 60.71%, specificity 70.37%, diagnostic accuracy 67.89%, PPV 41.46%, and NPV 83.82%. Among female patients, sensitivity was 68.18%, specificity 69.33%, diagnostic accuracy 69.07%, PPV 39.47%, and NPV 88.14%. In cases where the duration of illness was 7 days or less, the sensitivity was 68.18%, specificity 69.33%, diagnostic accuracy 69.07%, PPV 39.47%, and NPV 88.14%. When the illness lasted for more than 7 days, sensitivity was 58.33%, specificity 81.54%, diagnostic accuracy 75.28%, PPV 53.85%, and NPV 84.13% (as shown in Table-V).

Table V

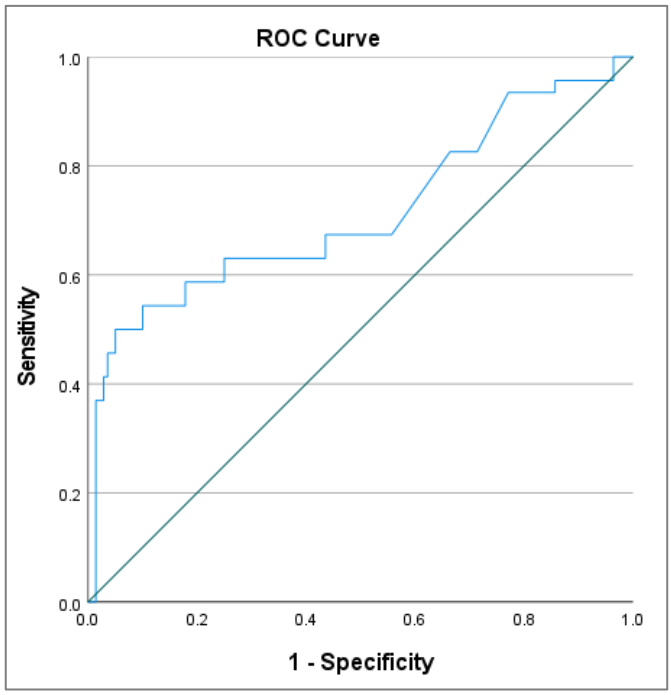
Stratified Analysis of Sensitivity, Specificity, Diagnostic Accuracy, PPV, and NPV of Serum Ferritin in Predicting Adverse Outcome (Non-Survivor) by demographic variables

Variables	Groups	Diagnostic Parameter	Result
Age (years)	≤8	Sensitivity	63.33%
		Specificity	74.75%
		Diagnostic Accuracy	72.10%
		PPV	43.18%
		NPV	87.06%
	>8	Sensitivity	62.50%
		Specificity	75.61%
		Diagnostic Accuracy	71.93%
		PPV	50%
		NPV	83.78%
Gender	Male	Sensitivity	60.71%
		Specificity	70.37%
		Diagnostic Accuracy	67.89%
		PPV	41.46%
		NPV	83.82%
	Female	Sensitivity	68.18%
		Specificity	69.33%
		Diagnostic Accuracy	69.07%
		PPV	39.47%
		NPV	88.14%
Duration of Illness (days)	≤7	Sensitivity	68.18%
		Specificity	69.33%
		Diagnostic Accuracy	69.07%
		PPV	39.47%
		NPV	88.14%
	>7	Sensitivity	58.33%
		Specificity	81.54%
		Diagnostic Accuracy	75.28%
		PPV	53.85%
		NPV	84.13%

The ROC curve analysis for serum ferritin levels in predicting adverse outcomes in children with severe sepsis showed an AUC of 0.714, indicating moderate predictive ability. The optimal cutoff value for serum ferritin was not explicitly stated, but the analysis provided various cutoff points with corresponding sensitivity and specificity values. For example, at a cutoff of 402.850 ng/mL, sensitivity was 82.6% and 1 - specificity was 71.4% (Graph-I).

Graph I

ROC Curve



DISCUSSION

The results demonstrated that serum ferritin levels were significantly associated with adverse outcomes, as evidenced by the ROC curve analysis with an AUC of 0.714. This would also incriminate higher ferritin levels themselves as biomarkers for the recognition of children who are also at higher risk of adverse outcomes. The values thus obtained for sensitivity and specificity indicate the consideration of serum ferritin as an imperfect but valuable predictor in the overall clinical assessment.

The analysis of stratification revealed that the diagnostic performance varied across different demographic groups. For instance, children ≤8 years of age and illness duration ≤7 days had modestly improved sensitivity and specificity compared to children of higher age and of longer duration of illness. It is probable that the difference is explained by the difference in the pattern of the immune responses and of the course of the diseases in younger children compared to older children and also the impact of earlier intervention in altering the outcome.

The results also pointed to the value of taking gender into account, which displayed greater sensitivity and NPV than male gender. It is possibly attributable to the gender differences in basal ferritin level and body immunity. It is also probable that the difference in diagnostic precision in relation to duration of the illness could allow the timing of the serum ferritin test to influence its predictive value.

Our study results align with those of Dewa Ayu Angga Rainingsih et al. [14] who found that elevated serum ferritin levels are associated with increased mortality risk in

pediatric septic shock patients. Rainingsih et al. [14] identified a ferritin cut-off of 660.78 ng/ml with high sensitivity (85.7%) and specificity (77.8%) for predicting mortality, similar to our findings of a significant association between serum ferritin levels and adverse outcomes (chi-square = 22.20, p-value = 0.000). However, our study found a lower mean serum ferritin level (515.600 ng/mL) compared to their cut-off value, suggesting that the threshold for predicting adverse outcomes may vary based on population characteristics and study design.

Manjushree S Kulkarni et al. [15] also found that serum ferritin levels are a helpful predictive marker of mortality in severe sepsis, with higher ferritin levels associated with increasing organ dysfunction. Our study's sensitivity (63.04%) and specificity (75%) for diagnosing adverse outcomes are comparable to Kulkarni et al.'s findings, reinforcing the prognostic value of serum ferritin in pediatric sepsis. However, our study's diagnostic accuracy (72.04%) was slightly lower than their reported accuracy, which may be attributed to differences in patient demographics and clinical settings.

Mansi Lal et al. [16] demonstrated that high serum ferritin levels (>504 ng/mL) and a pSOFA score >12 are excellent predictors of mortality in children with severe sepsis. Our study's mean serum ferritin level (515.600 ng/mL) is within the range identified by Lal et al. [16] as predictive of adverse outcomes. The significant association between serum ferritin levels and adverse outcomes in our study supports the use of ferritin as a prognostic marker, similar to the findings of Lal et al. [16] However, our study did not incorporate the pSOFA score, which could have provided additional insights into the prognostic utility of ferritin in conjunction with clinical scoring systems.

Gulrej Nisar Shaikh et al. [13] found that serum ferritin levels within five days of illness onset predicted poor outcome in critically ill children with severe sepsis. Their identified cut-off value of 558 ng/mL had a sensitivity of 74.1% and specificity of 67.7%, which are comparable to our study's sensitivity (63.04%) and specificity (75%). The consistency in sensitivity and specificity across these studies underscores the robustness of serum ferritin as a prognostic marker in pediatric sepsis. However, our study's mean serum level of ferritin (515.600 ng/mL) was slightly higher than their threshold value, which would indicate possible differences in ferritin levels due to reasons of regional difference and patient population.

The similarity in results in these studies also highlights the prognostic predictability of serum ferritin in childhood sepsis. Differences between studies in the cut-off values and diagnostic performance indices are to be anticipated owing to variation between the populations of patients, state of illness, and study designs. For instance, the higher end of the cut-off value in Rainingsih et al. [14] would suggest the possibility of having a sicker patient population or variation in the inflammatory response in the study population. Likewise, the low end of the cut-off value in Shaikh et al. [13] would be attributable to the inclusion of children presenting with microcytic anemia, which would arguably have different initial ferritin levels.

Our study's comparatively slightly less diagnostic accuracy than in some of the studies listed above may be due to our broader age range and varying illness duration in the study population. Stratification analysis in our study revealed age- and duration-dependent variation in diagnostic performance in support of the suggestion that the factors may also decide the prognostic value of serum ferritin. Future studies should attempt to determine ferritin cut-off values standardized to various populations and the impact of comorbidities on ferritin level and outcome in children with sepsis.

Our study also had several limitations. We could only conduct the study in a single center, which could restrict the generalizability of our results to the wider population. We also had a comparatively small sample size, which would impact our precision of estimates and the strength of our conclusions. We also did not include other clinical scores like the pSOFA score, which would have given us a better idea of the prognostic value of serum ferritin. Larger multicentric studies in the future should correct for the first two limitations by being larger in number and multicentric in nature. Multiple prognostic indicators also should be included in the studies in order to enhance the predictive value of serum ferritin in children with sepsis.

CONCLUSION

Our study concluded that serum ferritin is of considerable prognostic value for the predictability of undesirable events in children presenting with severe sepsis. The consistent observation of raised ferritin in association with increased risk of death in several demographic and clinical analyses highlights its potential for application as a biomarker in the relevant setting. The current observation is in accordance with the literature, validating the utility of serum ferritin in the risk assessment and clinical decision-making for the condition of pediatric sepsis. For further refinement of prognostic accuracy, future research would do well to define ferritin cut-off values in normalized fashion and study its co-use in conjunction with other indexes of clinical severity.

Acknowledgments

We are extremely thankful for the department's medical staff's wholehearted dedication. Their attentive diligence in keeping appropriate details of records and dealing with patient information have been crucial to our operations.

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