Serum ferritin as a predictor of duration of paediatric intensive care unit stay in critically ill children: a prospective observational study from eastern India

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ABSTRACT

Background: Critically ill children impose a heavy demand on limited paediatric intensive care unit (PICU) resources, and early identification of those likely to require a prolonged stay could aid triage and counselling. Serum ferritin is an acute-phase reactant that rises in sepsis and hyperinflammation. We evaluated whether admission serum ferritin predicts the duration of PICU stay and compared it with C-reactive protein (CRP) and the Paediatric Risk of Mortality (PRISM-III) score.

Methods: In this single-centre prospective observational study conducted over one year (November 2022–October 2023) in a tertiary care PICU in Kolkata, 57 critically ill children aged 1 month to 18 years were enrolled. Serum ferritin and CRP were measured on day 1 and on the day before shifting out of the PICU; PRISM-III was calculated at 24 hours. Correlations were assessed by Spearman's rho, group differences by the Mann–Whitney U test, categorical associations by the chi-square test, and predictive performance by receiver operating characteristic (ROC) analysis. A p-value <0.05 was significant.

Results: The mean age was 6.59 ± 4.91 years and 64.9% were male. The median PICU stay was 5 days (range 1–29); mortality was 5.3%. Ferritin was elevated (>500 µg/L) in 77.2% of children on day 1. Duration of PICU stay correlated significantly with PRISM-III at 24 h ($r=0.60$, $p<0.001$), delta ferritin ($r=0.49$, $p<0.001$), day-1 ferritin ($r=0.32$, $p=0.003$) and day-1 CRP ($r=0.32$, $p=0.01$). Children staying ≥5 days had significantly higher day-1 ferritin (26,262 vs 13,051 µg/L; $p=0.003$) and day-1 CRP (10.46 vs 6.59 mg/dL; $p=0.02$). For predicting a stay ≥5 days, day-1 ferritin (cut-off 500 µg/L) yielded an AUC of 0.72 ($p=0.003$; sensitivity 83.3%, specificity 37.5%) and ferritin measured before shifting an AUC of 0.80 ($p<0.001$; sensitivity 80%, specificity 81.9%). Neither ferritin nor CRP was significantly associated with blood-culture positivity.

Conclusions: Elevated day-1 serum ferritin was significantly associated with a longer PICU stay and performed comparably to CRP, though PRISM-III remained the strongest correlate. Ferritin is an inexpensive, widely available adjunct that may help flag critically ill children at risk of a prolonged intensive-care course, but it did not predict culture-positive sepsis.

Keywords: *serum ferritin; C-reactive protein; paediatric intensive care unit; length of stay; PRISM-III; critically ill children; biomarker.*

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1. Introduction

Admissions of critically ill children to intensive care units range from roughly 75 to 166 per 100,000 children-years, with respiratory, infectious, congenital and perioperative conditions being the commonest reasons for admission. Intensive care is resource-intensive and costly, and in resource-limited settings the shortage of paediatric intensive care unit (PICU)

infrastructure remains a major barrier to access. Sepsis is a leading cause of childhood morbidity and mortality worldwide, with reported PICU case-fatality exceeding 50% in some developing countries.

Because clinical scoring alone is subjective, laboratory biomarkers are increasingly used to gauge severity and prognosis. C-reactive protein (CRP) is a widely available acute-phase protein that rises within 4–8 hours of an inflammatory stimulus and peaks by 36–50 hours, but it does not reliably distinguish bacterial from viral infection. Serum ferritin, a ubiquitous 24-subunit iron-storage protein, is also an acute-phase reactant that increases in response to inflammatory cytokines such as interleukin-1 and tumour necrosis factor. During infection, iron is sequestered within hepatocytes and macrophages, enhancing ferritin translation; markedly elevated ferritin (hyperferritinaemia) is now recognised across the hyperferritinaemic-syndrome spectrum, including macrophage activation syndrome and septic shock.

Since the seminal observation by Garcia et al. that ferritin above 500 µg/L in paediatric septic shock carried a threefold higher mortality, ferritin has attracted interest as a prognostic marker. However, evidence for its value in predicting resource utilisation—specifically the duration of PICU stay—remains limited and inconsistent. We therefore undertook this study to determine whether admission serum ferritin predicts the length of PICU stay in critically ill children aged 1 month to 18 years, and to compare its performance with CRP and the Paediatric Risk of Mortality (PRISM-III) score.

2. Materials and methods

2.1 Study design, setting and population

This was a time-framed, single-centre, prospective observational study conducted in the PICU of Apollo Multispeciality Hospitals, Kolkata, over one year (November 2022 to October 2023). Consecutive critically ill children aged 1 month to 18 years admitted to the PICU with fever of any duration and fulfilling the inclusion criteria were enrolled after written informed consent from a parent or guardian and age-appropriate assent.

Children with hereditary hyperferritinaemia, known haemophagocytic lymphohistiocytosis or macrophage activation syndrome, transfusion-dependent thalassaemia (who have baseline hyperferritinaemia), immunosuppression, and neonates (<1 month) or adults (>18 years) were excluded.

2.2 Sample size

Assuming an alpha risk of 0.05 and a beta risk of 0.20 in a two-sided test with an anticipated correlation coefficient of 0.364 (derived from prior data on paediatric septic shock) and no dropout, the minimum required sample was 57 (GRANMO). Fifty-seven children were enrolled.

2.3 Data collection and measurements

For each child the duration of illness and of fever, and the dates of PICU admission and of shifting to the ward, were recorded. Serum ferritin and CRP were measured from 2 mL of clotted blood on day 1 and on the day before shifting out of the PICU; delta values (day 1 minus pre-shifting) and trends were computed. In the study laboratory, ferritin >500 µg/L and CRP >0.5 mg/dL were regarded as elevated. PRISM-III was calculated at 24 hours from a standard 14-parameter table. Ventilator- and vasopressor-free days (28 minus days on support), the maximal mode of respiratory support, need for renal replacement therapy, and culture positivity from blood, urine, cerebrospinal fluid and endotracheal aspirate were documented.

2.4 Statistical analysis

Data were summarised as frequencies, percentages and mean ± standard deviation (SD); because the distribution of ferritin and CRP was markedly skewed on the Shapiro–Wilk test, these variables are additionally reported as median and range. Correlations between continuous variables used Spearman's rho. The Mann–Whitney U test compared PRISM-III, ferritin and CRP between children with a PICU stay <5 days and ≥5 days. The chi-square test assessed the association of ferritin and CRP status with blood-culture positivity. ROC analysis was performed and the area under the curve (AUC) with sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) derived. A p-value <0.05 was considered significant. Analyses were performed in SPSS v16.0 (SPSS Inc., Chicago, IL, USA).

2.5 Ethics

The study was approved by the Institutional Ethics Committee, Apollo Multispeciality Hospitals, Kolkata (Ref. IEC/DNB/2022/11/52; approval 21 November 2022). Written informed consent and assent were obtained, and confidentiality of records was maintained throughout.

3. Results

3.1 Baseline characteristics

Fifty-seven critically ill children were studied. About one-third were aged 1–5 years (31.6%), followed by

6–10 years (29.8%), >10 years (24.6%) and <1 year (14.0%); the mean age was 6.59 ± 4.91 years (Table 1). Boys predominated (64.9%). The duration of PICU stay was 1–6 days in the majority (78.9%), 7–14 days in 15.8% and >14 days in 5.3%, with a median of 5 days (range 1–29). Fever most often lasted 3–4 days (40.4%). The mean PRISM-III at 24 hours was 10.4 ± 9.9 (median 6). Overall PICU mortality was 5.3%; 93.0% were discharged and 1.8% left against medical advice (Figure 1).

Table 1. Baseline demographic and clinical characteristics (n = 57).

Variable	n	%
Age <1 year	8	14.0
Age 1–5 years	18	31.6
Age 6–10 years	17	29.8
Age >10 years	14	24.6
Male sex	37	64.9
PICU stay 1–6 days	45	78.9
PICU stay 7–14 days	9	15.8
PICU stay >14 days	3	5.3
Mechanical ventilation	9	15.8
Inotrope support	6	10.5
Renal replacement therapy	3	5.3
Mortality	3	5.3

PICU, paediatric intensive care unit. Mean age 6.59 ± 4.91 years; median PICU stay 5 days (range 1–29); mean PRISM-III at 24 h 10.4 ± 9.9.

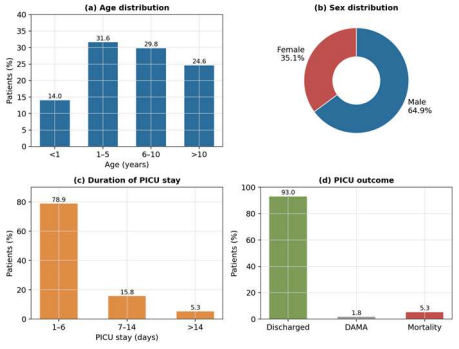

Figure 1. Distribution of the cohort by (a) age, (b) sex, (c) duration of PICU stay and (d) outcome (n = 57).

3.2 Ferritin and CRP profile

Ferritin and CRP were markedly skewed. Median serum ferritin was 5,996 µg/L (range 69–100,000) on day 1 and 1,108 µg/L (range 46–76,540) before shifting; median CRP fell from 4.10 mg/dL (range 0.3–42.9) to 0.90 mg/dL (range 0.3–6.2). The proportion of children with an elevated marker declined from day 1 to the day before shifting—from 77.2% to 45.6% for ferritin and from 93.0% to 61.4% for CRP—consistent with clinical recovery (Table 2, Figure 2). Blood culture was positive in 14.0%, endotracheal aspirate in 5.3%, and urine and cerebrospinal fluid in 1.8% each. The maximal respiratory support was heated humidified high-flow nasal cannula in 22.8%, invasive ventilation in 15.7% and non-invasive ventilation in 3.5%, while 57.9% needed none.

Table 2. Serum ferritin and CRP on day 1 versus the day before shifting from the PICU (n = 57).

Parameter	Day 1, median (range)	Before shifting, median (range)
Ferritin (µg/L)	5,996 (69–100,000)	1,108 (46–76,540)
Ferritin elevated (>500 µg/L)	44 (77.2%)	26 (45.6%)
CRP (mg/dL)	4.10 (0.3–42.9)	0.90 (0.3–6.2)
CRP elevated (>0.5 mg/dL)	53 (93.0%)	35 (61.4%)

CRP, C-reactive protein. Median delta ferritin 4,342 µg/L (range −131 to 94,760); median delta CRP 3.40 mg/dL (range −1 to 38.4).

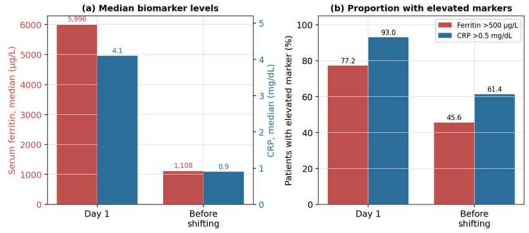

Figure 2. (a) Median serum ferritin and CRP and (b) the proportion of children with elevated markers, on day 1 versus before shifting from the PICU.

3.3 Correlation with duration of PICU stay

Duration of PICU stay correlated most strongly with PRISM-III at 24 hours (r=0.60, p<0.001), followed by delta ferritin (r=0.49, p<0.001), day-1 ferritin (r=0.32, p=0.003), day-1 CRP (r=0.32, p=0.01) and delta CRP (r=0.32, p=0.01). PRISM-III on the day of shifting (r=0.01) and CRP before shifting (r=0.17, p=0.19) were not significantly correlated (Table 3, Figure 3).

Table 3. Spearman correlation of PRISM-III, ferritin and CRP with duration of PICU stay.

Variable	r	p-value
PRISM-III at 24 h	0.60	<0.001*

Variable	r	p-value
Delta ferritin	0.49	<0.001*
Ferritin, day 1	0.32	0.003*
CRP, day 1	0.32	0.01*
Delta CRP	0.32	0.01*
CRP, before shifting	0.17	0.19
PRISM-III on day of shifting	0.01	0.93

**Significant at p<0.05 (Spearman's rho). PRISM-III, Paediatric Risk of Mortality III; CRP, C-reactive protein.*

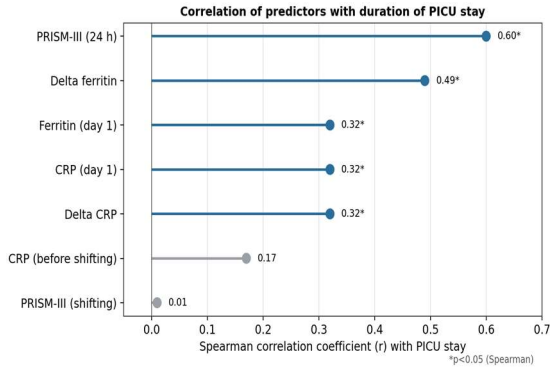

Figure 3. Spearman correlation coefficients of candidate predictors with duration of PICU stay. Blue bars indicate statistically significant associations (*p<0.05).

3.4 Comparison by length of stay (<5 vs ≥5 days)

Children staying ≥5 days in the PICU had significantly higher day-1 ferritin (26,262 ± 25,864 vs 13,051 ± 7,721 µg/L; p=0.003) and day-1 CRP (10.46 ± 10.02 vs 6.59 ± 5.38 mg/dL; p=0.02) than those staying <5 days. CRP before shifting also differed (p=0.03). Notably, ferritin before shifting was higher in the shorter-stay group, and the difference in PRISM-III at 24 h did not reach significance (p=0.07) (Table 4, Figure 4).

Table 4. Comparison of PRISM-III, ferritin and CRP between children with PICU stay <5 days and ≥5 days (mean ± SD).

Variable	<5 days (n=27)	≥5 days (n=30)	p
PRISM-III at 24 h	6.67 ± 6.01	12.93 ± 12.73	0.07
Ferritin day 1 (µg/L)	13,051 ± 7,721	26,262 ± 25,864	0.003*
Ferritin before shifting (µg/L)	14,960 ± 4,384	5,852 ± 5,566	0.009*
CRP day 1 (mg/dL)	6.59 ± 5.38	10.46 ± 10.02	0.02*
CRP before shifting (mg/dL)	1.07 ± 1.31	1.47 ± 1.16	0.03*

**Significant at p<0.05 (Mann–Whitney U test). SD, standard deviation.*

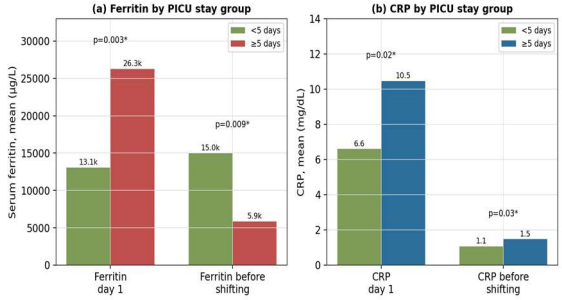

Figure 4. (a) Ferritin and (b) CRP in children with a PICU stay <5 days versus ≥5 days. Day-1 values were significantly higher in the longer-stay group.

3.5 Predictive performance and culture association

On ROC analysis for predicting a stay ≥5 days, day-1 ferritin (cut-off 500 µg/L) yielded an AUC of 0.72 (p=0.003) with sensitivity 83.3% and specificity 37.5%, while ferritin measured before shifting achieved an AUC of 0.80 (p<0.001; sensitivity 80.0%, specificity 81.9%, PPV 80.0%). Day-1 CRP (cut-off 0.5 mg/dL) gave an AUC of 0.67 (p=0.02) and CRP before shifting 0.66 (p=0.03), whereas PRISM-III (cut-off 10) reached an AUC of 0.62 that was not significant (p=0.11) (Table 5, Figure 5).

In contrast, neither marker discriminated culture-positive sepsis. Blood-culture positivity was numerically higher when ferritin was elevated (15.9% vs 7.7% on day 1) and when CRP was elevated (15.1% vs 0% on day 1), but neither association was statistically significant on chi-square testing (ferritin p=0.45 and p=0.07; CRP p=0.40 and p=0.10 on day 1 and before shifting, respectively).

Table 5. ROC performance of predictors for a PICU stay ≥5 days.

Predictor (cut-off)	AUC	p	Sens. (%)	Spec. (%)
Ferritin before shifting (500 µg/L)	0.80	<0.001*	80.0	81.9
Ferritin day 1 (500 µg/L)	0.72	0.003*	83.3	37.5

Predictor (cut-off)	AUC	p	Sens. (%)	Spec. (%)
CRP day 1 (0.5 mg/dL)	0.67	0.02*	40.0	81.4
CRP before shifting (0.5 mg/dL)	0.66	0.03*	63.0	60.0
PRISM-III at 24 h (10)	0.62	0.11	81.5	43.3

**Significant at p<0.05. AUC, area under the receiver operating characteristic curve; Sens., sensitivity; Spec., specificity.*

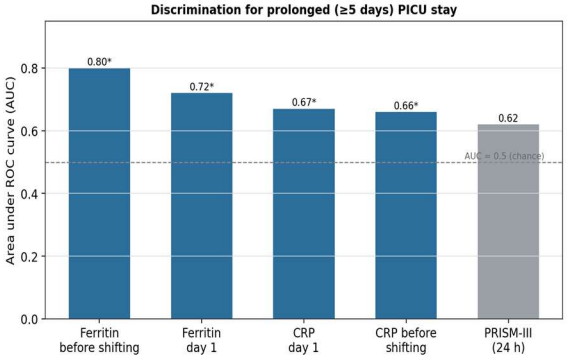

Figure 5. Area under the ROC curve of each predictor for a prolonged (≥5 days) PICU stay. Blue bars denote statistically significant discrimination (*p<0.05).

4. Discussion

In this prospective cohort of 57 critically ill children, admission serum ferritin was significantly associated with the duration of PICU stay: day-1 ferritin correlated modestly with length of stay (r=0.32) and was substantially higher in children who stayed ≥5 days. Its discrimination for a prolonged stay was fair for the day-1 value (AUC 0.72) and good for the pre-shifting value (AUC 0.80). These findings support the concept that the intensity and persistence of the acute-phase and hyperinflammatory response, reflected by ferritin, tracks with the clinical trajectory in the PICU.

Our results align with several paediatric studies linking ferritin to adverse outcomes. Tonial et al. reported that ferritin ≥300 ng/mL was associated with longer hospitalisation and mechanical ventilation, and Carcillo et al. showed that a combined CRP–ferritin contingency table stratified mortality risk in severe sepsis. Manjushree et al. found higher ferritin among non-survivors with longer PICU stay, and Shaikh et al. and Ghanate et al. observed that ferritin within five days of illness onset predicted poor outcome. Conversely, in tropical-infection sepsis, Williams et al. found that serial ferritin predicted neither organ dysfunction nor mortality, with organ-dysfunction scores outperforming ferritin—mirroring our observation that PRISM-III at 24 hours was the single strongest correlate of PICU stay (r=0.60).

Both ferritin and CRP fell markedly between admission and discharge from the PICU (median ferritin 5,996→1,108 µg/L; median CRP 4.10→0.90 mg/dL), and the proportion with elevated markers roughly halved, in keeping with resolving inflammation as reported by Vani et al. and Ismail et al. The comparable performance of CRP (day-1 AUC 0.67) and ferritin in our cohort suggests these acute-phase reactants carry overlapping prognostic information; ferritin's advantage lies in its low cost and wide availability relative to procalcitonin in resource-limited settings.

Importantly, neither ferritin nor CRP was significantly associated with blood-culture positivity, and blood cultures were positive in only 14.0% of children. This reinforces that these markers reflect the host inflammatory response rather than microbiological confirmation of infection, and that they should complement—not replace—clinical judgement and culture-based diagnosis. The apparently paradoxical higher pre-shifting ferritin in the shorter-stay group likely reflects the small number of longer-stay children, deaths that truncated stay while ferritin remained high, and the grossly skewed distribution, and should be interpreted cautiously.

5. Limitations

This was a single-centre study with a modest sample size and no control group. Timing of transfer out of the PICU depended on clinical judgement and local protocol, which may vary. Three deaths truncated PICU stay despite high ferritin, and a few children who developed ventilator-associated pneumonia had prolonged stays, both of which can distort the ferritin–stay relationship. Ferritin and CRP values were extremely high in some children and very low in others, producing a grossly skewed distribution that necessitated non-parametric summaries. Finally, more frequent serial sampling was limited by cost and the need for repeated venepuncture. Larger, multicentre studies with a control group and serial measurements are warranted.

6. Conclusion

Elevated serum ferritin measured on Day 1 of PICU admission was significantly associated with a longer PICU stay in critically ill children aged 1 month to 18 years. It also predicted a prolonged PICU stay (≥ 5 days) with fair-to-good discriminative accuracy, performing comparably to CRP. However, PRISM-III

at 24 hours remained the strongest correlate of length of stay, and neither ferritin nor CRP predicted culture-positive sepsis. Serum ferritin is an inexpensive, widely available biomarker that may serve as a useful adjunct for flagging critically ill children at risk of a protracted intensive-care course, provided it is interpreted alongside validated severity scores and clinical assessment.

Declarations

Ethics approval and consent: Approved by the Institutional Ethics Committee, Apollo Multispeciality Hospitals, Kolkata (IEC/DNB/2022/11/52). Written informed consent and assent were obtained.

Funding: None.

Conflicts of interest: The authors declare no conflicts of interest.

Data availability: The de-identified dataset is available from the corresponding author on reasonable request.

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