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ORIGINAL RESEARCH ARTICLE

Association Between Serum Ferritin Levels and Disease Severity in Hospitalized Patients with Acute Febrile Illness

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Abstract: Background: Serum ferritin is an inflammatory biomarker that may reflect disease severity in acute infectious illnesses. This study evaluated the association between admission ferritin and organ dysfunction in hospitalized adults with acute febrile illness.**Methods:** A total of 320 adults with acute febrile illness were analyzed. Admission ferritin was assessed in relation to Sequential Organ Failure Assessment (SOFA) score, subsequent ICU admission, hospital length of stay, and other clinical outcomes. Multivariable regression adjusted for age, sex, comorbidity burden, and etiology.**Results:** Median admission ferritin was 400.2 ng/mL. Ferritin increased progressively across SOFA categories and correlated with SOFA score (Spearman ρ=0.395; $p<0.001$). Each doubling of ferritin was associated with a 0.66-point higher adjusted SOFA score (95% CI 0.46–0.86). Higher ferritin was also associated with subsequent ICU admission (OR 1.59, 95% CI 1.14–2.22) and longer hospitalization. Ferritin alone showed modest discrimination for subsequent ICU admission (AUC 0.615).**Conclusion:** Higher admission ferritin was associated with greater organ dysfunction, ICU requirement, and longer hospitalization, supporting its role as an adjunctive severity marker.

Keywords: acute febrile illness; ferritin; SOFA score; intensive care unit; disease severity

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Introduction

Acute febrile illness is a diverse group of infectious syndromes that can be self-limited or a systemic inflammatory process with progressive organ dysfunction. The identification of patients at risk for severe disease is still difficult due to the fact that clinical deterioration may occur before definitive microbiological diagnosis. Conventional physiological assessment may therefore be complemented by biomarkers that reflect the intensity of the inflammatory response of the host.

Ferritin is an iron storage protein that is found inside cells, and its blood level increases significantly in inflammation, infection, oxidative stress, and cell injury [1]. In addition to its established role as a marker of iron stores, hyperferritinemia has also been associated with immune activation and cytokine induced inflammatory conditions such as septic shock and macrophage activation syndromes [2]. The Sequential Organ Failure Assessment (SOFA) score is a standardized measure to quantify organ dysfunction in the respiratory, cardiovascular, hepatic, coagulation, renal and neurological systems [3] and has become a central part of modern organ failure assessment in the context of infection [4].

There is growing evidence that serum ferritin may have prognostic value for a number of infectious

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diseases. In critically ill patients with community-acquired pneumonia (CAP), severe hyperferritinemia has been linked to a macrophage activation-like inflammatory phenotype and poor outcome [5]. Ferritin levels ≥500 ng/mL have been independently correlated with complicated disease and long hospital stay in scrub typhus [6]. Likewise, a systematic review and meta-analysis showed significantly higher ferritin levels in severe dengue, which could be used as a marker of severity in acute viral infection [7]. In patients with sepsis, higher levels of ferritin have also been linked to higher short- and longer-term mortality, but the discriminatory power of ferritin alone seems to be modest [8].

These findings indicate that ferritin may be a general measure of the inflammatory and cellular-injury burden, not specifically linked to a disease process. Its association with graded organ dysfunction in a diverse group of hospitalized adults with acute febrile illness, however, is not fully characterized. In addition, clinical utility of admission ferritin for predicting future intensive care unit (ICU) admission and hospital outcome needs to be further assessed.

The present study thus investigated the relationship between admission serum ferritin level and organ dysfunction defined by SOFA score in hospitalized adults with acute febrile illness. Secondary aims included assessment of its associations with subsequent admission to the intensive care unit, hospital stay and other clinically relevant outcomes.

Methods

Study design and eligibility

This study was a prospective observational cohort of 320 consecutive adult admissions for acute febrile illness. The study area was Balvir Singh Tomar Institute of Medical Science Research & Hospital, Jaipur-Delhi Highway, Jaipur, Rajasthan, India and the study period was from December 2025 to March 2026. Patients were included if they were ≥18 years old, had a febrile illness of ≤14 days, fever ≥38 °C or a credible recent history of fever, suspected or confirmed acute infection, had a serum ferritin level available within 24 hours of admission, and had adequate data to calculate the admission Sequential Organ Failure Assessment (SOFA) score. Exclusion criteria included known iron-overload disorders, and previous hemophagocytic lymphohistiocytosis or macrophage activation syndrome. Common chronic comorbidities were allowed.

Exposure and outcomes

The exposure was serum ferritin (ng/mL) within 24 hours of admission. The main outcome was the total SOFA score at the initial assessment, which was the sum of six organ subscores. The respiratory subscore included ventilatory support status and arterial PaO_2/FiO_2. Admission creatinine was used for the renal subscore; urine output was measured over 24 hours. The scores were categorized descriptively as 0-1, 2-5 and ≥6. The causes were categorized as confirmed, probable, or undifferentiated. Secondary outcomes included admission to the intensive care unit, invasive mechanical ventilation, vasopressor use, hospital length of stay, and in-hospital mortality.

Statistical analysis

Medians and interquartile ranges were used to summarize continuous variables and n (%) for categorical variables. All observations available were used for each analysis. The unadjusted ferritin–SOFA association was quantified using Spearman rank correlation. Kruskal–Wallis tests were used to compare ferritin levels between categories of SOFA and between etiologic groups having ≥15 observations. The Mann–Whitney U tests with Holm adjustment were used for pairwise comparisons of SOFA categories. The difference in SOFA points per doubling of ferritin was estimated using multivariable linear regression adjusted for age, sex, comorbidity count, and etiology with HC3 heteroskedasticity-robust standard errors.

The odds ratio for each doubling of ferritin, among those without an ICU admission at or before the time of ferritin sampling, was estimated by unadjusted logistic regression. Linear regression of log-transformed length of stay with HC3 standard errors adjusted for age, sex, and number of comorbidities. The ferritin coefficient was exponentiated to obtain the ratio of geometric mean stays per doubling. Ventilation, vasopressor support and death were reported descriptively. ICU admissions at or before either ferritin sampling or the first SOFA assessment were not included in organ support summaries.

In the same eligible records as the logistic model, an exploratory receiver operating characteristic (ROC) analysis estimated the area under the curve (AUC) for ferritin and subsequent ICU admission. The Spearman correlation and AUC were presented with 95% percentile bootstrap confidence intervals using 2,000 resamples. The 95% confidence intervals for regression estimates were reported. Analyses were performed in SPSS version 22.

Results

Cohort characteristics

The analysis included 320 adults with acute febrile illness. Respiratory and urinary tract infections were the most frequent identified etiologies. Overall, 49 (15.3%) records included an ICU

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admission (Tables 1 and 2).

Ferritin and admission organ dysfunction

Higher admission ferritin was associated with higher SOFA scores (Figure 1). Each doubling of ferritin was associated with a 0.66-point higher SOFA score (95% CI 0.46 to 0.86) after adjustment for age, sex, comorbidity count, and etiology. Ferritin concentrations differed across SOFA categories and across the etiologies included in the omnibus comparison (Tables 2 and 3).

Hospital outcomes

Among the 298 records eligible for the subsequent ICU admission analysis, 27 (9.1%) included an ICU admission after ferritin sampling. Higher ferritin was associated with greater odds of subsequent ICU admission and a longer hospital stay. Ferritin alone had an AUC of 0.615 (95% CI 0.494 to 0.732) for subsequent ICU admission (Table 4 and Figure 2).

Table 1. Baseline characteristics

Characteristic	Overall (n = 320)
Age, years	49.0 (38.0–61.2)
Female sex	164 (51.2%)
Body mass index, kg/m²	23.9 (20.9–26.6)
Fever duration, days	5 (4–6)
Hypertension	114 (35.6%)
Diabetes mellitus	83 (25.9%)
Cardiovascular disease	30 (9.4%)
Chronic kidney disease	25 (7.8%)
Admission ferritin, ng/mL	400.2 (208.0–712.6)
Admission SOFA score	1 (0–3)

Values are median (IQR) or n (%). SOFA, Sequential Organ Failure Assessment.

Table 2. Admission ferritin by etiology

Etiology	n (%)	Confirmed, n	Ferritin, ng/mL, median (IQR)
Dengue	17 (5.3%)	17	843.30 (563.10–1032.90)
Enteric fever	38 (11.9%)	23	361.40 (173.25–624.98)
Leptospirosis	6 (1.9%)	5	488.15 (364.12–844.15)
Malaria	28 (8.8%)	24	426.95 (327.95–796.90)
Other confirmed acute infection	32 (10.0%)	32	415.95 (198.45–618.35)
Respiratory tract infection	57 (17.8%)	39	354.20 (200.80–604.10)
Scrub typhus	18 (5.6%)	11	497.70 (394.25–946.40)
Undifferentiated	64 (20.0%)	0	259.90 (160.35–498.62)
Urinary tract infection	60 (18.8%)	42	370.65 (221.38–666.48)

Kruskal–Wallis H(7) = 28.39, p <0.001 across eight categories (n = 314). Leptospirosis (n = 6) was summarized descriptively.

Table 3. Ferritin and admission SOFA score

Measure or comparison	n	Summary or estimate	Statistic	p
SOFA 0–1	165	299.00 (174.40–485.60)	—	—
SOFA 2–5	124	488.65 (306.10–893.00)	—	—
SOFA ≥6	31	592.30 (488.40–1003.65)	—	—
SOFA categories, overall	320	$\varepsilon^2 = 0.125$	H(2) = 41.67	<0.001
SOFA 0–1 vs 2–5	289	Rank-biserial r = -0.37	U = 6,398.5	<0.001
SOFA 0–1 vs ≥6	196	Rank-biserial r = -0.53	U = 1,208.0	<0.001
SOFA 2–5 vs ≥6	155	Rank-biserial r = -0.21	U = 1,516.0	0.070
Unadjusted association	320	0.30 to 0.49 (95% CI)	$\rho = 0.395$	<0.001
Ferritin per doubling	320	0.66 (0.46 to 0.86)	t = 6.44	<0.001
Age per 10 years	320	0.27 (0.10 to 0.44)	t = 3.12	0.002
Male vs female	320	-0.68 (-1.19 to -0.17)	t = -2.65	0.009
Comorbidity count	320	0.10 (-0.23 to 0.43)	t = 0.60	0.549

SOFA category rows show ferritin in ng/mL as median (IQR). Pairwise Mann–Whitney p-values use Holm adjustment. The Spearman ρ interval is bootstrap-based. The four adjusted estimates are regression coefficients with 95% CIs in SOFA points from one linear model with HC3 standard errors and etiology included as a covariate.

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Table 4. Ferritin and hospital outcomes

Outcome	n	Events, n (%) or median (IQR)	Estimate per ferritin doubling (95% CI)	Statistic	p
Subsequent ICU admission	298	27 (9.1%)	1.59 (1.14 to 2.22)	z = 2.72	0.006
Invasive mechanical ventilation	294	4 (1.4%)	—	—	—
Vasopressor support	294	4 (1.4%)	—	—	—
In-hospital death	320	12 (3.8%)	—	—	—
Hospital length of stay	320	5 (4–7) days	1.11 (1.06 to 1.17)	t = 4.53	<0.001

Estimates are an unadjusted odds ratio for subsequent ICU admission and an adjusted ratio of geometric mean lengths of stay. The latter model included age, sex, and comorbidity count. Ventilation, vasopressor use, and death are summarized descriptively. ICU risk sets excluded admission to ICU at or before the relevant baseline assessment.

Figures

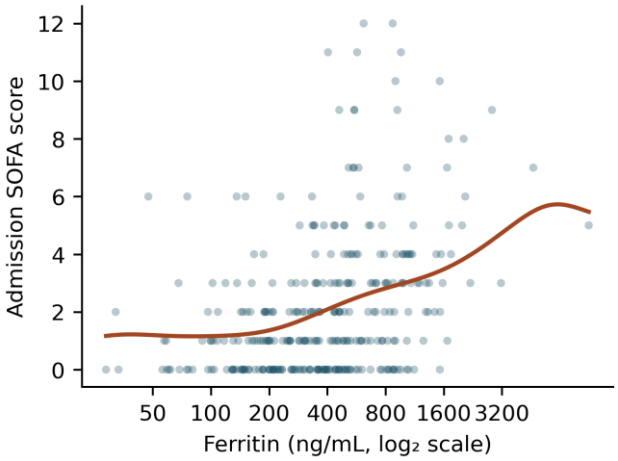

Figure 1. Admission ferritin and SOFA score. The curve shows a smoothed mean SOFA score.

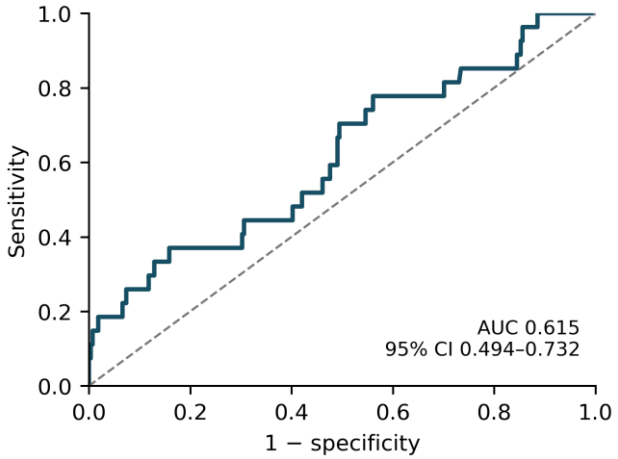

Figure 2. Receiver operating characteristic curve for ferritin and subsequent ICU admission (27 events among 298 records).

Discussion

Serum ferritin was found to have a graded association with organ dysfunction in 320 adults admitted to hospital with acute febrile illness. The median ferritin level was 299 ng/mL in patients with SOFA 0–1, 488.7 ng/mL in patients with SOFA 2–5, and 592.3 ng/mL in patients with SOFA ≥6. The correlation with SOFA was moderate (ρ=0.395) and remained significant with each doubling of ferritin (0.66 points higher SOFA score after adjusting for age, sex, comorbidity burden, and etiology). Higher ferritin was also associated with longer hospitalization and subsequent ICU admission, but discrimination for subsequent ICU admission was modest (AUC 0.615). The results indicate that ferritin is not a single test for triage but is primarily a marker of the severity of systemic disease.

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This interpretation is in line with the large sepsis cohort reported by He et al. [9]. In 1,947 patients, the highest quartile of ferritin was associated with the highest 28-day and 1-year mortality rates (29.5% and 42.4%, respectively). After multivariable adjustment, each 1,000 ng/mL increment in ferritin was also associated with increased mortality, and ferritin alone resulted in AUCs of around 0.59–0.60. The presence of a clear outcome gradient and limited discrimination is similar to our findings of ferritin being a marker of SOFA and ICU risk with only moderate predictive accuracy for ICU admission.

Gunasekaran et al. [10] also confirm the relation with the hospital course. Ferritin level was higher at admission to the ICU and 24 hours after admission in septic shock patients compared to cardiac surgical patients after surgery (372 versus 198 μg/L, and 457 versus 264 μg/L, respectively). There was no linear correlation between ferritin and mortality or severity of illness, but ferritin levels above the median at 24 hours were correlated with longer ICU and hospital stays. In our cohort, the geometric mean hospital stay increased by 11% for every doubling of ferritin, indicating that ferritin is associated with increased duration of illness, not a specific outcome.

Data from the heterogeneous sepsis population further highlight the importance of using ferritin in conjunction with the existing severity assessment. Ferritin was elevated in nonsurvivors (964.7 vs 828.4 μg/L) in 89 Vietnamese patients with sepsis, but the AUC for 28-day mortality was only 0.662, versus 0.757 for SOFA [11]. Ferritin-related indices were combined with SOFA to obtain a discrimination of 0.80. This supports our finding that ferritin was associated with SOFA, but this should not be used as a substitute for organ failure assessment.

The different ferritin levels in the different etiologies of the cohort are also biologically and clinically significant. Dengue showed one of the highest median ferritin concentrations (843.3 ng/mL). In a prospective study of 70 dengue patients, Goyal et al. [12] found a mean ferritin level of ~1,469 ng/mL, which was significantly higher in severe dengue. The correlation of ferritin with platelet count was negative ($r=-0.35$) and positive with hospital stay ($r=0.50$). More recently, Mettananda et al. [13] studied 209 patients with dengue and observed plasma leakage in 33.5% of the cases. The ferritin level on days of illness 3 and 4 was significantly elevated in patients who went on to develop leakage and had an AUC of 0.78 and a negative predictive value of 84% for early ferritin. These results together indicate that the level and predictive value of ferritin is influenced by the infectious syndrome and the time of the measurement.

High ferritin levels may be useful to distinguish more inflammatory phenotypes. Jha et al. [14] measured the peak ferritin level in 144 children with severe dengue and reported a median peak ferritin of 6,732 ng/mL, with levels >10,000 ng/mL associated with disease-related complications, and a cut-off of >15,691 ng/mL predicting mortality with AUC of 0.826. Likewise, FerriPedS study by Pai et al. [15] consisted of 115 critically ill children with severe sepsis of which 52% had ferritin >500 ng/mL.Nonsurvivors had median ferritin of 1,355 versus 233 ng/mL in survivors, and mortality was 38.3% versus 16.4% in those with and without hyperferritinemia. Ferritin was also associated with organ-dysfunction and mortality-risk scores. These pediatric data are not directly comparable to our adult cohort, but do support the idea that as ferritin increases, so does systemic dysfunction.

There is similar evidence from adult sepsis data. In an analysis of 2,339 patients admitted to an ICU, Li et al. [16] identified ferritin ≥500 ng/mL in 39.4% and found that hyperferritinemia was associated with increased in-hospital mortality and decreased 28- and 90-day survival, with platelet count accounting for approximately 12.6% of the ferritin–mortality association. These results indicate that ferritin could be a reflection of several inflammatory, hematological and organ injury pathways, not just one.

There are some restrictions to be taken into account. Ferritin is non-specific and can be affected by inflammation, liver damage, iron status and underlying comorbid conditions. The subsequent ferritin kinetics could not be captured by a single admission measurement and the relatively small number of subsequent ICU admissions resulted in limited precision for that endpoint. Ferritin distributions may also be affected by etiologic heterogeneity. However, the relationship between ferritin and SOFA remained significant after adjustment for etiology and comorbidity, and this indicates that ferritin could be a useful, low-cost marker to complement clinical severity assessment.

Conclusion

In acute febrile illness, higher admission ferritin was independently linked to increased SOFA-defined organ dysfunction and was also associated with subsequent admission to the intensive care unit (ICU) and longer hospital stay. The modest stand-alone discrimination it demonstrated suggests that ferritin should be used as an additional marker of systemic disease burden in addition to clinical assessment and established organ-failure scores.

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