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Serum Iron Profile Dynamics and Short-Term Mortality in Critically Ill Patients: A Retrospective Cohort Study

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Abstract

Iron metabolism dysregulation is a common feature of critical illness and may affect outcomes through its roles in oxygen transport, immune regulation, and oxidative stress. Although serum iron and ferritin have been proposed as prognostic biomarkers in intensive care unit (ICU) patients, their temporal changes and associations with short-term mortality remain unclear. This study evaluated the relationship between serial measurements of serum iron and ferritin and in-hospital mortality. To evaluate the association between serial (day-1 and day-7) serum iron and ferritin measurements and 7-day in-hospital mortality in a cohort of critically ill patients, and to assess the discriminative performance of a multivariable model including these biomarkers. This retrospective cohort study included 413 consecutive adult patients admitted to the intensive care unit (ICU) of a tertiary referral teaching hospital between January and December 2025. Clinical and laboratory data were retrospectively extracted from electronic medical records. Serum iron and ferritin concentrations measured on ICU admission (day 1) and on day 7, or at the last available assessment for patients discharged or deceased before day 7, were evaluated for their association with 7-day in-hospital mortality using multivariable logistic regression analysis. The overall 7-day mortality rate was 23.0% (95/413). After adjustment for age, sex, body mass index, and ICU length of stay, higher day 1 iron (OR: 0.517; 95% CI: 0.390–0.686; P<0.001) and ferritin levels (OR: 0.896; 95% CI: 0.857–0.937; P<0.001) were independently associated with lower mortality. In contrast, elevated day 7 iron (OR: 1.858; 95% CI: 1.426–2.421; P<0.001) and ferritin levels (OR: 1.115; 95% CI: 1.066–1.166; P<0.001) were associated with increased mortality. The model demonstrated high discrimination (AUROC 0.996; 95% CI 0.988–1.000). Serum iron and ferritin demonstrate a time-dependent biphasic association with short-term mortality. Serial monitoring may improve risk stratification in critically ill patients.

Keywords: Iron, Ferritin, Intensive Care Units, Mortality, Prognosis, SOFA, Critical Illness

1. Introduction

Critically ill patients admitted to intensive care units (ICUs) face mortality rates reaching up to 40% depending on illness severity and case mix (1). Despite therapeutic advancements, the identification of reliable, cost-effective biomarkers for early risk stratification remains a clinical priority.

Iron is an essential trace element fundamental to oxygen transport, mitochondrial respiration, DNA synthesis, and immune regulation. However, iron is a double-edged sword: its ability to catalyse reactive oxygen species via the Fenton reaction makes iron overload particularly detrimental, contributing to oxidative stress, mitochondrial dysfunction, and tissue injury (2). Hepcidin, the master regulator of systemic iron homeostasis, is upregulated by inflammatory cytokines—particularly interleukin-6—leading to ferroportin degradation, functional iron deficiency (hypoferraemia), and increased ferritin synthesis. Ferritin thus serves a dual role as both an iron storage protein and a positive acute-phase reactant (3).

Recent meta-analyses have reinforced the prognostic significance of iron parameters in critical illness. A 2024 meta-analysis encompassing 19 studies demonstrated a significant negative correlation between serum iron levels and mortality in sepsis (relative risk: 1.567; 95% CI: 1.208–1.925) (4). In acute kidney injury (AKI), elevated ferritin independently predicts 28-day mortality (5). Shu et al. reported that elevated serum iron was significantly associated with increased 28-day and 90-day mortality in 483 ICU patients with AKI (6). During the COVID-19 pandemic, ferritin >490 ng/mL was associated with a 3.4-fold increased risk of death and a 2.78-fold increased risk of ICU admission (7). Emerging machine learning-based studies have further confirmed elevated ferritin and serum iron as independent predictors of one-year mortality in critically ill patients with atrial fibrillation (8).

Despite this evidence, several critical gaps remain. First, most studies rely on single time-point measurements at ICU admission, failing to capture the dynamic changes of iron metabolism during the disease course (8). Second, the simultaneous assessment of both iron and ferritin at multiple time points in a general ICU population—rather than a single disease subgroup—has been limited. Third, non-transferrin-bound iron (NTBI) has emerged as a key mediator of oxidative injury, yet its clinical utility remains under investigation (9, 10). Fourth, data from Middle Eastern populations remain scarce, with most evidence derived from Western cohorts or large databases such as MIMIC-IV.

Given these gaps, the present study aimed to evaluate the association between serial serum iron and ferritin measurements—on day 1 and day 7 of ICU admission—and short-term (7-day) in-hospital mortality in a cohort of critically ill patients from a tertiary care centre in northern Iran, addressing critical temporal and regional gaps in the literature.

2. Methods

Study design

This retrospective cohort study was conducted in the intensive care unit (ICU) of a tertiary referral university-affiliated teaching hospital in northern Iran. Consecutive adult patients admitted between January and December 2025 were identified through the hospital electronic medical record system. Demographic, clinical, laboratory, and outcome data were retrospectively extracted from medical records after completion of patient care. The study is reported in accordance with the STROBE statement for cohort studies.

Setting and participants

All adult patients (≥18 years) admitted to the ICU with an expected length of stay exceeding 24 hours were screened for eligibility. Patients were enrolled using a consecutive sampling method. Exclusion criteria were: (1) blood transfusion within 7 days prior to admission or during the first 7 days of ICU stay (to avoid confounding the iron profile), (2) incomplete medical records preventing extraction of key clinical or laboratory variables, and (3) refusal to provide written informed consent. A total of 413 patients met the inclusion criteria and were enrolled in the final analysis. A flow diagram illustrating patient screening, eligibility assessment, and inclusion is presented in **Figure 1.**

Variables and data collection

Demographic and clinical data were extracted from electronic medical records using a standardised data collection form. Demographic characteristics included age (years), sex (male/female), and body mass index (BMI, kg/m2). Clinical characteristics included the primary underlying disease, categorised as pneumonia, pancreatitis, acute kidney injury (AKI), liver failure, urinary tract infection (UTI), severe gastrointestinal bleeding (GIB), or others; length of ICU stay (days); and the modified Sequential Organ Failure Assessment

(SOFA) score calculated on day 1 of admission (range 0–20; higher scores indicate greater organ dysfunction; it evaluates respiratory, coagulation, hepatic, cardiovascular, neurological, and renal systems). Laboratory parameters included serum iron (µg/dL) and serum ferritin (ng/mL), each measured on day 1 (within 24 hours of ICU admission) and on day 7. For patients discharged or deceased before day 7, the last available measurement was recorded as the day-7 value. All blood samples were collected in the morning after an overnight fast (when clinically feasible) using standard hospital laboratory protocols. Serum iron was measured using the colorimetric method, and serum ferritin was measured using the chemiluminescent immunoassay method, following the manufacturer's instructions.

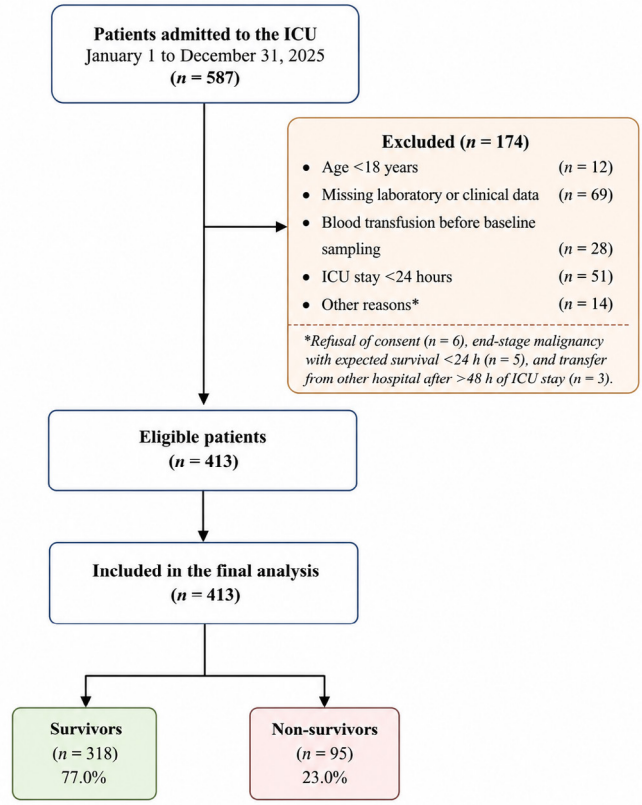


Figure 1. STROBE flow diagram of patient selection and study progression. Flow diagram illustrating the selection of patients included in this retrospective cohort study. Consecutive adult patients admitted to the intensive care unit (ICU) between January 1 and December 31, 2025, were screened for eligibility. After applying predefined inclusion and exclusion criteria (excluding prior blood transfusions, incomplete records, or lack of consent), 413 patients were included in the final analysis, comprising 318 survivors and 95 non-survivors at 7 days.

Outcome measures

The primary outcome was all-cause in-hospital mortality within seven days after ICU admission. This time frame was selected to capture early mortality directly related to the acute critical illness and to minimise the confounding effects of prolonged ICU complications. No formal sample size calculation was performed because this was a retrospective cohort study; all consecutive eligible patients admitted during the study period were included (a minimum of 323 patients was estimated based on an expected mortality rate of 25–30%, a 95% confidence level, and 5% precision; 413 patients were enrolled to allow for dropouts). To minimize selection bias, all consecutive eligible patients admitted during the study period were included, and data were extracted using standardized electronic medical records by trained investigators according to a predefined protocol. Owing to the retrospective design, residual confounding and information bias cannot be completely excluded.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY, USA). Continuous variables were assessed for normality using the Kolmogorov–Smirnov test together with visual inspection of Q–Q plots and histograms. Normally distributed variables are presented as mean ± standard deviation (SD), whereas non-normally distributed variables are expressed as median and interquartile range (IQR). Categorical variables are summarized as frequencies and percentages. Baseline characteristics were compared between survivors and non-survivors using independent-samples t tests, the Mann–Whitney U test, or the chi-square/Fisher's exact test as appropriate. To identify factors independently associated with 7-day in-hospital mortality, multivariable logistic regression analysis (enter method) was performed; variables with $P < 0.20$ in univariable analysis, together with clinically relevant variables identified a priori (age, sex, BMI, ICU length of stay, day-1 serum iron, day-1 serum ferritin, day-7 serum iron, and day-7 serum ferritin), were entered into the model. The modified SOFA score resulted in quasi-complete separation of the data and was excluded from the final model. Multicollinearity was assessed using variance inflation factors (VIF < 5 acceptable). Model calibration was evaluated with the Hosmer–Lemeshow test and discrimination with the area under the ROC curve (AUROC) with 95% confidence intervals. Odds ratios (ORs) with 95% CIs were reported; all tests

were two-sided and $P < 0.05$ was considered statistically significant. Because this was a retrospective cohort study, associations should be interpreted as measures of association rather than causality, and day-7 measurements were analyzed as time-dependent clinical variables associated with mortality rather than baseline prognostic predictors.

3. Results

Patient characteristics

A total of 413 consecutive adult patients admitted to the intensive care unit (ICU) between January and December 2025 were included in the analysis. The mean age of the study population was 75.8 ± 16.2 years, and 230 patients (55.7%) were female. The overall 7-day in-hospital mortality rate was 23.0% (95/413). Pneumonia (20.8%), pancreatitis (18.6%), acute kidney injury (17.9%), liver failure (17.2%), urinary tract infection (16.0%), and severe gastrointestinal bleeding (9.4%) were the most common admission diagnoses. The baseline demographic and clinical characteristics of the study population are presented in **Table 1.**

Primary outcome analysis

The comparison of laboratory findings between survivors and non-survivors is presented in **Table 2**. No statistically significant differences were observed in day-1 serum iron concentrations (58.6 ± 19.1 vs. 58.3 ± 16.7 μg/dL, $P = 0.892$) or day-1 serum ferritin concentrations (337.1 ± 166.8 vs. 331.1 ± 153.9 ng/mL, $P = 0.763$). In contrast, patients who died within 7 days had significantly higher day-7 serum iron levels than survivors (71.5 ± 18.1 vs. 58.7 ± 20.0 μg/dL, $P < 0.001$). Likewise, day-7 serum ferritin concentrations were significantly higher among non-survivors (392.7 ± 157.1 vs. 338.1 ± 167.9 ng/mL, $P < 0.001$). Modified SOFA scores were also significantly higher in non-survivors than survivors (6.68 ± 1.63 vs. 3.01 ± 0.96, $P < 0.001$). Multivariable logistic regression (**Table 3**) showed that higher day-1 serum iron (OR 0.517, 95% CI 0.390–0.686, $P < 0.001$) and day-1 ferritin (OR 0.896, 95% CI 0.857–0.937, $P < 0.001$) were independently associated with lower odds of 7-day mortality, whereas higher day-7 iron (OR 1.858, 95% CI 1.426–2.421, $P < 0.001$) and day-7 ferritin (OR 1.115, 95% CI 1.066–1.166, $P < 0.001$) were associated with increased odds. Age, sex,

Table 1. Baseline characteristics and clinical features of critically ill patients stratified by 7-day mortality status (n = 413)

Variable	Total (n = 413)
Age (years), mean ± SD	75.8 ± 16.2
Female sex, n (%)	230 (55.7)
Body mass index (kg/m²), mean ± SD	26.4 ± 4.8
Modified SOFA score on admission, mean ± SD	3.8 ± 1.8
Primary underlying disease, n (%)	
Pneumonia	86 (20.8)
Pancreatitis	77 (18.6)
Acute kidney injury	74 (17.9)
Liver failure	71 (17.2)
Urinary tract infection	66 (16.0)
Severe gastrointestinal bleeding	39 (9.4)
ICU length of stay ≤7 days, n (%)	318 (77.0)
7-day in-hospital mortality, n (%)	95 (23.0)

Data are presented as mean ± standard deviation (SD) for continuous variables and frequency (percentage) for categorical variables. Abbreviations: BMI, body mass index; ICU, intensive care unit; SD, standard deviation; SOFA, Sequential Organ Failure Assessment.

Table 2. Comparison of serum iron biomarkers and SOFA score between survivors and non-survivors at Day 1 and Day 7

Parameter	Survivors (n = 318)	Non-survivors (n = 95)	P value
Day-1 serum iron (μg/dL)	58.6 ± 19.1	58.3 ± 16.7	0.892
Day-1 serum ferritin (ng/mL)	337.1 ± 166.8	331.1 ± 153.9	0.763
Day-7 serum iron (μg/dL)	58.7 ± 20.0	71.5 ± 18.1	<0.001
Day-7 serum ferritin (ng/mL)	338.1 ± 167.9	392.7 ± 157.1	<0.001
Modified SOFA score on admission	3.01 ± 0.96	6.68 ± 1.63	<0.001

Data are presented as mean ± standard deviation (SD). P values were calculated using independent-samples t-tests. Abbreviations: SOFA, Sequential Organ Failure Assessment.

Table 3. Multivariable binary logistic regression model predicting 7-day mortality in critically ill patients

Variable	β	SE	Wald	P value	Odds Ratio (OR)	95% CI for OR
Age (years)	−0.016	0.021	0.607	0.436	0.984	0.944–1.025
Sex (male)	0.436	0.791	0.304	0.582	1.546	0.328–7.290
Body mass index (kg/m²)	−0.040	0.071	0.381	0.537	0.957	0.832–1.101
ICU length of stay (days)	0.025	0.042	0.343	0.558	1.025	0.944–1.113
Day-1 serum iron (μg/dL)	−0.660	0.144	21.010	<0.001	0.517	0.390–0.686
Day-1 serum ferritin (ng/mL)	−0.110	0.023	22.845	<0.001	0.896	0.857–0.937
Day-7 serum iron (μg/dL)	0.619	0.135	21.025	<0.001	1.858	1.426–2.421
Day-7 serum ferritin (ng/mL)	0.109	0.023	22.457	<0.001	1.115	1.066–1.166

Hosmer–Lemeshow goodness-of-fit test: $\chi^2 = 4.12$, df = 8, P = 0.845. Area under the ROC curve (AUROC) = 0.996 (95% CI: 0.988–1.000). The modified SOFA score was excluded due to quasi-complete separation. Abbreviations: β, regression coefficient; CI, confidence interval; ICU, intensive care unit; OR, odds ratio; SE, standard error; SOFA, Sequential Organ Failure Assessment.

BMI, and ICU length of stay were not significantly associated with 7-day mortality in the adjusted model.

Model performance and sensitivity analyses

The multivariable logistic regression model demonstrated a high level of discrimination, with an AUROC of 0.996 (95% CI 0.988–1.000) (**Figure 2**). The model showed adequate calibration according to the Hosmer–Lemeshow goodness-of-fit test ($\chi^2 = 4.12$, df = 8, P = 0.845). The modified SOFA score was initially entered into the regression model but resulted in quasi-complete separation with failure of maximum likelihood estimation; therefore, SOFA was excluded from the final model to obtain stable parameter estimates. Given that the model incorporated serial laboratory measurements obtained during ICU follow-up, this discriminatory performance should be interpreted within the context of longitudinal biomarker assessment rather than baseline prognostic prediction.

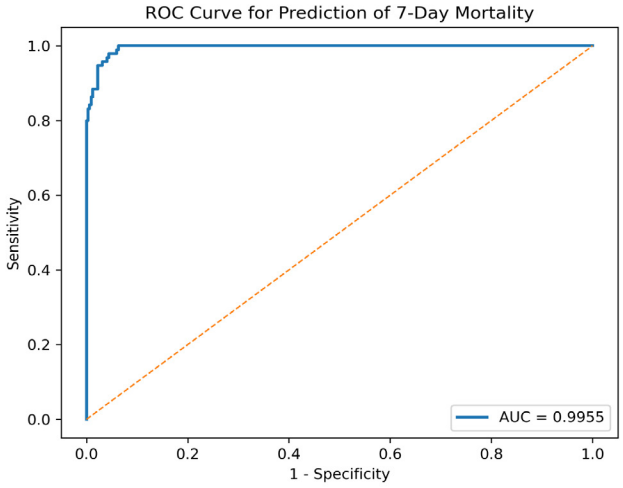


Figure 2. Receiver operating characteristic (ROC) curve analysis for the multivariable predictive model. Receiver operating characteristic (ROC) curve of the multivariable binary logistic regression model evaluating the association between serial iron profile parameters and 7-day in-hospital mortality in critically ill patients. The final model included age, sex, body mass index, ICU length of stay, day-1 serum iron, day-1 serum ferritin, day-7 serum iron, and day-7 serum ferritin. The model demonstrated excellent discriminative capability with an area under the curve (AUROC) of 0.996 (95% CI: 0.988–1.000).

4. Discussion

Principal findings

In this retrospective cohort of 413 critically ill patients, serial serum iron and ferritin measurements demonstrated a time-dependent biphasic association with 7-day in-hospital mortality: higher day-1 levels were independently associated with lower mortality, whereas higher day-7 levels were associated with increased mortality, after adjustment for age, sex, BMI, and ICU length of stay.

Comparison with existing literature

The protective association of higher iron and ferritin concentrations at admission may initially appear paradoxical given the established links between iron overload, oxidative stress, and adverse outcomes. Previous studies have reported similar observations. Xia et al. demonstrated that low serum iron levels on ICU admission independently predicted in-hospital mortality among critically ill patients (12). Likewise, Tacke et al. reported that markers reflecting iron availability were

strongly associated with survival in intensive care populations (11). Studies in ARDS, sepsis, and severe viral infections have consistently demonstrated strong associations between hyperferritinemia and mortality (13, 16, 17).

Biological plausibility and mechanistic insights

This finding is biologically plausible and consistent with the concept that adequate iron availability reflects preserved physiological reserve, nutritional status, and hematopoietic capacity before the onset of critical illness (3, 11, 12). Patients presenting with higher baseline iron stores may be better equipped to tolerate the profound metabolic demands imposed by acute systemic stress. In addition, moderate ferritin elevation during the early phase of critical illness may represent an appropriate host-defense response rather than a pathological process: ferritin synthesis is rapidly upregulated by pro-inflammatory cytokines, facilitating intracellular iron sequestration and limiting iron availability to invading pathogens (13). In contrast, the marked elevation of serum iron and ferritin on day 7 among non-survivors likely reflects progressive dysregulation of iron homeostasis in the setting of persistent inflammation and organ dysfunction. Inflammatory cytokines, particularly interleukin-6, stimulate hepcidin production, resulting in ferroportin degradation and functional iron sequestration (14, 15). When this regulatory mechanism becomes overwhelmed, ongoing tissue injury, hemolysis, and impaired erythropoietic utilization may lead to the release and accumulation of circulating catalytic iron (10). Excess free iron promotes reactive oxygen species generation through Fenton chemistry, contributing to mitochondrial dysfunction, endothelial injury, and multiple organ failure. Hyperferritinemia in advanced critical illness reflects excessive macrophage activation and dysregulated systemic inflammation (13, 16, 17).

Clinical implications

Serial assessment of iron-related biomarkers may provide additional prognostic information for early risk stratification in critically ill patients. Although this study was conducted in a single tertiary referral ICU, the observed associations are biologically plausible and consistent with previous reports. Nevertheless, external validation in multicenter cohorts with different case mixes is required before generalizing these findings to broader critically ill populations or implementing them in routine clinical practice.

Strengths and Limitations

This study has several limitations. First, its retrospective single-center design limits causal inference and may reduce generalizability. Second, biomarkers such as hepcidin, transferrin saturation, C-reactive protein, and interleukin-6 were not routinely available and therefore could not be incorporated into the analyses. Third, external validation of the regression model was not performed. Finally, because serial day-7 biomarkers were included in the analyses, the observed associations should not be interpreted as baseline prognostic predictions. The main strengths include the consecutive enrollment of a relatively large general ICU cohort and the use of serial (day-1 and day-7) biomarker measurements, which capture the dynamic course of iron metabolism during critical illness.

5. Conclusion

In conclusion, serial serum iron and ferritin measurements were independently associated with short-term mortality in critically ill patients. These findings suggest that dynamic changes in iron metabolism may provide clinically useful information for early risk stratification. Nevertheless, prospective multicenter studies incorporating additional biomarkers of iron homeostasis are required to validate these observations before implementation in routine clinical practice.

6. Declrations

Ethical Approval and Consent to Participate

The study protocol was approved by the Ethics Committee of Guilan University of Medical Sciences (Approval No. IR.GUMS.REC.1404.039). The study was conducted in accordance with the principles of the Declaration of Helsinki. Owing to the retrospective design of the study and the use of anonymized routinely collected clinical data, the requirement for informed consent was waived by the Ethics Committee.

Availability of Data and Materials

The datasets generated and/or analyzed during the current study are not publicly available due to institutional and patient privacy restrictions but are available from the corresponding author on reasonable request.

Conflict of Interest

The authors declare that they have no competing interests.

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This research was Self-funded.

Author's Contributions

PGZ conceptualized the study, developed the methodology, collected and curated the data, performed the formal analysis, and drafted the original manuscript. SA contributed to the study conceptualization, supervised the project, validated the findings, and critically reviewed and edited the manuscript. MH contributed to the study conceptualization, supervised the project, and critically reviewed and edited the manuscript. ZAR contributed to the methodology, formal analysis, validation of the results, and critical revision of the manuscript. MF contributed to the study conceptualization, methodology, project supervision, and critical revision of the manuscript. All authors contributed to the interpretation of the findings, approved the final version of the manuscript, and agree to be accountable for all aspects of the work.

All authors have read and approved the final version of the manuscript.

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Artificial Intelligence Statement

The authors used an artificial intelligence (AI)-assisted language tool solely to improve the readability and language of the manuscript. All scientific content, study design, data collection, data analysis, interpretation of the findings, and final editorial decisions were performed entirely by the authors. The authors have reviewed and approved the final manuscript and accept full responsibility for its accuracy and integrity.

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