

Prognostic Value of Transferrin Saturation in Hyperferritinemic Patients with Acute Heart Failure: A Retrospective Cohort Study from the MIMIC-IV Database

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Research Article

Keywords: acute heart failure, iron metabolism, transferrin saturation, hyperferritinemia, MIMIC-IV, prognosis

Posted Date: August 12th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10565304/v1>

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Additional Declarations: No competing interests reported.

Abstract

Background

Iron deficiency management in acute heart failure (AHF) relies on ferritin and transferrin saturation (TSAT), yet the prognostic significance of TSAT within the hyperferritinemic range (ferritin ≥ 300 ng/mL) —where patients are currently classified as iron-sufficient—has not been systematically examined in critically ill AHF populations.

Methods

We conducted a retrospective cohort study using the MIMIC-IV database (2008–2019), including 1,395 adult patients admitted to the intensive care unit (ICU) with AHF who had ferritin and TSAT measured within 48 hours of admission. Patients were classified into five iron metabolism phenotypes using European Society of Cardiology (ESC) guideline thresholds. The primary analysis compared HyperF+HighTSAT (ferritin ≥ 300 ng/mL, TSAT $\geq 20\%$, $n = 306$) versus HyperF+LowTSAT (ferritin ≥ 300 ng/mL, TSAT $< 20\%$, $n = 332$). The primary outcome was in-hospital all-cause mortality, analyzed via multivariable logistic regression with sequential covariate adjustment (Model 0–3). Secondary outcomes included 28-day and 1-year mortality assessed by Cox proportional hazards models and Kaplan-Meier curves.

Results

In-hospital mortality showed a clear gradient across phenotypes: 6.6% (absolute iron deficiency), 11.9% (functional iron deficiency), 8.8% (normal iron), 14.8% (HyperF+LowTSAT), and 27.8% (HyperF+HighTSAT). Among the 638 hyperferritinemic patients, those with high TSAT had significantly higher in-hospital mortality than those with low TSAT (adjusted OR 1.71, 95% CI 1.06–2.75, $P = 0.027$). One-year survival was significantly worse in the high-TSAT group (adjusted HR 1.45, 95% CI 1.12–1.86, $P = 0.004$). Subgroup analyses showed consistent directional associations across all strata.

Conclusions

Among AHF patients classified as iron-sufficient by current ferritin-based criteria, an elevated TSAT ($\geq 20\%$) identifies a subgroup with substantially increased in-hospital and 1-year mortality, independent of established illness severity markers.

Introduction

Acute heart failure (AHF) remains one of the leading causes of hospitalization worldwide, with in-hospital mortality rates of 4–10% and 1-year mortality exceeding 20% [1, 2]. Despite advances in

pharmacological and device therapy, risk stratification in the acute setting remains challenging [3].

Iron deficiency is the most prevalent nutritional deficiency in heart failure, affecting up to 50% of patients with chronic heart failure (CHF) and approximately 40% of those with AHF [4, 5]. Its clinical significance has been firmly established by randomized trials demonstrating that intravenous iron supplementation reduces heart failure hospitalizations and improves quality of life. The FAIR-HF trial showed that ferric carboxymaltose improved symptoms and functional capacity in iron-deficient CHF patients [6], and the CONFIRM-HF trial confirmed sustained benefit over one year [7]. The AFFIRM-AHF trial subsequently demonstrated a reduction in heart failure hospitalizations with intravenous iron initiated during AHF hospitalization [8], and the IRONMAN trial provided further evidence in a broader HF population [9]. A recent meta-analysis of these trials confirmed the benefit of intravenous iron across heterogeneous definitions of iron deficiency [10].

Based on this evidence, the European Society of Cardiology (ESC) guidelines recommend systematic assessment of iron status in heart failure and define iron deficiency as serum ferritin < 100 ng/mL or ferritin 100–299 ng/mL with TSAT < 20% [11]. However, this classification was developed and validated in stable CHF populations where low-grade systemic inflammation allows ferritin to reliably reflect iron stores [4, 5]. In these cohorts, patients with ferritin $\geq$ 300 ng/mL are considered iron-sufficient and are typically excluded from iron supplementation trials. Whether this classification retains its validity in AHF—a state characterized by acute systemic inflammation and hemodynamic instability—has not been established.

Ferritin is an established acute-phase reactant markedly upregulated by pro-inflammatory cytokines including interleukin-6 (IL-6), independently of iron status [12, 13]. Hepcidin, the master regulator of iron homeostasis, is itself induced by IL-6 and mediates the hypoferrremia of inflammation [14, 15]. In AHF, elevated ferritin may therefore reflect systemic inflammation or cellular injury rather than true iron reserves [16, 17], and the assumption that ferritin $\geq$ 300 ng/mL uniformly indicates favorable iron status has not been directly tested. Several recent studies using the MIMIC database have examined iron markers and outcomes in heart failure. Zhou et al. demonstrated that extreme hyperferritinemia ($\geq$ 1000 ng/mL) was associated with elevated short-term mortality in critically ill CHF patients [18]. Hourani et al. found that combined ferritin–TSAT classification outperformed the binary guideline definition in CHF [19], and Cai et al. reported that multiple iron homeostasis derangements were associated with worse long-term prognosis [20]. These studies, using the same database and disease population, established that iron marker phenotyping is feasible and prognostically informative in this context. However, none specifically tested whether TSAT provides incremental prognostic information within the hyperferritinemic range—the population for whom current guidelines consider ferritin alone sufficient for classification and who are excluded from iron supplementation by design.

We aimed to determine whether TSAT stratifies mortality risk among hyperferritinemic AHF patients, independent of established illness severity measures.

Methods

Data Source and Study Population

We conducted a retrospective cohort study using the Medical Information Mart for Intensive Care (MIMIC-IV) database (v3.1), a publicly available database of de-identified electronic health records from Beth Israel Deaconess Medical Center (2008–2019) [21]. The institutional review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center approved the use of MIMIC-IV; informed consent was waived. One of the authors (Yakupjiang Maimaiti) completed the Collaborative Institutional Training Initiative (CITI) "Data or Specimens Only Research" course to obtain credentialed access to the database (Record ID: 71972596). Reporting follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for observational studies [22].

Adult patients (18–89 years) admitted to an ICU with a diagnosis of AHF were identified using International Classification of Diseases (ICD) codes (ICD-9 [428.x] and ICD-10 [I50.x] codes (full code list in Table S1). The validity of ICD coding for heart failure identification in administrative databases has been previously established [23]. Patients aged ≥ 90 years were excluded due to MIMIC-IV age truncation. Only the first ICU admission with length of stay ≥ 24 hours was included. Eligible patients had serum ferritin, serum iron, and total iron-binding capacity (TIBC) measured within 48 hours of ICU admission. The final analytical cohort comprised 1,395 patients.

Iron Metabolism Phenotype Classification

The first iron panel within 48 hours of ICU admission was used. TSAT was calculated as (serum iron / TIBC) $\times 100$. All classification thresholds were fixed a priori based on ESC guideline definitions [11]; data-driven optimization was not performed. Patients were classified as follows:

Absolute iron deficiency (AID): ferritin < 100 ng/mL

Functional iron deficiency (FID): ferritin 100–299 ng/mL and TSAT $< 20\%$

Normal iron status: ferritin 100–299 ng/mL and TSAT $\geq 20\%$

Hyperferritinemia with low TSAT (HyperF+LowTSAT): ferritin ≥ 300 ng/mL and TSAT $< 20\%$

Hyperferritinemia with high TSAT (HyperF+HighTSAT): ferritin ≥ 300 ng/mL and TSAT $\geq 20\%$

Outcomes

The primary outcome was in-hospital all-cause mortality. Secondary outcomes were 28-day and 1-year all-cause mortality. Follow-up for time-to-event analyses was calculated from hospital admission until death or censoring.

Covariates

Demographics, vital signs, laboratory values (first within 48 hours), comorbidities (ICD-coded from the full hospitalization), and illness severity measures were extracted. The Sequential Organ Failure Assessment (SOFA) score was calculated using the worst values within the first 24 hours [24].

Comorbidities included hypertension, diabetes, chronic kidney disease, atrial fibrillation, coronary artery disease, chronic obstructive pulmonary disease, and liver insufficiency. Heart failure subtypes (HFrEF vs. HFpEF) were classified based on ICD diagnosis codes rather than echocardiographic ejection fraction measurements, which are not reliably extractable from MIMIC-IV. Heart failure subtypes (HFrEF vs. HFpEF) were classified based on ICD diagnosis codes rather than echocardiographic ejection fraction measurements, which are not reliably extractable from MIMIC-IV.

Variables with < 5% missingness were imputed with the median. For lactate (27.4% missing) and albumin (33.2% missing), median imputation with a missing indicator was used [25].

Statistical Analysis

Baseline characteristics were compared across phenotypes using Kruskal-Wallis and chi-square tests.

The primary analysis was restricted to hyperferritinemic patients (ferritin ≥ 300 ng/mL, N = 638) and compared HyperF+HighTSAT versus HyperF+LowTSAT. Kaplan-Meier curves were constructed for 1-year survival, and differences were assessed using the log-rank test. Multivariable logistic regression was performed for in-hospital mortality with sequential adjustment: Model 0 (unadjusted), Model 1 (age + sex), Model 2 (Model 1 + comorbidities + eGFR), Model 3 (Model 2 + SOFA score + mechanical ventilation + vasoactive drugs + hemoglobin + creatinine + albumin + lactate). Cox proportional hazards regression was used for 1-year mortality, with the assumption of proportional hazards verified by Schoenfeld residuals. A secondary analysis examined the full five-group gradient using AID as reference.

Subgroup analyses were performed stratified by age (≤ 70 vs. >70 years), sex, SOFA score (≤ 5 vs. >5), renal function, anemia, and liver insufficiency. Sensitivity analyses included a complete-case analysis excluding patients with imputed values. All analyses used Python 3.11 (statsmodels, lifelines). Two-sided $P < 0.05$ was considered significant.

Results

Study Population and Baseline Characteristics

From 15,926 ICU admissions with a primary diagnosis of AHF, we identified 1,395 patients (8.8%) who had both serum ferritin and TIBC measured within 48 hours of ICU admission (Fig. 1). The final cohort had a median age of 70 years (IQR 59–80), 55.5% were male, and 203 patients (14.6%) died during hospitalization. Of these, 638 (45.7%) had hyperferritinemia (ferritin ≥ 300 ng/mL) and constituted the

primary analysis cohort; the remainder were classified as AID (n = 332, 23.8%), FID (n = 312, 22.4%), or normal iron status (n = 113, 8.1%).

Baseline characteristics across the five phenotypes are shown in Table 1. A gradient of increasing illness severity was evident from AID to HyperF+HighTSAT: mean SOFA score rose from 4.2 ± 3.0 to 7.4 ± 4.5 ($P < 0.001$), mechanical ventilation uses from 13.0% to 25.8%, and continuous renal replacement therapy (CRRT) use from 0.9% to 8.5% (all $P < 0.001$). Liver insufficiency was substantially more prevalent in the HyperF+HighTSAT group (23.2% vs. 7.7–15.9%, $P < 0.001$), and pre-admission use of guideline-directed cardiovascular medications was consistently lower (Table 1).

In-Hospital Mortality

During hospitalization, 203 of the 1,395 patients (14.6%) died. In-hospital mortality increased across phenotypes in a stepwise manner: AID 6.6% (22/332), normal iron 8.8% (10/113), FID 11.9% (37/312), HyperF+LowTSAT 14.8% (49/332), and HyperF+HighTSAT 27.8% (85/306). In the hyperferritinemic subgroup (n = 638), HyperF+HighTSAT was associated with significantly higher odds of in-hospital death in the unadjusted model (OR 2.22, 95% CI 1.50–3.29, $P < 0.001$; Table 2). After sequential adjustment, the association remained significant: Model 1 (age + sex) OR 2.25 (1.52–3.34, $P < 0.001$), Model 2 (+ comorbidities + eGFR) OR 1.98 (1.32–2.99, $P = 0.001$), and Model 3 (+ SOFA, mechanical ventilation, vasoactive drugs, hemoglobin, albumin, creatinine, lactate) OR 1.71 (1.06–2.75, $P = 0.027$). The attenuation from Model 2 to Model 3 was driven primarily by SOFA score and albumin. In the five-group fully adjusted model with AID as the reference, HyperF+HighTSAT carried the highest risk (OR 3.15, 95% CI 1.72–5.78, $P < 0.001$), followed by FID (OR 1.98, 1.07–3.66, $P = 0.030$), HyperF+LowTSAT (OR 1.94, 1.05–3.60, $P = 0.035$), and normal iron (OR 1.51, 0.64–3.57, $P = 0.35$).

28-Day and 1-Year Mortality

Although the 28-day mortality gradient mirrored the in-hospital pattern (AID 11.4% to HyperF+HighTSAT 28.8%), the association was attenuated and no longer statistically significant after full adjustment (OR 1.31, 95% CI 0.85–2.02, $P = 0.22$; Cox HR 1.20, 0.85–1.70, $P = 0.31$). At 1 year, mortality ranged from 26.5% (normal iron) to 51.3% (HyperF+HighTSAT). The Kaplan-Meier curves showed significant separation among phenotypes (log-rank $P < 0.001$; Fig. 2). Within the hyperferritinemic subgroup, HyperF+HighTSAT was associated with significantly worse 1-year survival (adjusted HR 1.45, 95% CI 1.12–1.86, $P = 0.004$; Table 2).

Subgroup and Sensitivity Analyses

In subgroup analyses (Fig. 3), the association between HyperF+HighTSAT and in-hospital mortality was most pronounced among patients aged > 70 years (adjusted OR 2.23, 95% CI 1.07–4.65, $P = 0.033$), those with SOFA > 5 (OR 1.80, 1.02–3.18, $P = 0.042$), and those without liver insufficiency (OR 1.71, 1.02–2.88, $P = 0.043$). The direction of the association was consistent across all 12 subgroups examined;

statistical significance was reached only in the oldest, most severely ill, and non-liver-insufficiency strata. A complete-case analysis excluding 264 patients with imputed lactate or albumin values (n = 374) yielded consistent results (OR 2.12, 95% CI 1.19–3.77, P = 0.011). All subgroup analyses were exploratory; no correction for multiple comparisons was applied, and subgroup results should be interpreted as hypothesis-generating.

Discussion

Summary of main findings

In this retrospective cohort of 1,395 ICU-admitted AHF patients, in-hospital mortality ranged from 6.6% to 27.8% across five guideline-defined iron phenotypes. Among hyperferritinemic patients—classified as iron-sufficient by current ESC criteria—TSAT $\geq$ 20% identified a subgroup with nearly doubled in-hospital mortality compared to those with low TSAT (adjusted OR 1.71, 95% CI 1.06–2.75, P = 0.027), independent of SOFA score and other severity measures.

The finding that ferritin $\geq$ 300 ng/mL masks substantial prognostic heterogeneity has implications for the application of current iron status classification in AHF. The ESC guideline was developed in chronic HF populations where IV iron trials showed clinical benefit across a range of ferritin and TSAT thresholds [6–10]; ferritin $\geq$ 300 ng/mL was adopted as the upper boundary for iron deficiency based on its correlation with bone marrow iron stores in stable CHF [4]. In the acute setting, however, the picture differs. Ferritin behaves as an acute-phase reactant, upregulated by inflammation [12–15]; its relationship to true iron stores is therefore less straightforward [16,17]. Our data show that within the guideline-defined iron-sufficient range, in-hospital mortality varies two-fold depending on concurrent TSAT. This heterogeneity is invisible when ferritin is used alone. The Kaplan-Meier curves further illustrate that the survival disadvantage of the HyperF+HighTSAT group persists throughout 1-year follow-up.

The sequential adjustment models help separate the contribution of illness severity from the TSAT signal. The unadjusted OR of 2.22 changed minimally after accounting for demographics and comorbidities (Models 1–2) but decreased to 1.71 after adding SOFA, mechanical ventilation, vasoactive drugs, and laboratory values (Model 3). This pattern indicates that the excess risk partly overlaps with critical illness, but a residual association persists.

Subgroup and time-course findings

The subgroup analyses provide additional insight into where the prognostic signal is concentrated. The association between HyperF+HighTSAT and in-hospital mortality was most prominent in patients aged > 70 years (OR 2.23, P = 0.033) and those with higher illness severity (SOFA > 5: OR 1.80, P = 0.042), as well as in patients without liver insufficiency (OR 1.71, P = 0.043). In younger patients, those with lower SOFA scores, and across sex, renal function, and anemia strata, the point estimates were attenuated and did not reach statistical significance, although the direction of association remained consistent across all

subgroups. Subgroup analyses involving fewer events—for example, the no-anemia and no-liver-insufficiency strata—produced unstable estimates with wide confidence intervals. These strata were therefore not suitable for independent interpretation. Overall, these findings suggest that TSAT-based risk stratification within hyperferritinemia may be most informative in older, more severely ill patients—precisely the subgroup in whom additional prognostic tools are most needed. However, all subgroup analyses should be interpreted with caution given the reduced sample sizes and limited statistical power in individual strata.

However, the association was attenuated and not statistically significant for 28-day mortality (OR 1.31, $P = 0.220$), in contrast to the results at in-hospital and 1-year follow-up. This divergence is consistent with the nature of the study endpoints. The 28-day window captures predominantly early deaths, which in an ICU population are heavily driven by acute organ failure and the immediate sequelae of critical illness—factors explicitly adjusted for in Model 3. The in-hospital endpoint captures the full hospitalization course, including deaths occurring after the acute phase when the prognostic information from iron phenotyping may become more apparent. At 1 year, the association is strongest (HR 1.45, $P = 0.004$), suggesting that the HyperF+HighTSAT phenotype identifies a persistent risk state that extends beyond the index admission.

Comparison with previous studies

Our study can be positioned within the existing MIMIC-based literature on iron markers in heart failure. Zhou et al. examined ferritin ≥ 1000 ng/mL as a binary exposure and reported a 1.5-fold increase in short-term mortality in critically ill CHF patients [18]. While conceptually related, they focused exclusively on extreme hyperferritinemia without considering TSAT, and their threshold (≥ 1000 ng/mL) captured only the far tail of the distribution. Hourani et al. compared three iron status definitions in 3,074 CHF patients and found that a four-category ferritin–TSAT classification had better prognostic discrimination than the binary guideline definition [19]. However, their hyperferritinemic group (ferritin > 300 ng/mL, $n = 661$) showed a paradoxically lower hazard (HR 0.50) compared with the reference group—a finding that appears to contradict our observation of markedly elevated mortality in HyperF+HighTSAT patients. This discrepancy likely reflects differences in study population (CHF vs. AHF), outcome definition (long-term composite vs. in-hospital mortality), and the fact that Hourani et al. did not stratify by TSAT within the hyperferritinemic group. Cai et al. assessed the relationship between iron homeostasis and prognosis in 1,758 HF patients and reported that lower TSAT was associated with worse outcomes in the overall cohort [20]; they did not examine effect modification by ferritin level. Aslan et al. examined 387 AHF patients and reported that those with ferritin > 200 ng/mL plus TSAT $< 20\%$ had the highest 1-year mortality [27], using different cutoffs from guideline-defined thresholds. Collectively, these studies established the relevance of iron phenotyping in heart failure. Our study extends this work by demonstrating that TSAT provides incremental risk stratification specifically within the hyperferritinemic range—the population that current guidelines classify as iron-sufficient.

Furthermore, our findings are consistent with evidence from randomized trials that TSAT modifies the clinical response to intravenous iron therapy independently of ferritin. In a patient-level meta-analysis of

four major trials (FAIR-HF, CONFIRM-HF, AFFIRM-AHF, IRONMAN), TSAT < 20% was associated with significant benefit from intravenous iron (RR 0.81 for cardiovascular death or HF hospitalization), whereas TSAT $\geq$ 20% showed no benefit (RR 0.98, P for interaction = 0.05), while ferritin did not modify the treatment effect (P for interaction = 0.96) [28]. Both lines of evidence—prognostic from our observational data and therapeutic from randomized data—suggest that TSAT provides clinically relevant information beyond ferritin alone in heart failure. Importantly, our data are observational and do not support or oppose any specific iron management strategy.

Clinical implications

Clinically, a high TSAT in AHF patients with elevated ferritin should not be assumed to indicate favorable prognosis. Combined ferritin–TSAT assessment may identify patients at elevated risk who warrant closer monitoring.

Strengths and limitations

This study has several strengths. First, it leveraged a large, multicenter critical care database (MIMIC-IV) with granular laboratory data. Second, iron phenotypes were defined strictly according to ESC guideline thresholds, ensuring clinical translatability. Third, the sequential adjustment strategy (Models 0–3) explicitly separated the TSAT signal from illness severity, and sensitivity analyses confirmed the robustness of the primary findings. Nevertheless, several limitations should be noted. First, this is a single-center retrospective analysis, and residual confounding is possible. Second, the requirement for iron markers within 48 hours of ICU admission may select for patients with greater clinical suspicion for iron disorders. Third, hepcidin, IL-6, and C-reactive protein were not available, precluding assessment of the inflammatory contribution to ferritin–TSAT patterns [29,30]. Fourth, only admission iron parameters were analyzed; serial measurements might provide additional information, as iron markers are known to evolve during the early course of AHF [31]. Fifth, ICD-code-based identification of AHF and comorbidities may introduce misclassification, and HF subtype classification (HFrEF vs. HFpEF) was based on ICD diagnosis codes rather than echocardiographic ejection fraction measurements, which are not available in MIMIC-IV [23,32].

External validation in independent multicenter AHF cohorts is needed. Prospective studies incorporating inflammatory and iron-regulatory biomarkers may clarify the biological basis of the HyperF+HighTSAT phenotype.

Conclusions

In ICU-admitted AHF patients classified as iron-sufficient by ferritin criteria, TSAT $\geq$ 20% identifies a subgroup with nearly doubled in-hospital mortality independent of illness severity. TSAT provides incremental prognostic information within the hyperferritinemic range.

Abbreviations

AHF
acute heart failure
AID
absolute iron deficiency
BMI
body mass index
BUN
blood urea nitrogen
CHF
chronic heart failure
CI
confidence interval
CKD
chronic kidney disease
COPD
chronic obstructive pulmonary disease
CRRT
continuous renal replacement therapy
EF
ejection fraction
eGFR
estimated glomerular filtration rate
ESC
European Society of Cardiology
FID
functional iron deficiency
HF
heart failure
HFpEF
heart failure with preserved ejection fraction
HFrEF
heart failure with reduced ejection fraction
HR
hazard ratio
ICD
International Classification of Diseases
ICU
intensive care unit
IL-6
interleukin-6

IQR
interquartile range
KM
Kaplan-Meier
MIMIC
Medical Information Mart for Intensive Care
MRA
mineralocorticoid receptor antagonist
MV
mechanical ventilation
OR
odds ratio
RDW
red cell distribution width
RR
relative risk
SGLT2
sodium-glucose cotransporter 2
SOFA
Sequential Organ Failure Assessment
STROBE
Strengthening the Reporting of Observational Studies in Epidemiology
TIBC
total iron-binding capacity
TSAT
transferrin saturation
WBC
white blood cell.

Declarations

Ethics approval and consent to participate:

The MIMIC-IV database contains de-identified data. The institutional review boards of Beth Israel Deaconess Medical Center (Boston, MA) and the Massachusetts Institute of Technology (Cambridge, MA) waived the requirement for informed consent. Access was obtained under CITI Program certification.

Clinical trial number

not applicable.

Consent for publication:

Not applicable.

Competing interests:

The authors declare that they have no competing interests.

Artificial Intelligence Declaration

During the preparation of this manuscript, the authors used DeepSeek (深度求索, Hangzhou, China) to assist with language editing and improving clarity. The authors reviewed and approved all content and are fully responsible for the final manuscript.

Funding:

Jilin Provincial Health Science and Technology Capacity Building Program (Grant No. 2025WS-2A001). The funder had no role in study design, data collection, analysis, interpretation, or manuscript preparation.

Author Contribution

Yakupjiang Maimaiti: Conceptualization, Data curation, Formal analysis, Writing – original draft. Guo Zhen: Data curation, Visualization. Yulin Tian: Methodology, Validation. Lu Peng: Software, Investigation. Nannan Wang: Resources, Data curation. Shipeng Wang: Writing – review & editing. Hanchi Xu: Visualization, Investigation. Haoxuan Chu: Writing, Investigation. Yushi Wang: Supervision, Project administration, Writing – review & editing, Funding acquisition, Correspondence.

Acknowledgements:

Not applicable.

Availability of data and materials:

The MIMIC-IV database (v3.1) is publicly available through PhysioNet (<https://physionet.org/content/mimiciv/>). The analysis code is available from the corresponding author upon reasonable request.

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Tables

Table 1. Baseline Characteristics by Iron Metabolism Phenotype

Characteristic	AID (n=332)	FID (n=312)	Normal (n=113)	HyperF LowTSAT (n=332)	HyperF HighTSAT (n=306)	P value
Demographics						
Age, years	70.2 ± 14.8	69.3 ± 15.2	67.7 ± 15.7	67.0 ± 14.6	66.8 ± 14.0	0.001
Male sex	145 (43.7)	173 (55.4)	69 (61.1)	206 (62.0)	181 (59.2)	<0.001
BMI, kg/m ²	30.2 ± 8.4	30.5 ± 10.6	29.4 ± 8.4	30.3 ± 8.1	29.1 ± 8.8	0.308
Vital signs on ICU admission						
Heart rate, bpm	84 ± 16	86 ± 17	84 ± 16	86 ± 16	85 ± 16	0.346
Systolic BP, mmHg	118 ± 17	115 ± 16	117 ± 16	116 ± 16	115 ± 17	0.050
Diastolic BP, mmHg	62 ± 11	61 ± 10	64 ± 12	61 ± 11	61 ± 11	0.272
Mean arterial pressure, mmHg	77 ± 11	76 ± 9	79 ± 11	76 ± 10	77 ± 10	0.261
Respiratory rate, /min	19 ± 3	20 ± 3	19 ± 3	21 ± 4	20 ± 4	<0.001
Temperature, °C	36.7 ± 0.4	36.8 ± 0.4	36.7 ± 0.4	36.8 ± 0.4	36.7 ± 0.4	<0.001
SpO ₂ , %	96 ± 2	96 ± 2	97 ± 2	97 ± 2	97 ± 2	<0.001
Comorbidities						
Hypertension	151 (45.5)	135 (43.3)	45 (39.8)	130 (39.2)	107 (35.0)	<0.001
Diabetes mellitus	152 (45.8)	121 (38.8)	48 (42.5)	146 (44.0)	117 (38.2)	<0.001
Coronary artery disease	151 (45.5)	144 (46.2)	57 (50.4)	156 (47.0)	123 (40.2)	<0.001
Atrial fibrillation	168 (50.6)	159 (51.0)	60 (53.1)	162 (48.8)	165 (53.9)	<0.001
COPD	96 (28.9)	70 (22.4)	24 (21.2)	58 (17.5)	64 (20.9)	<0.001
Chronic kidney disease	138 (41.6)	127 (40.7)	50 (44.2)	150 (45.2)	140 (45.8)	<0.001
Liver insufficiency	28 (8.4)	24 (7.7)	18 (15.9)	33 (9.9)	71 (23.2)	<0.001

Characteristic	AID (n=332)	FID (n=312)	Normal (n=113)	HyperF LowTSAT (n=332)	HyperF HighTSAT (n=306)	P value
Anemia	293 (88.3)	261 (83.7)	89 (78.8)	279 (84.0)	253 (82.7)	<0.001
HFrEF	148 (44.6)	136 (43.6)	52 (46.0)	157 (47.3)	157 (51.3)	<0.001
HFpEF	149 (44.9)	139 (44.6)	44 (38.9)	135 (40.7)	112 (36.6)	<0.001
Laboratory values						
Ferritin, ng/mL	54.5 (33.0–78.0)	179.5 (131.8–235.2)	188.0 (140.0–239.0)	603.5 (424.5–1012.8)	890.5 (487.8–2124.5)	<0.001
Serum iron, µg/dL	29.0 (19.0–48.2)	26.0 (17.0–37.0)	73.0 (56.0–99.0)	24.0 (17.0–32.0)	68.5 (46.0–122.0)	<0.001
TIBC, µg/dL	330.0 (281.0–384.2)	255.5 (219.5–299.2)	243.0 (207.0–289.0)	200.0 (170.0–242.0)	178.5 (142.0–240.5)	<0.001
TSAT, %	9.2 (5.8–14.9)	10.3 (7.4–13.8)	29.4 (23.7–41.6)	12.4 (9.2–15.7)	37.4 (26.4–67.3)	<0.001
Hemoglobin, g/dL	9.9 ± 1.7	10.2 ± 1.7	10.6 ± 2.1	10.3 ± 1.9	10.2 ± 2.1	0.096
WBC, ×10 ⁹ /L	9.4 (7.0–12.5)	10.1 (7.7–13.7)	9.3 (6.9–13.5)	11.2 (8.3–15.5)	10.4 (7.2–15.8)	<0.001
Platelets, ×10 ⁹ /L	220 (169–289)	210 (155–286)	203 (151–268)	212 (146–298)	169 (117–240)	<0.001
RDW, %	16.6 ± 2.7	15.8 ± 2.6	15.5 ± 2.1	15.5 ± 2.5	16.1 ± 2.7	<0.001
Creatinine, mg/dL	1.3 (0.9–1.8)	1.3 (0.9–2.3)	1.3 (0.9–1.9)	1.4 (1.0–2.8)	1.8 (1.1–3.4)	<0.001
BUN, mg/dL	14.0 (12.0–16.0)	15.0 (13.0–17.2)	14.0 (12.0–17.0)	16.0 (13.0–18.0)	16.0 (13.0–20.0)	<0.001
Albumin, g/dL	3.3 ± 0.4	3.2 ± 0.4	3.3 ± 0.5	3.1 ± 0.5	3.0 ± 0.6	<0.001
Lactate, mmol/L	1.6 (1.4–1.8)	1.6 (1.2–1.9)	1.6 (1.3–1.9)	1.6 (1.3–2.0)	1.6 (1.4–2.8)	0.005
Illness severity and organ						

Characteristic	AID (n=332)	FID (n=312)	Normal (n=113)	HyperF LowTSAT (n=332)	HyperF HighTSAT (n=306)	P value
support						
SOFA score	4.2 ± 3.0	5.0 ± 3.3	4.9 ± 3.3	5.8 ± 3.8	7.4 ± 4.5	<0.001
SOFA > 5	78 (23.5)	113 (36.2)	37 (32.7)	151 (45.5)	183 (59.8)	<0.001
Mechanical ventilation	43 (13.0)	52 (16.7)	18 (15.9)	73 (22.0)	79 (25.8)	<0.001
Vasoactive drugs	72 (21.7)	63 (20.2)	27 (23.9)	81 (24.4)	85 (27.8)	<0.001
CRRT	3 (0.9)	6 (1.9)	0 (0.0)	11 (3.3)	26 (8.5)	<0.001
Pre-admission medications						
Beta-blocker	250 (75.3)	225 (72.1)	91 (80.5)	249 (75.0)	210 (68.6)	<0.001
MRA	49 (14.8)	51 (16.3)	17 (15.0)	46 (13.9)	16 (5.2)	<0.001
Loop diuretic	283 (85.2)	273 (87.5)	89 (78.8)	272 (81.9)	224 (73.2)	<0.001
ACEi/ARB	159 (47.9)	129 (41.3)	58 (51.3)	143 (43.1)	90 (29.4)	<0.001
Digoxin	42 (12.7)	40 (12.8)	14 (12.4)	41 (12.3)	25 (8.2)	<0.001
SGLT2 inhibitor	3 (0.9)	7 (2.2)	2 (1.8)	4 (1.2)	1 (0.3)	0.177
Statin	226 (68.1)	205 (65.7)	74 (65.5)	220 (66.3)	150 (49.0)	<0.001
Clinical outcomes						
In-hospital death	22 (6.6)	37 (11.9)	10 (8.8)	49 (14.8)	85 (27.8)	<0.001
28-day death	38 (11.4)	51 (16.3)	12 (10.6)	64 (19.3)	88 (28.8)	<0.001
1-year death	109 (32.8)	113 (36.2)	30 (26.5)	120 (36.1)	157 (51.3)	<0.001

Values are mean ± SD, median (IQR), or n (%). AID = absolute iron deficiency; FID = functional iron deficiency; HyperF = hyperferritinemia (ferritin ≥300 ng/mL). SOFA = Sequential Organ Failure Assessment; MRA = mineralocorticoid receptor antagonist; CRRT = continuous renal replacement therapy; RDW = red cell distribution width. HFrEF and HFpEF were classified by ICD diagnosis codes (echocardiographic ejection fraction data were not available in MIMIC-IV). HFrEF and HFpEF were classified by ICD diagnosis codes (echocardiographic ejection fraction data were not available in MIMIC-IV).

Table 2. Multivariable Regression: HyperF+HighTSAT vs HyperF+LowTSAT

Outcome / Model	Events/N	OR/HR	95% CI	P
In-hospital mortality				
Unadjusted	134/638	2.22	1.50–3.29	<0.001
Model 1: Age + Sex	134/638	2.25	1.52–3.34	<0.001
Model 2: + Comorbidities	134/638	1.98	1.32–2.99	0.001
Model 3: + Severity measures	134/638	1.71	1.06–2.75	0.027
28-day mortality				
Unadjusted	152/638	1.69	1.17–2.44	0.005
Model 3 (fully adjusted)	152/638	1.31	0.85–2.02	0.220
Cox HR (fully adjusted)	152/638	1.20	0.85–1.70	0.307
1-year mortality				
Unadjusted	277/638	1.86	1.36–2.56	<0.001
Model 3 (fully adjusted)	277/638	1.63	1.13–2.35	0.010
Cox HR (fully adjusted)	277/638	1.45	1.12–1.86	0.004
5-group comparison (Model 3, ref: AID)				
Functional ID	37/312	1.98	1.07–3.66	0.030
Normal iron	10/113	1.51	0.64–3.57	0.347
HyperF + Low TSAT	49/332	1.94	1.05–3.60	0.035
HyperF + High TSAT	85/306	3.15	1.72–5.78	<0.001

Model 3 adjusts for age, sex, SOFA, mechanical ventilation, vasoactive drugs, hemoglobin, albumin, creatinine, lactate, and comorbidities. OR = odds ratio; HR = hazard ratio.

Figures

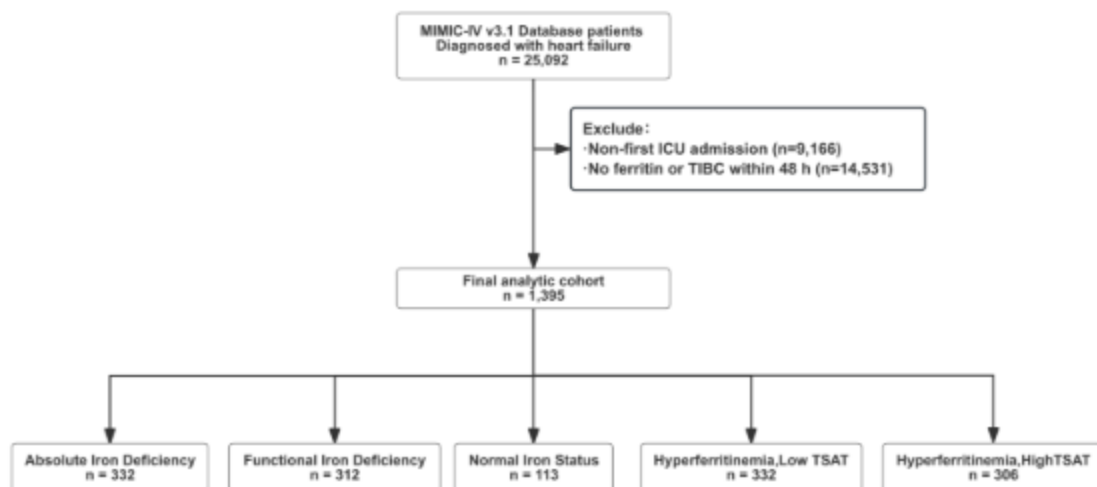


Figure 1

Patient selection flow diagram.

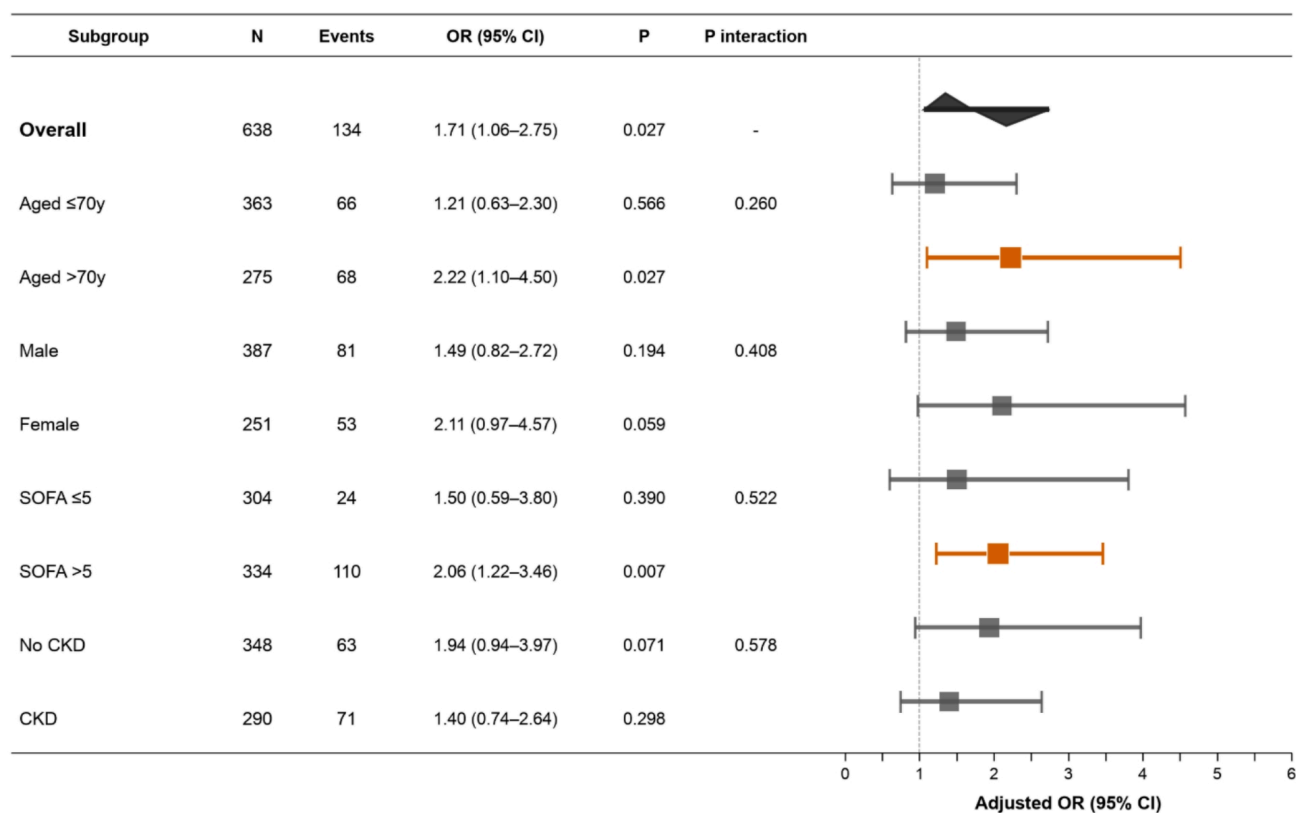


Figure 2

Subgroup analysis: adjusted odds ratios for in-hospital mortality in HyperF+HighTSAT vs HyperF+LowTSAT. Adjusted for age, sex, and available covariates. Diamond = overall estimate (Model 3). Horizontal lines = 95% CI.

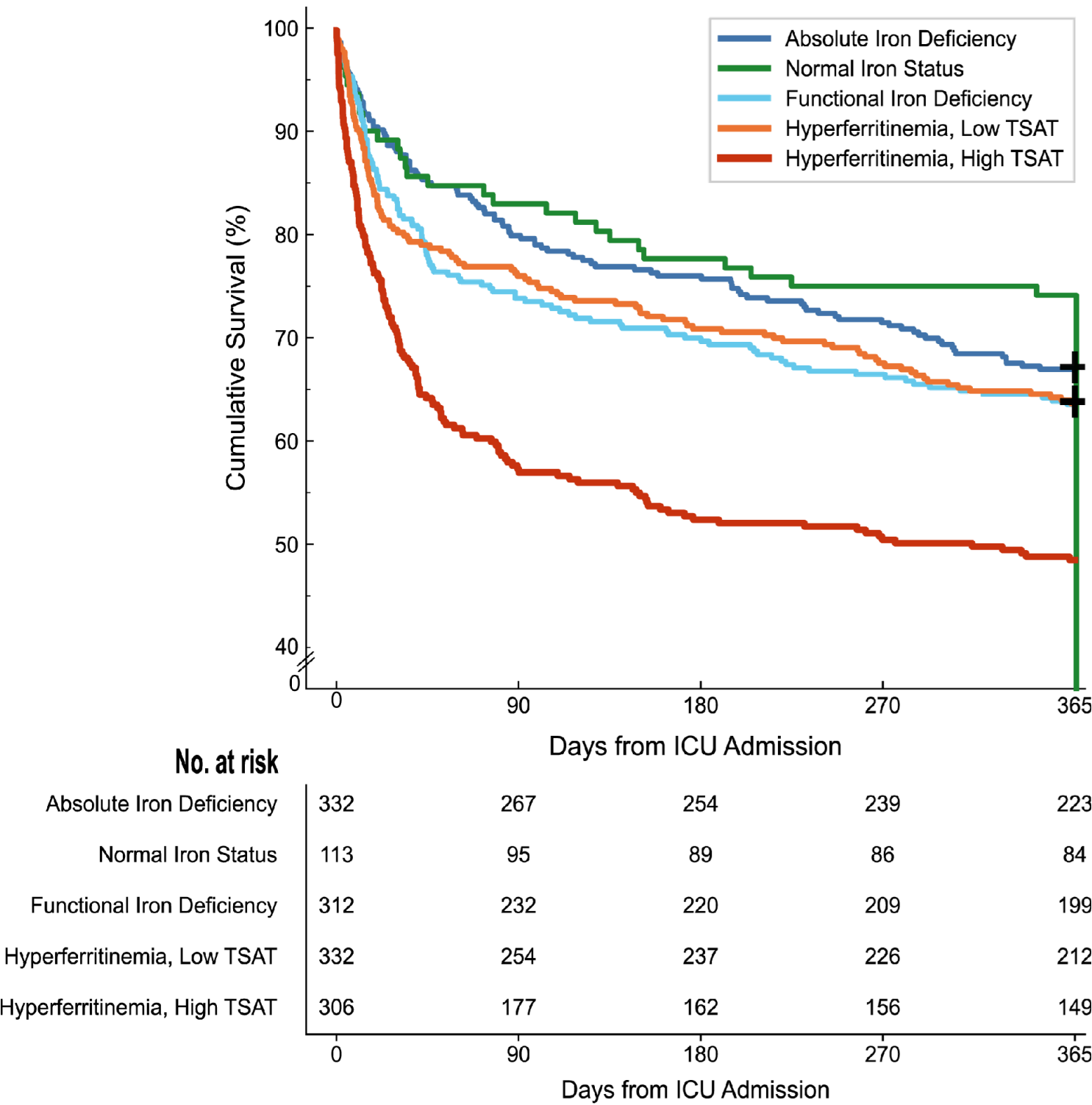


Figure 3

Kaplan-Meier 1-year survival curves by iron metabolism phenotype.

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