

Transferrin Saturation Provides Prognostic Information Beyond Ferritin in Hyperferritinemic Heart Failure: A MIMIC-IV Retrospective Cohort Study

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Abstract

Patients with heart failure and ferritin ≥ 300 ng/mL are classified as iron-sufficient and excluded from intravenous iron trials regardless of transferrin saturation (TSAT). We studied ICU-admitted, iron-tested adults with heart failure in MIMIC-IV whose iron panel was measured within 48 h of ICU admission, and classified them using European Society of Cardiology thresholds. Among 909 patients, 443 were hyperferritinemic. Comparing TSAT $\geq 20\%$ with $< 20\%$, 1-year mortality in the landmark cohort ($n = 440$) was 51.8% versus 31.4% (adjusted hazard ratio 1.84, 95% CI 1.34–2.53), and the association persisted after adjustment for guideline-directed medical therapy and log-ferritin (1.57, 1.12–2.20; $P = 0.009$). Ferritin alone was not associated with mortality. In-hospital and 28-day associations were directionally consistent, though they attenuated after additional adjustment for guideline-directed medical therapy and ferritin, and TSAT improved 1-year discrimination modestly ($\Delta C + 0.013$). In this single-center retrospective cohort, high TSAT identified a subgroup of hyperferritinemic patients with higher 1-year mortality beyond ferritin concentration alone. Because iron parameters reflect a single early-ICU measurement and only 8.2% of eligible patients underwent iron testing, these observational findings do not imply a causal or therapeutic role for TSAT.

Introduction

Heart failure (HF) remains one of the leading causes of hospitalization and death worldwide^{1,2}. Iron deficiency is the most prevalent nutritional deficiency in heart failure, affecting up to 50% of patients with chronic HF and a substantial proportion of those with acute HF^{3–5}. Randomized trials show that intravenous iron improves symptoms and functional capacity in iron-deficient patients with HF, whereas the effect on hospitalizations has been more variable: AFFIRM-AHF and pooled analyses support a reduction in heart failure hospitalizations, whereas IRONMAN and HEART-FID were neutral on their primary composite endpoints^{6–11}. Assessment of iron status is therefore recommended in all patients with HF¹².

Current guidelines define iron deficiency as serum ferritin < 100 ng/mL (absolute iron deficiency) or ferritin 100–299 ng/mL with TSAT $< 20\%$ (functional iron deficiency)¹². Patients with ferritin ≥ 300 ng/mL are classified as ferritin-defined iron-sufficient regardless of TSAT, and are excluded from iron supplementation trials by design. This classification derives from stable, ambulatory HF populations with low-grade inflammation³. Notably, when ferritin-based criteria were validated against the gold standard of bone-marrow iron staining, TSAT and serum iron rather than ferritin showed the best diagnostic performance, and the diagnostic value of ferritin itself was questioned¹³. In ambulatory HF, low TSAT has been more consistently associated with mortality than ferritin-based definitions of iron deficiency^{14,15}. The same pattern has been reported in acutely decompensated heart failure, where a lower TSAT (but not ferritin) was associated with 30-day death or heart failure readmission¹⁶.

Ferritin is an acute-phase reactant whose serum concentration increases substantially in response to inflammation^{17–21}, and its relationship to true iron status is less straightforward in acutely ill patients. Whether ferritin ≥ 300 ng/mL reliably identifies favorable iron status in critically ill patients with HF remains uncertain. Several recent studies using the MIMIC database have examined iron markers and outcomes in heart failure. Zhou et al. demonstrated that extreme hyperferritinemia (≥ 1000 ng/mL) was associated with elevated short-term mortality in critically ill patients with chronic HF²². Hourani et al. found that a combined ferritin–TSAT classification outperformed the binary guideline definition in patients with congestive HF²³, and Cai et al. reported that multiple iron homeostasis derangements were associated with worse long-term prognosis²⁴. Collectively, these studies

suggest that iron-status phenotyping in MIMIC-IV is feasible and may provide prognostic insights. However, none specifically tested whether TSAT stratifies mortality risk within the hyperferritinemic range in ICU-admitted patients with HF.

We therefore examined whether TSAT stratifies mortality risk among ICU-admitted patients with HF and ferritin ≥ 300 ng/mL, and whether any association persists after accounting for ferritin concentration, illness severity, and medical therapy.

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 public, single-center electronic health record dataset from Beth Israel Deaconess Medical Center (2008–2019)²⁵. The institutional review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center approved its use; informed consent was waived, and one author (YM) completed CITI certification (Record ID 71972596). Reporting follows the STROBE statement²⁶. During the preparation of this manuscript, the authors used DeepSeek (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.

Adult patients (18–89 years) admitted to an intensive care unit (ICU) with HF by International Classification of Diseases (ICD) codes (ICD-9 428.x or ICD-10 I50.x, any position; Supplementary Table S5) were identified. We included the first ICU admission lasting ≥ 24 h, ensuring a stable observation window; a sensitivity analysis included shorter stays. Serum ferritin, serum iron, and total iron-binding capacity (TIBC) were required to be measured within 48 h of ICU admission, before in-hospital interventions such as red-cell transfusion or iron supplementation could substantially alter the panel. Patients aged ≥ 90 years were excluded due to MIMIC-IV age truncation. Because iron studies in the ICU are ordered on clinical grounds, we compared included and excluded patients (Supplementary Table S1); the two groups were broadly similar in illness severity, sex, and mortality.

Iron phenotype classification

TSAT was calculated as $(\text{serum iron} / \text{TIBC}) \times 100$ using measurements from the same 48-hour window; in 98.7% of patients the three analytes were measured in the same blood draw. TSAT was selected as the exposure because it is the guideline-endorsed marker of iron availability and distinguishes functional from absolute iron deficiency. Classification thresholds were fixed a priori according to European Society of Cardiology (ESC) definitions¹²: absolute iron deficiency (AID, ferritin < 100 ng/mL), functional iron deficiency (FID, ferritin 100–299 ng/mL with TSAT $< 20\%$), normal iron status (ferritin 100–299 ng/mL with TSAT $\geq 20\%$), hyperferritinemia with low TSAT (HyperF+LowTSAT, ferritin ≥ 300 ng/mL with TSAT $< 20\%$), and hyperferritinemia with high TSAT (HyperF+HighTSAT, ferritin ≥ 300 ng/mL with TSAT $\geq 20\%$). Throughout this manuscript, "high TSAT" denotes TSAT $\geq 20\%$, the prespecified threshold, and does not imply markedly elevated TSAT. The term "phenotype" is used descriptively to denote risk strata defined by ferritin and TSAT thresholds; no biological mechanism is implied.

Outcomes

The primary outcome was 1-year all-cause mortality; secondary outcomes were in-hospital and 28-day mortality. Time zero was the first iron panel; the 5 patients who died before it (1 in the HyperF+HighTSAT, 2 in the HyperF+LowTSAT, and 2 in the FID group) were excluded (landmark approach), leaving 904 of 909 patients overall and 440 of 443 hyperferritinemic patients. Follow-up was censored at 365 days (28 days for the 28-day outcome) or at death.

Covariates

Demographics, comorbidities (hypertension, diabetes, coronary artery disease, atrial fibrillation, COPD, chronic kidney disease, liver insufficiency [mild or severe liver disease on the Charlson comorbidity index]), the Sequential Organ Failure Assessment (SOFA) score²⁷ (worst value in 24 h), laboratory values (hemoglobin, creatinine, albumin, lactate; first within 48 h), and cardiovascular medications recorded in the inpatient pharmacy record during the hospital admission (beta-blockers, mineralocorticoid receptor antagonists [MRAs], renin-angiotensin system inhibitors [ACEi/ARB/ARNI], sodium-glucose cotransporter 2 [SGLT2] inhibitors, statins) were extracted. Hemoglobin and creatinine were available in virtually all patients (missing < 1%); albumin and lactate were missing in 24–47% and 16–34% of patients across groups (overall 33% and 23%). Detailed missingness for all analysis variables is provided in Supplementary Table S2. Missing laboratory values were handled by multiple imputation²⁸ (20 imputations with chained equations; imputation models incorporated the exposure, the event indicator and follow-up time, and all analysis covariates; Rubin's rules for pooling). Complete-case and single-median-imputation analyses are reported as sensitivity analyses in the Supplementary Information.

Statistical analysis

Baseline characteristics were compared across phenotypes using Kruskal–Wallis tests for continuous and chi-square tests for categorical variables; standardized mean differences (SMD) were calculated for the HyperF+HighTSAT group versus all other phenotypes combined. 28-day and 1-year mortality were modeled with multivariable Cox proportional hazards, and in-hospital mortality (an admission-bounded outcome with minimal censoring) with multivariable logistic regression. In the exploratory acute heart failure subset, in which events were few, 1-year mortality was likewise estimated with logistic regression. Models were fit sequentially: Model 0 (unadjusted), Model 1 (age, sex), Model 2 (Model 1 + comorbidities), Model 3 (Model 2 + SOFA, laboratory values). Additional models adjusted for a guideline-directed medical therapy (GDMT) score (number of the above drug classes recorded during the admission: beta-blockers, MRA, ACEi/ARB/ARNI, SGLT2 inhibitors, statins; range 0–5) and log-transformed ferritin to test whether the TSAT association persists after accounting for ferritin elevation. Fully adjusted models were repeated with a statin-free GDMT score (0–4) as a sensitivity analysis (Supplementary Table S3). To avoid reliance on dichotomization, the dose–response relationships of TSAT and ferritin with 1-year mortality were examined using restricted cubic splines²⁹ (3 and 4 knots), with nonlinearity tested by joint Wald tests. Incremental prognostic value was assessed by change in the C statistic and likelihood ratio tests comparing nested models. Interaction between ferritin and TSAT was tested with a multiplicative term. Subgroup analyses (age > 70 vs ≤ 70 years, sex, SOFA > 5 vs ≤ 5, CKD, anemia [hemoglobin < 12 g/dL], liver insufficiency, and HF subtype by ICD code [systolic (HFrEF; 428.2x/I50.2x) vs diastolic (HFpEF; 428.3x/I50.3x)]) were performed as prespecified exploratory analyses. Interaction terms were tested for each stratum without adjustment for multiple comparisons. Proportional-hazards assumptions were assessed with Schoenfeld residuals³⁰, and E-values quantified the unmeasured confounding required to explain the association³¹. Sensitivity analyses included a subset with acute or acute-on-chronic HF codes, an analysis with hospital admission as the time origin (including the 3 patients who

died before the iron panel), the full-hospital (non-ICU-restricted) cohort, inclusion of ICU stays shorter than 24 h, exclusion of patients with red-cell transfusion or iron supplementation before the iron panel, restriction to same-draw iron panels, iron-panel windows of 24 h and 72 h (in addition to the primary 48-h window), additional adjustment for bilirubin, white blood cell count, and platelet count, and inverse probability weighting for iron testing³² (propensity score derived from age, sex, SOFA, comorbidities, ICU unit, and hospital service; weights stabilized and capped at the 99th percentile). Two-sided $P < 0.05$ was considered significant.

Results

Study population

Of 26,034 ICU admissions with an HF diagnosis, 14,814 were first ICU admissions, 13,059 were aged 18–89 years, and 11,041 had an ICU stay ≥ 24 h; of these, 909 (8.2%) had the full iron panel within 48 h and constituted the study cohort (Fig. 1). Compared with the 10,132 eligible patients without iron testing, the included patients were slightly younger (67.8 vs 71.2 years) with similar sex distribution (58.1% male), illness severity (SOFA 5.3 vs 5.4), and in-hospital mortality (15.5% vs 13.5%) (Supplementary Table S1). Detailed cohort-construction criteria are described in the Supplementary Information. Among the 909 patients, 198 (21.8%) had AID, 193 (21.2%) FID, 75 (8.2%) normal iron status, 222 (24.4%) HyperF+LowTSAT, and 221 (24.3%) HyperF+HighTSAT.

Baseline characteristics across phenotypes are shown in Table 1. The HyperF+HighTSAT group had higher ferritin (median 1015 vs 600 ng/mL) and SOFA (7 vs 5) than the HyperF+LowTSAT group, more liver insufficiency (20.4% vs 10.8%), comparable albumin (median 3.0 g/dL in both groups), higher creatinine (median 1.9 vs 1.4 mg/dL), and considerably lower use of guideline-directed medications (ACEi/ARB 24.0% vs 45.9%, MRA 5.9% vs 15.8%, statins 48.9% vs 64.9%). Hypertension, diabetes, atrial fibrillation, and CKD did not differ across phenotypes ($P = 0.08$ – 0.91 ; Table 1).

Table 1
Baseline characteristics by iron phenotype (n = 909)

Variable	AID (n = 198)	FID (n = 193)	Normal (n = 75)	HyperF+LowTSAT (n = 222)	HyperF+HighTSAT (n = 221)	P	SMD
Age, years	72.0 [62.1–80.8]	71.6 [61.7–78.8]	69.6 [61.4–79.5]	66.7 [57.3–78.7]	68.1 [59.2–76.1]	0.029	–0.12
Male, %	43.4	57.5	72.0	64.4	60.6	< 0.001	0.07
Ferritin, ng/mL	53.5 [30.2–77.8]	183.0 [135.0–239.0]	175.0 [142.0–242.5]	600.0 [426.2–1049.0]	1015.0 [540.0–2212.0]	< 0.001	0.43
TSAT, %	8.3 [5.9–14.4]	10.0 [7.3–13.8]	30.2 [23.7–42.2]	12.4 [9.2–15.6]	39.4 [26.4–68.0]	< 0.001	1.52
Serum iron, µg/dL	28.0 [20.0–47.5]	26.0 [18.0–37.0]	74.0 [56.0–108.0]	23.0 [16.2–32.0]	71.0 [46.0–123.0]	< 0.001	1.03
TIBC, µg/dL	330.0 [281.0–386.0]	259.0 [222.0–313.0]	246.0 [212.0–289.0]	202.5 [170.0–243.8]	174.0 [142.0–231.0]	< 0.001	–1.02
Hypertension, %	73.7	75.1	74.7	73.9	69.2	0.684	–0.11
Diabetes, %	49.5	40.9	41.3	41.4	35.7	0.084	–0.16
CAD, %	71.2	67.4	69.3	64.9	62.4	0.379	–0.11
Atrial fibrillation, %	51.0	51.8	56.0	49.1	54.3	0.777	0.06
COPD, %	44.9	38.3	26.7	27.5	36.2	0.002	0.02
CKD, %	40.9	38.3	40.0	41.4	43.0	0.914	0.06
Liver insufficiency, %	11.6	8.3	20.0	10.8	20.4	0.001	0.25
SOFA	4.0 [2.0–6.0]	4.0 [2.0–6.0]	4.0 [3.0–6.0]	5.0 [3.0–8.0]	7.0 [4.0–10.0]	< 0.001	0.61
Hemoglobin, g/dL	9.2 [7.9–11.0]	10.1 [8.4–11.6]	10.1 [8.4–12.6]	9.6 [8.5–11.4]	9.9 [8.0–11.2]	0.014	–0.05

Values are median [IQR] or %. P: Kruskal–Wallis/chi-square. SMD: standardized mean difference (HyperF+HighTSAT vs all others). Iron markers: first values within 48 h of ICU admission; TSAT = serum iron/TIBC × 100. Missing: hemoglobin/creatinine < 1%; albumin/lactate 24–47%/16–34% (overall 33%/23%); observed data only. In-hospital death: all 909 patients; 28-day/1-year rows: landmark cohort (n = 904; 198/191/75/220/220 for AID/FID/Normal/LowTSAT/HighTSAT; iron panel as index; 5 pre-panel deaths excluded). Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; AID, absolute iron deficiency; ARB, angiotensin-receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; FID, functional iron deficiency; HyperF, hyperferritinemia (ferritin ≥ 300 ng/mL); IQR, interquartile range; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SMD, standardized mean difference; SOFA, Sequential Organ Failure Assessment; TIBC, total iron-binding capacity; TSAT, transferrin saturation.

Variable	AID (n = 198)	FID (n = 193)	Normal (n = 75)	HyperF+LowTSAT (n = 222)	HyperF+HighTSAT (n = 221)	P	SMD
Creatinine, mg/dL	1.2 [0.9–1.8]	1.3 [0.9–2.2]	1.3 [0.9–1.9]	1.4 [1.0–2.8]	1.9 [1.0–3.7]	< 0.001	0.43
Albumin, g/dL	3.4 [3.0–3.7]	3.2 [2.9–3.6]	3.3 [2.7–3.6]	3.0 [2.7–3.4]	3.0 [2.6–3.4]	< 0.001	–0.31
Lactate, mmol/L	1.7 [1.2–2.4]	1.5 [1.1–2.1]	1.5 [1.1–2.3]	1.6 [1.2–2.3]	1.8 [1.3–3.2]	0.006	0.37
Beta-blocker, %	79.3	78.8	78.7	78.8	70.1	0.122	–0.20
MRA, %	16.2	19.7	14.7	15.8	5.9	0.001	–0.35
ACEi/ARB/ARNI, %	51.0	47.2	50.7	45.9	24.0	< 0.001	–0.52
SGLT2i, %	0.0	3.6	1.3	0.9	0.0	0.003	–0.17
Statin, %	68.2	69.4	62.7	64.9	48.9	< 0.001	–0.37
In-hospital death, %	7.6	10.9	9.3	14.4	29.9	< 0.001	0.48
28-day death, %	10.6	12.0	13.3	17.7	30.9	< 0.001	0.42
1-year death, %	30.8	31.4	28.0	31.4	51.8	< 0.001	0.43
Values are median [IQR] or %. P: Kruskal–Wallis/chi-square. SMD: standardized mean difference (HyperF+HighTSAT vs all others). Iron markers: first values within 48 h of ICU admission; TSAT = serum iron/TIBC × 100. Missing: hemoglobin/creatinine < 1%; albumin/lactate 24–47%/16–34% (overall 33%/23%); observed data only. In-hospital death: all 909 patients; 28-day/1-year rows: landmark cohort (n = 904; 198/191/75/220/220 for AID/FID/Normal/LowTSAT/HighTSAT; iron panel as index; 5 pre-panel deaths excluded). Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; AID, absolute iron deficiency; ARB, angiotensin-receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; FID, functional iron deficiency; HyperF, hyperferritinemia (ferritin ≥ 300 ng/mL); IQR, interquartile range; MRA, mineralocorticoid receptor antagonist; SGLT2i, sodium-glucose cotransporter 2 inhibitor; SMD, standardized mean difference; SOFA, Sequential Organ Failure Assessment; TIBC, total iron-binding capacity; TSAT, transferrin saturation.							

Primary outcome: 1-year mortality

One-year mortality varied across phenotypes, with the highest rate in the HyperF+HighTSAT group (AID 30.8%, FID 31.4%, normal iron 28.0%, HyperF+LowTSAT 31.4%, HyperF+HighTSAT 51.8%; log-rank $P < 0.001$; Fig. 2). With normal iron status as the reference in the fully adjusted model, only the HyperF+HighTSAT group showed significantly higher 1-year mortality (HR 2.07, 95% CI 1.28–3.35, $P = 0.003$), whereas AID (HR 1.10, 95% CI 0.67–1.84), FID (HR 1.29, 95% CI 0.78–2.14), and HyperF+LowTSAT (HR 1.14, 95% CI 0.69–1.88) did not differ (all $P > 0.3$). Excess mortality was therefore concentrated in the HyperF+HighTSAT group. Within the hyperferritinemic subgroup (n = 440; 3 deaths before the iron panel excluded), HyperF+HighTSAT was associated with significantly higher 1-year mortality (Table 2): unadjusted HR 1.98 (95% CI 1.47–2.67), Model 3 HR 1.84 (95% CI 1.34–2.53, $P <$

0.001). The association persisted after additional adjustment for GDMT (HR 1.61, 95% CI 1.17–2.23, $P = 0.004$) and after further adjustment for log-transformed ferritin (HR 1.57, 95% CI 1.12–2.20, $P = 0.009$), whereas log-ferritin itself was not associated with mortality (HR 1.06 per log-unit, 95% CI 0.91–1.23, $P = 0.48$). There was no evidence of interaction between the degree of ferritin elevation and the TSAT group ($P = 0.54$). Complete-case (HR 2.11, 95% CI 1.43–3.10) and single-median-imputation (HR 1.85, 95% CI 1.35–2.52) analyses gave similar results.

Table 2

Association of HyperF+HighTSAT (vs HyperF+LowTSAT) with mortality (n = 440; landmark, iron panel as index time)

Outcome	Model	Effect (95% CI)	P
In-hospital	M0 (unadjusted)	OR 2.66 (1.64–4.30)	< 0.001
In-hospital	M1 (age, sex)	OR 2.70 (1.66–4.38)	< 0.001
In-hospital	M2 (+ comorbidities)	OR 2.52 (1.52–4.15)	< 0.001
In-hospital	M3 (fully adjusted)	OR 2.02 (1.16–3.52)	0.014
In-hospital	M3 + GDMT	OR 1.62 (0.90–2.92)	0.107
In-hospital	M3 + GDMT + log-ferritin	OR 1.38 (0.75–2.55)	0.301
28-day	M0	HR 1.92 (1.29–2.84)	0.001
28-day	M1	HR 1.94 (1.31–2.87)	0.001
28-day	M2	HR 1.81 (1.21–2.70)	0.004
28-day	M3	HR 1.63 (1.08–2.46)	0.021
28-day	M3 + GDMT	HR 1.36 (0.89–2.08)	0.152
28-day	M3 + GDMT + log-ferritin	HR 1.22 (0.78–1.92)	0.382
1-year	M0	HR 1.98 (1.47–2.67)	< 0.001
1-year	M1	HR 2.03 (1.51–2.74)	< 0.001
1-year	M2	HR 1.98 (1.46–2.70)	< 0.001
1-year	M3	HR 1.84 (1.34–2.53)	< 0.001
1-year	M3 + GDMT	HR 1.61 (1.17–2.23)	0.004
1-year	M3 + GDMT + log-ferritin	HR 1.57 (1.12–2.20)	0.009

Model 3 adjusts for age, sex, comorbidities (hypertension, diabetes, CAD, atrial fibrillation, COPD, CKD, liver insufficiency), SOFA, and laboratory values (hemoglobin, creatinine, albumin, lactate). Events among the 440 patients: 95 in-hospital, 107 at 28 days, 183 at 1 year (events per covariate $\approx 6.3/7.1/12.2$ for Model 3 [15 covariates], ≈ 5.6 for the fully adjusted 17-covariate in-hospital model). Estimates from models including imputed values (M3 onward) are pooled across 20 imputations; sensitivities are reported in Supplementary Table S3. Abbreviations: CI, confidence interval; GDMT, guideline-directed medical therapy (score 0–5); HR, hazard ratio; HyperF, hyperferritinemia (ferritin ≥ 300 ng/mL); OR, odds ratio; SOFA, Sequential Organ Failure Assessment; TSAT, transferrin saturation.

Dose–response and component analyses

In restricted cubic spline models adjusted as in Model 3, the association of TSAT with 1-year mortality was approximately linear (nonlinearity $P = 0.56$ with 3 knots and 0.12 with 4 knots), indicating the association was not an artifact of the prespecified 20% threshold. By contrast, ferritin showed significant nonlinearity with 3 knots ($P = 0.013$) that was not reproduced with 4 knots ($P = 0.56$), without a monotonic dose–response; this nonlinearity appeared driven by extreme upper-tail values (35 patients with ferritin > 5000 ng/mL in the high-TSAT group; Supplementary Fig. S1); results were unchanged when ferritin values above 5000 ng/mL were excluded (fully adjusted HR 1.58, 95% CI 1.14–2.18). Twenty-one patients (4.8%) had TSAT values exceeding 100%, which is physiologically impossible, indicating measurement error in iron or TIBC; excluding them did not change the association (Model 3 HR 1.85, 95% CI 1.34–2.54). To identify which component of the TSAT ratio drives the association, serum iron and TIBC were entered separately and jointly as standardized continuous variables (Table 2). When both were included, higher serum iron showed a nominally significant association with 1-year mortality (HR 1.21 per SD, 95% CI 1.00–1.46, $P = 0.047$), whereas TIBC was not associated (HR 0.90 per SD, 95% CI 0.74–1.10, $P = 0.30$), and the categorical exposure term was attenuated (HR 1.39, 95% CI 0.85–2.27, $P = 0.11$). These exploratory findings suggest that the observed association may have been driven more by variation in serum iron than by TIBC; however, the three indices are mathematically coupled, limiting mechanistic interpretation.

Secondary outcomes

In-hospital mortality was 29.9% in the HyperF+HighTSAT group versus 14.4% in the HyperF+LowTSAT group (unadjusted OR 2.66, 95% CI 1.64–4.30; Model 3 OR 2.02, 95% CI 1.16–3.52, $P = 0.014$). The association attenuated after further adjustment for GDMT and log-ferritin (OR 1.38, 95% CI 0.75–2.55, $P = 0.30$), consistent with limited in-hospital events for full adjustment (95 events; ≈ 6.3 events per covariate with 15 Model 3 covariates, ≈ 5.6 with GDMT and log-ferritin added). 28-day mortality was directionally consistent (Model 3 HR 1.63, 95% CI 1.08–2.46, $P = 0.021$).

Incremental prognostic value

Adding log-TSAT to the baseline 1-year Cox model (demographics, comorbidities, SOFA, laboratory values) improved discrimination modestly (C statistic 0.731–0.744; $\Delta C + 0.013$) and fit significantly (likelihood ratio $P < 0.001$); a binary TSAT indicator likewise improved fit ($P < 0.001$). For the in-hospital outcome, discrimination improved (C statistic 0.814–0.824; $\Delta C + 0.010$; likelihood ratio $P = 0.001$; Supplementary Table S3).

Subgroup and sensitivity analyses

There was no evidence of effect modification across strata of age, sex, SOFA, CKD, anemia, or liver insufficiency (all P -interaction > 0.15 ; Fig. 3). Stratum-specific estimates suggested a numerically stronger association with systolic HF codes (1-year Model 3 HR 2.68, 95% CI 1.64–4.38, $P < 0.001$) than diastolic codes (HR 1.61, 95% CI 0.90–2.89, $P = 0.11$), although the interaction was not significant ($P = 0.085$); subgroup analyses are hypothesis-generating.

In the subset of patients with acute or acute-on-chronic HF codes ($n = 100$ hyperferritinemic patients), the association was directionally consistent but not significant (in-hospital OR 2.53, 95% CI 0.51–12.44; 1-year OR 2.15, 95% CI 0.84–5.49). In the full-hospital cohort ($n = 2,185$ patients with iron panels, not restricted to the ICU), where SOFA scores are ICU-derived and were unavailable, limiting adjustment to Model 2, the association remained significant (1-year Model 2 HR 1.49, 95% CI 1.18–1.90, $P = 0.001$; Supplementary Table S4). When hospital admission was used as the time origin and the 3 patients who died before the iron panel were included ($n = 443$), the association was similar (Model 3 HR 1.81, 95% CI 1.32–2.48; Supplementary Table S3). Inclusion of ICU stays shorter than 24 h (Model 1 HR 1.97, 95% CI 1.50–2.60) and exclusion of pre-panel red-cell transfusion or iron

supplementation (Model 3 HR 1.68, 95% CI 1.21–2.34) did not materially change the association; the remaining pre-specified sensitivity analyses (same-draw panels, 24- and 72-h windows, bilirubin or inflammatory-cell adjustment, penalized Cox regression) produced consistent estimates (Supplementary Table S3). In a propensity-score-weighted analysis of the probability of iron testing (pseudo- $R^2=0.06$), the weighted estimate was similar to the primary analysis (1-year Model 3 HR 1.81, 95% CI 1.30–2.52, $P < 0.001$): measured selection into testing did not account for the association; however, the low pseudo- R^2 means measured factors explained little of the variation, so unmeasured predictors of testing cannot be excluded. Proportional-hazards assumptions were satisfied (Schoenfeld $P = 0.88$); E-values indicated that unmeasured confounding would require a risk ratio of at least 3.1 (lower bound 2.0; 3.0 [1.9] for the IPW estimate) to explain the association.

Discussion

In this cohort of 909 iron-tested ICU patients with HF, TSAT $\geq 20\%$ identified a hyperferritinemic subgroup, currently classified as ferritin-defined iron-sufficient by ESC criteria, with an approximately 1.6- to 1.8-fold higher 1-year mortality. These findings do not indicate that high TSAT is intrinsically harmful; rather, concurrent TSAT provides additional risk stratification within the ferritin ≥ 300 ng/mL range. The association persisted after full adjustment, and TSAT improved model fit beyond established predictors, extending prior MIMIC-based work by showing that TSAT retains prognostic value precisely where current guidelines consider ferritin alone sufficient^{22–24}.

Strengths

This study drew on a large public critical care database; the cohort was rebuilt from raw data under pre-specified criteria. The sequential adjustment separated the TSAT signal from illness severity, and the primary finding withstood extensive sensitivity analyses (multiple imputation, alternative time origins, short ICU stays, pre-panel interventions, hospital-wide cohort).

The attenuated short-term associations

In-hospital and 28-day associations attenuated after full adjustment, consistent with short-term ICU deaths being driven largely by acute organ failure (adjusted in Model 3), whereas 1-year mortality captures the post-discharge course.

Interpretation

Ferritin ≥ 300 ng/mL may therefore encompass substantial prognostic heterogeneity that ferritin measurement alone does not capture. In acute illness ferritin behaves as an acute-phase reactant^{17–21}, attenuating its relationship to iron stores. Within the ferritin-defined iron-sufficient range, 1-year mortality ranged from 31% to 52% with TSAT, heterogeneity ferritin alone did not capture. The association's persistence after log-ferritin adjustment, with ferritin itself null ($P = 0.48$), suggests that TSAT carries prognostic information beyond the degree of ferritin elevation. The high-TSAT group was also more severely ill and received less guideline-directed therapy at baseline (Table 1); the E-value of 3.1 (lower bound 2.0) indicates that an unmeasured confounder of at least this strength would be required to explain the association, so residual confounding by illness severity cannot be excluded.

Mechanistic considerations

The biological basis of this association remains uncertain, and our data are descriptive rather than mechanistic. The group had more liver insufficiency and lower TIBC (Table 1); in exploratory component analyses the association appeared more closely related to variation in serum iron than in TIBC, although these mutually related iron indices

limit mechanistic interpretation. One possible explanation is that hyperferritinemia accompanied by higher TSAT may, in selected patients, reflect iron overload or altered hepatic iron handling; however, the present dataset cannot distinguish among these potential mechanisms. Because TSAT is a ratio, elevated values may also reflect reduced transferrin availability rather than replete iron stores; the association did not differ between patients with and without liver insufficiency (P-interaction > 0.15; Fig. 3).

Comparison with previous studies

This study extends the MIMIC literature on iron markers in HF. Zhou et al., examining ferritin ≥ 1000 ng/mL as a binary exposure, reported a 1.5-fold higher short-term mortality among critically ill patients with chronic HF, without considering TSAT²². Hourani et al., in 1,839 patients with congestive HF, found that a three-category ferritin–TSAT classification (iron-deficient, iron-replete, and hyperferritinemic) better distinguished prognostic subgroups than the binary guideline definition²³. Their hyperferritinemic group had a paradoxically lower hazard than their reference, contrasting with our findings; importantly, their ferritin ≥ 300 ng/mL category was not further stratified by TSAT, and the discrepancy likely reflects population (hospital-wide vs ICU) and outcome differences. Cai et al. assessed iron homeostasis and prognosis in 3,483 patients with HF and reported that fourth-quartile serum iron and ferritin were associated with worse long-term outcomes, whereas fourth-quartile transferrin and TIBC were protective²⁴; although they did not stratify by ferritin level, the component-level direction is consistent with our results. In an emergency-department cohort with acute HF, Aslan et al. reported the highest in-hospital mortality (42.5% vs 13.8%) among patients with ferritin ≥ 300 ng/mL and TSAT < 20%³³. In patients hospitalized for worsening heart failure (n = 661), TSAT < 20% likewise identified the subgroup with the worst prognosis over a mean follow-up of 1.9 years³⁴. In ambulatory older adults with HF and anemia, Ambrosy et al. also found low TSAT associated with higher mortality within the ferritin > 300 ng/mL stratum (adjusted HR 1.33, 95% CI 1.06–1.69), while ferritin > 300 ng/mL alone was not³⁵. These analyses and ours concur that ferritin ≥ 300 ng/mL encompasses prognostically heterogeneous patients but disagree on the direction of the TSAT association, likely reflecting clinical setting and acuity; given the consistent association of low TSAT with adverse outcomes in ambulatory HF^{14,15}, the prognostic meaning of TSAT is context-dependent. Together with prior MIMIC-based work, they support TSAT providing incremental risk stratification within the hyperferritinemic range that guidelines classify as ferritin-defined iron-sufficient. A consistent picture emerges once clinical setting and acuity are taken into account: low TSAT marked worse prognosis in ambulatory cohorts^{14,15,35}, whereas high TSAT within the ferritin-defined iron-sufficient range marked worse prognosis in our ICU cohort; in an emergency-department cohort with acute HF, by contrast, the highest in-hospital mortality occurred in patients with ferritin ≥ 300 ng/mL and TSAT < 20%³³. The three-category ferritin–TSAT model likewise found lower risk in its hyperferritinemic group but did not stratify that group by TSAT²³. Because these cohorts differ in care setting, acuity, outcome window and in whether the iron panel was obtained on clinical indication, the apparent disagreement is more plausibly explained by case mix and by the context-dependence of a single early measurement than by a genuine reversal of effect.

The low mortality of the AID group

Absolute iron deficiency had the lowest mortality (30.8% at 1 year), counterintuitive given the adverse prognostic role of iron deficiency in ambulatory HF and likely reflecting ICU selection effects; the AID group may include patients with less inflammation or different comorbidity profiles.

Clinical implications

In hyperferritinemic patients with HF, a high TSAT should not be assumed to indicate favorable prognosis: combined ferritin–TSAT assessment may improve prognostic stratification here and merits external validation. In a meta-analysis of randomized intravenous iron trials, benefit was confined to TSAT < 20% (P for interaction = 0.05), whereas ferritin did not modify treatment effect³⁶. These observational data neither support nor oppose any specific iron management strategy.

Limitations

First, this is a single-center retrospective analysis of an iron-tested subset (8.2% of eligible patients), and although included and excluded patients were broadly similar, residual selection and indication bias is possible. Second, iron parameters reflect a single early-ICU measurement; serial values, which fluctuate during acute HF³⁷, were not available. Third, hepcidin, IL-6, and CRP were not available, precluding direct assessment of inflammatory iron regulation. Fourth, HF subtypes were classified by ICD codes rather than ejection fraction, which is not reliably extractable from MIMIC-IV. Fifth, the hyperferritinemic subgroup available for fully adjusted models was modest (n = 440), limiting power for secondary outcomes and subgroup inference. Sixth, 4.8% of patients had physiologically impossible TSAT values (> 100%), indicating measurement error in iron or TIBC; exclusion left the association unchanged, but residual measurement error cannot be excluded. Seventh, cardiovascular medication use was ascertained from the inpatient pharmacy record across the whole admission rather than at a fixed baseline time point; because it may partly reflect the acute course, the attenuation seen after adjustment for medical therapy should not be interpreted as an isolated treatment effect.

Conclusions

Among iron-tested ICU patients with HF and ferritin ≥ 300 ng/mL, TSAT $\geq 20\%$ was associated with higher 1-year mortality after adjustment for ferritin elevation, severity, and guideline-directed medical therapy, suggesting TSAT provides incremental prognostic information within the hyperferritinemic range and may aid risk stratification. These findings warrant external validation and do not imply a causal or therapeutic role for TSAT.

Declarations

Competing interests:

The authors declare that they have no competing interests.

Use of large language models

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.

Ethics approval:

The MIMIC-IV database contains de-identified data; the institutional review boards of Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology waived the requirement for informed consent.

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Author Contribution

Yakupjiang Maimaiti: Conceptualization, Data curation, Formal analysis, Writing – original draft. Zhen Guo: Data curation, Visualization. Yulin Tian: Methodology, Validation. Peng Lu: 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.

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Data Availability

The MIMIC-IV database (version 3.1) used in this study is publicly available through PhysioNet to credentialed users (<https://physionet.org/content/mimiciv/>). Due to privacy restrictions, the original patient-level data are not directly available from the authors. The cohort-construction SQL queries, analysis scripts, and STROBE checklist supporting the findings of this study are available from the corresponding author upon reasonable request.

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Figures

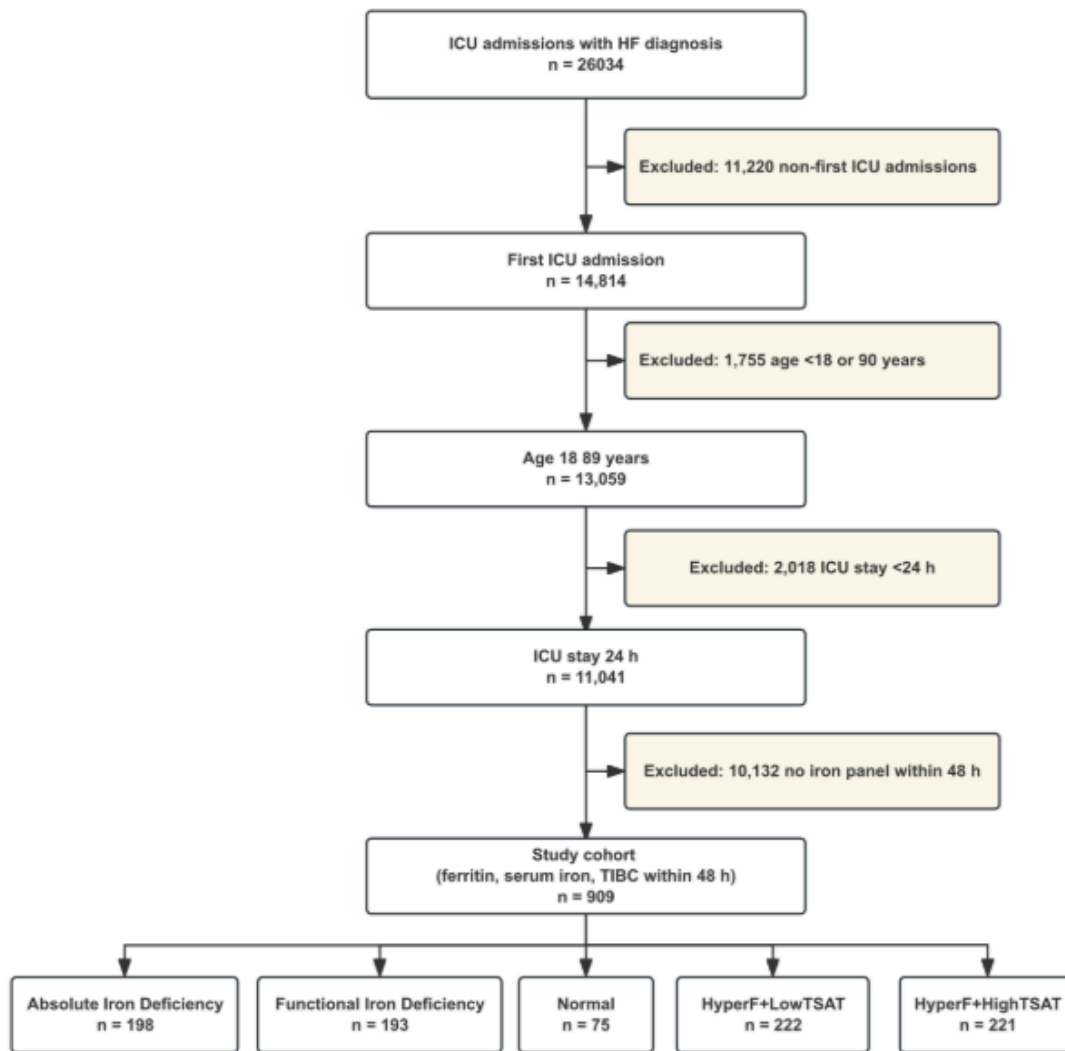


Figure 1

Study flow diagram. Abbreviations: AID, absolute iron deficiency; FID, functional iron deficiency; HF, heart failure; HyperF, hyperferritinemia (ferritin ≥ 300 ng/mL); ICD, International Classification of Diseases; ICU, intensive care unit; TIBC, total iron-binding capacity; TSAT, transferrin saturation.

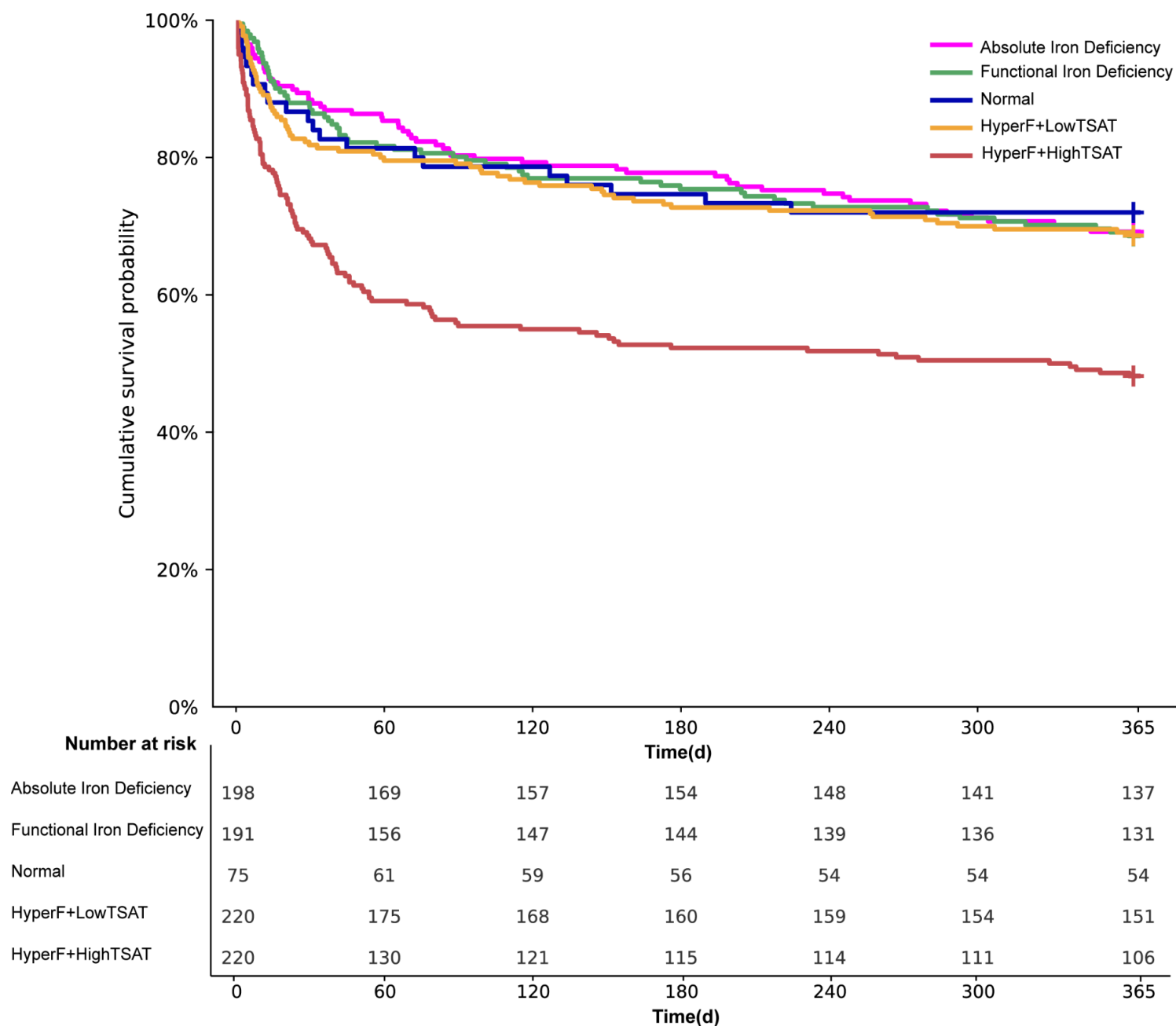


Figure 2

One-year survival by iron phenotype in the landmark cohort (n=904; log-rank $P < 0.001$ across five groups). Time origin: first iron panel (landmark); plus signs mark censoring at 365 days; numbers at risk below the x-axis. Primary comparison: HR 1.84, 95% CI 1.34–2.53 (Table 2). Abbreviations: AID, absolute iron deficiency; FID, functional iron deficiency; HyperF, hyperferritinemia (ferritin ≥ 300 ng/mL); TSAT, transferrin saturation.

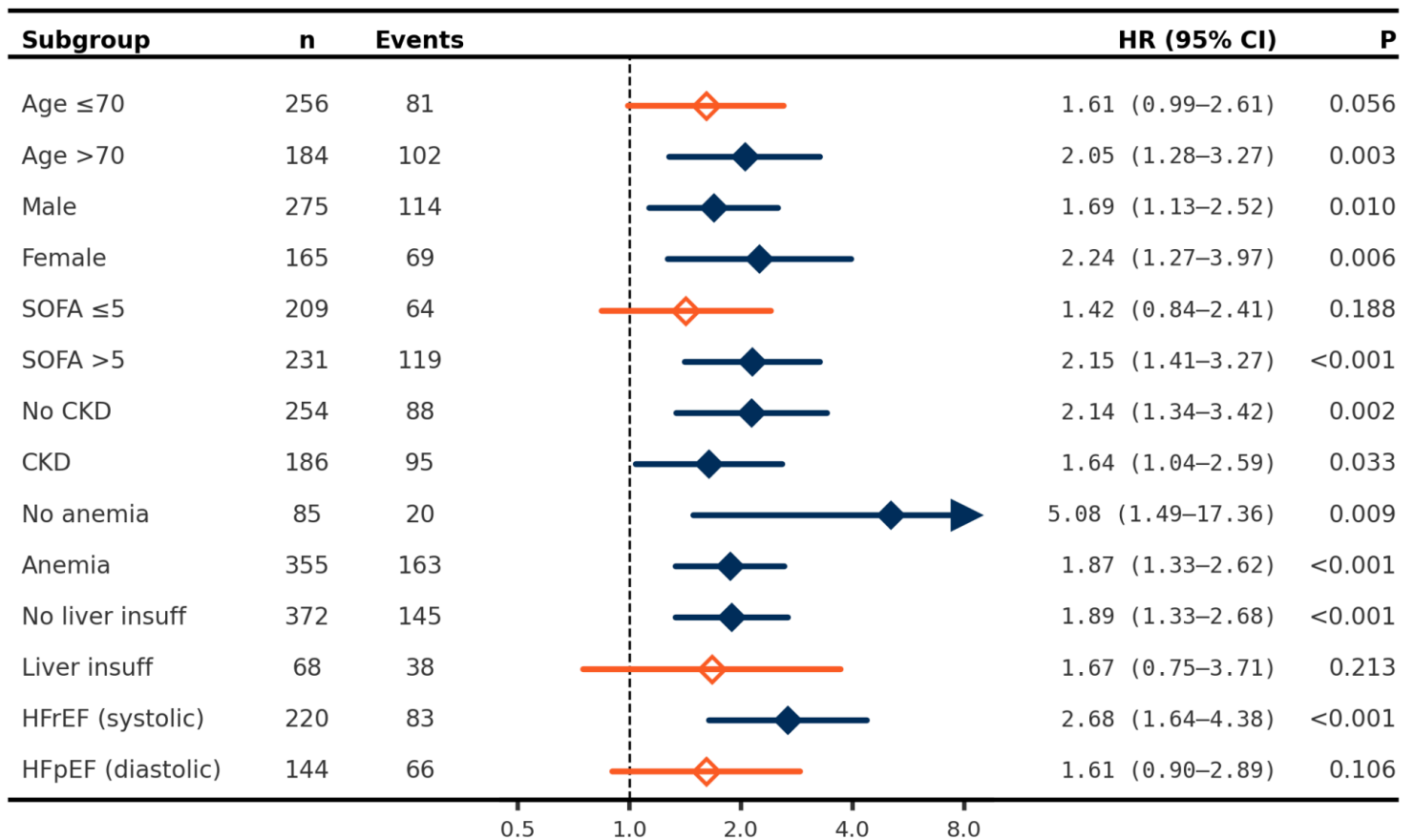


Figure 3

Subgroup analysis of 1-year mortality (HyperF+HighTSAT vs HyperF+LowTSAT). Model 3-adjusted hazard ratios are shown; n and Events are patients and 1-year deaths per stratum. Hazard ratios use a logarithmic scale; arrows mark confidence intervals extending beyond the axis. Colors: blue P<0.05, orange not significant; "unstable": <30 patients or <5 events. Abbreviations: CKD, chronic kidney disease; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HyperF, hyperferritinemia (ferritin ≥300 ng/mL); SOFA, Sequential Organ Failure Assessment; TSAT, transferrin saturation.

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