

Supplementary Material

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

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Supplementary Table S1. Characteristics of included versus excluded patients

Patients with a full iron panel (ferritin, serum iron, and total iron-binding capacity) measured within 48 h of ICU admission were included (n=909). Excluded patients were those eligible by the remaining inclusion criteria (first ICU admission $\geq$ 24 h, age 18–89 years, HF by ICD code) without iron testing within 48 h (n=10,132).

Characteristic	Included (n=909)	Excluded (n=10,132)
Age, years, mean	67.8	71.2
Male, %	58.1	58.1
SOFA score, mean	5.3	5.4
In-hospital death, %	15.5	13.5

Abbreviations: HF, heart failure; ICD, International Classification of Diseases; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment.

Supplementary Table S2. Missingness of analysis variables

Values refer to the full cohort (n=909) unless stated otherwise. Phenotype groups: AID, FID, Normal, HyperF+LowTSAT, HyperF+HighTSAT.

Variable	Role in analysis	Overall missing, n (%)	Range across phenotype groups (%)	Handling
Ferritin, serum iron, TIBC	Iron phenotype definition (inclusion criterion)	0 (0)	0	Required for inclusion (full iron panel within 48 h)
Hemoglobin	Model 3 covariate; anemia subgroup definition	1 (0.1)	0–0.5	Observed values in Table 1; multiple imputation (m=20) in adjusted models
Creatinine	Model 3 covariate	1 (0.1)	0–0.5	As above
Albumin	Model 3 covariate	298 (32.8)	23.5–46.5	Observed values in Table 1; multiple imputation (m=20) in adjusted models; complete-case and single-median-imputation sensitivity analyses
Lactate	Model 3 covariate	211 (23.2)	15.8–34.3	As above
SOFA score	Model 3 covariate	0 (0)	0	Derived from first-24-h data (mimiciv_derived.first_day_sofa)
Comorbidities and pre-admission medications	Model 2/3 covariates	0 (0)	0	Derived from official Charlson comorbidity and pharmacy tables; absence coded as not present
HF subtype (systolic vs diastolic by ICD code)	Pre-specified subgroup	0 (0); systolic or diastolic code present in 364 of 440 hyperferritinemic patients (82.7%)	—	Remaining patients (other or mixed HF codes) excluded from subtype strata

Values in Table 1 are from observed data only. Multiple imputation used chained equations (20 imputations) with the exposure, survival outcomes, and all analysis covariates included in the imputation models; estimates from adjusted models were pooled with Rubin's rules.

Abbreviations: HF, heart failure; ICD, International Classification of Diseases; TIBC, total iron-binding capacity.

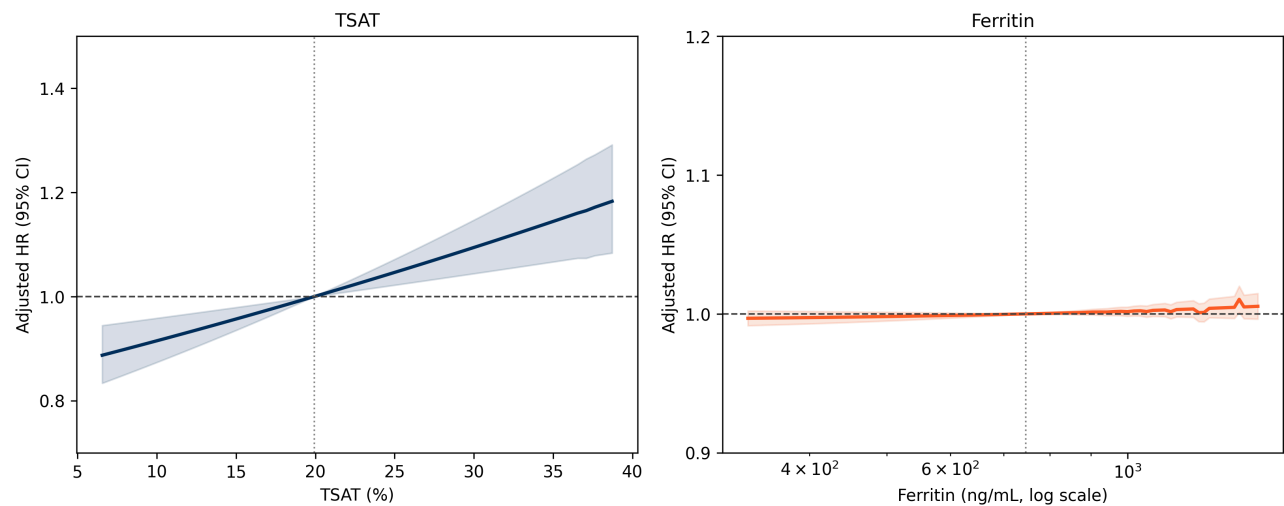
Supplementary Table S3. Sensitivity analyses for the association of HyperF+HighTSAT (vs HyperF+LowTSAT) with mortality

All estimates refer to 1-year mortality in the hyperferritinemic subgroup (n=440, landmark analysis) unless stated otherwise. Model 3 adjusts for age, sex, comorbidities, SOFA score, and laboratory values (hemoglobin, creatinine, albumin, and lactate). Hemoglobin and creatinine were available in virtually all patients; albumin and lactate were missing in 33% and 23% overall. In the primary analyses, missing laboratory values were handled by multiple imputation with chained equations (20 imputations; imputation models incorporated the exposure, the event indicator and follow-up time, and all analysis covariates), and estimates from models including imputed variables were pooled using Rubin's rules. Sensitivity rows state their own analytic approach.

Analysis	Definition (n hyperferritinemic)	Model	Estimate (95% CI)	P
Complete case	All four laboratory values observed (n=279; 79 in-hospital, 84 at 28 days, and 129 at 1-year events)	Model 3	HR 2.11 (1.43–3.10)	<0.001
Complete case	As above	Model 3 + GDMT + log-ferritin	HR 1.69 (1.12–2.56)	0.013
Single median imputation	Missing laboratory values replaced by medians	Model 3	HR 1.85 (1.35–2.52)	<0.001
Exclusion of extreme ferritin	Ferritin >5000 ng/mL (35 patients) excluded before imputation	Model 3 + GDMT + log-ferritin	HR 1.58 (1.14–2.18)	0.006
Exclusion of physiologically impossible TSAT	TSAT >100% (21 patients; measurement error in serum iron or TIBC), single median imputation	Model 3	HR 1.85 (1.34–2.54)	<0.001
GDMT score without statins	GDMT score restricted to beta-blockers, MRA, ACEi/ARB/ARNI, and SGLT2 inhibitors (0–4 classes), MI m=20 pooled	Model 3 + GDMT (0–4)	HR 1.57 (1.13–2.18)	0.007
GDMT score without statins	As above	Model 3 + GDMT (0–4) + log-ferritin	HR 1.55 (1.10–2.17)	0.012
Same-draw iron panel	All three analytes drawn within the same blood draw (n=432)	Model 3	HR 1.90 (1.38–2.62)	<0.001
Time origin: hospital admission	All hyperferritinemic patients with an iron panel (n=443; the 3 patients who died before the iron panel were included; 186 events at 1 year)	Model 3	HR 1.81 (1.32–2.48)	<0.001
24-h measurement window	Iron panel within 24 h of ICU admission (n=340)	Model 3	HR 1.75 (1.24–2.47)	0.001
72-h measurement window	Iron panel within 72 h of ICU admission (n=529)	Model 3	HR 1.87 (1.39–2.52)	<0.001

Additional adjustment for bilirubin	Model 3 + bilirubin	Model 3 + bilirubin	HR 1.81 (1.32–2.48)	<0.001
Additional adjustment for WBC and platelets	Model 3 + white blood cell count and platelet count as inflammatory markers	Model 3 + WBC/PLT	HR 2.02 (1.47–2.78)	<0.001
Penalized Cox (ridge, $\alpha=0.5$)	Ridge shrinkage at a moderate penalty	Model 3 penalized	HR 1.32	—
Discrimination (in-hospital)	C statistic change adding log-TSAT to the baseline logistic model	Model 3	ΔC +0.010 (0.814–0.824; likelihood ratio P=0.001)	—

Abbreviations: CI, confidence interval; GDMT, guideline-directed medical therapy (score 0–5); HR, hazard ratio; MI, multiple imputation; PLT, platelet; TSAT, transferrin saturation; WBC, white blood cell.



Supplementary Figure S1. Restricted cubic spline analyses of the association of TSAT and ferritin with 1-year mortality in the hyperferritinemic subgroup (n=440; knots at the 10th, 50th, and 90th percentiles; reference: group median; adjusted as in Model 3). Nonlinearity P values (joint Wald tests): TSAT P=0.56, consistent with an approximately linear association; ferritin P=0.013, reflecting a rise at extreme upper-tail values without a monotonic dose-response (see text). Abbreviations: CI, confidence interval; HR, hazard ratio; TSAT, transferrin saturation.

Supplementary Table S4. Sensitivity analysis in the full-hospital cohort (n=2,185)

All patients with an iron panel measured during hospitalization were analyzed regardless of ICU admission (n=2,185: AID 609, FID 490, normal iron status 266, HyperF+LowTSAT 414, HyperF+HighTSAT 406). The index time for time-to-event analysis was hospital admission; the 1-year outcome was all-cause death within 365 days (event definition identical to the primary analysis, verified against the original flag in all 2,185 patients). Models: Model 0, unadjusted; Model 1, age and sex; Model 2, Model 1 plus comorbidities (hypertension, diabetes, coronary artery disease, atrial fibrillation, COPD, CKD, liver insufficiency). In-hospital and 28-day outcomes were analyzed with logistic regression; the 1-year outcome with Cox proportional hazards regression (in time-to-event analysis the previously reported logistic estimate was replaced by a hazard ratio).

Outcome	Model	Estimate (95% CI)	P
In-hospital	M0	OR 2.62 (1.70–4.02)	<0.001
In-hospital	M1	OR 2.62 (1.70–4.02)	<0.001
In-hospital	M2	OR 2.29 (1.47–3.56)	<0.001
28-day	M0	OR 2.14 (1.45–3.16)	<0.001
28-day	M2	OR 1.88 (1.25–2.83)	0.002
1-year	M0	HR 1.63 (1.29–2.06)	<0.001
1-year	M1	HR 1.63 (1.29–2.07)	<0.001
1-year	M2	HR 1.49 (1.18–1.90)	0.001

Abbreviations: AID, absolute iron deficiency; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; FID, functional iron deficiency; HR, hazard ratio; HyperF, hyperferritinemia (ferritin ≥ 300 ng/mL); OR, odds ratio; TSAT, transferrin saturation.

Supplementary Table S5. International Classification of Diseases (ICD) codes used to identify heart failure and heart failure subtypes in the MIMIC-IV database

Adult patients admitted to an intensive care unit with heart failure were identified using ICD-9 and ICD-10 codes recorded in the diagnoses_icd table of MIMIC-IV (any position). Heart failure subtype was classified according to diagnosis codes (systolic: 428.2x/150.2x; diastolic: 428.3x/150.3x) because echocardiographic ejection fraction measurements were not reliably extractable from MIMIC-IV; patients with mixed systolic–diastolic codes or codes without systolic/diastolic specification were included in the cohort but not assigned to either subtype.

Part A. ICD-9 codes

ICD-9 Code	Description	HF subtype
428.0	Congestive heart failure, unspecified	Unspecified
428.1	Left heart failure	Unspecified
428.20	Systolic heart failure, unspecified	HFrEF
428.21	Acute systolic heart failure	HFrEF
428.22	Chronic systolic heart failure	HFrEF
428.23	Acute on chronic systolic heart failure	HFrEF
428.30	Diastolic heart failure, unspecified	HFpEF
428.31	Acute diastolic heart failure	HFpEF
428.32	Chronic diastolic heart failure	HFpEF
428.33	Acute on chronic diastolic heart failure	HFpEF
428.40	Systolic and diastolic heart failure, unspecified	Mixed
428.41	Acute systolic and diastolic heart failure	Mixed
428.42	Chronic systolic and diastolic heart failure	Mixed
428.43	Acute on chronic systolic and diastolic heart failure	Mixed
428.9	Heart failure, unspecified	Unspecified

Part B. ICD-10 codes

ICD-10 Code	Description	HF subtype
I50.0	Congestive heart failure, unspecified	Unspecified
I50.1	Left ventricular failure	Unspecified
I50.20	Unspecified systolic (congestive) heart failure	HFrEF
I50.21	Acute systolic (congestive) heart failure	HFrEF
I50.22	Chronic systolic (congestive) heart failure	HFrEF
I50.23	Acute on chronic systolic (congestive) heart failure	HFrEF
I50.30	Unspecified diastolic (congestive) heart failure	HFpEF
I50.31	Acute diastolic (congestive) heart failure	HFpEF
I50.32	Chronic diastolic (congestive) heart failure	HFpEF
I50.33	Acute on chronic diastolic (congestive) heart failure	HFpEF

I50.40	Unspecified combined systolic and diastolic heart failure	Mixed
I50.41	Acute combined systolic and diastolic heart failure	Mixed
I50.42	Chronic combined systolic and diastolic heart failure	Mixed
I50.43	Acute on chronic combined systolic and diastolic heart failure	Mixed
I50.810	Right heart failure, unspecified	Unspecified
I50.811	Acute right heart failure	Unspecified
I50.812	Chronic right heart failure	Unspecified
I50.813	Acute on chronic right heart failure	Unspecified
I50.814	Right heart failure due to left heart failure	Unspecified
I50.819	Right heart failure, unspecified	Unspecified
I50.82	Biventricular heart failure	Unspecified
I50.83	High output heart failure	Unspecified
I50.84	End stage heart failure	Unspecified
I50.89	Other heart failure	Unspecified
I50.9	Heart failure, unspecified	Unspecified

HF subtype: HFrEF, heart failure with reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; Mixed, combined systolic and diastolic heart failure; Unspecified, codes without systolic/diastolic specification (including right, biventricular, and high-output failure). Echocardiographic ejection fraction was not reliably extractable from MIMIC-IV; subtypes were therefore classified from diagnosis codes.