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RESEARCH ARTICLE

Prognostic value of three iron deficiency definitions in patients with advanced heart failure

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Aims There is uncertainty about the definition of iron deficiency (ID) and the association between ID and prognosis in patients with advanced heart failure. We evaluated three definitions of ID in patients referred for heart transplantation.

Methods and results Consecutive patients assessed for heart transplantation at a single UK centre between January 2010 and May 2022 were included. ID was defined as (1) serum ferritin concentration of <100 ng/ml, or 100–299 ng/ml with transferrin saturation <20% (guideline definition), (2) serum iron concentration ≤13 μmol/L, or (3) transferrin saturation <20%. The primary outcome measure was a composite of all-cause mortality, urgent heart transplantation or need for mechanical circulatory support. Overall, 801 patients were included, and the prevalence of ID was 39–55% depending on the definition used. ID, defined by either serum iron or transferrin saturation, was an independent predictor of the primary outcome measure (hazard ratio [HR] 1.532, 95% confidence interval [CI] 1.264–1.944, and HR 1.595, 95% CI 1.323–2.033, respectively), but the same association was not seen with the guideline definition of ID (HR 1.085, 95% CI 0.8827–1.333). These findings were robust in multivariable Cox regression analysis. ID, by all definitions, was associated with lower 6-min walk distance, lower peak oxygen consumption, higher intra-cardiac filling pressures and lower cardiac output.

Conclusions Iron deficiency, when defined by serum iron concentration or transferrin saturation, was associated with increased frequency of adverse clinical outcomes in patients with advanced heart failure. The same association was not seen with guideline definition of ID.

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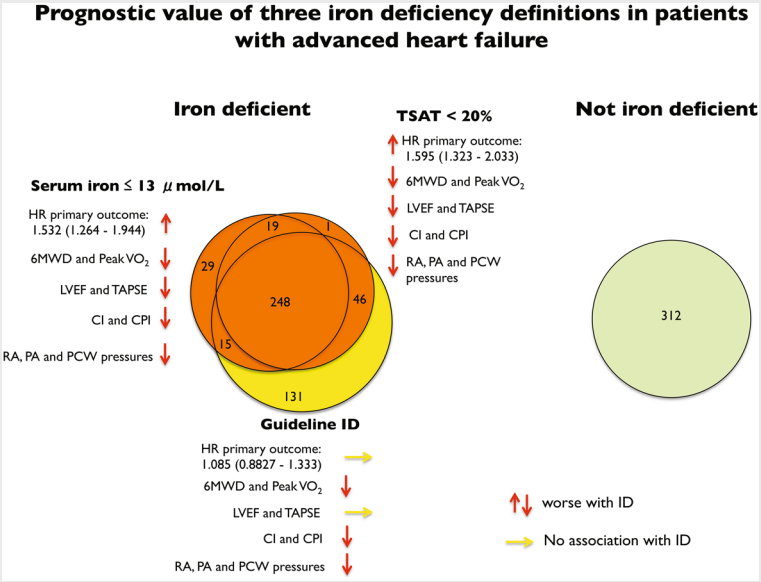
Graphical Abstract



Venn diagram of iron deficiency (ID) according to various definitions and associated outcomes. Non-scaled VENN diagram. Data for hazard ratio (HR) is mean (95% confidence interval). Red circles indicate worst prognosis, yellow intermediate prognosis and green best prognosis. 6MWD, 6-min walk distance; CI, cardiac index; CPI, cardiac power index; LVEF, left ventricular ejection fraction; PA, pulmonary artery; PCW, pulmonary capillary wedge; RA, right atrial; TAPSE, tricuspid annular plane systolic excursion; TSAT, transferrin saturation; VO_2, oxygen consumption.

Keywords Iron deficiency • Advanced heart failure • Heart transplant

Introduction

Iron deficiency (ID) is a common comorbidity in patients with chronic heart failure (HF) and other cardiovascular diseases and is an independent predictor of adverse prognosis including quality of life and exercise capacity.[1–3] Intravenous iron replacement has been shown to improve outcomes in HF patients including exercise capacity, quality of life, rate of HF hospitalization and possibly mortality.[1–4]

Different definitions of ID are used in clinical practice. European HF guidelines define ID as a serum ferritin concentration of <100 ng/ml, or a serum ferritin of concentration of 100–299 ng/ml with a transferrin saturation (TSAT) <20%[5] because this definition was used in most large trials of iron replacement in HF.[1–3] However, other criteria to diagnose ID have been proposed based on comparison to the gold standard of bone marrow biopsy including serum iron ≤13 μmol/L and TSAT <20%.[6] Overreliance on serum ferritin concentrations to diagnose ID has been criticized because inflammation can lead to extracellular release of ferritin and increased serum ferritin concentrations even in patients who would fulfill ID criteria based on alternative definitions.[7] Another confounding factor in determining ID with current definitions is the increased use of sodium–glucose cotransporter 2 (SGLT2) inhibitors affecting iron homeostasis and subsequently ferritin concentrations and TSAT.[8]

The prognostic value of ID in patients with advanced HF, assessed for heart transplantation, is currently not well established. This patient population is characterized by relatively young age, single-organ pathology and prognosis is largely determined by the severity of heart disease rather than comorbidities. Without dedicated study, the prognostic value of ID in this cohort can therefore not be inferred. In this study we therefore investigated the prognostic value of various ID definitions in patients with advanced HF assessed for cardiac transplantation.

Methods

Study population

Consecutive ambulatory outpatients assessed for heart transplantation at Royal Papworth Hospital, a large national advanced HF centre in the United Kingdom, between January 2010 and May 2022 were included. All patients underwent echocardiography, right heart catheterization, 6-min walk distance (6MWD), cardiopulmonary exercise test and a series of blood tests as part of heart transplant assessment. Data were collected prospectively and supplemented by retrospective review of

patient records. The study was approved by our institutional review board.

Definitions

Three definitions of ID were used: (1) guideline definition of ID: serum ferritin concentration of <100 ng/ml, or 100–299 ng/ml with TSAT <20%; (2) serum iron concentration ≤13 μmol/L; or (3) TSAT <20%. Anaemia was defined using criteria from the World Health Organization with haemoglobin <12.0 g/dl in women and <13.0 g/dl in men.[9]

Outcomes

The primary outcome was a composite of all-cause mortality, urgent heart transplantation or mechanical circulatory support (MCS) with veno-arterial extracorporeal membrane oxygenation or any form of ventricular assist device. Support with an intra-aortic balloon pump was not a co-primary endpoint. Patients were followed up clinically and through use of electronic patient records up to May 2022. Secondary outcomes were echocardiographic parameters (left ventricular ejection fraction [LVEF], tricuspid annular plane systolic excursion [TAPSE] and left ventricular internal diameter in diastole), 6MWD and peak oxygen consumption (VO_2) derived from cardiopulmonary exercise testing, and parameters obtained from right heart catheterization (right atrial pressure, pulmonary artery pressure, pulmonary capillary wedge pressure, cardiac index, cardiac power index). The competing event of routine (non-urgent) heart transplantation was not part of the primary endpoint and follow-up was censored at the time of routine heart transplantation.

Statistical analysis

Categorical values are presented as numbers and percentages and compared through use of Fisher's exact tests or chi-square tests. Continuous variables were tested for normal distribution using D'Agostino and Pearson omnibus normality test, presented as median with 25th and 75th percentiles (interquartile range) or mean with standard deviation, and compared using Student's *t*-test or Mann–Whitney U test.

Kaplan–Meier cumulative endpoint curves were used to compare groups. The log-rank test was used to evaluate statistical significance. Cox proportional hazards models were used to estimate the effects of variables on the primary outcome all-cause mortality, urgent cardiac transplant or MCS. The multivariable model was adjusted for age, sex, body mass index (BMI), diabetes, smoking history, estimated glomerular filtration rate (eGFR), haemoglobin, N-terminal pro-B-type natriuretic peptide (NT-proBNP), HF phenotype, LVEF, severity of HF symptoms (New York Heart Association [NYHA] classification III or IV), beta-blocker, angiotensin-converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), angiotensin receptor–neprilysin inhibitor (ARNI), and loop diuretic use. Hazard ratios (HR) with 95% confidence interval (CI) are reported.

Results

Overall, 897 patients with advanced HF were assessed for heart transplantation between January 2010 and May 2022. Full iron studies were available for 801 patients. Baseline characteristics are described in *Table 1*. A total of 392 patients (49%) had dilated cardiomyopathy, 178 (22%) ischaemic cardiomyopathy, 113 (14%) hypertrophic cardiomyopathy, 32 (4%) restrictive cardiomyopathy, 34 (4%) congenital heart disease, 32 (4%) arrhythmogenic ventricular cardiomyopathy and 20 (2%) another cardiomyopathy.

Prevalence of iron deficiency and its association with patient subgroups

The prevalence of ID in this advanced HF population ranged from 39% to 55% depending on definition used. Stratified according to HF aetiology the prevalence of ID was 41–65% using guideline criteria, 29–48% using serum iron ≤13 μmol/L definition, and 34–55% using TSAT <20% definition (online supplementary *Table S1*). Each definition of ID defined a distinct patient population, albeit with considerable overlap between the definitions. Of the 489 patients identified as iron deficient by any definition, 51% fulfilled criteria for all three definitions, 16% for two definitions and 33% for only one of the definitions (*Graphical Abstract*). The prevalence of ID according to the three definitions in various patient subgroups is shown in *Figure 1*. ID was more common in female patients, those with anaemia and those with more severe symptoms.

Outcomes according to different iron deficiency criteria

The median follow-up duration was 1.64 years (interquartile range: 0.51–4.23 years) and the primary outcome occurred in 364 (45%) of patients. Of those patients reaching the primary endpoint, 178 (49%) died, 77 (21%) received MCS and 109 (30%) received an urgent cardiac transplant. No patients were lost to follow-up. There were numerically higher proportions of death as the determinant of the primary outcome in the ID groups but this was only statistically significant using the TSAT <20% definition. When patients with ID were compared across the three definitions, no statistical differences were observed (online supplementary *Table S2*).

The Kaplan–Meier curves for the primary outcome according to the three different ID definitions are shown in *Figure 2*. Whilst the guideline ID definition was not a predictor of the composite primary endpoint, serum iron ≤13 μmol/L and TSAT <20% were both strong predictors. Median event-free survival in the guideline ID group was 4.13 years and in the non-ID group (any definition) 4.79 years (p = NS). Median event-free survival in the serum iron ≤13 μmol/L group was 2.75 years (HR 1.53, 95% CI 1.26–1.94 compared to iron >13 μmol/L) and in the TSAT <20% it was 2.81 years (HR 1.60, 95% CI 1.32–2.03 compared to TSAT ≥20%) (*Figure 2*). Since May 2016 the European Society of Cardiology (ESC) guidelines for HF recommend the use of intravenous iron replacement in patients with HF who are iron deficient.[10] Following publication of this guideline, intravenous iron replacement therapy was initiated or advised to the regular HF team for 117/219 patients (53%) fulfilling guideline criteria of ID and 80/162 patients (49%) and 73/156 patients (47%) of patients fulfilling iron ≤13 μmol/L or TSAT <20% criteria, respectively (p = 0.4325).

Table 1 Patient characteristics according to iron deficiency criteria

	Missing	Guideline definition			Serum iron definition			TSAT definition			*p*-value*	*p*-value#
		ID	Non-ID	*p*-value	ID	Non-ID	*p*-value	ID	Non-ID	*p*-value		
Demographics and comorbidities												
Age, years	0 (0)	52 (41–58)	52 (42–58)	0.355	51 (41–58)	52 (42–58)	0.6062	51 (41–58)	52 (42–58)	0.4209	0.9854	0.9563
Female sex	0 (0)	151 (34)	82 (23)	0.0003	95 (31)	138 (28)	0.4736	107 (34)	126 (26)	0.0136	0.5107	0.2
BMI, kg/m^2	0 (0)	28 (4)	26 (4)	0.5797	27 (5)	26 (4)	0.0553	25 (5)	26 (4)	0.2114	0.3593	0.5243
Diabetes	0 (0)	59 (13)	48 (13)	>0.9999	40 (13)	67 (14)	0.8313	46 (15)	61 (13)	0.3964	0.7978	0.2905
COPD	0 (0)	26 (6)	17 (5)	0.5296	16 (5)	27 (6)	0.8735	17 (5)	26 (5)	>0.9999	0.8972	0.8664
Smoking	0 (0)	11 (3)	2 (1)	0.0455	10 (3)	3 (1)	0.0073	9 (3)	4 (1)	0.2618	0.8417	0.492
eGFR, ml/min/1.73 m^2	0 (0)	80 (61–104)	85 (64–108)	0.257	76 (57–101)	86 (66–109)	0.0002	76 (56–100)	87 (66–109)	<0.0001	0.0856	0.5665
ICM	0 (0)	115 (26)	63 (17)	0.0036	85 (27)	93 (19)	0.0068	79 (25)	99 (20)	0.1174	0.8259	0.5725
Blood group												
A	0 (0)	188 (43)	147 (41)	0.6144	123 (40)	212 (43)	0.3046	129 (41)	206 (42)	0.7693	0.6809	0.7582
B	0 (0)	49 (11)	38 (11)	0.8201	39 (13)	48 (10)	0.2445	37 (12)	50 (10)	0.5611	0.8405	0.9369
AB	0 (0)	12 (3)	10 (3)	>0.9999	9 (3)	13 (3)	0.8281	11 (4)	11 (2)	0.376	0.82	0.879
0	0 (0)	191 (43)	166 (46)	0.4757	140 (45)	217 (44)	0.8841	137 (44)	220 (45)	0.7159	0.9009	0.8845
Heart failure classification and LVEF												
NYHA class III–IV	0 (0)	361 (82)	272 (75)	0.0233	266 (86)	367 (75)	0.0003	270 (86)	363 (75)	<0.0001	0.2584	0.9646
LVEF, %	5 (<1)	22 (17–32)	22.5 (17–32)	0.8594	21 (17–30)	23 (17.5–32.5)	0.0344	20 (17–31)	23 (17.5–32)	0.0185	0.3233	0.6556
Laboratory values												
Haemoglobin, g/L	0 (0)	134 (17)	141 (17)	<0.0001	130 (17)	141 (16)	<0.0001	130 (16)	141 (16)	<0.0001	0.0006	0.8015
Anaemia	0 (0)	144 (33)	70 (19)	<0.0001	137 (44)	77 (16)	<0.0001	134 (43)	80 (16)	<0.0001	0.002	0.341
NT-proBNP, ng/L	252 (31)	2673 (1224–4892)	2114 (906–4678)	0.0493	3150 (1493–6115)	1922 (863–4128)	<0.0001	3145 (1679–5829)	1855 (833–4128)	<0.0001	0.0187	0.4606
Medications												
ACEi, ARB or ARNI	0 (0)	381 (87)	334 (93)	0.0081	274 (88)	441 (90)	0.4138	270 (86)	445 (91)	0.0192	0.7196	0.432
MRA	0 (0)	356 (81)	293 (81)	>0.9999	238 (77)	411 (84)	0.0124	249 (79)	400 (82)	0.3561	0.3454	0.5667
Beta-blocker	0 (0)	366 (83)	330 (91)	0.0007	257 (83)	439 (90)	0.0052	257 (83)	443 (91)	<0.0001	0.6382	0.6253
Loop diuretic	0 (0)	394 (90)	313 (87)	0.2261	279 (90)	428 (87)	0.3676	290 (92)	417 (86)	0.0035	0.3811	0.7292

Values are *n* (%), median (IQR), or mean (SD).

Guideline criteria for ID were ferritin <100 ng/ml or ferritin 100–299 ng/ml and TSAT <20%.

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; ICM, ischaemic cardiomyopathy; ID, iron deficient; LVEF, left ventricular ejection fraction; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; TSAT, transferrin saturation.

*p-value comparing various ID definitions.

#p-value comparing patients not fulfilling ID criteria according to various definitions.

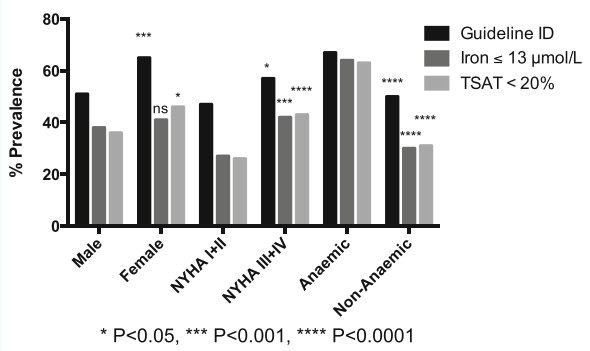


Figure 1 Prevalence of iron deficiency (ID) by definition and subgroup. NYHA, New York Heart Association; TSAT, transferrin saturation.

Prior to its publication, intravenous iron replacement therapy was not routinely recommended by our institution. To further assess whether the recommendation in the 2016 ESC guidelines could have biased our result, we dichotomized patients into two groups, before and after publication of the guidelines. Time to the primary endpoint was comparable in both groups for any definition of ID used and there was no suggestion that the introduction selectively benefited patients who fulfilled guideline criteria of ID (online supplementary *Figure S1*).

Of those patients fulfilling guideline criteria, patients with TSAT <20% (i.e. ferritin 0–299 ng/ml) had worse outcomes compared to those with TSAT ≥20% (i.e. ferritin <100 ng/ml but TSAT ≥20%) (median event-free survival 2.76 years vs. 11.84 years; HR 2.151, 95% CI 1.49–2.62). Further analysis identified a subgroup of 131 patients fulfilling guideline criteria of ID but not meeting criteria of the other definitions (*Graphical Abstract*) that had favourable outcomes compared to patients fulfilling both the guideline definition of ID and at least one of the other definitions (online supplementary *Figure S2*). These patients were also less symptomatic (NYHA class III–IV), had higher LVEF and lower NT-proBNP concentrations (online supplementary *Table S3*).

In univariable analysis, lower serum iron concentrations and lower TSAT were associated with the primary outcome (*Table 2*) but ferritin concentrations were not. In a multivariable model, including age, sex, BMI, diabetes, smoking history, eGFR, haemoglobin, NT-proBNP, HF phenotype, LVEF, HF severity (NYHA class III or IV), beta-blocker, ACEi, ARB, ARNI, and loop diuretic use, Ln (serum iron) was not statistically associated with the primary outcome (HR 0.76, 95% CI 0.56–1.03, $p = 0.07$) but the association between Ln (TSAT) and the primary outcome remained significant (HR 0.73, 95% CI 0.57–0.93, $p < 0.01$).

The categorical values of serum iron ≤13 µmol/L and TSAT <20% were associated with the primary outcome in univariable Cox regression analysis, but the guideline definition of ID was not (*Table 2*). In the multivariable model the predictive value of serum iron ≤13 µmol/L and TSAT <20% remained (HR 1.42, 95% CI 1.05–1.91, $p = 0.02$, and HR 1.38, 95% CI 1.03–1.84, $p < 0.03$, respectively).

The associations of the three ID definitions on the secondary outcomes 6MWD and peak VO_2, echocardiographic parameters and right heart catheterization are presented in *Table 3*. ID according to any definition was associated with worse 6MWD and peak VO_2. Only ID according to the serum iron ≤13 µmol/L and TSAT <20% definitions but not the guideline definition was associated with reduced LVEF and TAPSE. Finally, all definitions of ID were associated with elevated right atrial, pulmonary artery and pulmonary capillary wedge pressures, and associated with lower cardiac index.

Discussion

In this study we show that ID is associated with an adverse prognosis in patients with advanced HF. This population is characterized by young age, few comorbidities but incorporates a broad spectrum of cardiac diseases. A particular strength of the current study is the long follow-up for the primary endpoint and the wealth of cardiac investigations for the secondary endpoints. To our knowledge, we present the largest data set of patients with advanced HF and co-existing ID. This study, along with others,[6,7] suggests that the definition of iron deficiency in HF may benefit from being refined.

In this study, ID defined by serum iron concentrations and TSAT, but not the guideline definition of ID, was associated with the primary outcome of all-cause mortality, urgent heart transplantation or MCS. Death was the main driver of the primary outcome, particularly in patients with ID. The association was preserved over a wide range of HF aetiologies including dilated cardiomyopathy, hypertrophic cardiomyopathy and ischaemic cardiomyopathy as well as other acquired, inherited, or congenital cardiac conditions. Multivariable Cox regression analysis suggested that this association remained significant even after adjustment for age, sex, BMI, diabetes, smoking history, eGFR, haemoglobin, NT-proBNP, HF aetiology, LVEF, and HF severity (NYHA class III or IV) and beta-blocker, ACEi, ARB, ARNI, and loop diuretic use.

The current guideline definition of ID, centred around ferritin serum concentrations, as well as the two alternate ID criteria, predicted exercise capacity, peak VO_2, cardiac index and right heart pressures. In addition, ID according to the serum iron definition and the TSAT definition was also associated with adverse echocardiographic features such as reduced LVEF and TAPSE. These outcome measures are important. Previous studies have shown a strong correlation between poor exercise capacity in patients with HF, assessed by 6MWD, and worse outcomes including hospitalizations and mortality.[11] Similarly, peak VO_2 predicted the composite endpoint of mortality, MCS or transplant in patients with HF across the spectrum of LVEF but in particular in patients with HF with preserved ejection fraction.[12] In the advanced HF population TAPSE, cardiac index and pulmonary capillary wedge pressure are all important predictors of adverse clinical outcomes.[13]

The prevalence of ID is high in patients with HF,[1–3] acute coronary syndromes,[14] atrial fibrillation[15] and valvular heart disease.[16] ID is a well-established marker of adverse outcomes in the HF population and intravenous iron supplementation improves quality of life and exercise capacity.[1–3,17] The IRONMAN and AFFIRM-AHF

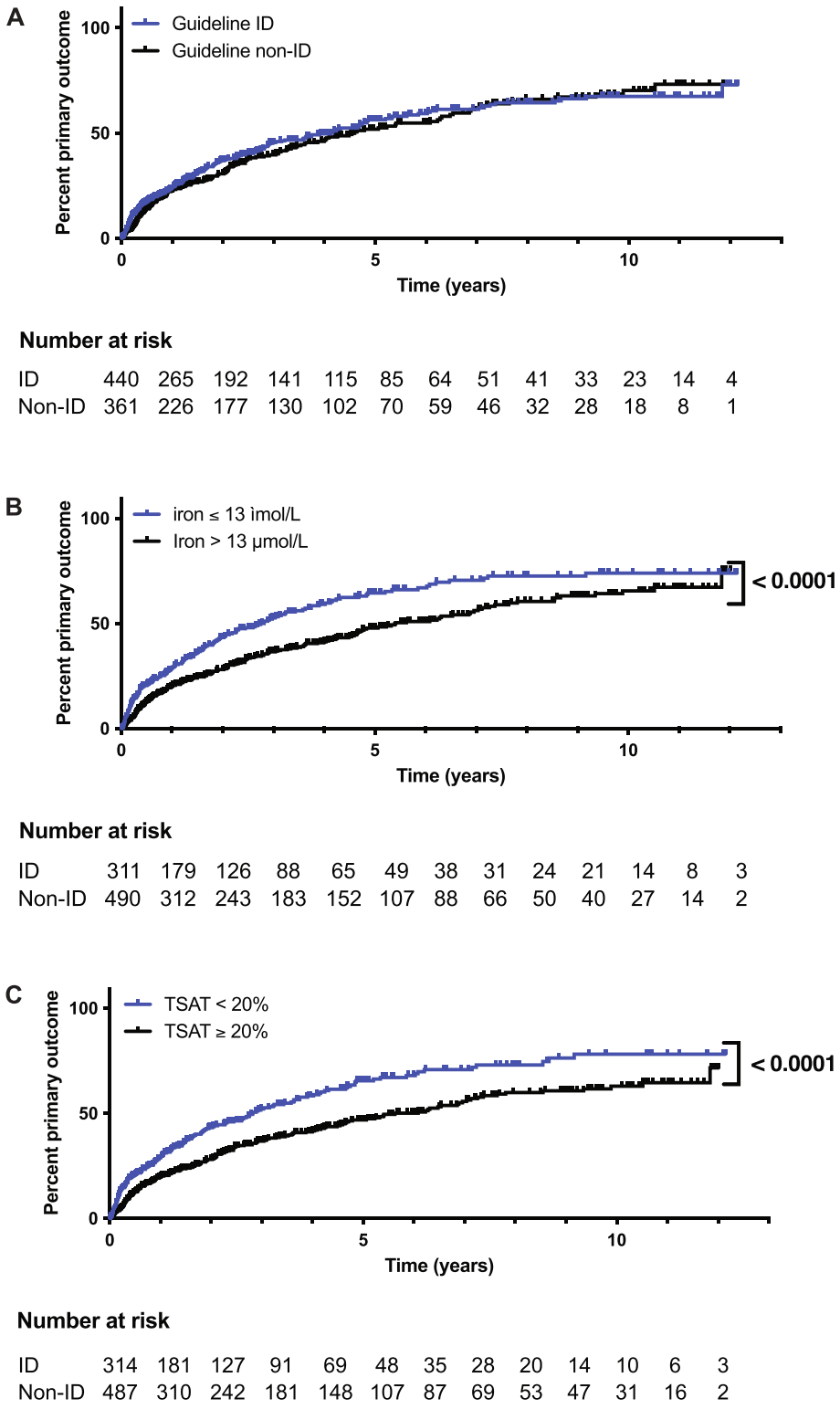


Figure 2 Inverse Kaplan–Meier curves for primary outcome all-cause mortality, urgent transplant or mechanical circulatory support. (*A*) Guideline definition of iron deficiency (ID); (B) iron ≤13 µmol/L definition; (C) transferrin saturation (TSAT) <20% definition. Number at risk in yearly intervals.

Table 2 Cox regression analysis for primary outcome

	Univariable model		Multivariable model[a]	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
Iron biomarkers				
Ln (serum iron), µmol/L	0.69 (0.57–0.85)	0.0003	0.76 (0.56–1.03)	0.0713
Ln (TSAT), %	0.66 (0.56–0.80)	<0.0001	0.73 (0.57–0.93)	0.0178
Ln (ferritin), ng/ml	1.05 (0.95–1.16)	0.3742	0.95 (0.82–1.10)	0.4897
ID definitions				
Iron ≤13 µmol/L	1.53 (1.25–1.89)	<0.0001	1.42 (1.05–1.91)	0.0223
TSAT <20%	1.60 (1.30–1.97)	<0.0001	1.38 (1.03–1.84)	0.0289
Guideline ID definition	1.09 (0.88–1.34)	0.4397	1.30 (0.97–1.73)	0.0743

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; ID, iron deficiency; Ln, natural logarithmic; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; TSAT, transferrin saturation.
[a]Multivariable model adjusted for age, sex, BMI, diabetes, smoking history, eGFR, haemoglobin, NT-proBNP, heart failure aetiology, LVEF, NYHA class III or IV, beta-blocker, ACEi, ARB, ARNI, and loop diuretic.

studies additionally suggested that intravenous iron replacement may reduce the rate of admission for HF and cardiovascular death.[4,18] It is therefore important to use an accurate biomarker of ID to correctly diagnose patients who may benefit most from iron supplementation. Although there is a 51% overlap in identifying ID by all three ID definitions, each one defines a unique subset of patients. Whilst the serum iron ≤13 µmol/L and the TSAT <20% definitions identify patient populations at particular high risk, the current guideline definition of ID describes a group of patients with mixed HRs for adverse outcomes. For example, patients with high ferritin (≥300 ng/ml), but low serum iron concentrations (≤13 µmol/L) or low TSAT (<20%), that is, those patients with a pro-inflammatory state, are at particular high risk of adverse outcomes in the current and previous studies[7] but are not captured by the guideline definition of ID. Vice versa, patients with low ferritin (<100 ng/ml) but high serum iron concentrations and high TSAT (≥20%) are defined as iron deficient by the guideline definition of ID but carry a relatively good prognosis. A pivotal study by Grote Beverborg and colleagues[6] suggests that an isolated low ferritin concentration, as found in our subgroup of 131 patients with favourable outcomes in the guideline ID group, has a poor diagnostic accuracy when compared to the gold standard of bone marrow biopsy, and a poor prognostic value when used on its own. Instead, similar to our present study, serum iron ≤13 µmol/L and TSAT ≤19.8% were found to have the best prognostic accuracy even when compared to the guideline definition of ID. Thus, an isolated low ferritin may identify patients that are not truly iron deficient, and therefore may not benefit from intravenous iron replacement.

Our study is not without limitations. Additional biomarkers of iron metabolism have been proposed, including hepcidin and soluble transferrin receptor.[19,20] In particular soluble transferrin receptor may be a promising candidate for the diagnosis of ID and to identify patients who could benefit from iron supplementation.[20] However, these newer biomarkers are not in routine clinical use at the moment and were not available in our patient population. Although many of the patients in this study were referred to us prior to the widespread use of intravenous iron as a treatment for HF, following the publication of the 2016 ESC HF guideline[10] a proportion of the ID population was treated with intravenous iron

Table 3 Correlation of iron deficiency with secondary outcomes

	Guideline definition			Serum iron definition			TSAT definition		
	ID	Non-ID	*p*-value	ID	Non-ID	*p*-value	ID	Non-ID	*p*-value
Exercise capacity (*n* = 757; missing 44 [5%]) and cardiopulmonary exercise testing (*n* = 693; missing 108 [13%])									
6MWD (m)	301.5 (104.1)	333.6 (110.7)	<0.0001	289.0 (106.0)	332.7 (106.4)	<0.0001	292.8 (106.6)	330.6 (106.9)	<0.0001
Peak VO_2 (ml/kg/min)	12.5 (10.0–15.0)	14.0 (11.0–17.4)	<0.0001	11.9 (9.5–14.5)	14.0 (11.2–17.0)	<0.0001	11.8 (9.5–14.0)	14.0 (11.6–17.1)	<0.0001
Peak VO_2 (%)	45 (35–55)	51 (41–61)	<0.0001	41 (33–52)	51 (41–61)	<0.0001	42 (33–52)	52 (41–61)	<0.0001
Echocardiography (*n* = 796; missing 5 [<1%])									
LVEF (%)	22 (17–32)	22.5 (17–32)	0.8594	21 (17–30)	23 (17.5–32.5)	0.0344	20 (17–31)	23 (17.5–32)	0.0185
LVIDD (mm)	62.13 (12.60)	63.20 (11.80)	0.2192	62.72 (12.37)	62.54 (12.18)	0.8362	62.24 (12.85)	62.85 (11.85)	0.4911
TAPSE (mm)	16 (13–19)	16 (14–19)	0.2896	16 (13–19)	16 (14–19)	0.0229	16 (12–19)	16 (14–20)	0.0043
Right heart catheterization (*n* = 790; missing 11 [1%])									
CI (TD) (L/m^2)	1.80 (1.50–2.20)	1.95 (1.60–2.20)	0.0008	1.74 (1.42–2.20)	1.90 (1.60–2.20)	0.0003	1.70 (1.60–2.23)	1.95 (2.23-)	<0.0001
CPI (TD) (W/m^2)	0.30 (0.25–0.39)	0.34 (0.28–0.41)	<0.0001	0.30 (0.24–0.38)	0.33 (0.27–0.41)	0.0004	0.29 (0.24–0.37)	0.34 (0.27–0.41)	<0.0001
RA mean pressure (mmHg)	11 (7–17)	8 (5–12)	<0.0001	12 (7–18)	8 (6–12)	<0.0001	13 (8–19)	8 (5–12)	<0.0001
PA mean pressure (mmHg)	31 (23–41)	26 (18–35)	<0.0001	33 (24–42)	27 (19–36)	<0.0001	34 (26–43)	26 (18–34)	<0.0001
PCWP mean pressure (mmHg)	23 (16–29)	18 (10–24)	<0.0001	23 (17–29)	18 (12–25)	<0.0001	24 (18–30)	18 (11–24)	<0.0001

6MWD, 6-min walk distance; CI, cardiac index; CPI, cardiac power index; ID, iron deficient; LVEF, left ventricular ejection fraction; LVIDD, left ventricular internal diameter in diastole; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; RA, right atrial; TAPSE, tricuspid annular plane systolic excursion; TD, thermo-dilution; TSAT, transferrin saturation; VO_2, oxygen consumption.

infusions, potentially reducing the effect size of the initial ID diagnosis on outcomes. Despite this, our analysis suggests that similar proportions of patients were treated with intravenous iron replacement in the three ID groups. In addition, dichotomized data comparing patients assessed before and after the introduction of the ESC guidelines did not show improvement in the primary outcome in the latter groups suggesting that the guideline recommendation of intravenous iron replacement did not cause significant bias in our study. Another limitation is that this study was conducted prior to the widespread use of SGLT2 inhibitors in HF which are known to interfere with iron homeostasis as well as ferritin concentrations and TSAT.[8]

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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