ESC European Society of Cardiology

European Journal of Heart Failure (2022) **24**, 807–817
doi:10.1002/ejhf.2251

RESEARCH ARTICLE

Natural history and prognostic significance of iron deficiency and anaemia in ambulatory patients with chronic heart failure

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Received 30 November 2020; revised 21 April 2021; accepted 25 May 2021; online publish-ahead-of-print 1 July 2021

Aims Iron deficiency (ID) and anaemia are common in heart failure; less is known about changes over time.

Methods and results We investigated prevalence, incidence and resolution of ID and anaemia in 906 patients with chronic heart failure (median age 73 (65–79) years, 70% men, 51% with heart failure with reduced ejection fraction) 1 year apart. ID was defined as serum iron ≤13 μmol/L and anaemia as haemoglobin <13.0 g/dL for men or <12.0 g/dL for women. FAIR-HF criteria for ID were also considered. At baseline, 10% had anaemia without ID, 23% had ID without anaemia, 20% had both, and 47% had neither. Percentages changed little over 1 year, but 157 (30%) patients had new-onset ID, 104 (16%) new-onset anaemia, whilst ID resolved in 173 (44%) and anaemia in 63 (23%). Compared to those who remained iron replete (iron >13 μmol/L), mortality was higher in those with persistent or incident ID at 1 year [hazard ratio (HR) 1.81 (1.23–2.67), and HR 1.40 (0.91–2.14), respectively] in multivariable models ($P = 0.02$). Compared to persistent ID, resolution of ID was associated with a lower mortality [HR 0.61 (0.44–0.86); $P = 0.004$]. Changes in ID defined by FAIR-HF criteria were not similarly associated with mortality. Anaemia was associated with a poor outcome even if it resolved.

Conclusions The prevalence and incidence of ID and anaemia are high in chronic heart failure but so is the rate of resolution. Persistent or incident ID, defined by a serum iron ≤13 μmol/L, is associated with higher mortality and resolution of ID with lower mortality.

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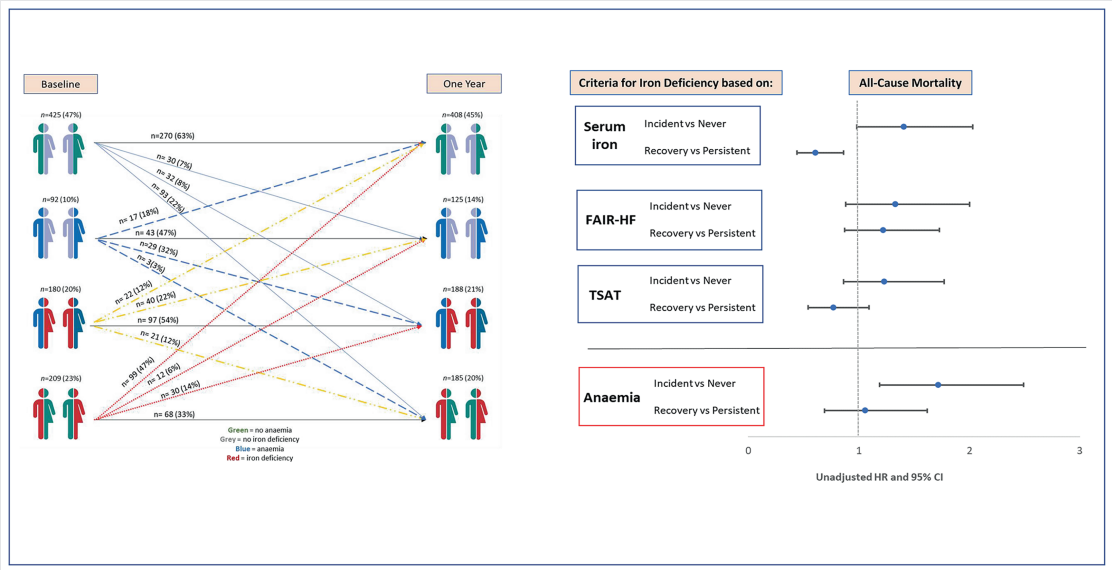
Graphical Abstract



Anaemia: Haemoglobin <13.0 g/dL (men), <12.0 g/dL (women); iron deficiency (ID): serum iron ≤13 μmol/L
Supplementary definitions of ID: ferritin <100 μg/L or TSAT <20% if ferritin 100-299 μg/L (FAIR-HF); TSAT <20%
Prevalence of ID was higher with the FAIR-HF definition but rates of incidence and recovery were similar regardless of how ID was defined.

Longitudinal data from 906 patients with chronic heart failure. Over 1 year most patients (70%) have or develop iron deficiency (ID), anaemia or both. Compared to those with either persistent ID or anaemia, only those who recovered from ID (achieving a serum iron >13 μmol/L) had lower all-cause mortality at 4 years, with transferrin saturation (TSAT) showing a similar trend. CI, confidence interval; HR, hazard ratio.

Keywords Iron deficiency • Anaemia • Heart failure • Natural history

Introduction

Anaemia is common in patients with chronic heart failure[1,2] and is often associated with iron deficiency (ID).[3–6] Both are thought to contribute to worsening symptoms and reduced exercise capacity,[7–9] and both are associated with an unfavourable prognosis.[2,3 9–11]

Several randomised trials have found that giving intravenous (IV) iron to patients with ID and chronic heart failure improves symptoms,[12,13] quality of life[13] and exercise capacity.[12,14] Meta-analyses suggest that IV iron might also improve prognosis.[15,16] These benefits may be independent of the presence of, or correction of, anaemia. Recent expert guidance suggests that haemoglobin and, perhaps, indices of ID should be checked once, or even twice a year in patients with heart failure and ongoing symptoms.[17] However, reports on the natural history of ID and anaemia in patients with heart failure that should inform these recommendations are scarce. Most research has focussed on prevalent anaemia and ID rather than their incidence or resolution. Additionally, disagreement exists on how ID should be defined in heart failure. Accordingly, we studied the natural history of anaemia and ID, according to various definitions, in a cohort of patients with chronic heart failure.

Methods

Study population

Between 2002 and 2014, consenting patients referred with suspected or confirmed heart failure from primary and secondary care physicians, were enrolled at a single clinic serving a local population of approximately 500 000 people (The Hull LifeLab). All patients enrolled gave written informed consent for their data to be stored electronically and used for research. Patients were reviewed by heart failure specialist nurses and doctors at regular intervals, usually at 4 and 12 months, and then annually, unless an appointment was requested sooner by the patient or a clinician. Information on demography, symptoms and signs, haematology and biochemistry profiles and electrocardiograms were systematically collected at each visit and recorded in a dedicated electronic health record which was stored on a secure server. Echocardiograms were performed routinely at baseline only. Patients were followed until 3 March 2019.

Heart failure was defined as typical symptoms and signs and either a measured or visually estimated left ventricular ejection fraction (LVEF) of <40% [heart failure with reduced ejection fraction (HFrEF)] or an elevated N-terminal pro brain natriuretic peptide (NT-proBNP; ≥125 ng/L) following the European Society of Cardiology (ESC) guidelines.[18] Those with an NT-proBNP ≥125 ng/L were further classified as those with an LVEF of 40–49% [heart failure mid-range ejection fraction (HFmrEF)] or ≥50% [heart failure with preserved ejection

Table 1 Definitions of iron deficiency and anaemia being investigated

	Iron deficiency			Anaemia
	FAIR-HF	Serum iron	TSAT	
Men	Ferritin <100 μg/L or TSAT <20% if ferritin 100–299 μg/L	≤13 μmol/L	<20%	Hb <13.0 g/dL
Women	Ferritin <100 μg/L or TSAT <20% if ferritin 100–299 μg/L	≤13 μmol/L	<20%	Hb <12.0 g/dL

Hb, haemoglobin; TSAT, transferrin saturation.

fraction (HFpEF)]. These simplified definitions were used as further echocardiographic data on structural or functional alterations were not always available. The clinic protocol indicated that all patients should have standard haematology and blood biochemistry checked, including NT-proBNP and iron indices, although this set of investigations was often incomplete. Only patients who had tests for ID and a haematology profile at baseline and 1 year were included in this analysis. Those treated with erythropoietin analogues or IV iron were excluded.

Anaemia was defined, using the World Health Organisation (WHO) criteria, as a haemoglobin of <12.0 g/dL in women and <13.0 g/dL in men.[19] Iron indices included: serum ferritin, serum iron, transferrin, and transferrin saturation (TSAT). As there are no universally accepted criteria for ID, we defined it as a serum iron ≤13 μmol/L, based on a study that used bone marrow iron depletion as a diagnostic 'gold-standard'.[20] However, we also considered other definitions of ID including the criteria employed in the FAIR-HF trial[13] and subsequently adopted by the ESC (ferritin <100 μg/L or TSAT <20% if ferritin 100–299 μg/L)[18] and by a TSAT of <20% alone (*Table 1*).

Patients were grouped at baseline according to the presence or absence of anaemia or ID, using the serum iron criterion. Those who had neither ID nor anaemia at baseline were grouped by whether they developed ID or anaemia, respectively. Those with ID or anaemia at baseline were grouped by whether ID and anaemia did or did not resolve. These groupings were repeated separately using the other definitions of ID described above.

Deaths were adjudicated based on medical records from primary and secondary care. Deaths in patients with advanced symptoms of heart failure (New York Heart Association class IV) or recurrent hospitalisations for heart failure were classified as due to heart failure unless another cause was clear (e.g. metastatic lung cancer). Deaths due to heart failure, myocardial infarction, stroke, or other major cardiovascular (CV) insult were grouped as CV deaths. Details on adjudication have been published.[21]

Statistical analysis

Continuous variables are presented using median, 25th and 75th percentiles and compared using one-way ANOVA if normally distributed or a Kruskal–Wallis test if not. Categorical variables are presented as numbers and percentages and compared using χ^2 tests. Non-normally distributed variables were transformed using either logarithms with base 10, or the square root as appropriate. No imputation was performed for missing data. Univariable and multivariable logistic regression analysis was used to identify predictors of incident ID at 1 year in those without ID at baseline, regardless of the presence of anaemia, and incident anaemia at 1 year, in those without anaemia at baseline, regardless of the presence of ID. Variables associated with outcome at the 10% significance level ($P \leq 0.1$) from the univariable models and/or clinically relevant variables (e.g. sex), were entered into multivariable models. Odds ratios (ORs), corresponding 95% confidence intervals (CI) and *P*-values are reported.

Kaplan–Meier curves for all-cause and CV mortality within 5 years of the baseline visit were constructed for patients grouped by change in ID or anaemia status between baseline and 1 year. Differences between groups were evaluated using the log-rank test. Univariable and multivariable Cox proportional hazards regression models were used to assess the association between ID and anaemia groups and mortality within 5 years of the baseline visit. Those who never developed ID or anaemia respectively were used as the reference group. Further exploratory analysis compared risk of death within 5 years between those whose ID resolved against those who remained iron deficient at 1 year for each definition of ID. Separate multivariable models were produced using baseline and updated (1 year) haematinic values, respectively. An enter method was applied for prognostic multivariable models. Hazard ratios (HRs) with 95% CI are reported. All analyses were performed with SPSS statistical software, version 26 (IBM Corp., Armonk, NY, USA). All tests were 2 sided and unless previously specified, used the 5% level to determine statistical significance.

Results

A complete set of blood tests was available at both baseline and follow-up for 906 (33%) of 2763 patients with confirmed heart failure who survived 12 months (online supplementary *Figure S1*). Those without available follow-up tests, and therefore not included in the analysis, were more likely to have HFmrEF or HFpEF (74%), be women (42%) and had lower plasma NT-proBNP [818 (312–1937) ng/L] (online supplementary *Table S1*).

Natural history of iron deficiency and anaemia and incident disease

Overall, the proportion of patients with anaemia and ID, whether defined by serum iron or FAIR-HF criteria, changed little over 1 year (*Figure 1* and online supplementary *Table S2*) but this concealed underlying dynamic changes in incidence and recovery: 428 (47%) patients changed their classification (*Figure 2* and *Graphical Abstract*). Only 270 patients (30%) had neither anaemia nor ID, defined as a serum iron ≤13 μmol/L, measured 1 year apart. At either baseline or 1 year, 546 (60%) had ID and 376 (42%) had anaemia. Of individuals with a serum iron >13 μmol/L who were not anaemic at baseline ($n = 425$), 22% developed ID alone, 8% ID and anaemia, and 7% anaemia only.

Patients whose serum iron was >13 μmol/L on both occasions were younger, more likely to be men, were less likely to have diabetes, had higher haemoglobin and estimated glomerular filtration rate (eGFR), lower NT-proBNP and were less likely to receive iron supplements (*Table 2*).

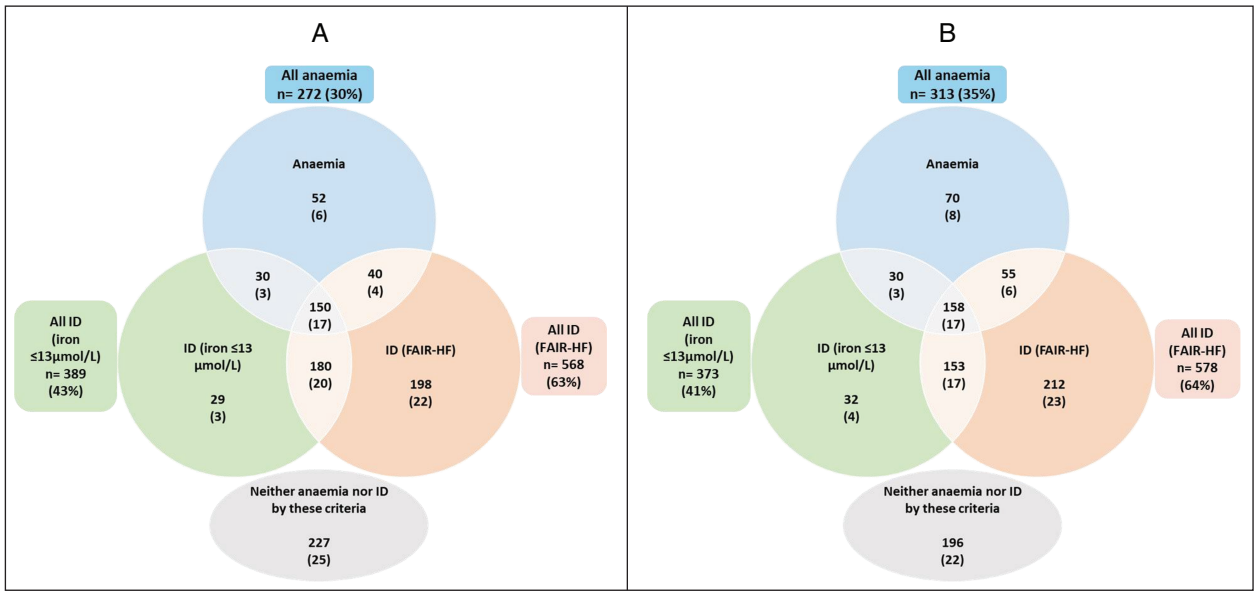


Figure 1 Venn diagrams demonstrating the distribution of iron deficiency (ID) (by both a serum iron ≤13 μmol/L and the FAIR-HF definition: ferritin <100 μg/L or transferrin saturation <20% if ferritin 100–299 μg/L) and anaemia at baseline (*A*) and 1-year follow-up visit (*B*). Presented as number and (%).

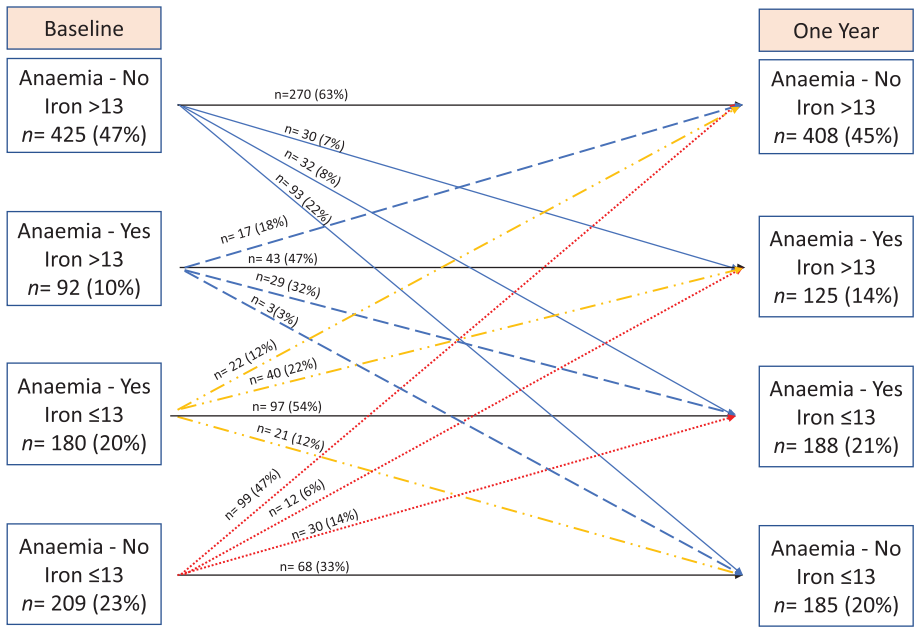


Figure 2 Classification of patients according to iron deficiency (serum iron ≤13 μmol/L) and anaemia (World Health Organisation definition: haemoglobin <13.0 g/dL in men and <12.0 g/dL in women) status at baseline and 1-year follow-up. Number and (%) on each line represent the count and (%) of patients moving between groups from baseline to follow-up.

Table 2 Characteristics at baseline of patients according to change in iron deficiency status (serum iron ≤13 μmol/L) between baseline and 1 year

Variable	Persists (*n* = 216; 24%)	Develops (*n* = 157; 17%)	Resolves (*n* = 173; 19%)	Never (*n* = 360; 40%)	*P*-value
Demographics					
Age (years)	76 (68–82)	73 (66–78)	74 (65–80)	71 (63–78)	0.004
Male sex	135 (63)	105 (67)	118 (68)	275 (76)	0.003
BMI (kg/m^2)	28 (25–33)	29 (25–32)	28 (26–32)	28 (25–32)	0.79*
IHD	137 (63)	92 (59)	98 (57)	209 (58)	0.52
Hypertension	120 (56)	90 (57)	80 (46)	178 (49)	0.11
Diabetes	73 (34)	40 (26)	49 (28)	68 (19)	0.001
NYHA class (III or IV)	91 (42)	51 (33)	63 (36)	87 (24)	<0.001
Blood results					
Haemoglobin (g/dL)	12.4 (11.3–13.4)	13.6 (12.6–14.6)	13.0 (11.9–14.0)	14.2 (13.3–15.3)	<0.001*
Iron (μmol/L)	10 (8–12)	17 (15–19)	11 (9–12)	19 (16–22)	NA
Ferritin (μg/L)	77 (39–136)	157 (64–188)	82 (41–142)	113 (62–203)	<0.001
TSAT (%)	16 (12–18)	26 (23–31)	16 (13–19)	29 (24–35)	<0.001
eGFR (mL/min/1.73 m^2)	53 (39–69)	61 (47–75)	63 (46–75)	65 (50–79)	<0.001*
NT-proBNP (ng/L) – all	1674 (662–3555)	1309 (517–2768)	1746 (498–3078)	926 (465–1886)	<0.001
NT-proBNP (ng/L) – SR	1402 (523–3292)	1060 (342–2769)	1095 (365–2770)	756 (372–1427)	<0.001
ECG and echo					
AF or flutter	56 (26)	41 (26)	53 (31)	102 (29)	0.72
Heart rate (bpm)	75 (63–85)	68 (59–81)	74 (62–89)	70 (61–81)	0.003
HFrEF	95 (44)	82 (52)	100 (58)	185 (51)	0.06
Treatment at baseline					
Loop diuretic	154 (72)	113 (72)	122 (71)	226 (63)	0.04
ACEi or ARB	162 (76)	135 (87)	134 (78)	293 (82)	0.06
MRA	38 (18)	54 (35)	43 (25)	120 (33)	<0.001
BB	116 (55)	113 (72)	109 (63)	263 (73)	<0.001
Anticoagulant	46 (21)	51 (33)	42 (24)	102 (28)	0.07
Antiplatelet	116 (64)	80 (51)	102 (59)	179 (50)	0.23
Oral iron treatment	21 (10)	8 (5)	6 (4)	7 (2)	<0.001

Values are expressed as count (%), or median (Q1–Q3) as appropriate.
ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BB, beta-blocker; BMI, body mass index; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; IHD, ischaemic heart disease; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro brain natriuretic peptide; NYHA, New York Heart Association; SR, sinus rhythm.
Iron deficiency defined as serum iron ≤13 μmol/L.
P-values provided from Chi-square tests for categorical variables and Kruskal–Wallis tests for non-normally distributed continuous variables, unless indicated by(*) in which case one-way ANOVA test has been used.

Of 517 patients who were iron replete at baseline, serum iron had dropped to ≤13 μmol/L in 157 (30%) at 1 year (*Figure 2*). The rate of incident ID did not differ between those with HFrEF (31%), HFmrEF (30%) or HFpEF (32%) ($P = 0.84$). The median (Q1, Q3) change in serum iron for those who developed ID was −5.0 (−8.5; −3.0) μmol/L (online supplementary *Table S3*); only eight (5%) patients received oral iron supplements. In univariable analysis, the baseline variables most strongly associated with incident ID were lower haemoglobin [OR (95% CI) 0.79 (0.70–0.90); $P < 0.001$] and serum iron [0.39 (0.25–0.60); $P < 0.001$] with weaker associations for higher plasma NT-proBNP [1.66 (1.07–2.56); $P = 0.02$] or high-sensitivity C-reactive protein (hsCRP) [1.73 (1.15–2.61); $P = 0.01$] (online supplementary *Table S4*). In multivariable analyses, only lower serum iron [0.55 (0.33–0.89); $P = 0.02$], or lower haemoglobin [0.83 (0.72–0.97); $P = 0.02$] and higher hsCRP [1.75 (1.10–2.78); $P = 0.02$] were significantly associated with incident ID.

Iron deficiency, defined as a serum iron ≤13 μmol/L, resolved in 173 (44%) of 389 patients who had ID at baseline, only 6 (4%) of whom received oral iron. Resolution of ID was more likely in the absence of anaemia at baseline (*Figure 2*). The median change of serum iron in those whose ID resolved by the serum iron criterion was +6.0 (+4.0; +9.0) μmol/L, for TSAT was +9.0 (+6.1; +14.1)% and for ferritin was +12 (−16; +59) μg/L (online supplementary *Table S3*).

Similar patterns of prevalence, development and resolution of ID were observed when applying TSAT <20% as the definition of ID (online supplementary *Figure S2A*). Applying the FAIR-HF criteria for ID, only 338 patients (37%) were iron replete at baseline and 38% of these developed ID at 1 year (online supplementary *Figure S2B*). Of those with ID at baseline ($n = 568$), 81% of whom had a serum ferritin <100 μg/L, ID resolved in only 117 (21%) by FAIR-HF criteria. Persistent ID was substantially higher by FAIR-HF criteria (50%) compared to serum iron ≤13 μmol/L

Table 3 Characteristics at baseline of patients according to change in anaemia status between baseline and 1 year

Variable	Persists (*n* = 209; 23%)	Develops (*n* = 104; 12%)	Resolves (*n* = 63; 7%)	Never (*n* = 530; 58%)	*P*-value
Demographics					
Age (years)	76 (70–82)	77 (70–82)	73 (69–79)	71 (61–78)	<0.001
Male sex	155 (74)	66 (64)	44 (70)	368 (69)	0.27
BMI (kg/m^2)	27 (24–31)	28 (25–31)	27 (24–32)	29 (25–33)	0.014*
IHD	128 (61)	69 (66)	36 (57)	303 (57)	0.31
Hypertension	109 (52)	54 (52)	26 (41)	279 (53)	0.40
Diabetes	67 (32)	28 (27)	20 (32)	115 (22)	0.02
NYHA class (III or IV)	77 (37)	35 (34)	31 (49)	149 (28)	0.002
Blood results					
Haemoglobin (g/dL)	11.5 (10.8–12.1)	13.4 (12.7–13.9)	11.9 (11.3–12.5)	14.2 (13.5–15.2)	NA
Iron (μmol/L)	12 (9–15)	15 (12–19)	12 (8–15)	16 (12–20)	<0.001
Ferritin (g/L)	90 (46–176)	111 (57–172)	85 (35–179)	100 (53–176)	0.26
TSAT (%)	19 (14–24)	23 (17–29)	17 (11–24)	24 (18–31)	<0.001
eGFR (mL/min/1.73 m^2)	49 (35–64)	58 (43–70)	58 (38–72)	66 (54–80)	<0.001*
NT-proBNP (ng/L) – all	1903 (745–3937)	1666 (710–2867)	2132 (729–4080)	1014 (413–2047)	<0.001
NT-proBNP (ng/L) – SR	1496 (632–3472)	1454 (604–3040)	1192 (464–3559)	656 (310–1663)	<0.001
ECG and echo					
AF or flutter	45 (22)	25 (26)	18 (29)	164 (31)	0.08
Heart rate (bpm)	70 (60–83)	68 (59–80)	73 (59–92)	72 (62–84)	0.04
HFrEF	101 (48)	56 (54)	37 (59)	268 (51)	0.48
Treatment at baseline					
Loop diuretic	162 (78)	84 (81)	45 (73)	324 (62)	<0.001
ACEi or ARB	161 (78)	86 (83)	48 (77)	429 (81)	0.59
MRA	62 (30)	30 (29)	20 (32)	143 (27)	0.77
BB	129 (62)	65 (63)	41 (66)	366 (69)	0.22
Anticoagulant	44 (21)	25 (24)	14 (22)	158 (30)	0.07
Antiplatelet	123 (59)	53 (51)	36 (57)	265 (50)	0.15
Oral iron treatment	22 (11)	7 (7)	4 (6)	9 (2)	<0.001

Values are expressed as count (%), or median (Q1–Q3) as appropriate.
ACEi, angiotensin-converting enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; BB, beta-blocker; BMI, body mass index; ECG, electrocardiogram; eGFR, estimated glomerular filtration rate; HFrEF, heart failure with reduced ejection fraction; IHD, ischaemic heart disease; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro brain natriuretic peptide; NYHA, New York Heart Association; SR, sinus rhythm.
Anaemia defined as haemoglobin <12.0 g/dL (women) or <13.0 g/dL (men).
P-values provided from Chi-square tests for categorical variables and Kruskal–Wallis tests for non-normally distributed continuous variables, unless indicated by (*) in which case one-way ANOVA test has been used.

(24%) (online supplementary *Table S2*). Baseline characteristics by category of ID (persistent, incident, resolved or never) and predictors of incident ID according to the FAIR-HF criteria are presented in online supplementary *Tables S5 and S6*.

Patients who were not anaemic on either occasion were younger, had a higher body mass index (BMI) but were less likely to have diabetes, had higher serum iron and eGFR and lower NT-proBNP. They were less likely to be treated with loop diuretics or oral iron (*Table 3*). Of 634 patients who were not anaemic at baseline, 104 (16%) developed anaemia at 1 year (*Figure 2*). The rate of incident anaemia did not differ for patients with HFrEF (17%), HFmrEF (17%) and HFpEF (15%) ($P = 0.81$). The median change in haemoglobin from baseline in those who developed anaemia was −1.5 (−0.9; −2.0) g/dL; seven (7%) patients received oral iron supplements. On univariable analysis, the baseline variables most strongly associated with incident anaemia were increasing age [1.87 (1.48–2.38); $P < 0.001$] and plasma NT-proBNP [2.37 (1.46–3.84); $P < 0.001$], lower eGFR [0.98 (0.97–0.99); $P < 0.001$] and haemoglobin [0.41 (0.32–0.52); $P < 0.001$] and treatment with loop diuretics [2.63 (1.57–4.42); $P < 0.001$]; indices of ID at baseline were only weakly associated with incident anaemia (online supplementary *Table S7*). On multivariable analyses, increasing age [1.67 (1.23–2.28); $P = 0.001$] and lower haemoglobin [0.26 (0.17–0.41); $P < 0.001$] were strongly associated with the risk of incident anaemia. Even when haemoglobin was excluded from the model, iron indices measured at baseline were not associated with incident anaemia.

Anaemia resolved in 63 (23%) of 272 patients with anaemia at baseline. Of those in whom anaemia resolved, 43 (68%) had ID at baseline which persisted in 21 (49%) by 1 year (*Figure 2*). The median change in haemoglobin in those whose anaemia resolved was +1.7 (+1.0; +2.6) g/dL. Only four patients received oral iron supplements.

In general, prescriptions of evidence-based heart failure therapies increased across all patient groups over the course of 1 year, with corresponding improvements in symptoms and plasma NT-proBNP concentrations (online supplementary *Tables S8 and S9*).

Survival

Within 5 years, 274 (30%) patients had died: 58% from CV causes, 39% from non-CV causes and 3% from uncertain causes.

Iron deficiency

In univariable analysis, higher serum iron measured at 1 year was associated with a better subsequent survival, both for all-cause [HR (95% CI) 0.69 (0.58–0.83); $P < 0.001$] and CV mortality [0.68 (0.53–0.85); $P = 0.001$] but not in multivariable models (online supplementary *Tables S10* and *S11*). Analysis by category of ID (persistent, incident, resolved or never), unadjusted for other variables, found significant differences in all-cause mortality ($P < 0.001$). Compared to those who never had ID, patients with persistent ID had the highest all-cause mortality [2.37 (1.76–3.20); $P < 0.001$) (*Figure 3A*).

After adjusting for age, sex, diabetes, ischaemic heart disease, NYHA class, BMI, atrial fibrillation/flutter, heart rate, systolic blood pressure, left ventricular phenotype, NT-proBNP, hsCRP, eGFR, baseline haemoglobin and therapy with loop diuretics, differences persisted in mortality related to ID ($P = 0.02$) (*Figure 3A*). Compared to those who never had ID, those with persistent ID had the greatest risk of death [1.81 (1.23–2.67); $P = 0.003$]. There was a similar pattern for CV mortality in both unadjusted and adjusted models (online supplementary *Figure S3*). Regardless of baseline values, patients who had a serum iron >17 μmol/L at 1 year had a better prognosis than those who had a value <10 μmol/L (*Figure 4A*, online supplementary *Figure S4*).

Serum ferritin measured at 1 year was not associated with mortality on univariable or multivariable analyses but an increase in serum ferritin between baseline and 1 year was associated with a higher all-cause mortality [1.01 (1.00–1.03); $P = 0.04$] (online supplementary *Table S10*). When the FAIR-HF criteria were used to classify patients, mortality was similar for patients who had persistent, incident or resolved ID compared to those that never had ID in both unadjusted and adjusted models (online supplementary *Figure S5*).

A higher TSAT at 1 year was associated with a lower subsequent all-cause [0.98 (0.97–0.99); $P = 0.02$] and CV mortality [0.98 (0.96–0.99); $P = 0.03$] in univariable analysis but not in multivariable models. The association between the absence, persistence, development, or resolution of ID defined by a TSAT <20% and all-cause and CV mortality was similar to that for ID defined as a serum iron ≤13 μmol/L (online supplementary *Figure S6*), although these relationships were no longer statistically significant after adjustment.

Compared to patients with persistent ID, resolution of ID according to the serum iron criterion was associated with better survival [0.61 (0.44–0.86); $P = 0.004$] (*Graphical Abstract*). In contrast, resolution of ID defined by either of the other two criteria was not associated with a better prognosis (online supplementary *Table S12* and *Figure S7*).

Anaemia

Higher haemoglobin measured at 1 year was associated with lower all-cause [0.82 (0.77–0.89); $P < 0.001$] and CV mortality [0.81 (0.73–0.89); $P < 0.001$] in univariable analysis, but not in multivariable models (online supplementary *Tables S10* and *S11*).

In univariable models, analysis by category of anaemia (persistent, incident, resolved, or never), unadjusted for other variables, found significant differences in all-cause mortality ($P < 0.001$). Anaemia at baseline, regardless of whether it persisted [2.32 (1.77–3.06); $P < 0.001$] or resolved [2.47 (1.65–3.71); $P < 0.001$], was associated with higher all-cause mortality compared to those who were neither anaemic at baseline nor follow-up (*Figure 3B*). New-onset anaemia was associated with an intermediate outcome [1.72 (1.19–2.49); $P = 0.004$], but mortality was higher for those whose anaemia was more severe at follow-up (*Figure 4B*). Adjusting for the 15 baseline variables specified above, but with baseline iron and ferritin rather than haemoglobin in the model, similar trends were observed but statistical significance was lost. There was a similar pattern for CV mortality in both unadjusted and adjusted models (online supplementary *Figure S3B*). Patients who were neither anaemic at baseline nor follow-up had the best survival (*Figure 4B*). The survival of individual men and women according to haemoglobin at baseline and 1 year are shown in online supplementary *Figure S8*.

Discussion

This is the first analysis, to our knowledge, to provide a comprehensive report of the natural history of ID and anaemia in patients with heart failure representative of clinical practice. The picture is highly dynamic. Most patients with heart failure (70%) have or develop ID, anaemia, or both, with 47% changing their status within 1 year. There was little difference according to left ventricular phenotype (HFrEF, HFmrEF or HFpEF). The rate of new-onset anaemia (16%) and incident ID (30%) were both individually substantial. Current ESC and American College of Cardiology/American Heart Association guidelines give no indication as to how frequently iron indices or haemoglobin should be checked,[18,22] but, in keeping with more recent expert advice,[17] our study suggests that it would be prudent to re-check haemoglobin and markers of ID at least once a year.

We chose to define ID as a serum iron ≤13 μmol/L based on a recent study of patients with HFrEF, which reported a strong relationship between low serum iron and the absence of iron on bone-marrow histology ($n = 42$) and with mortality,[20] whilst a low ferritin, in the absence of a low serum iron, was associated with neither. In our analysis, the prevalence of ID (defined as a serum iron ≤13 μmol/L) at baseline (43%) was similar to previous reports despite differences in the criteria for ID.[5,20] Persistent ID was associated with a poor prognosis and resolution of ID, based on serum iron measurements, was associated with an improved survival. In contrast, patients who had anaemia at any time, even if it resolved, had a worse long-term outcome, perhaps because they were more likely to also have ID or because anaemia indicates other underlying risk, including worse renal function and more severe heart failure.

The current ESC guideline-recommended definition of ID, based on the inclusion criteria of the FAIR-HF trial,[13] has not been

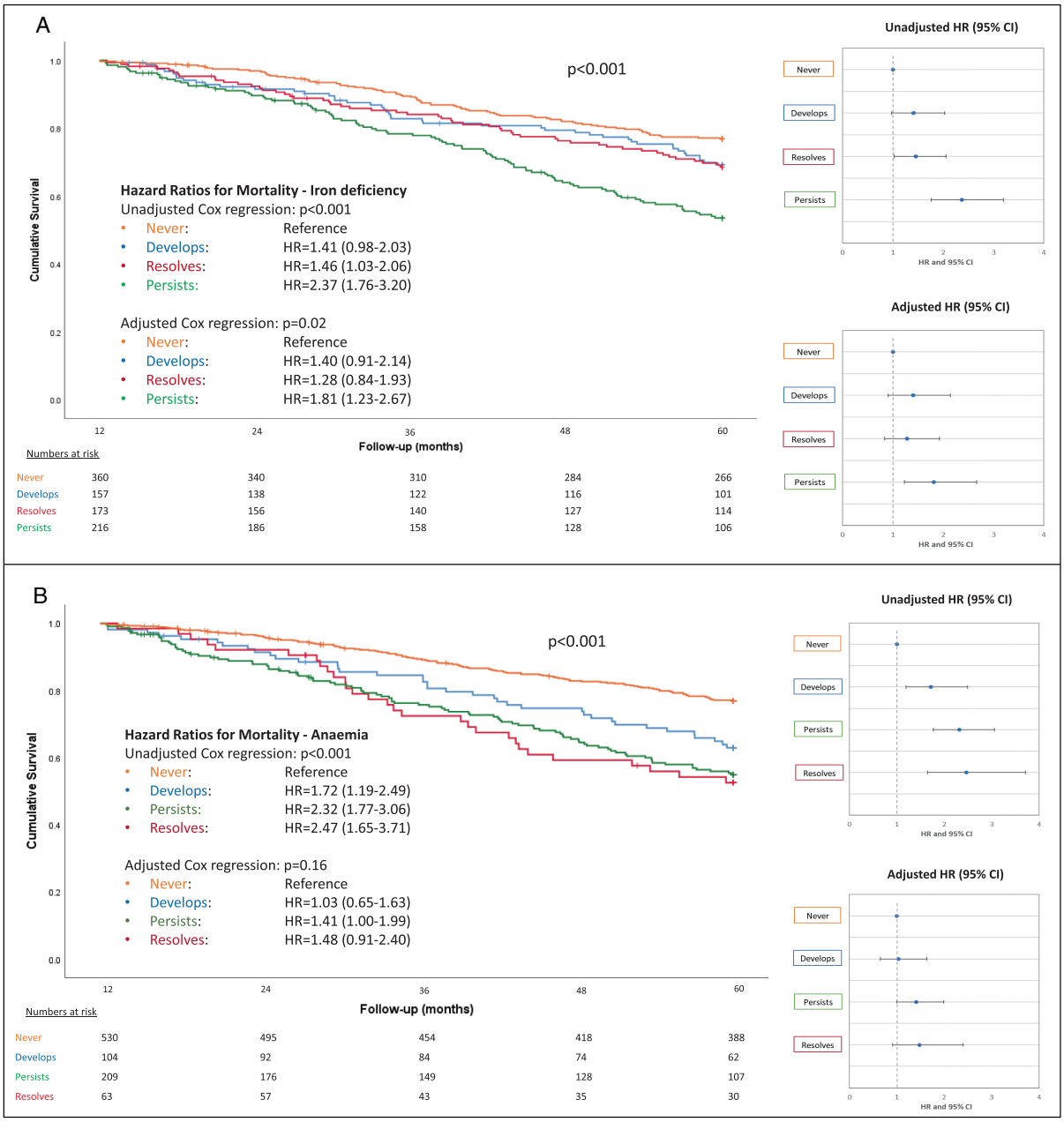


Figure 3 Kaplan–Meir survival analysis of all-cause mortality 5 years from baseline visit according to whether iron deficiency (serum iron ≤13 μmol/L) (*A*) or anaemia (World Health Organisation definition) (*B*) was never present at either baseline or 1 year, or whether either developed, resolved, or persisted at 1 year. Never developing iron deficiency or anaemia respectively used as the reference. Differences between changes in status compared using the log-rank test. Unadjusted and adjusted hazard ratios (HR) with 95% confidence intervals (CI) also reported. Models adjusted for age, sex, diabetes, ischaemic heart disease, New York Heart Association class, body mass index, atrial fibrillation/flutter, heart rate, systolic blood pressure, left ventricular phenotype, log 10 N-terminal pro brain natriuretic peptide, log 10 high-sensitivity C-reactive protein, estimated glomerular filtration rate, therapy with loop diuretics and baseline haemoglobin (*A*) or baseline sq root iron and log 10 ferritin (*B*). Forest plots of HRs with 95% CI for each group in unadjusted and adjusted models also presented.

universally accepted, nor validated against the gold standard of bone-marrow histology. When applying the ESC (or the FAIR-HF) definition to our cohort, the prevalence of ID was 63% but it was not associated with a higher mortality, nor was it associated with an improved survival when it resolved. Data previously published from the Hull LifeLab reported that serum iron and TSAT are highly correlated ($r > 0.9$), with strong, linear associations between lower levels and worse outcome. In contrast, the relation between ferritin

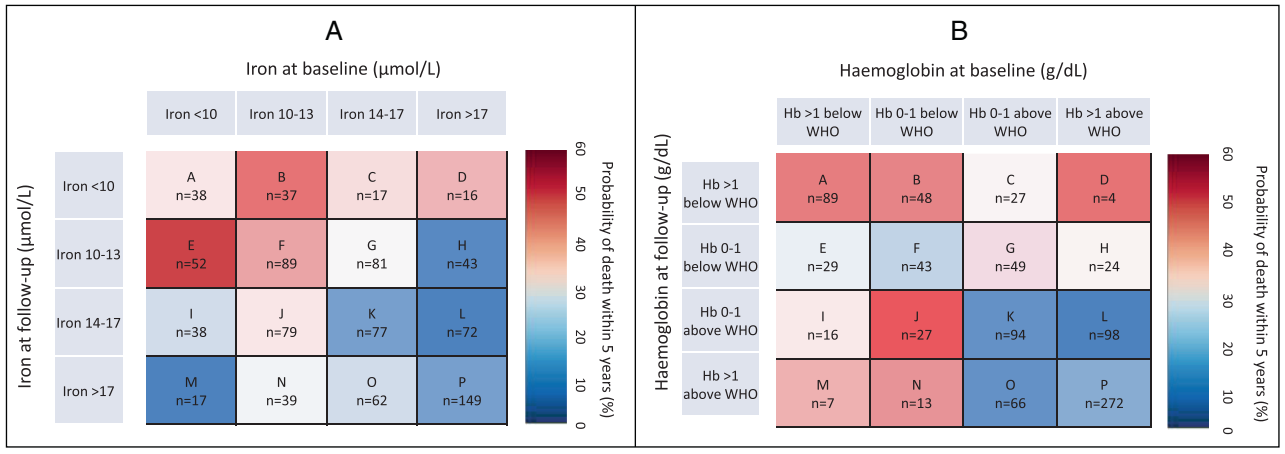


Figure 4 Heat maps depicting survival 5 years from baseline classified by baseline and 1-year follow-up measurements of (*A*) serum iron (μmol/L) and (*B*) haemoglobin (g/dL). Number of patients within each cell reported. WHO, World Health Organisation definition of anaemia: haemoglobin <13.0 g/dL in men and <12.0 g/dL in women.

and mortality was non-linear and weaker in both the Hull LifeLab and other cohorts.[6,11,23]

Serum ferritin concentrations increase as a result of inflammation and cell damage, including that associated with heart failure.[24,25] The WHO requires a ferritin <15 μg/L to diagnose ID and many clinical laboratories define it as <30 μg/L.[26] The FAIR-HF criteria for ID may have been successful not because it is either sensitive or specific but because ID is so common in patients with heart failure that testing for ID might not be required in order to achieve a positive result. However, an individual patient-data meta-analysis of trials of ferric carboxymaltose compared the effect of IV iron on outcome according to terciles of haemoglobin, ferritin and TSAT. Lower values of TSAT (which are highly correlated with serum iron) but not lower values of ferritin were associated with greater benefit from IV iron.[15] Serum iron is a measure of the total amount of transferrin-bound iron in blood serum. Although there are reports of diurnal variation of measured values within healthy populations due to post-prandial surges,[27] serum concentrations appear to be fairly stable in heart failure,[20] perhaps because iron absorption is impaired.[28] Despite the high correlation between serum iron and TSAT, a low serum iron may have performed better than either the FAIR-HF criteria or TSAT in prognostic models because serum iron might represent a summary-measure of ID and inflammation, which both cause a fall in serum iron.[29] Transferrin concentrations may decrease with chronic disease.[30] Because TSAT is calculated from transferrin and serum iron [(iron/transferrin × 25.2) × 100)], a decline in transferrin may attenuate the decline in TSAT as ID develops.

Predictors of incident ID at 1 year included, as might be expected, a lower serum iron or haemoglobin, reflecting borderline iron repletion. A higher hsCRP was also associated with incident ID. Heart failure and many of its comorbid conditions are associated with chronic low-grade inflammation which may increase hepatic secretion of hepcidin.[31] Hepcidin binds to and inactivates ferroportin, which is involved both in the translocation of iron from the gut epithelium to the circulation and in iron release from macrophages, thus reducing iron absorption and availability.[32]

In our analysis, changes in TSAT amongst patients whose ID resolved were of similar magnitude to those observed in the treatment arms (IV ferric carboxymaltose) of the FAIR-HF[13] and CONFIRM-HF[14] trials. In our cohort, few patients were prescribed oral iron therapy at baseline (n = 42; 5%). This suggests that many patients improve iron absorption following optimisation of treatment for heart failure. How iron stores are replenished may be of fundamental importance to clinical outcomes. Short-term randomised trials favour intravenous[13,14] rather than oral iron[28] in patients with heart failure. In health, the body contains about 4000 mg of iron, with about 1800 mg in red blood cells, 300 mg in muscle and other tissues and 2000 mg stored in the bone marrow, liver and reticulo-endothelial system.[33] Clinical ID will occur only once stores are exhausted or unavailable. In an otherwise healthy person with ID, the maximum absorption of iron is about 20 mg/day.[34] Assuming no iron losses and adequate iron ingestion, it would take 3–4 months to correct ID fully. For a patient with heart failure, absorption will be lower, and losses may be greater and therefore oral supplements may be ineffective. However, once ID is corrected, good treatment of heart failure, with or without oral supplements, may reduce the need for further IV iron.

Prevalent ID and anaemia are both associated with a worse mortality in patients with heart failure.[3,9] Similar trends were observed for incident ID or anaemia. Some patients required only a small change in values in order to be classified as incident cases. The lesser severity of ID and anaemia and greater chance of later resolution may account for the weaker relationship with outcome of incident compared to prevalent ID or anaemia. Also, some patients may have developed ID or anaemia between these visits and died before 1 year.

Resolution of ID was associated with a lower mortality, but resolution of anaemia was not. In contrast to our findings, a retrospective cohort study (n = 1393) reported better survival for those whose anaemia resolved.[1] Differences may reflect the play of chance, variations in the population studied, covariates used for statistical modelling or frequent relapse after recovery. Patients with resolution of anaemia still had a lower haemoglobin at 1 year than those who never had anaemia, suggesting only partial recovery. A high prevalence of persistent ID in patients whose anaemia had recovered compared to those who had a normal haemoglobin throughout, might also explain their poor outcome. Changes in haemoglobin concentration could also reflect changes in plasma volume or red cell mass or perhaps splenic sequestration and thus the severity of heart failure rather than ID. Additionally, despite increasing haemoglobin concentrations, treatment of anaemia with erythropoietin analogues does not seem to improve prognosis.[35]

Several trials are exploring whether IV iron in those with ID, defined by the FAIR-HF diagnostic criteria, improves morbidity and mortality in patients with HFrEF or, for HFpEF, symptoms and exercise capacity.[36] The recently reported AFFIRM-AHF trial failed to demonstrate a reduction in CV mortality with IV iron in patients admitted with worsening heart failure, an LVEF <50% and ID defined by the FAIR-HF criteria.[37] Intravenous iron was, however, associated with a lower rate of first and recurrent hospitalisations for heart failure. No significant differences were reported in subgroup analysis for those with a ferritin above or below 100 μg/L, those with a TSAT above or below 20% or for those with a haemoglobin above or below 12.0 g/dL. No subgroup analysis based on serum iron concentrations was reported. Given our results, exploring the effects of IV iron in subgroups with and without a low serum iron or TSAT and in those with and without anaemia will be of particular interest in future trials.

Limitations

This is an analysis of a clinical service. Only 906 of 2763 patients with a follow-up visit at 1 year had a full set of measurements at both time-points. The main reason for a lack of repeat measurements was deviation from the clinic protocol, which may have been more likely in those who were clinically stable. Patients were recruited over a period of 18 years, during which time treatments for heart failure have evolved. However, other than IV iron, none has been shown to have a substantial influence on haemoglobin or iron status. Patients prescribed oral iron (<5% of the population studied) were not excluded as this reflects common clinical practice. Most of the enrolment to the study and follow-up was done before guidelines recommended IV iron for treating symptoms in patients with HFrEF and ID (class IIa, level A) in 2016. No data on blood loss or blood transfusion were available and we did not implement a 'minimum-change' rule to define resolution of anaemia or ID (e.g. requirement for haemoglobin to change by at least 0.5 g/dL to allow reclassification), as implemented by Tang *et al.*[1] This might have ensured a more definitive change in status and avoided patients being reclassified when close to classification thresholds. However, such a criterion might be difficult to implement in clinical practice. Some curves on Kaplan–Meier analysis cross each other suggesting that risk in these groups may not be proportional over time. Yet the only sub-group that is of any concern is also the smallest in number which is likely to have an influence.

Conclusions

Most patients with heart failure have or will develop ID and a substantial proportion of these will also have anaemia. Patients with persistent ID have a worse outcome compared to those in whom it resolves but resolution of anaemia is not associated with a lower mortality compared to those in whom it persists. Serum iron ≤13 μmol/L is more strongly associated with prognosis than ID defined by the FAIR-HF criteria.

Supplementary Information

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

Conflict of interest: F.J.G. reports receipt of sponsorship from Vifor to attend an international meeting. J.G.F.C reports receipt of personal honoraria for lectures and advisory boards from Pharmacosmos and Vifor, and from AstraZeneca, Amgen, Bayer, Novartis and Servier. The University of Glasgow has received research grants from Pharmacosmos and Vifor. P.P. and J.G.F.C. are supported by the British Heart Foundation Centre of Research Excellence (RE/18/6134217). All other authors have nothing to disclose.

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