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Prevalence and Outcomes of Anemia and Hematinic Deficiencies in Patients With Chronic Heart Failure

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IMPORTANCE Detailed information on the prevalence, associations, and consequences of anemia and iron deficiency in epidemiologically representative outpatients with chronic heart failure (HF) is lacking.

OBJECTIVE To investigate the epidemiology of anemia and iron deficiency in a broad range of patients referred to a cardiology clinic with suspected HF.

DESIGN, SETTING, AND PARTICIPANTS We collected clinical data, including hemoglobin, serum iron, transferrin saturation, and serum ferritin concentrations, on consecutive patients referred with suspected HF to a single outpatient clinic serving a local community from January 1, 2001, through December 31, 2010. Follow-up data were censored on December 13, 2011. Patients underwent phenotyping by echocardiography and plasma N-terminal pro–brain natriuretic peptide measurement and were followed for up to 10 years.

MAIN OUTCOME MEASURES Prevalences of anemia and iron deficiency and their interrelationship, all-cause mortality, and cardiovascular mortality.

RESULTS Of 4456 patients enrolled in the study, the median (interquartile range) age was 73 (65-79) years, 2696 (60.5%) were men, and 1791 (40.2%) had left ventricular systolic dysfunction (LVSD). Of those without LVSD, plasma N-terminal pro–brain natriuretic peptide concentration was greater than 400 pg/mL in 1172 (26.3%), less than 400 pg/mL in 841 (18.9%), and not measured in 652 (14.6%). Overall, 1237 patients (27.8%) had anemia, with a higher prevalence (987 [33.3%]) in patients who met the criteria for HF with or without LVSD. Depending on the definition applied, iron deficiency was present in 270 (43.2%) to 425 (68.0%) of patients with and 260 (14.7%) to 624 (35.3%) of patients without anemia. Lower hemoglobin (hazard ratio 0.92; 95% CI, 0.89-0.95; $P < .001$) and serum iron (hazard ratio 0.98; 95% CI, 0.97-0.99; $P = .007$) concentrations were independently associated with higher all-cause and cardiovascular mortality in multivariable analyses.

CONCLUSIONS AND RELEVANCE Anemia is common in patients with HF and often associated with iron deficiency. Both anemia and iron deficiency are associated with an increase in all-cause and cardiovascular mortality and might both be therapeutic targets in this population.

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Anemia is common in patients with heart failure (HF) and associated with more severe symptoms and an adverse prognosis[1]; further investigation often reveals blood indexes that suggest iron deficiency, which may also be associated with an adverse outcome.[1,2] However, not all patients who appear iron deficient have anemia. The prevalence and association of anemia and iron deficiency depend on how they are defined. Blood hemoglobin and iron indexes have a continuous distribution. Small changes in values used to define what is abnormal can have marked effects on the prevalence of anemia or iron deficiency, making it difficult to understand the association between these conditions.

Anemia and iron deficiency not only indicate an adverse prognosis but also are potential targets for therapy in patients with HF.[3-5] If anemia persists despite correction of iron deficiency, then erythropoiesis-stimulating peptides may be administered to stimulate erythrocyte production.[6-9] Whether anemia or iron deficiency is the key driver of worsening symptoms and prognosis in patients with HF or whether each is important in its own right is currently uncertain. A large trial revealed that darbepoeitin alfa could increase hemoglobin concentrations, but this resulted only in a modest improvement in quality of life and no reduction in hospitalizations or death.[10] However, two medium-sized randomized clinical trials[4,11] of intravenous iron suggested improvements in symptoms, functional class, and morbidity, which did not appear to be related to the severity of anemia.

Understanding the interplay of HF, anemia, and iron deficiency is also hampered by the lack of universally accepted diagnostic criteria for HF. Anemia might simply be a manifestation of age and comorbidity in this population. Accordingly, we investigated the epidemiology of anemia and iron deficiency in a broad range of patients referred to a cardiology clinic with suspected HF.

Key Points

Questions What is the prevalence, using various definitions, of anemia and hematinic deficiencies in patients with heart failure and how are they related to prognosis?

Findings In this observational study of 4456 patients referred to a community-based heart failure clinic, anemia was present in one-third of patients, of whom two-thirds had iron deficiency. Both anemia and markers of iron deficiency, except ferritin, were associated with a poorer prognosis, including an excess of cancer deaths.

Meaning In patients with heart failure, anemia is commonly associated with iron deficiency, and anemia and iron deficiency may both be therapeutic targets.

Methods

Patients referred with suspected HF to a cardiology outpatient clinic serving a mixed urban-rural community (Kingston-upon-Hull and East Riding of Yorkshire, United Kingdom; population, approximately 550 000) from January 1, 2001, through December 31, 2010, were invited to participate in this study. Follow-up data were censored on December 13, 2011. The only exclusion criterion was the inability to provide valid informed consent because of age younger than 18 years or important cognitive dysfunction. Patients with severe renal disease were not excluded, but no patient undergoing dialysis was referred or included. Patients gave written informed consent for their data to be stored electronically and used for research. Precise records were not kept, but less than 2% of patients approached are thought to have refused to participate or were excluded. The study was approved by the Hull and East Yorkshire Local Research Ethics Committee.

Patients provided written informed consent. Patient information was held confidentially by the clinical research team who also cared for them. Personal identifiers were removed before analysis. Consenting patients received a standardized symptom questionnaire and underwent clinical examination, electrocardiography, and echocardiography. Venous blood samples were taken for standard hematologic and biochemical testing. Most patients had N-terminal pro-brain natriuretic peptide (NT-proBNP) and high-sensitivity C-reactive protein (hsCRP) measured. Anemia was defined according to the World Health Organization (WHO) criteria as a hemoglobin concentration of less than 12.0 g/dL in women and less than 13.0 g/dL in men (to convert to grams per liter, multiply by 10).[1] Anemia was subclassified as mild if the hemoglobin concentration was less than 1 g/dL, moderate if 1 to 2 g/dL, and marked if more than 2 g/dL below the WHO definition. Patients with hemoglobin concentrations less than 1 g/dL above the WHO definition were considered to have borderline anemia. Hematinic factors were serum iron and transferrin saturation (TSAT), ferritin, vitamin B_{12}, and red blood cell or serum folate. Because the clinic was designed to deliver one-stop investigations, hematinic factors were measured without knowledge of the hemoglobin concentration or clinical diagnosis. The local laboratory-defined lower limits are less than 45 µg/dL for serum iron (to convert to micromoles per liter, multiply by 0.179), less than 30 ng/mL for ferritin (to convert to picomoles per liter, multiply by 2.247), less than 15% for TSAT, less than 180 pg/mL for vitamin B_{12} (to convert to picomoles per liter, multiply by 0.7378), less than 3 ng/mL for serum folate (to convert to nanomoles per liter, multiply by 2.266), and less than 147 ng/mL for red blood cell folate (to convert to nanomoles per liter, multiply by 2.266). Additional cut points of less than 67 µg/dL for serum iron, less than 100 ng/mL for ferritin, and less than 20% for TSAT were used to explore different possible threshold definitions for iron deficiency used in a previous study.[4]

There is also a spectrum of cardiac dysfunction and hierarchy of evidence to support a diagnosis of HF. In 2008, the European Society of Cardiology guidelines indicated that a diagnosis of HF was unlikely if the plasma NT-proBNP concentration was less than 400 pg/mL (to convert to nanograms per liter, multiply by 1).[12] Accordingly, patients were assigned to 1 of the following 5 cardiac phenotypes based on echocardiography and measurement of NT-proBNP: (1) left ventricular systolic dysfunction (LVSD) defined as a left ventricular ejection fraction less than 40%; (2) left ventricular ejection fraction

greater than 40% but left ventricular diastolic dysfunction or hypertrophy and plasma NT-proBNP concentration greater than 400 pg/mL (HFnEF type 1); (3) no substantial echocardiographic abnormality with a plasma NT-proBNP concentration greater than 400 pg/mL (HFnEF type 2); (4) no substantial echocardiographic abnormality with a plasma NT-proBNP concentration less than 400 pg/mL (not HF); and (5) no substantial echocardiographic abnormality but no measurement of NT-proBNP (HF uncertain).

Patients were followed up clinically and by electronic records in primary and secondary care. Follow-up was censored at last contact or death. Deaths were adjudicated based on available records before and surrounding the time of death. Patients with symptoms of HF at rest or minimal exertion (New York Heart Association Class IV) or recurrent hospitalization for HF were generally classified as deaths attributable to HF. Out-of-hospital deaths that could not be attributed to cancer, HF, or other end-stage disease were considered sudden.

Continuous variables were summarized using median and interquartile range (IQR) and compared using Kruskal-Wallis rank tests; categorical variables were expressed as numbers and percentages and compared using χ^2 tests. Univariate analyses were based on data without imputation. Multiple regression models were used to investigate correlation among variables. Missing values were imputed based on 10 imputations using a chained equation[13,14] similar to the Gibbs sampler.[15] Multivariable linear regression was used for continuous variables and ordinal logistic regression for ordered categorical variables. Variables with a high percentage of missing values were not included in multivariable analysis to reduce uncertainty. Standardized (or β) coefficient was used to measure the strength of the association of independent to dependent variables.[16,17] Logistic regression models were used to identify variables associated with anemia and iron deficiency, and Cox proportional hazards regression models were used to identify variables associated with all-cause or cardiovascular mortality. Models were not overfitted.[18,19] For each cardiac phenotype, the association between predicted probabilities of all-cause mortality at 2 years and predictor were constructed based on multivariable logistic regression models adjusted for age and sex and illustrated using probability curves. Venn diagrams were used to illustrate the associations between anemia and indexes of iron deficiency. Statistical analyses were performed with STATA statistical software, version 12.1 (StataCorp). The 2-tailed level of statistical significance was set at $P < .05$.

Results

Of 4456 patients, the median (IQR) age was 73 (65-79) years, 1760 (39.5%) were women, 1791 (40.2%) had LVSD, 707 (15.9%) had HFnEF type 1, 465 (10.4%) had HFnEF type 2, 841 (18.9%) were considered not to have HF, and 652 (14.6%) had no major echocardiographic abnormality but did not have NT-proBNP measured. Patients with HFnEF by either definition were older; those with LVSD were more likely to be men (**Table**). The median potential duration of follow-up was 7.7 (IQR, 4.8-9.0) years or, if censored at time of death, which occurred in 1964 patients (44.1%), 4.7 (IQR 2.5-7.6) years; 4261 patients (95.6%) were followed up, dead or alive, for a minimum of 3 years.

Overall, 1237 patients (27.8%) had anemia, which was mild in 643 (14.4%), moderate in 354 (7.9%), and marked in 240 (5.4%) (**Figure 1**). The prevalence of anemia was higher in patients with LVSD (597 [33.3%]) or with either definition of HFnEF (232 [32.8%] and 148 [34.0%] in types 1 and 2, respectively) than in those who lacked echocardiographic and biomarker criteria for HF (113 [13.4%]) (**Figure 2**). An additional 1022 patients (22.9%) had borderline anemia, but the prevalence was similar in patients with and without HF. There was a strong association between the prevalence of anemia and age, especially in men, but only a weak association with sex (**Figure 3**A).

A serum iron concentration was available in 3545 patients (79.6%) and was less than 45 µg/dL in 497 (14.0%) and less than 67 µg/dL in 1296 (36.6%). Patients with anemia were much more likely to have low serum iron concentrations regardless of cardiac phenotype. Less than 5% of patients with a hemoglobin concentration lower than 1 g/dL above the WHO threshold had a serum iron concentration less than 45 µg/dL compared with greater than 45% of those with a hemoglobin concentration greater than 1 g/dL below the WHO threshold. For a given serum iron concentration or TSAT, patients with HF, regardless of cardiac phenotype, had a higher prevalence of anemia than patients without HF (Figure 3B and C). Thus, patients with HF were more likely to have a low serum iron concentration and more likely to have anemia when serum iron concentration was low. Serum iron was highly correlated with TSAT ($r = 0.906$; $P < .001$), mean corpuscular hemoglobin ($r = 0.462$; $P < .001$), and mean corpuscular volume ($r = 0.273$; $P = .001$) but only weakly with ferritin ($r = 0.207$; $P = .01$).

Serum ferritin was measured in 3373 patients (75.7%) and was less than 30 ng/mL in 478 (10.7%) and less than 100 ng/mL in 1951 (43.8%) (Figure 3D). Despite a higher prevalence of anemia, patients with LVSD were less likely to have a low serum ferritin concentration than those without HF. Many patients had a serum ferritin concentration less than 100 ng/mL but did not have anemia. The prevalence of anemia was poorly related to serum ferritin.

Vitamin B_{12} was measured in 3805 patients (85.4%), red blood cell folate in 2553 patients (57.3%), and serum folate in 1191 patients (26.7%). Patients with vitamin B_{12} or folate concentration below the laboratory reference range were uncommon, and prevalence did not differ by cardiac phenotype (Figure 3E and F). The prevalence of anemia increased slightly with higher, rather than lower, serum vitamin B_{12} and folate concentrations. Patients with HF had a slightly higher prevalence of macrocytosis regardless of hemoglobin category (Figure 2). There was also a strong association between the prevalence of anemia and estimated glomerular filtration rate, hsCRP, and NT-proBNP (Figure 3G-I).

Overall, amongst 2395 patients with complete hematinic data, 1020 patients (42.6%) had anemia or fulfilled 1 or more of the more conservative criteria for iron deficiency and 1808 (75.5%) if more liberal criteria for iron deficiency were

Table. Clinical Characteristics and Hematologic Profile by Cardiac Phenotype[a]

Variable	No. of Patients (% Missing)	Overall (n = 4456)	LVSD (n = 1791)	HFnEF Type 1 (n = 707)	HFnEF Type 2 (n = 465)	Not HF (n = 841)	No LVSD but Missing NT-proBNP (n = 652)	*P* Value[b]
Age, y	4456 (0)	73 (65-79)	72 (64-78)	77 (69-82)	76 (69-82)	69 (61-76)	72 (65-78)	<.001
Men	4456 (0)	2696 (60.5)	1330 (74.3)	315 (44.6)	283 (60.9)	440 (52.3)	328 (50.3)	<.001
IHD	4456 (0)	2132 (47.8)	1174 (65.5)	224 (31.7)	220 (47.3)	293 (34.8)	221 (33.9)	<.001
COPD	4456 (0)	480 (10.8)	187 (10.4)	64 (9.1)	49 (10.5)	95 (11.3)	85 (13.0)	.19
Diabetes	4456 (0)	845 (19.0)	380 (21.2)	117 (16.5)	97 (20.9)	133 (15.8)	118 (18.1)	.004
NYHA Class III/IV	4456 (0)	1126 (25.3)	646 (36.1)	176 (24.9)	105 (22.6)	110 (13.1)	89 (13.7)	<.001
BMI	4359 (2.2)	28 (25-32)	27 (24-31)	27 (24-31)	28 (26-33)	30 (26-34)	29 (26-33)	<.001
Heart rate (ECG), /min	4227 (5.1)	71 (61-84)	74 (63-88)	72 (60-84)	70 (60-82)	69 (60-78)	69 (61-80)	<.001
Rhythm (ECG) sinus	4456 (0)	3230 (72)	1206 (67)	410 (58)	257 (55)	803 (95)	554 (85)	<.001
Systolic BP, mm Hg	4279 (4.0)	139 (121-157)	128 (112-144)	146 (128-163)	141 (126-160)	147 (130-165)	147 (130-164)	<.001
Edema (more than trivial)	4456 (0)	873 (20)	382 (21)	175 (25)	94 (20)	127 (15)	95 (15)	<.001
NT-proBNP, pg/mL	2963 (33.5)	748 (195-2182)	1759 (726-3964)	1252 (638-2575)	959 (629-1811)	122 (60-214)	NA	Not done
hsCRP, mg/L	3062 (31.3)	3.90 (1.70-8.10)	4.7 (1.9-9.1)	4.1 (1.6-8.7)	3.7 (1.7-9.9)	3.3 (1.4-6.0)	4.0 (1.6-7.6)	<.001
Sodium, mEq/L	4049 (9.1)	139 (137-141)	139 (136-141)	139 (137-141)	139 (137-141)	139 (138-141)	139 (137-141)	<.001
eGFR (4-variable), mL/min/1.73 m^2	4049 (91)	61.8 (47.8-76.4)	58 (45-72)	59 (46-71)	58 (44-73)	72 (59-84)	66 (50-81)	<.001
Hemoglobin, g/dL	4456 (0)	13.5 (12.3-14.6)	13.5 (12.2-14.5)	13.0 (11.9-14.2)	13.2 (12.1-14.4)	13.8 (12.9-14.8)	13.7 (12.5-14.7)	<.001
Anemia (WHO definition)	4456 (0)	1237 (28%)	597 (33%)	232 (33%)	158 (34%)	113 (13%)	137 (21%)	<.001
MCHC, pg/cell	4363 (2.1)	29.8 (28.5-31.0)	29.8 (28.3-31.1)	29.6 (28.0-31.0)	29.9 (28.5-31.0)	29.9 (28.8-31.0)	30.0 (28.7-31.1)	.01
MCV, μm^3	4432 (0.5)	91.5 (87.9-95.1)	91.6 (87.8-95.6)	91.7 (87.8-95.6)	91.7 (88.0-95.3)	91.0 (87.9-94.1)	91.8 (88.1-94.9)	.11
Iron, µg/dL	3545 (20.4)	84 (61-101)	78 (56-101)	73 (56-101)	78 (84-101)	89 (67-106)	84 (89-106)	<.001
Transferrin saturation, %	2751 (38.3)	23.0 (17.0-29.0)	22.0 (16.0-30.0)	19.0 (14.0-27.0)	23.0 (17.8-30.0)	24.0 (18.0-29.0)	23.0 (18.0-30.0)	<.001
Ferritin, ng/mL	3373 (24.3)	83 (45-150)	92 (50-169)	68 (39-130)	96 (50-167)	76 (41-139)	79 (42-135)	<.001
Red blood cell folate, ng/mL	2553 (42.7)	364 (254-523)	372 (260-533)	354 (239-501)	393 (263-558)	350 (248-480)	358 (248-525)	.02
Serum folate, ng/mL	1191 (73.3)	6.5 (4.3-10.1)	6.4 (4.1-10.0)	7.5 (4.8-10.7)	6.5 (4.3-10.7)	6.2 (4.4-10.1)	6.6 (4.4-10.0)	.28
Vitamin B_{12}, pg/mL	3805 (14.6)	325 (243-437)	332 (249-454)	345 (243-467)	334 (252-435)	307 (234-418)	309 (231-416)	<.001
Loop diuretic	4456 (0)	2565 (57.6)	1313 (73.3)	405 (57.3)	299 (64.3)	303 (36.0)	245 (37.6)	<.001
Thiazide diuretic	4456 (0)	273 (6.1)	55 (3.1)	45 (6.4)	34 (7.3)	91 (10.8)	48 (7.4)	<.001
Loop or thiazide diuretic	4456 (0)	2766 (62.1)	1335 (74.5)	442 (63.5)	321 (69.0)	382 (45.4)	286 (43.9)	<.001
MRA	4456 (0)	639 (143)	456 (25.5)	60 (8.5)	53 (11.4)	32 (3.8)	38 (5.8)	<.001
β-Blocker	4456 (0)	1967 (44.1)	952 (53.2)	274 (38.8)	230 (49.5)	282 (33.5)	229 (35.1)	<.001
ACE or ARB	4456 (0)	2737 (61.4)	1351 (75.4)	390 (55.2)	285 (61.3)	394 (46.8)	317 (48.6)	<.001
Digoxin	4456 (0)	608 (13.6)	292 (16.3)	169 (23.9)	91 (19.6)	18 (2.1)	38 (5.8)	<.001
Aspirin	4456 (0)	1948 (43.7)	835 (46.6)	257 (36.4)	203 (43.7)	377 (44.8)	276 (42.3)	<.001
Warfarin sodium	4456 (0)	823 (18.5)	419 (23.4)	179 (25.3)	131 (28.2)	26 (3.1)	68 (10.4)	<.001

Abbreviations: ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index (calculated as the weight in kilograms divided by height in meters squared); BP, blood pressure; COPD, chronic obstructive pulmonary disease; ECG, electrocardiography; eGFR, estimated glomerular filtration rate; HF, heart failure; HFnEF, HF with preserved left ventricular ejection fraction (type 1 is defined as echocardiographic abnormalities that could account for symptoms and NT-proBNP concentration >400 pg/mL, and type 2 is defined as no LVSD but NT-proBNP concentration >400 pg/mL); hsCRP, high-sensitivity C-reactive protein; IHD, ischemic heart disease; IQR, interquartile range; LVSD, left ventricular systolic dysfunction; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; MRA, mineralocorticoid antagonist; NT-proBNP, N-terminal pro–brain natriuretic peptide; NYHA, New York Heart Association.

SI conversion factors: To convert NT-proBNP to nanograms per liter, multiply by 1; hsCRP to nanomoles per liter, multiply by 9.524; sodium to millimoles per liter, multiply by 1; hemoglobin to grams per liter, multiply by 10; MCV to femtoliters, multiply by 1; iron to micromoles per litre, multiply by 0.179; ferritin to picomoles per liter, multiply by 2.247; folate to nanomoles per liter, multiply by 2.266; and vitamin B_{12} to picomoles per liter, multiply by 0.7378.

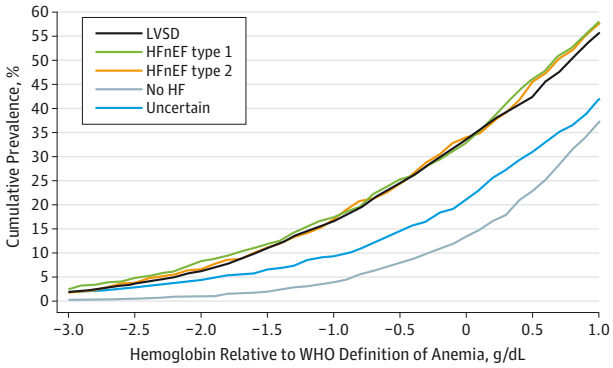
[a] Continuous variables are presented as median (IQR), and categorical variables are presented as number (percentage).

[b] The χ^2 test or Kruskal-Wallis rank test was used for comparisons among the LVSD, HFnEF type 1, HFnEF type 2, not HF, and missing NT-proBNP groups.

applied. Of patients with anemia using either conservative and liberal criteria, 270 (43.2%) to 425 (68.0%) had a low serum iron concentration or TSAT, compared with 260 (14.7%) to 624 (35.2%) of the patients without anemia (eFigures 1-4 in the Supplement). The pattern was similar if confined only to patients who fulfilled the criteria for HF.

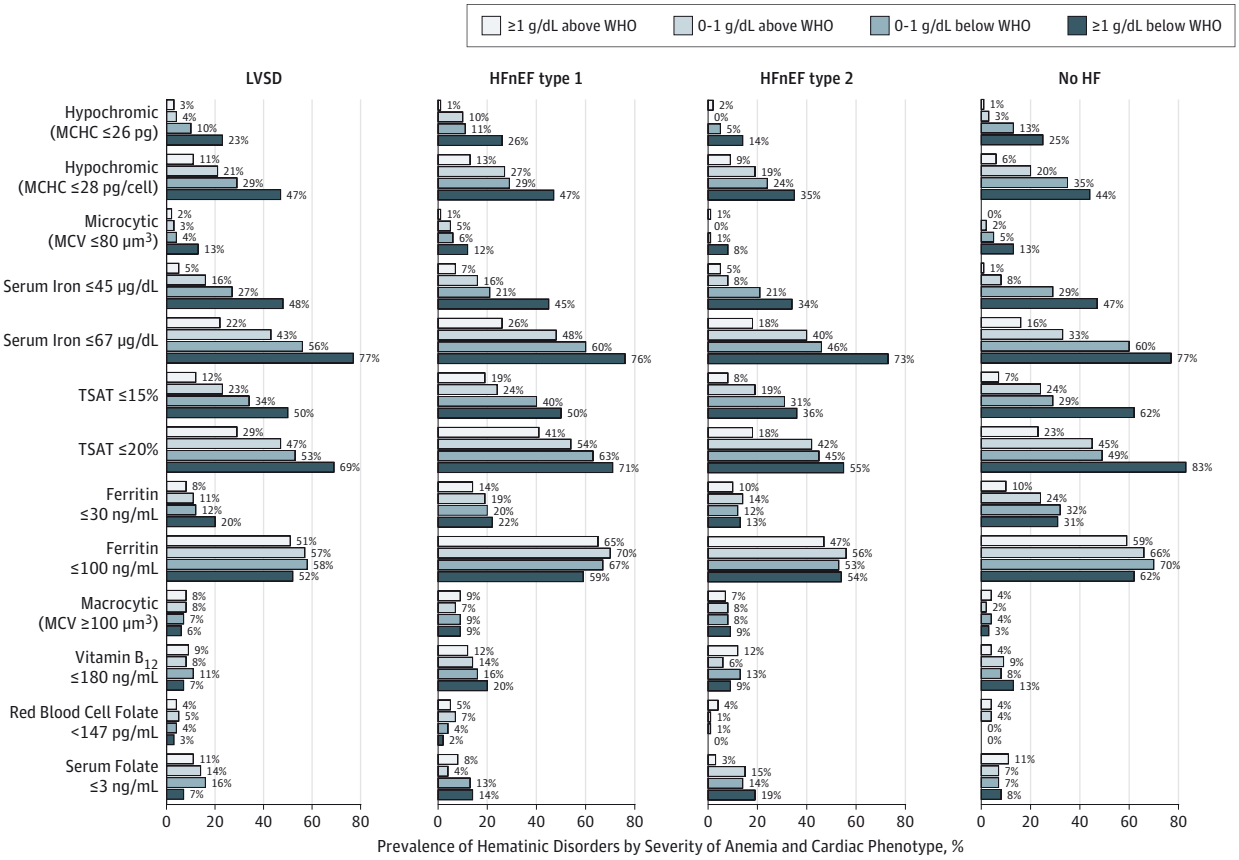
In a multivariable analysis (eTable 1 in the Supplement), the characteristics that were strongly independently and directly associated with hemoglobin concentration were serum iron (coefficient, 0.11; 95% CI, 0.10-0.12; $P < .001$), followed by serum sodium (coefficient, 0.05; 95% CI, 0.04-0.07; $P < .001$), heart rate (coefficient, 0.10; 95% CI, 0.07-0.13; $P < .001$), and estimated glomerular filtration rate (coefficient, 0.01; 95% CI, 0.005-0.01; $P < .001$). A strong inverse association between hemoglobin and logNT-proBNP was observed, whereas women and those with confirmed HF had lower hemoglobin concentrations. In further multivariable analysis (eTable 2 in the Supplement), there were strong, independent inverse associations between serum iron and both hsCRP (coefficient, −0.23; 95% CI, −0.25 to −0.21; $P < .001$) and NT-proBNP (coefficient, −0.08; 95% CI, −0.11 to −0.05; $P < .001$). Female sex (coefficient, −0.15; 95% CI, −0.20 to −0.10; $P < .001$), diabetes (coefficient, −0.18; 95% CI, −0.24 to −0.17; $P < .001$), peripheral edema (coefficient, −0.13; 95% CI, −0.20

Figure 1. Prevalence of Anemia by Severity and Cardiac Phenotype



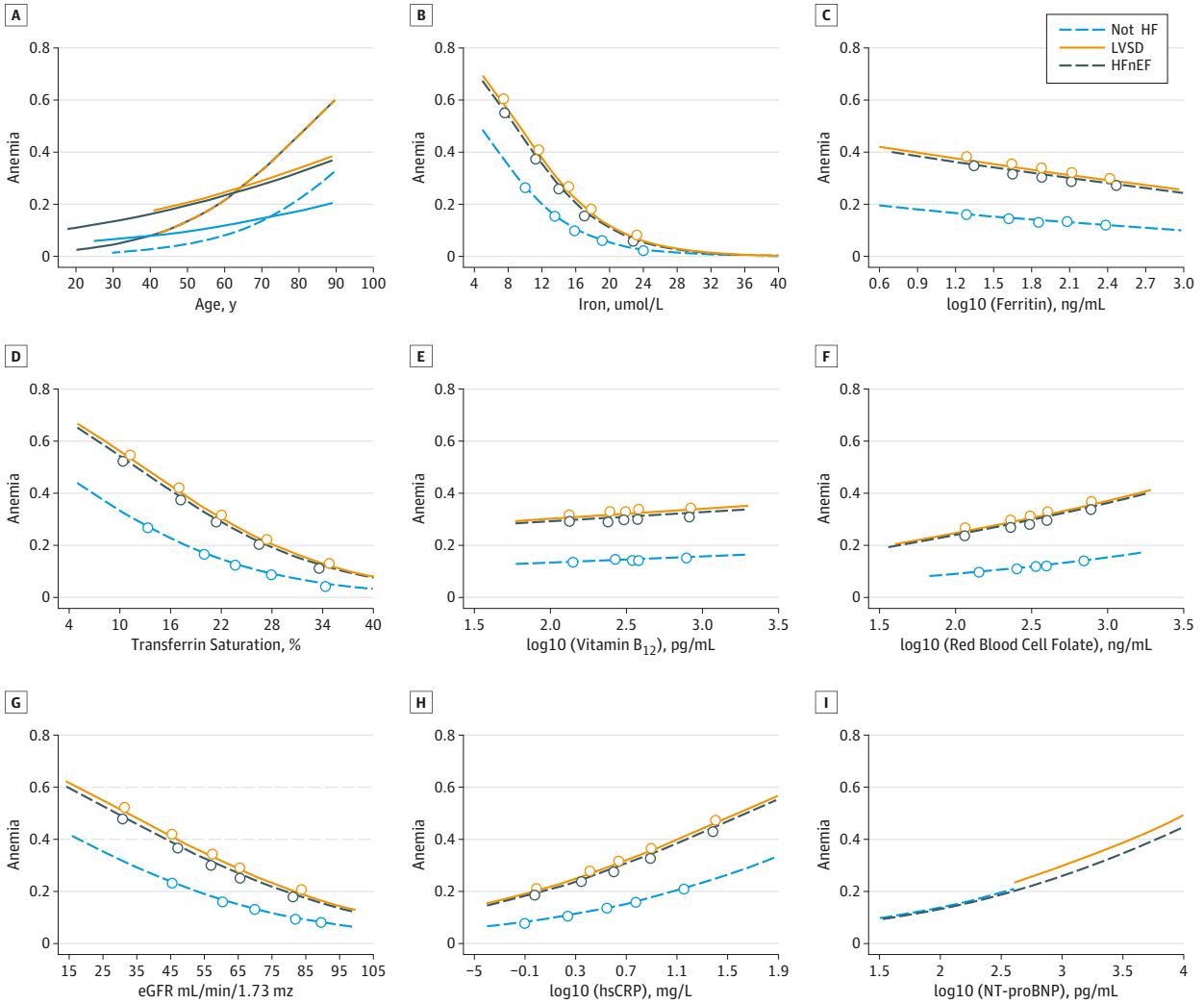
Anemia is defined as a hemoglobin concentration below the World Health Organization (WHO) thresholds of 12 g/dL for women and 13 g/dL for men. Heart failure (HF) with preserved left ventricular ejection fraction (HFnEF) type 1 is defined as echocardiographic abnormalities that could account for symptoms and N-terminal pro–brain natriuretic peptide (NT-proBNP) concentration greater than 400 pg/mL. HFnEF type 2 is defined as no substantial echocardiographic abnormality but NT-proBNP concentration greater than 400 pg/mL. Not HF is defined as no obvious echocardiographic abnormality but NT-proBNP concentration less than 400 pg/mL. Uncertain is defined as no obvious echocardiographic abnormality and NT-proBNP not measured. LVSD indicates left ventricular systolic dysfunction (defined as a left ventricular ejection fraction <40%).

Figure 2. Prevalence of Hematinic Disorders by Severity of Anemia and Cardiac Phenotype



See Figure 1 legend for definitions of HFnEF types 1 and 2. LVSD indicates left ventricular systolic dysfunction; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; TSAT, transferrin saturation.

Figure 3. Association of Variables to the Probability of Anemia by Cardiac Phenotype Using Logistic Regression Models

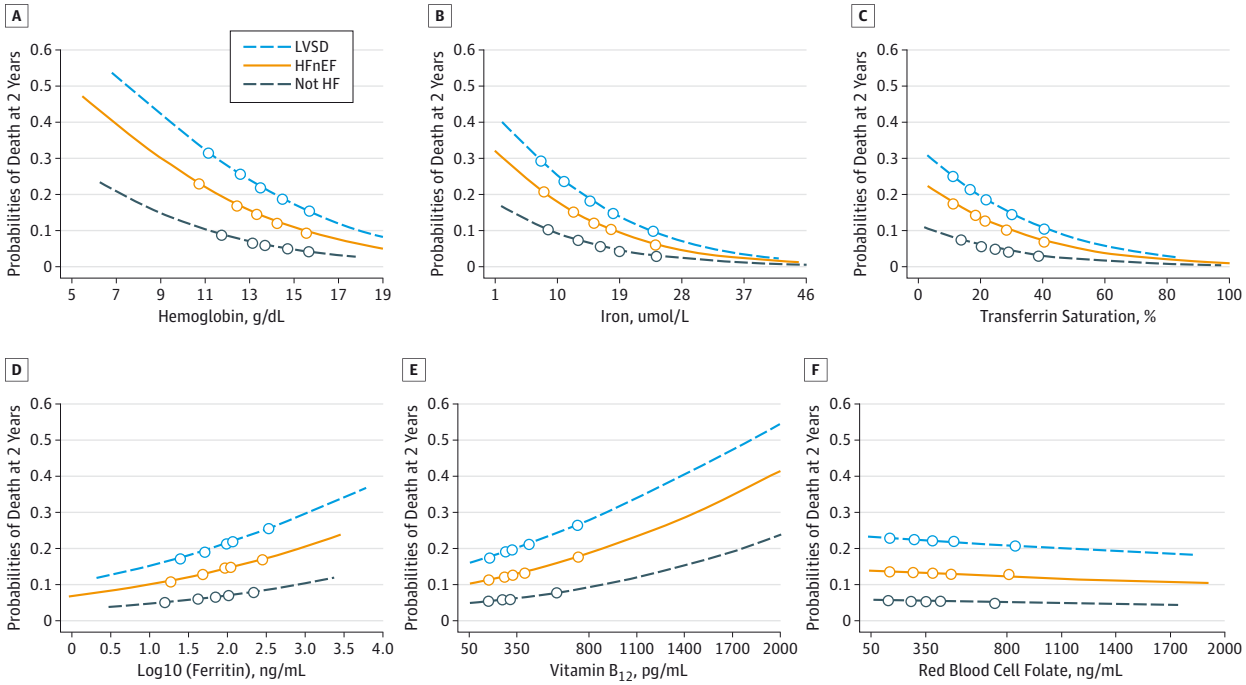


HFnEF types 1 and 2 have been conflated and the uncertain group omitted for clearer illustration. HF indicates heart failure; HFnEF, heart failure with preserved left ventricular ejection fraction; LVSD, left ventricular systolic dysfunction; NT-proBNP, N-terminal pro-brain natriuretic peptide. To convert iron to micrograms per deciliter, divide by 0.179. Circles denote rate at each quintile of the distribution.

to −0.07; $P < .001$), and use of mineralocorticoid antagonists (coefficient, 0.12; 95% CI, 0.05 to 0.19; $P < .001$) were all strongly related to lower serum iron concentration. In similar multivariable models, ferritin was most strongly associated with hsCRP (coefficient, 0.19; 95% CI, 0.15-0.22; $t = 10.5$; $P < .001$), and vitamin B_{12} was most strongly associated with lower body mass index (calculated as weight in kilograms divided by height in meters squared) (coefficient, −0.01; 95% CI, 0.01 to −0.004; $t = -4.55$; $P < .001$) and higher serum ferritin concentration (coefficient, 0.05; 95% CI, 0.03-0.07; $t = 4.41$; $P < .001$).

In univariate analyses, lower concentrations of hemoglobin and iron, lower TSAT, and higher concentrations of vitamin B_{12} were strongly associated with all-cause and cardiovascular mortality (eTables 3 and 4 in the Supplement; **Figure 4**A-F). The association between ferritin and prognosis was nonlinear, with the lowest and highest quintiles having the worst outcome. In a multivariable model restricted to hematinic variables and key clinical characteristics, the following were associated with higher all-cause and cardiovascular mortality: lower hemoglobin and serum iron concentrations, the highest quintile of ferritin, and higher serum vitamin B_{12} concentrations. If the model was extended to include comorbidities, such as findings on physical examination, other biochemical testing, and therapy (the last may be confounded by indication and will change during follow-up), the independent association between serum iron and all-cause mortality was lost, but hemoglobin and vitamin B_{12} concentrations remained weakly associated with outcome. If the analysis was confined to cardiovascular mortality, then only serum iron concentration but neither hemoglobin nor vitamin B_{12} concentration was associated with outcome in the extended model. Elimination of hemoglobin from the extended model strengthened the association of serum iron with outcomes and vice versa.

Figure 4. Association Between Hematinic Variables and All-Cause or Cardiovascular Mortality at 2 Years by Cardiac Phenotype



Association between hematinic variables and all-cause mortality at 2 years adjusted for age and sex. Heart failure (HF) with preserved left ventricular ejection fraction subtypes have been conflated. Circles denote rate at each quintile of the distribution. To convert hemoglobin to grams per liter, multiply by 10; iron to micrograms per deciliter, divide by 0.179; vitamin B_{12} to picomoles per liter, multiply by 0.7378; and folate to nanomoles per liter, multiply by 2.266.

All but 294 patients were followed up for at least 3 years. By 3 years, mortality was similar in patients with LVSD (586 [32.7%]) and HFnEF type 1 (228 [32.3%]), somewhat lower in HFnEF type 2 (105 [22.6%]), and markedly lower among those thought not to have HF (70 [8.3%]; median age, 69 years at referral) (eFigure 5 in the Supplement). Mortality increased progressively as hemoglobin concentration decreased (eFigure 6 in the Supplement). A similar pattern was observed for serum iron concentration (eFigure 7 in the Supplement). Among patients with HF, most patients died suddenly or of worsening HF. Mode of death was similar in those with or without anemia. Among patients who were considered not to have HF, there were few cardiovascular and no HF deaths, but those who had anemia or iron deficiency had a slightly higher cancer-related mortality (eFigure 8 and eFigure 9 in the Supplement). Fatal or nonfatal gastrointestinal malignant tumors were reported in 32 (2.6%) of 1237 patients with anemia and 47 (1.5%) of 3219 patients without anemia, with similar rates across cardiac phenotypes and according to iron deficiency.

Discussion

This analysis confirms that anemia is common in patients referred for investigation of suspected HF, especially if the diagnosis of HF is subsequently confirmed by objective evidence of cardiac dysfunction. The prevalence of anemia is similar regardless of the underlying HF phenotype and, even if borderline, is often associated with iron deficiency. However, the prevalence of anemia and iron deficiency is highly dependent on how these terms are defined; by some definitions, most patients will have at least one or the other. Bone marrow histologic analysis reveals a high prevalence of iron depletion in patients with HF,[20] reinforcing the belief that iron deficiency makes an important contribution to the development of anemia in this setting.

An essential function of the circulation is to deliver oxygen to tissues. The flow required will depend on local metabolic activity and the amount of oxygen per unit of blood, which is strongly related to the concentration of hemoglobin. Thus, anemia, regardless of its cause, will increase cardiac demand, which could have a deleterious effect on symptoms and prognosis. Iron deficiency may also be important in HF because it is an essential component of myoglobin and the mitochondrial respiratory chain.[21,22]

The causes of anemia in patients with HF are complex.[6] Anemia denotes a low hemoglobin concentration. Plasma volume expansion or a decrease in red blood cell mass may cause the hemoglobin concentration to decrease and the patient to become anemic[20,23]; plasma volume expansion may contribute to both anemia and an increase in natriuretic peptides and partly account for why patients with HF have a lower hemoglobin concentration for a given level of iron deficiency. Worsening congestion can cause anemia, which diuretics might correct, but diuretics could also conceal reductions in red blood cell mass by causing dehydration.[24] Reductions in red blood cell mass may

reflect reduced hematopoiesis due to iron deficiency or erythropoietin deficiency or resistance, associated with renal dysfunction and activation of inflammatory pathways.[1,25] Pharmacologic therapy for HF, including angiotensin-converting enzyme inhibitors, carvedilol, and mineralocorticoid antagonists, is associated with a decrease in hemoglobin concentration, although the extent to which this reflects plasma volume expansion or a reduction in red blood cell mass is uncertain. Iron deficiency may be related to impaired nutrition, reduced absorption attributable to increased production of hepcidin,[26,27] a key regulator of iron homeostasis, or attributable to increased losses from the gastrointestinal or urinary tracts aggravated by antithrombotic therapies.[2] However, neither aspirin nor warfarin was strongly linked to the presence of anemia in the present study. Importantly, we identified a rather low incidence of gastrointestinal cancers regardless of whether the patient had anemia. Our analysis shows that serum iron concentration and TSAT, have a strong inverse association with hsCRP, a marker of inflammation, although whether this is a cause or consequence of iron deficiency we cannot tell. In contrast, serum ferritin was directly related to hsCRP, suggesting that high levels may reflect inflammation rather than iron repletion in the setting of HF. Thus, there is a high risk that iron deficiency will be missed if based on serum ferritin concentration. On the other hand, a threshold for serum ferritin concentration of less than 100 ng/mL identifies many patients with no other evidence of iron deficiency. Accordingly, for patients with HF, its further use in clinical practice or for selecting patients for clinical trials should be questioned.

The severity of anemia and iron deficiency were both strongly related to all-cause and cardiovascular mortality on univariate analyses. Patients with anemia were at increased risk of sudden and HF-related death. Elimination of iron or hemoglobin from the multivariable model strengthened the association of the other with outcome. Therefore, it is likely that both the severity of anemia and iron deficiency contribute to an adverse outcome in patients with HF.

The lack of a robust blood test for iron deficiency creates uncertainty about its role in the development of anemia.[1] An observational study such as this can help identify how sensitive the prevalences of anemia and iron deficiency are to changes in definition and their association with outcome. However, demonstrating an association between a variable and an outcome does not prove causality. A series of trials demonstrated that giving erythropoietin to patients with HF increased hemoglobin concentrations and perhaps improved well-being,[5,7,8,28] but this did not translate into a benefit on morbidity or mortality. Studies of intravenous iron have also found an increase in hemoglobin concentration, symptoms,[4] and exercise capacity,[29,30] with hints that this might translate into better long-term outcome.[4,9]

This was a single-center study serving a predominantly white population but including a population of mixed ethnicity. Data should be extrapolated with care to centers that serve populations different from ours or if different criteria are used to define HF. However, we enrolled consecutive patients, which may make this study more epidemiologically representative than many multicenter studies that enroll patients in a selective and nonconsecutive fashion.

Conclusions

In patients with heart failure, with or without a reduced left ventricular ejection fraction, anemia and iron deficiency are common and many patients have both, suggesting that iron deficiency could be an important cause of anemia in this setting. Serum concentrations of iron and transferrin saturation are more strongly associated with anemia than are serum concentrations of ferritin, which may be greatly influenced by activation of inflammatory pathways. Both anemia and iron deficiency are associated with a higher all-cause mortality, mostly driven by cardiovascular deaths. The incidence of gastrointestinal malignant tumors is fairly low in patients with heart failure and only slightly higher in patients with anemia or iron deficiency. These data should help with the planning, execution, and interpretation of future interventional trials designed to treat iron deficiency and/or anemia.

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