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ORIGINAL ARTICLE

Iron deficiency in Taiwanese patients with heart failure and reduced ejection fraction

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Abstract

Background: Iron deficiency (ID) is a common comorbidity among patients with heart failure and reduced ejection fraction (HFrEF), and is associated with poorer outcomes independent of anemia. This study aimed to evaluate the prevalence and prognostic significance of ID in Taiwanese patients with HFrEF.

Methods: We included HFrEF patients from two multicenter cohorts at different periods. The multivariate Cox regression analysis was applied to assess the risk of outcomes associated with ID, accounting for the varying risk of death.

Results: Of the 3612 patients with HFrEF registered from 2013 to 2018, 665 patients (18.4%) had available baseline iron profile measurements. Of these, 290 patients (43.6%) were iron deficient; 20.2% had ID+/anemia+, 23.4% ID+/anemia–, 21.5% ID–/anemia+, and 34.9% ID–/anemia–. Regardless of anemia status, patients with coexisting ID had a higher risk than those without ID (all-cause mortality: 14.3 vs 9.5 per 100 patient-years, adjusted hazard ratio [HR] 1.33; 95% confidence interval [CI], 0.96-1.85; $p = 0.091$; cardiovascular mortality: 10.5 per 100 patient-years vs 6.1, adjusted HR 1.54 [95% CI, 1.03-2.30; $p = 0.037$]; cardiovascular mortality or first unplanned hospitalization for HF: 36.7 vs 19.7 per 100 patient-years, adjusted HR 1.57 [95% CI, 1.22-2.01; $p < 0.001$]). Among patients eligible for treatment in the IRONMAN trial design (43.9%), parenteral iron therapy was estimated to reduce heart failure hospitalizations and cardiovascular deaths by 13.7 per 100 patient-years.

Conclusion: Iron profiles were tested in less than one-fifth of the Taiwanese HFrEF cohort. ID was present in 43.6% of tested patients and was independently associated with poor prognosis in these patients.

Keywords: Anemia; Heart failure with reduced ejection fraction (HFrEF); Hospitalization; Iron deficiency; Mortality; Taiwan

1. INTRODUCTION

Iron deficiency (ID) is an important but often overlooked comorbidity in patients with heart failure and reduced ejection fraction (HFrEF).[1] The prevalence of ID ranged from 35% to 50% in Western cohorts.[2,3] ID is independently associated with decreased functional capacity, decreased quality of life, and increased mortality, regardless of anemia.[1,4]

Recent clinical trials have demonstrated the beneficial effects of parenteral iron therapy in patients with reduced left ventricular ejection fraction (LVEF) and ID,[5-8] emphasizing the importance of real-world ID detection. The European Society of Cardiology guidelines recommend ID[9] testing for all patients with heart failure (HF), but this comorbidity is undertested in Taiwan.

The prevalence of ID is unclear in Taiwanese patients with HFrEF, as well as its effects on their clinical outcomes. This study aimed to investigate: (1) factors associated with the iron profile, (2) the prevalence of ID, anemia, or both, and (3) the prognostic value of ID among Taiwanese HFrEF patients, with the joint participation of two Taiwanese multicenter HFrEF cohorts.

2. METHODS

2.1. Study design and patient characteristics

The current study adopted data from two multicenter HFrEF cohorts in Taiwan. (1) Taiwan Society of Cardiology-Heart Failure Registry with Reduced Ejection Fraction Registry,[10]

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which is a prospective multicenter observational survey of patients with HFrEF recently admitted for HF in 21 hospitals from 2013 to 2014. (2) The Treatment with angiotensin receptor neprilysin inhibitor for Taiwan Heart Failure patient study,[11,12] which was a principal investigator-initiated multicenter retrospective HFrEF study that recruited symptomatic patients with HFrEF from 10 hospitals from 2017 to 2018.

HFrEF includes symptoms of HF with New York Heart Association (NYHA) functional class II, III, or IV, and an LVEF of <40%. A total of approximately 60 variables were collected from each patient in both cohorts at baseline, including age, sex, body mass index, HF etiology, blood pressure, heart rate, NYHA functional class, LVEF, estimated glomerular filtration rate (eGFR), comorbidities, medications, laboratory data, and use of cardiac implantable devices. The Institutional Ethics Committee of each hospital approved the study which complied with the Helsinki Declaration of Ethical Principles. Supplementary Fig. 1 (http://links.lww.com/JCMA/A196) shows the flowchart of the study.

2.2. Definitions and study outcomes

ID is defined as ferritin levels of <100 μg/L or 100–299 μg/L with transferrin saturation (TSAT) of <20%. TSAT is measured by iron/ total iron binding capacity (TIBC) × 100.[9,13] Anemia is defined by World Health Organization (WHO) as hemoglobin of <13.0 g/dL in males and <12.0 g/dL in females [9]. Five clinical outcomes were assessed during follow-up, including (1) all-cause mortality, (2) cardiovascular mortality, (3) composite of cardiovascular death or first unplanned HF hospitalization, (4) first unplanned HF hospitalization, and (5) total HF hospitalizations.

2.3. Statistical analysis

Continuous variables are expressed as mean ± standard deviation while categorical variables as percentages. Chi-square tests for categorical variables were used to assess differences in baseline characteristics and clinical variables. Student's *t*-test or the Wilcoxon rank-sum test was used to compare continuous data. Multivariate logistic regression models were used to assess factors associated with iron profile testing, and results were expressed as odds ratios (OR) and 95% confidence intervals (CIs).

Survival analysis with the Kaplan–Meier method and the log-rank test was used to analyze the risks of all-cause mortality, cardiovascular death, and HF hospitalization. Cox regression models using univariate and multivariable models were used to compare hazard ratios (HRs) for clinical outcomes in patients with and without ID. HRs were adjusted for the following variables: age, sex, HF etiology, systolic blood pressure, eGFR, presence or absence of WHO-defined anemia, LVEF, hypertension, diabetes, HF drug prescription, and device therapy at discharge. A *p*-value of <0.05 was considered statistically significant. All statistical analyzes were performed using IBM Statistical Package for the Social Sciences Statistics version 24.0 software (IBM SPSS, IBM Corp, Armonk, NY, USA).

3. RESULTS

3.1. Factors associated with iron profiles measuring in Taiwan

Of the 3612 patients with HFrEF, 665 (18.4%) had complete ferritin and TSAT measurements at baseline. Iron profile testing was performed in 21.8% and 18.4% of patients with and without anemia, respectively ($p < 0.001$). Fig. 1 shows the predictors for the iron profile test. Patients enrolled from 2017 to 2018, recipients of implanted cardioverter-defibrillators, renin–angiotensin system inhibitors users, hospitalization registry, and chronic kidney disease history were key patient characteristics independently associated with a higher likelihood of iron profile testing among Taiwanese patients with HFrEF.

3.2. Characterization of iron deficiency

The mean age of the study cohort was 62.3 years, and the mean LVEF was 27.6%. Of 665 patients with baseline iron profiles, 290 (43.6%) were iron deficient. Table 1 shows the detailed baseline characteristics of patients with and without ID. At baseline, patients with and without ID had similar characteristics in terms of age, sex, vital signs, comorbidities, LVEF, and HF treatment. However, iron, TIBC, TSAT, and ferritin levels were significantly lower in patients with ID than in patients without ID. Additionally, patients with ID had significantly lower hemoglobin, albumin, and high-density lipoprotein cholesterol levels, but similar eGFR, triglycerides, and low-density lipoprotein cholesterol levels.

3.3. Outcome analysis according to iron deficiency, anemia, and renal functional status

A total of 232 (34.9%) patients had neither ID nor anemia (ID–/anemia–), while 23.4% had only ID (ID+/anemia–), 21.5% had only anemia (ID–/anemia+), and 20.2% had ID and anemia (ID+/anemia+), as shown in Supplementary Fig. 1 (http://links.lww.com/JCMA/A196). Patients with ID were at higher risk for all outcomes compared with patients without ID during a mean follow-up period of 24.5 months: all-cause mortality (14.3 vs 9.5 per 100 patient-years, adjusted HR: 1.33; 95% CI: 0.96–1.85, $p = 0.091$, Fig. 2A), cardiovascular mortality (10.5 vs 6.1 per 100 patient-years, adjusted HR: 1.54; 95% CI: 1.03–2.30, $p = 0.037$, Fig. 2B), cardiovascular mortality or first unplanned hospitalization for HF (36.7 vs 19.7 per 100 patient-years, adjusted HR: 1.57; 95% CI: 1.22–2.01, $p < 0.001$), and first unplanned hospitalization for HF (34.3 vs 18.5 per 100 patient-years, adjusted HR: 1.48; 95% CI: 1.14–1.92, $p = 0.003$). The reference group was patients with neither ID nor anemia (ID–/anemia–), and the outcomes of patients with ID–/anemia+ and ID+/anemia– were significantly higher, while those with ID+/anemia+ had the highest risk, as shown in Figs. 3A and 4.

The study included 195 (29.3%) patients with normal renal function (eGFR of ≥60 mL/min/1.73 m²) without ID, as well as 22.6% with normal renal function and ID, 27.1% with impaired renal function (eGFR of <60 mL/min/1.73 m²) but without ID, and 21.1% with impaired renal function and ID. Worse clinical outcomes were seen in patients with impaired renal function than those with preserved renal function. Additionally, patients with both impaired renal function and ID had the worst prognosis, with an all-cause mortality rate of 18.4 per 100 patient-years and a cardiovascular mortality rate of 13.9 per 100 patient-years, with cardiovascular mortality or first unplanned hospitalizations of 52.3 per 100 patient-years, and the total number of unplanned hospitalizations due to HF of 71.2 per 100 patient-years (Fig. 3B).

3.4. Eligibility for an intravenous iron supplement

Table 2 shows the eligibility of patients with HFrEF in Taiwan for intravenous iron therapy according to the inclusion and exclusion criteria of different randomized trials. The IRONMAN study used relatively broad ID inclusion criteria and recruited inpatients and outpatients with HF,[8] resulting in 43.9% of Taiwanese patients with HFrEF having tested iron profiles who were eligible for intravenous iron supplementation. Parenteral iron therapy in these eligible patients was estimated to reduce overall HF hospitalizations by 11.4 per 100 patient-years and reduce overall HF hospitalizations and the incidence of cardiovascular death by 13.7 per 100 patient-years.

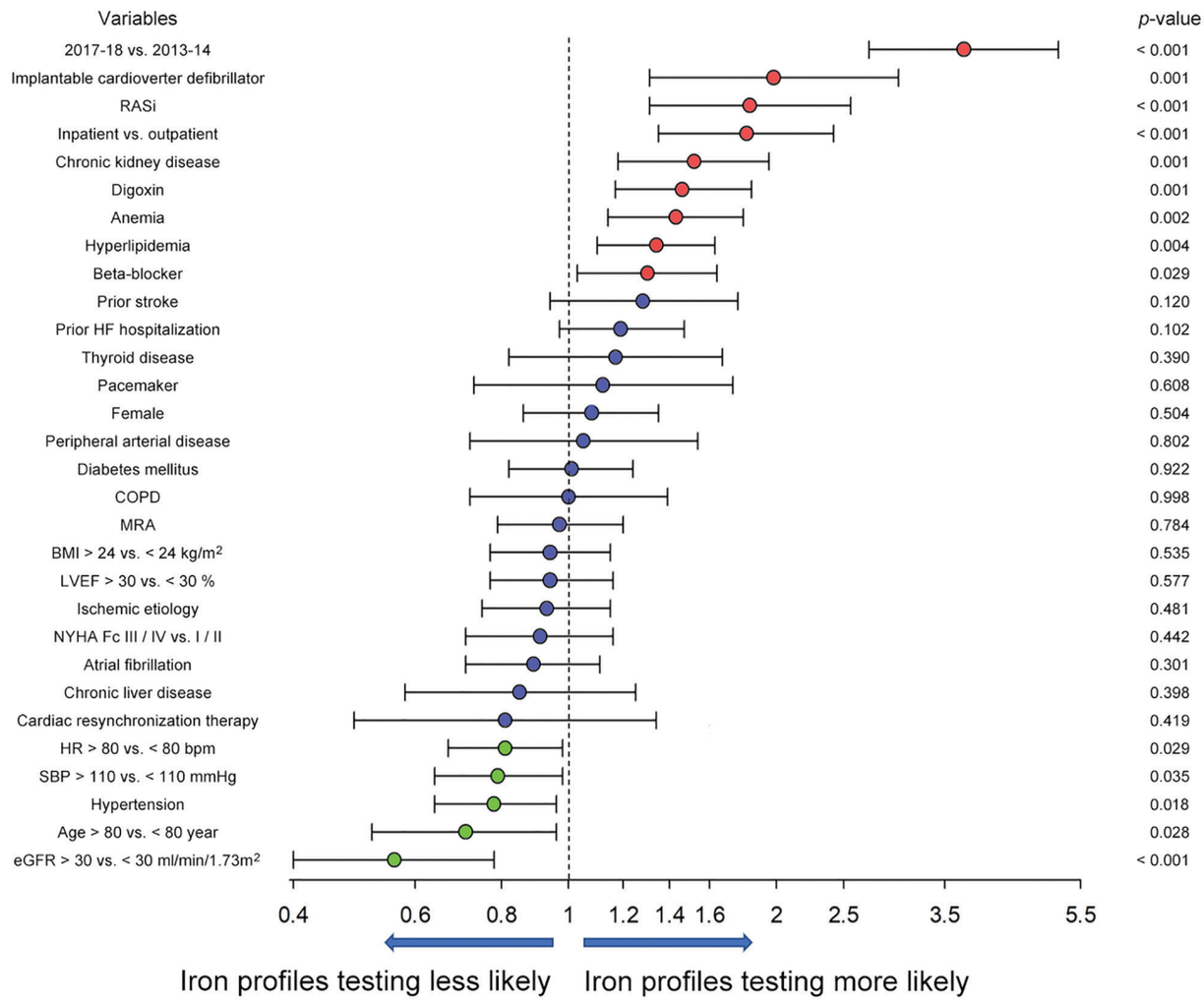

Fig. 1 Predictors for iron profiles testing use. BMI = body mass index; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; HR = hazard ratio; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA Fc = New York Heart Association functional class; RASi = renin-angiotensin system inhibitor; SBP = systolic blood pressure.

4. DISCUSSION

Our study revealed that among Taiwanese patients with HF, (1) <20% underwent ID diagnostic testing, (2) 43.6% had ID, and (3) patients with coexisting ID were more likely to have worse clinical outcomes than those without.

Iron plays a crucial role in maintaining cellular energy, and its impact on patients with HF is multifactorial. First, cardiac myocytes, which require high energy levels, are sensitive to limited iron utilization and decreased iron supply.[14] Second, ID can contribute to skeletal muscle weakness by affecting energetic metabolism and disrupting carbohydrate and fat catabolic processes.[15] Low ferritin levels have been associated with respiratory muscle weakness in patients with HFrEF.[16] Third, ID at the cellular level is linked to a decreased total number of mitochondria, reduced mitochondrial volume density, and declined mitochondrial cristae surface density. However, intravenous iron supplementation can restore muscle energy levels and improve mitochondrial function.[17]

Analysis from this multicenter HFrEF cohort revealed that patients enrolled from 2017 to 2018 were more likely to have undergone iron profile testing than those enrolled from 2013 to 2014, indicating an increased awareness of detecting ID among patients with HF in recent years. Enrolled inpatients were also more likely than enrolled outpatients to undergo iron profile testing, indicating that physicians tend to fully assess patients during hospitalization.

Overall, <20% of Taiwanese patients received iron profile testing, highlighting the importance of regular iron status assessment in patients with HF, as recommended by international guidelines, regardless of their care setting.[9,13] Several studies have demonstrated the beneficial effects of ID correction by parenteral iron therapy in both inpatients and outpatients with chronic HF. Ferric carboxymaltose in AFFIRM-AHF reduced HF hospitalization and cardiovascular death compared with placebo only in patients with HF with an ischemic etiology,[18] emphasizing the importance of patient selection and individualized treatment strategies. However, the current analysis revealed no association between the presence of an ischemic etiology for HF and a higher likelihood of iron profile testing. An ongoing Taiwan multicenter registry aims to recruit patients with HF with full-spectrum LVEFs, thereby providing more accurate information on patients with different phenotypes.

The ferritin and TSAT criteria recommended in modern HF guidelines.[9,13] reported that the prevalence of ID in HF was 42.5%, 49.0%, 37.8%, and 58.8% in German, Swedish,

Table 1

Baseline characteristics of patients

	Iron deficiency, n = 290	No iron deficiency, n = 375	*p*
Age (y)	62.1 ± 16.2	62.5 ± 14.1	0.741
Gender			
Male	205 (70.7)	286 (76.3)	0.105
Female	85 (29.3)	89 (23.7)	
Body mass index (kg/m^2)	25.8 ± 4.9	25.1 ± 4.7	0.060
Systolic blood pressure (mmHg)	118.3 ± 18.9	120.0 ± 20.7	0.297
Diastolic blood pressure (mmHg)	72.0 ± 13.4	72.1 ± 15.0	0.908
Heart rate (beats/min)	80.8 ± 15.6	78.7 ± 14.7	0.087
New York Heart Association functional class			0.615
II	206 (71.0)	273 (72.8)	
III/IV	84 (29.0)	102 (27.2)	
Principal cause of heart failure			
Ischemic etiology	118 (40.7)	168 (44.8)	0.288
Nonischemic etiology	172 (59.3)	207 (55.2)	
Left ventricular ejection fraction (%)	27.1 ± 7.9	28.0 ± 7.4	0.141
eGFR (mL/min/1.73 m^2)	62.2 ± 35.9	60.0 ± 33.9	0.409
Hemoglobin (g/dL)	12.6 ± 2.3	13.1 ± 2.5	0.008
Albumin (g/dL)	3.4 ± 0.5	3.5 ± 0.5	0.042
Triglyceride (mg/dL)	123 ± 91	125 ± 88	0.874
Total cholesterol (mg/dL)	159 ± 43	167 ± 43	0.085
HDL-C (mg/dL)	39 ± 13	43 ± 14	0.010
LDL-C (mg/dL)	98 ± 33	99 ± 35	0.904
Iron (μg/dL)	46 ± 26	87 ± 42	<0.001
Total iron binding capacity (μg/dL)	333 ± 85	288 ± 76	<0.001
Transferrin saturation (%)	14 ± 7	31 ± 13	<0.001
Ferritin (ng/mL)	107 ± 77	505 ± 503	<0.001
Medical history			
Diabetes mellitus	122 (42.1)	153 (40.8)	0.742
Hypertension	132 (45.5)	172 (45.9)	0.929
Peripheral arterial disease	21 (7.2)	29 (7.7)	0.811
Stroke	35 (12.1)	40 (10.7)	0.571
Atrial fibrillation/flutter	87 (30.0)	117 (31.2)	0.739
Hyperlipidemia	130 (44.8)	177 (47.2)	0.543
Chronic obstructive pulmonary disease	35 (12.1)	32 (8.5)	0.133
Prior hospitalization for heart failure	170 (58.6)	233 (62.1)	0.358
Chronic kidney disease	105 (36.2)	127 (33.9)	0.530
Chronic liver disease	16 (5.5)	26 (6.9)	0.457
History of thyroid disease	29 (10.0)	34 (9.1)	0.684
Device therapy			
Pacemaker	17 (5.9)	21 (5.6)	0.885
Implantable cardioverter-defibrillator	17 (5.9)	36 (9.6)	0.078
Cardiac resynchronization therapy	17 (5.9)	13 (3.5)	0.140
Heart failure medication			
ACEi/ARB/ARNI	254 (87.6)	343 (91.5)	0.101
Beta-blocker	222 (76.6)	291 (77.9)	0.750
Mineralocorticoid receptor antagonist	175 (60.3)	222 (59.2)	0.765
Ivabradine	43 (14.8)	69 (18.4)	0.222
Digoxin	84 (29.0)	90 (24.0)	0.149

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin-receptor neprilysin inhibitor; eGFR = estimated glomerular filtration rate; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

Australian, and Indian databases, respectively.[2,3,19,20] The prevalence of ID in the DAPA-HF trial was 43.7%.[21] Our analysis of a multicenter cohort revealed that ID was observed in 43.6% of patients with HFrEF in Taiwan, which is consistent with the global burden of ID in HF.

The current findings revealed that patients with ID are at significantly higher risk of cardiovascular death and/or unplanned HF hospitalization, as well as a numerically higher risk of all-cause mortality. The Swedish Heart Failure Registry[19] reported that Swedish patients had a similar mortality rate to Taiwanese patients in this cohort (ie, all-cause death, neither ID nor anemia, Sweden: 6.2 vs Taiwan: 6.0 per 100 patient-years; both ID and anemia, Sweden: 19.0 vs Taiwan: 19.4 per 100 patient-years).

Regardless of anemia status, worse symptoms and quality of life, more severe functional impairment, and higher rates of HF hospital admission and mortality were seen in patients with ID than in patients without ID.[1–4] Further, the risk of adverse cardiovascular events was highest in patients with both ID and anemia, intermediate in those with either ID or anemia alone, and lowest in those without either ID or anemia. However, many Taiwanese adults had ID but were not anemic (23.4%), emphasizing the importance of not only

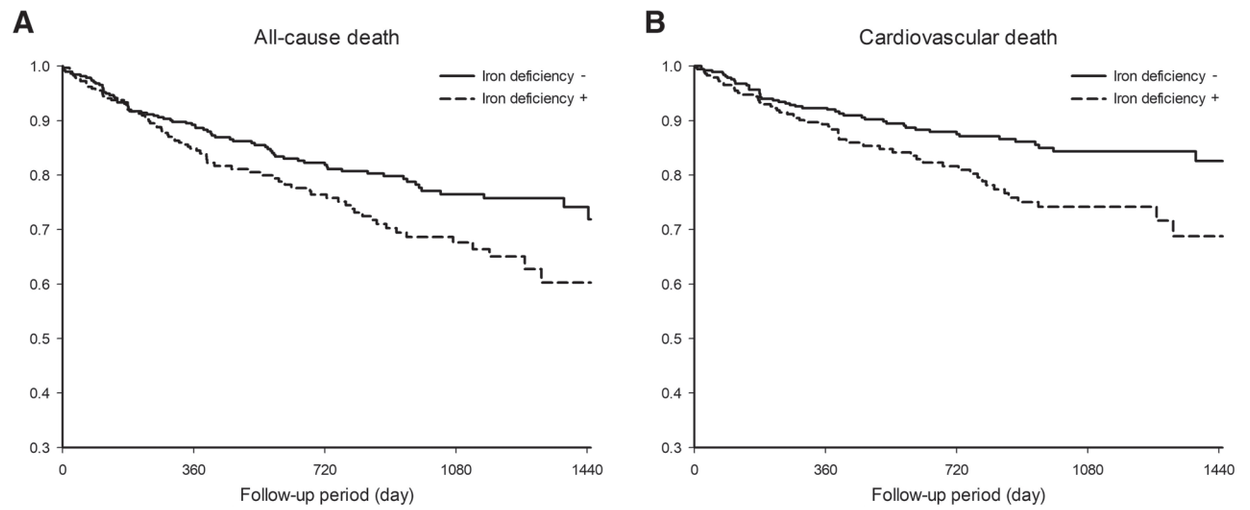

Fig. 2 Kaplan-Meier curves for death from any causes, death from cardiovascular causes, stratified by iron deficiency status, and renal function.

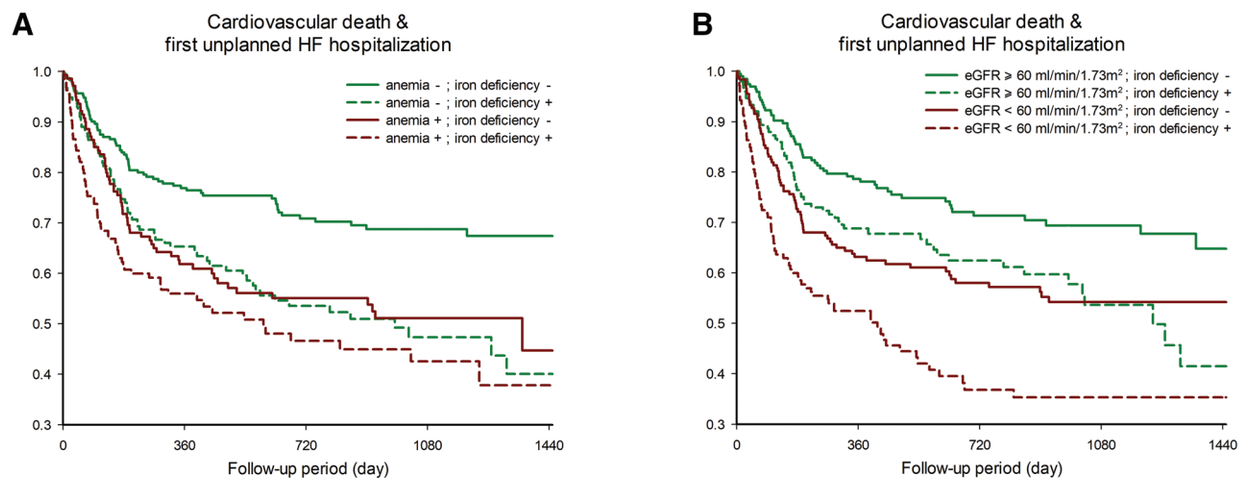

Fig. 3 Kaplan-Meier curves of cardiovascular death or first unexpected hospitalization for heart failure, stratified by iron deficiency status, anemia status, and renal function. eGFR = estimated glomerular filtration rate; HF = heart failure.

measuring iron levels to evaluate anemia, which may miss important prognostic and treatment factors. In addition, our study demonstrates iron testing as a valuable tool in patients with varying renal function levels, including those with impaired renal function (ie, eGFR of <60 mL/min/1.73 m^2), who typically have a poorer prognosis compared to those with preserved renal function.

A pooled analysis of randomized trials revealed that parental iron treatment reduces the risk of all-cause mortality or hospitalization for cardiovascular causes, as well as reduces HF symptoms, and improves exercise capacity and quality of life.[22] The AFFIRM-AHF study revealed that ferric carboxymaltose was highly cost-effective in patients with ID and acutely decompensated HF.[23] Later, the IRONMAN study revealed that intravenous administration of iron derisomaltose could reduce the risk of HF admission and cardiovascular death in both inpatients and outpatients with reduced ejection fraction and ID.[8]

The European and American guidelines recommend intravenous iron therapy for symptomatic HFrEF patients with ID,[9,13] but intravenous iron supplementation is not widely available in Taiwan. Our analysis revealed that 28.7% and 43.9% of patients were eligible for intravenous iron therapy according to the AFFIRM-AHF and IRONMAN trials, respectively. Notably, treatment-eligible patients with ID were at high risk, with observed rates of overall HF hospitalization and cardiovascular death event rates of 84.9 and 57.2 per 100 patient-years, respectively. Intravenous iron therapy is estimated to reduce the risk by 21%–24% based on the trials mentioned above. These findings indicate the benefit of this new treatment modality. Real-world data should be collected in the future to determine the effectiveness of intravenous iron therapy in patients with HF in Taiwan.

In conclusion, ID under-detection in patients with HFrEF is common in Taiwan. Our study revealed that only 18.4% of patients with HFrEF had their iron profile measured, and 43.6% of those tested had ID. Patients with ID had worse clinical outcomes compared with those without ID regardless of anemia and renal function status. An estimated 30%–40% of Taiwanese patients with HFrEF could benefit from intravenous iron therapy based on eligibility criteria. These findings emphasize the need to increase ID awareness and detection in Taiwanese patients with HFrEF.

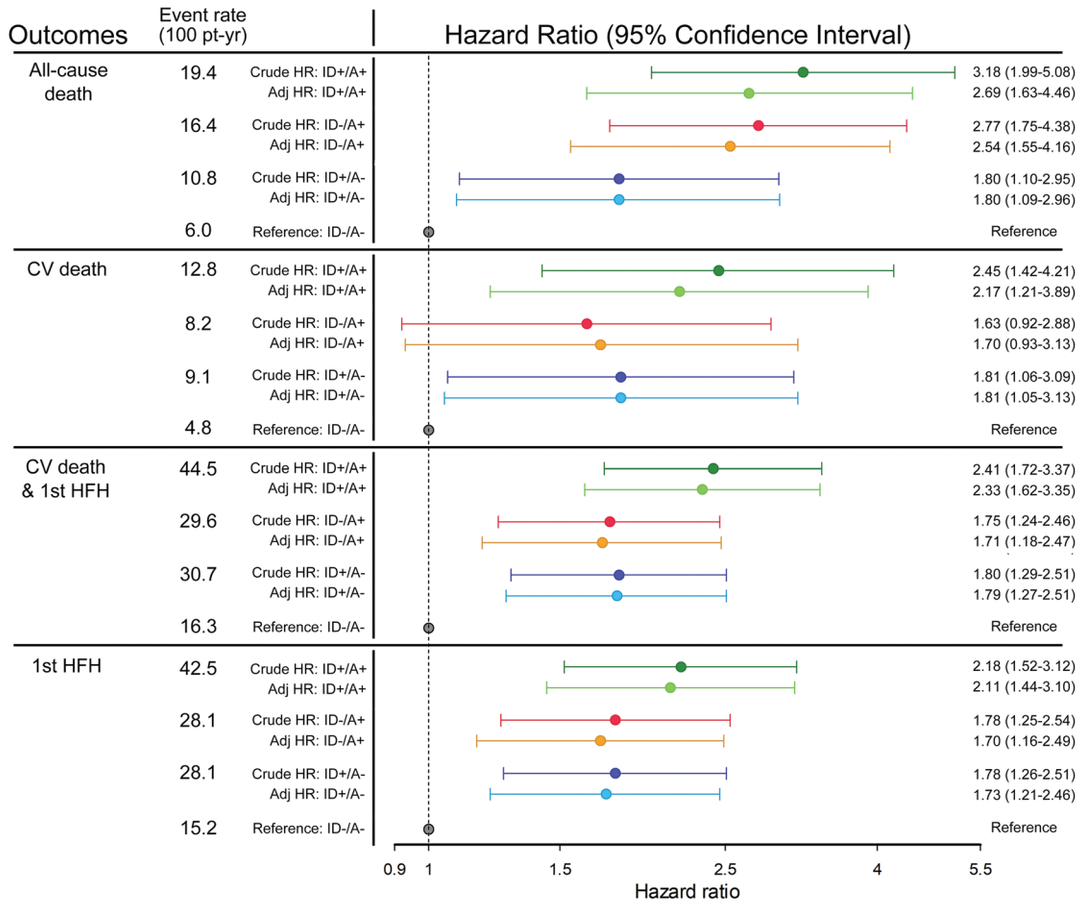

Fig. 4 Outcome analysis according to iron deficiency/anemia (ID/A) status. CV death = cardiovascular death; HFH = heart failure hospitalization.

Table 2

Eligibility of intravenous iron therapy for Taiwanese heart failure patients based on different trials

Trial	IRONMAN	AFFIRM-AHF	CONFIRM-HF
Reference	*Lancet* (2022)	*Lancet* (2020)	*Eur Heart J* (2015)
Enrollment	Hospitalized or ambulatory HF patients	Hospitalized HF patients	Stable ambulatory HF patients
LVEF criteria	≤45%	<50%	≤45%
Iron criteria	Serum ferritin level <100 ng/mL, or TSAT <20%, exclude if ferritin >400	Serum ferritin level < 100 ng/mL, or 100–299 ng/mL with TSAT <20%	Serum ferritin level <100 ng/mL, or 100–300 ng/mL with TSAT <20%
Hemoglobin criteria	Exclude if hemoglobin < 9 g/dL		Hemoglobin < 15 g/dL
Main finding	Reduces the risk of HF hospitalizations and cardiovascular death	Reduces the risk of HF hospitalizations, no apparent effect on the risk of cardiovascular death	Improves symptoms, functional capacity, and quality of life
Estimated treatment effect for total HF hospitalization and cardiovascular death (%)	↓24	↓21	↓47
Estimated treatment effect for total HF hospitalization (%)	↓24	↓26	↓61
Eligible proportion among Taiwanese HF patients with ID testing (%)	43.9	28.7	11.6
Event rate of total HF hospitalization and cardiovascular death of eligible patients (per 100 patient-years)	57.2	84.9	35.2
Estimated event rate of total HF hospitalization and cardiovascular death if iron therapy given (per 100 patient-years)	43.5	67.1	18.7
Event rate of total HF hospitalization of eligible patients (per 100 patient-years)	47.3	71.6	27.4
Estimated event rate of total HF hospitalization if iron therapy given (per 100 patient-years)	35.9	53.0	10.7

AHF = acute heart failure; HF = heart failure; ID = iron deficiency; LVEF = left ventricular ejection fraction; TSAT = transferrin saturation.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://links.lww.com/JCMA/A196.

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