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Iron Deficiency in Korean Patients With Heart Failure

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ABSTRACT

Background: Although iron deficiency (ID) is an important and treatable risk factor for heart failure (HF), data on ID are scarce in Asian patients with HF. Therefore, we sought to determine the prevalence and clinical characteristics of ID in hospitalized Korean patients with HF.

Methods: In this prospective, multicenter cohort study, 461 patients with acute HF seen at five tertiary centers from January to November 2019 in Korea were enrolled. ID was defined as serum ferritin < 100 μg/L or ferritin 100–299 μg/L in combination with transferrin saturation < 20%.

Results: The patients' mean age was 67.6 ± 14.9 years, and 61.8% were male. Among total 461 patients, ID was present in 248 patients (53.8%). The prevalence of ID was significantly higher in women than in men (65.3% vs. 47.3%, $P < 0.001$). In a multivariable logistic regression analysis, the independent predictors of ID were female sex (odds ratio [OR], 2.19; 95% confidence interval [CI], 1.47–3.30), valvular heart disease (OR, 2.10; 95% CI, 1.10–4.17), higher heart rate (OR, 1.10; 95% CI, 1.01–1.21), anemia (OR, 1.60; 95% CI, 1.07–2.40), and the use of clopidogrel (OR, 1.56; 95% CI, 1.00–2.45). Among women, the prevalence of ID did not significantly differ between younger and older women (< 65 years: 73.7% vs. ≥ 65 years: 63.0%, $P = 0.222$), those with low and high body mass index (BMI < 25 kg/m^{2}: 66.2% vs. BMI ≥ 25 kg/m^{2}: 69.6%, $P = 0.703$), or those with low and high natriuretic peptide (NP) levels (NP < median: 69.8% vs. NP ≥ median: 61.1%, $P = 0.295$). Only 0.2% patients with acute HF received intravenous iron supplementation in Korea.

Conclusion: The prevalence of ID is high in hospitalized Korean patients with HF. Because ID cannot be diagnosed by clinical parameters, routine laboratory examinations are necessary to identify patients with ID.

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Keywords: Iron Deficiency; Iron Deficiency Anemia; Heart Failure; Anemia

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INTRODUCTION

Iron is an important trace element and an essential component of hemoglobin, myoglobin, cytochromes, and proteins responsible for oxygen storage, transport, and utilization.[1-3] It is critical for oxidative energy generation. Therefore, cells with high energy demand, such as cardiac myocytes, are especially sensitive to iron underutilization.[4] Iron deficiency (ID), regardless of the presence of anemia, can manifest as reduced quality of life, exercise capacity,[5] and survival.[6]

The prevalence of ID ranges between 2% and 10% in the general population.[7,8] In patients with heart failure (HF), dietary iron intake[9] and enteral absorption are reduced[10] and systemic inflammation is elevated,[11] with prevalence of ID being as high as 50–60%.[12-14] Patients with ID had worse prognosis,[13,15,16] but its correction with intravenous (IV) iron supplementation improved the clinical outcomes.[17-20]

Despite the clinical importance of ID in HF, data on its prevalence are scarce, especially in East Asians.[21] Therefore, in this prospective, multicenter study, we sought for the first time to determine the prevalence and risk factors of ID and ID anemia (IDA) in Korean patients with HF.

METHODS

Study population

In the FErrous Renown and UpShot in Korean Acute Heart Failure Patients (FERUS-HF) study, we prospectively enrolled patients hospitalized for acute HF at five tertiary university hospitals from January to November 2019 in Korea (clinical trials.gov: NCT04812873). Patients ≥ 19 years of age who had objective findings of structural and/or functional disorder of the heart with one of the following criteria were enrolled: 1) symptoms of HF, 2) signs of HF, or 3) lung congestion in chest X-ray. Patients who declined consent were excluded. Total 465 patients were enrolled initially in this study, and 4 patients were additionally excluded because of missing laboratory tests.

Study variables and definitions

Routine blood sampling and tests were conducted by laboratories at each center that were certified by the Korean Association of Quality Assurance for Clinical Laboratory at the index admission. Laboratory measurements regarding iron status were performed in laboratories of the participating centers after study enrollment and before discharge. Hematological measurements were performed using fresh venous blood with ethylenediaminetetraacetic acid. Ferritin (ng/mL), serum iron (μg/dL), total iron binding capacity (TIBC, μg/dL), and transferrin (mg/dL) were measured directly. Transferrin saturation was calculated as the ratio of serum iron and TIBC multiplied by 100. ID was defined as serum ferritin < 100 μg/L or ferritin 100–299 μg/L in combination with transferrin saturation of < 20%.[18,19] Anemia was defined as a hemoglobin concentration of < 12 g/dL in women and < 13 g/dL in men. IDA was defined as the presence of both ID and anemia. Chronic kidney disease (CKD) was defined as estimated glomerular filtration rate < 60 mL/min/1.73 m^2.

All echocardiographic studies were performed using a standard ultrasound machine with a 2.5-MHz probe. Left ventricular ejection fraction (LVEF) was measured using Simpson's biplane method unless this method was not possible. Based on the echocardiographic

findings performed at the index acute HF hospitalization, patients were classified into those with HF with reduced ejection fraction (LVEF ≤ 40%), HF with mildly reduced ejection fraction (LVEF, 41–49%), and HF with preserved ejection fraction (LVEF ≥ 50%).[22-24] Valvular heart disease was defined as greater than mild stenosis or regurgitation, and previous valve surgery.

The primary endpoint was the prevalence of ID and IDA. Anemia and ID treatment was investigated between study enrollment and discharge.

Statistical analysis

Categorical variables are reported as frequencies (percentages). Continuous variables are expressed as means ± standard deviations or medians with interquartile ranges. For comparison between groups, the χ^2 test (or Fisher's exact test when any expected cell count was < 5 for a 2 × 2 table) was used for categorical variables, while the unpaired Student's t-test or Mann-Whitney U test were used for continuous variables. A logistic regression model was used to determine the predictor of ID and IDA. Variables found to be statistically significant ($P < 0.1$) in the univariable analysis were included in the final multivariable model, except for variables with > 10% missing values or variables that were closely related to the other variables.

All tests were two-tailed, and a P value < 0.05 was considered statistically significant. Statistical analyses were performed by using R version 4.2.0 (The R Foundation for Statistical Computing, Vienna, Austria) and SAS Version 9.4 (SAS Institute, Cary, NC, USA) by a professional statistician.

Ethics statement

The present study protocol was reviewed and approved by the Institutional Review Board of Seoul National University Bundang Hospital (B-1811/504-302). Informed consent was submitted by all subjects when they were enrolled. This study complied with the principles of the Declaration of Helsinki.

RESULTS

Patients

Finally, we analyzed 461 patients with acute HF (**Table 1**). The mean age was 67.6 ± 14.9 years, and 61.8% were male. Furthermore, 53.2% had hypertension, 38.6% had diabetes, 37.6% had atrial fibrillation, 60.1% had CKD, and 17.8% were current smokers. The mean LVEF was 35.4 ± 16.1%. Based on the hematological measurements, the following mean values were noted: hemoglobin, 12.1 ± 2.4 g/dL; iron, 65.0 ± 39.3 µg/dL; TIBC, 290.5 ± 82.7 µg/dL; transferrin saturation, 23.6 ± 14.6% and ferritin, 224.6 ± 453.8 ng/mL. Regarding antithrombotic medication, 11.3%, 34.5%, 36.9%, and 28.6% received warfarin, new oral anticoagulants, aspirin, and P2Y$_{12}$ inhibitors, respectively.

ID

Among total patients, 53.8% of patients had ID (**Fig. 1**). **Table 1** shows the baseline characteristics of patients with and without ID. Patients with ID were more likely to be female (46.4% vs. 28.6%, $P < 0.001$), have diabetes (43.2% vs. 33.3%, $P = 0.031$), have a valvular heart disease (14.1% vs. 7.0%, $P = 0.015$), and have a higher heart rate (87.2 ± 22.8 beats/min vs. 83.0 ± 21.3 beats/min, $P = 0.046$). Regarding laboratory findings, patients with ID had lower hemoglobin levels (11.8 ± 2.3 mg/dL vs. 12.5 ± 2.5 mg/dL, $P = 0.001$) and ferritin levels (80.5 ±
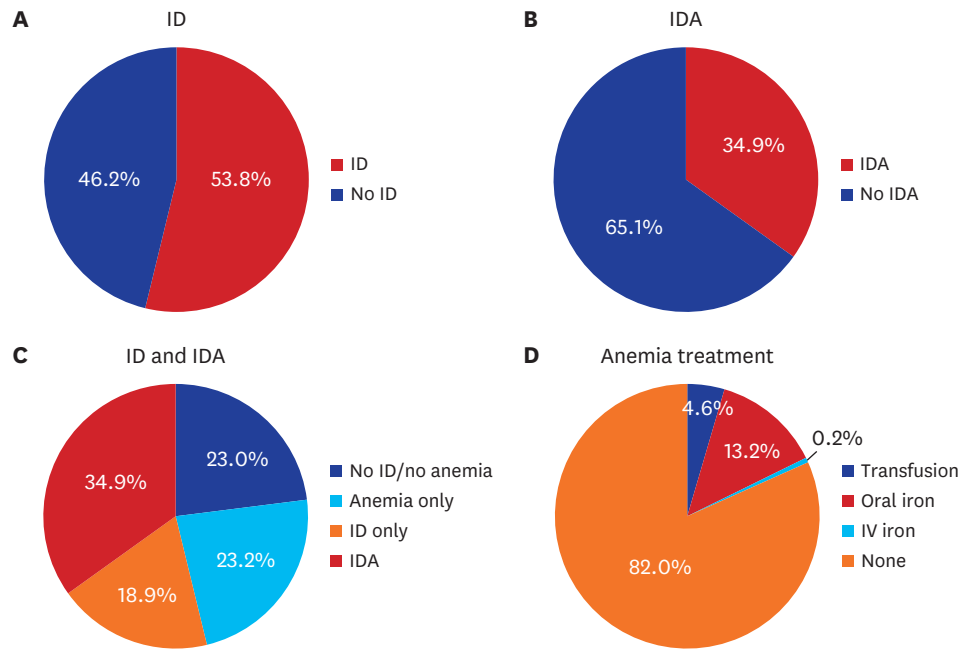
Fig. 1. Prevalence of various parameters regarding iron deficiency and anemia. (**A**) Prevalence of ID. (**B**) Prevalence of IDA. (**C**) Prevalence of ID and IDA. (**D**) Treatment pattern of anemia.
ID = iron deficiency, IDA = iron deficiency anemia, IV = intravenous.

Table 1. Baseline characteristics of the study population

Characteristics	All patients (N = 461)	ID			IDA		
		ID (n = 248)	No ID (n = 213)	P value	IDA (n = 161)	No IDA (n = 300)	P value
Age, yr	67.6 ± 14.9	68.0 ± 14.9	67.2 ± 15.0	0.445	71.5 ± 12.1	65.51 ± 15.9	< 0.001
Men	285 (61.8)	133 (53.6)	152 (71.4)	< 0.001	87 (54.0)	198 (66.0)	0.012
Body mass index, kg/m² (n = 291)	24.7 ± 5.0	24.5 ± 4.8	25.0 ± 5.3	0.445	23.5 ± 3.8	25.26 ± 5.4	0.012
De novo HF	169 (36.7)	100 (40.3)	69 (32.4)	0.096	55 (34.2)	114 (38.0)	0.475
Ischemic etiology	110 (23.8)	65 (26.2)	45 (21.1)	0.243	46 (28.6)	64 (21.3)	0.105
Comorbidities							
Hypertension	245 (53.2)	135 (54.4)	110 (51.6)	0.549	88 (54.7)	157 (52.3)	0.633
Diabetes mellitus	178 (38.6)	107 (43.2)	71 (33.3)	0.031	78 (48.5)	100 (33.3)	0.002
Chronic kidney disease	277 (60.1)	145 (58.5)	132 (62.0)	0.503	104 (66.2)	173 (56.9)	0.066
Ischemic heart disease	159 (34.5)	90 (36.3)	69 (32.4)	0.380	64 (39.8)	95 (31.7)	0.082
Valvular heart disease	50 (10.9)	35 (14.1)	15 (7.0)	0.015	27 (16.8)	23 (7.7)	0.003
Atrial fibrillation	173 (37.6)	90 (36.4)	83 (39.0)	0.577	59 (36.9)	114 (38.0)	0.813
COPD	53 (11.5)	27 (10.9)	26 (12.2)	0.658	19 (11.8)	34 (11.3)	0.881
Cerebrovascular disease	38 (8.2)	19 (7.7)	19 (8.9)	0.624	18 (11.2)	20 (6.7)	0.093
Malignancy	39 (8.5)	24 (9.7)	15 (7.0)	0.311	16 (9.9)	23 (7.7)	0.404
Current smoking	82 (17.8)	37 (14.9)	45 (21.1)	0.082	15 (9.3)	67 (22.3)	< 0.001
Physical exam (at admission)							
Systolic BP, mmHg	121.2 ± 25.7	123.1 ± 27.5	119.1 ± 23.4	0.310	123.6 ± 27.6	119.9 ± 24.6	0.371
Diastolic BP, mmHg	73.0 ± 17.8	74.0 ± 17.7	71.9 ± 18.0	0.214	70.8 ± 15.4	74.2 ± 18.9	0.089
Heart rate, beats/min	85.3 ± 22.2	87.2 ± 22.8	83.0 ± 21.3	0.046	83.6 ± 21.1	86.2 ± 22.7	0.265
Laboratory test results							
Iron, μg/dL	65.0 ± 39.3	52.0 ± 33.3	80.2 ± 40.4	< 0.001	45.9 ± 33.2	75.3 ± 38.6	< 0.001
TIBC, μg/dL	290.5 ± 82.7	316.7 ± 85.0	260.0 ± 68.6	< 0.001	301.5 ± 68.0	284.6 ± 89.2	0.008
Transferrin saturation, %	23.6 ± 14.6	16.7 ± 9.4	31.6 ± 15.4	< 0.001	15.5 ± 9.6	27.9 ± 15.0	< 0.001
Ferritin, ng/mL	224.6 ± 453.8	80.5 ± 60.3	392.4 ± 624.5	< 0.001	81.6 ± 63.2	301.4 ± 545.6	< 0.001
Hemoglobin, mg/dL	12.1 ± 2.4	11.8 ± 2.3	12.5 ± 2.5	0.001	10.4 ± 1.3	13.0 ± 2.4	< 0.001
Anemia	268 (58.1)	161 (64.9)	107 (50.2)	0.001	161 (100.0)	107 (35.7)	< 0.001

(continued to the next page)

Table 1. (Continued) Baseline characteristics of the study population

Characteristics	All patients (N = 461)	ID (n = 248)	No ID (n = 213)	P value	IDA (n = 161)	No IDA (n = 300)	P value
WBC, 10^9/L	7.47 ± 2.94	7.24 ± 2.85	7.73 ± 3.03	0.121	6.91 ± 2.79	7.77 ± 2.98	0.002
Platelet, 10^9/L	213.5 ± 82.3	218.5 ± 79.5	207.8 ± 85.2	0.152	216.6 ± 85.7	211.9 ± 80.4	0.911
BUN, mg/dL	28.8 ± 17.1	28.6 ± 16.5	29.1 ± 17.8	0.787	31.3 ± 18.3	27.5 ± 16.3	0.021
Creatinine, mg/dL	1.56 ± 1.32	1.49 ± 1.17	1.65 ± 1.47	0.432	1.66 ± 1.37	1.51 ± 1.29	0.062
eGFR, mL/min/1.73 m²	62.6 ± 34.2	61.8 ± 33.2	63.5 ± 35.4	0.657	57.2 ± 34.4	65.5 ± 33.9	0.004
BNP, pg/mL (n = 207)	843 (476–2,060)	843 (522–1,793)	844 (367–3,013)	0.837	852 (540–1,980)	834 (439–2,263)	0.205
NT-proBNP, pg/mL (n = 269)	4,430 (2,211–10,533)	4,394 (2,320–11,437)	4,448 (2,131–10,480)	0.979	5,467 (2,283–12,890)	4,249 (2,147–96,587)	0.205
NP above median (n = 459)	230 (50.1)	124 (50.4)	106 (49.8)	0.965	86 (55.1)	144 (47.5)	0.149
Echocardiography (n = 346)							
LVEF, %	35.4 ± 16.1	36.1 ± 16.5	34.4 ± 15.6	0.352	37.9 ± 16.6	33.9 ± 15.7	0.024
Heart failure type				0.362			0.225
HF with reduced EF	233 (67.3)	122 (64.6)	111 (70.7)		77 (61.6)	156 (70.6)	
HF with mildly reduced EF	39 (11.3)	25 (13.2)	14 (8.9)		16 (12.8)	23 (10.4)	
HF with preserved EF	74 (21.4)	42 (22.2)	32 (20.4)		32 (25.6)	42 (19.0)	
Medication at admission							
ARNI/ACEi/ARB (n = 382)	278 (72.8)	153 (73.2)	125 (72.3)	0.835	94 (67.6)	184 (75.7)	0.087
Beta-blocker (n = 382)	263 (68.9)	140 (67.0)	123 (71.1)	0.388	91 (65.5)	172 (70.8)	0.281
MRA (n = 382)	208 (54.5)	120 (57.4)	88 (50.9)	0.201	73 (52.5)	135 (55.6)	0.566
Ivabradine (n = 382)	30 (7.9)	21 (10.1)	9 (5.2)	0.080	11 (7.9)	19 (7.8)	0.974
Loop diuretics (n = 382)	322 (84.3)	185 (88.5)	137 (79.2)	0.013	123 (88.5)	199 (81.9)	0.088
Warfarin	52 (11.3)	26 (10.5)	26 (12.2)	0.560	18 (11.2)	34 (11.3)	0.961
NOAC	159 (34.5)	91 (36.7)	68 (31.9)	0.283	56 (34.8)	103 (34.3)	0.923
Aspirin	170 (36.9)	93 (37.5)	77 (36.2)	0.765	71 (44.1)	99 (33.0)	0.019
P2Y$_{12}$ inhibitors	132 (28.6)	79 (31.9)	53 (24.9)	0.099	62 (38.5)	70 (23.3)	< 0.001
Clopidogrel	123 (26.7)	76 (30.7)	47 (22.1)	0.038	60 (37.3)	63 (21.0)	< 0.001
SGLT2 inhibitors	25 (5.4)	15 (6.1)	10 (4.7)	0.522	9 (5.6)	16 (5.3)	0.908
Anemia and ID treatment							
Transfusion	21 (4.6)	10 (4.0)	11 (5.2)	0.561	8 (5.0)	13 (4.3)	0.755
Iron supplement							
Oral	61 (13.2)	38 (15.3)	23 (10.8)	0.153	36 (22.4)	25 (8.3)	< 0.001
Intravenous	1 (0.2)	1 (0.4)	0 (0)	> 0.999	1 (0.6)	0 (0)	0.349
In-hospital death	6 (1.3)	3 (1.2)	3 (1.4)	> 0.999	3 (1.9)	3 (1.0)	0.414

Values are expressed as number (%), mean ± standard deviation, or median (interquartile range).
ACEi = angiotensin-converting enzyme inhibitor, ARNI = angiotensin receptor-neprilysin inhibitor, ARB = angiotensin II receptor blocker, BNP = B-type natriuretic peptide, BP = blood pressure, BUN = blood urea nitrogen, COPD = chronic obstructive pulmonary disease, EF = ejection fraction, eGFR = estimated glomerular filtration rate, HF = heart failure, ID = iron deficiency, IDA = iron deficiency anemia, LVEF = left ventricular ejection fraction, MRA = mineralocorticoid receptor antagonist, NOAC = non-vitamin K oral anticoagulants, NP = natriuretic peptide, NT-proBNP = N-terminal pro-B-type natriuretic peptide, SGLT2 = sodium glucose cotransporter 2, TIBC = total iron binding capacity, WBC = white blood cell.

60.3 mg/dL vs. 392.4 ± 624.5 mg/dL, P < 0.001) than patients without ID. The prescription of clopidogrel was more prevalent in the ID group (30.7% vs. 22.1%, P = 0.038). The prevalence of CKD and malignancy did not differ significantly between patients with and without ID. The prevalence of ID was not significantly different between patients with ischemic HF or non-ischemic HF (59.1% vs. 52.1%, P = 0.243).

Regarding the treatment of anemia and ID, 4.6%, 13.2%, and 0.2% received blood transfusion, oral iron replacement, and IV iron replacement, respectively. The treatment did not differ between patients with and without ID. Among total 461 patients, 6 patients died before discharge. The in-hospital mortality rate did not differ between ID and non-ID patients (3/248 vs. 3/213; P > 0.999).

Logistic regression models to determine the predictor of ID are shown in **Table 2**. In the multivariable logistic regression analysis, the independent predictors of ID were female sex (odds ratio [OR], 2.19; 95% confidence interval [CI], 1.47–3.30), valvular heart disease (OR,

2.10; 95% CI, 1.10–4.17), heart rate (OR, 1.10; 95% CI, 1.01–1.21), anemia (OR, 1.60; 95% CI, 1.07–2.40), and the use of clopidogrel (OR, 1.56; 95% CI, 1.00–2.45) (**Table 2**).

ID in women

Because female sex was the most important predictor of ID, we performed various post-hoc analyses according to sex, age, body mass index (BMI), NP levels and menopause, among others (**Table 3**). The prevalence of ID was significantly higher in females than in males (65.3% vs. 47.3%, $P < 0.001$). Interestingly, when stratifying the patients according to age, both the younger and older subgroups of females had a higher prevalence of ID than their male counterparts. Furthermore, there was no difference in the ID prevalence between the younger and older women. Similar findings were observed in subgroups stratified by different BMI cutoffs; females classified with low and high BMI had a trend toward higher ID prevalence than their male counterparts. Again, there was no difference in the ID prevalence between the women with low and high BMI. Similar findings were observed when stratified based on the

Table 2. Predictors of ID and IDA

Variables	Univariable analysis			Multivariable analysis		
	OR	95% CI	P value	OR	95% CI	P value
Predictor of ID						
Age, per 10 yr	1.03	0.92–1.18	0.538			
Female	2.15	1.47–3.19	< 0.001	2.19	1.47–3.30	< 0.001
BMI, kg/m²	0.98	0.94–1.02	0.360			
Ischemic heart disease	1.19	0.81–1.75	0.380			
Diabetes mellitus	1.51	1.03–2.22	0.031	1.47	0.98–2.21	0.060
Chronic kidney disease	0.86	0.59–1.26	0.444			
Valvular heart disease	2.17	1.17–4.20	0.017	2.10	1.10–4.17	0.028
Malignancy	1.41	0.73–2.82	0.313			
Smoking	0.65	0.40–1.06	0.084			
Heart rate, per 10 b.p.m	1.09	1.00–1.19	0.049	1.10	1.01–1.21	0.025
Anemia	1.83	1.26–2.67	0.002	1.60	1.07–2.40	0.021
Above NP	1.03	0.71–1.48	0.891			
LVEF, per %	1.01	0.99–1.02	0.346			
Warfarin	0.84	0.47–1.50	0.560			
NOAC	1.23	0.84–1.82	0.283			
Aspirin	1.06	0.73–1.55	0.765			
Clopidogrel	1.56	1.03–2.39	0.039	1.56	1.00–2.45	0.049
Predictor of IDA						
Age, per 10 yr	1.35	1.17–1.56	< 0.001	1.24	1.06–1.46	0.008
Female	1.77	1.19–2.62	0.005	1.45	0.93–2.26	0.103
BMI, kg/m²	0.92	0.88–0.97	0.002			
Ischemic heart disease	1.39	0.93–2.08	0.105			
Diabetes mellitus	1.78	1.21–2.65	0.004	1.62	1.07–2.47	0.024
Chronic kidney disease	1.46	1.00–2.23	0.053			
Valvular heart disease	2.54	1.40–4.63	0.002	3.03	1.62–5.76	< 0.001
Malignancy	1.37	0.70–2.69	0.339			
Smoking	0.37	0.20–0.66	0.001	0.54	0.27–0.98	0.044
Heart rate, per 10 b.p.m	0.95	0.87–1.04	0.306			
Above NP	1.36	0.92–2.00	0.123			
LVEF, per %	1.02	1.00–1.03	0.017			
Warfarin	1.03	0.55–1.87	0.928			
NOAC	1.08	0.72–1.62	0.702			
Aspirin	1.51	1.02–2.24	0.040	1.26	0.81–1.97	0.300
Clopidogrel	2.06	1.34–3.14	< 0.001	1.96	1.22–3.15	0.005

Variables found to be statistically significant ($P < 0.1$) in the univariable analysis were included in the final multivariable model, except for variables with > 10% missing values or variables that were closely related to the other variables.
BMI = body mass index, CI = confidence interval, ID = iron deficiency, IDA = iron deficiency anemia, LVEF = left ventricular ejection fraction, NOAC = non-vitamin K oral anticoagulants, NP = natriuretic peptide; OR = odds ratio.

Table 3. Prevalence of iron deficiency according to subtype

Variables	All (N = 461)	Men (n = 285)	Women (n = 176)	P value
Overall	248 (53.8)	135 (47.3)	115 (65.3)	< 0.001
Age, yr				
< 50 (n = 60)	33 (55.0)	24 (50.0)	9 (75.0)	0.120
≥ 50 (n = 401)	215 (53.6)	109 (46.0)	106 (64.6)	< 0.001
P value	0.951	0.612	0.547	
< 65 (n = 168)	88 (52.4)	60 (46.2)	28 (73.7)	0.003
≥ 65 (n = 293)	160 (54.6)	73 (47.1)	87 (63.0)	0.006
P value	0.716	0.874	0.222	
Body mass index, kg/m² (n = 291)				
< 20 (n = 42)	22 (52.4)	14 (51.9)	8 (53.3)	0.927
≥ 20 (n = 249)	144 (57.8)	71 (49.3)	73 (69.5)	0.001
P value	0.623	0.808	0.244	
< 23 (n = 118)	70 (59.3)	35 (54.7)	35 (64.8)	0.265
≥ 23 (n = 173)	96 (55.5)	50 (46.7)	46 (69.7)	0.003
P value	0.598	0.314	0.570	
< 25 (n = 177)	103 (58.2)	54 (52.4)	49 (66.2)	0.067
≥ 25 (n = 114)	63 (55.3)	31 (45.6)	32 (69.6)	0.012
P value	0.710	0.381	0.703	
Natriuretic peptide (n = 459)				
< Median (n = 229)	122 (53.3)	62 (43.4)	60 (69.8)	< 0.001
≥ Median (n = 230)	124 (53.9)	69 (49.3)	55 (61.1)	0.105
P value	0.965	0.378	0.295	

Values are expressed as number (%).

median NP levels. Lastly, the prevalence of ID did not differ between those with and without menopause (menopause: 103/157 [65.6%] vs. no menopause: 12/19 [63.2%], P = 0.832).

IDA

In this study, 34.9% of patients had IDA. They were older, more likely to be female, have diabetes, have valvular heart disease, and use clopidogrel, among others (**Table 1**). The independent predictors of IDA were older age, diabetes mellitus, valvular heart disease, non-smoking, and the use of clopidogrel (**Table 2**).

Stratification according to ID and anemia

Next, we classified the patients according to the presence of anemia and ID. Overall, 193 (41.9%) patients had no anemia, while 268 (58.1%) patients had anemia (**Table 4**). Patients with anemia were older and had a lower BMI than those without anemia. Interestingly, the

Table 4. Baseline characteristics according to anemia and iron deficiency

Characteristics	All patients	No anemia		Anemia	
		No ID/No anemia	ID only	Anemia only	IDA
Total	461 (100)	106 (23.0)	87 (18.9)	107 (23.2)	161 (34.9)
Age, yr	67.6 ± 14.9	63.3 ± 16.7	61.5 ± 17.3	70.9 ± 11.9	71.5 ± 12.1
Men	285 (61.8)	82 (77.4)	46 (52.9)	70 (65.4)	87 (54.0)
Body mass index, kg/m²	24.7 ± 5.0	25.8 ± 5.7	25.8 ± 5.6	23.9 ± 4.7	23.5 ± 3.8
De novo HF	169 (36.7)	43 (40.1)	45 (51.7)	26 (24.3)	55 (34.2)
Ischemic etiology	110 (23.8)	21 (19.8)	15 (17.2)	24 (22.4)	50 (31.1)
Comorbidities					
Hypertension	245 (53.2)	52 (49.1)	47 (54.0)	58 (54.2)	88 (54.7)
Diabetes mellitus	178 (38.6)	30 (28.3)	29 (33.3)	41 (38.3)	78 (48.5)
Chronic kidney disease	277 (60.1)	51 (48.1)	39 (44.8)	81 (75.7)	106 (65.8)
Ischemic heart disease	159 (34.5)	25 (23.6)	26 (29.9)	44 (41.1)	64 (39.8)
Valvular heart disease	50 (10.9)	3 (2.8)	8 (9.2)	12 (11.2)	27 (16.8)
Atrial fibrillation	173 (37.6)	47 (44.3)	31 (35.6)	36 (33.6)	59 (36.8)
COPD	53 (11.5)	13 (12.3)	8 (9.2)	13 (12.2)	19 (11.8)

(continued to the next page)

Table 4. (Continued) Baseline characteristics according to anemia and iron deficiency

Characteristics	All patients	No anemia		Anemia	
		No ID/No anemia	ID only	Anemia only	IDA
Cerebrovascular disease	38 (8.2)	7 (6.6)	1 (1.2)	12 (11.2)	18 (11.2)
Malignancy	39 (8.5)	5 (4.7)	8 (9.2)	10 (9.4)	16 (9.9)
Current smoking	82 (17.8)	26 (24.5)	22 (25.3)	19 (17.8)	15 (9.3)
Physical exam (at admission)					
Systolic BP, mmHg	121.2 ± 25.7	118.0 ± 22.2	122.1 ± 27.4	120.1 ± 24.6	123.6 ± 27.6
Diastolic BP, mmHg	73.0 ± 17.8	73.8 ± 18.9	79.9 ± 20.0	70.0 ± 16.8	70.8 ± 15.4
Heart rate, beats/min	85.3 ± 22.2	84.9 ± 22.9	93.9 ± 24.5	81.2 ± 19.5	83.6 ± 21.1
Laboratory test results					
Iron, µg/dL	65.0 ± 39.3	86.0 ± 37.5	63.1 ± 30.8	74.5 ± 42.4	45.9 ± 33.2
TIBC, µg/dL	290.5 ± 82.7	290.9 ± 60.2	344.7 ± 104.5	229.4 ± 62.6	301.5 ± 68.0
Transferrin saturation, %	23.6 ± 14.6	29.9 ± 12.2	18.9 ± 8.7	33.2 ± 18.0	15.5 ± 9.6
Ferritin, ng/mL	224.6 ± 453.8	295.1 ± 252.6	78.6 ± 54.8	488.7 ± 835.4	81.6 ± 63.2
Hemoglobin, mg/dL	12.1 ± 2.4	14.5 ± 1.4	14.2 ± 1.4	10.5 ± 1.6	10.4 ± 1.3
Anemia	268 (58.1)	0 (0.0)	0 (0.0)	107 (100.0)	161 (100.0)
WBC, 10^9/L	7.47 ± 2.94	7.83 ± 2.44	7.86 ± 2.87	7.63 ± 3.53	6.91 ± 2.79
Platelet, 10^9/L	213.5 ± 82.3	210.2 ± 68.5	222.1 ± 66.2	205.5 ± 99.1	216.6 ± 85.7
BUN, mg/dL	28.8 ± 17.1	23.1 ± 11.5	23.6 ± 10.7	34.8 ± 20.8	31.3 ± 18.3
Creatinine, mg/dL	1.56 ± 1.32	1.16 ± 0.46	1.16 ± 0.53	2.13 ± 1.91	1.66 ± 1.37
eGFR, mL/min/1.73 m^2	62.6 ± 34.2	74.6 ± 29.6	70.5 ± 29.3	52.6 ± 37.4	57.2 ± 34.4
BNP, pg/mL (n = 207)	843 (476–2,060)	392 (219–1,259)	828 (500–1,346)	2,015 (753–3,601)	851 (534–1,978)
NT-proBNP, pg/mL (n = 269)	4,430 (2,211–10,533)	3,056 (1,518–5,872)	3,483 (2,194–7,750)	7,561 (3,788–20,498)	5,467 (2,320–13,162)
NP above median (n = 459)	230 (50.1)	34 (32.1)	36 (41.9)	72 (67.3)	88 (55.0)
Echocardiography (n = 346)					
LVEF, %	35.4 ± 16.1	30.3 ± 13.1	32.6 ± 15.9	38.1 ± 16.8	37.9 ± 16.6
Heart failure type					
HF with reduced EF	233 (67.3)	60 (81.1)	45 (70.3)	51 (61.5)	77 (61.6)
HF with mildly reduced EF	39 (11.3)	6 (8.1)	9 (14.1)	8 (9.6)	16 (12.8)
HF with preserved EF	74 (21.4)	8 (10.8)	10 (15.6)	24 (28.9)	32 (25.6)
Medication at admission					
ARNI/ACEi/ARB (n = 382)	278 (72.8)	65 (78.3)	59 (84.3)	60 (66.7)	94 (67.6)
Beta-blocker (n = 382)	263 (68.9)	66 (79.5)	49 (70.0)	57 (63.3)	91 (65.5)
MRA (n = 382)	208 (54.5)	55 (66.3)	47 (67.1)	33 (36.7)	73 (52.5)
Ivabradine (n = 382)	30 (7.9)	3 (3.6)	10 (14.3)	6 (6.7)	11 (7.9)
Loop diuretics (n = 382)	322 (84.3)	74 (89.2)	62 (88.6)	63 (70.0)	123 (88.5)
Warfarin	52 (11.3)	12 (11.3)	8 (9.2)	14 (13.1)	18 (11.2)
NOAC	159 (34.5)	40 (37.7)	35 (40.2)	28 (26.2)	56 (34.8)
Aspirin	170 (36.9)	33 (31.1)	22 (25.3)	44 (41.1)	71 (44.1)
P2Y$_{12}$ inhibitors	132 (28.6)	24 (22.6)	17 (19.5)	29 (27.1)	62 (38.5)
Clopidogrel	123 (26.7)	21 (19.8)	16 (18.4)	26 (24.3)	60 (37.3)
SGLT2 inhibitors	25 (5.4)	9 (8.5)	6 (6.9)	1 (0.9)	9 (5.6)
Anemia and ID treatment					
Transfusion	21 (4.6)	3 (2.8)	2 (2.3)	8 (7.5)	8 (5.0)
Iron supplement					
Oral iron	61 (13.2)	6 (5.7)	2 (2.3)	17 (15.9)	36 (22.4)
Intravenous	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
In-hospital death	6 (1.3)	2 (1.9)	0 (0.0)	1 (0.9)	3 (1.9)

Values are expressed as number (%), mean ± standard deviation, or median (interquartile range).
ACEi = angiotensin-converting enzyme inhibitor, ARNI = angiotensin receptor-neprilysin inhibitor, ARB = angiotensin II receptor blocker, BNP = B-type natriuretic peptide, BP = blood pressure, BUN = blood urea nitrogen, COPD = chronic obstructive pulmonary disease, EF = ejection fraction, eGFR = estimated glomerular filtration rate, HF = heart failure, ID = iron deficiency, IDA = iron deficiency anemia, LVEF = left ventricular ejection fraction, MRA = mineralocorticoid receptor antagonist, NOAC = non-vitamin K oral anticoagulants, NP = natriuretic peptide, NT-proBNP = N-terminal pro-B-type natriuretic peptide, SGLT2 = sodium glucose cotransporter 2, TIBC = total iron binding capacity, WBC = white blood cell.

baseline characteristics were comparable between non-anemic patients with and without ID. The same was true for anemic patients with and without ID. Also, among patients with ID, patients with IDA were more likely to be older and had a lower BMI, higher prevalence of diabetes and CKD, and higher use of aspirin and clopidogrel, and oral iron supplementation than those with non-anemic ID (**Supplementary Table 1**).

DISCUSSION

The main findings of the current study were as follows: 1) more than half and one-third of the patients hospitalized for acute HF had ID and IDA, respectively; 2) the most important predictor of ID was female sex; and 3) the treatment with IV iron supplementation was very low in these patients. In this study of patients with acute HF in Korea, 53.8% had ID, similar to previous reports. In patients with chronic HF, the prevalence of ID was 50% in an international pooled cohort from Poland, Spain, and the Netherlands,[12] 61% in 574 community-dwelling HF patients in the United States,[25] and 61% among Southeast Asian HF patients.[26] Meanwhile, in patients with acute HF, ID was present in up to 80%.[27,28]

We showed that female sex, valvular heart disease, high heart rate, anemia, and the use of clopidogrel were independent predictors of ID. The use of clopidogrel is associated with an increased risk of bleeding, anemia, and iron loss.[29] Interestingly, the use of aspirin was not the predictor of ID, which has been reported in other study as well.[30] A higher heart rate may be more of a marker rather than a mediator of ID. In our study, CKD and malignancy were not a predictor of ID and IDA. Also, median value of NP and prevalence of NP above the median were not significantly different between patients with ID or without. Furthermore, neither LVEF nor HF type was associated with ID. NP level, which reflects the disease severity of HF, was a powerful predictor of ID in previous studies,[13] and the same finding was seen for LVEF.[26] The reason for the different results between ours and those may be due to ethnic difference or relatively small sample size of our study. Previous studies suggested that inflammation was associated with ID, and there was more inflammatory milieu in women.[31,32] Further researches are needed to evaluate the relationship between ID and inflammation.

Our study confirmed that female sex is an important predictor of ID, which is in line with previous studies.[12,26] To elucidate the reasons for this, we performed a few subgroup analyses. The main causes of ID include decreased dietary intake, reduced absorption, and blood loss. The possible causes of ID in HF include cachexia/malnutrition, decreased iron resorption in the intestine due to congestion in the splanchnic area, and decreased iron utilization due to inflammation because HF itself is an inflammatory disease.[33]

It has been a well-accepted concept that menstruation is the leading cause of ID in females; however, when stratifying the patients according to age (i.e., 50 years and 65 years), the prevalence of ID did not differ between younger and older females, as well as between those with and without menopause. The median age of menopause in Korean women is 50 years.[34] These results suggest that blood loss from menstruation is a unlikely cause of ID.[26]

We believe that stratification by BMI may infer the association between nutritional status and ID. Also, not only malnutrition but obesity is known to be associated with ID.[35-37] Females had a higher prevalence of ID than males, regardless of their BMI. In addition, there was no difference in the prevalence of ID between females with high and low BMI.

Reduced iron absorption can occur in patients with HF who have poor visceral circulation, i.e., congestion. NP is a hormone that is secreted in the ventricles in response to increased myocardial wall stress, which is proportional to the intra-cardiac pressure.[38] As such, the NP level can be used as a surrogate for congestion. Interestingly, females had more ID than males, regardless of NP level. In addition, there was no difference in the ID prevalence between females with high and low NP levels.

Taken together, it is unclear why females have more ID than men with HF. Because ID is an important risk factor for outcomes in HF, further research is warranted.

ID occurs in three stages: 1) depletion of iron storage without causing anemia, 2) followed by iron-restricted erythropoiesis, and 3) finally by hypochromic and microcytic anemia. Therefore, one may expect a gradual "aggravation" of the characteristics from normal (no ID/no anemia) to IDA. In this study, the anemic patients had more unfavorable clinical characteristics than the non-anemic patients. More importantly, among the anemic patients, those with and without ID had similar characteristics. The same was observed in the non-anemic patients with and without ID. For example, the mean age of anemic patients with and without ID was 70.9 ± 11.9 years and 71.5 ± 12.1 years, respectively, whereas that of non-anemic patients with and without ID was 63.3 ± 16.7 and 61.5 ± 17.3 years, respectively. These findings have important clinical implications. Because there is no obvious clinical factor that makes the presence of ID highly likely, routine laboratory tests should be performed to detect ID in HF, especially since HF is a disease with increasing prevalence and is associated with high morbidity and mortality.[21,39]

A striking finding was that only 0.2% of patients received IV iron replacement, and 13.2% received oral iron supplements. Oral iron supplementation did not improve the clinical outcomes,[40] whereas IV iron replacement with ferric carboxymaltose improved outcomes in both chronic[17,18,20,41] and acute HF.[19] Consequently, current practice guidelines recommend IV iron in patients with HF and ID.[22-24] Although this study enrollment was performed in 2019, the low prescription rate is alarming. Because the prescription rates of renin-angiotensin system modulators and beta-blockers in Korea are comparable to those of the United States and Europe,[21,42] both the lack of knowledge and inertia to administer IV iron may be the reasons for the unacceptably low application of adequate ID management.

This study has several limitations. First, since this study was conducted at tertiary university hospitals, the results might not be generalized to other settings (e.g., community or primary settings). Second, our study had a relatively small number of patients, and statistical insignificance of prevalence of ID according to age, BMI, median NP levels, and menopause might be due to small sample size. Third, we could not evaluate the impact of presence of ID in the clinical course of HF except for in-hospital mortality because our study focused on the cross-section of patients' characteristics. It is expected that further research will be possible in the future by collecting long-term clinical outcomes. Fourth, information on co-morbidities including previous surgery, chemotherapy, liver disease, or thyroid disease was missing, although these co-morbidities are likely to be associated with ID and anemia. Fifth, because not all patients were de-novo HF in our study, some patients might already have an oral or IV iron supplement before the index admission which may have affected the iron profile at the index admission. Despite these limitations, this study had certain strengths, showing prevalence of ID in Asian patients with HF.

In conclusion, the prevalence of ID is high in hospitalized Korean HF patients. Because ID cannot be diagnosed by clinical parameters, routine laboratory examinations are necessary to identify patients with ID.

ACKNOWLEDGMENTS

SUPPLEMENTARY MATERIAL

Supplementary Table 1
Baseline characteristics between patients with IDA and ID only

Click here to view

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