



## Iron Deficiency and the Risk of Incident Left Ventricular Dysfunction in Patients with Coronary Artery Disease: A Single-center Cohort Study

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**Background:** Heart failure (HF) is a complex and life-threatening condition that often coexists with comorbidities such as hypertension, type 2 diabetes mellitus, coronary artery disease (CAD), and iron deficiency (ID). However, the relationship between ID and the development of HF remains poorly understood. **Aim:** This study aimed to investigate the correlation between ID and the development of left ventricular dysfunction. **Methods:** A total of 64,661 patients diagnosed with CAD at a tertiary hospital between 2011 and 2023 were recruited. Of these, 4813 patients who underwent iron status evaluation, including serum iron (SI), total iron-binding capacity (TIBC), and ferritin within 30 days, were included in the analysis. We compared the incidence and hazard ratio (HR) of new-onset left ventricular (LV) dysfunction (LV ejection fraction <50%) between patients with and without ID, defined as SI/TIBC or transferrin saturation (TSAT) <20% or ferritin <100 ng/mL. **Results:** The incidence of new-onset LV dysfunction was higher in patients with ID, defined by TSAT <20% compared to those with normal TSAT (HR, 1.40; 95% confidence interval [CI], 1.14–1.72) over a 13-year follow-up. In multivariable analysis, TSAT <20% retained its predictive value for new-onset LV dysfunction (adjusted HR, 1.24; 95% CI, 1.01–1.54), while ferritin levels were not correlated with the incidence of new-onset LV dysfunction in this cohort. The all-cause mortality rate was also higher in patients with ID, defined by TSAT <20% compared to those with normal TSAT. A subgroup analysis revealed no significant difference in predicting new-onset LV dysfunction between patients with ID, with or without coexisting anemia ( $P = 0.165$ ). **Conclusion:** In patients with CAD, ID, particularly defined by TSAT <20%, was predictive of future LV dysfunction and associated outcomes. Further studies are needed to investigate the underlying mechanisms and causal relationship between ID and the risk of LV dysfunction.

**Key words:** Coronary artery disease, iron deficiency, left ventricular dysfunction, heart failure, transferrin saturation

### INTRODUCTION

Heart failure (HF) is a multifaceted and often fatal condition, with its prevalence escalating with age. Despite significant advancements in prevention and treatment strategies, HF continues to impose a substantial burden on global public health, characterized by a staggering mortality rate that can reach 75% within 10 years.<sup>1</sup> This condition frequently coexists with various comorbidities, including hypertension (HTN), type 2 diabetes mellitus (DM), coronary artery disease (CAD), and iron deficiency (ID).<sup>2</sup>

Numerous studies have demonstrated the efficacy of various interventions for HF in patients with DM, HTN, and CAD. For

instance, sodium-glucose cotransporter-2 (SGLT2) inhibitors have been shown to reduce the risk of first hospitalization for HF by 29%.<sup>3</sup> Similarly, angiotensin–neprilysin inhibitor has been associated with an 18% reduction in all-cause mortality and a 21% decrease in hospitalization rates for HF.<sup>4</sup> However, ID has received comparatively less attention, despite clinical studies indicating that ferric carboxymaltose significantly improves outcomes, including the 6-min walk test distance, peak oxygen consumption, quality of life, and the New York Heart Association functional classification.<sup>5–8</sup> This oversight

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may be attributed to the suboptimal diagnostic criteria for ID in HF patients, as current biomarkers exhibit certain limitations.<sup>9</sup>

ID is notably more prevalent than anemia in HF, affecting up to 59% of nonanemic ambulatory HF patients. Furthermore, approximately 60% of individuals with CAD also present with ID.<sup>2</sup> The presence of ID and ID anemia correlates with poorer prognoses, with increasing severity linked to elevated mortality rates.<sup>9</sup> Although ID has traditionally been associated with anemia, the two conditions do not necessarily coexist. The prevalence of ID may be underestimated, as the current guidelines do not advocate for regular monitoring, and there is no consensus on the most appropriate biomarkers for assessment.

Iron serves as a critical cofactor for numerous enzymes involved in essential cellular and organismal functions, making it vital for all living cells, particularly those with high energy demands, such as cardiomyocytes, hepatocytes, neurons, renal, and skeletal muscle cells, as well as cells with high mitogenic activity, including hematopoietic and immune cells.<sup>10</sup> The underlying mechanisms linking ID and HF remain poorly elucidated; however, recent mechanistic studies underscore the potential benefits of intravenous iron supplementation.

The European Society of Cardiology (ESC) adopts a widely accepted definition of ID, characterized by a ferritin level of <100 µg/L or a ferritin level between 100 and 300 µg/L with a transferrin saturation (TSAT) of <20%.<sup>11</sup> Historically, the diagnosis of ID has heavily relied on ferritin levels. However, these levels can be significantly influenced by various factors, including inflammation, infection, chronic kidney disease, and malignancy, often resulting in elevated ferritin levels during inflammatory states, thereby obscuring the true availability of iron. TSAT, defined as the ratio of serum iron (SI) to the total iron-binding capacity of transferrin, provides a more accurate reflection of iron availability for cellular metabolism in both hematopoietic and extra hematopoietic cells. A TSAT of <20% is indicative of depleted iron reserves for target cells.<sup>2,10</sup> In this study, we aimed to utilize TSAT as a biomarker to evaluate the association with new-onset LVD and prognostication in patients with CAD.

## MATERIALS AND METHODS

### Study population

This retrospective cohort study utilized a clinical database of electronic medical records (EMRs) maintained by the Tri-Service General Hospital, a tertiary care center located in Taiwan. Approval for the study was obtained from the Institutional Review Board of Tri-Service General Hospital (IRB NO A202405127). The informed consent was waived

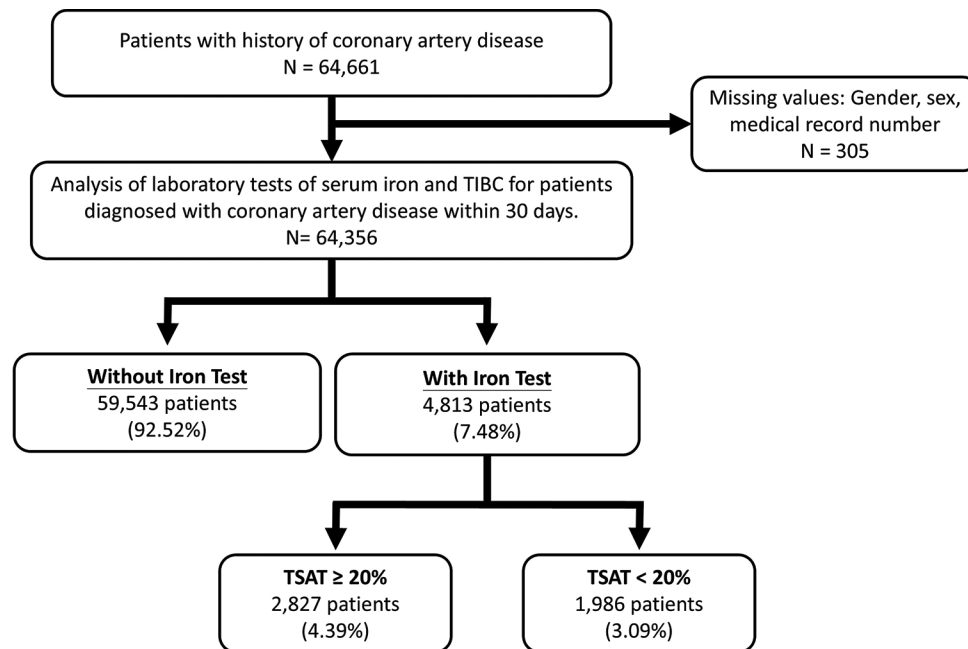
by IRB. The dataset included 64,661 patients diagnosed with CAD from January 2011 to July 2023. The extracted patient data encompassed demographic variables such as gender, age, and body mass index (BMI), along with laboratory results from SI panel tests, which included SI levels, total iron-binding capacity (TIBC), and ferritin. In addition, baseline comorbidities were identified using the International Classification of Diseases, Ninth and Tenth Revision (ICD-9 and ICD-10) codes, and other relevant baseline biochemical parameters were recorded, including serum creatinine, alanine aminotransferase, cholesterol, uric acid, fasting glucose, glycated hemoglobin (HbA1c), B-type natriuretic peptide (BNP), and N-terminal pro b-type natriuretic peptide (Pro-BNP).

All patients included in the study were required to have undergone at least one SI panel test, which could include measurements of SI levels, TIBC, or ferritin. Patients with missing records for age or gender were excluded, as were those who did not have SI panel tests during the follow-up period, as these individuals could not be included in the outcome analysis. ID was defined based on a TSAT of <20% (calculated as SI divided by TIBC) or ferritin levels below 100 ng/mL, consistent with established guidelines.<sup>12,13</sup> In addition, given that some recommendations suggest using a serum ferritin threshold of 30 µg/L to define ID,<sup>14</sup> we also assessed whether a ferritin level lower than 30 µg/L could serve as a predictor of clinical outcomes. Since TSAT is the primary focus of analysis in this study, patients were categorized into two groups: those with TSAT <20% and TSAT ≥20%, as illustrated in Figure 1.

### Observational variables

The primary endpoint of this study was the occurrence of new-onset LVD, defined as an LV ejection fraction (LVEF) of <50%, assessed by M-mode, two-dimensional imaging, or the biplane Simpson method through echocardiography. Severe LVD was defined as an LVEF of 40% or lower. Patients with a previously documented LVEF of <50% were excluded. Patients who did not undergo echocardiographic evaluation during the follow-up periods were excluded from the primary analysis. In addition, all-cause mortality, as recorded in the electronic medical records, was analyzed as a secondary clinical outcome. Patients were followed from the date of their first SI panel test until the development of LVD, mortality, or until December 31, 2023.

Data on gender, age, BMI, baseline biochemical markers, and pre-existing comorbidities were gathered for the purpose of risk assessment and comparison. Baseline biochemical measurements were collected within 30 days before or after



**Figure 1:** Flowchart of study population enrollment. N = Number of patients; TSAT: Transferrin saturation

the date of enrollment. In addition, baseline medications, such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, and SGLT2 inhibitors, were evaluated based on their corresponding Anatomical Therapeutic Chemical codes. Baseline comorbidities were identified using ICD-9 and ICD-10 codes. These included type 2 DM (ICD-9 code 250 and ICD-10 code E11), CAD (ICD-9 codes 412–414 and ICD-10 codes I20–I25), HTN (ICD-9 codes 401–404 and ICD-10 codes I10–I16), and dyslipidemia (ICD-9 code 272 and ICD-10 code E78). Atrial fibrillation (AF) was captured using ICD-9 codes 427.31–427.32 and ICD-10 code I48. Acute myocardial infarction was defined using ICD-9 codes 410–411 and ICD-10 codes I21–I24, whereas peripheral arterial occlusion disease was identified using ICD-9 code 443.9 and ICD-10 code I73.9. Stroke was recorded under ICD-9 code 434 and ICD-10 code I63. Chronic obstructive pulmonary disease (COPD) was classified using ICD-9 codes 490–492 and ICD-10 codes J40–J44, and chronic kidney disease was identified using ICD-9 code 585 and ICD-10 code N18. Liver cirrhosis was defined by ICD-9 code 571 and ICD-10 code K74, whereas cancer was captured under ICD-9 codes 140–209 and ICD-10 codes C00–C96. The presence of a pacemaker was indicated by ICD-9 codes V45.00–V45.09 and ICD-10 code Z95.0. Thyroid diseases were classified using ICD-9 codes 240–246 and ICD-10 codes E00–E07. Finally, HF was defined using ICD-9 codes 428, 398.91, and 402.1–402.91, and ICD-10 code I50.

### Statistical analysis

The patient characteristics are reported as means with standard deviations for continuous variables, and as numbers or percentages for categorical variables, as appropriate. Comparisons between groups were performed using the Chi-square test for categorical variables and analysis of variance for continuous variables, where applicable. To assess the impact of different iron panel results on the development of LVD, ferritin levels and TSAT were evaluated using Cox proportional hazards regression models. Hazard ratios (HRs) were adjusted for several covariates, including gender, age, type 2 DM, HTN, dyslipidemia, AF, acute myocardial infarction, peripheral arterial occlusion disease, stroke, COPD, chronic kidney disease, liver cirrhosis, cancer, presence of a pacemaker, thyroid disease, and anemic status (defined as hemoglobin levels below 14 g/dL in males and below 12 g/dL in females).

Cox proportional hazards regression models and the Kaplan–Meier method were employed to compare the risk of new-onset LVD and all-cause mortality across different iron panel test results. Given that pre-existing anemia has been shown to potentially influence the development of LVD in prior research, we further stratified patients into subgroups based on their anemic status. All statistical analyses were conducted using R software (R Foundation for Statistical Computing, Vienna, Austria, version 3.4.4), with two-tailed  $P < 0.05$  considered indicative of statistical significance.

Table 1: Baseline characteristics of patients with coronary artery disease with and without test for iron deficiency

| Variables                             | Without iron test (n=59,543), n (%) | With iron test (n=4813), n (%) | P      |
|---------------------------------------|-------------------------------------|--------------------------------|--------|
| Gender (male)                         | 35,602 (59.8)                       | 2499 (51.9)                    | <0.001 |
| Age                                   | 61.37±15.60                         | 70.85±14.55                    | <0.001 |
| BMI (kg/m <sup>2</sup> )              | 28.83±33.35                         | 27.18±20.14                    | 0.008  |
| Comorbidities                         |                                     |                                |        |
| Anemia                                | 11,316 (40.3)                       | 3738 (81.0)                    | <0.001 |
| Type 2 DM                             | 14,360 (24.1)                       | 2410 (50.1)                    | <0.001 |
| HTN                                   | 30,644 (51.5)                       | 3701 (76.9)                    | <0.001 |
| Dyslipidemia                          | 24,009 (40.3)                       | 3279 (68.1)                    | <0.001 |
| AF                                    | 2776 (4.7)                          | 694 (14.4)                     | <0.001 |
| Acute myocardial infarction           | 6348 (10.7)                         | 982 (20.4)                     | <0.001 |
| Peripheral arterial occlusion disease | 1197 (2.0)                          | 303 (6.3)                      | <0.001 |
| Stroke                                | 4093 (6.9)                          | 879 (18.3)                     | <0.001 |
| COPD                                  | 5702 (9.6)                          | 1318 (27.4)                    | <0.001 |
| Chronic kidney disease                | 3745 (6.3)                          | 1876 (39.0)                    | <0.001 |
| Liver cirrhosis                       | 5987 (10.1)                         | 1106 (23.0)                    | <0.001 |
| Cancer                                | 4170 (7.0)                          | 911 (18.9)                     | <0.001 |
| Pacemaker implantation                | 400 (0.7)                           | 107 (2.2)                      | <0.001 |
| Thyroid disease                       | 3630 (6.1)                          | 708 (14.7)                     | <0.001 |
| HF                                    | 5640 (9.5)                          | 1456 (30.3)                    | <0.001 |
| History of LVEF <50                   | 3325 (6.0)                          | 1179 (24.5)                    | <0.001 |
| Laboratory data                       |                                     |                                |        |
| WBC (10 <sup>3</sup> /μL)             | 7.94±4.98                           | 6.99±3.90                      | <0.001 |
| Hemoglobin (g/dL)                     | 13.20±2.25                          | 10.45±2.51                     | <0.001 |
| Platelet (10 <sup>3</sup> /μL)        | 223.51±74.95                        | 215.18±96.77                   | <0.001 |
| Albumin (g/dL)                        | 3.66±0.59                           | 3.62±0.66                      | 0.014  |
| Triglyceride (mg/dL)                  | 134.69±85.21                        | 126.23±81.98                   | <0.001 |
| Total cholesterol (mg/dL)             | 174.50±44.39                        | 151.02±44.13                   | <0.001 |
| HDL-cholesterol (mg/dL)               | 46.93±14.00                         | 44.13±15.45                    | <0.001 |
| LDL-cholesterol (mg/dL)               | 107.16±36.74                        | 85.07±34.33                    | <0.001 |
| Creatinine (mg/dL)                    | 1.23±1.42                           | 2.53±3.03                      | <0.001 |
| ALT (U/L)                             | 29.36±81.54                         | 27.95±86.02                    | 0.320  |
| Uric acid (mg/dL)                     | 5.97±1.83                           | 5.88±2.17                      | 0.007  |
| HbA1c (%)                             | 6.84±1.65                           | 6.42±1.33                      | <0.001 |

Anemia is defined as hemoglobin level lower than 14 mg/dL in men and 12 mg/dL in women. BMI=Body mass index; LVEF=Left ventricular ejection fraction; DM=Diabetes mellitus; HTN=Hypertension; AF=Atrial fibrillation; COPD=Chronic obstructive pulmonary disease; WBC=White blood cell; HDL=High-density lipoprotein; LDL=Low-density lipoprotein; ALT=Alanine transaminase; HbA1c=Glycated hemoglobin; HF=Heart failure

## RESULTS

We identified 4813 (7.18%) patients with at least one SI panel measurement within our CAD cohort. Table 1 presents the characteristics of patients with and without iron panel tests. Patients who underwent iron panel testing were 51.9% male, with an average age of 70 years. Compared to patients without iron panel tests, those receiving iron panel testing

were older (mean age: 70.85 years vs. 61.37 years), had a higher prevalence of anemia (81.0% vs. 40.3%), and exhibited a greater proportion of chronic comorbidities, including type 2 DM, HTN, and chronic kidney disease. Among patients with iron panel tests, 2827 (58.7%) had a TSAT ≥20%, whereas 1986 (41.3%) had ID, defined by TSAT < 20%. Patients with ID defined by TSAT <20% were more likely to have underlying conditions such as DM, AF, stroke, and HF compared to those

Table 2: Characteristics and future events in patients with and without iron deficiency

| Variable                              | TSAT $\geq 20\%$ ( $n=2827$ ), $n$ (%) | TSAT $< 20\%$ ( $n=1986$ ), $n$ (%) | $P$      |
|---------------------------------------|----------------------------------------|-------------------------------------|----------|
| Gender (male)                         | 1564 (55.3)                            | 935 (47.1)                          | $<0.001$ |
| Age                                   | 70.68 $\pm$ 13.98                      | 71.09 $\pm$ 15.33                   | 0.346    |
| BMI                                   | 27.40 $\pm$ 22.41                      | 26.88 $\pm$ 16.51                   | 0.478    |
| Comorbidities                         |                                        |                                     |          |
| Anemia                                | 1994 (74.0)                            | 1744 (90.9)                         | $<0.001$ |
| Type 2 DM                             | 1339 (47.4)                            | 1071 (53.9)                         | $<0.001$ |
| HTN                                   | 2197 (77.7)                            | 1504 (75.7)                         | 0.108    |
| Dyslipidemia                          | 1977 (69.9)                            | 1302 (65.6)                         | 0.001    |
| AF                                    | 359 (12.7)                             | 335 (16.9)                          | $<0.001$ |
| Acute myocardial infarction           | 579 (20.5)                             | 403 (20.3)                          | 0.873    |
| Peripheral arterial occlusion disease | 190 (6.7)                              | 113 (5.7)                           | 0.147    |
| Stroke                                | 483 (17.1)                             | 396 (19.9)                          | 0.012    |
| COPD                                  | 795 (28.1)                             | 523 (26.3)                          | 0.171    |
| Chronic kidney disease                | 1143 (40.4)                            | 733 (36.9)                          | 0.014    |
| Liver cirrhosis                       | 684 (24.2)                             | 422 (21.2)                          | 0.017    |
| Cancer                                | 545 (19.3)                             | 366 (18.4)                          | 0.459    |
| Pacemaker                             | 59 (2.1)                               | 48 (2.4)                            | 0.445    |
| Thyroid disease                       | 438 (15.5)                             | 270 (13.6)                          | 0.067    |
| HF                                    | 809 (28.6)                             | 647 (32.6)                          | 0.003    |
| Laboratory data                       |                                        |                                     |          |
| SI (ug/dL)                            | 94.38 $\pm$ 40.89                      | 35.23 $\pm$ 17.19                   | $<0.001$ |
| TIBC (ug/dL)                          | 280.13 $\pm$ 76.49                     | 316.79 $\pm$ 98.63                  | $<0.001$ |
| SI/TIBC (TSAT)                        | 0.35 $\pm$ 0.15                        | 0.12 $\pm$ 0.05                     | $<0.001$ |
| Ferritin (ng/mL)                      | 567.53 $\pm$ 1205.25                   | 266.53 $\pm$ 518.79                 | $<0.001$ |
| Ferritin $<100$ ng/mL                 | 365 (16.1)                             | 766 (47.8)                          | $<0.001$ |
| Ferritin $<30$ ng/mL                  | 65 (2.9)                               | 445 (27.7)                          | $<0.001$ |
| Hemoglobin (mg/dL)                    | 11.02 $\pm$ 2.63                       | 9.63 $\pm$ 2.07                     | $<0.001$ |
| Creatinine (mg/dL)                    | 2.72 $\pm$ 3.19                        | 2.26 $\pm$ 2.75                     | $<0.001$ |
| ACEi/ARB                              | 1584 (56.0)                            | 1173 (59.1)                         | 0.036    |
| Beta blocker                          | 1840 (65.1)                            | 1336 (67.3)                         | 0.115    |
| SGLT2i                                | 190 (6.7)                              | 211 (10.6)                          | $<0.001$ |
| Adverse events                        |                                        |                                     |          |
| Future LVEF $<50\%$ event             | 211 (14.7)                             | 165 (17.9)                          | 0.038    |
| Future LVEF $\leq 40\%$ event         | 114 (6.9)                              | 80 (7.5)                            | 0.560    |
| Future event for all-cause mortality  | 335 (11.9)                             | 281 (14.2)                          | 0.019    |

Anemia is defined as hemoglobin level lower than 14 mg/dL in men and 12 mg/dL in women. BMI=Body mass index; LVEF=Left ventricular ejection fraction; TIBC=Total iron-binding capacity; ACEi=Angiotensin-converting enzyme inhibitor; ARB=Angiotensin II receptor blocker; SGLT2i=Sodium-glucose co-transporter 2 inhibitor; DM=Diabetes mellitus; HTN=Hypertension; AF=Atrial fibrillation; COPD=Chronic obstructive pulmonary disease; TSAT=Transferrin saturation; SI=Serum iron; HF=Heart failure

with TSAT  $\geq 20\%$ , as shown in Table 2. The average TSAT was 35% in patients with normal TSAT levels and 12% in those with TSAT  $< 20\%$ . The average ferritin levels were 567 ng/mL and 266 ng/mL in patients with normal and low TSAT levels, respectively. The majority of patients undergoing iron tests

had anemia, accounting for 74.0% and 90.9% of those with normal and low TSAT levels, respectively.

The incidence rate of new-onset LVD was higher in patients with ID, defined by TSAT  $< 20\%$  compared to those with TSAT  $\geq 20\%$  (17.9% vs. 14.7%,  $P = 0.038$ ). However, the

incidence of severe LVD (LVEF  $\leq 40\%$ ) showed no significant difference between the two groups [Table 2]. Figure 2 illustrates that the HR for the incidence of new-onset LVD was 1.40 (95% confidence interval [CI], 1.14–1.72) for patients with ID, defined by TSAT  $<20\%$  compared to those with TSAT  $\geq 20\%$  during the 13-year follow-up period. In addition, all-cause mortality was significantly higher in patients with low TSAT levels (14.2% in the TSAT  $<20\%$  group vs. 11.9% in the TSAT  $\geq 20\%$  group,  $P = 0.019$ ). The HR for all-cause mortality was 1.22 (95% CI, 1.04–1.43) for patients with ID, defined by TSAT  $<20\%$  compared to those with TSAT  $\geq 20\%$ .

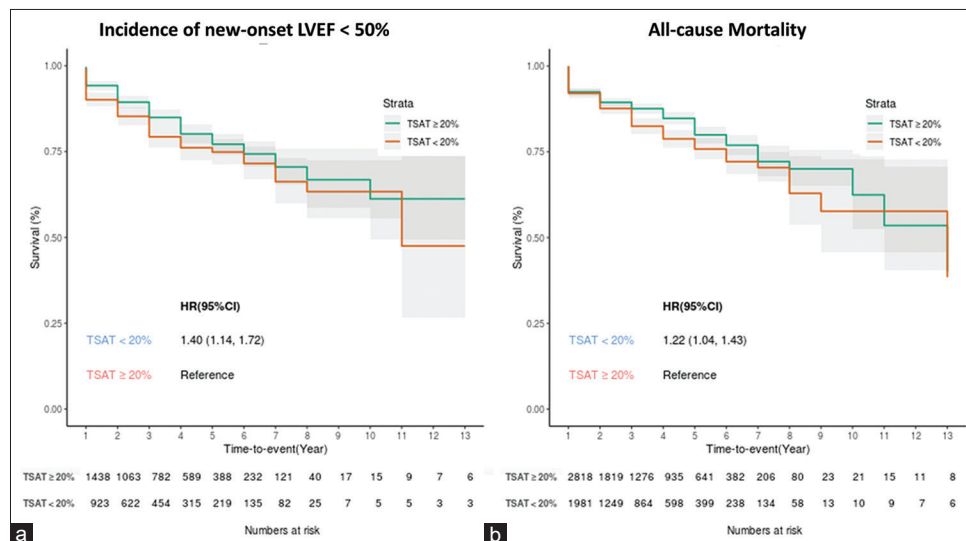
We evaluated the impact of different iron panel results on the risk of incident LVD using a univariate Cox regression model [Model 1 in Table 3]. ID defined by TSAT  $<20\%$  was associated with a higher risk of developing LVD, whereas ID defined by ferritin levels below 30 ng/mL were found to have a protective effect against LVD (HR, 0.65; 95% CI, 0.45–

0.92). ID defined by ferritin levels  $<100$  ng/mL did not show a significant association with incident LVD. However, after adjusting for confounding comorbidities (Model 2) and anemic status (Model 3), ID defined by TSAT  $<20\%$  maintained its predictive value for future LVD development (adjusted HR, 1.37; 95% CI, 1.11–1.69 in Model 2 and adjusted HR, 1.24; 95% CI, 1.01–1.54 in Model 3). In contrast, ID defined by ferritin levels, whether below 100 ng/mL or 30 ng/mL, were not significantly associated with new-onset LVD after adjustment. The predictive value of ID, defined as TSAT  $<20\%$ , for all-cause mortality remained significant after adjusting for confounding comorbidities [Table 4]. In addition, given that anemia affects heart function and increases the risk of incident LVD, we compared the HRs for new-onset LVD in subgroups stratified by the presence or absence of anemia [Table 5]. Although the HR for new-onset LVD associated with ID defined by TSAT  $<20\%$  was lower in patients without anemia compared to

Table 3: Hazard ratio of baseline iron status for new-onset left ventricular dysfunction (left ventricular ejection fraction  $<50\%$ )

| Independent variable      | Model 1 - Crude-HR (95% CI) | <i>P</i> | Model 2 - Adjusted-HR (95% CI) <sup>#</sup> | <i>P</i> | Model 3 - Adjusted-HR (95% CI) <sup>#</sup> | <i>P</i> |
|---------------------------|-----------------------------|----------|---------------------------------------------|----------|---------------------------------------------|----------|
| TSAT $\geq 20\%$          | 1.00                        |          | 1.00                                        |          | 1.00                                        |          |
| TSAT $<20\%$              | 1.32 (1.08–1.62)            | 0.007    | 1.37 (1.11–1.69)                            | 0.003    | 1.24 (1.01–1.54)                            | 0.045    |
| Ferritin $\geq 100$ ng/mL | 1.00                        |          | 1.00                                        |          | 1.00                                        |          |
| Ferritin $<100$ ng/mL     | 0.86 (0.68–1.10)            | 0.225    | 0.89 (0.69–1.13)                            | 0.339    | 0.82 (0.64–1.05)                            | 0.123    |
| Ferritin $\geq 30$ ng/mL  | 1.00                        |          | 1.00                                        |          | 1.00                                        |          |
| Ferritin $<30$ ng/mL      | 0.65 (0.45–0.92)            | 0.017    | 0.86 (0.59–1.24)                            | 0.406    | 0.71 (0.49–1.04)                            | 0.080    |

<sup>#</sup>All result of Model 2 Adjusted-HR were adjusted by gender, age, type 2 DM, HTN, dyslipidemia, AF, acute myocardial infarction, peripheral arterial occlusion disease, stroke, COPD, chronic kidney disease, liver cirrhosis, cancer, pacemaker, thyroid disease. Model 3 Adjusted-HR was adjusted by Model 2 plus anemia. Anemia is defined as hemoglobin level lower than 14 mg/dL in men and 12 mg/dL in women. TSAT=Transferrin saturation; CI=Confidence interval; HR=Hazard ratio; DM=Diabetes mellitus; HTN=Hypertension; AF=Atrial fibrillation; COPD=Chronic obstructive pulmonary disease



**Figure 2:** Kaplan–Meier curve for new-onset left ventricular ejection fraction lower than 50% (a) and all-cause mortality (b) for patients stratified with transferrin saturation  $<20\%$ . TSAT = Transferrin saturation; CI: Confidence interval; HR = Hazard ratio

Table 4: Hazard ratio of baseline transferrin saturation for all-cause mortality events

| Independent variables | Model 1 - crude-HR (95% CI) | <i>P</i> | Model 2 - Adjusted-HR (95% CI) <sup>#</sup> | <i>P</i> | Model 3 - Adjusted-HR (95% CI) <sup>#</sup> | <i>P</i> |
|-----------------------|-----------------------------|----------|---------------------------------------------|----------|---------------------------------------------|----------|
| TSAT $\geq 20\%$      | 1.00                        |          | 1.00                                        |          | 1.00                                        |          |
| TSAT $< 20\%$         | 1.24 (1.06–1.45)            | 0.008    | 1.22 (1.04–1.43)                            | 0.014    | 1.18 (1.01–1.39)                            | 0.040    |

<sup>#</sup>All result of Model 2 Adjusted-HR were adjusted by gender and age. Model 3 Adjusted-HR was adjusted by Model 2 plus type 2 DM, HTN, dyslipidemia, AF, acute myocardial infarction, peripheral arterial occlusion disease, stroke, COPD, chronic kidney disease, liver cirrhosis, cancer, pacemaker, thyroid disease. TSAT=Transferrin saturation; CI=Confidence interval; HR=Hazard ratio; DM=Diabetes mellitus; HTN=Hypertension; AF=Atrial fibrillation; COPD=Chronic obstructive pulmonary disease

Table 5: Hazard ratio of iron status for new-onset left ventricular dysfunction (left ventricular ejection fraction  $< 50\%$ ) stratified with anemia

| Stratified variable             | Crude-HR (95% CI) | <i>P</i>  | <i>P</i> (interaction) | Adjusted-HR (95% CI) <sup>#</sup> | <i>P</i>  | <i>P</i> (interaction) |
|---------------------------------|-------------------|-----------|------------------------|-----------------------------------|-----------|------------------------|
| Without anemia ( <i>n</i> =492) | 1.00              |           | 0.227                  | 1.00                              |           | 0.165                  |
| With anemia ( <i>n</i> =1768)   | 4.15 (2.78–6.18)  | $< 0.001$ |                        | 2.32 (1.53–3.53)                  | $< 0.001$ |                        |
| Without anemia ( <i>n</i> =491) |                   |           |                        |                                   |           |                        |
| TSAT $\geq 20\%$                | 1.00              |           |                        | 1.00                              |           |                        |
| TSAT $< 20\%$                   | 0.57 (0.17–1.89)  | 0.354     |                        | 0.76 (0.20–2.87)                  | 0.681     |                        |
| With anemia ( <i>n</i> =1267)   |                   |           |                        |                                   |           |                        |
| TSAT $\geq 20\%$                | 1.00              |           |                        | 1.00                              |           |                        |
| TSAT $< 20\%$                   | 1.14 (0.92–1.41)  | 0.227     |                        | 1.28 (1.03–1.59)                  | 0.028     |                        |

<sup>#</sup>All results of Adjusted-HR were adjusted by gender, age, type 2 DM, CAD, HTN, dyslipidemia, AF, acute myocardial infarction, peripheral arterial occlusion disease, stroke, COPD, chronic kidney disease, liver cirrhosis, cancer, pacemaker, thyroid disease, heart failure. Anemia is defined as hemoglobin level lower than 14 mg/dL in men and 12 mg/dL in women. TSAT=Transferrin saturation; CI=Confidence interval; HR=Hazard ratio; CAD=Coronary artery disease; DM=Diabetes mellitus; HTN=Hypertension; AF=Atrial fibrillation; COPD=Chronic obstructive pulmonary disease

those with anemia, no statistically significant interaction ( $P$  for interaction  $> 0.05$ ) was observed either before or after adjusting for confounding comorbidities. The presence of anemia alone was a predictor of new-onset LVD, irrespective of iron status (adjusted HR: 2.32; 95% CI: 1.53–3.53).

## DISCUSSION

The relationship between ID and LVD has not been extensively studied, particularly in patients with CAD, who are at increased risk for developing LVD. Historically, ferritin has been the commonly used biomarker to assess ID and LVD in the literature,<sup>15,16</sup> but the comparison between ferritin and TSAT has not been well explored. In this study, we found that TSAT was a stronger predictor of new-onset LVD than ferritin, even when using different ferritin cutoff values. Moreover, TSAT was also linked to an increased risk of mortality, highlighting the critical metabolic role of SI in the body. Although ID can contribute to anemia, which is a known risk factor for HF, our findings showed that the presence or absence of anemia did not significantly impact the predictive value of TSAT for future heart function decline. These results suggest that evaluating iron status, particularly TSAT, could be beneficial in the routine clinical management of patients with CAD.

According to the current studies, ID was not only relevant to the prognosis in patients with HF, and it was also associated with the risk for new-onset HF. Several studies dedicated to using ferritin as predictor for new-onset HF have, however, demonstrated quite different results. In the PREVENT study, elevated ferritin levels independently predict the higher risk of developing new-onset HF, especially in HFpEF, in apparently healthy women.<sup>16</sup> In contrast, the ARIC study found that lower plasma ferritin levels are linked with an increased risk of incident HF, including HFpEF in older population (mean age: 75 years).<sup>15</sup> A U-shaped relationship between ferritin levels and the risk of incident HF has also been reported by other studies.<sup>17,18</sup> The abovementioned findings demonstrated that ferritin is a susceptible factor, influenced by age, gender, inflammation, and more, which makes using this marker to predict HF unreliable. In addition, previous studies were all community based, with only a minority of the population consisting of those with CAD. Our research specifically targets the CAD population, which was thought to have increased ferritin concentrations.<sup>19</sup> Otherwise, the study population was followed up or admitted to our hospital due to chronic or acute diseases, which have the potential to influence ferritin levels to varying degrees.<sup>20–22</sup> All of these make our findings different from previous studies. We identified TSAT as an independent predictor of new-onset

LVD, regardless of ferritin levels, age, gender, and even underlying comorbidities.

The mechanisms behind the development of ID in HF have not been thoroughly explored. However, ID is likely linked to factors such as impaired iron absorption, increased gastrointestinal losses, and decreased availability of usable iron from the reticuloendothelial system.<sup>7</sup> Among ambulatory patients with HF, the prevalence of ID reaches up to 50%. ID is an independent predictor of reduced exercise capacity, diminished quality of life, and decreased survival rates. Risk factors include female gender, more advanced stages of HF, elevated levels of NT-proBNP, and higher serum concentrations of C-reactive protein.<sup>23</sup> ID in HF patients is linked to decreased exercise capacity, diminished quality of life, and a poor prognosis, independent of anemia and LVEF.<sup>24</sup> The ESC guidelines recommend intravenous iron supplementation for symptomatic HF patients with LVEF below 50%, while the American Heart Association guidelines do not specifically address this recommendation.<sup>25,26</sup> There are still uncertainties about the optimal use of iron supplementation therapy and its role in HF patients. Although current guidelines do not recommend iron supplementation in CAD patients with ID, this study may provide a direction for future research on this prevalent population to improve patient care.<sup>27</sup>

We found that TSAT was a stronger predictor of new-onset LVD compared to ferritin, even when applying different ferritin cutoff values. This is likely because serum ferritin, being both an acute-phase protein and an indicator of iron stores, often has limited value as its levels are elevated in the presence of inflammation.<sup>28</sup> TSAT, compared to serum ferritin, is a more reliable predictor of iron status and response to erythropoiesis-stimulating agent treatment in dialysis patients.<sup>29</sup> Low TSAT and high ferritin levels are significant predictors of cerebrovascular and cardiovascular disease and mortality in maintenance hemodialysis patients.<sup>30</sup> In cancer patients, especially those undergoing chemotherapy, ferritin can be elevated due to the inflammatory state induced by the malignancy or treatment. A study highlighted that TSAT is a more reliable indicator for assessing iron status.<sup>31</sup> The study also has shown that among the traditionally used markers of iron status, reduced TSAT, particularly TSAT <10%, is most strongly associated with an increased risk of adverse outcomes in chronic kidney disease patients, regardless of serum ferritin levels.<sup>32</sup> In conclusion, TSAT consistently emerges as a more reliable predictor of ID and related adverse outcomes across various conditions, including LVD, chronic kidney disease, and cancer, especially in the presence of inflammation, where ferritin may be elevated and less reflective of true iron status.

This study identifies a potential screening target for ID in patients with CAD, addressing a gap in the existing evidence for this population. A large randomized trial is warranted

to validate this hypothesis. This study also has several limitations. First, although adjustments were made for gender, age, and baseline comorbidities to reduce confounding factors, the retrospective nature of the study inherently limits causal inferences. Second, as this study was conducted at a single institution in Taiwan, the generalizability of the results to other populations should be approached with caution due to the small sample size, lack of ethnic diversity, and potential patient selection bias arising from various indications for iron testing in this study. Further research is necessary to validate these findings in diverse ethnic groups. Third, the effect of treatment for ID on the incidence of LVD was not evaluated due to the unavailability of ferric carboxymaltose and ferric derisomaltose – both recommended by current guidelines – in our healthcare system, warranting future large-scale studies to address this gap. Fourth, since current evidence primarily illustrates the relationship between ID and iron supplementation therapy in patients with reduced EF, analyses of other echocardiographic characteristics were not performed. Finally, analyzing the causes of loss to follow-up and their outcomes was challenging in this electronic medical record-based retrospective study. However, the large sample size and extended follow-up period may have mitigated this limitation.

## CONCLUSION

Our study highlights the differential predictive value of TSAT and ferritin levels for incident LVD. In patients with CAD, TSAT levels below 20% were predictive of incident LVD. These findings provide practical insights for screening ID in patients with CAD.

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## Data availability statement

The data that support the findings of this study are available from the corresponding author, Wei-Ting Liu, upon reasonable request.

## Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used ChatGPT in order to proofread the document. After using this

tool, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

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### Conflicts of interest

There are no conflicts of interest.

### REFERENCES

- Hung CL, Chao TF, Tsai CT, Liao JN, Lim SS, Tuan TC, *et al.* Prevalence, incidence, lifetime risks, and outcomes of heart failure in Asia: A nationwide report. *JACC Heart Fail* 2023;11:1454-6.
- Savarese G, von Haehling S, Butler J, Cleland JG, Ponikowski P, Anker SD. Iron deficiency and cardiovascular disease. *Eur Heart J* 2023;44:14-27.
- Usman MS, Bhatt DL, Hameed I, Anker SD, Cheng AY, Hernandez AF, *et al.* Effect of SGLT2 inhibitors on heart failure outcomes and cardiovascular death across the cardiometabolic disease spectrum: A systematic review and meta-analysis. *Lancet Diabetes Endocrinol* 2024;12:447-61.
- McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, *et al.* Angiotensin-neprilysin inhibition versus enalapril in heart failure. *N Engl J Med* 2014;371:993-1004.
- Anker SD, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H, *et al.* Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Engl J Med* 2009;361:2436-48.
- Jankowska EA, Kirwan BA, Kosiborod M, Butler J, Anker SD, McDonagh T, *et al.* The effect of intravenous ferric carboxymaltose on health-related quality of life in iron-deficient patients with acute heart failure: The results of the AFFIRM-AHF study. *Eur Heart J* 2021;42:3011-20.
- Ponikowski P, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V, *et al.* Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency†. *Eur Heart J* 2015;36:657-68.
- van Veldhuisen DJ, Ponikowski P, van der Meer P, Metra M, Böhm M, Doletsky A, *et al.* Effect of ferric carboxymaltose on exercise capacity in patients with chronic heart failure and iron deficiency. *Circulation* 2017;136:1374-83.
- Cleland JG, Zhang J, Pellicori P, Dicken B, Dierckx R, Shoaib A, *et al.* Prevalence and outcomes of anemia and hematinic deficiencies in patients with chronic heart failure. *JAMA Cardiol* 2016;1:539-47.
- Alnuwaysir RI, Hoes MF, van Veldhuisen DJ, van der Meer P, Grote Beverborg N. Iron deficiency in heart failure: Mechanisms and pathophysiology. *J Clin Med* 2021;11:125.
- McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al.* 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021;42:3599-726.
- McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al.* 2023 focused update of the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2023;44:3627-39.
- Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, *et al.* 2022 AHA/ACC/HFSA guideline for the management of heart failure: A report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Circulation* 2022;145:e895-1032.
- Garcia-Casal MN, Pasricha SR, Martinez RX, Lopez-Perez L, Peña-Rosas JP. Serum or plasma ferritin concentration as an index of iron deficiency and overload. *Cochrane Database Syst Rev* 2021;5:CD011817.
- Aboelsaad IA, Claggett BL, Arthur V, Dorbala P, Matsushita K, Lennep BW, *et al.* Plasma ferritin levels, incident heart failure, and cardiac structure and function: The ARIC study. *JACC Heart Fail* 2024;12:539-48.
- Klip IT, Voors AA, Swinkels DW, Bakker SJ, Kootstra-Ros JE, Lam CS, *et al.* Serum ferritin and risk for new-onset heart failure and cardiovascular events in the community. *Eur J Heart Fail* 2017;19:348-56.
- Dong F, Zhang X, Culver B, Chew HG Jr., Kelley RO, Ren J. Dietary iron deficiency induces ventricular dilation, mitochondrial ultrastructural aberrations and cytochrome c release: Involvement of nitric oxide synthase and protein tyrosine nitration. *Clin Sci (Lond)* 2005;109:277-86.
- Silvestre OM, Gonçalves A, Nadruz W Jr., Claggett B, Couper D, Eckfeldt JH, *et al.* Ferritin levels and risk of heart failure-the atherosclerosis risk in communities study. *Eur J Heart Fail* 2017;19:340-7.
- Sung KC, Kang SM, Cho EJ, Park JB, Wild SH, Byrne CD. Ferritin is independently associated with the presence of coronary artery calcium in 12,033 men. *Arterioscler Thromb Vasc Biol* 2012;32:2525-30.
- Bayih A, Dedefo G, Kinde S, Alem M, Negesso AE, Baye A, *et al.* Serum ferritin level and associated factors among uncontrolled adult type II diabetic follow-up patients: Comparative based cross-sectional study. *BMC Endocr Disord* 2024;24:144.
- Cheng L, Li H, Li L, Liu C, Yan S, Chen H, *et al.*

- Ferritin in the coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. *J Clin Lab Anal* 2020;34:e23618.
22. Fertrin KY. Diagnosis and management of iron deficiency in chronic inflammatory conditions (CIC): Is too little iron making your patient sick? *Hematology Am Soc Hematol Educ Program* 2020;2020:478-86.
23. von Haehling S, Ebner N, Evertz R, Ponikowski P, Anker SD. Iron deficiency in heart failure: An overview. *JACC Heart Fail* 2019;7:36-46.
24. Anand IS, Gupta P. Anemia and iron deficiency in heart failure: Current concepts and emerging therapies. *Circulation* 2018;138:80-98.
25. Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, *et al.* 2022 AHA/ACC/HFSA guideline for the management of heart failure: A report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. *J Am Coll Cardiol* 2022;79:e263-421.
26. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, *et al.* 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2021;42:3599-726.
27. Vrints C, Andreotti F, Koskinas KC, Rossello X, Adamo M, Ainslie J, *et al.* 2024 ESC guidelines for the management of chronic coronary syndromes. *Eur Heart J* 2024;45:3415-537.
28. Cullis JO. Diagnosis and management of anaemia of chronic disease: Current status. *Br J Haematol* 2011;154:289-300.
29. Gaweda AE, Bhat P, Maglinte GA, Chang CL, Hill J, Park GS, *et al.* TSAT is a better predictor than ferritin of hemoglobin response to Epoetin alfa in US dialysis patients. *Hemodial Int* 2014;18:38-46.
30. Kuragano T, Joki N, Hase H, Kitamura K, Murata T, Fujimoto S, *et al.* Low transferrin saturation (TSAT) and high ferritin levels are significant predictors for cerebrovascular and cardiovascular disease and death in maintenance hemodialysis patients. *PLoS One* 2020;15:e0236277.
31. Aapro M, Österborg A, Gascón P, Ludwig H, Beguin Y. Prevalence and management of cancer-related anaemia, iron deficiency and the specific role of I.V. iron. *Ann Oncol* 2012;23:1954-62.
32. Eisenga MF, Nolte IM, van der Meer P, Bakker SJ, Gaillard CA. Association of different iron deficiency cutoffs with adverse outcomes in chronic kidney disease. *BMC Nephrol* 2018;19:225.