# SIGNIFICANT ASSOCIATION OF CIRCULATORY IRON STATUS WITH ENLARGED HEART IN END-DTAGE KIDNEY DISEASE PATIENTS

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## Introduction

1. High prevalence of morphological and functional cardiac abnormalities are observed at the initiation of dialysis. In a Canadian study, echocardiography revealed concentric left ventricular (LV) hypertrophy in 42%, eccentric LV hypertrophy in 23%, isolated LV dilation in 4%, and systolic dysfunction in 16% of 432 ESKD patients who survived at least 6 months on dialysis (*J Am Soc Nephrol,* 10**:** 1606-1615, 1999).

2. Iron is known to play a crucial role in oxygen transport as a component of Hb, in oxygen storage as a component of myoglobin, and in cardiac and skeletal muscle metabolism as a component of oxidative enzymes (*European heart journal,* 34**:** 816-829, 2013). These physiological roles of iron led us to hypothesize that iron deficiency in itself may directly contribute to cardiac morphological and functional abnormalities independent of anemia.

3. A recent study revealed that among 546 patients with systolic dysfunction, iron deficiency (ID) was observed in 32% of anemic patients and 57% of non-anemic patients (*European heart journal,* 31**:** 1872-1880, 2010). Moreover, the FERRIC-HF study (*Journal of the American College of Cardiology,* 51**:** 103-112, 2008) demonstrated that intravenous iron therapy for patients with heart failure improved exercise tolerance and symptoms.

4. We already know that higher prevalences of ID (*Clin J Am Soc Nephrol,* 4**:** 57-61, 2009), anemia (*Cardiorenal medicine,* 4**:** 189-200, 2014), and cardiac remodeling (*Kidney international,* 47**:** 186-192, 1995) are observed simultaneously in incident dialysis patients. ID might result in cardiac enlargement independent of anemia, which indicates cardiac remodeling in patients with ESKD.

## Aim

The purpose of this study was to clarify the association between ID and cardiac remodeling at the start of maintenance dialysis

## Participants and Methods

*Study design and patients*
We conducted a cross-sectional study of information obtained from the database of the Japanese Study Group for Assessing Initiation of Renal Replacement Therapy (J-START), which includes the nephrology units at nine teaching hospitals in Japan. Between January 2006 and October 2015, a total of 2,643 patients with ESKD started chronic dialysis at the nine hospitals. We excluded those with ESKD for whom no data were available on Hb, Fe, total iron-binding capacity (TIBC), ferritin, or cardiothoracic ratio (CTR). We therefore analyzed data from 1974 patients with ESKD (Fig. 1). Clinical factors associated with CTR were also determined. The Ethics Committee for Clinical Research at Toho University Ohashi Medical Center approved the study protocol [Permission no. 13-52]. Written informed consent was obtained from all participants for participation in J-START.

*Data collection*
Clinical information was collected from all patients at each nephrology unit immediately before the first HD session. The estimated glomerular filtration rate (eGFR) was calculated using the new Japanese equation: eGFR (mL/min/1.73 m$^2$) = 1.94×Cr$^{-1.094}$ × age$^{-0.287}$ (× 0.739 for women). Body mass index (BMI) at optimal weight was calculated as weight in kilograms divided by the square of height in meters.

*Definition of comorbid disease and ID*
The presence or absence of cardiac and cerebral diseases was determined from a review of the medical record. Cardiac diseases were defined as ESKD patients with valvular heart disease, any cause of cardiomyopathy or myocarditis, pericarditis, endocarditis, or ischemic heart disease including myocardial infarction, acute coronary syndrome, or history of coronary revascularization therapy. ESKD patients with cerebrovascular diseases were defined as those with cerebral bleeding and infarction. Circulatory ID was defined as transferrin saturation (TSAT) (Fe divided by TIBC × 100) < 20%, and stored ID was defined as ferritin level < 100 ng/dL.

*Reasons for starting dialysis*
The J-START database includes information about the clinical reasons for deciding whether a patient should start chronic dialysis therapy. "Overhydration" means that patients with ESKD started dialysis due to excessive fluid retention such as lung congestion or massive edema.

*Cardiothoracic ratio*
Standard chest radiography proceeded on the day of the first HD session. The CTR was determined by dividing the maximum horizontal width of the heart by the horizontal inner width of the rib cage. To ensure accurate measurement, a vertical line was drawn on the radiograph through the midpoint of the spine from the sternum to the diaphragm. The maximum transverse diameter of the heart was then determined by adding the widest distance of the right and left heart borders from and to the midline, respectively. This value was then divided by the maximum transverse diameter of the thorax.

*Statistical analysis*
Data are expressed as mean ± standard deviation or median [interquartile range]. Patient characteristics were compared between the 4 patient groups in combination with TSAT above or below 20% and ferritin above or below 100 ng/dL using the chi-square test for categorical variables, analysis of variance (ANOVA) for normally distributed variables, and the Kruskal-Wallis tests for non-normally distributed variables. Associations between various factors and CTR category were assessed using logistic regression analysis. Numbers of available data are presented in Table 1. A probability (*P*) value < 0.05 was considered to indicate statistically significant differences in all tests. All data were statistically analyzed using SPSS for Windows version 20 (IBM, Armonk, NY).

## Summary

The main findings in this study were:
1) a high prevalence of ID was seen at the initiation of dialysis, as reported previously;
2) a marker of circulatory iron TSAT was inversely correlated with CTR, as a surrogate marker of cardiac enlargement;
3) ferritin showed no significant relationship with CTR;
4) a significantly higher odds ratio for cardiac enlargement was observed in patients with TSAT <20%

## Conclusion

Deficiency of circulatory iron is closely correlated with enlarged heart in ESKD patients. Iron supplementation in the predialysis phase of CKD may help prevent cardiac remodeling independent of Hb level in CKD patients with ID.
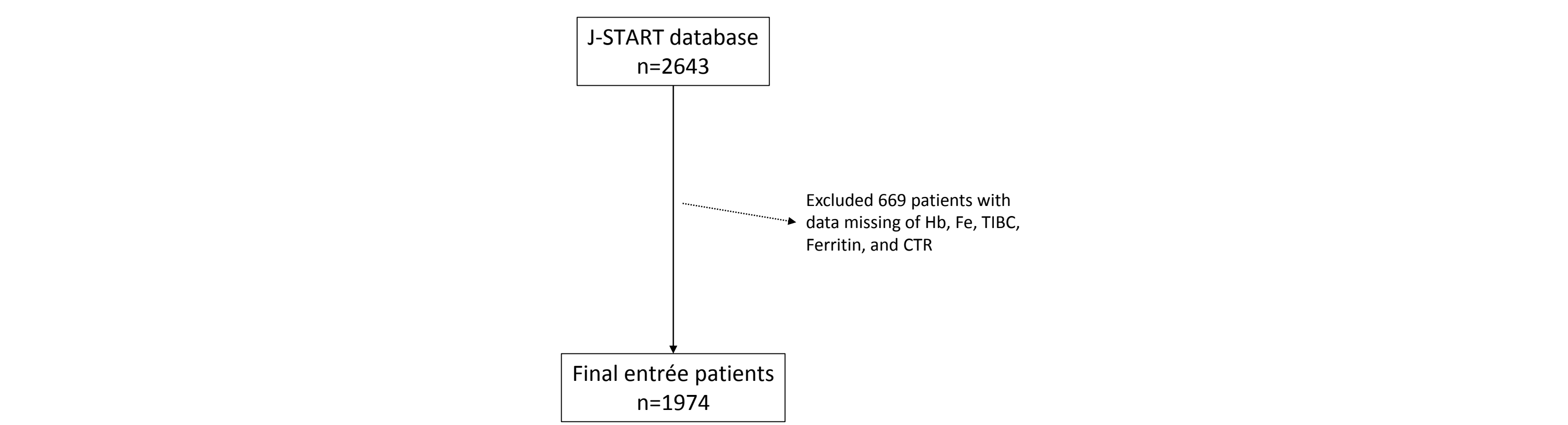
**Figure 1. Subject flow diagram**



**Table 1. Characteristics of patients in four groups devided by iron status**

| | | Total | TSAT <20% | | TSAT ≥20% | | p value |
|---|---|---|---|---|---|---|---|
| | | | Ferritin <100ng/dL | Ferritin ≥100ng/dL | Ferritin <100ng/dL | Ferritin ≥100ng/dL | |
| Patients number (%) | | 1974 | 341 (17.3) | 409 (20.7) | 339 (17.2) | 885 (44.8) | |
| Age, years | 1974 | 67.1±13.7 | 67.3±14.3 | 66.7±13.4 | 66.5±14.0 | 67.5±13.4 | 0.65 |
| Male, % | 1974 | 67 | 54 | 72 | 61 | 72 | <0.001 |
| Diabetes, % | 1974 | 42 | 43 | 43 | 39 | 41 | 0.69 |
| BMI, kg/m$^2$ | 1904 | 22.9±4.7 | 22.9±4.3 | 22.9±4.9 | 23.1±5.3 | 22.7±4.6 | 0.64 |
| Primary disease, % | 1974 | | | | | | 0.65 |
| Diabetic nephropathy | | 41.5 | 43.4 | 42.5 | 39.2 | 41.2 | |
| Glomerulonephritis | | 26 | 24.6 | 22 | 29.8 | 26.9 | |
| Nephrosclerosis | | 17.8 | 18.5 | 17.4 | 18.6 | 17.5 | |
| PCK | | 3.2 | 2.9 | 3.9 | 2.9 | 3.1 | |
| Others | | 5.1 | 4.7 | 5.9 | 3.5 | 5.4 | |
| Unknown | | 6.4 | 5.9 | 8.3 | 5.9 | 5.9 | |
| Cardiac disease, % | 1974 | 18 | 21 | 19 | 15 | 17 | 0.13 |
| Cerebrovascular disease, % | 1974 | 13 | 13 | 17 | 12 | 12 | 0.055 |
| Overhydration, % | 1940 | 34 | 33 | 47 | 21 | 33 | <0.001 |
| Systolic BP, mmHg | 1920 | 150±25 | 151±23 | 150±25 | 149±24 | 151±25 | 0.86 |
| Diastolic BP, mmHg | 1921 | 77±15 | 76±15 | 77±16 | 77±13 | 77±15 | 0.79 |
| CTR, % | 1974 | 54.3±6.9 | 55.0±7.2 | 55.9±6.8 | 53.3±6.8 | 53.7±6.7 | <0.001 |
| CTR>54%, % | 1974 | 49 | 51 | 57 | 44 | 46 | <0.001 |
| Hemoglobin, g/dL | 1974 | 8.7±1.5 | 8.8±1.3 | 8.5±1.4 | 9.2±1.5 | 8.6±1.5 | <0.001 |
| Albumin, g/dL | 1969 | 3.1±0.6 | 3.2±0.5 | 3.0±0.5 | 3.3±0.6 | 3.1±0.6 | <0.001 |
| Creatinine, mg/dL | 1973 | 9.2±3.4 | 8.7±3.0 | 9.2±3.4 | 9.5±3.3 | 9.3±3.5 | 0.01 |
| eGFR, mL/min/1.73$^2$ | 1971 | 5.4±2.5 | 5.4±2.3 | 5.5±2.6 | 5.1±2.8 | 5.4±2.5 | 0.22 |
| Total cholesterol, mg/dL | 1719 | 166±47 | 167±48 | 161±44 | 169±43 | 166±50 | 0.14 |
| Triglyceride, mg/dL | 1781 | 121±69 | 121±92 | 117±51 | 115±57 | 125±70 | 0.095 |
| HDL-C, mg/dL | 1743 | 44±16 | 46±15 | 42±16 | 46±15 | 43±16 | <0.001 |
| Calcium, mg/dL | 1966 | 7.7±0.9 | 7.8±0.9 | 7.7±0.8 | 7.8±1.0 | 7.7±1.0 | 0.01 |
| Phosphate, mg/dL | 1966 | 6.2±1.8 | 5.9±1.6 | 6.3±1.7 | 6.2±1.6 | 6.2±1.8 | 0.024 |
| i-PTH, pg/mL | 1810 | 271 [171, 399] | 273 [186, 390] | 263 [172, 393] | 303 [170, 465] | 266 [163, 390] | 0.16 |
| CRP, mg/dL | 1942 | 0.28 [0.09, 1.57] | 0.2 [0.09, 1.01] | 1.29 [0.20, 4.89] | 0.14 [0.02, 0.31] | 0.26 [0.70, 1.35] | <0.001 |
| glucose, mg/dL | 1863 | 142±53 | 151±61 | 142±54 | 138±42 | 141±53 | 0.011 |
| Fe, μg/dL | 1974 | 58±35 | 31±10 | 28±10 | 76±30 | 76±34 | <0.001 |
| TIBC, μg/dL | 1974 | 217±50 | 250±44 | 206±47 | 239±44 | 201±48 | <0.001 |
| TSAT, % | 1974 | 27.9 | 12.7 | 13.8 | 32.4 | 38.6 | <0.001 |
| Ferritin, ng/dL | 1974 | 145 [74, 258] | 50 [31, 71] | 191 [139, 31] | 60 [41, 80] | 225 [156, 363] | <0.001 |
| ESA, % | 1947 | 76 | 84 | 72 | 84 | 73 | <0.001 |
| ARB/ACE-I, % | 1956 | 59 | 55 | 54 | 65 | 61 | 0.005 |
| Vitamin D, % | 1952 | 24 | 26 | 21 | 29 | 23 | 0.02 |
| Iron, % | 1603 | 13 | 14 | 13 | 19 | 10 | 0.005 |

**Table 2. Multivariate logistic regression analysis for the factors associated with cardiothoracis ratio.**

| | | | Odds ration (95% CI) | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Binary | | Cardiothoracis ratio, % | | | | |
| | | | | | | Multinominal | | | |
| | | | >54 (median) | <45 (reference) | 45-<50 | 50-<55 | 55-<60 | 60-<65 | >=65 |
| TSAT, 1% increase | crude | TSAT, 1% increase | 0.991 | **0.986-0.996** | 1 | 0.994 0.984-1.003 | 0.99 0.980-0.999 | 0.986 0.976-0.996 | 0.982 0.971-0.993 | 0.965 0.951-0.980 |
| | adjusted* | TSAT, 1% increase* | 0.994 0.988-1.001 | 1 | 0.991 0.979-1.003 | 0.989 0.977-1.000 | 0.986 0.974-0.998 | 0.984 0.971-0.997 | 0.964 0.947-0.981 |
| TSAT, <20% | crude | TSAT, <20% | 1.427 1.189-1.713 | 1 | 1.154 0.756-1.762 | 1.375 0.921-2.054 | 1.63 1.084-2.453 | 1.971 1.278-3.039 | 2.745 1.689-4.461 |
| | adjusted* | TSAT, <20%* | 1.253 1.013-1.550 | 1 | 1.245 0.783-1.979 | 1.369 0.872-2.150 | 1.572 0.987-2.505 | 1.755 1.067-2.886 | 2.712 1.542-4.771 |
| Ferritin, 50g/dL increae | crude | Ferritin, 50g/dL increae | 1.02 1.004-1.036 | 1 | 1.003 0.981-1.025 | 0.983-1.069 1.033 | 0.991-1.078 1.046 | 1.003-1.091 1.033 | 0.986-1.082 |
| | adjusted** | Ferritin, each 50g/dL increae** | 1.01 0.991-1.029 | 1 | 1.018 0.963-1.076 | 1.024 0.971-1.080 | 1.031 0.977-1.087 | 1.042 0.987-1.099 | 1.04 0.984-1.099 |
| Ferritin, <100 ng/dL | crude | Ferritin, <100 ng/dL | 0.919 0.763-1.106 | 1 | 1.283 0.852-1.931 | 1.113 0.753-1.646 | 1.135 0.761-1.694 | 0.796 0.513-1.234 | 1.199 0.738-1.948 |
| | adjusted** | Ferritin, <100 ng/dL** | 0.994 0.794-1.245 | 1 | 1.365 0.848-2.198 | 1.316 0.825-2.100 | 1.352 0.833-2.193 | 0.97 0.573-1.643 | 1.079 0.593-1.964 |

TSAT; transferrin saturation

*adjusted by age, sex, diabetic nephropathy, BMI, eGFR, cardiac disease, overhydration, sBP, albumin, Hb, CRP, ferritin

**adjusted by age, sex, diabetic nephropathy, BMI, eGFR, cardiac disease, overhydration, sBP, albumin, Hb, CRP, TSAT

**Figure 2. Differences in CTR between four combination groups with Hb above or below 10 g/dL and TSAT above or below 20%.**
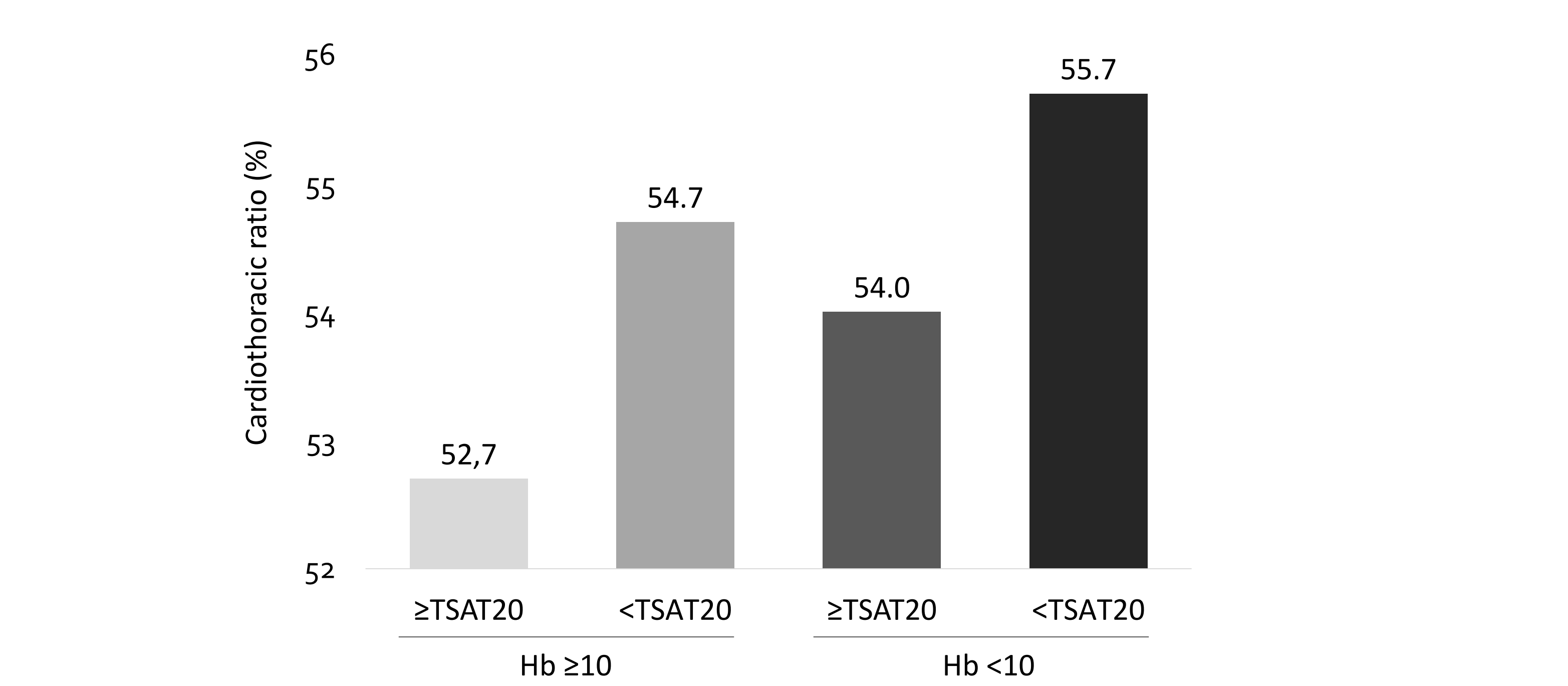


In each of the anemia (Hb <10 g/dL) and non-anemia groups (Hb ≥10 g/dL), CTR was significantly higher in the ID group with TSAT <20% than in the non-ID group with TSAT ≥20% (non-anemia group, p<0.01; anemia group, p<0.001). Regardless of TSAT above or below 20%, CTRs in the anemia group were significantly higher than those with TSAT ≥20% in the non-anemia group (p<0.01). No interaction effect of TSAT with Hb was identified.

**Table 3. Odds ratio for CTR>54% in stratification of TSAT levels**

| TSAT | No. of patients (%) | Model 1* | | | | Model 2** | | | | Model 3*** | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | 95%CI | | | | 95%CI | | | | 95%CI | | |
| | | Odds | lower | upper | p | Odds | lower | upper | p | Odds | lower | upper | p |
| <10% | 187 (9.5) | 1.503 | 1.074 | 2.104 | 0.017 | 1.629 | 1.132 | 2.343 | 0.009 | 1.423 | 0.951 | 2.127 | 0.086 |
| 10-<20 | 563 (28.5) | 1.301 | 1.025 | 1.649 | 0.03 | 1.276 | 0.99 | 1.645 | 0.06 | 1.195 | 0.902 | 1.584 | 0.21 |
| 20-<30 (reference) | 531 (26.9) | 1 | | | | 1 | | | | 1 | | | |
| 30-<40 | 338 (17.1) | 1.085 | 0.826 | 1.425 | 0.55 | 1.122 | 0.838 | 1.503 | 0.43 | 1.01 | 0.731 | 1.397 | 0.95 |
| 40-<50 | 162 (8.2) | 0.627 | 0.436 | 0.902 | 0.012 | 0.704 | 0.478 | 1.036 | 0.075 | 0.623 | 0.408 | 0.95 | 0.028 |
| ≥50 | 193 (9.8) | 0.885 | 0.635 | 1.232 | 0.46 | 0.843 | 0.585 | 1.214 | 0.35 | 0.717 | 0.478 | 1.074 | 0.1 |

TSAT; transferrin saturation, CI; confidence interval
* crude
** adjusted by age, sex, diabetes, BMI, Hb, ferritin, cardiac dsiease
*** adjusted by the factors in Model 2 + usage of Iron agents