

# Iron deficiency in heart failure patients: the French CARENFER prospective study

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## Abstract

**Aims** Iron deficiency (ID) is reported as one of the main co-morbidities in patients with chronic heart failure (CHF), which then influences quality of life and prognosis. The CARENFER study aimed to assess the prevalence of ID in a large panel of heart failure (HF) patients at different stages of the disease.

**Methods and results** This prospective cross-sectional nationwide study was conducted in 48 medical units in France in 2019. Serum ferritin concentration and transferrin saturation (TSAT) index were determined in all eligible patients with a diagnosis of HF. ID diagnosis was based on the European Society of Cardiology (ESC) 2016 guidelines. Patients were classified as having either a decompensated HF or a CHF. Left ventricular ejection fraction (LVEF) was categorized as preserved ( $\geq 50\%$ ), mildly reduced (40–49%), or reduced ( $< 40\%$ ). ID diagnosis was determined in 1661 patients, of whom 1475 could be classified as having a decompensated HF or a CHF. Patients' median age was 78 years. Decompensated HF represented 60.1% of cases. The overall prevalence of ID was 49.6% (47.1–52.1). In CHF and decompensated HF patients, respectively, ID prevalence was 39.0% (35.1–43.1) and 58.1% (54.7–61.4),  $P < 0.001$ ; TSAT  $< 20\%$  was respectively reported in 34.7% and 70.0% of patients ( $P < 0.001$ ). Patients with preserved LVEF were more likely to have an ID (57.5%) compared with patients with mildly reduced (47.4%) or reduced LVEF (44.3%) ( $P < 0.001$ ).

**Conclusions** Iron deficiency was highly prevalent in patients with decompensated HF or CHF with preserved LVEF. ID prevalence defined by TSAT was higher than by the ESC criteria in decompensated HF patients, questioning the importance of ID definition to assess its prevalence.

**Keywords** Iron deficiency; Heart failure; Prevalence; Cross-sectional studies; Epidemiology; Adults

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See CARENFER Study Group members in Appendix A.

One-sentence summary: Half of patients with decompensated heart failure or chronic heart failure with preserved left ventricular ejection fraction suffer from iron deficiency.

## Introduction

Iron loss and/or chronic inflammation predisposes patients with chronic heart failure (CHF) to develop iron deficiency (ID), in whom it is reported as one of the main non-cardiovascular co-morbidities.<sup>1</sup> Progressive ID can result in

iron-deficient erythropoiesis and, eventually, ID-associated anaemia. All heart failure (HF) subtypes as described in the European Society of Cardiology (ESC) guidelines exhibit ID.<sup>2</sup> Prevalence of ID has been found to range from 35–40% in stable ambulatory CHF patients<sup>3</sup> to more than 60% in patients with acute decompensated heart failure (AHF).<sup>4,5</sup> Most

of these studies have addressed the prevalence of ID in CHF patients or those with HF with reduced ejection fraction (HFrEF). Fewer data are available in AHF, HF with preserved ejection fraction (HFpEF), or HF with mildly reduced ejection fraction (HFmrEF),<sup>6,7</sup>

Importantly, even in the absence of anaemia, ID in patients with HF is associated with clinical signs and symptoms including fatigue<sup>8</sup> and impaired physical performance,<sup>9</sup> all contributing to a reduced quality of life.<sup>10,11</sup> Observational studies have shown that the presence of ID in patients with HF is also significantly associated with a worse prognosis and a higher mortality independently of anaemia.<sup>3,12</sup>

Despite the demonstrable adverse effects of ID in HF patients and their reversibility under iron therapy, systematic screening and subsequent treatment of ID in HF patients with or without anaemia remain inconsistent. In 2016, and more recently in 2021, the ESC has reaffirmed the importance of detecting and treating ID in HF patients.<sup>2,13</sup> ID definition has been updated based on both serum ferritin level and iron saturation of transferrin (TSAT) index to account for inflammation. In France, the recommendations of the National Authority for Health (Haute Autorité de Santé) are in line with those of the ESC, recommending the combined use of serum ferritin concentration and TSAT index.<sup>14</sup> Despite these recommendations, ID remains largely under-diagnosed in France as recently shown in a cohort study of 100 000 patients undergoing iron replacement therapy.<sup>15</sup>

In this prospective multicentre study conducted in France, we aimed to assess the prevalence of ID based on the ESC guidelines in a large panel of HF patients at different stages of the disease.

## Materials and methods

### Study sites and population

The CARENFER study was conducted in France between May 2019 and March 2020. It is a cross-sectional, prospective, nationwide study carried out in 48 cardiology and geriatric wards, which were selected based on a voluntary basis. Based on the conservative assumption that the prevalence of ID is 75% in HF patients,<sup>4</sup> we calculated that 1800 patients had to be recruited to estimate the overall prevalence of ID with a precision of 2%, with an alpha risk of 5%. This sample size allowed estimating the prevalence of ID in males and females separately with a precision of no more than 3%.

All patients present in the medical unit during the study period, whether inpatient or outpatient, with a diagnosis of HF regardless of left ventricular ejection fraction (LVEF) were eligible. Few inclusion criteria were considered in order to

limit selection bias: 18 years old or more, registration with a social security system, and signed written informed consent. Patients under guardianship or curatorship as well as pregnant or breastfeeding women were not included.

### Study procedures

For all included patients, a standardized questionnaire was conducted. The following information was retrieved from the patient's medical record: patient's demographic and clinical data (age, gender, weight, and height), date and type of hospitalization (geriatric vs. cardiology ward, inpatient vs. outpatient, and traditional vs. day hospitalization), reason for admission (decompensation vs. scheduled check-up), HF characteristics [New York Heart Association (NYHA) status before current admission and LVEF before current admission], ongoing treatment for HF and ID, and reported co-morbidities (diabetes, hypertension, chronic kidney disease, and coronary artery disease). For patients who had a recent (i.e. within 7 days before their inclusion in the present study) determination of haemoglobin (Hb) level, as well as serum ferritin and TSAT measurements, no additional biochemical assessment was performed at inclusion. A data quality control was performed throughout the study to ensure that individual data collection was complete and consistent with the patient's medical record and hospital registers.

In addition, in all participating medical units, a standardized questionnaire was sent to investigators in order to document general practices within the unit regarding the assessment of ID in patients with CHF or decompensated HF. The following information was collected: iron status assessment recommended (yes/no), time of assessment (before admission or at patient's admission/discharge), and iron parameters measured.

### Definitions

In this study, ID and functional/absolute ID definitions were based on the 2016 ESC guidelines: absolute ID was defined as serum ferritin < 100 µg/L, and functional ID as the combination of a serum ferritin level between 100 and 299 µg/L and a TSAT index < 20%. Anaemia was defined according to World Health Organization guidelines as an Hb level of ≤13 and ≤12 g/dL, in males and females, respectively. According to the reason for admission, patients were classified as having either a CHF or a decompensated HF corresponding to patients with acute HF or CHF with an unplanned hospitalization for decompensation. HF was classified according to LVEF as HFrEF (<40%), HFmrEF (40–49%), and HFpEF (≥50%).

## Statistics

Descriptive statistics included patients' demographic, main clinical characteristics, distribution of iron parameter measurements, and Hb level: first, in the overall study population, then according to the type of HF (decompensated vs. chronic, as defined above) and LVEF profile. Continuous variables with a Gaussian distribution are presented as mean  $\pm$  standard deviation (SD). For variables distributed in a non-Gaussian manner, the data are shown as medians with interquartile ranges (IQRs). Normality was checked by the Shapiro–Wilk statistic. Categorical data were expressed as percentages. Comparisons between variables were assessed using the  $\chi^2$  test for categorical variables and Wilcoxon's or Kruskal's test for quantitative variables. The level of significance was set at  $P < 0.05$ .

The prevalence of ID, absolute/functional ID, and anaemia was calculated and then analysed according to the type of HF (decompensated vs. chronic) and LVEF profile. Comparisons between variables were assessed using the  $\chi^2$  test. Given the significant differences expected between males and females,<sup>16</sup> secondary analyses were conducted in the two subgroups separately. The prevalence of events was estimated with the Agresti–Coull 95% confidence interval (CI).<sup>17</sup> Finally, the level of agreement between TSAT  $<$  20% and ID (based on the ESC criteria) was assessed among patients with CHF and those with decompensated HF using Cohen's kappa statistic.

All statistics were performed using both SAS® Version 9.4 and R (v 4.1.0).

## Ethics

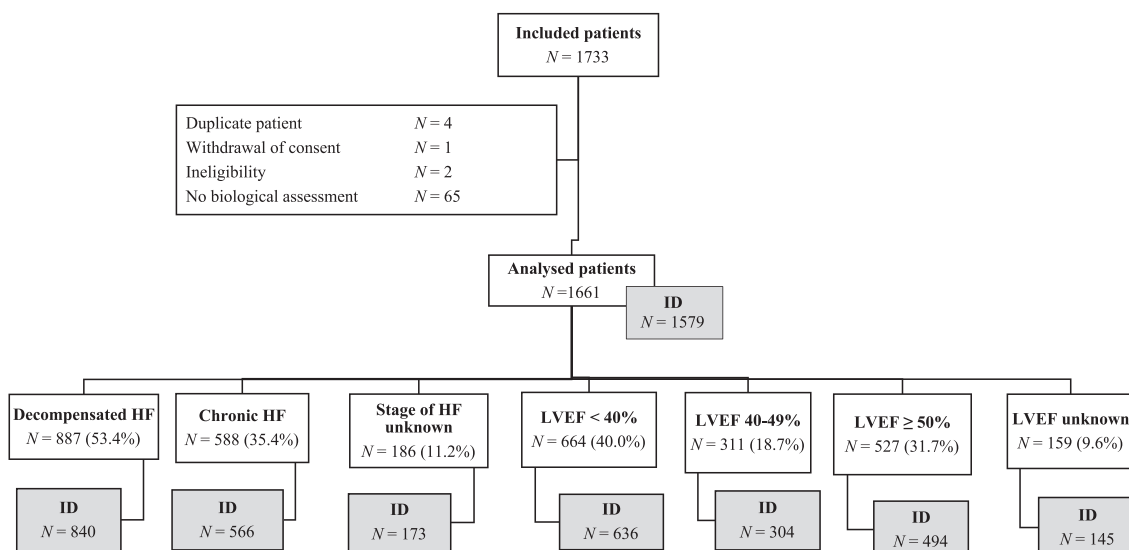
The protocol complied with recommendations of the Declaration of Helsinki, and the International Conference on Harmonization (ICH) guidelines for good clinical practice (GCP), all applicable laws, rules, and regulations. The protocol also complied with the French laws and regulations. Ethical approval was granted by an Ethics Committee (Comité de Protection des Personnes) designated by the French Ministry of Health. All subjects provided written informed consent. ClinicalTrials.gov Identifier: NCT03924258.

## Results

### Study population and patients' baseline characteristics

A total of 1733 patients were included in 48 centres, with a median (IQR) of 29 (21–43) patients by centre. Seventy-two patients were excluded from the analysis because of consent withdrawal ( $n = 1$ ), duplicate inclusion ( $n = 4$ ), no fulfilment of inclusion criteria ( $n = 2$ ), and absence of biological assessment ( $n = 65$ ), leaving 1661 patients for the present analysis (Figure 1). Among them, 16.1% (267/1661) were outpatients seen at a hospital consultation and 83.9% (1394/1661) were inpatients hospitalized either in a cardiology ward [78.9% (1100/1394)] or in a geriatric ward [21.1% (294/1394)]. The type of HF (decompensated vs. chronic) was documented in

**Figure 1** Flow chart of CARENFER study. This graph displays the number (%) of patients with a documented stage of HF (decompensated vs. chronic) as well as a documented LVEF before admission. According to the reason for admission, patients were classified as having either a chronic HF or a decompensated HF corresponding to patients with acute or chronic HF with an unplanned hospitalization for decompensation. ID refers to the number of patients who were classified as iron deficient or not based on both iron saturation of transferrin and serum ferritin level. HF, heart failure; ID, iron deficiency; LVEF, left ventricular ejection fraction.



1475 out of the 1661 patients; for the 186 other patients, the reason for admission reported in the questionnaire was not precise enough to decide whether the patient had been hospitalized for cardiac decompensation or not.

Patient's and HF characteristics stratified on the type of HF are presented in *Table 1*. Males represented 61.6% of the study population. The patients' median age was 78 years. More than 83.3% of the patients had at least one

co-morbidity, with hypertension reported in more than 60% of patients. Decompensated HF represented 60.1% (887/1475) of cases and CHF 39.9% (588/1475) of cases. The characteristics of patients who could not be classified as having a CHF or a decompensated HF are presented in Supporting Information, *Table S1*.

Patients with a decompensated HF were significantly older than patients with a CHF; they were more likely to be females,

**Table 1** Patients' baseline characteristics, and according to the type of heart failure

	Total (N = 1661)	Type of heart failure <sup>a</sup>		P-value <sup>b</sup>
		Decompensated (N = 887)	Chronic (N = 588)	
<b>Age (years), n</b>	<b>1661</b>	<b>887</b>	<b>588</b>	<0.001
Median (Q1–Q3)	78.0 (67.0–86.0)	80.0 (70.0–87.0)	72.0 (62.0–82.0)	
<b>Age (in class), n (%)</b>	<b>1661</b>	<b>887</b>	<b>588</b>	<0.001
<60 years	225 (13.5)	89 (10.0)	121 (20.6)	
[60–70] years	280 (16.9)	125 (14.1)	139 (23.6)	
[70–80] years	380 (22.9)	205 (23.1)	138 (23.5)	
[80–90] years	585 (35.2)	354 (39.9)	151 (25.7)	
≥90 years	191 (11.5)	114 (12.9)	39 (6.6)	
<b>Gender, n (%)</b>	<b>1661</b>	<b>887</b>	<b>588</b>	0.002
Male	1023 (61.6)	528 (59.5)	398 (67.7)	
Female	638 (38.4)	359 (40.5)	190 (32.3)	
<b>Co-morbidities<sup>c</sup></b>				
Hypertension, n (%)	<b>1661</b>	<b>887</b>	<b>588</b>	<0.001
No	618 (37.2)	293 (33.0)	263 (44.7)	
Yes	1043 (62.8)	594 (67.0)	325 (55.3)	
Diabetes, n (%)	<b>1661</b>	<b>887</b>	<b>588</b>	<0.001
No	1118 (67.3)	562 (63.4)	428 (72.8)	
Yes	543 (32.7)	325 (36.6)	160 (27.2)	
Chronic kidney failure, n (%)	<b>1661</b>	<b>887</b>	<b>588</b>	<0.001
No	1219 (73.4)	624 (70.3)	468 (79.6)	
Yes	442 (26.6)	263 (29.7)	120 (20.4)	
Coronary insufficiency, n (%)	<b>1661</b>	<b>887</b>	<b>588</b>	0.454
No	991 (59.7)	523 (59.0)	359 (61.1)	
Yes	670 (40.3)	364 (41.0)	229 (38.9)	
Overweight or obesity <sup>d</sup> , n (%)	<b>1616</b>	<b>855</b>	<b>581</b>	0.126
No	644 (39.9)	346 (40.5)	211 (36.3)	
Yes	972 (60.1)	509 (59.5)	370 (63.7)	
<b>Number of co-morbidities, n (%)<sup>e</sup></b>	<b>1661</b>	<b>887</b>	<b>588</b>	<0.001
No co-morbidity	278 (16.7)	130 (14.6)	127 (21.6)	
1 co-morbidity	541 (32.6)	259 (29.2)	215 (36.6)	
2 co-morbidities	464 (27.9)	263 (29.7)	148 (25.2)	
3 co-morbidities	283 (17.0)	179 (20.2)	69 (11.7)	
4 co-morbidities	95 (5.7)	56 (6.3)	29 (4.9)	
<b>NYHA class before admission, n (%)</b>	<b>1601</b>	<b>836</b>	<b>579</b>	<0.001
I	196 (12.2)	27 (3.2)	136 (23.5)	
II	604 (37.7)	222 (26.5)	297 (51.3)	
III	567 (35.4)	390 (46.7)	120 (20.7)	
IV	234 (14.6)	197 (23.6)	26 (4.5)	
<b>LVEF before admission (%)</b>	<b>1502</b>	<b>820</b>	<b>546</b>	0.741
Median (Q1–Q3)	40.0 (30.0–55.0)	40.0 (30.0–55.0)	40.0 (30.0–52.0)	
<b>LVEF in class, n (%)</b>				0.148
<40%	664 (44.2)	371 (45.2)	240 (44.0)	
[40–50]%	311 (20.7)	153 (18.7)	125 (22.8)	
≥50%	527 (35.1)	296 (36.1)	181 (33.2)	

HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Analysable population N = 1661.

<sup>a</sup>Patients were classified as having either a chronic HF or a decompensated HF corresponding to patients with acute or chronic HF with an unplanned hospitalization for decompensation.

<sup>b</sup>Comparison of clinical characteristics between patients with chronic HF and decompensated HF; Wilcoxon's rank sum test or Pearson's  $\chi^2$  test.

<sup>c</sup>Hypertension, diabetes, chronic kidney failure, and coronary insufficiency are diagnoses that were extracted from patients' medical records.

<sup>d</sup>Overweight and obesity were defined as body mass index 25.0–30.0 and  $\geq 30$  kg/m<sup>2</sup>, respectively.

<sup>e</sup>Including hypertension, diabetes, chronic kidney failure, and coronary insufficiency.

to have co-morbidities, and to display NYHA III–IV (Table 1). HF was classified as HF<sub>r</sub>EF, HF<sub>m</sub>rEF, and HF<sub>p</sub>EF in 44.2% (664/1502), 20.7% (311/1502), and 35.1% (527/1502), respectively. These proportions were not statistically different in patients with a decompensated HF or a CHF. The clinical characteristics of patients according to LVEF profile are presented in Supporting Information, Table S2. Patients with a preserved LVEF were older, more likely to be females, and to have co-morbidities such as hypertension, diabetes, and chronic kidney failure. Proton pump inhibitors and antithrombotic medications used are listed in Supporting Information, Table S3. Ongoing or completed oral iron therapy was recorded in approximately 5% of patients (Supporting Information, Table S3). Intravenous (IV) iron replacement therapy was recorded in 8.5% of patients with CHF, and 13.3% of patients with decompensated HF during the hospital stay; IV ferric carboxymaltose (FCM) was the main treatment.

### Body iron parameters, haemoglobin level, and prevalence of iron deficiency

Table 2 presents the distribution of iron parameters stratified on type of HF. Overall, patients were more likely to have a TSAT index < 20% than a ferritin level < 100 µg/L. The

proportion of TSAT < 20% was statistically higher in decompensated HF (70.0%) than in CHF (34.7%) patients ( $P < 0.001$ ), as was the proportion of patients with a ferritin level < 100 µg/L (32.3% vs. 26.5%, respectively,  $P = 0.02$ ) (Figure 2). ID based on the ESC 2016 guidelines could be assessed in 95.1% (1579/1661) of patients. Overall, ID was found in 49.6% (783/1579, 95% CI: 47.1–52.1) of HF patients; females were more likely to have ID than males (57.9% vs. 44.4%,  $P < 0.001$ ) (Supporting Information, Table S3). ID prevalence was not statistically different in patients from cardiology [49.1% (46.4–51.8)] and geriatric [51.8% (45.9–57.7)] units ( $P = 0.45$ ) (data not shown).

### Prevalence of iron deficiency according to both types of heart failure and ejection fraction

Iron deficiency prevalence was statistically higher in decompensated HF (488/840, 58.1%, 95% CI: 54.7–61.4) than in CHF (221/566, 39.0%, 95% CI: 35.1–43.1) (Figure 2, Table 2). A similar trend was observed when stratifying by gender (Supporting Information, Table S4). Anaemia was reported in 59.5% and 36.1% of patients with decompensated HF and CHF, respectively (Table 2). The proportion of patients with TSAT < 20% and that of patients identified as iron

**Table 2** Iron parameters and haemoglobin levels according to type of heart failure (decompensated vs. chronic)

	Total (N = 1661)	Type of heart failure <sup>a</sup>		P-value <sup>b</sup>
		Decompensated HF (N = 887)	Chronic HF (N = 588)	
<b>Serum iron (mg/L), n</b>	<b>1583</b>	<b>846</b>	<b>561</b>	<0.001
Median (IQR)	0.58 (0.39–0.84)	0.49 (0.33–0.68)	0.78 (0.57–1.00)	
<b>Haemoglobin level (g/dL), n</b>	<b>1611</b>	<b>875</b>	<b>554</b>	<0.001
Mean (SD)	12.4 (2.1)	12.1 (2.1)	13.0 (2.0)	
<b>Hb level categories, n (%)</b>		<b>875</b>	<b>554</b>	<0.001
<8 g/dL	21 (1.3)	10 (1.1)	9 (1.6)	
[8–10] g/dL	225 (14.0)	151 (17.3)	36 (6.5)	
[10–12] g/dL for females, [10–13] g/dL for males	589 (36.6)	360 (41.1)	155 (28.0)	
>12 g/dL for females, >13 g/dL for males	776 (48.2)	354 (40.5)	354 (63.9)	
<b>Serum ferritin level (µg/L), n</b>	<b>1582</b>	<b>842</b>	<b>567</b>	0.193
Median (IQR)	195.5 (85.0–375.0)	174.0 (78.0–364.0)	209.0 (93.0–367.0)	
<b>Serum ferritin level categories, n (%)</b>	<b>1582</b>	<b>842</b>	<b>567</b>	0.022
<100 µg/L	459 (29.0)	272 (32.3)	150 (26.5)	
≥100 µg/L	1123 (71.0)	570 (67.7)	417 (73.5)	
<b>TSAT (%), n</b>	<b>1593</b>	<b>848</b>	<b>568</b>	<0.001
Median (IQR)	18.0 (12.0–26.0)	15.0 (10.0–21.0)	23.0 (17.0–30.0)	
<b>TSAT categories, n (%)</b>	<b>1593</b>	<b>848</b>	<b>568</b>	<0.001
<20%	894 (56.1)	594 (70.0)	197 (34.7)	
≥20%	699 (43.9)	254 (30.0)	371 (65.3)	
<b>ID prevalence<sup>c</sup></b>	<b>1579</b>	<b>840</b>	<b>566</b>	<0.001
No, n (%)	796 (50.4)	352 (41.9)	345 (61.0)	
Yes, n (%) [95% CI]	783 (49.6) [47.1–52.1]	488 (58.1) [54.7–61.4]	221 (39.0) [35.1–43.1]	

CI, confidence interval; Hb, haemoglobin; HF, heart failure; ID, iron deficiency; IQR, interquartile range; SD, standard deviation; TSAT, iron saturation of transferrin.

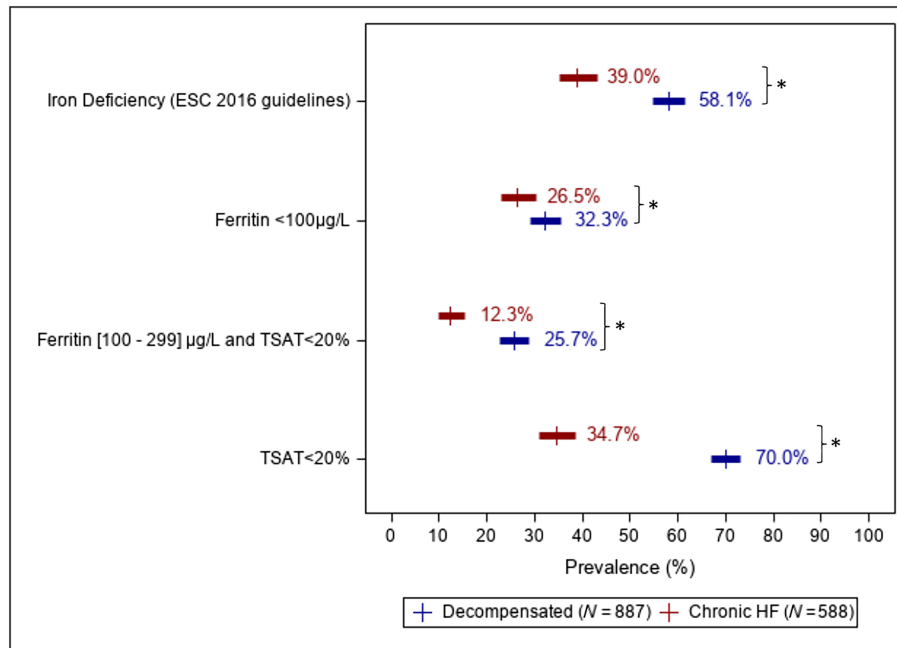
Analysable population N = 1661.

<sup>a</sup>Patients were classified as having either a chronic HF or a decompensated HF corresponding to patients with acute or chronic HF with an unplanned hospitalization for decompensation.

<sup>b</sup>Comparison of biological characteristics between patients with chronic HF and decompensated HF; Wilcoxon's rank sum test or Pearson's  $\chi^2$  test.

<sup>c</sup>Based on the European Society of Cardiology 2016 guidelines.

**Figure 2** Prevalence of iron deficiency (ID), absolute and functional ID, and TSAT < 20% according to the stage of heart failure (decompensated vs. chronic HF). Analysable population  $N = 1475$ . ESC, European Society of Cardiology; TSAT, iron saturation of transferrin.



deficient based on the ESC criteria were compared: among CHF patients, the level of agreement between TSAT < 20% alone and ID was considered as substantial [kappa coefficient, 95% CI: 0.65 (0.58–0.72)], while it was considered as moderate among patients with decompensated HF [kappa coefficient, 95% CI: 0.58 (0.52–0.63)], with a higher proportion of patients with a TSAT < 20% (70.0%) than with ID based on the ESC criteria (58.1%).

Iron deficiency prevalence was determined in 1434/1502 (95.5%) of patients with a documented LVEF. Patients with a preserved LVEF were significantly more likely to have an ID (284/494, 57.5%, 95% CI: 53.1–61.8) compared with patients with mildly reduced (144/304, 47.4%, 95% CI: 45.7–65.0) or reduced LVEF (282/636, 44.3%, 95% CI: 40.5–48.2) (Figure 3, Supporting Information, Table S2).

### Clinical practices

Clinical practices regarding iron assessment were documented in all participating centres. Twenty-eight out of the 48 centres (58.3%) reported a systematic iron assessment for patients with CHF; 25 centres (25/47, 53.2%) reported a systematic iron assessment in patients with decompensated HF. Iron assessment was most likely performed on admission than at the end of hospitalization both in patients with decompensated HF (21/28, 80.8%) and in those with CHF (20/25, 80.0%); only two centres (2/28, 7.7%) reported iron assessment before admission for patients with CHF. Most of

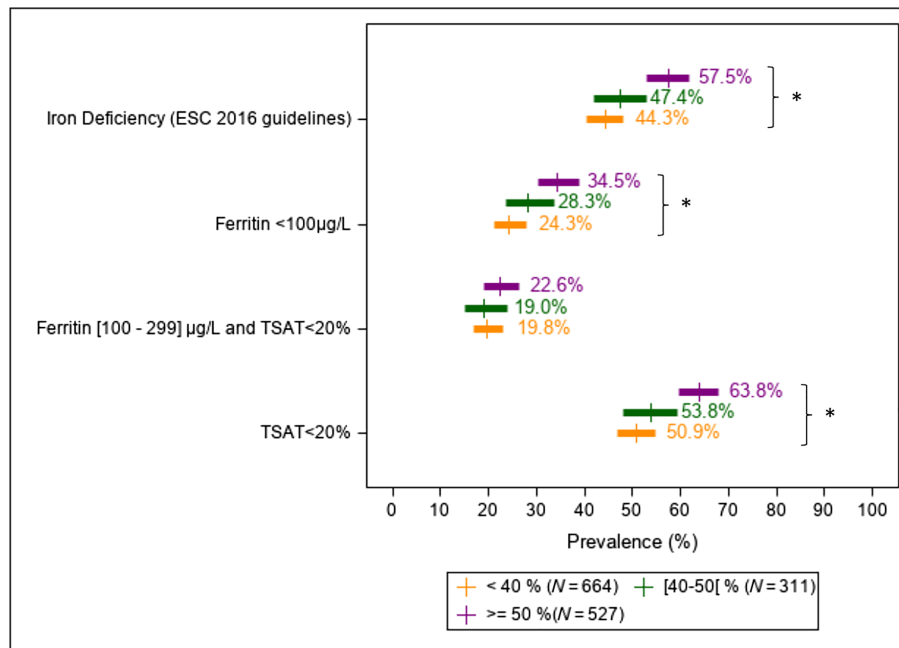
the centres declared measuring serum ferritin, TSAT, and Hb levels both in patients with decompensated HF (between 96% and 100% of the centres) and in patients with CHF (100% of the centres); serum iron was documented in only 58.3% and 62.5% of centres in case of CHF and decompensated HF, respectively.

### Discussion

We prospectively assessed ID prevalence in a large cohort of patients presenting at hospital with diverse HF types, with a systematic measurement of both ferritin level and TSAT index. We showed that as many as 49.6% of HF patients presented with ID based on the 2016 ESC definition. Absolute ID accounted for the majority (59%) of all ID cases. ID prevalence was significantly higher in decompensated HF than in CHF. In decompensated HF, the agreement between a TSAT index < 20% and ID based on the ESC criteria was considered as moderate. Importantly, patients with a mildly reduced LVEF were significantly more likely to have an ID compared with patients with reduced LVEF. Patients with preserved LVEF had even higher rates of ID than patients with HFmrEF.

The prevalence of ID has mainly been estimated in stable CHF patients, ambulatory or hospitalized, in whom it is considered as one of the most common non-cardiovascular co-morbidities. In these patients, it has been shown that the prevalence of ID varies according to gender, NYHA

**Figure 3** Prevalence of iron deficiency (ID), absolute and functional ID, and TSAT < 20% according to left ventricular ejection fraction (LVEF). Analysable population  $N = 1502$ . LVEF before admission was categorized as preserved ( $\geq 50\%$ ), mildly reduced (40–49%), or reduced (<40%). ID was defined as a serum ferritin level < 100  $\mu\text{g/L}$  or the combination of a serum ferritin level between 100 and 299  $\mu\text{g/L}$  and a TSAT index < 20%; absolute ID was defined as a serum ferritin < 100  $\mu\text{g/L}$ ; and functional ID was defined as the combination of a serum ferritin level between 100 and 299  $\mu\text{g/L}$  and a TSAT index < 20%. Prevalence estimates were compared between patients according to LVEF profile using the  $\chi^2$  test; an asterisk indicates a  $P$ -value < 0.05. ESC, European Society of Cardiology; TSAT, iron saturation of transferrin.



category, anaemia, and LVEF, ranging from 30% to 55%,<sup>3,18</sup> and that the figures are higher than those for chronic obstructive pulmonary disease, renal failure or diabetes, and other common co-morbidities in HF. In accordance with the literature, we found that 39.0% of CHF patients had an ID. There are less data available on the prevalence of ID in decompensated HF patients, who represented 60.1% of our study population. Compared with CHF patients, those with a decompensated HF had a much higher prevalence of ID (58.1%) that is in concordance with previously reported prevalence estimates.<sup>4,19,20</sup> Recently, it has been shown that treatment of ID in patients with LVEF < 50% hospitalized for HF decompensation (AFFIRM-HF study) resulted in a reduction in HF hospitalizations.<sup>21</sup> There is now a class IIa level B in the 2021 ESC guidelines to consider IV FCM in patients hospitalized for acute HF before discharge to improve symptoms and reduce rehospitalization.<sup>13</sup> Thirty-six per cent (524/1475) of our study population had similar characteristics than patients included in the AFFIRM-HF trial and may have benefited from IV FCM based on the 2021 ESC guidelines.

We showed that prevalence estimates of ID were higher in patients with HFpEF and HFmrEF compared with patients with HFrEF. This finding is in line with those of recent publications<sup>7,22</sup> and meta-analyses.<sup>6</sup> Recently, Martens *et al.* reported ID prevalence as high as 64% and 61% in CHF patients with HFpEF and HFmrEF, respectively.<sup>7</sup> The reason

for this is not clear. Higher age and a higher proportion of women and patients with co-morbidities alone do not explain this finding. In patients with HFpEF and HFmrEF, ID has been associated with reduced exercise capacity and quality of life as in HFrEF.<sup>7,22</sup> Systematic assessment of iron status and iron supplementation may therefore be relevant in these patients, for whom there is no clear recommendation for management.

Indeed, there is now clear evidence that IV iron therapy in CHF patients has positive effects on both symptoms related to ID, including quality of life, and risk of HF-related hospitalization.<sup>23,24</sup> The ESC guidelines propose that this treatment should be offered in symptomatic patients with HFrEF and ID.<sup>2</sup> There are currently no recommendations for CHF patients with HFpEF.<sup>13</sup> Three clinical trials (NCT03074591, NCT03833336, and NCT04945707) are underway to assess the efficacy of IV iron therapy in these patients—who represent a significant proportion of the iron-deficient population and have similar morbidity and mortality rates than HFrEF patients<sup>6</sup> on exercise capacity and quality of life. In particular, the large FAIR-HFpEF trial will assess the effect of FCM on exercise tolerance, symptoms, and quality of life in patients with HFpEF and ID (NCT03074591).

We found a higher prevalence of ID defined by TSAT alone than by the ESC criteria in patients with decompensated HF. Among these patients, 70% had a TSAT index < 20% while

58.1% were diagnosed iron deficient based on the ESC 2016 criteria, reflected by only a moderate level of agreement between TSAT alone and the ESC criteria. Among patients with CHF, the level of agreement between TSAT < 20% and ID (ESC criteria) was higher and considered as substantial. Although a higher prevalence of TSAT < 20% compared with the ESC criteria does not imply that the former definition is the most accurate, our results are in line with recent publications highlighting the diagnostic and predictive value of TSAT. Recently, Beverborg *et al.* reported that low TSAT better correlated than ferritin to characterize ID when taking bone marrow iron content as reference.<sup>25</sup> Also, Cleland *et al.* showed that serum concentrations of iron and TSAT were more strongly associated with anaemia than were serum concentrations of ferritin.<sup>26</sup> Finally, a low TSAT has been independently associated with higher rates of morbidity and death.<sup>25–28</sup> All together, these results reinforce the idea of using a TSAT < 20% for the identification of ID in patients with HF and question the value of serum ferritin in the assessment of ID.<sup>29,30</sup>

Despite the demonstrated adverse effects of ID in HF patients, the diagnosis and management of HF patients with ID remain largely suboptimal.<sup>15,31</sup> A recent study based on French healthcare databases including more than 100 000 patients undergoing iron therapy from 2006 to 2015 showed that ID was highly under-detected, with iron assessment reported in only 33% of patients before iron therapy.<sup>15</sup> In the present study, clinical practices were evaluated in each of the 48 participating centres. Just over 50% of them reported a systematic iron assessment in both CHF patients and those with decompensated HF. Although these results may not be representative of the clinical practices of all practitioners in the centres, they highlight the strong under-detection of ID even in highly specialized units. This may be partially due to the lack of practical advice on how to screen, diagnose, and treat ID, in particular in acute HF.<sup>32</sup>

We acknowledge some limitations to the present study. First, our prevalence estimates are not based on a representative sample of HF patients. However, they are based on a very large number of participants recruited from 48 centres across France. The diagnosis of HF was based on the patient's medical record and did not have to meet any specific criteria for the study. However, as most of the participants were inpatients in cardiology units, we are confident in the validity of the HF diagnosis. Eleven per cent of the participants could not be classified as having a decompensated HF or a CHF based on the reason for admission but still contributed to the estimated prevalence of ID in the overall study population. Second, biochemical assessment was not centralized, with possibly different biological cut-offs across participating centres. Therefore, misclassifications cannot be excluded. Only serum ferritin and TSAT levels were determined because they are the two biomarkers recommended by the ESC and the French National Authority for Health to define ID. Finally,

the values of the iron parameters prior to decompensation were not reported. Therefore, it is not known whether ID in patients with decompensated HF was already present before decompensation.

## Conclusion

In this large, nationwide study, we found a high prevalence of ID in patients with HF. While most studies have addressed the prevalence of ID in patients with CHF and low EF, we found that ID prevalence was significantly higher in HFmrEF and HFpEF or in decompensated HF. We also found that ID when defined only by low TSAT, a definition supported by recent studies and overcoming the limitation of ferritin assessment in case of inflammation, was higher than when defined by the ESC criteria in patients with decompensated HF. Finally, our study reveals an insufficient application of the ESC guidelines regarding systematic detection of ID and anaemia in all HF patients using both serum ferritin concentration and TSAT.<sup>13</sup>

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## Conflict of interest

P. Cacoub received grants from Alnylam and MSD; royalties from Iltoo; consulting fees from Vifor Pharma and Servier; honoraria from Vifor Pharma, Servier, and Alnylam; and support for attending meetings from Abbvie. J.N. Trochu received consulting fees and clinical research grant from Vifor Pharma for the present work; institutional grants from Novartis, Akcea, and Boston Scientific; consulting fees from Novartis, Bayer, Resmed, Astra Zeneca, and Abbott; and honoraria from Abbott and Novartis. A. Korichi has a full-time position at Vifor Pharma Group. Alain Cohen Solal received in the last 3 years fees for expertises, boards, and studies from Novartis, Vifor Pharma, We Health, Bayer, Abbott, Merck, Astra Zeneca, Leo, Boehringer Ingelheim, and Sanofi. F. Picard received personal fees from Vifor Pharma for the present study. All remaining authors have declared no conflicts of interest.



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## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1.** Patients' baseline characteristics according to whether the type of heart failure (decompensated vs. chronic) was determined. Analyzable population  $N = 1661^{\S}$ .

**Table S2.** Patients' clinical characteristics and iron parameters and haemoglobin levels according to LVEF profile. Analyzable population  $N = 1502$ .

**Table S3.** Current treatment for heart failure (HF) and current or completed treatment for iron deficiency (ID) according to the type of heart failure (decompensated vs. chronic HF). Analyzable Population  $N = 1475$ .

**Table S4.** Iron parameters and haemoglobin levels according to gender and type of heart failure <sup>¶</sup>. Analyzable Population  $N = 1475$ .

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