Ironing out the iron profile in heart failure patients: A single centre, outpatient-based cross-sectional study in South Africa

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ABSTRACT

Background: Iron deficiency is the most common nutritional deficiency globally, affecting up to 55% of patients with heart failure. Iron deficiency is an independent predictor of poor outcomes in heart failure patients. Screening for iron deficiency is recommended by the European Society of Cardiology (ESC) and adopted locally.

Objectives: To provide insight into the burden of iron deficiency in patients with heart failure in South Africa by measuring the iron profile and analysing differences in the iron profile between sexes and subgroups of heart failure.

Methods: A single-centre descriptive cross-sectional study was performed. Demographic, clinical, echocardiographic and laboratory data of patients with heart failure attending Universitas Academic Hospital in Bloemfontein for 3 months in 2023 were collected and analysed.

Results: We included 147 patients, 127 of whom had iron profile results. Over half (60.6%, 77/127) had iron deficiency, while the majority (74.0%, 57/77) had non-anaemic iron deficiency. Iron deficiency was more prevalent in females than males (p-value = 0.0006).

Conclusion: A high prevalence of iron deficiency in heart failure was noted. Even though their haemoglobin levels were normal, most patients were iron deficient. Routine screening of heart failure patients, as adopted from the ESC Guidelines 2021, is recommended.

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INTRODUCTION

Heart failure is a complex, multifactorial syndrome resulting from impaired heart function due to a structural or functional abnormality of the heart.[1] Globally, heart failure affects 64.3 million people, of whom 29.5 million are males and 34.8 million are females.[2] Iron deficiency was recently recognised as a heart failure-associated comorbidity, and its presence independently predicts a poor outcome in acute and chronic heart failure patients.[1]

The heart has the highest energy expenditure of all organs, and cardiomyocytes depend highly on effective mitochondrial function. Iron deficiency leads to mitochondrial damage by altering the mitochondrial morphology, as well as functioning. Dysfunctional mitochondria lead to decreased ATP production, damage to mitochondrial DNA, increased gluconeogenesis, increased lactic acid production, impaired mitophagy, increased apoptosis and oxidative stress. Cardiomyocytes, deprived of iron, lead to decreased contractility and structural changes in the heart. Iron deficiency further alters calcium handling with a shift towards lactic acid-producing glycolytic metabolism.[3]

Iron deficiency leads to a deterioration in exercise capacity, precipitates circulatory decompensation and promotes skeletal muscle dysfunction in an already failing heart, leading to an increase in hospitalisations and death.[1]

The impact of iron deficiency in patients with heart failure is so profound that the ESC, in their 2021 guideline, recommended that all patients with heart failure are periodically screened for anaemia and iron deficiency with a full blood count, serum

ferritin and transferrin saturation.[4-7] Screening for iron deficiency has thus become the standard of care.

Heart failure patients are at risk of developing iron deficiency as they gradually decrease iron stores due to many factors, including loss of appetite, poor nutrition, and decreased gastrointestinal absorption of iron from intestinal oedema and chronic inflammation.[8] Gastrointestinal bleeding, secondary to medications such as antithrombotics and anticoagulants, is another proposed mechanism for developing iron deficiency.[8]

The European Society of Cardiologists classify heart failure according to the left ventricular ejection fraction (LVEF).[1] There are three distinct groups, namely heart failure with a reduced ejection fraction (HFrEF, LVEF ≤40%), heart failure with a midrange ejection fraction (HFmrEF, LVEF 41% - 49%), and heart failure with a preserved ejection fraction (HFpEF, LVEF ≥50% with objective evidence of cardiac abnormalities). Intravenous iron supplementation is recommended in symptomatic iron-deficient heart failure patients with a reduced or midrange ejection fraction to alleviate symptoms and improve quality of life.[9] Intravenous ferric carboxymaltose or ferric derisomaltose should be considered in symptomatic iron-deficient heart failure patients with a reduced or midrange ejection fraction to reduce the risk of hospitalisation.[9] No iron supplementation is currently recommended in heart failure patients with a preserved ejection fraction,[1,9] and therefore, we did not include this group in our study.

According to European studies, iron deficiency is present in up to 36% - 55% of chronic heart failure patients.[5,6,10,11] A similar prevalence of 49% - 60% is seen in sub-Saharan heart failure patients.[12,13] However, to our knowledge, minimal data to date describes the iron profile of heart failure patients in South Africa. The prevalence and characteristics of iron deficiency in our context are unknown.

This study, therefore, aims to explore the iron profile of patients with heart failure (HFrEF and HFmrEF) attending the Cardiology Clinic at Universitas Academic Hospital. The study's objectives are firstly to measure the iron profile in patients with heart failure and determine the prevalence of iron deficiency in this population. Secondly, we aim to analyse iron profile differences between sexes and subgroups of heart failure and explore associations between CRP, nT-proBNP and iron deficiency. We hope to provide knowledge and insight into the burden of iron deficiency in heart failure in a South African setting, as limited data on this topical topic exist.

METHODS

Study design

We conducted a single-centre descriptive cross-sectional study that enrolled heart failure patients with a reduced or midrange ejection fraction to measure their iron profile. We reviewed their clinical, echocardiographic and laboratory data.

Setting

The study was performed at the Cardiology Clinic at Universitas Academic Hospital (UAH) in Bloemfontein, South Africa. UAH is a 636-bed hospital. It is the only centre providing specialist cardiology services for patients primarily from the Free State, Northern Cape Province, and Lesotho.

Study size

The study size was determined by the time set out to do the study, i.e. 3 months. On average, 20 patients are seen in the Cardiology Clinic per day. About a quarter of these patients have heart failure. Our estimated study size was 240 patients for the 3 months.

Participants

The study population consisted of all patients 18 years and older with a confirmed diagnosis of heart failure who attended the clinic during the data collection period of 3 months (1 March - 31 May 2023). We defined heart failure as a clinical syndrome with symptoms of dyspnoea, lower limb swelling and fatigue, and signs of raised jugular venous pressure, pulmonary congestion, and peripheral oedema with echocardiographical evidence of a decreased left ventricular ejection fraction (LVEF).

A field worker screened patients according to the inclusion criteria, obtained informed consent from eligible patients, and completed the data forms. We included all consenting heart failure patients with an LVEF of 49% or less. We divided heart failure into subgroups based on the LVEF, namely, heart failure with a reduced ejection fraction (LVEF ≤40%) and heart failure with a midrange ejection fraction (LVEF 41% - 49%).

Definitions

Heart failure was graded according to LVEF, as found on the echocardiographic report. Heart failure with a reduced ejection fraction is defined as an LVEF ≤40%, and heart failure with a mildly reduced ejection fraction is defined as an LVEF between 41% - 49%.

Heart failure symptoms were classified according to the NYHA Functional Classification.[1] Class I patients have no limitations of physical activity and are asymptomatic. Class II patients have

slight limitations in physical activity. Class III patients have marked limitations in physical activity. Class IV patients cannot continue physical activity without discomfort and have symptoms at rest.

Iron deficiency was defined as either a serum ferritin concentration of less than <100ng/mL or 100 - 299ng/mL with transferrin saturation of less than 20%.[1] Anaemia was defined as a haemoglobin of <12g/dL in females and <13g/dL in males.[14]

Variables

Categorical and numerical data were collected. Age, sex, LVEF, haemoglobin, mean corpuscular volume and haemoglobin, ferritin, transferrin saturation, C-reactive protein (CRP) and N-terminal pro-brain natriuretic peptide (nT-proBNP) were collected as numerical variables. Each participant's home province, New York Heart Association (NYHA) functional classification, and concomitant medications were captured as categorical variables. Preceding iron studies and iron supplementation were captured as categorical data.

Sources / measurement

An electronic data form was created to capture data. The researcher collected clinical data from participant files. Echocardiography data were collected from relevant records in patient files, and laboratory data were collected from the National Health Laboratory (NHLS) Trakcare. Research Electronic Data Capture (REDCap) facility hosted by the University of the Free State (UFS) was used to process all data. REDCap is a secure, web-based software platform that supports data capture for research studies.[15] A p-value of less than 0.05 was considered statistically significant.

Data analysis

Numerical variables were summarised by medians, ranges, or percentiles. Categorical variables were summarised by frequencies and percentages. Differences between groups were evaluated using the Chi-Square test. The Department of Biostatistics, Faculty of Health Sciences, UFS, analysed the data using SAS version 9.4.

Ethical considerations

The Health Sciences Research Ethics Committee of the University of Free State provided ethical approval to conduct the study. (Reference no. UFS-HSD2022/1969/2802) The head of the Department of Internal Medicine, School of Clinical Medicine, UFS. The Free State Province Department of Health granted permission to conduct the research at a provincial facility.

Participation in the study was voluntary, and written consent was obtained before inclusion. No identifiable data was used, and a number was allocated to each patient in the study to ensure anonymisation.

Data management

This study adhered to ethical data management practices. REDCap employs access controls to restrict access to raw data to authorised members only. Only the research team was granted access to the project. De-identified data will be securely stored on REDCap for at least 5 years, after which it will be securely deleted.

RESULTS

Description of the study population

We pre-screened 156 patients during the 3-month period that fulfilled our study's inclusion criteria. We enrolled 144 patients, as 12 did not sign informed consent to participate in the study. A further 17 patients were excluded from the study because of incomplete blood results. We studied the iron profile in 127 patients (Figure 1).

Of the 127 patients, 60.6% (77/127) had iron deficiency as defined by the ESC definition of iron deficiency in heart failure. Table 1 compares the baseline characteristics of the iron-

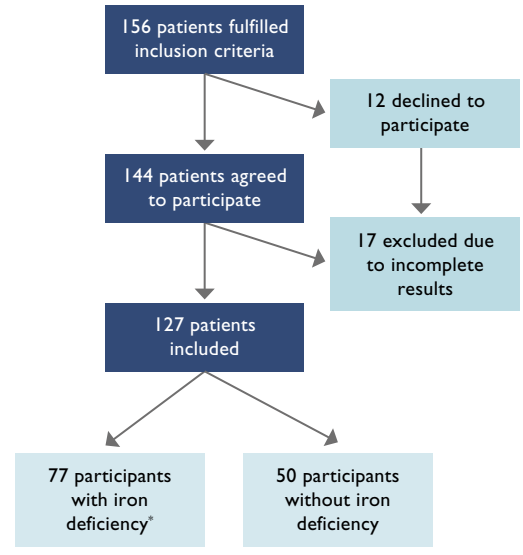

FIGURE 1: Scheme for determining the study population.
*as defined by Ferritin <100ng/mL or Ferritin 100 - 299ng/mL with Transferrin Saturation of <20%.

TABLE I: Baseline characteristics of iron-deficient and non-iron-deficient heart failure patients.

Variable	Iron-deficient n=77	Non-iron-deficient n=50
Age		
20 - 29 (freq; %)	7 (9.1%)	0 (0%)
30 - 39 (freq; %)	10 (12.9%)	4 (8.0%)
40 - 49 (freq; %)	14 (18.2%)	11 (22.0%)
50 - 59 (freq; %)	21 (27.3%)	10 (20.0%)
60 - 69 (freq; %)	13 (16.9%)	18 (36.0%)
70 - 79 (freq; %)	11 (14.3%)	6 (12.0%)
80 - 89 (freq; %)	1 (1.3%)	1 (2.0%)
Sex		
Male (freq; %)	27 (35.1%)	33 (66.0%)
Female (freq; %)	50 (64.9%)	17 (34.0%)
Home province		
Free State (freq; %)	70 (90.9%)	43 (86.0%)
Northern Cape (freq; %)	7 (9.1%)	6 (12.0%)
Eastern Cape (freq; %)	0 (0%)	1 (2.0%)
Iron studies performed in the last 6 months		
Yes (freq; %)	3 (3.9%)	6 (12.0%)
No (freq; %)	71 (92.2%)	44 (88.0%)
Unsure (freq; %)	3 (3.9%)	0 (0%)
Taking iron supplementation		
Yes (freq; %)	3 (3.9%)	1 (2.0%)
No (freq; %)	72 (93.5%)	48 (96.0%)
Unsure (freq; %)	2 (2.6%)	1 (2.0%)
NYHA functional classification		
Class I (freq; %)	19 (24.7%)	15 (30.0%)
Class II (freq; %)	40 (51.9%)	27 (54.0%)
Class III (freq; %)	16 (20.8%)	8 (16.0%)
Class IV (freq; %)	2 (2.6%)	0 (0%)
Heart failure classification		
HFrEF (freq; %)	48 (62.3%)	33 (66.0%)
HFmrEF (freq; %)	29 (37.7%)	17 (34.0%)

deficient and non-iron-deficient patients. More females (64.9%, 50/77) were affected than males (35.1%, 27/77). Iron deficiency was most prevalent in the 50 - 59 age group, with 27.3% (21/77) of the iron-deficient patients falling into this age category.

Most iron-deficient patients (92.2%, 71/77) had no iron studies performed before the index clinic visit. Of the iron-deficient patients, only 4.2% (3/77) took iron supplementation at the time of the clinic visit. These patients were all taking oral ferrous sulphate.

TABLE II: Presence of concomitant anaemia in iron-deficient heart failure patients.

Variable	Males n=27	Females n=50	Total n=77
Anaemic (freq; %)	6 (22.2%)	14 (28.0%)	20 (26.0%)
Non-anaemic (freq; %)	21 (77.8%)	36 (72.0%)	57 (74.0%)

Of the 77 patients, 24.7% (n=19) had NYHA Functional Class I heart failure, 51.9% (n=40) Class II, 20.8% (n=16) Class III, and 2.6% (n=2) Class IV. Heart failure with a reduced ejection fraction was present in 62.3% (48/77) of iron-deficient patients. The rest of the iron-deficient patients had heart failure with a midrange ejection fraction.

Almost three-quarters (74%, 57/77) of iron-deficient patients had a normal haemoglobin level, as previously defined. Concomitant anaemia was present in 26% (20/77) of iron-deficient patients; therefore, most iron-deficient patients with heart failure had normal haemoglobin (Table II).

Iron deficiency and sex

Iron deficiency was more prevalent in females than males (p-value = 0.0006). There was no statistically significant difference in the median MCV between males and females (p-value = 0.0945). We also found that ferritin and transferrin saturation were lower in females than males (p-value = 0.0015 and p-value = 0.0032, respectively).

Iron deficiency and left ventricular ejection fraction

We explored differences within the iron profile in the subgroups of heart failure (Table III). Females were more affected by iron deficiency than males in both subgroups. The median ages of the patients within the subgroups ranged from 48.5 - 59 years. Most of the patients had NYHA functional class II heart failure.

In both groups, the females' MCV were lower than the males' MCV. The median transferrin saturation ranged between 13.5% - 15%, with median ferritin of 46.5 - 56.5µg/L in the females, as opposed to 13% - 14.5% and 68.5 - 69µg/L in the males. Females' ferritin was lower than their male counterparts. The median CRP was low in both subgroups.

There was no association between the left ventricular ejection fraction and iron deficiency (p-value = 0.6748). No association was noted between NYHA functional class and anaemia (p-value = 0.5926) or NYHA functional class and iron deficiency (p-value = 0.5703).

TABLE III: Differences in iron profile within subgroups of heart failure patients, based on the left ventricular ejection fraction.

	LVEF ≤40%		LVEF 41% - 49%	
	Males n=20	Females n=28	Males n=7	Females n=22
Age (mean; range)	54.5 (50.0 - 62.5)	48.5 (33.5 - 60.0)	59.0 (40.0 - 70.0)	54.5 (41.0 - 68.0)
NYHA Functional Class				
I (freq; %)	3 (15.0%)	7 (25.0%)	3 (42.9%)	6 (27.3%)
II (freq; %)	12 (60.0%)	13 (46.4%)	3 (42.9%)	12 (54.6%)
III (freq; %)	4 (20.0%)	8 (28.6%)	1 (14.3%)	3 (13.6%)
IV (freq; %)	1 (5.0%)	0 (0%)	0 (0%)	1 (4.6%)
MCV (mean; range)	94.5 (92.1 - 100.6)	91.6 (84.4 - 95.2)	96.9 (86.8 - 99.5)	93.2 (88.4 - 94.3)†
MCH (mean; range)	29.6 (29.1 - 32.2)	29.1 (26.4 - 30.3)	30.4 (27.3 - 33.4)	28.4 (27.7 - 29.8)†
TSAT (mean; range)	13.0 (10.5 - 18.5)	15.0 (12.0 - 17.0)*	14.5 (13.0 - 19.0)†	13.5 (10.0 - 17.0)
Ferritin (mean; range)	68.5 (37.0 - 139.5)	56.5 (33.5 - 96.0)	69.0 (38.0 - 126.0)	46.5 (20.0 - 88.0)
CRP (mean; range)	6 (4 - 13)***	5 (2 - 9)**	5 (2 - 7)†	1 (1 - 3)^

**2 patients' results missing, **6 patients' results missing, ***3 patients' results missing, †1 patient's results missing, ^3 patients' results missing.*
LVEF: Left ventricular ejection fraction, NYHA: New York Heart Association, TSAT: Transferrin saturation, CRP: C-reactive protein.

Iron deficiency and C-reactive protein

We found that the CRP does not affect the iron profile in heart failure patients. The median CRP in the iron-deficient group was 4 and 3.5mg/L in the non-iron-deficient group. We could not find any statistical association between CRP and iron deficiency (p-value = 0.8475).

Iron deficiency and N-terminal prohormone of brain natriuretic peptide

Only 4 patients in our study had nT-proBNP done. These patients' results were 1028, 3935, 5046 and 560ng/L, respectively. Three patients with positive nT-proBNP results had iron deficiency. We could not assess any association between nT-proBNP and iron deficiency as the results were incomplete.

Iron deficiency and concomitant anticoagulants

Most patients with iron deficiency were on warfarin (31.2%, 24/77), aspirin (29.9%, 23/77) and rivaroxaban (9.1%, 7/77). Only 3 patients were taking clopidogrel, and only 2 were on enoxaparin. There was no difference between the iron-deficient and non-iron-deficient groups related to the use of these medications (p=0.1704, p=0.6245, p=0.7131, p=0.055, p=0.7024, respectively).

DISCUSSION

Our study found that more than half of our heart failure patients had iron deficiency, as defined by the ESC definition for iron deficiency in heart failure.[1] Iron deficiency was missed in most of these patients, as most had no previous iron studies before the clinic visit. Nearly three-quarters of heart failure patients with iron deficiency had normal haemoglobin values. These results are important because iron deficiency is common in heart failure patients, and normal haemoglobin should not exclude heart failure patients from having their iron studies checked, as patients with iron deficiency are eligible for intravenous iron supplementation as per ESC guidelines.[1] There is a need for further studies to determine the optimal treatment of iron deficiency considering conflicting results regarding improvements in symptoms, functional capacity and safety.[16-17] Side effects and alternatives to intravenous iron repletion warrant careful consideration.

Iron deficiency is common in heart failure patients and is associated with adverse cardiovascular outcomes.[18-19] Our study is one of the first studies in South Africa to report on the iron profile in heart failure patients. Our finding is in keeping with European data, which suggest a 36% - 55% prevalence of iron deficiency in heart failure patients.[5,6,10,11] Our findings were also comparable to data from sub-Saharan Africa, which found a prevalence of 49% in Tanzania and 60% in Nigeria, respectively.[12,13]

We found that iron deficiency is often missed in heart failure patients as they often have a normal haemoglobin count despite being iron deficient. Possible reasons why routine iron studies are not done might be because doctors are not familiar with the new ESC Guidelines or that doctors feel no need to investigate the iron profile as the patient might have had normal

haemoglobin at the time of consultation. Cost constraints may also influence the uptake of laboratory tests in smaller institutions; however, as the study site is an academic hospital, this is not likely a factor. Our study highlights the need for routine iron studies in all South African heart failure patients.

It is important to note that iron deficiency and anaemia do not necessarily need to coexist. One may be anaemic without ID, but also and perhaps more importantly, one may have ID without anaemia. It has been noted that in heart failure ID does not correlate closely with anaemia.[20]

There was a statistically significant association between iron deficiency and sex, consistent with European data, showing that females are more likely to develop iron deficiency.[5,6] Our findings failed to show statistically significant associations between iron deficiency and left ventricular ejection fraction, NYHA functional class and CRP. Literature,[1,5,6] however, suggests that these associations exist, and our relatively small study population might be a possible reason we could not prove the existence of these associations. Because of incomplete data, we could not assess the association between iron deficiency and nT-proBNP.

Strengths and limitations

The study's strengths include that it is one of the first studies reporting on the prevalence and characteristics of iron deficiency in heart failure patients in South Africa. We recruited heart failure patients with a confirmed echocardiographic diagnosis of heart failure and used validated assays for our laboratory data. These measures ensured good quality data. However, several limitations should be highlighted. One limitation is that our study was conducted in a single-centre outpatient department for 3 months. Our results only give a 3-month glimpse of the burden of iron deficiency in heart failure patients and do not represent South Africa or the Free State as a whole, as not all patients with heart failure are referred to Universitas Cardiology. Our relatively small study population is another limitation, as patients were excluded from the study because of incomplete results and not agreeing to participate.

CONCLUSION

We conclude that iron deficiency is common in heart failure patients in the South African context. Furthermore, iron deficiency can occur in patients with normal haemoglobin; therefore, the diagnosis is often missed. A normal haemoglobin should not exclude patients from having their iron status routinely checked. Iron deficiency is treatable, and by diagnosing these patients, treatment can be offered, improving symptoms and quality of life in these patients. We support the adoption of ESC Guidelines 2021, which advocate for routine screening for iron deficiency in heart failure with treatment thereof in managing South African heart failure patients, and we appeal to South African doctors to screen for iron deficiency in heart failure patients. This recommendation is particularly important to female patients with heart failure given the higher prevalence of ID in that population.

Further research is needed on iron deficiency in heart failure patients in South Africa. This can be done by conducting bigger, multicentre studies for longer periods to ensure the generalisability of results. We believe that larger numbers will provide more insight into the prevalence and characteristics of iron deficiency in South African heart failure patients, leading to the development of our own guidelines on screening and managing iron-deficient heart failure patients.

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DISCLOSURES

The views and opinions expressed in this article are those of the authors and are the product of professional research. It does not necessarily reflect the official policy or position of the University of the Free State. The authors are responsible for this article's results, findings, and content.

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