ORIGINAL ARTICLE

Iron Deficiency in Heart Failure Patients with Reduced Ejection Fraction and the Correlation with Left Ventricular Ejection Fraction

Kok Leng Tan[1,2], Seng Loong Ng[2], Soon Eu Chong[1], W Yus Haniff W Isa[2], Hady[2], Jun Jie Tan[1], Zurkurnai Yusof[2]

[1] Advanced Medical and Dental Institute, Universiti Sains Malaysia, Bertam, 13200, Kepala Batas, Penang, Malaysia
[2] Cardiology Unit, Department of Medicine, School of Medical Sciences, Universiti Sains Malaysia, 16150 Kubang Kelian, Kelantan, Malaysia

ABSTRACT

Introduction: Iron deficiency (ID) has recently been identified as a threat to patients with heart failure with reduced ejection fraction (HFrEF). This study was conducted to determine the occurrence of ID among HFrEF patients in a Malaysian tertiary hospital and its correlation between left ventricular ejection fraction (LVEF). **Methods:** Stable patients with LVEF less than 45% were included. Demographic data, LVEF (Simpsons) and cardiac functional status were studied, along with full blood count and iron profile. **Results:** 81 patients with a mean LVEF of 33.6% were recruited. 43.2% of them were NYHA class II patients, followed by 38.3% class III, 13.6% class I and 4.9% class IV patients. About 2/5 of the study population were anaemic, and of those, 48.5% were iron deficient. Majority of these anaemic patients (87.5%) had an absolute iron deficiency. Pearson's statistical analysis showed positive correlation between ejection fraction and serum ferritin ($r=0.624$, $p< 0.001$), serum iron ($r= 0.302$, $p<0.05$), transferrin saturation ($r= 0.346$, $p<0.001$) and haemoglobin ($r=0.528$, $p <0.001$). Among the HFrEF patients, mean LVEF of those without anaemia and without ID were the highest (35.75+4.35%), followed by anaemic patients without ID (31.71+4.47%) and anaemic patients with ID (28.94+2.57%). There was also a trend showing that anaemic patients with ID were associated with higher NYHA functional class. **Conclusions:** ID is correlated with HFrEF in this single tertiary centre of a developing country. Further studies are needed to explore this potential nutritional therapeutic target that may be used in the updates of existing advisory.

Keywords: Iron Deficiency, Heart Failure, Ejection Fraction, Anaemia

Corresponding Author:
Jun Jie Tan, D.Phil
Email: jjtan@usm.my
Tel: +604-5622422

KokLeng Tan, MMed
Email: tankl@usm.my
Tel: +604-5622029

INTRODUCTION

Despite significant improvement in treatment of heart failure with reduced ejection fraction (HFrEF) over the years, the functional status remains impaired among many patients. Anaemia has been associated with increased disease severity in HFrEF patients and is believed to contribute to a poorer outcome (1) and earlier onset of the disease (2). The pathophysiology contributing to the adverse outcome in HFrEF is generally complex and involving multiple aetiology (3-5). One of the common key factors involved is iron deficiency (ID) (6-8).

Traditionally, ID is only considered clinically relevant when a patient is anaemic. However, a chronic and gradual reduction in iron storage may be a preventable cause of anaemia (9). New studies have shown that even if patients are non-anaemic, ID is still common among HFrEF patients (1, 10).Regardless whether a patient is anaemic, ID is associated with a decreased physical fitness and reduced effort tolerance (11-13). The frequency and clinical significance of ID, regardless of haemoglobin level in patients with HFrEF is unclear and more data is needed (1, 14, 15). This study was conducted to determine the occurrence of ID among HFrEF patients in a Malaysian tertiary hospital, the correlation between left ventricular ejection fraction (LVEF) and serum iron profile.

MATERIALS AND METHODS

Inclusion & Exclusion Criteria

This cross-sectional study was conducted after the approval of the Human Research and Ethic Committee

of Universiti Sains Malaysia (USM/JEPeM/14080293). Patients were recruited during echocardiography assessment. Inclusion criteria were age above 18 years old, LVEF ≤ 45% (Simpson's method), and clinically stable for the past 6 months. Exclusion criteria include acute coronary syndrome or any major surgery within the last 3 months. Patients with acute or chronic illness that may affect iron metabolism (e.g. malignancy, infection, chronic liver disease, severe kidney disease requiring haemodialysis and haematological diseases) were excluded. Venous blood (10 ml) was drawn from each consented patient and sent for iron profiling (serum ferritin, serum iron level, total iron binding capacity, transferrin saturation and haemoglobin level). Demographic data, LVEF (Simpson's planimetric method) and New York Heart Association (NYHA) functional classification for each patient were recorded. The researcher who recorded the NYHA classification was different from the one who performed echocardiography and each of them was blinded from the findings of patients including NYHA and LVEF which had been recorded. Patients with ID were those with serum ferritin level < 100µg/L, or ferritin level from 100-300 µg/L with transferrin saturation (Tsat) < 20%. Patients with haemoglobin level < 12g/ dL in women or < 13g/dL in men were considered anaemic.

Statistical analysis

All data was processed and analysed using IBM Statistical Package for Social Sciences (SPSS) version 22.0. The frequency of anaemia and iron deficiency state in HFrEF were analysed. Relationship between LVEF with serum haemoglobin, ferritin and transferrin saturation were analysed using Pearson's correlation analysis.

RESULTS

A total of 62 male and 19 female patients with HErEF (n= 81), with age ranging from 29 to 87 and mean LVEF of 33.6±4.9% were recruited (Table I). Average weight was 65±5.3 kg with BMI 22.6±1.5 kg/m2. Of the 81 recruited patients, 11 (13.6%) were diagnosed as class I, while class II and III were 35 (43.2%) and 31 (38.3 %) respectively, based on NYHA functional classification. Only 4 patients (4.9%) were in NYHA class IV (Table I). In addition, 33 patients (40.7%) were found to be anaemic, and 48.5% of the anaemic patients were deficient in iron. However, all ID cases were found in patients with anaemia, which accounted for 19.8% of the whole study population. Among the iron deficient patients, absolute ID was found in 14 patients (87.5%) and 2 (12.5%) were having functional ID.

With Pearson's correlation analysis, serum haemoglobin, serum ferritin, serum iron level and transferrin saturation were found positively correlated with LVEF ($p < 0.05$) (Figure 1A-D). Serum ferritin was better correlate with LVEF ($r = 0.624$, $p<0.01$) (Figure 1D) compared to serum haemoglobin ($r = 0.528$, $p<0.001$) (Figure 1C). However, total iron binding capacity does not statistically correlate with LVEF (Figure 1E).

Table I: Socio-demographic and clinical characteristics of participated patients

Socio-demographic characteristics			
Variable		**Mean (SD)**	**n (%)**
Gender	Male		62 (76.5%)
	Female		19 (23.5%)
Age	(years)	60.8 (10.2)	
Weight	(kg)	65.0 (5.3)	
Height	(cm)	169.5 (2.6)	
BMI	(kg/m)	22.6 (1.5)	
Clinical Characteristics			
Variables		**Mean (SD)**	**n (%)**
New York Heart Association Functional Class			
Class I			11 (13.6)
Class II			35 (43.2)
Class III			31 (38.3)
Class IV			4 (4.9)
Left ventricular ejection fraction (%)		33.6 (4.9)	
Blood parameter			
Serum iron (µmol/L)		9.8 (2.5)	
Total iron binding capacity (µmol/L)		53.52 (67.1)	
Transferrin saturation (%)		24.4 (6.4)	
Serum ferritin (µg/L)		253.5 (67.1)	
Serum hemoglobin (g/dL)		12.8 (1.8)	
Outcome			
Anemia			33 (40.7)
Iron deficiency			16 (19.8)
Absolute iron deficiency			14 (17.3)
Functional iron deficiency			2 (2.5)
Diabetes Mellitus			28 (34.6)
Hypertension			40 (49.4)
Chronic Kidney Disease (Creatinine Clearance <30 ml/min)			10 (12.3)
Diabetes + Hypertension			23 (28.4)
Diabetes + Chronic Kidney Disease			8 (9.9)
Hypertension + Chronic Kidney Disease			8 (9.9)
Hypertension + Diabetes + Chronic Kidney Disease			6 (7.4)

Among the recruited HFrEF patients, mean LVEF of those without anaemia were the highest (35.8±4.4%), followed by anaemic patients without ID (31.7±4.5%), and anaemic patients with ID (28.9±2.6%) (Figure 2A). 64.6% of the non-anaemic patients were in NYHA class I and class II. For anaemic patients with no iron deficiency, more than half were in NYHA class I and II (52.9%), and 47.1% of them were in NYHA class III and IV. Among the patients who were anaemic and iron deficient, all of them were having symptoms of heart failure, with a majority (56.3%) having dyspnoea on mild exertion (Figure 2B). Noteworthy, among all the anaemic patients, those with functional class III and IV had significantly lower level of serum iron (8.7±2.4

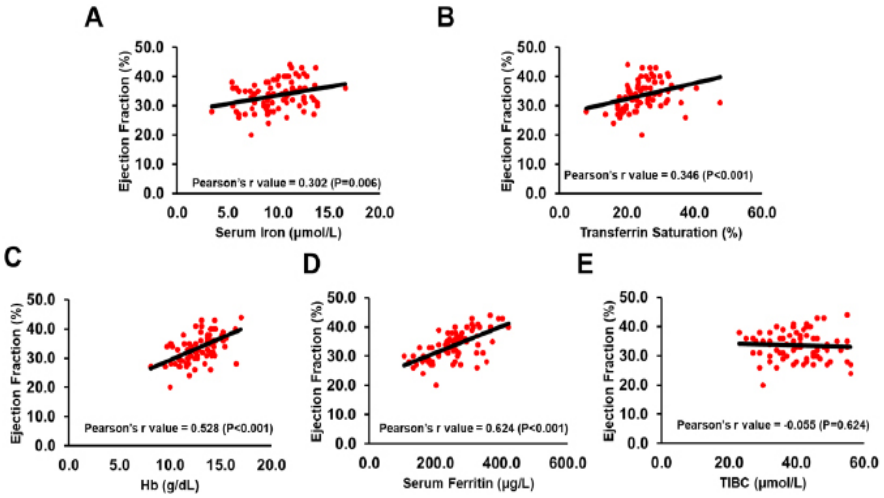

Figure 1: Relationship between left ventricular ejection fraction and (A) serum iron, (B) transferrin saturation, (C) Hb, (D) serum ferritin and (TIBC) in HFrEF patients.

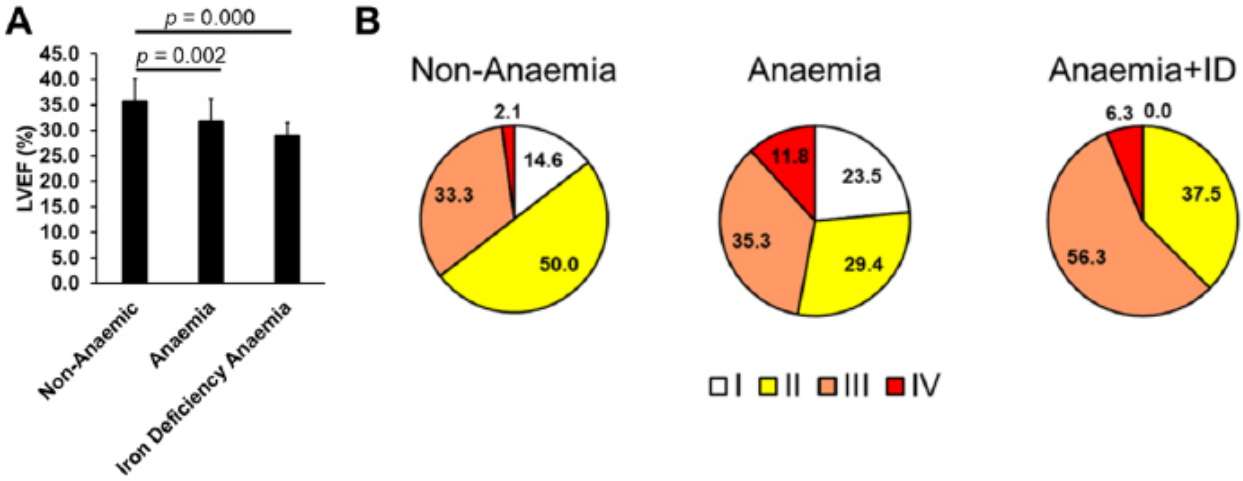

Figure 2: (A) Mean LVEF of HFrEF patients without anaemia, with anaemia and with iron deficiency anaemia. (B) Distribution of patient NYHA functional class in different subgroup of patients

µg/L) and serum ferritin (210.9±61.0 µg/L) than those with NYHA class I and II (10.6±2.4 µg/L and 285.9±52.1 µg/L, respectively; p<0.001).

DISCUSSION

Anaemia and Iron Deficiency in Heart Failure with reduced Ejection Fraction

Iron deficiency is one of the most common chronic nutritional deficiency that affects almost 2 billion people worldwide (16), which could affect erythropoiesis and thus may present concomitantly with anaemia. Hence, patients with ID would have higher risk of developing anaemia. Although ID without anaemia is relatively uncommon, it poses a significant diagnostic challenge as iron profiles are usually investigated only when anaemia is not responding to haematinics. It occasionally presents in parturient, or patients with menorrhagia, blood donations, as well as history of celiac disease (17). Most of the past studies on iron deficiency and heart failure were from developed countries. Hence, this study provides a new insight for the disease comorbidity and its correlation in a developing country like Malaysia, which has lifestyle and dietary behavior.

Yet, the significance and the consequence of ID in heart failure patients are often neglected (18). Our study showed that that 48.5% of the anaemic HFrEF populations were iron deficient, with majority of them were having absolute iron deficiency. This is also similar to an international study involving multi-ethic Asian which concluded that anaemia represents nearly half of their study population (19). Iron is also a metabolically active micronutrient and is known for its vital role in oxygen storage, transport and mitochondrial oxidative metabolism in heart muscle (20). The postulated pathogenesis of ID could be correlated to the initial activation of sympathetic pathway (21), left ventricular (LV) hypertrophy and finally LV dilation (22). Subsequently, ID could affect cardiac muscle contractility and the global heart function (23).

Studies have shown that iron deficiency in patients with HFrEF is correlated with poorer quality of life, reduced functional capacity and increased mortality (24, 25). A study involved international pooled cohorts concluded

that ID, but not anaemia, is a strong independent predictor of mortality, with a greater predictor power than anaemia (26). They demonstrated that up to 42% heart failure patients with iron deficiency despite having normal haemoglobin level (26). This was not observed in our cohort and thus a future study with larger sample size may help to confirm this. However, we consistently observed a strong positive correlation between haemoglobin, ferritin, transferrin saturation and ejection fraction in our study, with serum ferritin correlated better with LVEF as compared to serum haemoglobin. Furthermore, the mean LVEF among the HFrEF patients was the highest among patients without anaemia, followed by anaemic patients without ID, and the lowest was among patients with Iron deficiency anaemia.

Iron deficiency can also lead to anaemia in heart failure patients, and the cause of iron deficiency in these patients can also be a result of progressive heart failure. In this study, only the total iron binding capacity, or "transferrin" iron-binding capacity (TIBC) which measures the binding capacity of transferrin to iron, was found to be uncorrelated with LVEF. This is because chronic inflammation in heart failure may lead to overactivity of sympathetic nervous system and renin-angiotensin-aldosterone system, subsequently blocking transferrin receptor causing inhibition of iron intake (27, 28). In addition, the binding of iron with transferrin may be reduced due to increased hepcidin production (29). Low serum iron can couple with high TIBC in patients with IDA, but low in anaemia of chronic disease with normal transferrin saturation. Hence, changes in TIBC may not represent the true status of iron deficiency due to the net effect of ID and anaemia of chronic disease in HFrEF patients. Nonetheless, with the double antiplatelet agents commonly prescribed to patients with heart disease, it also imposes the risk of mucosal breaks and occult bleeding in the upper and lower gastrointestinal tract (30), thus contributes to ID anaemia in HFrEF population.

Anaemia and Iron Deficiency and Symptoms of Heart Failure

NYHA is a simple and widely accepted way of grading the severity of functional limitation in heart failure. It has been widely employed as a risk stratification tool in clinical practice, as well as an important outcome measure. A strong association has been reported between NYHA functional class and outcomes in patients with heart failure (31).

In this study, more than half of the non-anaemic patients were in NYHA class I and class II. For anaemic patients who were not iron deficient, half of them were in NYHA class I and II and others were in class III and IV. None of the patients with both ID and anaemia was in NYHA class I. This suggests that all of them were at least having some symptoms of heart failure, i.e. they suffered, at least, from dyspnoea on moderate exertion. More than 60 % of them were in moderate to severe symptoms of heart failure (NHYA functional class III or IV). This is in agreement with a study by Martens et al. (2018) which suggested that higher prevalence of iron deficiency was noted in patients with more functional limitations (24). The study also found that iron status is closely related to a reduced in VO2 max than the severity of anaemia.

This study was limited by small number of NYHA class IV patients, as these patients were mostly unstable and thus unfit for this 6-month study. The small sample size in the experiment also fails to capture patients with absolute ID without anaemia, thus unable to represent the disease comorbidity pattern. Future study with larger sample size and improved experimental design including patients' aetiology and treatment may provide better representation of the disease comorbidity and justify whether ID anaemia can be a target of HF management in this country.

CONCLUSION

In conclusion, this study revealed a high frequency of ID among HFrEF patients in this tertiary hospital of a fast-developing country. Serum ferritin, serum iron, transferrin saturation and haemoglobin level were positively correlate with LVEF. Knowing the prevalence of ID in HFrEF patients and with increasing understanding of these notorious comorbidities from past studies, emphasizing haemoglobin and ferritin levels as equally important therapeutic target could be an alternative management strategy to improve LVEF and functional status in HFrEF patients. In cases of which patient is intolerant to oral haematinics, intravenous iron should be recommended as soon as possible. Further action should be taken to update the existing advisories and emphasise the importance of treating ID aggressively in managing chronic heart failure.

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