

IRON DEFICIENCY IN HEART FAILURE

Dr. Kulbhushan Badyal¹, Dr. Shivani Panhotra²

MD., Medicine, Department of Cardiology, Batra Hospital and Medical Research Centre, New Delhi, India

MD., Pathology, Department of Pathology, Hamdard Institute of Medical Sciences, New Delhi, India

Article Info: Received 07 February 2020; Accepted 21 March 2020

DOI: <https://doi.org/10.32553/ijmbs.v4i3.1063>

Corresponding author: Dr Shivani Panhotra

Conflict of interest: No conflict of interest.

Abstract

Background: Data on the burden of Iron deficiency (ID) in Heart failure (HF) patients in India are sparse and there is very little information available about the prevalence of iron deficiency in heart failure with mid-range (HFmrEF) and preserved ejection fraction (HFpEF) in comparison to heart failure with reduced ejection-fraction (HFrEF).

Aims and Objective: This study was carried out with aim to evaluate iron profile in HF patients and to know the prevalence of ID in HFpEF, HFmrEF and HFrEF in our region.

Materials and Methods: Patients with clinically diagnosed HF were enrolled in the study. This was a single tertiary care centre, prospective, observational study carried out from December 2017 to November 2018. Patients were classified into HFrEF, HFmrEF and HFpEF on echocardiography. Serum ferritin (micrograms per liter), serum iron (micrograms per liter), total iron binding capacity (micrograms per liter), transferrin (milligrams per deciliter), and transferrin saturation were measured to assess iron status. Absolute ID was defined as serum ferritin < 100 mg/L and functional ID was defined as normal serum ferritin (100–300 mg/L) with low TSAT (<20%).

Results: A total of 120 patients of HF (66.7% males and 33.3% females) were studied. Out of 120 patients, 78 (65%) patients of HF had ID. Absolute ID was in 38.3% and functional ID was seen in 26.7% patients. 62.5% of males had ID, whereas, 70% of females had ID in HF. Patients with ID had higher NYHA Class, 35.9% compared to 23.8% patients without ID. ID was high in all subsets of HF. ID was found in 61.11% in HFrEF, 67.44% in HFmrEF and 69.57% in HFpEF. P=0.71. 14.1% patients had ID, but no anemia (p= 0.02). In anemic patients, ID was more (85.2%) than non anemic patients (69%).

Conclusion: In our study, prevalence of ID was higher in patients of HF than that reported from western literature. HFpEF had higher prevalence of ID followed by HFmrEF and HFrEF, respectively. Literature is scanty about HFmrEF, our study has given an insight of ID in this subset of HF. ID can occur even without anemia and females are more prone to have ID in HF. Our study highlights the importance of diagnosis and treatment of ID in all subsets of HF, in order to improve quality of life, morbidity and mortality in patients of HF.

Keywords: Iron deficiency, Heart Failure, Anemia, HFrEF, HFmrEF, HFpEF

Introduction

Heart failure (HF) is a global pandemic affecting an estimated 26 million people worldwide.¹ Prevalence of HF is approximately 1–2% of the adult population in developed countries, rising to more than 10% among people 70 years of age. The lifetime risk of HF at age 55 years is 33% for men and 28% for women.²⁻⁵ Contemporary data on the burden of HF in India are sparse. India has undergone rapid epidemiological and demographic transitions in the last two decades. As a result, the burden of cardiovascular disease is increasing in India. At present, the burden of HF in India is around 2–5 million patients with an estimated prevalence of 2–3/1000 population.⁶

HF is a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac

abnormality, resulting in a reduced cardiac output and/or elevated intra cardiac pressures at rest or during stress.⁷

Iron is an important micronutrient that is required by every cell in the body for metabolism. It has a number of important roles that contribute to metabolic health. Being a component of haemoglobin, it plays a key role in tissue oxygenation. It is also a component of myoglobin, which is an oxygen-binding protein found in skeletal muscle and myocytes, allowing oxygen release in hypoxic conditions.⁸ Iron plays a key role in erythropoiesis, via hepcidin, which is produced in the liver and regulates iron absorption in the gastrointestinal tract and iron release from reticuloendothelial tissue. Iron Deficiency (ID) leads to a reduction in maturation of haematopoietic cells and resistance to erythropoietin, a renally produced cytokine that increases red blood cell development.⁹ Once absorbed, intracellular iron exists in the ferrous form (Fe²⁺), while extracellular aerobic performance and is

accompanied by the reports iron is in the ferric form (Fe^{3+}). Iron is described as either stored (as ferritin within the liver, bone marrow and spleen) or utilised (circulating and intracellular iron).¹⁰ Circulating iron is bound to transferrin, which delivers iron to tissues for utilisation or storage, while most intracellular iron is within haemoglobin.

Anemia and ID are common in HF, and both may worsen symptoms. Traditionally, ID has been considered to have clinical consequences only in the presence of anemia. However, ID, even in the absence of anemia, attenuate of fatigue and exercise intolerance.^{11,12} It has been found that ID may occur in HF patients with or without anemia and it increases morbidity in terms of frequent hospital admissions, impaired exercise capacity, poor quality of life and increased mortality.¹³ In patients with New York Heart Association (NYHA) class II, III HF and ID, intravenous iron replacement has been found to improve functional status and quality of life.^{14,15} Iron is the key cofactor in oxidative metabolism in skeletal muscle and Krebs's cycle. Besides helping in erythropoiesis, it plays a key role in oxygen uptake, transport and storage as well as in oxidative metabolism.¹⁶ It has been recognized that patients with HF are prone to the development of ID due to multiple mechanisms. This can be due to depletion of the iron store due to dietary deficiency, low intake and decreased absorption from gastrointestinal congestion or blood loss from gastrointestinal tract, leading to absolute ID. Chronic inflammation, commonly observed in chronic HF, may also play a role. Inflammation causes reduced iron absorption and availability of iron recycled in the reticuloendothelial system which leads to functional ID.^{10,17,18} A decreased iron status is associated with disease severity and is a strong and independent predictor of outcome.¹⁹ Recent American and European guidelines also advise evaluation of all patients with HF for anemia and ID, in addition to other baseline laboratory measurements.^{7,20}

Iron Deficiency (ID) may occur in HF patients with or without anemia and it increases morbidity in terms of frequent hospital admissions, impaired exercise capacity, poor quality of life and increased mortality. Data on the burden of ID in HF patients in India are sparse and there is very little information available about the prevalence of ID in HF with mid range ejection fraction (HFmrEF) and preserved ejection fraction (HFpEF) in comparison to HF with reduced ejection fraction (HFrEF)

Aims and Objectives

1. To study iron profile in HF patients
2. To find prevalence of ID in HFpEF, HFmrEF and HFrEF

Material and Methods

The study was carried out in the Cardiology Department of Batra Hospital and Medical Research Centre, New Delhi, India from December 2017 to November 2018.

STUDY DESIGN: This study was a prospective, single arm, cross sectional, observational study.

Inclusion Criteria-

- Age ≥ 18 years
- Patients hospitalized for HF or Patients coming for follow up in Out Patient Department clinically diagnosed with HF

Exclusion Criteria-

- Patients having Chronic Kidney Disease or Chronic Liver Disease or Congenital Heart Disease or any Malignancy.
- History of therapy for anemia in form of repeated blood transfusions or iron therapy in the previous 12 months.
- Patients who do not give consent for study

Baseline characteristics, details of functional status i.e. NYHA class and LVEF were recorded. All patients were subjected to blood tests for Hb level, BNP and Iron study. The following blood biomarkers reflecting iron status were measured:

- Serum Ferritin ($\mu\text{g/L}$),
- Serum Iron ($\mu\text{g/dL}$),
- Total Iron Binding Capacity ($\mu\text{g/dL}$) and
- Transferrin saturation (TSAT- calculated as the ratio of serum iron ($\mu\text{g/dL}$) and TIBC ($\mu\text{g/dL}$) multiplied by 100 and expressed as a percentage).

Transthoracic 2D-ECHO was done on all patients with Philips EPIQ 7C with a 3.5 MHz transducer. LVEF was measured by Simpson's planimetry method. Accordingly patients were categorised into-

- HFrEF- LVEF $< 40\%$
- HFmrEF- LVEF = 40-50%
- HFpEF- LVEF $> 50\%$

Diagnosis of HF was established based on validated clinical criteria from the ESC guidelines for the diagnosis of HF. Patients were required to have a plasma B-type natriuretic peptide (BNP) level ≥ 100 pg/mL (or an N-terminal pro-BNP [NT-proBNP] level ≥ 300 pg/mL).²¹

- ID was defined as a (as per ESC guidelines) ferritin level < 100 $\mu\text{g/L}$ or serum ferritin 100–299 $\mu\text{g/L}$ in combination with a TSAT $< 20\%$.²¹

-Absolute ID was diagnosed as ferritin level < 100 $\mu\text{g/L}$.

-Functional ID was diagnosed as normal serum ferritin (serum ferritin 100–299 µg/L) in combination with a TSAT <20%.

- Anemia was defined as Hb < 13 g/dl for males and <12 g/dl for females, based on World Health Organization definition.²²

Statistical Method

The statistical analysis was conducted following the principles as specified in International Council for Harmonization (ICH) Topic E9 (ICH 1998). For continuous measurements - mean, median, standard deviation, minimum and maximum were used to tabulate the data. For the categorical measurements - absolute/relative frequencies and percentages were used to compute the data. Qualitative data was compared by chi square test. While for quantitative data (mean) comparison between two groups, student t test was used. For all statistical analysis, p value of less than or equal to 0.05 was considered to indicate a significant difference at 5% level of significance. All statistical analysis were performed by using software SPSS version 20.0.

Ethical Considerations

The Research was carried out after approval from Ethics Committee of the Hospital.

Results

1. Iron deficiency in study subjects

Among 120 patients, 78 (65%) patients had Iron deficiency. 46 (38.3%) had Absolute ID and 32 (26.7%) had Functional ID. Figure 1 depicts Iron deficiency in study subjects.

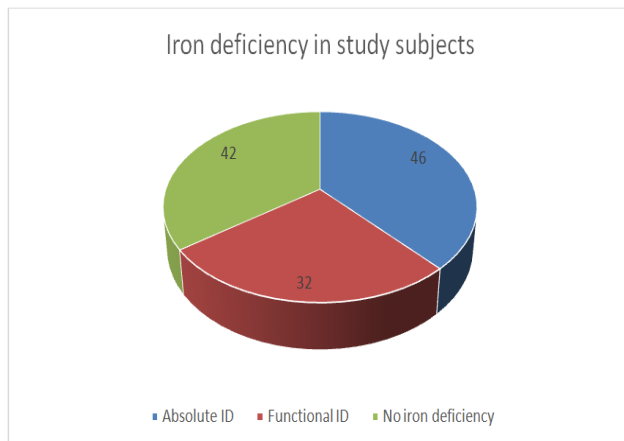


Figure 1: Iron deficiency in study subjects

2. Distribution of Iron deficiency in male and female

50 (62.5%) males had ID, whereas, 28 (70%) females had ID. Among males, 37.5% had Absolute ID and 25% had Functional ID. Among females, 40% had Absolute ID and 30% had Functional ID. It shows females had more

tendency for ID ($p = 0.81$). Figure 2 shows distribution of ID in male and female.

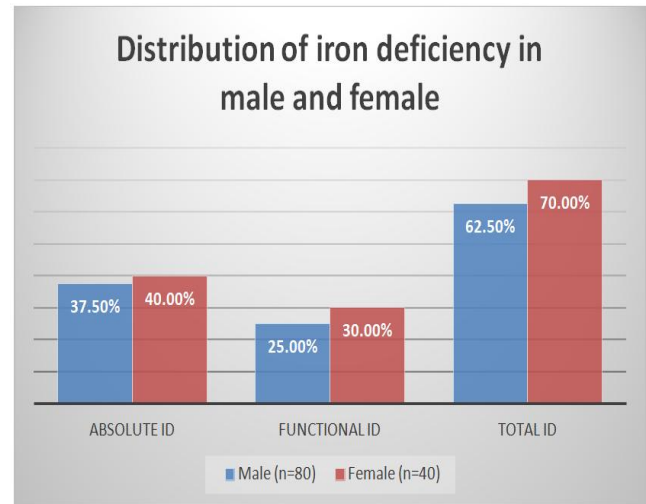


Figure 2: Distribution of ID in male and female.

3. Subsets of HF on basis of LVEF and ID

Among patients with HFrEF, 21 (38.89%) patients did not have ID, whereas, 33 (61.11%) patients had ID. Among patients with HFmrEF, 14 (32.56%) patients did not have ID, whereas, 29 (67.44%) patients had ID. Similarly, among patients of HFpEF, 7 (34.43%) patients did not have ID, whereas, 16 (69.57%) patients had ID. It shows that high prevalence of ID is present in any subset of HF ($p = 0.71$). Figure 3 show distribution in Subsets of HF on basis of LVEF in patients with or without iron deficiency.

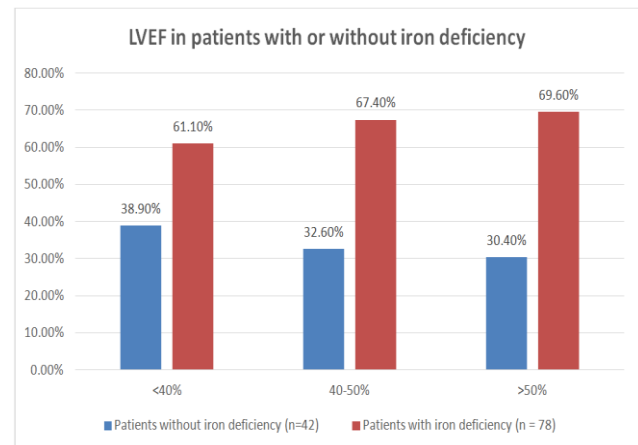


Figure 3: Subsets of HF on basis of LVEF in patients with or without iron deficiency

4. Anemia status and ID

In patients without ID, 29 (69%) patients had anemia and in patients with ID, 67 (85.2%) patients had anemia. 11 (14.1%) patients had no anemia, but ID was present ($p = 0.02$). Figure 4 show anaemia status in patients with or without iron deficiency.

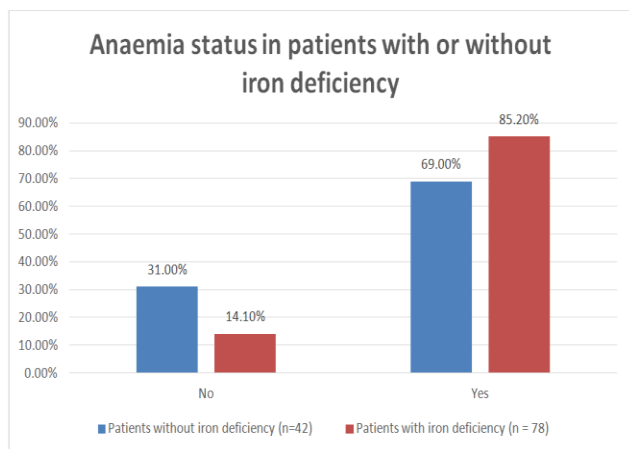


Figure 4: Anaemia status in patients with or without iron deficiency

Discussion

In this study, we found that ID is very common in Indian patients with HF, affecting more than half of the HF population. Absolute ID was more common than functional ID (38.3% vs 26.7%). This study also confirmed that ID can occur in the absence of anemia. In recent years, there is increasing awareness worldwide of the significance of ID in patients of HF. In USA, a prospective study of community-dwelling adults with self-reported HF revealed a prevalence rate of 61.3%.²³ In Europe, prevalence rates ranging from 37% to 50% have been reported.^{11,24} Another study, reported a prevalence of 61% among community dwelling HF patients.²⁵

In our study, we found the prevalence of ID being 65%, which is significantly higher than these studies, but comparable to two studies done in Indian population by **Sharma et al.**²⁶ and **Verma et al.**²⁷ This also highlights the burden of this condition in Indian HF patients. A study by **Yeo et al.**²⁸ done in multiethnic Asian population, suggesting HF patients of Indian ethnicity having highest rates of ID, also support our findings.

Most of previous studies have taken chronic HF and HFrEF as well as HFpEF patients. In our study, we also tried to look for ID among subsets of HF patients, which included HFrEF, HFpEF and HFmrEF. HFmrEF subset has been considered for the first time in our region. Moreover, very little is known about this new entity in HF at present. ESC 2016 guidelines⁷ have emphasised on this subset of HFmrEF and in coming time, more and more literature will be available about HFmrEF. According to our study, most patients had HFrEF (45%), followed by HFmrEF (35.8%) and HFpEF (19.2%). Among patients with HFrEF, 21 (38.89%) patients did not have ID, whereas, 33 (61.11%) patients had ID. Among patients with HFmrEF, 14 (32.56%) patients did not have ID, whereas, 29 (67.44%) patients had ID. Similarly, among patients of HFpEF, 7 (34.43%) patients did

not have ID, whereas, 16 (69.57%) patients had ID. Therefore, ID was found in 61.11% in HFrEF, 67.44% in HFmrEF and 69.57% in HFpEF. This suggests that HFmrEF and HFpEF have even higher prevalence of ID than total HF patients. These group of patients need to be identified and treated. Although large multicentre studies are needed before generalisation of these results. These results are similar to a study conducted by **Martens P et al.**²⁹ in 2018 in which ID was seen in 50% in HFrEF; 61% in HFmrEF and 64% in HFpEF, but the overall prevalence of ID was 53%, which in our study is higher (65%) overall.

In Indian population, elderly population has prevalence of ID anemia in about 32.6% population. In our study, ID is significantly higher in HF patients (65%). This clearly indicates the burden of ID in HF patients in India and the need for its correction. On gender-based analysis, we found that ID was significantly higher in women with HF as compared to men. This finding is in accordance with previous studies that suggested female gender as an independent correlate of ID in HF.^{19,28} Iron is essential not only for erythropoiesis but also for several bioenergetic processes in the skeletal muscle and in the Krebs cycle. Hence, chronic ID may not only lead to anemia but, by itself, reduce exercise capacity and lead to problems, including fatigue, restless legs, memory loss, skin problems, etc. A vegetarian diet, GI losses, malabsorption, and various illnesses can be a cause of ID. In recent years, the prevalence and prognosis of ID in chronic HF have received greater attention. The mechanisms of ID are multifactorial. Functional ID may occur despite adequate iron stores, whereas iron stores are depleted in absolute ID. In our study, absolute ID was the most common cause of ID, which can be explained by wide prevalent nutritional ID in India along with defective absorption in HF. Studies have shown that ID is associated with advanced symptoms.¹⁹

Recent studies have found that different clinical characteristics have been associated with the disorder of iron metabolism in patients with HF. These include advance NYHA class, female sex, lower MCV, and anemia. However, our study failed to identify any independent predictors of ID. This might be related to the small size of our study population. In this study, 65% patients were having ID and among these patients, 85.2% had ID with anemia. A significant number of patients (14.1%) were having ID but no anemia. Thus, only Hb levels should not be taken into consideration for workup of ID in HF patients. With 26.7% prevalence, functional ID is also making a significant part of disease burden. This subset will remain unrevealed unless care is taken to consider TSAT and serum ferritin in the workup. A recent article by **Yeo et al.** also stressed regarding assessment of functional ID and correlated it with symptoms regardless of ejection

fraction. These findings lay emphasis on getting a complete iron profile (including TSAT) in HF patients, a practice still missing in the developing world, including India.

As our study indicates, ID is a common neglected burden in Indian HF patients, and this requires the need for more routine testing in future Indian guidelines. In this study, we did not find any significant difference regarding NYHA functional class among HF patients with or without ID. Prior large-scale studies have established that ID in HF patients correlates with NYHA functional class and work capacity of patients. This difference may be attributed to higher baseline NYHA class of our study patients. Being a single-center study, the number of patients was also less compared to these large-scale studies. Furthermore, this was an observational study, so effect of iron supplementation on improvement of NYHA class could not be analyzed. Various studies with beneficial effect of Iron supplementation in HF have been published including two open, non controlled trials,^{30,31} and four randomized, placebo-controlled trials.^{14,15,32,33}

Limitations of the study

The sample size of our study was small, and since there was no control group, it was difficult to predict whether the ID is more prevalent in the HF group than the general population in India. Being a single-center study & India being a vast country, it is difficult to generalize the findings, necessitating multicenter larger studies. Our study was a cross-sectional observational study and long term effect of ID on mortality and morbidity has not been addressed. A larger study that includes age and sex matched controls is required to address the above mentioned concerns. Third, only data from a single measurement in time were available, so the present study cannot comment on the effects of changes in iron status over time. So, more studies with serial measurements of iron indices over time are required in Indian population.

Conclusion

In our study, prevalence of ID was higher in patients of HF than that reported from Western literature. HFpEF had highest prevalence of ID followed by HFmrEF and HFrfEF, respectively. Literature is scanty about HFmrEF, our study has given an insight of ID in this subset of HF. ID can occur even without anemia and females are more prone to have ID in HF. Our study highlights the importance of diagnosis and treatment of ID in all subjects of HF, in order to improve quality of life, morbidity and mortality in patients of HF.

References

1. GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980- 2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet Lond Engl* 2016; 388: 1459-1544.
2. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. *Heart* 2007; 93: 1137-1146.
3. Redfield MM, Jacobsen SJ, Burnett JC et al. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA* 2003; 289: 194-202.
4. Bleumink GS, Knetsch AM, Sturkenboom MC et al. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam Study. *Eur Heart J England* 2004; 25: 1614-1619.
5. Ceia F, Fonseca C, Mota T et al. Prevalence of chronic heart failure in Southwestern Europe: the EPICA study. *Eur J Heart Fail* 2002; 4: 531-539.
6. Huffman MD, Prabhakaran D. Heart failure: Epidemiology and prevention in India. *Natl Med J India* 2010; 23: 283-288.
7. Ponikowski P, Voors AA, Anker SD et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016; 18: 891-975.
8. Ordway GA, Garry DJ. Myoglobin: an essential hemoprotein in striated muscle. *J Exp Biol.* 2004; 207: 3441-3446.
9. Adamson JW. The relationship of erythropoietin and iron metabolism to red blood cell production in humans. *Semin Oncol.* 1994; 21: 9-15.
10. Jankowska EA, von Haehling S, Anker SD et al. Iron deficiency and heart failure: diagnostic dilemmas and therapeutic perspectives. *Eur Heart J* 2013; 34: 816-829.
11. Tang YD, Katz SD. Anemia in chronic heart failure: Prevalence, etiology, clinical correlates, and treatment options. *Circulation* 2006; 113: 2454-2461.
12. Haas JD, Brownlie T. Iron deficiency and reduced work capacity: A critical review of the research to determine a causal relationship. *J Nutr* 2001; 131: 676S-688S.
13. De Silva R, Rigby AS, Witte KK et al. Anaemia, renal dysfunction and their interaction in patients with chronic heart failure. *Am J Cardiol* 2006; 98: 391-398.
14. Anker SD, Comin CJ, Filippatos G et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. *N Eng J Med* 2009; 361: 2436-2448.
15. Ponikowski P, van Veldhuisen DJ, Comin-Colet J 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: 657-668.
16. Dunn LL, Rahmanto YS, Richardson DR. Iron uptake and metabolism in the new millennium. *Trends Cell Biol* 2007; 17(2): 93-100.
17. Alexandrakis MG, Tsirakis G. Anemia in heart failure patients. *ISRN Hematol* 2012; 2012: 246915.
18. Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med* 2005; 352: 1011-1023.
19. Klip IT, Comin-Colet J, Voors AA et al. Iron deficiency in chronic heart failure: an international pooled analysis. *Am Heart J* 2013; 165: 575-582.
20. Yancy CW, Jessup M, Bozkurt B et al. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation* 2017; 136(6): e137-e161.
21. Ponikowski P, Voors AA, Anker SD et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2016; 18: 891-975.

22. WHO. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Vitamin and Mineral Nutrition Information System. Geneva, World Health Organization, 2011 (WHO/NMH/NHD/MNM/11.1)
23. Parikh A, Natarajan S, Lipsitz SR, Katz SD. Iron deficiency in community-dwelling US adults with self-reported heart failure in the National Health and Nutrition Examination Survey III: prevalence and associations with anemia and inflammation. *Circ Heart Fail* 2011; 4: 599-606.
24. Jankowska EA, Rozentryt P, Witkowska A et al. Iron deficiency: an ominous sign in patients with systolic chronic heart failure. *Eur Heart J* 2010; 31: 1872-1880.
25. Zimmermann MB, Hurrell RF. Nutritional iron deficiency. *Lancet* 2007; 370: 511-20.
26. Sharma SK, Agarwal SK, Bhargava K et al. Prevalence and spectrum of iron deficiency in heart failure patients in south Rajasthan. *Indian heart journal* 2016; 68: 493-497
27. Verma S, Dua P, Saini A, Chakraborty P. Iron deficiency in chronic systolic heart failure(INDIC study). *J Pract Cardiovasc Sci* 2016; 2: 99-102
28. Yeo TJ, Yeo PS, Ching-Chiew Wong R et al. Iron deficiency in a multi-ethnic Asian population with and without heart failure: prevalence, clinical correlates, functional significance and prognosis. *Eur J Heart Fail* 2014; 16: 1125-1132
29. Martens P, Nijst P, Verbrugge FH et al. Impact of iron deficiency on exercise capacity and outcome in heart failure with reduced, mid-range and preserved ejection fraction. *Acta Cardiol.* 2018; 73(2): 115-123.
30. Bolger AP, Bartlett FR, Penston HS, et al. Intravenous iron alone for the treatment of anemia in patients with chronic heart failure. *J Am Coll Cardiol.* 2006; 48: 1225-1227.
31. Usmanov RI, Zueva EB, Silverberg DS, et al. Intravenous iron without erythropoietin for the treatment of iron deficiency anemia in patients with moderate to severe congestive heart failure and chronic kidney insufficiency. *J Nephrol.* 2008; 21: 236-242.
32. Okonko DO, Grzeslo A, Witkowski T, et al. Effect of intravenous iron sucrose on exercise tolerance in anemic and non-anemic patients with symptomatic chronic heart failure and iron deficiency FERRIC-HF: a randomized, controlled, observer-blinded trial. *J Am Coll Cardiol.* 2008; 51: 103-112.
33. Toblli JE, Lombrana A, Duarte P. Intravenous iron reduces NT-pro-brain natriuretic peptide in anemic patients with chronic heart failure and renal insufficiency. *J Am Coll Cardiol.* 2007; 50: 1657-1665.