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Original Article

Prevalence, risk factors, and significance of iron deficiency and anemia in nonischemic heart failure patients with reduced ejection fraction from a Himachal Pradesh heart failure registry

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ABSTRACT

Background: The study aimed to estimate the prevalence, risk determinants, and its clinical significance of iron deficiency and anemia in patients of nonischemic heart failure with reduced ejection fraction (HFrEF).

Methods: Serum ferritin, transferrin saturation, and the hemoglobin (Hb) levels were measured in 226 consecutive patients with HFrEF diagnosed based on the left ventricular ejection fraction ≤ 45% and absence of coronary artery luminal narrowing of more than 50%, in a prospective tertiary care hospital-based heart failure registry. Patients with the New York Heart Association functional class III/IV were classified as patients with advanced heart failure. Multivariable logistic regression modeling was performed to assess the risk determinants of iron deficiency and anemia and their clinical significance as the risk factors for advanced heart failure. Odds ratio with 95% confidence interval (CI) was reported as the estimates of the strength of association between exposure and outcome variables.

Results: Iron deficiency and anemia were prevalent in 58.8% (52.2%–65.1%) and 35.8% (29.8%–42.3%) of patients, respectively. Female gender [OR 3.5 (95% CI 1.9–6.5)], history of bleeding [OR 11.7 (95% CI 1.4–101.2)], and vegetarian diet [OR 2.5 (95% CI 1.4–4.6)] were significantly associated with iron deficiency, while diabetes [OR 3.0 (95% CI 1.40–6.5)], estimated glomerular filtration rate [OR 0.98 (95% CI 0.97–0.99)], history of bleeding [OR 13.0 (95% CI 2.3–70.9)], and female gender [OR 2.9 (95% CI 1.5–5.7)] had significant association with anemia. The Hb level (OR 0.82 (95% CI 0.70–0.96) and transferrin saturation (OR 0.98 (95% CI 0.96–0.99)] had a significant inverse association with symptoms of advanced heart failure.

Conclusion: Iron deficiency and anemia are common comorbidities associated with HFrEF. Low Hb and transferrin saturation are significantly associated with advanced heart failure. The findings have important implications in the management of heart failure.

1. Introduction

Nonischemic heart failure with reduced ejection fraction (HFrEF) is a common cause of morbidity and mortality in low-income countries.[1] Although significant progress has been made in the management of HFrEF and its outcome, prognosis still remains grim. The annual mortality rate after hospitalization for heart failure is about 20%–25%.[2,3] Thus, the search for the newer treatment target continues. The trace element iron is metabolically an active element as it is the core component of oxygen transport and storage protein, hemoglobin (Hb) and myoglobin, respectively. It is a cofactor of oxidative enzymes and also an element of structural protein of the electron transport chain in mitochondria.[4] Thus, iron has a role both in providing oxygen to the body fuel and enhancing the oxidative capacity of energy manufacturing factory of the myocytes. Thus, the iron deficiency state could have role in pathogenesis of progression of heart failure.

Iron deficiency with and without anemia has been reported in a number of studies in patients with heart failure.[5–10] The iron deficiency state is associated with poor exercise capacity, quality of

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life, decreased New York Heart Association (NYHA) functional class, and increased mortality, and intravenous supplementation of iron has been demonstrated to improve the exercise capacity and NYHA functional class, although mortality benefits have not been evaluated.[11–14]

The state of iron deficiency is also determined by dietary habits. The dietary patterns in turn are influenced by socioeconomic and geographical characteristics and cultural practices. There is a paucity of data reporting the prevalence and risk determinants of the iron deficiency state in patients with nonischemic HFrEF from low-income countries.[15,16]

We aimed to estimate the prevalence, risk determinants of the iron deficiency state and anemia, and its consequence on severity of heart failure in patients with nonischemic HFrEF by estimating the serum iron markers and the Hb level.

2. Methods

2.1. Setup and study design

The study is the part of an ongoing single-center prospective tertiary care hospital-based registry of patients with nonischemic HFrEF started since 2011.

2.2. Study population, selection, and sample size

Patients with the left ventricular ejection fraction (LVEF) of equal or less than 45% without documented myocardial infarction and absence of regional wall motion abnormalities formed the target population to be screened for enrollment in the study. The sources of the target patient population were from indoor and outdoor services of the department of cardiology and from the echo laboratory referred for evaluation of symptoms of heart failure from the department of cardiology, internal medicine, and pediatrics. Ischemic etiology was excluded based on the presence of normal or nonobstructive coronary artery disease (CAD) with luminal narrowing of $\leq$50% of any one or more epicardial coronary arteries in conventional coronary angiography study in patients older than 40 years and in patients younger than 40 years with a history of angina. All consecutive eligible patients visiting IGMC hospital from June 2016 to Dec 2017 were enrolled after obtaining informed consent.

The study protocol was approved by IGMC Shimla ethical committee.

2.3. Data collection

The self-reported data of demographics and risk factors, e.g., history of hypertension, diabetes, hypothyroidism, hyperthyroidism, alcohol intake and so on, were recorded systematically using a structured data recording format. The NYHA functional class, history of bleeding from any sites, and intake of iron supplements were also recorded. The physical examination included recording of the weight, height, and blood pressure using validated tools and following standard guidelines. The general physical examination also focused on any signs of hypothyroidism, hyperthyroidism, and the right heart failure (elevated jugular venous pressure, congestive hepatomegaly, and/or dependent edema). The cardiovascular system examination also looked for evidence of valvular heart disease.

The 12-lead surface electrocardiogram was recorded to document any evidence of atrial fibrillation and bundle branch block and to measure QRS duration. The transthoracic echocardiography examination was performed in the left lateral decubitus position using appropriate frequency phased array probes with a Philips echo machine model I 133. The left ventricular (LV) dimensions and ejection fraction (EF) were calculated by recording 2D-guided M-mode tracing at the tip of mitral valve leaflets in the parasternal long-axis view. The chamber dimensions were measured following guidelines of the American society of Echocardiography.[17] LVEF was calculated by the Teichholtz method.[18] Three consecutive tracings were analyzed to record LVEF, and the average was taken as the value for the analysis. The presence of regional wall motion abnormalities was excluded by evaluating LV segments in the parasternal short-axis view at the base, mid, and apical segment of LV and in the apical four- and two-chamber view of LV. LV diastolic function was evaluated by recording mitral inflow velocities during the early diastolic E wave and late diastolic atrial A wave with pulse wave Doppler at the mitral valve annular plane and early diastolic medial septal annular motion with tissue doppler imaging ($e^{'}$). The cutoff value of the ratio of E wave to $e^{'}$ of equal to or more than 15 was used for diagnosing diastolic dysfunction. The right ventricular (RV) systolic function was measured by recording the tricuspid annular point systolic excursion (TAPSE) in the modified four-chamber view to intersect the sound beam perpendicular to the lateral tricuspid annulus to record the annular excursion in the longitudinal plane.

The blood sample was drawn in the fasting state to measure glucose and serum creatinine. The estimation was performed in a fully automatic auto analyzer using standard kits. The thyroid function test and other biochemical tests were performed if clinically indicated. The iron status was estimated by measuring serum ferritin using the chemiluminescent microparticle immunoassay method. The serum iron was measured by the TPTZ deproteinization method, and total iron-binding capacity (TIBC), the spectrophotometric nitroso-PSAP method. The transferrin saturation was derived from serum iron and TIBC. The Hb level was measured by the colorimetric method.

3. Definitions

3.1. Iron deficiency

Iron deficiency was labeled if the serum ferritin level was less than 100 μg/L (absolute iron deficiency) or was of 100–299 μg/L with transferrin saturation of $\leq$20% (functional iron deficiency).[19,20]

3.2. Anemia

According to the World Health Organization definition, the Hb level <13 gm/dl in men and <12 gm/dl in women was used to label anemia.[21]

3.3. Nonischemic HFrEF

Symptomatic patients with LVEF of equal to or less than 45% with the absence of regional wall motion abnormalities and obstructive CAD, i.e., coronary artery narrowing in any one or more of the epicardial coronary arteries of equal or greater than 50% of the luminal diameter were considered as those with nonischemic HFrEF.

3.4. NYHA functional class

The NYHA functional class is stratified as follows: NYHA class I, patients with asymptomatic LV systolic dysfunction during routine physical activity; NYHA class II, mildly breathless on routine physical activity; NYHA class III, severely breathless on routine activity; and NYHA class IV, the patient is breathless even at rest and unable to perform any activity without symptoms.

3.5. Advanced heart failure

Patients with NYHA functional class III or IV were labeled as having advanced heart failure.

3.6. Severity of LV systolic dysfunction

LV systolic dysfunction was classified into mild, moderate, and severe based on LVEF of 40–45%, 31–39%, and ≤30%, respectively.

3.7. Pulmonary artery hypertension

Patients with a peak tricuspid regurgitation (TR) velocity of greater than 3.0 m/sec was labeled as having pulmonary artery hypertension (PAH).

3.8. RV dysfunction

The cutoff value of 17 mm of the TAPSE was used for diagnosis of RV systolic dysfunction.

3.9. Data analysis

The data were transferred to the excel sheet from an electronic recording format. The accuracy of data entered was checked by filtering the data entered under each variable, and any data falling out of the range were crosschecked from the data source for any error and was corrected if found wrongly entered. The characteristics of the study population were described as absolute counts and percentages for categorical variables and mean ± standard deviation for continuous variables with normal distribution and median and interquartile range for not normally distributed data. The demographics, vegetarian diet, history of bleeding, diabetes, hypertension, symptoms of advanced heart failure, and estimated glomerular filtration rate (eGFR) were analyzed as the potential risk factors for iron deficiency and anemia using univariate and multivariable logistic regression modeling. The strength of association and level of uncertainty was expressed as odds ratio with 95% confidence interval (CI). The clinical significance of iron deficiency and anemia as the risk factor for advanced heart failure was analyzed by taking the subgroup without iron deficiency and anemia as the reference group and comparing the odds ratio with the group with iron deficiency, anemia, and iron deficiency with anemia, in multivariable logistic regression by modeling variables found to have significant association in univariate analysis for calculating adjusted odds ratio with 95% CI. Statistical analysis of data was analyzed using STATA, version 13. Two-sided p value of <0.05 was considered as statistically significant.

4. Results

4.1. Characteristics of the study population

The detailed description of clinical characteristics of the study sample was reported in Table 1. The patients with nonischemic HFrEF were characterized by middle-aged population with mean age of 58.8 years affecting both the genders equally; 42.9% had severe LV systolic dysfunction (LVEF<30%), and the mean LVEF was 32.5 ± 7.8%. The PAH was observed in 38.0%, while 37.4% had moderate to severe TR. RV systolic dysfunction was recorded in 17.7% of patients.

Hypertension and diabetes were the most common risk factors associated with HFrEF, while a small proportion of the patients had associated valvular heart disease and hypothyroidism. One-third had primary heart muscle disease without any apparent associated risk factors. The symptoms of advanced heart failure were recorded in 40% of patients. The left bundle branch block was the commonest form of bundle branch block (27.4%); and 16.8% had atrial fibrillation.

4.2. Prevalence of iron deficiency and anemia

Detailed description of the prevalence of iron deficiency, iron deficiency with anemia, anemia, and absolute and functional iron deficiency is reported in Table 1. Iron deficiency was prevalent in 58.8% (95% CI of 52.2%–65.1%) and was significantly higher in women than in men (72.2% vs. 42.0% p < 0.001). About one-third of the patients had anemia. Iron deficiency was significantly higher in patients with anemia compared with those without anemia (91.4% vs. 40.6%).

Absolute iron deficiency is more common than functional iron deficiency. Iron deficiency and anemia were significantly more common in women than in men, although functional iron deficiency was equally prevalent in both genders.

4.3. Risk factors of iron deficiency

The association of demographics, symptoms of advanced heart failure, diabetes, and eGFR with anemia and iron deficiency is reported in Table 2. Iron deficiency had significant and independent association with female gender (odds ratio, 3.5 and 95% CI, 1.9–6.5), consumption of vegetarian diet (odds ratio, 2.5 and 95% CI, 1.4–4.6), and history of blood loss (odds ratio, 11.7 and 95% CI, 1.4–101.2). Although there was a trend of association among patients with symptoms of advanced heart failure with iron deficiency, the association was not statistically significant (odds ratio, 1.45 and 95% CI, 0.79–2.65).

4.4. Risk factors of anemia

The female gender, self-reported history of bleeding, eGFR, and diabetes had significant and independent association with anemia. The odd of anemia in female gender was significantly high 3.0 (1.6–5.7). One-unit increase in eGFR decreases the risk of anemia by 2% with 95% CI of 1%–3%. There was a trend of increased odds of anemia in patients with advanced heart failure 1.5 (0.81–2.7).

4.5. Consequences of iron deficiency and anemia

The association of iron deficiency with advanced heart failure, diastolic heart failure, and severe LV systolic dysfunction (LVEF ≤30%) is reported in Table 3. There was no significant independent association between iron deficiency with symptoms of advanced heart failure [1.04 (0.54–2.01)], diastolic heart failure [1.09 (0.55–2.09)], and severe LV systolic dysfunction [1.38 (0.72–2.64)]. However, the odds of having symptoms of advanced heart failure and diastolic heart failure decreased by 18% and by 15% with 95% CI of 4%–30% and 1%–27%, respectively, for one-unit increase in the Hb level and was statistically significant. The Hb level had no significant association with severe LV systolic dysfunction. The association between iron deficiency and iron deficiency with anemia with advanced heart failure and diastolic heart failure was graded but was statistically not significant; however, one-unit increase in transferrin saturation odd of advanced heart failure decreased by 2% with 95% CI of 1%–4%. The transferrin saturation had no significant association with diastolic heart failure and severe LV systolic dysfunction.

5. Discussion

In the present cohort of 226 patients with nonischemic HFrEF registered in a tertiary care hospital-based heart failure registry

Table 1
Clinical characteristics of the study population of nonischemic systolic heart failure.

Characteristics	Total study group($n = 226$)	Male	Female	*P* value
		$n = 100$	$n = 126$	
		(44.2%)	(55.8%)	
Age	58.2 ± 14.1	61.0 ± 12.9	56.0 ± 14.6	0.007
Risk factors of nonischemic systolic heart failure				
Overweight/obese	30(13.3%)	12(12.0%)	18(14.3%)	0.81
Hypertension	101(44.7%)	44(44.0%)	57(45.2%)	0.85
Diabetes	39(17.3%)	19(19.0%)	20(15.9%)	0.53
Valvular heart disease	15(6.6%)	5(5.0%)	10(7.9%)	0.06
Hypothyroidism	10(4.4%)	3(3.0%)	7(5.5%)	0.35
Primary cardiomyopathy	75(33.2%)	33(33.0%)	42(33.3%)	0.958
Risk factors of iron deficiency/anemia				
Nonvegetarian	112(49.6%)	58(58.0%)	54(42.9%)	0.02
History of bleeding	9(3.9%)	7(7.0%)	2(1.5%)	0.04
Severity of heart failure				
NYHA functional class II	132(58.4%)	65(65.0%)	67(53.2%)	0.073
NYHA functional class III	85(37.6%)	34(34.0%)	51(40.4%)	0.346
NYHA functional class IV	9(4.0%)	1(1.0%)	8(6.35%)	0.04
ECG features				
Left bundle branch block	62(27.4%)	25(25.0%)	37(29.4%)	0.89(trends)
Right bundle branch block	5(2.2%)	3(3.0%)	2(1.6%)	0.47
Intraventricular conduction defect	9(4.0%)	5(5.0%)	4(3.2%)	0.48
Left ventricular hypertrophy	61(27.0%)	29(29.0%)	32(25.4%)	0.54
QRS duration (msec)	104.2	100(104.3 ± 25.5)	126(104.1 ± 25.9)	0.48
Atrial fibrillation	38(16.8%)	14(14.0%)	24(19.0%)	0.31
Echocardiography				
Moderate MR	51(22.6%)	18(18.0%)	33(26.2%)	0.14
Severe MR	24(10.6%)	8(8.0%)	16(12.7%)	0.25
LVEF (%)	226(32.5 ± 7.8)	100(32.3 ± 7.7)	126(32.6 ± 7.9)	0.62
LVEF ≤30%	97(42.9%)	46(46.0%)	51(40.4%)	0.4
31–40%	88(38.9%)	38(38.0%)	50(39.7%)	0.8
>41%	41(18.1%)	16(16.0%)	25(19.8%)	0.46
Diastolic heart failure E/E'>15	90(39.8%)	43(43.0%)	47(37.3%)	0.38
PAH (TR gradient ≥36 mmHg)	86(38.0%)	41(41.0%)	45(35.7%)	0.41
RV systolic dysfunction (TAPSE<17 mm)	40(17.7%)	24(24.0%)	16(12.7%)	0.03
Moderate TR	43(30.9%)	21(33.9%)	22(29.6%)	0.50
Severe TR	9(6.5%)	2(3.2%)	7(3.1%)	0.17
Renal function				
eGFR	75.1 ± 29.8	100(74.7 ± 28.5)	126(75.4 ± 30.7)	0.42
CKD (eGFR <60 ml/kg/minute/1.73 m^2)	65(28.7%)	28(28.0%)	37(29.3%)	0.82
Drug treatment				
Beta-blockers	198(87.6%)	87(87.0%)	111(88.1%)	0.80
Use of ACE inhibitor	154(68.1%)	65(65.0%)	89(70.6%)	0.36
Use of ARB	57(25.2%)	28(28.0%)	29(23.0%)	0.39
Use of MRA	206(91.0%)	86(86.0%)	120(95.2%)	0.05
Loop diuretics	180(79.6%)	80(80.0%)	100(79.4%)	0.90
Trimetazidine	96(42.0%)	47(47.0%)	49(38.9%)	0.22
Digitalis	31(13.7%)	13(13.0%)	18(14.3%)	0.78
Use of hematinics	43(19.0%)	13(13.0%)	30(23.8%)	0.04
Status of Hb levels and iron stores/levels				
Anemia	81(35.8%) (29.8%–42.3%)	25(25.0%)	56(44.4%)	0.002
Iron deficiency	133(58.8%) (52.2%–65.1%)	42(42.0%)	91(72.2%)	0.000
Absolute iron deficiency	85(37.6%)	19(19.0%)	66(52.4%)	0.000
Functional iron deficiency	48(21.2%) 16.3%–27.1%	23(23.0%)	25(19.8%)	0.56
Anemia with iron deficiency	74(91.4%) 82.7%–95.9%	23(92.0%)	51(91.1%)	0.89
Normal Hb level with iron deficiency	59(40.6%) (32.9%–48.9%)	19(25.3%)	40(50.1%)	0.001
Iron deficiency with anemia	74 (55.6%)	23(54.8%)	51(56.0%)	0.89
Normal iron state with anemia	7(7.5%)	2(3.45%)	5(14.2%)	0.055

Hb, hemoglobin; TAPSE, tricuspid annular point systolic excursion; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; PAH, pulmonary artery hypertension; RV, right ventricle; eGFR, estimated glomerular filtration rate; TR, tricuspid regurgitation; CKD, chronic kidney disease; ARB, angiotensin receptor blocker; MRA, mineralocorticoid receptor antagonist; ACE, angiotensin converting enzyme.

observed a high prevalence of iron deficiency and anemia. The female gender, vegetarian diet, diabetes, low eGFR, and history of bleeding had significant association with iron deficiency and or anemia. Low Hb and transferrin saturations levels were significantly associated with advanced heart failure.

Iron deficiency in heart failure has been reported in a number of studies, and the prevalence reported varied from 37% to 76%.[15,16,22] In the present study, 58.8% (95% CI 52.2%–65.1%) had iron deficiency, and about 40% of patients with a normal Hb level were having iron deficiency. Iron deficiency was significantly higher

Table 2
Risk factors of anemia and iron deficiency and crude odds ratio and adjusted odds ratio with 95% CI (adjusted for variables found to have significant association or trends of association in univariate logistic regression modeling).

Characteristics	Anemia		Iron deficiency	
	Odds ratio (95% CI)		Odds ratio (95% CI)	
	Crude odds ratio	adjusted odds ratio	Crude odds ratio	adjusted odds ratio
Age	0.99 (0.98–101)	1.00(0.98–1.02)	0.98(0.96–1.00)	0.99(0.97–1.01)
Gender (female)	2.4(1.3–4.2)	3.0(1.6–5.7)	3.5(2.0–6.3)	3.5(1.9–6.5)
Vegetarian (yes)	1.5(0.86–2.6)	1.4(0.75–2.5)	2.6(1.5–4.5)	2.5(1.4–4.6)
DM	2.8(1.38–5.67)	3.3(1.5–6.9)	1.30(0.64–2.67)	–
NYHA class III/IV	1.51(0.87–2.63)	1.48(0.81–2.7)	1.66(0.96–2.67)	1.4(0.79–2.6)
RHF	0.85(0.46–1.58)	–	0.63(0.31–1.28)	–
Bleeding	6.7(1.37–33.3)	11.7(2.2–62.1)	5.88(0.72–47.9)	11.7(1.4–101.2)
ACE inhibitors	0.82(0.46–1.47)	–	0.94(0.53–1.67)	–
Antiplatelet	0.92(0.44–1.91)		0.50(0.24–1.01)	0.53(0.23–1.17)
eGFR	0.98(0.98–0.99)	0.98(0.97–0.99)	0.99(0.98–1.00)	0.99(0.98–1.00)

CI, confidence interval; NYHA, New York Heart Association; eGFR, estimated glomerular filtration rate; DM, diabetes mellitus; RHF right heart failure.

Table 3
Iron deficiency as the risk factor of advanced heart failure, diastolic heart failure, and severe LV systolic dysfunction adjusted for age, gender, hypertension, diabetes, Hb level, and renal function.

Factors/exposure	Advanced heart failure	Diastolic heart failure	Severe LV systolic dysfunction, odds ratio (95% CI)
	Odds ratio (95% CI)	Odds ratio (95% CI)	
Age	0.98(0.99–1.01)	1.02(1.00–1.04)	1.01(0.99–1.03)
Gender (men)	0.87(0.48–1.59)	1.49(0.81–2.74)	1.17(0.64–2.14)
HTN	1.01(0.57–1.81)	0.68(0.38–1.25)	0.66(0.37–1.17)
DM	0.82(0.38–1.75)	0.97(0.45–2.05)	1.28(0.61–2.77)
eGFR	1.00(0.99–1.01)	1.00(0.99–1.01)	1.01(1.00–1.02)
Hb	0.82(0.70–0.96)	0.85(0.73–0.99)	1.05(0.91–1.22)
Absolute iron deficiency	1.44(0.80–2.49)	1.30(0.72 = 2.37)	1.08(0.60–1.95)
Functional iron deficiency	1.06 (0.55–2.06)	1.15(0.60–2.22)	1.17(0.61–2.26)
No iron deficiency, no anemia	Reference	Reference	Reference
Iron deficiency without anemia	1.20(0.59–2.43)	1.26(0.61–2.60)	1.15(0.57–2.32)
Iron deficiency with anemia	1.76(0.89–3.50)	1.91(0.96–3.83)	1.05(0.53–2.08)
Ferritin	0.99(0.99–1.00)	0.99(0.99–1.00)	0.99(0.99–1.00)
Transferrin saturation	0.98(0.96–0.99)	0.99(0.97–1.01)	1.00(0.98–1.01)

LV, left ventricular; CI, confidence interval; Hb, hemoglobin; eGFR, estimated glomerular filtration rate; HTN, hypertension.

among female patients without anemia (50.1% vs. 25.3% $p < 0.01$). The severity of heart failure and renal dysfunction had no significant association with iron deficiency although there was a trend.

The risk factors for iron deficiency and anemia in patients with heart failure have been investigated by a number of investigators.[23,24] The gender and severity of heart failure and renal dysfunction have been found to have significant association.[22,25–27]

Iron is not excreted through kidneys; it is lost from the body through sloughing of duodenal enterocytes, normal cyclic menstrual blood loss in women, and through pathological bleeding. Thus, the iron loss is more in women than in men. The iron homeostasis is maintained by hepcidin hormone that regulates iron absorption. The state of iron stores and cytokines regulates the synthesis and release of hepcidin. The severe heart failure induces systemic inflammatory response. Thus, elevated levels of cytokines induce expression of hepcidin hormone in the liver that inhibits membrane transport protein, ferroportin on cell membrane of enterocytes and in iron storage organs resulting in trapping of iron and depriving the circulatory pool from iron to be available for its utilization in the target organs resulting in the state of functional iron deficiency.[28–31] Thus, functional iron deficiency may be a marker of severity of heart failure. The data from the present study, however, do not suggest any significant association between functional iron deficiency with severity of heart failure [1.00 (0.52–1.91)], while there was a trend of association with absolute iron deficiency [odds ratio (95% 1.62; CI 0.96–2.88)]. The ferritin level used for diagnosing iron deficiency has its limited sensitivity, and specificity as ferritin is an acute-phase reactant. The acute-phase reactant is increased in chronic inflammatory conditions such as heart failure. Thus, the validity of the arbitrary cutoff value of the ferritin level used for diagnosing iron deficiency, as the categorical outcome, is uncertain. To overcome this uncertainty, association between advanced heart failure, diastolic heart failure, and severe LV systolic dysfunction with ferritin and transferrin saturation levels as the continuous exposure variable was analyzed using logistic regression model adjusting for age, gender, eGFR, and diabetes. The association between transferrin saturation and advanced heart failure was statistically significant. One-unit increase in transferrin saturation odds of advanced heart failure was decreased by 2% (1%–4%); however, its association with the ferritin level was not statistically significant. The ferritin level reflects the status of the iron content in the storage organ, while the transferrin saturation levels are the measures of iron available in the circulating pool for utilization by target organs such as erythroid tissue, heart, skeletal muscles, and so on. The absence of association between transferrin saturation with diastolic heart failure and severity of LV systolic dysfunction is not clear, although some of the intervention studies demonstrated improvement in LV systolic functions after supplementation of iron.[11–14]

Heart failure may contribute to the state of iron deficiency owing to the decreased intake and impaired absorption due to decreased appetite and congested gut as the manifestation of congestive heart failure. Thus, iron deficiency may have contributory role in progression of heart failure.

The clinical significance of iron deficiency with and without anemia was analyzed using multivariable logistic regression modeling, taking the group without iron deficiency and anemia as the reference exposure group and advanced heart failure, diastolic heart failure, and severe LV systolic dysfunction as the outcomes, adjusted for age, gender, eGFR, diabetes, and hypertension. There was a trend of graded association among the group with iron deficiency without anemia and with anemia compared with the group without iron deficiency and anemia (odds ratio 1.20; 95% CI 0.59–2.43 and odds ratio 1.76; 95% CI 0.89–3.5), respectively.

The anemia has been reported to be a common comorbid condition associated with heart failure.[16] In the present study, 35.8% of patients with nonischemic HFrEF were anemic. The anemia was significantly associated with female gender, history of blood loss, presence of diabetes, and low eGFR. The anemia in heart failure could be multifactorial: dilutional anemia, absolute iron deficiency, functional iron deficiency, and/or nonresponsive bone marrow to erythropoietin and erythropoietin deficiency due to frequently associated renal dysfunction.[32–34]

Thus, anemia may be a marker of severity of heart failure and/or a mediator of progression of heart failure. The patients with heart failure associated with anemia have been reported to have increased mortality in follow-up studies.[7,8] The present study reported significant association of advanced heart failure with anemia and iron deficiency. The odds of severe heart failure were decreased by 18% (4%–30%) for 1-g increase in the Hb level. Similarly, odd of advanced heart failure was reduced by 2% (1%–4%) per 1-g increase in transferrin saturation.

The clinical significance of association between iron deficiency and heart failure has also been reported in intervention studies where intravenous supplementation of iron in patients with heart failure with iron deficiency has resulted in improvement in the quality of life, exercise capacity, increase in 6-min walk distance, and LVEF.[11–14] However treatment of anemia with erythropoietin in patients with heart failure has resulted in variable results. This is expected as anemia is due to diverse mechanisms and may be of benefit in only patients with deficiency of erythropoietin or its resistance.

6. Limitations

The present study has a number of limitations due to the study design and methods used for diagnosis of iron deficiency and LV systolic function. The findings reported are based on single-center, tertiary care hospital-based registry data, thus have inherent element of selection bias and may not provide reliable estimate of prevalence of iron deficiency and anemia in the patient population studied in general population. The study design does not allow assessing the heart failure as the risk factor for iron deficiency and anemia. The iron deficiency state has been estimated by serum marker–based criteria that are not very reliable markers for identifying the state of true iron deficiency as bone marrow biopsy is the gold standard. The LV systolic dysfunction was assessed by Teichholtz formula, thus having limitations of its sensitivity as the calculation of LV volumes, and EF is derived from LV dimensions in end diastole and end systole with assumptions, thus may not be reliable methods in distorted LV geometry. Second, the LV shortening in the radial plane is the last to be affected than in the longitudinal plane, thus has limitations in assessing the true severity of LV systolic dysfunction.

7. Summary

Iron deficiency and anemia are common comorbid conditions associated with nonischemic HFrEF. Female gender, history of bleeding, vegetarian diet, diabetes, and renal dysfunction are risk factors for iron deficiency and/or anemia. Patients with anemia and iron deficiency have increased risk of having symptoms of advanced heart failure. Future studies are required to understand the relationship between the iron deficiency state and anemia with heart failure as an exposure and outcome or vice versa in appropriately designed studies to explore the role of supplementation of iron and correction of anemia as the potential targets for improving outcomes in patients of heart failure. The studies are also required to evaluate the iron levels in myocardium and skeletal muscles to assess the role of iron as the determinant of cardiac function, symptoms of heart failure, and their prognostic indicator.

7.1. Scope for future studies

The clinical significance of functional and absolute iron deficiency needs to be investigated in future studies in terms of risk marker or risk mediator so that the role of iron supplementation and erythropoietin could be clearly defined in different subsets of patients with iron deficiency with and without anemia.

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Conflicts of interest

All authors have none to declare.

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