

## Iron Deficiency in Heart Failure with Reduced Ejection Fraction - A Hospital Based Study

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### ABSTRACT

**INTRODUCTION:** Heart failure is a major cause of mortality and morbidity worldwide and a public health problem. Iron deficiency is one of the most frequent co-morbidities in patients with heart failure. Iron deficiency is a strong independent predictor of heart failure outcomes. It is associated with reduced exercise capacity and reduced quality of life and is an independent predictor of worse functional capacity and survival. Within a heart failure population iron deficiency is associated with worse prognosis.

**METHODS:** A hospital based cross sectional study was conducted at tertiary care hospital, Assam for a duration of one year. A total of 90 subjects above 13 years of age who were symptomatic heart failure patients with reduced ejection fraction <40% were taken up for study. Iron deficiency status in heart failure patients with reduced ejection fraction and the severity of heart failure was assessed. Chi square test and Fischer's exact test was used to calculate the p value. For all analyses statistical significance was fixed at 5% level (p value <0.05)

**CONCLUSION:** It was observed that there is a large burden of iron deficiency in heart failure patients, more prevalent in female patients and presented with higher functional NYHA class. our results were statistically significant.

**Key Words:** Heart failure, Iron Deficiency, Anemia, reduced ejection fraction

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### I. INTRODUCTION:

Heart failure is defined as a complex clinical syndrome that results from structural or functional impairment of ventricular filling or ejection of blood which in turn leads to cardinal symptoms of dyspnea, fatigue and signs of heart failure namely edema and rales. Heart failure is a major cause of morbidity and mortality worldwide and a public health problem. Overall about 2 % of adult population suffers and the prevalence increases with rising age of about 6-10% in people over age of 65 years<sup>1</sup>. Cardiovascular and Non cardiovascular comorbidities often complicate the natural course of heart failure with deleterious impact on clinical status, symptoms and heart failure progression, thus constituting targets for potential intervention.<sup>2</sup> Iron deficiency is one of the most common nutritional deficiencies worldwide, affecting one third of the general population<sup>3</sup> and is one of the most frequent co-morbidities in patients with heart failure. It is estimated to be present in 50% of outpatients and is a strong independent predictor of heart failure outcomes.<sup>4</sup>

Iron deficiency with or without anemia is associated with reduced exercise capacity, physical wellbeing, reduced quality of life and is an independent predictor of worse functional capacity and survival.<sup>5</sup> Within a heart failure population, Iron deficiency is associated with worse prognosis. It is an emerging problem in patients with Chronic heart failure and can be a potential therapeutic target.

### II. AIMS AND OBJECTIVES:

1. To assess iron deficiency status in heart failure patients with reduced ejection fraction.
2. To assess the association between iron deficiency and heart failure with reduced ejection fraction.
3. To assess the severity of heart failure in patients with iron deficiency (assessed by NYHA classification)

### III. MATERIALS AND METHODS:

The study was a hospital based observational study carried out in 90 patients with heart failure with reduced ejection of one year duration in tertiary care hospital, Assam.

**Study population :** The study was conducted on all patients above the age of 13 yrs who are symptomatic heart failure patients with reduced ejection fraction <40% attending outpatient department or admitted in the department of Medicine/Cardiology in tertiary care hospital of Assam.

**Sample size:** After considering the inclusion and exclusion criteria at total number of 90 cases were taken up for the study.

**INCLUSION CRITERIA :** Male or female patients above the age of 13 years with documented history of heart failure with reduced ejection fraction <40% as assessed by echocardiography.

**EXCLUSION CRITERIA:**

Patients not willing to give informed consent.

Acute coronary syndrome presenting with heart failure.

Any acute or chronic illness that might influence iron metabolism (including known malignancy, infection, active bleeding, hematological disorders).

Other conditions causing fluid overload stage; Renal failure, non cardiac cause of pulmonary edema, acute respiratory distress syndrome. Congenital heart disease.

Patients with history of therapy for anemia or iron therapy in the previous 12 months (blood transfusions, erythropoietin therapy, iron supplements).

**Method of collection of Data:**

- Data were collected from all heart failure patients with ejection fraction <40% attending Outpatient Department or admitted in the Medicine Department tertiary care Hospital. Patients were selected according to the inclusion and exclusion criteria mentioned above.

- All the patients were given an explanation of the study and informed written consent was taken from them or their attendants before enrollment into the study.

**ETHICAL CLEARANCE:** Ethical Clearance was obtained from the Ethical Clearance committee of tertiary care Hospital.

**CONSENT:** Informed written consent was taken from the patients or their attendant after explaining about the purpose of the study.

**CASE DEFINITION:**

- The current American College of Cardiology Foundation / American Heart Association defines heart failure as a complex clinical syndrome that results from structural or functional impairment of ventricular filling or ejection of blood, which in turn leads to cardinal symptoms of dyspnea, fatigue and signs of heart failure namely edema and rales.<sup>1</sup> Heart failure patients with reduced ejection fraction <40% were included in the study.

- Iron deficiency was defined according to 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure.<sup>6</sup>

Serum Ferritin <100 microgram / liter (absolute)

Serum Ferritin 100-299 microgram/liter and Transferrin saturation <20% (functional).

All the details, obtained from clinical history, physical examination and investigations done in all patients were filled up in pre-designed proforma. Detailed history and meticulous clinical examination was done for all patients

- Echocardiography was done for patients in tertiary care hospital. The machine used in the department is Philips Affiniti 70C model release 3.03

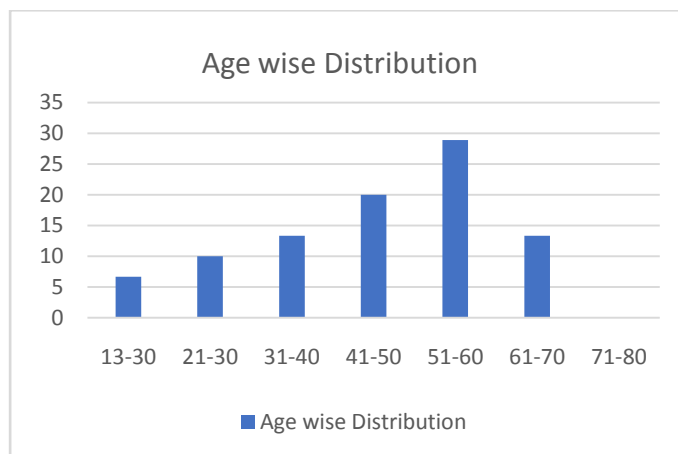
- Complete blood count, Iron Profile (Serum iron, Serum ferritin, TIBC, TSAT was done for all patients) done in Biochemistry and Pathology lab of our Medical College. Ortho Clinical Vitros 5600 Auto Analyzer was used to perform the test.

**STATISTICAL ANALYSIS:**

The statistical analysis of data was performed using the computer program, statistical package for Social Services (SPSS for windows, version 20.0 Chicago Inc.) and Microsoft Excel 2010. Results on continuous measurements are presented as mean  $\pm$  standard deviation and are compared using t test. Discrete data are expressed as number (%) and are analysed using Chi square test and Fischer's exact test (where the cell counts were <5 or 0) For all analyses, the statistical significance was fixed at 5% level (p value <0.05)

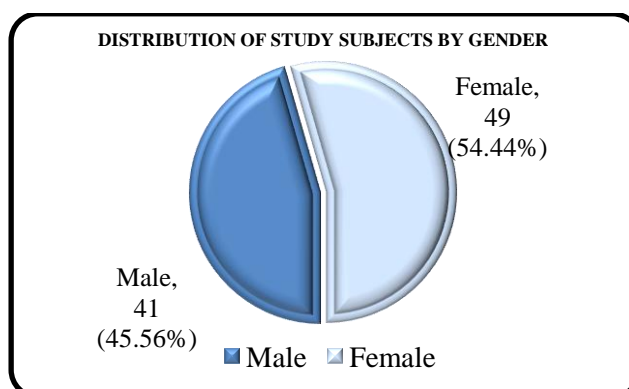
**IV. RESULTS AND OBSERVATIONS**

In our study population, the most common age group was 51-60 years (28.89%) followed by 41-50 years (20%). The mean age was  $57.77 \pm 16.26$  years. The maximum age was 77 years and the minimum age was 17 years



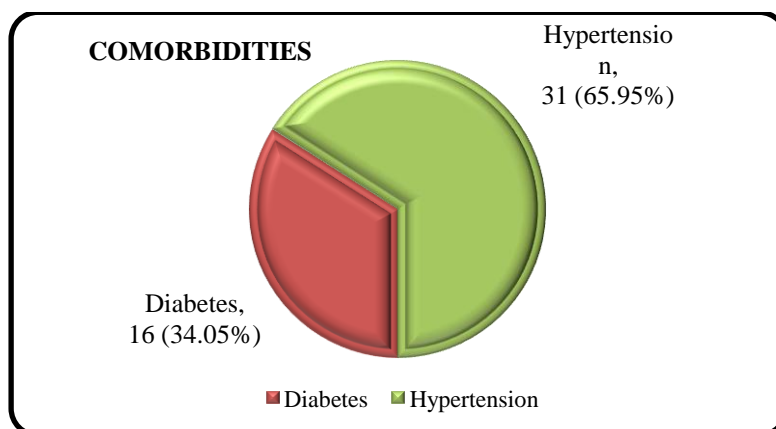
**SEX DISTRIBUTION :**

The above table shows the gender wise distribution of the study group. Out of the 90 cases, 49 were female (54.44%) and 41 were male (45.56%). The male:female ratio was 1:1.2.



**IRON DEFICIENCY IN HEART FAILURE WITH REDUCED EJECTION FRACTION:**

The above table shows that out of the 90 cases, number of subjects with iron deficiency were 58 (64.44%) and subjects without iron deficiency were 32 (35.56%).



**LABORATORY PARAMETERS :**

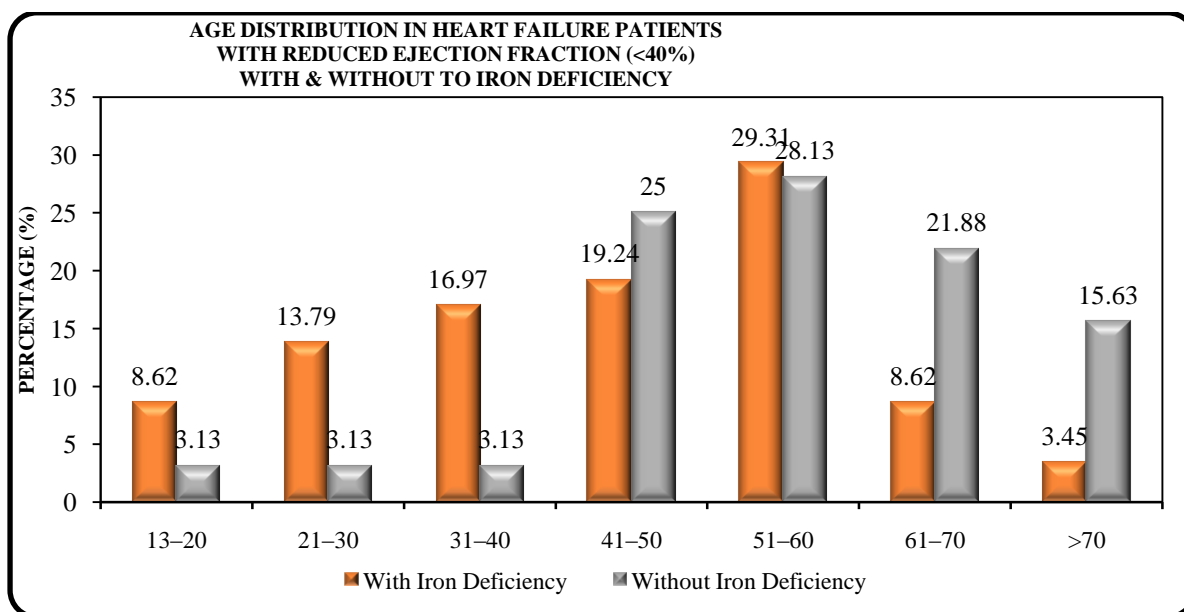
INVESTIGATION	WITH IRON DEFICIENCY		WITHOUT IRON DEFICIENCY		pvalue*
	Mean	±S.D.	Mean	±S.D.	
Hb(gm/dl)	10.38	2.51	11.80	1.53	<0.001

MCV(fl)	75.64	6.41	91.06	5.09	<0.001
MCH(pg)	25.61	4.06	32.72	2.82	<0.001
SerumIron(µg/dl)	27.93	11.50	74.03	19.33	<0.001
SerumFerritin(ng/ml)	71.88	23.68	218.76	86.28	<0.001
TIBC(µg/dl)	323.983	65.29	361.563	81.78	0.0296
TransferrinSaturation(TSAT %)	16.14	5.63	38.53	8.75	<0.001

**AGEDISTRIBUTIONOFHEARTFAILUREPATIENTSWITHREDUCEDEJECTIONFRACTION(<40%)WITH&WITHOUTIRONDEFICIENCY**

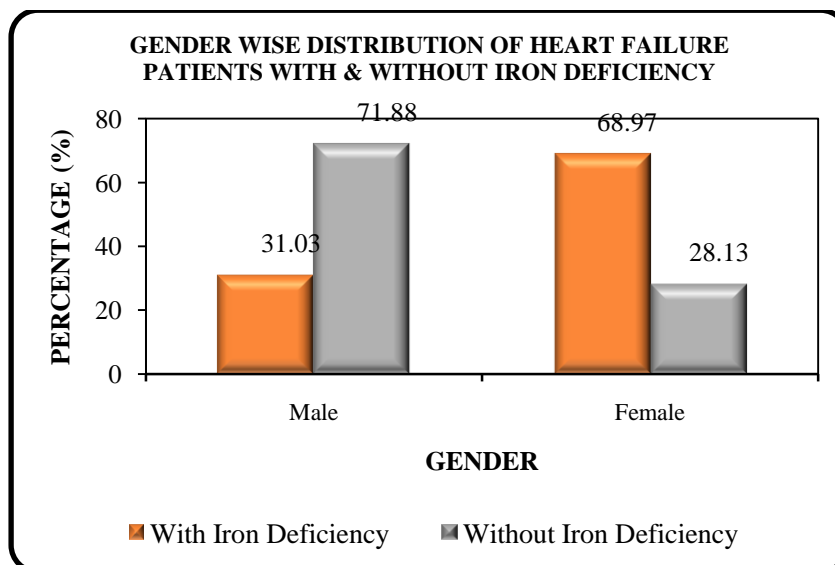
Out of 58 patients with Iron deficiency, majority were from the age group of 51-60 years (29.31%) followed by 41-50 years(19.24%).The number of subjects in the other age groups were:9 in the age group of 31-40 years(16.97%),7 in the age group of 21-30 years (13.79%),5 in two age group 13-20 and61-70 (8.62%) ,2 in the age group of > 70 years (3.45%). The mean age of this group was 57.19±15.<sup>51</sup>

Out of 32 patients without iron deficiency, majority were from the age group 51-60 years (29.31%) followed by 41-50 years (25%).The number of subjects in the group above 70 years of age(15.63%), 1 in the age group 13-20,21-30,31-40 years(3.13).The mean age of this group was 56.06±14.36.



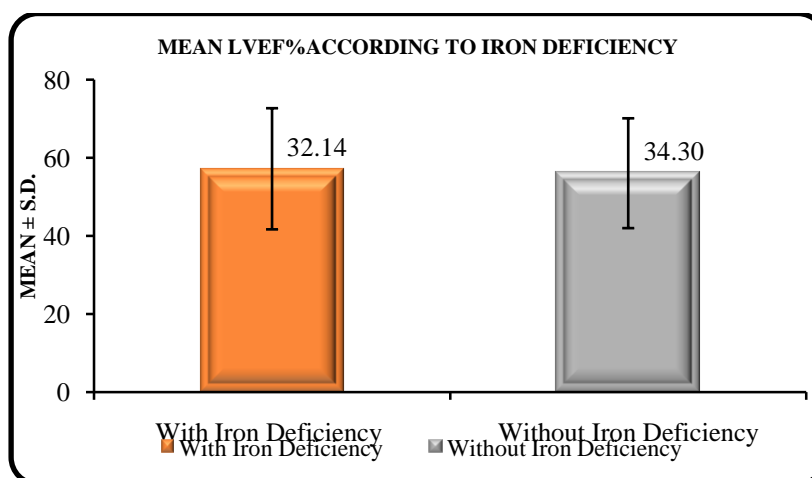
**GENDERWISEDISTRIBUTIONOFHEARTFAILUREPATIENTSWITH&WITHOUTIRONDEFICIENCY**

Out of the 58 cases with iron deficiency, there were 40 females (68.97%) while there were 18 males(31.03%).Out of 32 patients without iron deficiency, 23 were males(71.88%) and 9 were female(28.13%).There was a significant difference between the two groups in this regard



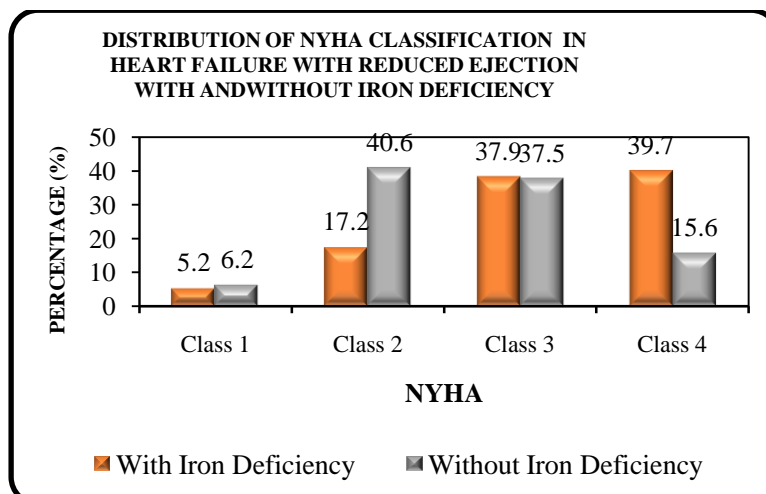
**LVEF Distribution in heart failure patients with reduced ejection fraction:**

we observed that there were 58 cases with iron deficiency. It was seen that 25 subjects(48.3%) had LVEF <30% followed by 33 subjects(51.7%) who had LVEF in the range 30-40% .The mean LVEF in the patients with iron deficiency was  $32.14 \pm 7.42$  %. While out of the 32 subjects without iron deficiency, 13 subjects(40.6%) had LVEF in the range <30% followed by 19 subjects(53.4%) who had LVEF <30%. Mean LVEF in the patients without iron deficiency was  $34.30 \pm 6.87$  %. There was no significant difference between the two groups in this regard.



**Distribution of NYHA classification in heart failure with reduced ejection fraction**

Out of 58 cases with iron deficiency, majority (23) of the subjects had NYHA class IV (39.7%) followed by 22 subjects (37.9%) who had NYHA class III. 10 subjects (17.2%) had NYHA class II and 3 subjects (5.2%) had NYHA class I. It can also be seen that out of 32 cases without iron deficiency, majority (13) had NYHA class II (40.6%) followed by 12 subjects (37.5%) who had NYHA class III. 5 subjects (15.6%) had NYHA class 4 and 2 subjects (6.2%) had NYHA class I.



## V. DISCUSSION:

The present study was undertaken to assess the association of iron deficiency in heart failure with reduced ejection fraction. After considering the inclusion and exclusion criteria, 90 cases who attended Cardiology outpatient department /Medicine and /or admitted in Department of Cardiology/Medicine, of our Medical College for duration of one year. This study was a hospital based observational study. In our study population, the most common age group was 51-60 years (28.89%) followed by 41-50 years (20%). The mean age was  $57.77 \pm 16.26$  years. The maximum age was 77yrs and the minimum age was 17yrs. In our study majority of the patients with Heart failure with reduced ejection fraction were females. Out of 90 patients, 49 were females (54.44%) and 41 were male (45.56%). We see that 65 cases (72.22%) were of normal weight, 17 cases (16.67%) were overweight, 7 cases (7.78%) were underweight and 1 case (1.11%) was obese. The mean BMI was  $22.04 \pm 5.6$ . Out of 90 patients, 47 patients had associated comorbidities out of these, 31 patients had hypertension (65.95%) and 16 patients had Diabetes (34.05%). In a study by Verma et al<sup>7</sup> 32.3% had hypertension whereas 20.5% had Diabetes. In a study by Negi et al<sup>8</sup> 44.7% subjects had hypertension while 17.3% had diabetes. Out of 90 subjects in our study it was seen that the number of subjects with iron deficiency was 58 (64.44%) and subjects without iron deficiency were 32 (35.56%). In a study by Akhil katna et al<sup>9</sup> out of 61 subjects, 48 subjects had iron deficiency and 31 subjects without iron deficiency. In a study by Jose Gonzales Castello et al<sup>10</sup> out of 1648 study population, iron deficiency was present in 898 subjects and 786 subjects without iron deficiency.

It is observed that the mean hemoglobin level in subjects with iron deficiency was  $10.38 \pm 2.51$  gm%). Mean MCV in the subjects with iron deficiency was  $75.64 \pm 6.41$  fl. Also mean MCH in subjects with iron deficiency was  $25.61 \pm 4.06$  pg. Mean serum iron was  $27.93 \pm 11.50$  microgram /dl, also the mean Serum Ferritin was  $71.88 \pm 23.68$  ng/ml. Mean TIBC was  $323.983 \pm 65.29$  mcg/dl. Also the mean transferrin saturation was  $16.14 \pm 5.63$ %. While in subjects without iron deficiency, it is observed that the mean hemoglobin level was  $11.80 \pm 1.53$  gm/dl. Mean MCV in the subjects without iron deficiency was  $91.06 \pm 5.09$  fl. Also the mean MCH were  $32.72 \pm 2.82$  pg. Mean serum iron was  $74.03 \pm 19.33$  mcg/dl. Mean Serum Ferritin was  $218.76 \pm 86.28$  ng/ml. Mean Serum TIBC was  $361.563 \pm 81$  mcg/dl. Mean Transferrin saturation was  $38.53 \pm 8.75$ %. There was significant difference between the two groups in this regard.

Out of 58 subjects with Iron deficiency, majority were from the age group of 51-60 years (29.31%) followed by 41-50 years (19.24%)

Out of 32 subjects without Iron deficiency, majority were from the age group of 51-60 years (29.31%) followed by 41-50 years (25%).

In a study conducted by Jankowska et al<sup>5</sup> the mean age in subjects with iron deficiency was  $56 \pm 11$  years while the mean age in subjects without iron deficiency was  $55 \pm 27$  years.

Out of 58 subjects with iron deficiency, there were 40 females (68.97%) while there were 18 males (31.03%). Out of 32 subjects without iron deficiency, there were 9 females (28.13%) while there were 23 males (71.88%). In a study by Jain et al<sup>11</sup> prevalence of iron deficiency in females were 51.3% whereas in males it was 46.5%.

It is observed that out of 58 cases with iron deficiency 25 subjects (48.3%) had LVEF <30% followed by 33 subjects (51.7%) who had LVEF in the range 30-40%. The mean LVEF in the subjects with iron deficiency was  $32.14 \pm 7.42$ % where as out of 32 cases without iron deficiency 13 subjects (40.6%) and LVEF <30% followed by 19 subjects (53.4%) who had LVEF in the range 30-40%. The mean LVEF in the subjects without iron deficiency was  $34.30 \pm 6.87$ %

It is seen that out of 18 males subjects with iron deficiency ,9 male subjects (50%) had LVEF <30% and 9 male subjects (50%) had LVEF in the range 30-40%. Out of 23 male subjects without iron deficiency ,9 male subjects (39.1%) had LVEF <30% and 14 male subjects (60.9%) had LVEF in the range 30-40%. It is seen that out of 40 females subjects with iron deficiency ,15 female subjects (37.5%) had LVEF <30% and 25 subjects (62.5%) had LVEF in the range 30-40%.

Out of 9 female subjects without iron deficiency, only 1 subject (11.1%) had LVEF <30% and 8 subjects (88.9%) had LVEF in the range 30-40%.

Out of 58 cases with iron deficiency ,Majority (23) of the subjects had NYHA class IV(39.7%) followed by 22 subjects (37.9%) who had NYHA class III .10 subjects (17.2%) had NYHA class II and 3 subjects (5.2%) had NYHA Class I.

Out of 32 cases without iron deficiency ,Majority (13) of the subjects had NYHA class II(40.6%) followed by 12 subjects (37.5%) who had NYHA class III .5 subjects (15.6%) had NYHA class IV and 2 subjects (6.2%) had NYHA Class I. There was significant difference between two groups in this regard ( $p=0.04$ ) In a study conducted by Klip et al <sup>12</sup> it was found that in subjects with iron deficiency ,39% subjects had NYHA class I/II ,53% subjects had NYHA Class III and 8% subjects had NYHA Class IV. Where as in subjects without iron deficiency 53% had NYHA class I/II ,42% had NYHA Class III and 5 % had NYHA class IV. In a study conducted by Okonko et al<sup>13</sup> it was found that in subjects with iron deficiency,18% subjects had NYHA class I/II ,54% subjects had NYHA Class III and 28% subjects had NYHA Class IV. Where as in subjects without iron deficiency 66% had NYHA class I/II ,30% had NYHA Class III and 3 % had NYHA class IV.

In a study conducted by Josep et al<sup>14</sup> it was found that in subjects with iron deficiency 15% subjects had NYHA class I,39% subjects had NYHA Class II 40% subjects had NYHA Class III and NYHA class IV..

Where as in subjects without iron deficiency 23 % had NYHA class I ,50% had NYHA Class II and 23 % had NYHA class III and 4% had NYHA class IV.

In a study conducted by Jacob et al <sup>15</sup> it was found that in subjects with iron deficiency 3% subjects had NYHA class I ,13% subjects had NYHA Class II 19% subjects had NYHA Class III and 20 % had NYHA class IV.

Where as in subjects without iron deficiency 5 % had NYHA class I ,15% had NYHA Class II and 13 % had NYHA class III and 9% had NYHA class IV.

## VI. SUMMARY:

**The various observations made from the study are summarized below:** The majority of the subjects in the study group belonged to the age group 51-60 years (28.89%) followed by 41-50 years (20%). The mean age group of the whole study group was  $57.77 \pm 6.26$  years. There were 49 female subjects (54.44%) and 41 male subjects (45.56%).

The sex ratio in the study group was 1:1.2. The majority of the subjects were normal weight (72.22%) while 17 subjects were overweight (16.67%), 7 subjects (7.78%) were underweight and only 1 subject was obese (1.11%). Out of the 90 patients, 47 patients had co-morbidities out of which 31 patients (65.95%) had hypertension and 16 patients had diabetes (34.05%) Out of the 90 subjects, 58 subjects had iron deficiency (64.44%) while 32 subjects without iron deficiency (35.56%). Significant differences were observed between subjects with or without iron deficiency in terms of Hb%, MCV, MCH, Serum iron, serum ferritin, TIBC and TSAT. The mean age for subjects with iron deficiency was  $57.19 \pm 15.51$  years, whereas the mean age for subjects without iron deficiency was  $56.06 \pm 14.36$  years. The majority of the subjects with iron deficiency were females (68.97%) while males were 31.03%. In subjects without iron deficiency majority were males (71.88%) while females were 28.13%. There was significant difference between the two groups.

The mean LVEF in subjects with iron deficiency was 32.14% while subjects without iron deficiency the mean LVEF was  $4.30 \pm 6.87$ %. In subjects with iron deficiency, majority had NYHA class IV (39.7%) followed by NYHA class III (37.9%), whereas subjects without iron deficiency majority had NYHA class II (40.6%) followed by NYHA class III (37.9%).

## VII. CONCLUSION:

In our hospital based observational study conducted among the heart failure patients with reduced ejection fraction, we observed a 64.44% prevalence of iron deficiency. We found the

prevalence of iron deficiency was significantly higher in the females (68.97%) than males (31.03%) and patients with iron deficiency had advanced NYHA class as compared to patients without iron deficiency.

This study showed that there is a large burden of iron deficiency in patients with heart failure with reduced ejection fraction, more prevalent in female patients and presented with higher functional NYHA class. Therefore screening of iron deficiency is recommended in all patients with heart failure and correction of iron status may help in improving the quality of life and decrease hospitalizations.

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