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Prospective Study to Evaluate the Effect of Optimal Medical Therapy on Iron Profile in Patients of Chronic Heart Failure in Tertiary Care Hospital in Kolkata

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Abstract: ***Introduction: Heart failure is considered a heterogeneous syndrome and is characterized by abnormalities in cardiac structure or function. In recent decades, our understanding of the heart failure syndrome has led to remarkable advances in terms of prevention, diagnosis and treatment possibilities. In recent years, iron deficiency has emerged as a newly recognized co-morbidity of chronic HF. Independently of anemia, iron deficiency occurs frequently in HF patients, contributing to cardiac and peripheral muscle dysfunction, and is a strong predictor of poor clinical outcome. Aims and objectives of the study: General Objectives: To evaluate the effect of optimal medical therapy in patients of chronic heartfailure over iron profile in parallel with disease progression. Specific Objectives: To examine the relationship between iron deficiency and Functional status in patient with chronic Heart Failure. Materials and methods: Place of study: Department of Cardiology, Medical college, Kolkata. Study Population: All consecutive patients admitted with HF in Medical College Kolkata. Study Period: One year (after ethics committee clearance). Sample Size: A total of 101 subjects. Sample Design: Consecutive eligible. Study Design: Single centre prospective study. Results: It can be observed that with more advancement of age the progression of heart failure worsens and elderly are more prone to advanced heart failure. In our study the mean level of hemoglobin was 10.95 ±1.71 g/dl and it has gradually increased to mean level of 11.57 ±1.61 g/dL after the optimal medical therapy with iron supplementation across all the NHYA functional class and is statistically highly significant (p value <0.0001).The correlation of gender with heart failurein our case is not significant. In our study, it can be clearly observed that with the progression of advanced heart failure classes the mean level of iron, ferritin and transferrin is worsening or is very low. The relationship between serum ferritin levels and new onset heart failure appears to be linear. The group treated with iron demonstrated a significant improvement in renal function and NYHAclass.***

Keywords: Heart failure, Iron deficiency, Optimal Medical Therapy, Functional Status

1. Introduction

Heart failure is considered a heterogeneous syndrome and is characterized by abnormalities in cardiac structure or function. This leads to decline of the heart's pumping capacity and subsequent inability to meet the body's circulatory demands[1]. In recent decades, our understanding of the heart failure syndrome has led to remarkable advances in terms of prevention, diagnosis and treatment possibilities. Despite this progress, heart failure prevalence is rising along with the ageing of the general population and is reaching epidemic proportions. In recent years, iron deficiency has emerged as a newly recognized co-morbidity of chronic HF. Independently of anemia, iron deficiency occurs frequently in HF patients, contributing to cardiac and peripheral muscle dysfunction, and is a strong predictor of poor clinical outcome [2,3,4]. Recent controlled randomized studies have shown that iron treatment in chronic HF has favorable effects on exercise capacity, New York Heart Association (NYHA) functional class, left ventricular ejection fraction (LVEF) and quality of life. Despite this, the diagnosis and management of HF patients with iron deficiency remains largely unrecognized in the cardiologist community. However, diagnostic tools and treatments already exist are relatively inexpensive and may lead to important health benefits for HF patients.

General Objectives
To evaluate the effect of optimal medical therapy in patients of chronic heartfailure over iron profile in parallel with disease progression.

Specific Objectives:
To examine the relationship between iron deficiency and Functional status in patient withchronic Heart Failure

Place of Study:
Department of Cardiology, Medical college, Kolkata

Study Population:
All consecutive patients admitted with HF in medical college Kolkata

Study Period:
One year (after ethics committee clearance)

Sample Size:
A total of 101 subjects

Sample Design:
Consecutive eligible

Study Design:
Single centre prospective study.

Inclusion Criteria:

1) Age more than 18
2) Admission with clinical diagnosis of HF.
3) One of the following abnormal investigation result
   a) Abnormal ECG showing LVH or evidence of old MI or abnormalventricular conduction
   b) Abnormal Chest X ray showing cardiomegaly or pulmonary venous hypertension or pulmonary oedema
   c) Raised natriuretic peptide levels (BNP or NT Pro BNP)
   d) Echocardiography
      - LV systolic dysfunction, EF < 40%
      - LV Diastolic dysfunction/ left ventricular hypertrophy.
      - Valvular heart disease.
4) Underlying heart disease diagnosed as one of the following
   a) Ischemic heart disease
   b) Non Ischemic dilated cardiomyopathy
   c) Valvular heart disease.
   d) Uncorrected or residual adult congenital heart disease
   e) Pulmonary vascular disease resulting from congenital heart diseaseor valvular heart disease.
   f) Heart failure with preserved ejection fraction (EF > 50%)
   g) Heart failure with mid-range ejection fraction (EF 40 – 50 %)

Exclusion Criteria:

1) Patients unwilling to participate
2) Pregnant patients
3) Admission with acute inflammatory process
4) Acute rheumatic fever

2. Methods

A total of 101 patients presenting with the symptoms of heart failure, admitted in the department of Cardiology, Medical College Kolkata were considered for the present study. The baseline characteristics including iron profile has been taken which includes hemoglobin, serum iron, serum ferritin, TIBC, Transferrin saturation, RDW and MCV has been recorded. The patients were followed up for 6 months after providing optimal medical therapy and the change in iron profile was measured.

2.1 Study Tools

Parameters under study:

1) History: Symptoms of dyspnea, fatigue, palpitation, chest pain and their NYHA classes; pedal/ facial swelling and other symptoms related to congestive cardiac failure (CCF); duration and severity of each symptom
2) Clinical examination: general examination with special impetus to pulse, blood pressure, JVP, dependant edema, precordial examination with special impetus to RV impulse and other features of RVH or RV dysfunction
3) Investigations to be done before supplementation of OMT and after supplementation of OMT:
   a) Hb
   b) Serum Iron
   c) Serum Ferritin
   d) Transferrin Saturation
   e) TIBC
   f) MCV
   g) RDW
4) **ECG:** standard 12 lead ECG with long lead II. ECG showing LVH or evidence of old MI or abnormal ventricular conduction
5) **Echocardiography:** General Electric (GE) Vivid 7 echocardiography machine belonging to the department of Cardiology, was used including 2D, M mode, color Doppler, pulsed wave Doppler , Doppler tissue imaging (DTI/ TDI). Views, measurements and calculations for different parameters to assess left ventricular (LV) function were done following recent recommendations of the American Society of Echocardiography and the European Society of Cardiovascular Imaging 68). Values of each parameter were obtained after averaging over three cardiac cycles (five to ten cycles in atrial fibrillation). A Doppler velocity range -15 to +15 cm/s and high frame count was selected for this study.

2.2 Statistical Analyses

Baseline variables are expressed as means with standard deviation (SD) when normally distributed, as medians with interquartile range (IQR) when distribution is skewed, or as numbers and percentages when categorical.
Inter-group differences were tested using the one-way analysis of variance (ANOVA) test, Kruskal-Wallis test or chi-square test, as appropriate. Correlation between values of two parameters were tested using Pearson's correlation coefficient. P value was considered significant when <0.05 and highly significant when <0.001

A total of 101 patients presenting with sign and symptoms of heart failure attending the Cardiology OPD or admitted in the Cardiology ward of Medical College, Kolkata during the period of the study were selected for the above study with informed consent and after ruling out the exclusion criteria

3. Results and Analysis

Among 101 patient with heart failure in our study there are 35.64% of female and 64.36% of male. In females, less than 65 years of age, the proportion of patients having LVEF <40% is 5.9% and LVEF >40% is 12.9%Aand the proportion of females more than 65 years of age having LVEF<40% is 11.9 % and LVEF >40% is 5% respectively. However there is almost similar proportion of male of 20.9 % having LVEF<40% in both below 65 years and above 65 years of age. And proportion of male with LVEF>40% having age below 65 years is 15.8 % and age above 65 years is 6.9%.

Baseline characteristics of the 101 patients are provided in table 1 below. It can be observed that older patients more often belong to NYHA class IV suggesting age is directly proportional to the degree of heart failure and it is statistically significant (p value 0.004). However there is no significant statistical correlation with the BMI of patients with heart failure. Iron profile both before the optimal

medical therapy (OMT) and after optimal medical therapy remains statistically highly significant across the classes of heart failure p value< 0.05 except the Red cell Distribution Width (RDW) which is not significant across heart failure classes in our study.

Table 1: Basic demographic statistics

	NYHA I	NYHA II	NYHA III	NYHA IV	Total	p Value
Age	58.63 ±12.56	58.2 ±12.57	64.89 ±13.48	72.18 ±15.73	63.14 ±14.21	0.004
BMI	26.26 ±3.19	26.57 ±3.51	26.81 ±3.43	27.14 ±3.03	26.71 ±3.32	0.884
Systolic BP	125.81 ±14.8	119.8 ±15.3	125.21 ±14.01	116.53 ±17.04	122.24 ±15.25	0.139
Diastolic BP	76.38 ±9.4	73.7 ±9.64	75.92 ±8.82	73.35 ±10.67	74.9 ±9.42	0.625
Heart Rate	82.06 ±14.83	83.5 ±13.28	83.29 ±14.79	92 ±16.67	84.62 ±14.86	0.162
Ejection Fraction	47.19 ±6.38	46.63 ±8.13	34.16 ±6.9	29.94 ±3.77	39.22 ±9.81	<0.0001
eGFR	79.27 ±18.41	71.02 ±21.57	66.18 ±29.71	49.72 ±15.96	66.92 ±25.16	0.004
Hemoglobin	11.96 ±1.51	10.84 ±1.52	11.22 ±1.81	9.59 ±1.05	10.95 ±1.71	<0.0001
MCV	87 ±1.93	84.3 ±3.7	85.53 ±5.1	82.94 ±6.3	84.96 ±4.7	0.061
RDW	13.69 ±0.97	13.75 ±0.9	13.8 ±1.17	14.35 ±1.04	13.86 ±1.05	0.207
Ferritin	35.5 ±7.06	36.5 ±13.59	31 ±12.68	27.88 ±6.88	32.82 ±11.78	0.051
Iron	62.75 ±14.37	57.97 ±13.47	50.03 ±17.68	42.41 ±8.89	53.12 ±16.03	<0.0001
TIBC	351.38 ±13.45	360.5 ±18.8	363.53 ±16.97	369.59 ±10.18	361.72 ±16.8	0.013
TransferrinSaturation	22.94 ±2.59	21.63 ±2.75	20.74 ±3.93	17.53 ±1.91	20.81 ±3.5	<0.0001
Hb after OMT	12.93 ±1.72	11.62 ±1.48	11.51 ±1.52	10.35 ±0.82	11.57 ±1.61	<0.0001
MCV after OMT	88.63 ±2.8	87.17 ±3.25	86.53 ±4.2	84.94 ±4.51	86.78 ±3.9	0.047
RDW after OMT	12.83 ±0.48	13.44 ±1.31	13.33 ±1.33	13.14 ±0.84	13.25 ±1.16	0.366
Ferritin afterOMT	39.81 ±12.08	40.43 ±14.41	33.13 ±14.54	32.65 ±9.05	36.28 ±13.66	0.067
Iron after OMT	71.44 ±24.71	62.23 ±12.38	55.05 ±19.47	52.53 ±14.06	59.36 ±18.67	0.007
TIBC after OMT	333 ±18.7	347.83 ±23.9	349.74 ±27.6	360.88 ±13.05	348.4 ±24.34	0.01
TSAT after OMT	26.13 ±4.5	24.13 ±3.89	22.58 ±5.75	19.29 ±2.66	23.05 ±5.01	<0.0001

The table shows that mean age of the patients across the study is 63.14 ±14.21, BMI is 26.71±3.32. The mean systolic and diastolic pressure and heart rate is 122.24 ±15.25, 74.9 ±9.42 and 84.62 ±14.86 which are not statistically significant across all the NYHA functional class. The mean Ejection fraction is 39.22 ±9.81, mean serum hemoglobin 10.95 ±1.71, mean Transferrin Saturation is 20.81 ±3.5 across the NYHA functional class and are statistically highly significant (P value <0.0001)

Table 2: Correlation of eGFR with NYHA functional Class

	eGFR<40	eGFR>40	Total	
NYHA I	2	14	16	P value 0.001
	12.5%	87.5%	100.0%	
NYHA II	7	23	30	
	23.3%	76.7%	100.0%	
NYHA III	17	21	38	
	44.7%	55.3%	100.0%	
NYHA IV	12	5	17	
	70.6%	29.4%	100.0%	
	38	63	101	
	37.6%	62.4%	100.0%	

Out of 101 patients, 37.6% have eGFR <60 ml/min and 62.4% have eGFR>60ml/min. In NYHA class I, 12.5% patients have eGFR<60 ml/min and 87.5% have eGFR>60 ml/min. In NYHA class II,23.3% patients have eGFR<60 ml/min and 76.7% have eGFR>60 ml/min. In NYHA classIII, 44.7% patients have eGFR<60ml/min and 55.3% have eGFR>60ml/min. In NYHA class IV, 70.6% patients have eGFR<60 ml/min and 29.4% have eGFR>60 ml/min. So across all classes the proportion of patients with eGFR<60 ml/min increases which is statistically significant (p value 0.001)

Table 3: Correlation of Ejection Fraction with NYHA functional Class

	EF<40	EF>40	Total	
NYHA I	2	14	16	P value <0.0001
	12.5%	87.5%	100.0%	
NYHA II	7	23	30	
	23.3%	76.7%	100.0%	
NYHA III	34	4	38	
	89.5%	10.5%	100.0%	
NYHA IV	17	0	17	
	100.0%	0.0%	100.0%	
	60	41	101	
	59.4%	40.6%	100.0%	

With respect to lower Ejection Fraction the patient become more symptomatic according toNYHA functional class. The proportion of patients with EF<40% gradually increases from NYHA functional class I to IV. Among 101 patients 59.4% of patients have LVEF <40% and 40.6 % of patients have LVEF >40% and is statistically highly significant (p value <0.0001).

Out of 16 patients in NYHA class I ,10 (62.5%) are non diabetic and 6(37.5%) belongs to diabetic patients, among 30 patients of NYHA class II 13(43.3 %) are non diabetic and 17(56.7%) corresponds to diabetic patient, among 38 patients of NYHA class III 18(47.4%) are non diabetic patients and 20(52.6%) belongs to diabetic patient, and among 17 NYHA class IV patients 5(29.4%) are non diabetic patients and 12(70.6%) belongs to diabetic patient. Diabetes is not statistically significant across heart failure classes (p value=0.290)

Table 4: Correlation of Hypertension with NYHA functional Class

	Non Hypertensive	Hypertensive	Total	
NYHA I	9	7	16	P value 0.022
	56.3%	43.8%	100.0%	
NYHA II	13	17	30	

	43.3%	56.7%	100.0%	
NYHA III	8	30	38	
	21.1%	78.9%	100.0%	
NYHA IV	3	14	17	
	17.6%	82.4%	100.0%	
	33	68	101	
	32.7%	67.3%	100.0%	

Among 16 NYHA class I patients 9 (56.3%) are non hypertensive patients and 7(43.8%) are hypertensive patients. Among 30 NYHA class II patients, 13(43.3%) are non hypertensive patients and 17(56.7%) are hypertensive patients. Among 38 NYHA class III patients, 8(21.1%) are non hypertensive patients and 30(78.9%) are hypertensive patients. Among 17 NYHA classIV patients, 3(17.6%) are non hypertensive patients and 14(82.4%) are hypertensive patients . Hypertension is statistically highly significant across heart failure classes (p value=0.022).

Table 5: Correlation of Atrial Fibrillation with NYHA functional Class

	NO AF	AF	Total	
NYHA I	16	0	16	
	100.0%	0.0%	100.0%	
NYHA II	27	3	30	
	90.0%	10.0%	100.0%	
NYHA III	31	7	38	P value 0.009
	81.6%	18.4%	100.0%	
NYHA IV	10	7	17	
	58.8%	41.2%	100.0%	
	84	17	101	
	83.2%	16.8%	100.0%	

Out of 101 patients,16(100%) patients, 27(90%) patients, 31(81.6%)patients,10(58.8%)patients with no Atrial fibrillation corresponds to NYHA class I, II, III and IV respectively.3 (10%) patients, 7(18.4%) and 7(41.2%) patients with Atrial fibrillation corresponds to NYHA class II, III and IV respectively. Atrial Fibrillation is statistically highly significant across the classes ofheart failure (p value 0.009).

Out of 101 patients,16(100%) patients,23(76.7%) patients,26(68.4%)patients,5(29.4%) ischemic patients corresponds to NYHA class I,II,III and IV respectively.7 (23.3%) patients, 12(31.6%) and 12(70.6%) non ischemic patients corresponds to NYHA class II,III and IV respectively.

Heart failure patients with Ischemic etiology is statistically highly significant across the classesof heart failure (p value <0.0001).

Comparison of Iron profile according to LVEF

The comparison between two groups (LVEF <40 and LVEF>40) of Ejection Fraction withrespect to iron profile in patients receiving optimal medical treatment is shown below.

Table 6: Comparison of Iron profile in patients receiving optimal medical treatment amongLVEF <40% Group

	Variables	Mean ± SD	p Value
LVEF<40	Hemoglobin	10.79 ± 1.79	0.016
	Hb after OMT	11.19 ± 1.44	
	MCV	85.08 ± 5.44	0.005
	MCV after OMT	86.35 ± 4	
	RDW	13.87 ± 1.17	0.039
	RDW after OMT	13.34 ± 1.26	
	Ferritin	32.22 ± 13.1	0.000
	Ferritin after OMT	35.75 ± 14.7	
	Iron	49.72 ± 16.3	0.002
	Iron after OMT	55.4 ± 17.57	
	TIBC	363.22 ± 16.79	0.000
	TIBC after OMT	349.08 ± 24.54	
	Transferrin Saturation	20.07 ± 3.68	0.000
	TSAT after OMT	22.37 ± 5.29	

Table 7: Comparison of Iron profile in patients receiving optimal medical treatment amongLVEF>40% Group

	Variables	Mean ± SD	p Value
LVEF>40	Hemoglobin	11.18 ± 1.57	0.001
	Hb after OMT	12.13 ± 1.7	
	MCV	84.78 ± 3.41	0.000
	MCV after OMT	87.41 ± 3.71	
	RDW	13.84 ± 0.87	0.001
	RDW after OMT	13.12 ± 0.99	
	Ferritin	33.71 ± 9.62	0.022
	Ferritin after OMT	37.05 ± 12.11	
	Iron	58.1 ± 14.4	0.000
	Iron after OMT	65.15 ± 18.94	
	TIBC	359.54 ± 16.77	0.007
	TIBC after OMT	347.39 ± 24.31	
	Transferrin Saturation	21.9 ± 2.94	0.003
	TSAT after OMT	24.05 ± 4.46	

Comparative analysis has been done to access the iron profile across two groups LVEF<40 % and LVEF>40% and has been presented in the table above. The values have been expressed as mean and standard deviation and it can be clearly seen that the iron profile across both the group after providing optimal medical therapy varied significantly (p value < 0.05)

Table 8: Comparison of Iron profile in patients receiving optimal medical treatment accordingto NYHA Class I

	Variables	Mean ± SD	p Value
NYHA Class I	Hemoglobin	11.18 ± 1.57	0.001
	Hb after OMT	12.13 ± 1.7	
	MCV	84.78 ± 3.41	0.000
	MCV after OMT	87.41 ± 3.71	
	RDW	13.84 ± 0.87	0.001
	RDW after OMT	13.12 ± 0.99	
	Ferritin	33.71 ± 9.62	0.022
	Ferritin after OMT	37.05 ± 12.11	
	Iron	58.1 ± 14.4	0.000
	Iron after OMT	65.15 ± 18.94	
	TIBC	359.54 ± 16.77	0.007
	TIBC after OMT	347.39 ± 24.31	
	Transferrin Saturation	21.9 ± 2.94	0.003
	TSAT after OMT	24.05 ± 4.46	

It can be observed from the table above that after supplementation of optimal medical therapy, there is gradual improvement in the iron profile across NYHA Class I and is statistically significant with p value <0.05

Table 9: Comparison of Iron profile in patients receiving

optimal medical treatment accordingto NYHA Class II

	Variables	Mean ± SD	p Value
NYHA Class II	Hemoglobin	10.84 ± 1.52	0.047
	Hb after OMT	11.62 ± 1.48	
	MCV	84.3 ± 3.7	0.002
	MCV after OMT	87.17 ± 3.25	
	RDW	13.75 ± 0.9	0.340
	RDW after OMT	13.44 ± 1.31	
	Ferritin	36.5 ± 13.59	0.023
	Ferritin after OMT	40.43 ± 14.41	
	Iron	57.97 ± 13.47	0.036
	Iron after OMT	62.23 ± 12.38	
	TIBC	360.5 ± 18.8	0.013
	TIBC after OMT	347.83 ± 23.9	
	Transferrin Saturation	21.63 ± 2.75	0.001
	TSAT after OMT	24.13 ± 3.89	

Upon supplementation of optimal medical therapy in our study, the iron prolife including hemoglobin, MCV, Transferrin saturation, TIBC significantly increased which is statistically significant (p value <0.05) except RDW which is not statistically significant (p value 0.340) in NYHA class II

Table 10: Comparison of Iron profile in patients receiving optimal medical treatment accordingto NYHA Class III

	Parameter	Mean ±SD	P value
NYHA Class III	Hemoglobin	11.22 ± 1.81	0.026
	Hb after OMT	11.51 ± 1.52	
	MCV	85.53 ± 5.1	0.048
	MCV after OMT	86.53 ± 4.2	
	RDW	13.8 ± 1.17	0.137
	RDW after OMT	13.33 ± 1.33	
	Ferritin	31 ± 12.68	0.045
	Ferritin after OMT	33.13 ± 14.54	
	Iron	50.03 ± 17.68	0.016
	Iron after OMT	55.05 ± 19.47	
	TIBC	363.53 ± 16.97	0.009
	TIBC after OMT	349.74 ± 27.6	
	Transferrin Saturation	20.74 ± 3.93	0.003
	TSAT after OMT	22.58 ± 5.75	

Upon supplementation of optimal medical therapy in our study, similarly like NYHA class II theiron prolife including hemoglobin, MCV, Transferrin saturation, TIBC significantly increased which is statistically significant (p value <0.05) given in table above, except RDW which is not statistically significant (p value 0.137) in NYHA class III

Table 11: Comparison of Iron profile in patients receiving optimal medical treatment accordingto NYHA Class IV

	Parameter	Mean ±SD	P value
NYHA Class IV	Hemoglobin	9.59 ± 1.05	0.032
	Hb after OMT	10.35 ± 0.82	
	MCV	82.94 ± 6.3	0.042
	MCV after OMT	84.94 ± 4.51	
	RDW	14.35 ± 1.04	0.008
	RDW after OMT	13.14 ± 0.84	
	Ferritin	27.88 ± 6.88	0.031
	Ferritin after OMT	32.65 ± 9.05	
	Iron	42.41 ± 8.89	0.012
	Iron after OMT	52.53 ± 14.06	
	TIBC	369.59 ± 10.18	0.009
	TIBC after OMT	360.88 ± 13.05	
	Transferrin Saturation	17.53 ± 1.91	0.026
	TSAT after OMT	19.29 ± 2.66	

Upon supplementation of optimal medical therapy in our study, similarly like NYHA class I, all the parameters of the iron prolife including hemoglobin, MCV, Transferrin saturation, TIBC andRDW increased significantly which is statistically significant (p value <0.05) given in table above.

Table 12: Comparison of Iron profile in patients receiving optimal medical treatment accordingto Non Ischemic Heart Disease

	Parameter	Mean ±SD	P value
Non Ischemic	Hemoglobin	11.22 ± 1.81	0.008
	Hb after OMT	11.51 ± 1.52	
	MCV	85.53 ± 5.1	0.006
	MCV after OMT	86.53 ± 4.2	
	RDW	13.8 ± 1.17	0.001
	RDW after OMT	13.33 ± 1.33	
	Ferritin	31 ± 12.68	0.001
	Ferritin after OMT	33.13 ± 14.54	
	Iron	50.03 ± 17.68	0.000
	Iron after OMT	55.05 ± 19.47	
	TIBC	363.53 ± 16.97	0.002
	TIBC after OMT	349.74 ± 27.6	
	Transferrin Saturation	20.74 ± 3.93	0.012
	TSAT after OMT	22.58 ± 5.75	

Table 13: Comparison of Iron profile in patients receiving optimal medical treatment accordingto Ischemic Heart Disease

	Variables	Mean ± SD	p Value
Ischemic	Hemoglobin	11.22 ± 1.81	0.003
	Hb after OMT	11.51 ± 1.52	
	MCV	85.53 ± 5.1	0.000
	MCV after OMT	86.53 ± 4.2	
	RDW	13.8 ± 1.17	0.122
	RDW after OMT	13.33 ± 1.33	
	Ferritin	31 ± 12.68	0.003
	Ferritin after OMT	33.13 ± 14.54	
	Iron	50.03 ± 17.68	0.001
	Iron after OMT	55.05 ± 19.47	
	TIBC	363.53 ± 16.97	0.000
	TIBC after OMT	349.74 ± 27.6	
	Transferrin Saturation	20.74 ± 3.93	0.000
	TSAT after OMT	22.58 ± 5.75	

The change in iron profile in both Ischemic and Non ischemic patients, upon supplementation of optimal medical therapy, including Hemoglobin, Ferritin, Iron, MCV, RDW, TIBC, TSAT showed favorable response as the level of iron profile improved in our study which is statistically significant. However in non ischemic patients, the change in iron is statistically highly significant (p value<0.0001) and in Ischemic patients, the change in MCV, TIBC and Transferrin in our study is found to be statistically highly significant (p value<0.0001).

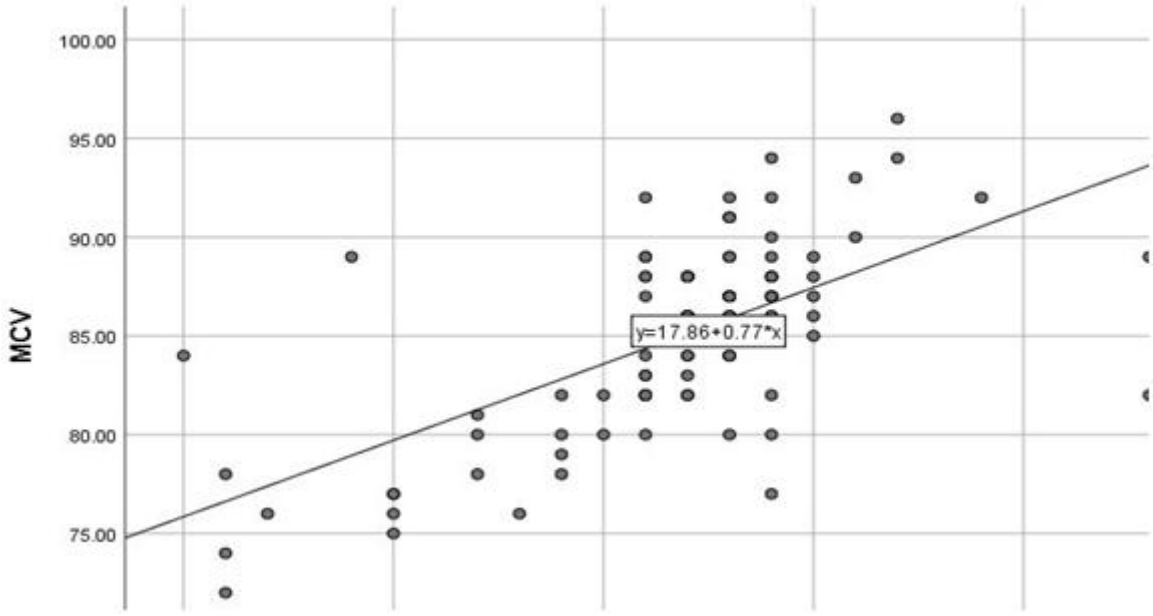

Figure 1: The figure shows that the level of MCV before supplementation of optimum medical therapy is positively correlated with the level of MCV after supplementation of optimum medical therapy. Correlation coefficient (r) = 0.641; R^2 Linear=0.0411 and y=17.86+0.77*x. The two-tailed P value being 0.0001, considered statistically highly significant.

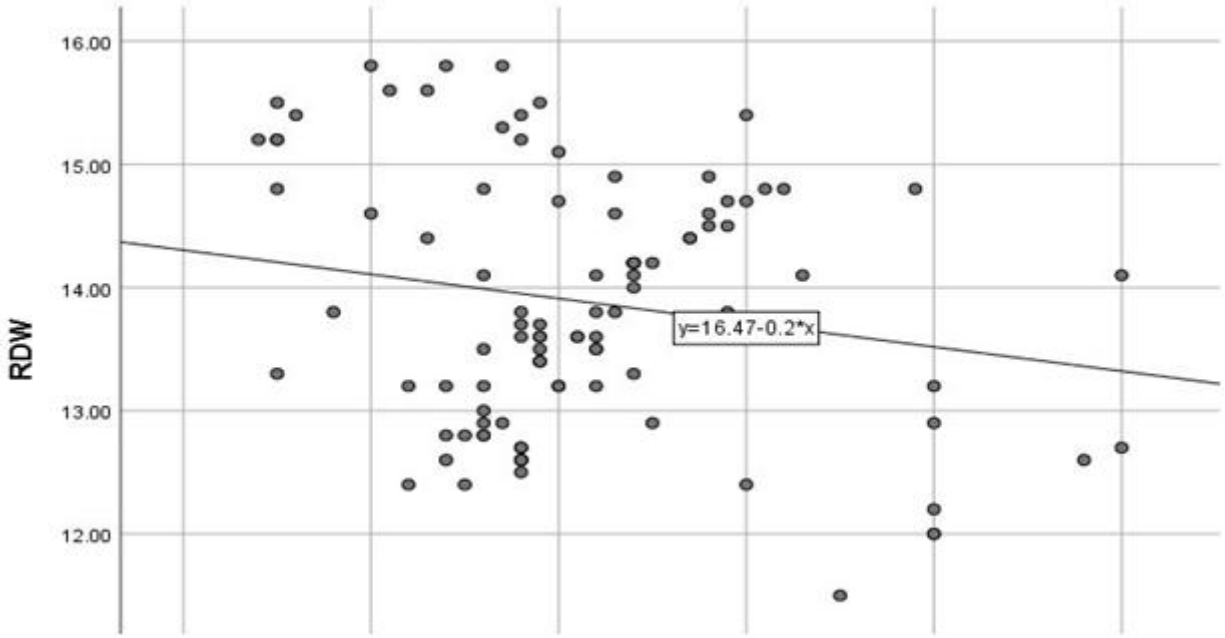

Figure 2: The figure shows that the level of RDW before supplementation of optimum medicaltherapy is negatively correlated with the level of RDW after supplementation of optimum medical therapy. Correlation coefficient (r) = -(0.216); R^2 Linear=0.0411 and y=16.47-0.2*x.

The two-tailed P value being 0.030, considered statistically highly significant.

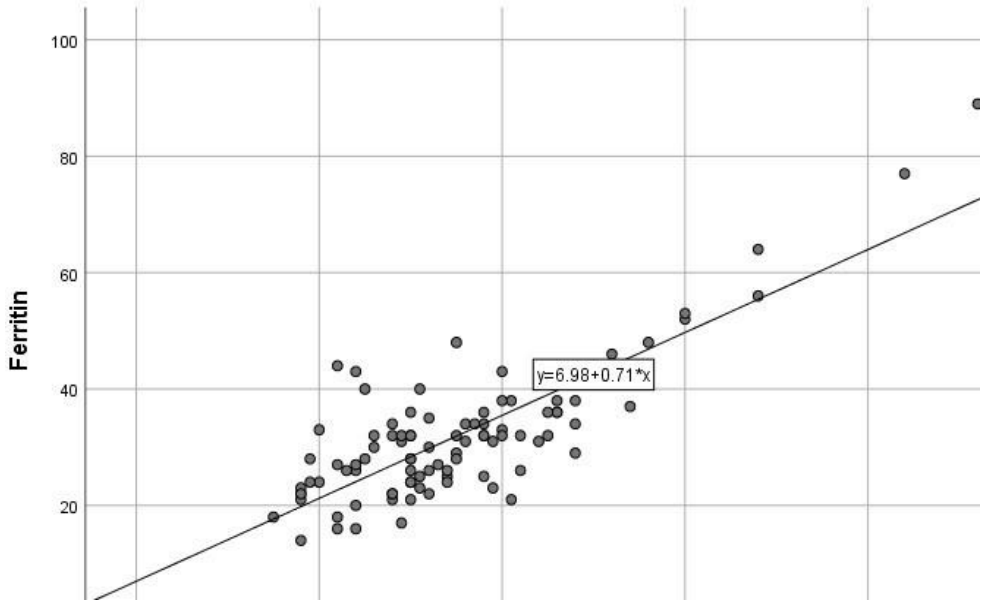

Figure 3: The figure shows that the level of Ferritin before supplementation of optimum medical therapy is positively correlated with the level of Ferritin after supplementation of optimum medical therapy. Correlation coefficient (r) = 0.826; R^2 Linear=0.683 and y=6.98+0.71*x. The two-tailed P value being 0.0001, considered statistically highly significant.

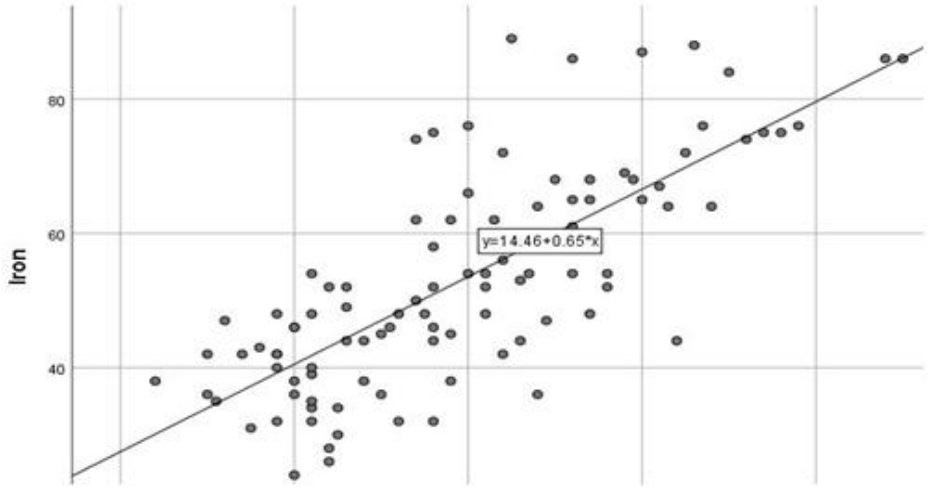

Figure 4: The figure shows that the level of Iron before supplementation of optimum medical therapy is positively correlated with the level of Iron after supplementation of optimum medical therapy. Correlation coefficient (r) = 0.759; R^2 Linear=0.576 and y=14.46+0.65*x. The two-tailed P value being 0.0001, considered statistically highly significant.

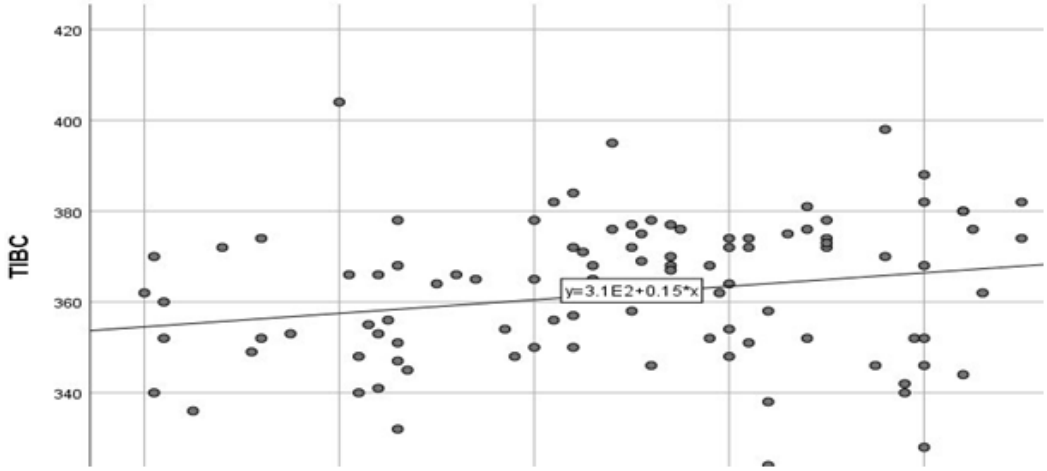

Figure 5: The figure shows that the level of TIBC before supplementation of optimum medical therapy is positively correlated with the level of TIBC after supplementation of optimum medicaltherapy. Correlation coefficient (r) = 0.216; R^2 Linear=0.046 and y=3.1+0.15*x. The two-tailed Pvalue being 0.030, considered statistically highly significant.

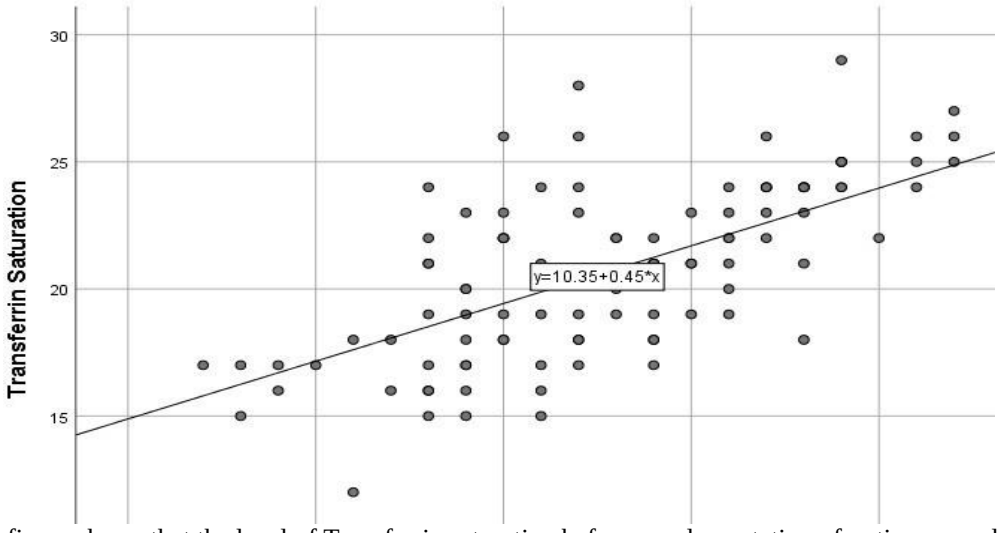

Figure 7: The figure shows that the level of Transferrin saturation before supplementation of optimum medical therapy is positively correlated with the level of Transferrin saturation after supplementation of optimum medical therapy. Correlation coefficient (r) = 0.650; R^2 Linear=0.046 and y=10.35+0.45*x. The two-tailed P value being 0.0001, considered statistically highly significant.

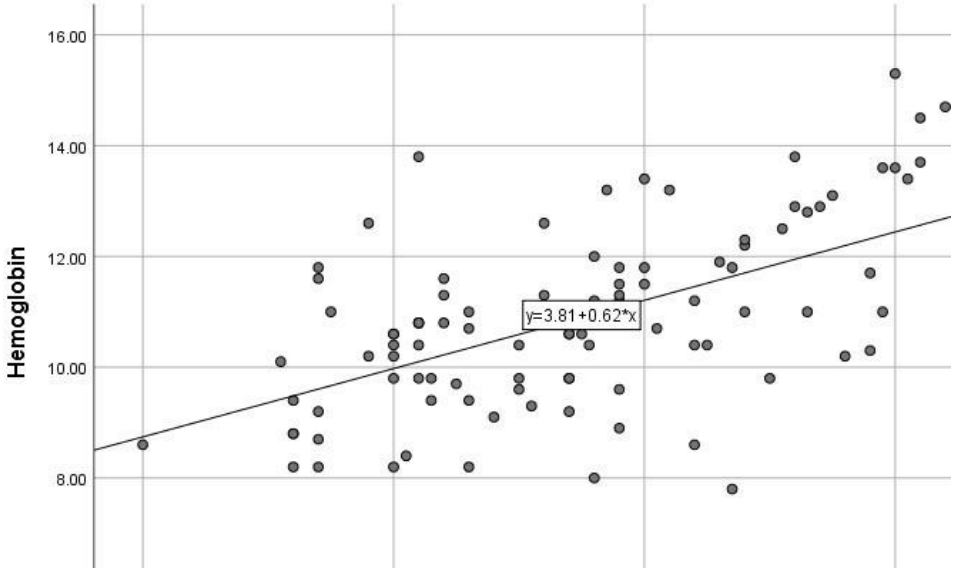

Figure 8: The figure shows that the level of Hemoglobin saturation before supplementation ofoptimum medical therapy is positively correlated with the level of Hemoglobin after supplementation of optimum medical therapy. Correlation coefficient (r) = 0.583; R^2 Linear=0.046 and y=3.81+0.62*x. The two-tailed P value being 0.001, considered statisticallyhighly significant.

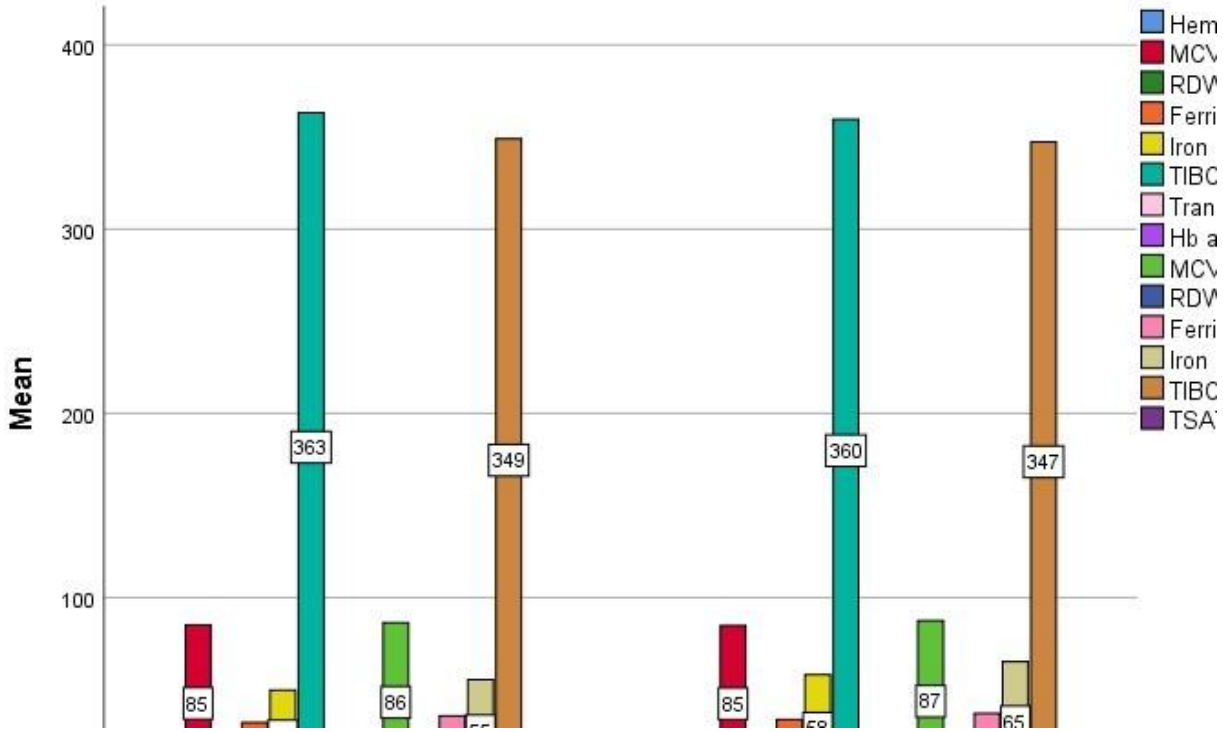

Figure 9: Comparison of Iron profile among two group of patients with LVEF<40% andLVEF>40%

The figure represents the iron profile in two groups characterized by Ejection fraction that is LVEF<40 and LVEF>40. It can be observed that the mean level of ferritin, Iron is lesser than inthe other group.

4. Discussion

In our study the mean age of the patients in NYHA class I is 58.63 ±12.56 years, NYHA class II is 58.2 ±12.57 years, NYHA class III is 64.89 ±13.48 years and NYHA class IV is 72.18 ±15.73 years and overall 63.14± 14.21 years. It can be observed that with the higher NYHA functional class, progression of age is more. This is in accordance with the age of patients in the study by Swedish HF registry [5], age of patient is 67.12± 12.3 years in the EVEREST II trial[6], age of patient is 62.4± 11.1 years in Valsartan heart failure (Val – HeFT) trial [7] and in IN – CHF registry.

In our study, In females, less than 65 years of age, the proportion of patients having LVEF <40% is 5.9% and LVEF >40% is 12.9% and the proportion of females more than 65 years of age having LVEF<40% is 11.9 % and LVEF >40% is 5% respectively. However there is almost similar proportion of male of 20.9 % having LVEF<40% in both below 65 years and above 65 years of age. And proportion of male with LVEF>40% having age below 65 years is 15.8 % and age above 65 years is 6.9%. This suggests that with more advancement of age the progression of heart failure worsens and elderly are more prone to advanced heart failure.

In our study the mean level of hemoglobin was 10.95 ±1.71 g/dL before providing optimal medical therapy and it has gradually increased to mean level of 11.57 ±1.61 g/dL after the optimal medical therapy across all the NHYA functional class and is statistically highly significant (p value <0.0001).

The group treated with iron demonstrated a significant increase in hemoglobin (10.360.6 g/dl21 to 11.860.7 g/dl21), improvement in renal function and NYHAclass. the association between levels of hemoglobin and the risk for new onset heart failure appears to be best described as "U-shaped". Interestingly, higher hemoglobin levels, already within the high-normal range, are associated with an increased heart failure incidence. This was in contrast to anemia, where a higher annual HF incidence was only observed for severe anemia. A total of 64.4% male and 35.6% female constituted the study. Among them, in NYHA class I 81.3% are males and 18.8% are females, in NYHA class II 60% are males and 40% are females,in NYHA class III 63.2% are males and 36.8% are females and in NYHA class IV 58.8% are males and 41.2% are females respectively. However, the correlation of gender with heart failure in our case is not significant (p value 0.477) Kilip[8] and Haas [9] have also reported they did not identify significant interaction with sex and is in accordancewith our findings. Iron deficiency in worsening heart failure is associated with reduced estimated protein intake, fluid retention, inflammation, and antiplatelet use.

The mean level of ferritin before OMT is 35.5 ±7.06, 36.5 ±13.59, 31±12.68 and 27.88 ±6.88 ng/ml and after the supplementation of iron and optimal medical therapy mean level of ferritin is 39.81 ±12.08, 40.43±14.41, 33.13 ±14.54, and 32.65 ±9.05 ng/ml, across NYHA class I, II, III and IV respectively and is statistically significant p value 0.051.

The mean level of iron before OMT is 62.75 ±14.37, 57.97 ±13.47, 50.03 ±17.68 and 42.41±8.89 µg/dL and after the supplementation of iron and optimal medical therapy mean level of iron is 71.44 ±24.71, 62.23 ±12.38, 55.05 ±19.47 and 52.53 ±14.06 µg/dL across NYHA class

I, II, III and IV respectively and is statistically highly significant p value <0.0001.

The mean level of transferrin saturation before OMT is 22.94 ±2.59, 21.63 ±2.75, 20.74 ±3.93, &17.53 ±1.91% and after the supplementation of iron and optimal medical therapy the mean level of transferrin saturation is 26.13 ±4.5, 24.13 ±3.89, 22.58 ±5.75 & 19.29 ±2.66% across NYHA class I, II, III and IV respectively and is statistically highly significant p value <0.0001.

In our study, it can be clearly observed that with the progression of advanced heart failure classesthe mean level of iron, ferritin and transferrin is worsening or is very low. The relationship between serum ferritin levels and new onset heart failure appears to be linear. Increasing ferritin levels independently amplify the risk for new onset heart failure.

Orynchak *et* al [10] also reported that worsening NYHA class was associated with lower serum iron, ferritin and transferrin saturation, regardless of anaemia status HF leads to worsening of kidney function by decreasing the stroke volume and thus a lower cardiac output leading to activation of the renin-angiotensin-aldosterone system (RAAS). This creates a low renal perfusion and a decreased eGFR also high central venous congestion due to right ventricular dysfunction leads to a decline in eGFR. In our study, Out of 101 patients, 37.6% have eGFR <60 ml/min and 62.4% have eGFR>60ml/min. In NYHA class I, 12.5% patients have eGFR<60 ml/min and 87.5% have eGFR>60 ml/min. In NYHA class II, 23.3% patients have eGFR<60 ml/min and 76.7% have eGFR>60 ml/min. In NYHA classIII,44.7% patients have eGFR<60ml/min and 55.3% have eGFR>60ml/min. In NYHA class IV,70.6% patients have eGFR<60 ml/min and 29.4% have eGFR>60 ml/min. So across all the NYHA functional class the proportion of patients with eGFR<60 ml/min increases, that is more worsening of kidney functions, which is statistically significant (p value 0.001). Mohinder R Vindhyal and Damman K [11] have reported more worsening of kidney function that with advanced NYHA functional class leading to re hospitalization. With respect to lower Ejection Fraction the patient become more symptomatic according to NYHA functional class. The proportion of patients with EF<40% gradually increases from NYHA functional class I to IV. Among 101 patients 59.4% of patients have LVEF <40% and 40.6 % of patients have LVEF >40% and is statistically highly significant (p value <0.0001). Solomon et al [12] have observed that lower LVEF is associated with adverse cardiovascular outcomes than those with preserved systolic function. LVEF was an important predictor of fatal and nonfatal cardiovascular outcomes, including heart failure death and hospitalization, sudden death, and fatal and nonfatal MI, in a broad spectrum of patients with symptomatic heart failure, but only in those with moderate to severe reductions in left ventricular systolic function. Ejection fraction was a poorer predictor of cardiovascular outcomes in those with an LVEF above 40%.

In our study out of 101 patients,16(100%) patients,27(90%) patients, 31(81.6%) patients, 10(58.8%) patients with no Atrial fibrillation corresponds to NYHA class I,II,III and IV respectively.3 (10%) patients, 7(18.4%) and 7(41.2%) patients with Atrial fibrillation corresponds to NYHA class II,III and IV respectively. Atrial Fibrillation is statistically highly significant across the classes of heart failure (p value 0.009).Our study is in accordance with Steven A. Lubitz et. al study, who have reported that Atrial Fibrillation in patients with systolic left ventricular dysfunction and CHF ranges from 6% for asymptomatic patients or for those with minimal symptoms, to between 15% and 35% for patients with New York Heart Association (NYHA) class II–IV symptoms.

5. Conclusion

Iron deficiency is common in patients with chronic HF, relates to disease severity, and is a strong and independent predictor of outcome. The high prevalence of iron deficiency in patients with chronic HF, even in the absence of anaemia, is now well-established. Despite this, iron deficiency is under diagnosed in HF patients, although it is recognized as a predictor of outcome in chronic HF. Cardiologists should be aware of the consequences of iron deficiency in these patients, and should routinely assess iron status with measurement of serum ferritin and TSAT. Several studies have shown improvement in exercise capacity, NYHA functional class and quality of life after correction of iron deficiency. The results of clinical trials should encourage cardiologists to consider iron deficiency as a therapeutic target in HF. The available evidence indicates that anemia in HF should be considered a marker and not a mediator, and further effort needs to be directed toward establishing the long-term effect of iron supplementation in patients with HF.

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