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Association of Serum Ferritin as a Iron marker in Heart Failure

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Abstract

Introduction: Heart failure is to be considered as a priority as it is a serious, life-threatening disease. Nearly twenty-six million people over the globe are surviving with heart failure at present. Despite the new availability of treatment modalities in heart failure treatment outcome of patients is not so good, prolonged hospital stay, frequent and recurrent admissions in hospital and quality of life are also not good. This study investigated the relationship between ferritin, a marker of iron status, and the incidence of HF in a community.

Results: The mean age was 73.36 ± 7.8 in the study population, the ranged between 48 years to 87 years. 32(32%) participants were heart failure according to Killip's classification of grade 2,33(33%) participants had grade 3 and 35(35%) participants had grade4 the mean pulse rate was 100.87 ± 19.59 in the study population, the ranged between 66 (beats per minute) to 138(beats per minute) in the study population.

Conclusion: Low serum ferritin was significantly associated with higher grades of Killip classification of heart failure.

Keywords: NIL

Introduction

Heart failure clinically defined when the heart fails to complete the metabolic needs of the body. Initially, the patient's body can tolerate small declines in output because the various compensatory mechanisms are presented in the body to overcome this mismatch. With time, these compensatory mechanisms start to have deleterious effects over heart function, and this will lead to further worsening of cardiac output, which will ultimately result in further activation and additional stress on a failing heart. As per the definition of The European Society of Cardiology Heart Failure is a clinical syndrome in which a patient presents with symptoms such as dyspnea, persistent cough, wheezing, bilateral lower limb swelling, and easy fatiguability, which may be associated with the following signs: raised jugular venous pressure; basal crepitations (crackles); tachycardia; and peripheral oedema.[1]Patients with HF frequently have many underlying co-morbid pathological conditions which are responsible for HF progression and symptoms. Iron deficiency and anemia are the most concurrent findings in cases of heart failure. As per World Health Organization guidelines hemoglobin <13 g/dL in men, <12 g/dL in women, considered as anemia, and at present approximately in 33 % of patients with heart failure have anemia.[2]. In a previous meta-analysis study Anemia prevalence was reported as 37.2%, including 153,180 patients with Heart Failure, these results indicate that anemia is a very notable problem in heart failure.[3] Iron deficiency and Anemia have become a principal consideration and a treatment target in heart failure during the last few years and they are associated with the severity of heart failure as well as serving as a prognostic indicator. An Iron deficiency in heart failure the value of serum ferritin levels <100 µg/L or transferrin saturation (TSAT)

less than 20% if the ferritin level is in range of 100-299 µg/L.[4] Primary and secondary causes of iron overload are most common manifestation is cardiomyopathy.[5] In disparity, severe iron deficiency has also been related with abnormalities in systolic and diastolic cardiac function, indicating a U-shaped relationship between body iron stores and the process leading to heart failure (HF).[6]

Heart failure definition and diagnosis

Heart failure can be defined as an oddity of cardiac structure or function responsible for the failure of oxygen delivery by heart at an amount requiring for normal functioning of the tissues for its metabolization in spite of normal filling pressures or only at the cost of increased filling pressures.[7] The diagnosis of Heart Failure can be difficult due to non-discriminating and because of limited diagnostic value of the symptoms of Heart failure.[8]

Diagnosis of heart failure:

Three conditions to be satisfied for the diagnosis of heart failure with reduced ejection fraction (HF-REF) are: -

1. Symptoms which are typically suggestive of Heart Failure.
2. Signs which are typically suggestive of Heart Failure.
3. Reduced Left Ventricular Ejection Fraction (LVEF)

Four conditions to be satisfied for the diagnosis of heart failure with preserved ejection fraction (HF-PEF) are: -

1. Symptoms which are typically suggestive of Heart Failure.
2. Signs which are typically suggestive of Heart Failure.
3. Normal or only mildly reduced Left Ventricular Ejection Fraction (LVEF) and Left Ventricle not dilated.
4. Pertinent underlying structural heart disease (Left Ventricular hypertrophy or Left Atrial enlargement) and diastolic dysfunction.

Killip's classification of heart failure:

In 1967 The Killip classification was first introduced to evaluate the severity of heart failure as a simple clinical tool in cases of myocardial infarction.[9] After that, this classification has been using to and frow to predict mortality of patients with acute myocardial infarction (AMI) in both short and long-term prediction. For e.g., the higher the value of the Killip class at the time of presentation chances of the mortality risk is also very high.[10]

Killip's classification of heart failure post MI.[11]

Table II – Clinical and hemodynamic subgroups in acute myocardial infarction

Killip Subgroup	Clinical characteristics	Hospital mortality
I	No congestion signs	<6%
II	S3, basal rales	<17%
III	Acute pulmonary edema	38%
IV	Cardiogenic shock	81%
Forrester subgroup	**Hemodynamic characteristics**	**Hospital mortality**
I	PCP <18, IC >2.2	3%
II	PCP >18, IC >2.2	9%
III	PCP <18, IC <2.2	23%
IV	PCP >18, IC <2.2	51%

PCP- pulmonary capillary pressure; CI- cardiac index.

Materials And Methods:

This cross sectional study was conducted in the department of General Medicine at Bharati

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Vidyapeeth (Deemed to be University) Medical College & Hospital, Sangli

All the eligible patients with heart failure and cardiomyopathy visiting Department of General Medicine at Bharati Vidyapeeth (Deemed to be University) Medical College & Hospital, Sangli were considered as the study population. Collection of the data for the study was done between January 2019 to June 2020 over a period of 1 year 6 months. Patients with heart failure and cardiomyopathy above 18 years of age who are willing for study were included in this study and patients who had already received iron supplements were excluded.

Anthropometric measurements:

Anthropometric measurements, including height, weight, waist circumference (WC), and blood pressure were obtained when the subject were in light clothing and no shoes, Body mass index (BMI) was calculated by dividing weight (kg) by height squared (m2). Blood pressure was measured twice by using a mercury sphygmomanometer after 10 min of rest, while the subjects were seated, and the average of the two measurements was used for analysis.

Definition groups:

Cardiovascular risk factors were as follows: 1) abdominal obesity, which is define as the presence of WC ≥90 CM IN MEN; 2) impaired glucose homeostasis, which is define as the fasting plasma glucose (FPG) ≥5.6 mmol/L and/or 2h plasma glucose (PPG- 2h) ≥7.8mmol/L; 3) Dyslipidemia, serum triglycerides (TG) ≥1.7 mmol/L, and/or serum high-density lipoprotein

cholesterol (HDL- C) <0.9 mmol/L in men; and 4) Blood pressure ≥ 130/85 mmHg. Subjects were considered to have clustering of cardiovascular high-risk factors when they had at least two of the above-mentioned four traits. History of MI or stroke was defined as a self-reported condition requiring hospitalization for at least 3 days.

Results:

Classifying of patients according to Killip's classification for heart failure:

All patients willing to take part in the study was classified according to Killip's classification[12], for heart failure:

1. Killip class I include individuals with no signs of heart failure.
2. Killip class II includes individuals, with rales or crackles in the lungs, and S3, and elevated jugular venous pressure
3. Killip class III describes individuals with frank acute pulmonary edema
4. Killip class IV describes individuals in cardiogenic shock or hypotension (measured as systolic blood pressure lower than 90 mmHg), and evidence of peripheral vasoconstriction (oliguria, cyanosis or sweating).

Ferritin measurement and definition of iron status

The immunoturbidimetric assay is used in the measurement of serum Ferritin level.

At −70 °C samples were frozen after collection of Plasma samples at visit 1. 3.4 ng/mL is the lower most limit of detection of ferritin.

Categorization of Participants was in three different groups as per ferritin serum levels:

low ferritin is said when serum levels below 30 ng/mL).

Normal ferritin levels are said when serum levels are 30–200 ng/mL in the female population and 30–300 ng/mL in male population;

and high ferritin is to be called when serum values are higher than 200 ng/mL in the female population and higher than 300 ng/mL in male population.

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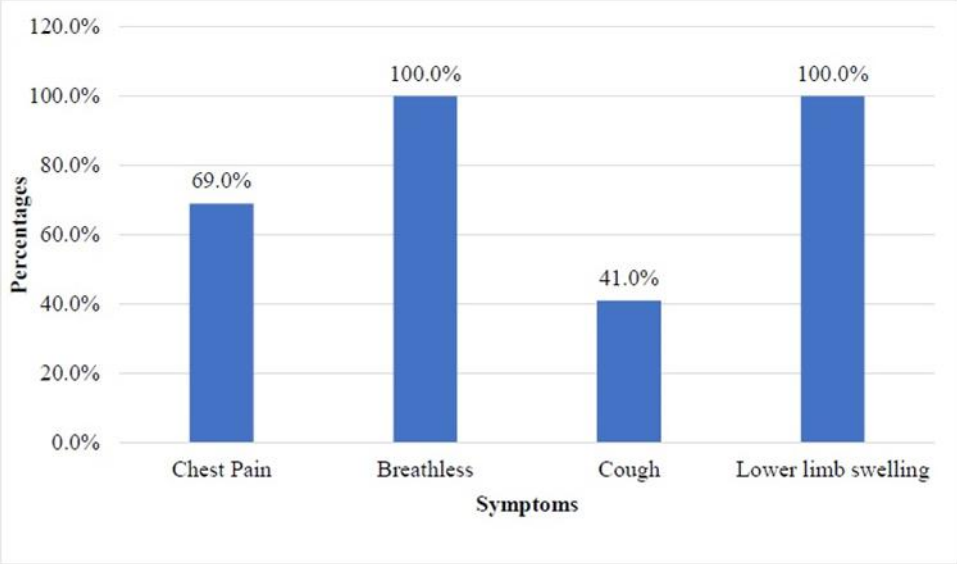
Table 1: Symptoms

Symptoms	Frequency	Percentages
Chest Pain	69	69%
Breathless	100	100%
Cough	41	41%
Lower limb swelling	100	100%



Among the study population, 69(69%) participants had chest pain, 100(100%) participants had breathless,41(41%) participants had a cough, and 100(100%) participants had lower limb swelling.

Table 2: Heart failure according to Killip's classification

Heart failure according to Killip's classification	Frequency	Percentages
Grade 2	32	32.00%
Grade 3	33	33.00%
Grade 4	35	35.00%

Among the study population, 32(32%) participants were heart failure according to Killip's classification of grade 2,33(33%) participants had grade 3 and 35(35%) participants had grade 4

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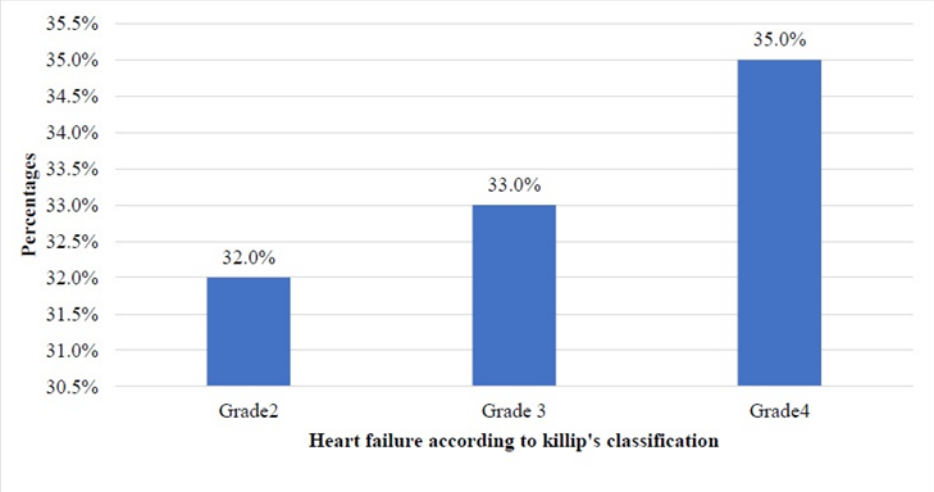
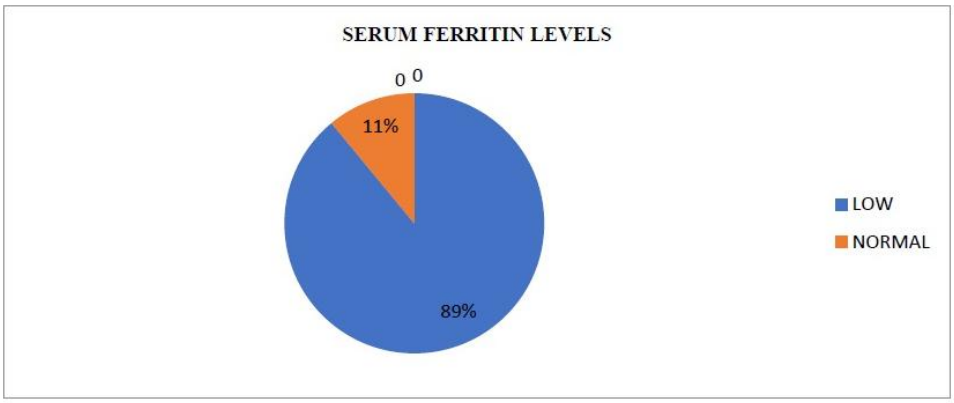


Table 3:

Serum Ferritin Levels	Frequency	Percentages
Low	89	89.00%
Normal	11	11.00%



Among the study population, 89 (89%) participants had low, and 11(11%) participants had Normal.

Table 4: 2Decho (LVEF)

Parameter	Mean ± SD	Minimum	Maximum
2Decho (LVEF)	40.05 ± 9.44	30.00	60.00

The mean 2D echo was 40.05 ± 9.44in the study population. They ranged between 30 to 60 in the study population

Table5: Serum Ferritin levels

Parameter	Grade 2 Median (IQR)	Grade 3 Median (IQR)	Grade 4 Median (IQR)	Kruskal Wallis test (P value)
Serum ferritin levels	25 (21.25, 29)	21 (18, 26)	22 (17, 25)	0.029*

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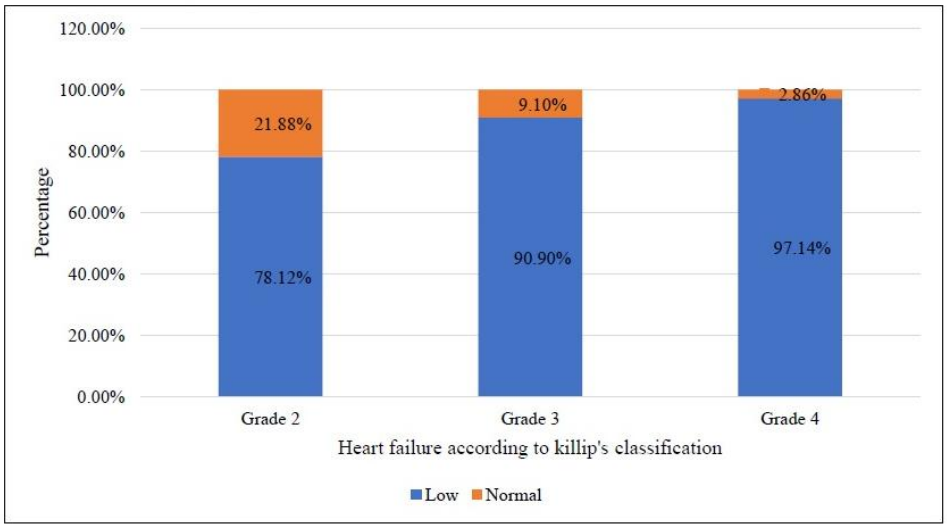
Among the people with heart failure according to Killip's classification, grade 2 median was 25(ng/mL) (IQR 21.25 to 29) of serum ferritin levels, grade 3 median was 21 (ng/ml) (IQR 18,26), and grade 4 median was 22 (ng/ml) (IQR 17,25). The difference in the median age across heart failure to Killip's classification was statistical significance (P Value 0.029

Table 6: Association between Serum Ferritin levels and heart failure according to Killip classification

Serum Ferritin Levels	Heart Failure According to Killip Classification			Chi square	P value
	Grade 2 (N=32)	Grade 3 (N=33)	Grade 4 (N=35)		
Low	25 (78.12%)	30 (90.90%)	34 (97.14%)	6.35	0.041 *
Normal	7 (21.88%)	3 (9.1%)	1 (2.86%)		



Among the people with heart failure as per the Killip classification of grade 2, 25 (78.12%) people had low and 7 (21.88%) normal. Among the people with heart failure as per the Killip classification of grade 3, 30 (90.90%) people had low and 3 (9.1%) normal. Among the people with heart failure as per the Killip classification of grade 4, 34 (97.14%) people had low and 1 (2.86%) normal. the difference in the proportion of serum ferritin levels across heart failure to Killip classification was statistically significant (p value 0.041).

Discussion

the mean age of diagnosis of HF was 70 years, and a greater incidence of HF in men at all ages, similar to our study.[12] Similarly, the American Heart Association (AHA) in 2016 found an increased incidence of HF in men with 52.9% and in women with 47.1%.47 A prospective Indian study by Sharma KS et al[13], with 150 subjects also found an increased incidence of HF in men (68%) compared to females (32%) with a mean age of 63.3 ± 14.4 years. The clinical presentation among our study population showed breathlessness and lower limb swelling in 100%, chest pain in 69%, cough in 41%. According to the Killip's classification of the grade of heart failure, the study population; 35% had grade 4, and 33% had grade 3 and 32% had grade 2. It is very crucial to note the symptom history as it indicates the severity of heart failure; for example, the severity of symptoms relates to deprived ventricular function. However, even mild symptoms have shown to be associated with risk of death and hospitalization.[14] The symptoms can also change its course from mild to all of a sudden shift to breathlessness at rest and taking a course of arrythmias and developing

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pulmonary edema. Worsening of clinical symptoms also indicate a greater risk of death and immediate medical help.[7] Use of The Killip's classification to describe the severity of the patient's condition in view of heart failure and the acute cases of post-myocardial infarction.[15]

The mean value of serum ferritin levels was 33.61 ± 41.76 in the study population; the ranged between 9 (ng/mL) to 223 (ng/mL). The incidence of low serum ferritin was 89% in our study population. In contrast, the association of serum ferritin levels in carotid artery atherosclerosis was studied by Haiyan Xu et al.[16] Heart failure can be explained by many different pathophysiological means in respect to a low serum ferritin level. There is a reduction in amount and activity of muscular oxidative enzymes and respiratory proteins which causes impairment of cellular energy production capacity in cases of iron deficiency.[17] Ultimately leading to structural changes such as irregularities in sarcomere organization and mitochondrial swelling.[6] In our study, we considered low-normal' ferritin group, with a cut-off of ferritin levels between 30 ng/mL and 100 ng/mL had no risk of HF but lower than 30ng/ml was shown to be associated with HF. Further few studies[18,19], have also shown no association of high serum iron with the incidence of Acute Coronary artery disease as serum iron levels were high in-group without atherosclerosis. Case study by Carolyn S.P. Lam et al[20], found low serum ferritin (<100 µg/L) to be associated with heart failure. Similarly, Silvestre, O et al[34], also found low serum ferritin <30ng/ml to be at greater risk of heart failure. In another study by Hiroki Nakano et al[21], found an increased death rate in heart failure patients with serum ferritin levels less than 100 µg/L. Among the study population, 89 (89%) participants had low, and 11(11%) participants had Normal. Among the study population, 93 (93%) participants had Raised JVP and 7 (7%) participants had Normal. The mean 2D echo was 40.05 ± 9.44 in the study population. They ranged between 30 to 60 in the study population. Among the people with heart failure according to Killip's classification, grade 2 median was 25 (ng/mL) (IQR 21.25 to 29) of serum ferritin levels, grade 3 median was 21 (ng/ml) (IQR 18,26), and grade 3 median was 22 (ng/ml) (IQR 17,25). The difference in the median age across heart failure to Killip's classification was statistical significance (P Value 0.029). The difference in the proportion of serum ferritin levels across heart failure to Killip classification was suggestive of statistically significant (p value 0.041).

Conclusion

Derangements in iron metabolism, as evidenced by either low or high ferritin serum levels, were associated with a higher risk of incident heart failure when compared with normal ferritin levels in this study population. These findings suggest that iron imbalance may play a role in the incidence of HF.

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