International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Anaemia Profile in Patients with Congestive Heart Failure in a Tertiary Care Centre in Kerala

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Abstract: ***Anaemia and Renal failure seem to be major risk factors recognized in the pathophysiology and progression of Congestive Heart Failure (CHF) with an adverse outcome. The cardio renal anaemia syndrome (CRAS) represents a pathological triangle in which the primary failing organ is the heart or the kidney and the dysfunction of one organ leads to dysfunction of the other (3)(4). The presence of anemia increases morbidity and mortality in patients with heart failure. It seems that there is an impaired mechanism operating between congestive heart failure, chronic kidney disease (CKD), and anemia, where each might cause or worsen the other. Anemia is independently associated with increased mortality and hospitalizations in patients with both Heart Failure with reduced Ejection Fraction (HFrEF) and HF with preserved ejection fraction. Therefore, correction of anemia would be a major part of this vicious circle in the reduction of the severity of the heart failure. This could be explained by the fact that a significant feature of congestive heart failure is impaired energy metabolism and therefore the failing heart is an energy-starved heart. Oxygen delivery through haemoglobin (Hb) is essential for energy production and improvement of Hb levels could also improve energy production in cardiomyocytes. (5) .This study is aiming to find the prevalence of anemia in heart failure in our set up.***

Keywords: Anemia, HFREF, Iron deficiency

1. Introduction

Heart failure is an enormous medical and societal burden and a leading cause of hospitalization. The overall prevalence of HF is thought to be increasing, in part because current therapies for cardiac disorders (e.g., myocardial infarction, valvular heart disease, arrhythmias) are allowing patients to survive longer. Worldwide, HF affects almost 23million people. Estimated prevalence of symptomatic HF in the general European population is similar to that in the United States and ranges from 0.4% to 2%(1).The current estimates about incidence of HF in India vary widely from 1.3 to 23 million as reported by Trivandrum Heart Failure Registry(2).

Anaemia and Renal failure seem to be major risk factors recognized in the pathophysiology and progression of Congestive Heart Failure (CHF) with an adverse outcome. The cardio renal anaemia syndrome (CRAS) represents a pathological triangle in which the primary failing organ is the heart or the kidney and the dysfunction of one organ leads to dysfunction of the other(3)(4).The presence of anaemia increases morbidity and mortality in patients with heart failure. It seems that there is an impaired mechanism operating between congestive heart failure, chronic kidney disease (CKD), and anemia, where each might cause or worsen the other. Anemia is independently associated with increased mortality and hospitalizations in patients with both Heart Failure with reduced Ejection Fraction (HFrEF) and HF with preserved ejection fraction. Therefore, correction of anaemia would be a major part of this vicious circle in the reduction of the severity of the heart failure. This could be explained by the fact that a significant feature of congestive heart failure is impaired energy metabolism and therefore the failing heart is an energy-starved heart. Oxygen delivery through haemoglobin (Hb) is essential for energy production and improvement of Hb levels could also improve energy production in cardiomyocytes. (5)

There is a paucity of data available about the prevalence and characteristics of anaemia in CHF patients in India. Previous Indian studies have found prevalence of anemia to vary considerably from 4%–55 % (6). However, not much is known about the prevalence, predictors, and prognosis of Iron Deficiency (ID) in patients with Congestive Heart Failure (CHF). ID is common in patients with heart failure, relates to disease severity, and is a strong and independent predictor of outcome (7). The present study was designed to know the prevalence of this important comorbidity and that of underlying nutritional deficiencies (Serum Iron, Vitamin B12 and Folate) in patients of CHF.

Aim of the study

- To evaluate Anemia profile in patients with Congestive Heart Failure.
- To evaluate clinical and laboratory profile of anemic and non anemic group

2. Materials and Methods

Study Setting

Government TD Medical College, Alappuzha is a tertiary level multispecialty Hospital in the coastal South India. Cardiac care is available 24hours, 7 days a week in Department of Cardiology . Patients coming to the institute either in OPD or in wards with CHF will be subjected to thorough clinical evaluation and complete laboratory evaluation for anemia profile.

Study Design

Descriptive Observational Study

Study Period

The study was conducted during 6 months period after ethical committee clearance.

Study Population

Sample size: Considering the prevalence of anemia in CHF patient as 37% (10-49%) from previous reference studies

and keeping α=0.05, for power of 90% a minimum sample size of 171 is assigned. In this study 200 patients were taken as sample size.

Inclusion Criteria

All consecutive patients having clinical criteria for heart failure (according to the Framingham criteria), who were 18 years or older in age and were in New York Heart Association (NYHA) functional class II- IV of more than three months duration at the time of enrolment were included in this study.

Diagnostic Criteria for Heart Failure (HF) in Population-Based Studies (FRAMINGHAM CRITERIA)

Major Criteria

1) Paroxysmal nocturnal dyspnea or orthopnea
2) Neck vein distension
3) Rales
4) Cardiomegaly
5) Acute pulmonary edema
6) S3 gallop
7) Increased venous pressure >16 cm H2O
8) Hepatojugular reflux

Minor Criteria

1) Ankle edema
2) Night cough
3) Dyspnea on exertion
4) Hepatomegaly
5) Pleural effusion
6) Vital capacity decreased One-third from maximal capacity
7) Tachycardia (rate >120/min)

Major or Minor Criteria

1) Weight loss >4.5 kg in 5 days in response to treatment

The diagnosis of HF using the Framingham criteria requires the simultaneous presence of at least 2 major criteria or 1 major criterion in conjunction with 2 minor criteria. Minor criteria are acceptable only if they cannot be attributed to another medical condition (e.g., Pulmonary Hypertension, Chronic Lung Disease, Cirrhosis, Ascites, Nephrotic Syndrome).[18]

Exclusion Criteria

Exclusion criteria are:

1) Acute coronary syndrome with heart failure.
2) Severe comorbidities like Chronic Kidney Disease, Chronic Lung Disease, Chronic Liver Disease, Nephrotic Syndrome.
3) Complex Cyanotic Congenital Heart Diseases.
4) Known malignant, haematological or other active neoplasia.
5) Immunosuppressive therapy, chemotherapy or radiotherapy within 3 months prior to enrolment.
6) Pregnant women

Methods

All consecutive patients having clinical criteria for heart failure (according to the Framingham criteria), who were 18 years or older in age and were in NYHA functional class II-IV for more than 3 month duration at the time of enrolment were included in this study.

Baseline Clinical and Laboratory Assessment

History and Clinical examination

In all enrolled patients satisfying the inclusion criteria, a detailed history was taken and complete physical examination was conducted by the investigator.

At time of admission, detailed history with special emphasis on time of onset and duration of heart failure, drug history, past history of Coronary Artery Disease (CAD), Type 2 Diabetes mellitus (T2DM), Hypertension (HTN), Bleeding disorder, Chronic Kidney Disease (CKD), Family history of CAD was taken.

Upon recruitment, all the patients underwent the Baseline clinical evaluation and following laboratory evaluation:

1) Haemoglobin concentration
2) Haematocrit
3) Mean corpuscular volume
4) Mean corpuscular haemoglobin concentration
5) Red cell distribution width
6) Serum iron concentration
7) Serum transferrin saturation
8) Serum ferritin saturation
9) Total iron binding capacity
10) Serum vitamin B12 level
11) Serum folate level

Definition of Anemia, iron, Vit B12 and folate deficiency

1) Haemoglobin<13 gm/dl (males) and < 12 gm/dl (females) - Anemia (WHO criteria)
2) Serum ferritin < 100 ng/ml- ID
3) Serum ferritin 100–300 ng/ml with transfer in saturation < 20%- ID
4) Serum Vit B12 < 200 pg/ml- Vitamin B12 deficiency
5) Serum folate< 4 ng/ml – Folate deficiency

Outcomes measurement: The study population was categorized into two groups;

1) Anemic Group
2) Non-anemic Group.

Each group was further sub categorized as having iron, B12 or folate deficiency or combined iron and B12/folate deficiency according to the definitions.

Follow up:
All patients included in the study were followed up at 30 day on OPD or telephonic basis. During follow up evaluation, patients were evaluated on basis of heart failure symptoms and anemia profile.

Statistical methods
Statistical testing was conducted with the statistical package for the social science system version SPSS 22.0. Data was presented as Mean, Standard deviation (SD), frequencies and percentages. All variables were expressed as mean±standard deviation. The Chi-square test was used to analyse categorical variables. Student's *t* test and analysis of variance was used for continuous variables.

Ethical Consideration
Study was conducted after getting approval from Institutional Research Committee. A written informed consent was taken from all patients / relatives participating in the study.

3. Results

200 patients admitted to hospital with clinical diagnosis of HF were studied, out of which 132 (66%) were males and 68 (34%) were females. Mean age of the study subjects was 59.12 years, mean EF of 38.5%.

Baseline Characteristics of Study Population:

Table 1

Total Patients	200
Males	132(66%)
Females	68(34%)
Mean Age	59.12
Males	59
Females	59.6
Age Group	
<50 YRS	56(28%)
50-70 YRS	112(56%)
>70 YRS	32(16%)
NYHA FC- MEAN	
NYHA FC I, II	64(32%)
NYHA FC III	90(45%)
NYHA FC IV	46(23%)
DM	88(44%)
Hypertension	72(36%)
Ischemic Heart Disease	136(68%)
Non Ichemic Heart Disease	64(32%)
Ejection Fraction -Mean	
<30%	42(21%)
31-40%	86(43%)
40-55%	34(17%)
>55 %	38(19%)
Atrial Fibrillation	38(19%)

Diabetes mellitus was seen in 88 (44 %) patients. Hypertension was seen in 72 (32%) patients. Ischemic cardiac disease was the predominant cause of heart failure constituting 68% (136) of patients and non-ischemic cause of heart failure seen in 32% (64) patients.

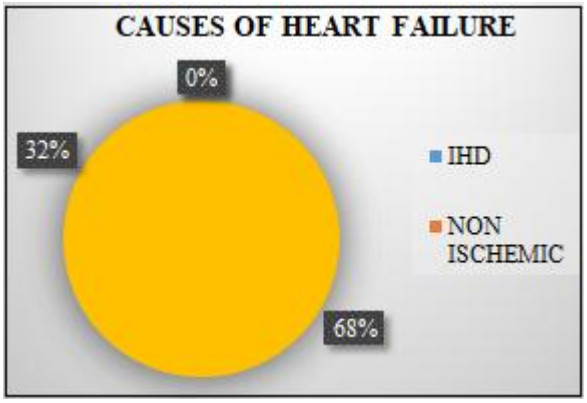


Table 2

	Anemic- 98 (46%)	Non Anemic - 102(54%)
Iron Deficeincey	54(27%)	30 (15%)
S.VIT B12 DEF	22(11%)	6(3%)
S. Folate DEF	12(6%)	2(1%)
Combined DEF	10(5%)	4(2%)

Overall, 46 % patients had anemia. In the anemic group, ID was found in 27% patients, 11% patients had Vitamin B12 deficiency and 12% patients had Folate deficiency. In the non-anemic group, ID was present in 15%, B12 deficiency seen in 3% and Folate deficiency seen in 1% of patients. Out of 200 patients, Vitamin B12 deficiency is seen in 14 % and Folate deficiency is seen in 7% of patients.

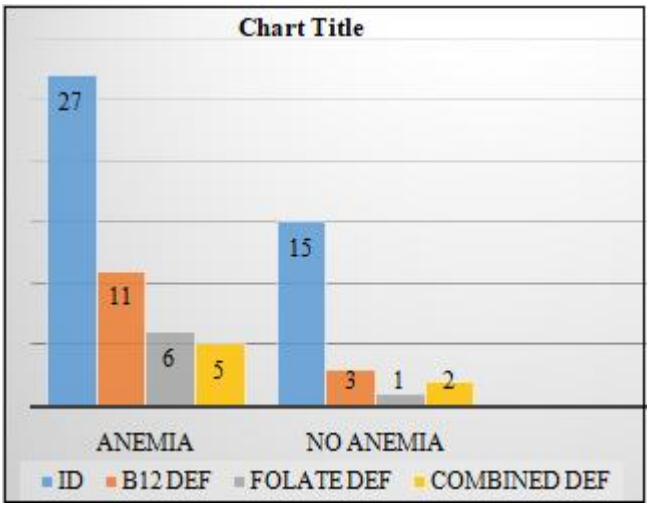
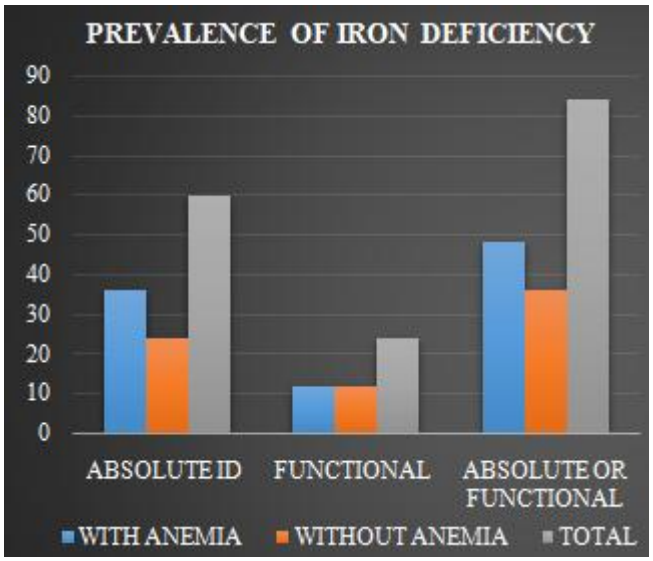


Table 3

	Males (132)	Females (68)	Total (200)
Absolute ID	36(27.27%)	24 (35.2%)	60(30%)
With anemia	26	14	40(20%)
Without anemia	10	10	20(10%)
Functional ID	12 (9.9%)	12(17.6%)	24(12%)
With anemia	6	8	14(7%)
Without anemia	6	4	10 (5%)
Absolute or functional ID	48 (36.6%)	36(52.9%)	84(42%)
With anemia	32	22	54(27%)
Without anemia	16	14	30(16%)

Absolute ID (serum ferritin < 100 mg/L) was present in 60 (30%) patients. Absolute ID with anemia (Hb< 13 g% for male and <12 g% for females) was present in 40 (20%) patients.Functional ID (serum ferritin 100–300 mg/L with TSAT < 20%) was present in 24 (12%) patients and

functional ID with anemia was present in 14 (7%) patients. Thus ID (either absolute or functional) was found in 84(42%) patients and ID with anemia was present in 54 (27%) patients



4. Discussion

Anemia is commonly present in CHF patients. ID in CHF isassociated with reduced iron stores in the bone marrow and the heart. ID is an independent risk factor for severity and worsening of the CHF.

Epidemiology of Anemia in CHF

A recent meta-analysis of 153, 180 patients with CHF, reported in 34 published studies from 2001 to 2007, estimated the prevalence of anemia to be 37.2% (10-49%). Estimates of the prevalence of anemia in patients with CHF and low ejection fraction range widely from 4% to 61% (median 18%) (8, 9).

In our study, we found the prevalence of ID being 42% which is correlated with the prevalence in STAMINA-HFP (Study of Anemia in a Heart Failure Population) Registry which estimated a prevalence of 34% (10). But prevalence of anemia is less compared to Arora et al study which was done in 275 patients and showed a prevalence of 76.7%(6) .

Iron Deficiency, Vitamin B12 Deficiency and Folate Deficiency

200 patients were enrolled in our study and complete evaluation of anemia was done. Our study found 46% prevalence of anemia as defined by the WHO criterion (Hb<13 gm/dL in males and < 12 gm/dL in females). Iron Deficiency was found in 42% patients in our study. The prevalence of ID was similar to that described by McDonagh et al (12), but it was lower than that described in a recent study by Sharma et al (13). This study had included 150 CHF patients and Iron Deficiency was present in 76% of the patients (Table 3). Our values are comparable to study done by Vander al Wal (14) which showed Iron Deficiency, vitamin B 12 deficiency, Folate deficiency of 58%, 4%, 5% respectively

In comparison to the study by Sharma et al, we also measuredthe prevalence of vitamin B12 and Folate deficiency in our patients.

Overall, 14% patients had vitamin B12 deficiency (defined asserum vitamin B12 < 200 pg/ml) and 7 % patients had Folate Deficiency (i.e. serum folate<4 ng/ml). Combined deficiency is seen in 7% of patients.

Pathophysiology of Anemia in CHF

The major factors contributing to CHF-related anemia involve CKD, renin-angiotensin system, hematinic abnormalities; mainly iron deficiency, chronic inflammation, and hemodilution (Figure 1).

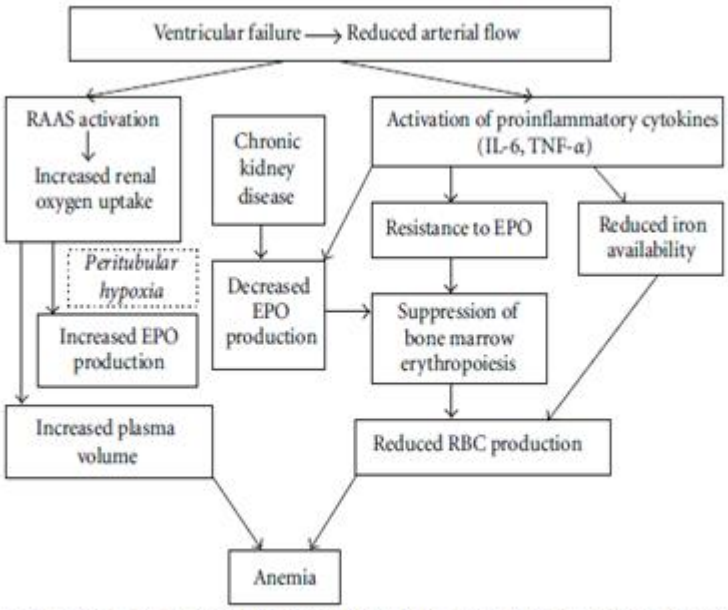


FIGURE 1: Pathophysiological mechanisms contributing to anemia in chronic heart failure patients. *(RAAS: renin-angiotensin-aldosterone system, IL-6: interleukin-6, TNF-α: tumor necrosis factor alpha, EPO: erythropoietin, RBC: red blood cells).*

Anemia in CHF is multifactorial. Two major factors contributing and exacerbating to its appearance are kidney dysfunction and iron deficiency. In 2003 this abnormality was described as cardio renal anemia syndrome (CRAS) (17), whereas the correction of anemia could play a major role in this vicious circle in improving the severity of CHF. In the last years, the role of iron has been recognized, as a major component of many energy-producing systems. In view of a possible independent association of iron deficiency and cardiac failure, renal failure and anemia, the same authors renamed the syndrome as cardio renal anemia iron deficiency (CRAID) syndrome (17).

Treatment of Anemia in CHF

CHF is not just a hemodynamic disorder. It is the final common pathway of other conditions, where renal failure and anemia contribute to the progression to a more severe disease status. They also could be potential targets for intervention. Since the two major components of CHF anemia are iron deficiency and reduced EPO activity (absolute or functional in both cases), the main goals of intervention would be to increase their levels. Anemia treatment strategies in heart failure patients include erythropoiesis-stimulating agents (ESAs) and Iron replacement(18). The role of blood transfusions remains understudied and unclear(19–21).Based on the results of the randomized trials with intravenous (IV) iron supplementation, the current American College of Cardiology, American Heart Association, and Heart Failure Society of America (ACC/AHA/HFSA) guidelines recommend (class IIb, level of evidence B-R) that IV iron replacement might be reasonable in patients with NYHA Class II and III HF and iron deficiency (ferritin <100 ng/mL or 100 to 300 ng/mL if transferrin saturation <20%) to improve functional status and quality of life(22)

5. Limitations of the Study

1) This study is a prospective observational study conducted at a tertiary care centre in South Kerala. It is difficult to generalize the findings for our entire nation with different cultures and food habits, necessitating multicenter large-scale studies.
2) No controls were taken to compare Iron Deficiency in subjects with or without Heart Failure.
3) Heart failure with reduced and preserved ejection fraction are included in the study. There is no separate analysis for HFpEF and HFrEF.
4) This was an observational study, so effect of iron supplementation on improvement of NYHA class could not be analysed.

6. Conclusion

Our study highlights the underestimated Iron Deficiency in Heart Failure patients and importance of doing complete iron profile in heart failure patients. This study suggests there is need to do large-scale studies for better evaluation of this easily treatable condition.

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