HAYDARPAŞA NUMUNE MEDICAL JOURNAL

DOI: 10.14744/hnhj.2023.03271
Haydarpasa Numune Med J 2024;64(2):179–186

ORIGINAL ARTICLE

Types of Anemias and Iron Deficiency Frequency in Hospitalized Patients with Decompensated Heart Failure: Internal Medicine Clinic Experience

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Abstract

Introduction: One of the most common comorbid conditions in heart failure is iron deficiency and anemia. Because the patients are mostly elderly and have comorbidities, many examinations cannot be performed for the etiology of anemia, and it is accepted as chronic disease anemia caused by chronic diseases. However, iron deficiency can occur frequently in these patients with or without anemia. We conducted this study to investigate this frequency in heart failure patients hospitalized in the internal medicine service.

Methods: This retrospective study comprised one hundred patients with decompensated heart failure (72.2±10.4 years; F/M: 41/59). Measurements of serum iron, ferritin, folic acid, vitamin B12, lactate dehydrogenase, bilirubin, reticulocyte, hemogram parameters, creatinine, ejection fraction, and cardiothoracic index of these patients were recorded from patients' files. The ESC 2016 guideline was used for the diagnosis of heart failure and diagnosis of iron deficiency in patients with heart failure.

Results: A total of 26 patients were NYHA III (26%), 74 patients were NYHA IV (74%), 16 patients were stage C (16%), and 84 patients were stage D (84%). Anemia was detected in 62 patients (62%), iron deficiency anemia in 45 patients (45%), and anemia of chronic disease in 56 patients (56%). Iron deficiency was present in 70% of all patients. Iron deficiency was found to be statistically significant in patients with coronary artery bypass graft ($p<0.05$).

Discussion and Conclusion: Considering that the functional capacities and quality of life of patients with intravenous iron therapy increase in patients with chronic heart failure, we suggest that more attention should be paid to the investigation and treatment of the etiology of anemia in this patient group.

Keywords: Anemia; heart failure; iron deficiency.

Chronic heart failure (CHF) is a disease with an increasing incidence and prevalence among the elderly. Despite advances in diagnosis and treatment, the prognosis remains poor[1-4]. The prevalence of heart failure is becoming an increasingly important public health problem due to the patients' low quality of life, high hospitalization rates, and poor prognosis[5-6]. Diseases accompanying heart failure negatively affect the clinical course, worsen the prognosis, complicate treatment, and control of the clinical picture. For this reason, the treatment and control of comorbid conditions along with the treatment for heart failure are emphasized. One of the most common

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Submitted Date: 01.11.2022 **Revised Date:** 01.11.2022 **Accepted Date:** 05.01.2023
Haydarpaşa Numune Medical Journal

comorbid conditions in heart failure is iron deficiency and anemia[7-10].

Anemia in CHF patients has many etiological causes and is associated with increased mortality in heart failure patients[3,4]. In various studies involving different patient populations and demographic characteristics, the incidence of anemia in CHF patients has been reported to be between 30% and 70%[11]. As the severity of CHF increases, the prevalence and severity of anemia also increase. The main causes of anemia in patients with CHF include malnutrition, concomitant renal failure, low erythropoietin (EPO) levels, bone marrow depression, erythropoietin resistance, increased oxidative stress, inflammation caused by tumor necrosis factor-alpha released during the CHF process, aspirin use, atherosclerosis, gastrointestinal iron loss, proteinuria, EPO loss, and parallel hemodilution with increased plasma volume[4,5].

Anemia, as defined by the World Health Organization (WHO) for the healthy population, is a hemoglobin (Hb) concentration of less than 13 g/dL in men and less than 12 g/dL in women[2,11]. Although anemia is a common condition in HF patients, a direct causal link with the presence of HF or other comorbidities has not yet been established[2]. Current data suggest that iron deficiency (ID) and anemia are common in both reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF) heart failure[7,12]. Additionally, iron deficiency and anemia in heart failure are independent predictors of poor prognosis.

The prevalence of iron deficiency, with or without anemia, in heart failure is reported to be 37% - 61%. Furthermore, iron deficiency is reported as an indicator of poor prognosis, independent of anemia. With or without anemia, mortality is four times higher in patients with iron deficiency than in those without iron deficiency. This indicates that iron deficiency is a stronger prognostic indicator than anemia[1]. Studies have shown that intravenous (IV) iron therapy (200 mg ferric carboxymaltose) improves cardiac function, exercise tolerance, and in this way increases quality of life and reduces symptoms without causing side effects in patients with class II and III heart failure and iron deficiency[7,13].

Another cause of anemia is chronic renal failure (CRF). Studies have found an association between anemia and chronic renal failure. CRF is one of the independent and strong predictors of anemia. The hemoglobin level decreases in parallel with the degree of renal dysfunction[1,4]. Diabetic patients have a higher prevalence of anemia compared to non-diabetic patients[1].

The Internal Medicine clinic, where the study was conducted, frequently encounters patients with decompensated heart failure, and among them, anemia is commonly seen. However, due to the elderly age and comorbidities of the patients, the etiology of the anemia is difficult to pinpoint and is generally attributed to chronic diseases. The most common type of anemia found in the world is iron deficiency anemia, and the symptoms of patients with iron deficiency with or without anemia in heart failure with IV iron treatment decrease. The present study aimed to investigate the frequency and type of anemia in patients with New York Heart Association (NYHA) class III–IV and American College of Cardiology / American Heart Association (ACC/AHA) stage C-D in hospitalized patients with decompensated heart failure in the Internal Medicine clinic.

Materials and Methods

Study Design and Patients' Selection

In this single-center retrospective cross-sectional observational study, patients hospitalized in the Internal Medicine clinic of Health Sciences University Haydarpaşa Numune Health Application and Research Center, Türkiye, who were diagnosed with decompensated heart failure, were studied. The study included patients who were admitted between October 2015 and December 2016. The study was carried out after the approval of the institutional Ethics Committee (HNEAH KAEK 2016/KK/118) and conducted in accordance with the Declaration of Helsinki.

Inclusion Criteria

A total of one hundred consecutive patients diagnosed with decompensated heart failure, according to NYHA (class III-IV) and ACC/AHA (stage C-D), were recruited for the study.

Exclusion Criteria

Patients younger than 18 and older than 90, who were pregnant, received a blood transfusion, had acute bleeding, NYHA class I-II, and ACC/AHA stage A-B were excluded from the study.

Patients' age, gender, physical examination, medications used before hospitalization, etiology of heart failure, comorbidities accompanying heart failure were recorded. Echocardiographic findings (ejection fraction [EF], heart valve disease, pulmonary artery pressure [PAP]), teleradiography (cardiothoracic index, pleural effusion) and complete blood count parameters, iron, iron-binding capacity, total iron-binding capacity, transferrin saturation, ferritin, vitamin

B12, folate, indirect bilirubin, lactate dehydrogenase (LDH), reticulocyte, corrected reticulocyte count, direct Coombs, haptoglobin, creatinine, sodium, and B-type natriuretic peptide (BNP) levels were recorded when patients were initially admitted to the hospital. If hemoglobin was <12 g/dL in women and <13 g/dL in men, it was accepted as anemia. Anemia was classified according to mean corpuscular volume (MCV), <80 fL as microcytic, between 80 and 100 fL as normocytic, and >100 fL as macrocytic anemia.

According to the European Society of Cardiology (ESC) 2016 guidelines for the diagnosis of iron deficiency in patients with heart failure, iron deficiency was considered present in patients with serum ferritin lower than 100 ng/dL, or serum ferritin between 100-299 ng/dL and transferrin saturation <20%[14].

Based on the reference values of the hospital laboratory, if B12 level was higher than 187 pg/mL, a diagnosis of B12 vitamin deficiency was established, and if folate level was lower than 3 ng/mL, a diagnosis of folate deficiency was made. In patients with high levels of indirect bilirubin and LDH, hemolytic anemia was diagnosed based on the corrected reticulocyte count, haptoglobin, and direct Coombs test values. Anemias that were not included in these groups and were not investigated further were classified as other anemias.

Patients were classified according to NYHA classification as III-IV[14], according to ACC/AHA as grade C-D[14], according to EF as reduced EF (less than 40%), mid-range (gray zone) EF (40-49%), preserved EF (50% and above), according to pulmonary artery pressure as 26-35 mmHg, 36-45 mmHg, and above 45 mmHg. Glomerular filtration rates (GFR) of patients were calculated using the MDRD (Modification of Diet in Renal Diseases Study) formula for patients with chronic renal failure (GFR = 186 x (serum creatinine)$^{-1.154}$ x (age)$^{-0.203}$ x (x 0.742 if female) (x 1.212 if Black race)).

Patients with chronic renal failure were those with glomerular filtration rates <60 mL/min/1.73 m^2 and with grade 3-4-5 chronic renal failure. Patients with heart failure concomitant chronic renal failure were also classified according to ferritin levels.

Statistical Analysis

Descriptive statistics were used to describe continuous variables (average, standard deviation, minimum, median, maximum). The Chi-Square test (or Fisher Exact test where appropriate) was used to examine the relationship between categorical variables. The statistical significance level was set at 0.05. The analyses were carried out using MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2013).

Results

One hundred patients (72.2±10.4 years; female/male: 41/59), aged 18-90 years, who were NYHA III-IV grade C-D with decompensated heart failure and hospitalized in the internal diseases service, were retrospectively included in this study. Baseline clinical characteristics, accompanying diseases, telecardiography, and echocardiographic findings of the patients and control group are shown in Table 1. The most common accompanying disease in patients with heart failure and anemia was diabetes mellitus, affecting 50% of patients. Eleven percent of the patients had multiple chronic diseases.

Hypertension (79%), and coronary artery disease (53%) were the most common etiologies of heart failure (Table 2). Pleural effusion was present in 76% of the patients. The

Table 1. Baseline clinical characteristics, accompanying diseases and telecardiography findings

Age (Years)	72.2±10.4
Female/Male (n)	59/41
Multiple disease (n)	11
Chronic Renal Failure (n)	35
Chronic Obstructive Pulmonary Disease (n)	20
Asthma bronchiale (n)	12
Leukemia (n)	2
Solid malignancy (n)	4
Diabetes Mellitus (n)	50
Thalassemia (n)	1
Cirrhosis (n)	2

Table 2. Etiology of heart failure (n)

Hypertension	79
Myocardial Infarction	26
Coronary Artery Diseases	53
Heart Valve Diseases	7
Heart Muscle Diseases	2
Congenital Diseases	0
Diabetes Mellitus	50
Hyperthyroidism	0
Arrhythmias	39
Atrial Fibrillation	34
Tachycardia	1
Surgical Intervention	1
Pulmonary Embolism	2
Cardiothoracic Rate>%50	98
Pleural effusion	76

cardiothoracic ratio was above 50% in 98% of the patients.

Patients' heart failure degree according to NYHA classification and ejection fraction are shown in Table 3. Overall, 74% of the patients were NYHA IV, 84% of the patients were stage D. There were 31 patients with pulmonary artery pressure (PAP) 26-35 mmHg, 15 with 36-45 mmHg, 23 with over 45 mmHg, and 4 with less than 26 mmHg.

Anemia was detected in 62% of the patients. The most common type of anemia was normocytic anemia (72.6%), with 5.8% of anemias being microcytic and 1.6% macrocytic. Iron deficiency without anemia was present

Table 3. Patients' degree of heart failure according to NYHA and ejection fraction

	NYHA III (n=26)	NYHA IV (n=74)
HFrEF (n=42)	14 (%33.3)	28 (%66.7)
HFmrEF (n=12)	1 (%8.3)	11(%91.7)
HFpEF (n=46)	11 (%23.9)	35 (%76.1)

Table 4. Types of anemia and iron deficiency (n)

Anemia	62
Iron Deficiency	70
Iron Deficiency Anemia	45
B12 Deficiency	4
Folate Deficiency	11
Hemolytic Anemia	1
Chronic Disease Anemia	56
Iron Deficiency Anemia+ Chronic Disease Anemia	26
Unclassified anemias	6

Table 5. Hematological, biochemical parameters and ecocardiography findings

Sodium (mEq/L)	136.1±5.9
EF (%)	43.6±14.5
PAB (mmHg)	42.6±13.1
BNP (pg/mL)	1900.7±1803.5
RBC (10^6/mL)	3.9±0.8
Hgb (g/dL)	11.2±2.4
Hct (%)	34.7±7.4
MCV (fl)	87.4±8.9
MCH (pg)	28.8±6.1
MCHC (g/dL)	32.2±1.9
RDW (%)	18.2±3.3
Plt (10^3/µL)	248.7±92
Iron (µg/dL)	41.2±29.1
IBC (µg/dL)	235.1±90.4
TIBC (µg/dL)	273.9±86.9
Ferritin (µg/mL)	219.4±383.2
Transferrin Saturation (%)	14.8±9.5
Vitamin B12 (pg/mL)	582±420.1
Folate (ng/mL)	6.5±3.6
LDH (IU/L)	340.7±330.3
Indirect Bilirubin (mg/dL)	0.6±0.5
Haptoglobulin (mg/dL)	151.9±98.1

EF: Ejection Fraction; PAP: Pulmonary Artery Pressure; BNP: B-type Natriuretic Peptide; RBC: Red Blood Cell; HG: Hemoglobin; HCT: Hematocrit; MCV: Mean Corpuscular Volume; MCH: Mean Corpuscular Hemoglobin; RDW: Red Cell Distribution Width; PLT: Platelet; IBC: Iron Binding Capacity; TIBC: Total Iron Binding Capacity; LDH: Lactate Dehydrogenase.

Table 6. Comparison of parameters according to anemia (n)

Parameters	No Anemia n (%)	Anemia n (%)	p (Fisher Exact test)
EF			
Reduced	21 (55.3)	21 (33.9)	0.11
Gray Zone	4 (10.5)	8 (12.9)	
Preserved	13 (34.2)	33 (53.2)	
NYHA classification			
III	11 (28.9)	15 (24.2)	0.64
IV	27 (71.1)	47 (75.8)	
ACC/AHA grade			
C	4 (10.5)	12 (19.4)	0.27
D	34 (89.5)	50 (80.6)	
PAP mmHg			
26-35	13 (52.0)	18 (40.9)	0.06
36-45	5 (20.0)	10 (22.7)	
> 45	7 (28.0)	16 (36.4)	
Concomitant Diseases	**n (%)**	**n (%)**	**p**
Diabetes Mellitus			
No	22 (57.9)	28 (45.2)	0.30
Yes	16 (42.1)	34 (54.8)	
Chronic renal failure			
No	32 (84.2)	33 (53.2)	<0.001
Yes	6 (15.8)	29 (46.8)	
Asthma bronchiale			
No	34 (89.5)	54 (87.1)	1.00
Yes	4 (10.5)	8 (12.9)	
COPD			
No	29 (76.3)	51 (82.3)	0.60
Yes	9 (23.7)	11 (17.7)	

Table 7. Classification according to ferritin for diagnosis of iron deficiency in HF patients (n=70)

Classification	n (%)
HF with iron deficiency	70 (70)
Ferritin< 41 ng/mL	14 (14)
Ferritin: 41-100 ng/mL	30 (30)
Ferritin: 100-299 ng/mL and Transferrin saturation< %20	26 (26)
HF without iron deficiency	30 (30)

in 70% of all patients. Iron deficiency anemia was present in 45%, and chronic disease anemia in 56% of all patients. Chronic disease anemia with iron deficiency coexisted in 26% of all patients (Table 4).

The mean level of hemoglobin was 11.2±2.4 g/dL, hematocrit was 34.7±7.4%, ferritin was 219.4±383.2 ng/mL, and transferrin saturation was 14.8±9.5%. Hematological, biochemical parameters, and echocardiography findings of patients are shown in Table 5.

Age positively correlated with ejection fraction (EF) (p=0.014, r=0.245). Anemia was detected in 50% of patients with HFrEF, 66.7% with HFmrEF (gray zone), and 71.7% with HFpEF. EF was inversely correlated with Hgb and Hct (p=0.004, r=-0.284 and p=0.006, r=-0.272, respectively). However, there was no correlation between EF and iron deficiency or iron deficiency anemia.

Anemia was present in 57.6% of those with NYHA III, 63.5% of those with NYHA IV; 75% of those with ACC/AHA grade C, and 59.5% of those with grade D. The frequency of anemia was 58.1% in patients with PAP 26-35 mmHg, 66.7% in patients with PAP 36-45 mmHg, and 69.6% in patients with PAP>45 mmHg (Table 6).

There was a negative correlation between age and iron deficiency anemia (p=0.026, r=-0.222). Classification according to ferritin for diagnosis of iron deficiency in HF patients is shown in Table 7.

There was a significant correlation between anemia and chronic renal failure (p<0.001). Anemia was found in 30 of 35 patients with CRF (86%), iron deficiency in 21 of 35 patients with CRF (60%), and iron deficiency anemia in 19 of 35 patients (54%). Classification according to ferritin for diagnosis of iron deficiency in patients with CRF and HF is shown in Table 8.

There was a statistically significant association between iron deficiency and the presence of a coronary artery bypass graft (p<0.05) (Table 9).

Table 8. Classification according to ferritin for the diagnosis of iron deficiency in patients with heart failure concomitant chronic renal failure (n=35)

Classification	n (%)
HF with CRF	35 (35)
CRF with of iron deficiency	21 (21)
CRF + Ferritin<41 ng/mL	3 (3)
CRF + Ferritin: 41-100 ng/mL	11 (11)
CRF + Ferritin: 100-299 ng/mL and Transferrin saturation<%20	7 (7)
CRF without iron deficiency	14 (14)
HF without CRF	65 (65)

Table 9. Comparison of parameters according to iron deficiency (n)

Parameters	No ID	ID	p
EF			
Reduced	13 (43.3)	29 (41.4)	0.64
Gray Zone	2 (6.7)	10 (14.3)	
Preserved	15 (50)	31 (44.3)	
NYHA			
III	11 (36.7)	15 (21.4)	0.13
IV	19 (63.3)	55 (78.6)	
Grade			
C	5 (16.7)	11 (15.7)	1.00
D	25 (83.3)	59 (84.3)	
PAP			
26-35	11 (57.9)	20 (40.0)	0.17
36-45	5 (26.3)	10 (20.0)	
> 45	3 (15.8)	20 (40.0)	
Concomitant Diseases	**n (%)**	**n (%)**	**p**
Diabetes Mellitus			
No	17 (56.7)	33 (47.1)	0.51
Yes	13 (43.3)	37 (52.9)	
Chronic renal failure			
No	16 (53.3)	49 (70.0)	0.11
Yes	14 (46.7)	21 (30.0)	
Asthma bronchiale			
No	26 (86.7)	62 (88.6)	0.74
Yes	4 (13.3)	8 (11.4)	
COPD			
No	25 (83.3)	55 (78.6)	0.78
Yes	5 (16.7)	15 (21.4)	
Etiology	**n (%)**	**n (%)**	**p**
Hypertension			
No	9 (30.0)	12 (17.1)	0.18
Yes	21 (70.0)	58 (82.9)	
Myocardial Infarction			
No	24 (80.0)	50 (71.4)	0.46
Yes	6 (20.0)	20 (28.6)	
Coronary Artery Diseases			
No	13 (43.3)	34 (48.6)	0.66
Yes	17 (56.7)	36 (51.4)	
Coronary Artery Bypass			
No	21 (70.0)	61 (87.1)	0.05
Yes	9 (30.0)	9 (12.9)	
Coronary Stent			
No	27 (90.0)	59 (84.3)	0.54
Yes	3 (10.0)	11 (15.7)	
Heart Valve Diseases			
No	28 (3.3)	65 (62.9)	1.00
Yes	2 (6.7)	5 (7.1)	
Heart Muscle Diseases			
No	29 (96.7)	69 (98.6)	0.51
Yes	1 (3.3)	1 (1.4)	

Table 9. CONT.

Etiology	n (%)	n (%)	p
Diabetes Mellitus			
No	17 (56.7)	32 (45.7)	0.38
Yes	13 (43.3)	38 (54.3)	
Arrhythmias			
No	16 (53.3)	45 (64.3)	0.37
Yes	14 (46.7)	25 (35.7)	
Atrial Fibrillation			
No	16 (53.3)	50 (71.4)	0.10
Yes	14 (46.7)	20 (28.6)	
Tachycardia			
No	30 (100)	69 (98.6)	1.0
Yes	0 (0.0)	1 (1.4)	
Surgical Intervention			
No	29 (96.7)	70 (100)	0.30
Yes	1 (3.3)	0 (0.0)	
Pulmonary Embolism			
No	30 (100.0)	68 (97.1)	1.00
Yes	0 (0.0)	2 (2.9)	

Among the 20 patients with COPD, 11 had anemia (55%), 15 had iron deficiency (75%), and 7 had iron deficiency anemia (35%).

Among the patients with normocytic anemia, there were 30 with chronic disease anemia—16 of the 30 patients had chronic renal failure (53%), and 5 of them had COPD (17%).

Discussion

Heart failure is one of the leading health problems worldwide due to its increasing frequency and prevalence. Although the prevalence of heart failure in the general population varies between 0.3-2%, this figure reaches 3-5% over the age of 65 and 25% over the age of 75 [15-17]. The most common cause of heart failure is coronary artery disease, responsible for 60-75% of cases. Hypertension is also a major cause and is present in 75% of those with coronary artery disease. In this cross-sectional study, the mean age of patients was 72.2±10.4 years, and hypertension (79%) and coronary artery disease (53%) were found to be the most frequent etiology of heart failure.

In a study among cardiomegaly patients, which was proven using echocardiography, a normal cardiothoracic ratio was found in 22% of patients[18]. In 98% of the patients, the cardiothoracic ratio was found to be above 50%. In a study that included 1658 elderly patients who were admitted to the emergency department for acute decompensated HF, the pleural effusion rate was reported to be 55% on chest radiographs[19]. Pleural effusion was detected in 74% of the patients in this study. These two findings may be due to the fact that the patients in the study had advanced heart failure.

Anemia is common in CHF patients and includes many etiological causes, increasing mortality. In the SOLVD study, 22% of the patients had hematocrit at 39% and below, and 4% had values below 35%[20]. In the present study, the mean hematocrit level was 34.7±7.4%. As there are different mechanisms that affect anemia in CHF patients, the prevalence of anemia differs in studies. The incidence of newly developed anemia in one year was found to be 9.6%[21]. As it is known, iron deficiency anemia is often seen as microcytic anemia, and chronic disease anemia as normocytic anemia[22]. In a study that included 153180 heart failure patients treated between 2001-2007, the prevalence of anemia was 37.2%[23]. In the present study, anemia was detected in 62% of the patients, although 72.6% of anemias were normocytic, iron deficiency anemia was detected in 45%, and chronic disease anemia in 56% of the patients. A total of 26% of the patients with chronic disease anemia had iron deficiency. The complexity of anemia mechanisms in patients with chronic diseases such as heart failure can also be understood from these findings.

In this study, 74% of the patients were NYHA IV, and 84% of the patients were stage D. Hospitalized patients tended to be of worse functional class. We think that the frequency of anemia is high due to the fact that the patients in the study had advanced HF.

In the RED-HF study, which was a double-blind, randomized, placebo-controlled, multicenter study where darbepoetin-alpha is used in patients with heart failure, it has been observed that treatment does not decrease mortality and does not improve the clinical status of patients[24]. Since agents used in the treatment of anemia in CKD patients were tested in HF patients, we also observed the relationship between renal failure concomitant anemia and iron deficiency in HF patients in the present observational study. There was a statistically significant correlation between anemia and chronic renal failure ($p<0.001$). Anemia was found in 30 of 35 patients with CRF (86%), iron deficiency in 21 of 35 patients with CRF (60%), and iron deficiency anemia in 19 of 35 patients (54%). Therefore, typing and treating anemia should be done in patients with cardiorenal syndrome.

The prevalence of iron deficiency in CHF patients has been reported to be between 5-21% in studies[25,26]. Iron deficiency may be more common in patients with HF, as

ferritin levels may not be proportional to low iron stores. This has been demonstrated in a series of 37 patients with advanced HF (mean left ventricular ejection fraction 22%, mean New York Heart Association class 3.7) and anemia. Bone marrow aspiration was performed in all hospitalized patients and iron deficiency was found in the bone marrow aspirates of 27 patients, with the iron deficiency prevalence calculated as 73%. Dilution anemia was found in 5.4% of the patients and drug-induced anemia in 2.7%. For 18.9% of the patients, no determination was made. According to another study conducted by Ezekowitz et al.[26], 17% of 12065 CHF patients were diagnosed with different etiologies, and 58% had chronic disease anemia.

In this study, anemia was found mostly among the HFpEF (71.7%) patients. The frequency of anemia was 50% in HFrEF, and 66.7% in HFmrEF. According to NYHA classification, the frequency of anemia increases as patients' symptoms increase. Anemia was detected in 57.6% of patients with NYHA III, and 63.5% with NYHA IV. This finding is compatible with the pathophysiology of heart failure. The frequency of anemia did not correlate with staging. Anemia was 75% in patients with grade C, while this rate was 59.5% in patients with grade D. As PAP increases, the frequency of anemia increases, but there was no statistical correlation. Anemia frequency was 58.1% in patients with PAP 26-35 mmHg, 66.7% in patients with PAP 36-45 mmHg, and 69.6% in patients with PAP above 45 mmHg. These data were consistent with Sutil-Vega et al.'s[27] review, highlighted as anemia and iron deficiency are also associated with increases in PAP.

According to this study, iron deficiency is mostly seen in those with HFpEF (44.3%) as well. While the iron deficiency rate was 14.3% in those with HFmrEF, 41.3% was found in those with HFrEF. Iron deficiency is higher in NYHA IV patients (78.6%) than in NYHA III (21.4%). As grading progresses, iron deficiency increases (15.7% in grade C, 84.3% in grade D). There was no correlation between iron deficiency and PAP. In the study of González-Costello et al.[9], iron deficiency was observed more frequently in cases where the etiology of heart failure was hypertension and diabetes mellitus rather than ischemic etiology. In this study, iron deficiency was found to be statistically significant in patients with coronary artery bypass grafts (Fisher's Exact $p<0.05$). It is probable that occult bleeding caused by the usage of acetylsalicylic acid in these patients led to this.

The prevalence of HFpEF has increased significantly over the past two decades, and it is thought to be the most common form of HF in the next decade[28]. HFpEF has significant morbidity and mortality, and although no clear therapy has been demonstrated to improve outcomes in HFpEF so far[28]. In this study, considering that there was a positive correlation between the age of the patients and EF, it will be concluded that HFpEF can be detected more frequently in the internal medicine clinic. Anemia and iron deficiency were detected mostly in HFpEF's patients in this study; the correction of signs such as anemia and iron deficiency in these patients is also important in reducing their symptoms.

The limitations of our study were that it was a retrospective and cross-sectional study, patients' weight and anemia due to antihypertensive drugs were not included in the study, and bone marrow biopsy was not performed for the definitive distinction of anemia etiology.

Conclusion

The findings indicate that anemia is frequently found in patients with heart failure with NYHA III-IV and grade C-D. The mean hemoglobin level in this anemia is usually between 9-10 g/dL. Given that the patients are mostly elderly and have comorbidities, it is often not possible to carry out many examinations for the etiology of the anemia, and it is generally considered to result from chronic diseases. However, iron deficiency is frequently detected in these patients, with or without anemia. It should be noted that the functional capacities and quality of life of patients with heart failure are potentially increased with intravenous iron treatment, especially where oral iron cannot be well absorbed due to intestinal edema, and erythropoiesis-stimulating agent (ESA) treatment does not decrease mortality nor improve the clinical status. We recommend more careful investigation of anemia etiologies and treatment in patients with chronic heart failure.

Ethics Committee Approval: The study included patients who were admitted between October 2015 and December 2016. The study was carried out after the approval of the institutional Ethics Committee (HNEAH KAEK 2016/KK/118) and conducted in accordance with the Declaration of Helsinki.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: G.H.G., D.R.; Design: D.R.; Supervision: D.R.; Fundings: None; Materials: G.H.G., D.R.; Data Collection or Processing: G.H.G., D.R.; Analysis or Interpretation: G.H.G., D.R.; Literature Search: G.H.G.; Writing: G.H.G., Critical Review: D.R.

Use of AI for Writing Assistance: Not declared.

Conflict of Interest: None declared.

Financial Disclosure: The authors declared that this study received no financial support.

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