Research Article

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Iron Deficiency Anemia and Mortality Rate in Heart Failure with Reduced Ejection Fraction

Murat Özmen

University of Health Sciences Türkiye, Erzurum Regional Training and Research Hospital, Department of Cardiology, Erzurum, Türkiye

Abstract

Objectives: Anemia is a common condition in heart failure (HF) patients and is associated with poor functional capacity and increased mortality and morbidity rates. However, the effect of different types of anemia on HF has not been adequately investigated in the literature In this study, we tried to determine the rate of iron deficiency anemia (IDA) and non-IDA of anemia of chronic disease (ACD) in HF patients followed in our clinic and discuss its effect on mortality.

Materials and Methods: Heart failure patients with reduced ejection fraction (HFrEF) who were admitted to the cardiology outpatient clinic between January 2021 and June 2021 were included in this study. Laboratory parameters, demographic characteristics, and clinical and echocardiographic data of the patients were examined retrospectively.

Results: A total of 521 patients were included in our study. The average age of the patients was 67±13 years. 70.6% of the patients are men. Mortality was observed to be statistically higher in the combination of HFrEF and IDA, than in the non-iron deficiency ACD groups. Cardiovascular and non-cardiovascular comorbidities were reported more frequently in the non-iron deficiency ACD group and were more particularly common in the chronic kidney disease ACD group. Statistical differences were observed in levels of serum iron metabolism parameters between IDA and ACD. Mortality rates among HFrEF patients with anemia during the total follow-up period were found to be higher than those in patients without anemia, as reported in the literature.

Conclusion: Mortality was observed to be quite high during the follow-up period in patients diagnosed with HFrEF and accompanied by ACD or IDA. The negative effects of IDA on mortality and prognosis in HF patients are well known. There are many causes of anemia in HF, although current studies and guidelines focus more on iron deficiency and IDA. In our study, iron deficiency without anemia in HF patients was shown to be an independent predictive factor for mortality.

Keywords: Heart failure, iron deficiency anemia, non-iron deficiency anemia, anemia of chronic disease, mortality

Address for Correspondence: Murat Özmen, University of Health Sciences Türkiye, Erzurum Regional Training and Research Hospital, Department of Cardiology, Erzurum, Türkiye
e-mail: drmuratt1987@gmail.com **ORCID:** orcid.org/0000-0002-6237-1398
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Introduction

As a clinical syndrome accompanied by comorbid conditions, heart failure (HF) is a chronic disease that develops when the heart muscle cannot send enough blood and oxygen the body needs[1]. HF, which affects approximately 26 million people globally and approximately 2 million people in our country, is a common healthcare issue. Its frequency is increasing both globally and in our country, with novel treatment modalities that reduce mortality rates[2]. The survival rates of individuals diagnosed with HF are lower than those of bowel cancer, prostate cancer, and breast cancer. The rate of at least one hospitalization for individuals who are living with HF is 83%, and 50% of these patients are monitored in intensive care units[2]. HF is accompanied by many comorbidities [e.g., coronary artery disease, hypertension (HT), diabetes mellitus, chronic kidney disease (CKD), and anemia], these aggravate the course of the disease[3]. Iron deficiency anemia (IDA) is a common comorbidity in patients with heart failure patients with reduced ejection fraction (HFrEF) and heart failure patients with preserved ejection fraction (HFpEF) and has been shown to be associated with increased mortality and morbidity rates[4]. The prevalence of anemia is around 17% in newly diagnosed chronic heart failure (CHF) patients, 30% in clinically stable CHF patients, and 50% in hospitalized CHF patients[5]. This means that the rate of iron deficiency (ID) is significantly higher than the rate of anemia, whether considering anemia alone or in conjunction with ID[6]. This means that mortality rates are higher in patients with ID. Significant benefits have recently emerged in clinical outcomes with intravenous (IV) iron treatment administered to HF patients who have ID. Improvements include quality of life, New York Heart Association class, 6-minute walking distance, peak oxygen consumption, and reduced HF hospitalization. These benefits have brought to the clinical agenda the importance of treating ID, which was considered a treatment target for the first time in the 2016 European Society of Cardiology (ESC) HF guideline. A limited number of studies in the literature examine HF patients regarding ID and IDA[7]. Examining IDA in patients with HF and determining the factors affecting are essential for clinical practices and the prognosis of patients. In light of this information, this study aims to examine ID, IDA, and other anemia conditions in low ejection fraction HF and to investigate their effects on mortality.

Materials and Methods

The study was conducted retrospectively at Erzurum City Hospital Clinic of Cardiology, which serves the Eastern Anatolian Region, with one faculty member and nine specialist doctors. In this study, 521 patients who applied to the City Hospital Clinic of Cardiology in the six months between January 2021 and June 2021 and met the inclusion criteria were included. These patients were screened retrospectively. Patients over the age of 18 who were diagnosed with HF and had hemogram, biochemistry, ferritin, iron, iron-binding capacity, and transthoracic echocardiography (TTE) data in the hospital system were included in the study. Among patients diagnosed with anemia, patients diagnosed with cancer, patients with hematological malignancies such as lymphoma-leukemia, patients with acute bleeding conditions (such as gastrointestinal bleeding), end-stage solid organ diseases (such as liver cirrhosis), and patients receiving dialysis treatment were excluded from the study. In this study, the anemia group defined outside IDA includes anemias not accompanied by ID, seen in chronic diseases, and other than the pathologies mentioned above. Additionally, those who did not have hemogram data, biochemistry data, ferritin, iron, iron-binding capacity, and TTE data were not included in the study. As determined by the World Health Organization and ESC HF guideline 2021, the hemoglobin (HGB) value for anemia was defined as less than 12 g/dL for women and less than 13 g/dL for men. IDA was defined as a serum Ferritin level <100 µg/L or transferrin saturation (TSAT) <20% if the Ferritin level was between 100-299 µg/L. TSAT was calculated using the following formula: serum iron (mg/dL)×100 / total iron-binding capacity (mg/dL)[8]. The

disease histories of the patients were recorded using the data in the hospital system. CKD: a known patient with CKD from medical records within six months prior to enrollment or when the estimated glomerular filtration rate (GFR) is <60 mL/min./1.73 m^2 by the CKD epidemiology collaboration formula using serum creatinine level[9]. This study was conducted in accordance with the Declaration of Helsinki, and ethical approval was obtained from the Local Ethics Committee of Erzurum Regional Training and Research Hospital (approval no: 16.05.2022/06-49, date: 16.05.2022).

Statistical Analysis

The data were analyzed with the IBM SPSS V23. Compliance with normal distribution was examined using the Kolmogorov-Smirnov and Shapiro-Wilk tests. The Pearson chi-square test and Yates's correction test were used to compare the categorical data according to the groups. The Mann-Whitney U test was used to compare the non-normally distributed data according to binary groups. The results of the analyses were presented as mean ± standard deviation and median (minimum-maximum) for quantitative data and as frequency and percentage for categorical data. The significance level was set at $p<0.05$.

Results

A total of 521 patients were included in this retrospective study. The average age of the patients was 67±13.70.6% were men. Particularly, patients in the IDA group were older than the mean age of the whole population (71.18±11.9). No statistically significant differences were detected between sex distributions according to anemia and IDA status (p=0.118). Comorbidities and mortality rates of the patients are shown in Table 1. Accordingly, statistical significance was observed in comparing mortality in patients with anemia due to ID *versus* anemia of chronic disease (ACD). Echocardiographically, the ejection fraction was observed to be lower in IDA (31.8±8.2).

Statistical analysis of the shaped elements and biochemical parameters of blood, according to whether or not ACD is present, is given in Table 2. Accordingly, statistically significant differences were detected between the hg (HGB, (10^9/L), mean corpuscular volume, neutrophil (10^9/L), lymphocyte (10^9/L), C-reactive protein, glucose, creatinine, albumin, triglyceride, high density lipoprotein, total cholesterol, and calcium values. ($p<0.001$) In Table 3, where patients with and without IDA are compared, iron metabolism parameters and

Table 1. The demographic characteristics of patients

	n=521 (%)	ACD (+) n=148 (%)	IDA (+) n=220 (%)	ID (+) n=41 (%)	p-value
ECHO (EF: %)	32.57±8.11	33±7.7	31.8±8.2	32.7±7.5	<0.001
Age (Mean ± SD)	67.32±13.37	68.68±13.04	71.18±11.9	70.23±12.2	<0.001
Female n (%)	153 (29.4)	46 (31.1)	60 (27.3)	13 (31.7)	0.118
CAD n (%)	139 (26.7)	51 (34.4)	59 (26.8)	18 (43.9)	0.16
AF n (%)	86 (16.5)	47 (31.7)	50 (22.7)	10 (24.3)	0.45
HT n (%)	339 (65.1)	99 (66.9)	151 (68.6)	12 (29.2)	0.33
DM n (%)	132 (25.3)	53 (35.8)	54 (24.5)	9 (21.9)	0.22
CVE n (%)	111 (21.3)	49 (33.1)	52 (23.6)	4 (9.7)	0.36
Mortality n (%)	117 (22.5)	23 (15.5)	65 (29.5)	15 (36.5)	0.02
CKD	95 (18.2)	47(31.7)	48 (21.8)	8 (19.5)	0.04

ACD: Anemia of chronic disease, IDA: Iron deficiency anemia, ID: Iron deficiency, ECHO: Echocardiography, EF: Ejection fraction, CAD: Coronary artery disease, AF: Atrial fibrillation, HT: Hypertension, DM: Diabetes mellitus, CVE: Cerebrovascular event, CKD: Chronic kidney disease

erythrocyte volume are compared, as expected, and found to be statistically significant in the IDA group. No significant differences were observed in other blood parameters. In evaluating patients without anemia in terms of ID, 41 (26.7%) had ID. In univariate and multivariate regression analyses, age, echocardiography, IDA, ID, and HGB were determined to be significant predictors of mortality in HFrEF (Table 4).

Discussion

HF is a clinical syndrome affecting millions of people on a global scale, accompanied by typical signs and symptoms developing as a result of structural and/or functional disorders of the heart[10]. The incidence of CHF is approximately 3/1000 person-years for all age groups in Europe. In adults, it is approximately 5/1000 person-years[11]. Since studies are generally evaluated on known/

Table 2. The comparison of the blood parameters according to ACD status

	ACD + (n=148)	ACD - (n=373)	
	+ , Mean ± SD	-, Mean ± SD	p-value
TSAT SAT	23.53±22.9	34.02±34.77	0.148
Iron (mg/dL)	58.32±38.17	60.56±45.54	0.988
FeBC (mg/dL)	28593.96±85233.65	41034.48±115537.12	0.056
Ferritin (mg/dL)	160.4±205.52	228.96±342.29	0.918
WBC(10^9/L)	8.36±3.55	8.35±3.21	0.780
HBG (10^9/L)	10.78±1.41	14.92±1.49	**<0.001**
PLT (10^9/L)	249.13±81.25	256.95±110.33	0.814
MCV (fL)	78.6±7.9	83.8±9.45	**<0.001**
MCH (pg)	24,6±2.83	29,8±1.45	**<0.001**
PDW (10^9/L)	12.7±2.2	13±2.67	0.420
Neutrophil (10^9/L)	6.06±3.64	7.33±6.42	**0.013**
Lymphocyte (10^9/L)	2.56±3.84	2±4.53	**<0.001**
Monocyte (10^9/L)	0.84±0.3	0.89±0.65	0.748
Glucose (mg/dL)	54±72.58	145.75±77.05161	**0.005**
Creatine (mg/dL)	1.72±1.33	1.12±0.48	**<0.001**
Albumin (g/L)	34.36±10.53	36.89±13.05	**<0.001**
Sodium (mmol/L)	139.78±3.88	139.68±5.88	0.205
Potassium (mmol/L)	4.4±0.56	4.5±0.77	0.340
Uric acid (mg/dL)	6.68±2.44	7.15±2.95	0.245
Triglyceride (mg/dL)	166.82±97.9	133.29±55.09	**0.010**
HDL (mg/dL)	26.74±2518.07	36.3±11.99	**0.005**
LDL (mg/dL)	158.17±69.58	148.16±68.14	0.392
Cholesterol (mg/dL)	171.43±46.2	153.2±45.64	**0.007**
Calcium (mg/dL)	9.31±0.72	8.81±0.79	**<0.001**
Magnesium (mg/dL)	1.95±0.3	1.89±0.4	0.052
VITB12 (pg/mL)	406.82±285.64	595.28±538.11	0.124

Mann-Whitney U-test, ACD: Anemia of chronic disease, TSAT SAT: Transferrin saturation, FeBC: Iron binding capacity, WBC: White blood cell, HGB: Hemoglobin, PLT: Platelet, MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, PDW: Platelet distribution width, HDL: High density lipoprotein, LDL: Low density lipoprotein, VITB12 : Vitamin B12

Table 3. The comparison of the blood parameters according to IDA status

	IDA (n=220)	non- IDA (n=301)	p-value
	+, Mean ± SD	-, Mean ± SD	
TSAT SAT	16.77±15.47	45.7±34.21	**<0.001**
Iron (mg/dL)	50.22±32.82	76.6±47.64	**<0.001**
FeBC (mg/dL)	39150.62±101116.47	12600.19±59826.7	**<0.001**
Ferritin (mg/dL)	67.55±70.09	342.42±324.54	**<0.001**
WBC (10^9/L)	8.82±3.55	8.26±3.81	**0.036**
HBG (10^9/L)	10.78±2.44	13.68±2.37	**<0.001**
PLT (10^9/L)	242.04±82.9	251.5±89.37	0.335
MCV (fL)	67.62±7.73	84.85±6.25	**<0.001**
MCH (pg)	21,7±3,4	30,6±1,47	**<0.001**
PDW (10^9/L)	13.01±2.71	12.73±2.23	0.781
Neutrophil (10^9/L)	6.9±3.51	6.54±5.84	**0.027**
Lymphocyte (10^9/L)	2.08±2.03	2.75±5.69	0.614
Monocyte (10^9/L)	0.85±0.38	0.88±0.5	0.424
Glucose (mg/dL)	159.82±79.38	149.3±78.91	0.121
Creatine (mg/dL)	1.4±1.13	1.25±0.68	0.339
Albumin (g/L)	36.22±11.35	37.49±11.25	0.104
Sodium (mmol/L)	140.33±5.09	139.64±4.21	0.194
Potassium (mmol/L)	4.49±0.63	4.43±0.64	0.385
Uric acid (mg/dL)	7.1±2.82	6.76±2.5	0.238
Triglyceride (mg/dL)	175.65±101.92	147.06±75.12	**0.018**
HDL (mg/dL)	36.57±11.2	41.26±11.78	**0.003**
LDL (mg/dL)	162.48±67.9	151.9±64.13	0.269
Cholesterol (mg/dL)	159.5±49.56	169.45±46.97	0.106
Calcium (mg/dL)	9.03±0.88	9.24±0.69	0.050
Magnesium (mg/dL)	1.95±0.36	1.93±0.33	0.647
VITB12 (pg/mL)	506.57±450.32	422.07±306.34	0.405

Mann-Whitney U test, Mean ± SD TSAT SAT: Transferrin saturation, FeBC: Iron binding capacity, WBC: White blood cell , HGB: Hemoglobin , PLT: Platelet , MCV: Mean corpuscular volume, MCH: Mean corpuscular hemoglobin, PDW: Platelet distribution width, HDL: High density lipoprotein, LDL: Low density lipoprotein, VITB12: Vitamin B12, IDA: Iron deficiency anemia

Table 4. Relationship between univariate and multivariate regression analysis and mortality

	Univariate			Multivariate		
	OR	95% CI	p	OR	95% CI	p-value
Age	1.050	1.030-1.070	**<0.001**	1.051	1.028-1.074	**<0.001**
ECHO-EF	0.95	0,920-0,980	**<0.001**	0.965	0.936-0.994	**0.018**
ACD	0.584	0.357-0.957	0.03	0.632	0.363-1.100	0.63
IDA	1.535	1.015-2.322	**0.04**	2.067	1.237-3.453	**0.006**
ID	1.410	1.002-1.830	**<0.001**	1.386	0.943-1.945	**<0.001**
HGB (g/dL)	0.810	0.739-0.887	**<0.001**	0.818	0.737-0.907	**<0.001**

OR: Odds ratio, CI: Confidence interval, ECHO-EF: Echocardiography-ejection fraction, ACD: Anemia of chronic disease, IDA: Iron deficiency anemia, ID: Iron deficieny, HGB: Hemoglobin

diagnosed CHF cases, the actual prevalence is probably higher[12]. Prevalence is estimated to be 1% among individuals under 55, and over 10% among those aged 70 and over[13]. With the development of treatment methods and the elucidation of the pathophysiology of the disease, significant improvements have been observed in prognosis and mortality. Still, hospitalization and mortality rates are quite high. Indeed, in the olmsted county cohort, post-diagnosis 1-year and 5-year mortality rates for all HF patients between 2000 and 2010 were 20% and 53%, respectively[14]. Study cohorts combining the Framingham Heart Study and Cardiovascular Health Study reported a 67% mortality rate at 5-year follow-up after diagnosis[15]. Our study supports existing studies, finding the mortality rate of patients with HF was found to be 22%. CHF patients are hospitalized on average once a year after initial diagnosis[16]. In another cohort, the average hospitalization rate from 2000 to 2010 was 1.3 per person-year. Interestingly, the majority of hospitalizations (63%) were for non-cardiovascular reasons[14]. In another study, age-adjusted first hospitalization rates increased by 28% for all-cause and CHF admissions, and 42% for non-cardiovascular admissions[17]. The risk of hospitalization due to HF is 1.5 times higher in patients with diabetes. AF, increased body mass index, glycated HGB, and low GFR are strong predictors of hospitalizations for CHF[18]. Due to a growing population, aging, and comorbidities, the number of hospital admissions for CHF is expected to increase by up to 50% over the next 25 years[19]. The severe nature of the disease, characterized by frequent hospitalizations and high mortality rates, with brings a great economic burden to countries and requires effective measures to tackle the factors that precipitate HF[20]. Anemia is one of the most common conditions resulting from these predisposing factors. Studies report that ACD and IDA are common in all types of HF, triggering decompensation and increasing mortality and morbidity[21]. Our study supports existing studies and finds IDA and ACD to be factors contributing to mortality in HF patients.The prevalence of anemia is around 17% in newly diagnosed CHF patients, 30% in clinically stable CHF patients, and 50% in hospitalized CHF patients[22]. In a meta-analysis that examined 34 studies covering approximately 153.180 patients, it was reported that the frequency of anemia in cases with HF was 37.2%[17]. However, this rate varies widely between 14 to 61% in different studies[23-24]. In our study, IDA was observed at 42.2% and ACD at 28.4% in patients with HF. A significant difference is observed between anemia and CHF regarding the development levels of countries, along with a negative relationship is observed[25]. In anemia, the decrease in HGB concentration lowers the oxygen-carrying capacity in the blood. As the anemia deepens, the compensatory capacity of the heart and skeletal muscle is exceeded and exercise intolerance develops. This process progresses faster in CHF[26]. Anemia is associated with poor prognosis in patients with HF[27]. Chronic anemia is an independent risk factor for mortality in patients with CHF. Although ID is a common cause of chronic anemia, other etiologies include CKD, inflammatory processes, and unexplained causes[28]. Although a specific cause cannot be found in most HF patients with anemia, it is recommended to perform the necessary tests to elucidate the etiology of anemia (hidden blood loss; iron, B12, and folate deficiency; blood dyscrasias)[10]. In our study, the effect of different types of anemia on CHF-related deaths was investigated, and mortality was found to be statistically significant in IDA patients compared to the ACD group. In comparing chronic cardiac and non-cardiac comorbidities associated with anemias in the IDA and ACD groups, comorbidities including chronic renal failure were more prevalent in chronic anemias, and statistical significance was observed. In another study conducted on a population of 90 people, an increase in uric acid levels was found to be correlated with HF mortality and was statistically significant. In our study, uric acid levels were not statistically significant[29]. Additionally, CKD was observed to be more prevalent in the ACD group. Although there are not enough data in the literature directly comparing the mortality of both groups in CHF patients, there are increased mortality rates in anemic patients with CHF[30]. In our study, ACD was observed at a rate of 28.4%

and IDA at 42.2%. Silverberg et al.[31] study found that the rate of chronic anemia due to all causes was 56%.31. In another study conducted by Tanner H[24], this rate was reported to be 15%. The reason for this low rate was due to a younger population being included in the study[24]. The average age of the patients was 54 in this study and was 67 in our study. In a prospective observational series of 546 cases, ID was detected in 32% of non-anemic cases[32]. Similarly, in our study, ID was observed in 41 (26.7%) patients without anemia. These results show that ID is present in a significant portion of HF cases without anemia. Our study supports studies in the literature. Although no statistically significant difference was detected between genders, it was determined that anemia and ID were more common in male CHF patients. Both groups ACD and IDA showed a statistically significant increase in mortality ($p<0.001$). CKD and HF frequently coexist. They share common risk factors, such as diabetes or HT. CKD may worsen coefficient of variation function, causing HT and vascular calcification. CKD is a major independent determinant of increased mortality and morbidity in HF[18]. Our study supports the current findings that CKD is more common in the ACD group and statistically significant. Both HF and CKD are increasing in prevalence as the population ages, and both conditions have been associated with ACD[33]. Anemia, even in the absence of renal disease, has also been associated with adverse clinical outcomes. However, the impact of HF, anemia, and CKD, alone or in combination, on mortality, adverse events, and hospitalization rates remains of clinical interest[34]. Certainly, ID is a common cause of anemia. However, various factors contribute to anemia, including malnutrition (iron, folic acid, and vitamin B12 deficiencies), renal dysfunction, inflammatory diseases, and unexplained anemia[35]. There are many causes of anemia in CHF, and current studies and guidelines focus more on ID and IDA[8]. Therefore, there is a need to expand the scope of research beyond ID. A thorough investigation of the mechanisms of anemia in HF may lead to new strategies in treatment. The optimal therapeutic target for anemia in CHF is currently uncertain. It has been found that mortality increases when the HGB level is <13-14g/dL or >16-17g/dL in CHF patients[36]. Additionally, repeated IV iron administration over time can lead to iron overload, which results in heart damage[5]. Therefore, there is a need to find a suitable therapeutic target for treating anemia and optimizing the prognosis of CHF. Although there are current treatment recommendations for anemia in CHF, studies showing the nature and boundaries of this complex comorbidity are still lacking[28]. It has been shown in the literature that anemia is an important factor mortality in HFrEF patients. Our study supports existing studies, and the results are consistent with the literature obtained in both anemia groups[37]. Improvements in functional capacity in quality of life in tissue oxygenation, and reduction in myocardial ischemia are achieved with treatment[37]. Blood transfusion to symptomatic patients with deficient HGB levels (<7g/dL), IV ferric carboxymaltose infusion to patients with ID with or without anemia, and treatment principles for other etiological factors must be planned by healthcare centers for HF patients[8]. Although preliminary studies showed a beneficial effect of erythropoietin (EPO) therapy on cardiac efficiency and in HF, more recent studies have not confirmed this positive impact of EPO, alluding to its side effect profile. Physical exercise significantly increases hemoglobhın levels and the response of anemia to treatment. In malnourished patients and chronic inflammatory processes, low levels of anabolic hormones, such as testosterone and insulin-like growth factor-1, contribute to the development of chronic anemia. In addition, exercise acts as a regulatory mechanism of chronic anemia and its cardiovascular consequences in patients with HF[38].

Study Limitations

The limitations of our study are that it was conducted in a single center and that patients with mid-range EF and HFpEF were not included.

Conclusion

In conclusion, initiating anemia tests and appropriate treatment modalities from primary health care institutions will benefit the prognosis of patients by correcting anemia. This study provides data that will contribute to the literature on the effects of ACD and IDA on mortality in HFrEF. Clarification of etiological factors is of vital importance in managing anemia in CHF, improving quality of life, and reducing the risk of hospitalization and death.

Ethics

Ethics Committee Approval: This study was conducted in accordance with the Declaration of Helsinki, and ethical approval was obtained from the Local Ethics Committee of Erzurum Regional Training and Research Hospital (approval no: 16.05.2022/06-49, date: 16.05.2022).

Informed Consent: These patients were screened retrospectively.

Footnotes

Authorship Contributions

Conflict of Interest: The authors declare no conflicts of interest concerning the authorship or publication of this article.

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