Original Article

Evaluation of the characteristics of iron metabolism markers in patients with CHF-related anemia in Jordan

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ABSTRACT

Congestive heart failure (CHF) frequently coexists with anemia, which is associated with negative results. To the best of our knowledge, this was the first study to evaluate the characteristics of iron metabolism markers in patients with CHF and anemia in Jordan. The current investigation included 150 CHF patients divided into 3 subgroups: 50 patients with absolute iron deficiency (AID) where (serum ferritin (SF) <100 µg/L), 50 patients with functional iron deficiency (FID) where (SF=100-300 µg/L and iron transferrin saturation coefficient (ITSC) <20%), and 50 other patients having anemia without ID. Among the total studied patients, hemoglobin values corresponded to a mild degree of anemia. Serum iron (SI), serum ferritin (SF), and soluble transferrin receptors (STR) matched reference levels, transferrin (TR) was below normal, and the median iron transferrin saturation coefficient (ITSC) <20% is an indication of ID. SI, SF, and TR conformed to reference values. TR, STR, ITSC, total iron-binding capacity (TIBC), endogenous erythropoietin (EPO), and C-reactive protein (CRP) all showed statistically significant variations among the studied subgroups, indicating important variations in iron metabolism of these subgroups. In the AID subgroup, CRP and hepcidin values were minimal, indicating a minor role in inflammation. Anemia in individuals with CHF was normocytic and normochromic, with low erythropoietin release and significant amounts of CRP and hepcidin. At later phases, iron supplements should be recommended for these two subgroups.

Keywords: Heart failure, Anemia, Iron deficiency, Ferritin, Erythropoietin, Hepcidin

Introduction

Cardiologists frequently encounter anemia in congestive heart failure (CHF) patients [1, 2]. Various papers state that it affects 7–79% of individuals with CHF [3, 4]. Anemia is more common as the functional class of CHF rises, from 8-33% for functional class II to 19-68% and even 80% for functional class III-IV [5-7]. In Jordan, 2,026 non-pregnant women between the ages of 15 and 49 participated in a national household-level micronutrient survey between 2002 and 2010. The incidences of iron deficiency and iron deficiency anemia were reported to be 35.2% and 19.6%, respectively [8]. In 21% of individuals with CHF, iron deficiency (ID) is identified as the primary cause of anemia. Inflammatory bowel disease, Parkinson's disease, rheumatic illnesses, and chronic renal failure are just a few of the chronic diseases that it has been shown to aggravate. Anemia of chronic disease takes the top spot, accounting for 58% of all cases [7]. Based on other statistics, anemia was considered to be caused by iron deficiency in 24–40% of patients, vitamin B12 insufficiency in 4-7%, and chronic heart disease in 46–69% of patients [9, 10]. Inflammation and the ID factor play a major role in the progression of anemia in CHF. The severity of CHF gets worse by iron deficiency anemia, which also decreases the efficiency of common medications, worsens the prognosis, boosts hospitalization rates, and raises patient mortality rates [11]. The

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functionality of the heart muscle is decreased in CHF patients who have ID anemia, and the progression of myocardial ischemia is accelerated [12].

Many believe that ID has a major role in the detrimental effects of iron-deficient anemia on the development of CHF. As a result of ID, the formation of the heme-containing protein myoglobin is altered, energy metabolism declines, mitochondrial dysfunction occurs, and cardiac function declines [13, 14]. ID anemia is linked to an improvement in cardiac output, hypertrophy, and dilatation of the left ventricle, as well as a decline in the performance of the myocardium and skeletal muscles. On the other hand, normal iron content is linked to a rise in the body's endurance and aerobic ability [15, 16]. The literature states that the ID-related poor prognosis is unaffected by the existence or absence of ID anemia [17]. In individuals who have CHF, ID is linked to higher mortality. According to these findings, the presence of ID is linked to a worse prognosis than the presence of anemia [18]. Currently, it is understood that anemia in addition to ID is a very bad situation for a patient with CHF.

Along with hemodilution, the etiology of anemia and ID in CHF is dependent on activities that may be brought on by a variety of factors:

- absolute ID (AID) connected to medication interactions, occult bleeding, and malnutrition;
- Functional iron deficiency (FID) is a condition in which there is persistent inflammation and iron is reallocated from the blood to the depot under the control of the key iron-regulatory protein hepcidin;
- Anemia in chronic disorders is characterized by a disruption of erythropoiesis caused by a reduction in endogenous erythropoietin (EPO) synthesis (the inhibitory influence of pro-inflammatory cytokines) [19, 20].

Hyponormochromic, micro-normocytic anemia, low serum iron (SI), and an iron transferrin saturation coefficient (ITSC) of less than 20% are the hallmarks of all iron deficiency diseases [3, 21]. A serum ferritin (SF) level of less than 100 µg/l, an increase in total iron-binding capacity (TIBC), transferrin levels (TR), soluble transferrin receptors (STR), and elevated concentrations of endogenous EPO are all indicators of AIDS. A SF level of less than 30 g/L is indicative of iron-deficiency anemia.

FID is diagnosed when SF levels are between 100 and 300 µg/l, inflammatory indicators (such as CRP and hepcidin levels) rise, EPO levels are normal or lowered, and low transferrin (TR) quantities are observed. These conditions are characteristic of anemia caused by chronic illnesses, which can also manifest as an isolated erythropoiesis problem without ID [22-26].

Considering the availability of clinical guidelines and several scientific studies, Jordan has not yet found a solution to the issue of the best method for treating anemia in patients with CHF.

Ferrotherapy is currently the most popular method for treating ID anemia in patients with CHF in outpatient clinics; typically, parenteral injection of iron preparations is employed [27, 28]. Jordan is a nation with a low to middle income [29], where it is thought that the financial load is fairly heavy. Jordan presently does not have any official educational or medical policies that address the problem of ID in CHF patients. To the best of our knowledge, this was the first study to evaluate the characteristics of iron metabolism markers in patients with CHF and anemia in Jordan. The primary outcome was to evaluate the erythrocyte parameters in patients with CHF and anemia. The secondary outcome was to recognize the characteristics of iron metabolism, erythropoiesis as well and inflammation markers among the studied patients.

Materials and Methods

Study design and setting

This was a retrospective cross-sectional study. The study included 150 patients with a diagnosis of CHF and anemia, who were in the hospital for decompensation of CHF or who applied on an outpatient basis in a large private hospital in Jordan during the period from January to March 2023.

Data collection

The diagnosis of CHF was established in accordance with the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines of 2022 [30]:

1. The stages of CHF were established according to the domestic classification [31].
2. Functional class CHF was determined according to the criteria of the New York Heart Association (NYHA — New York Heart Association) [32].
3. To assess the presence of CHF, the level of the N-terminal fragment of the precursor of the brain natriuretic peptide (NT-proBNP) was taken into account.
4. The diagnosis of anemia was established according to the criteria of the World Health Organization (WHO) according to the level of hemoglobin in men <130 g/l, and in women <120 g/l [33].

Patients

The study included 150 patients with a diagnosis of CHF and anemia.

Inclusion criteria

Patients not receiving iron preparations before the study for 3 months;

Exclusion criteria

- severe and acute anemia;
- proven causes of anemia (diseases of the gastrointestinal tract, bleeding, malabsorption, etc.);
- systemic inflammatory, oncological, autoimmune, infectious diseases;
- kidney disease, chronic kidney disease ≥III stage;

- blood diseases
- patients with CHF stages III and IV, according to NYHA.

Laboratory measurements

Anemia parameters were assessed in the total participants of patients before the start of CHF treatment. To obtain the main characteristics of anemia, erythrocyte indicators of a clinical blood test were used: hemoglobin (Hb), red blood cell count (RBC), hematocrit (Ht), mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), erythrocyte sedimentation rate (ESR). To assess the violation of iron metabolism, biochemical parameters were studied: SI, SF, TR, and soluble transferrin receptors (STR). The activity of erythropoiesis was assessed by the EPO index. The degree of systemic inflammation and its effect on iron metabolism was determined by the content of CRP and hepcidin.

In order to identify differences in the characteristics of anemia, participants were divided into 3 subgroups: patients with AID (SF <100 µg/L) (n=50), with FID (SF 100-300 µg/L and ITSC <20%) (n=50), and other patients (anemia without ID, n=50).

Treatment intervention

For the treatment of CHF, uniform standards were used, regardless of age and gender. Basic therapy for CHF in the total participants included: angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-blockers (with additional prescription of ivabradine according to indications), nitrates, diuretics, digoxin, as well as amiodarone in the presence of ventricular arrhythmias, oral anticoagulants, heparin or low molecular weight heparins (for venous thrombosis), omega-3 polyunsaturated fatty acids, etc. [34].

Ethical considerations

The research was carried out in conformity with the Declaration of Helsinki's tenets and Good Clinical Practice. The Research Ethics Committee at the University of Petra gave its approval to the study plan. Before enlisting in the research, all individuals gave written consent.

Statistical analysis

Statistical analysis was performed using the IBM SPSS Statistics-20 application package. The hypothesis about the normality of the distribution of indicators was tested using the Shapiro-Wilk test. With a distribution close to normal, the results were expressed as the mean and standard deviation (Mean ± SD), and differences were assessed using Student's t-test. With a distribution other than normal, the results were presented as a median and interquartile range [Median (min-max)], and non-parametric Wilcoxon and Mann-Whitney tests were used to assess differences. Friedman's test was used to determine the degree of difference between three dependent samples. Differences were considered statistically significant at $P \leq 0.05$.

Results and Discussion

The mean age (interquartile range) was 77.4 (66-82) years, of which 70 (46.7%) female patients and 80 (53.3%) males; more than half of the studied patients 85 (56.7%) had stage I of CHF (the least severe stage with no symptoms); patients with stage II were 65 (43.33%).

Table 1. Demographic and clinical data of the studied patients (n=150)

Variable	Parameter	N (%)
Age (years)	• Median (min-max)	77.4 (66-82)
Sex n (%)	• Male	80 (53.3%)
	• Female	70 (46.7%)
CHF Stage n (%)	• Stage I	85 (56.7%)
	• Stage II	65 (43.33%)

Erythrocyte parameters in patients of the total participants are presented in **Table 2**. Hb values corresponded to a mild degree of anemia, the characteristics of normochromic normocytic anemia were traced. Hb recorded 111 g/l ranging from 103 to 118 g/l. The median RBC was 3.8 10^{12}/l with a range from 3.6 to 3.99 10^{12}/l. The median value of MCH was 29 pg with a range of 25 to 331 pg. the median value of MCV was 87 fl with a range of 81 to 111fl.

Table 2. Erythrocyte parameters in patients of the total participants (n=150)

Index	Reference values	Median (min-max)
Hb (g/l)	M: 126-174, F: 117-161	111 (103-118)
RBC (10^{12}/l)	M: 3.9-5.8, F: 3.7-5.2	3.8 (3.6-3.99)
MCH (pg)	27-31	29 (25-331)
MCV (fl)	81-102	87 (81-111)

Note: M - male, F – female, Hb - hemoglobin, RBC - Red blood cell count, MCH – Mean Corpuscular Hemoglobin, MCV: Mean Corpuscular Volume.

Indicators of iron metabolism, erythropoiesis, and inflammation markers in the total participants are presented in **Table 3**. SI, SF, and soluble transferrin receptors (STR) matched reference levels, transferrin (TR) was below normal, which was not usual for ID, and the median ITSC <20% is an indication of ID. SI, SF, and TR conformed to reference values. High average values of CRP and hepcidin suggested the existence of systemic inflammation and blockage of iron circulation, while normal values of EPO indicated insufficient erythropoiesis in anemia and CHF.

Table 3. Indicators of iron metabolism and their reference values among total participants (n=150)

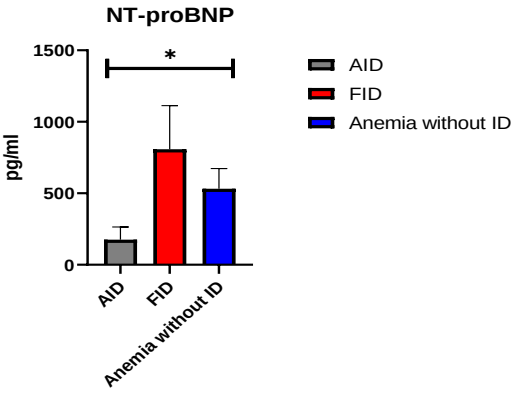
Index	Reference values	Median (min-max)
SF (ng/ml)	M: 20-60 years: 30-400 F: 17-60 years: 13-150	168 (75-352)

SI (µmol/l)	5.83-34.5	9 (5-11)
TR (g/l)	2.0-3.6	1.8 (1.7-2.5)
STR (mg/l)	M: 2.2-5.0. F: 1.9-4.4	3.9 (2.5-5.3)
ITSC (%)	20-55	18 (11-30)
TIBC (µmol/l)	45-76	42 (34-53)
EPO (mIU/ml)	4.3-29.0	16 (9-24)
CRP (mg/l)	<5	17 (5-46)
Hepcidin (ng/l)	<(60-85)	173 (76-485)

Note: M — male, F - female, SF - serum ferritin, SI — serum iron, TR — transferrin, STR — soluble transferrin receptors, ITSC - Iron transferrin saturation coefficient, TIBC - total iron-binding capacity of serum, EPO — erythropoietin, CRP — C-reactive protein.

When studying indicators of anemia, there were no statistical differences from functional class CHF in any of the studied parameters in the total participants of patients. A wide range of values was noteworthy, probably due to the small total group studied.

Characteristics of anemia, indicators of iron metabolism, erythropoiesis, and inflammation, according to the variant of anemia and ID (AID, FID, and anemia without ID) are presented in **Figure 1**. TR, STR, ITSC, TIBC, EPO, and CRP all showed statistically significant variations, indicating important variations in iron metabolism among these subgroups.



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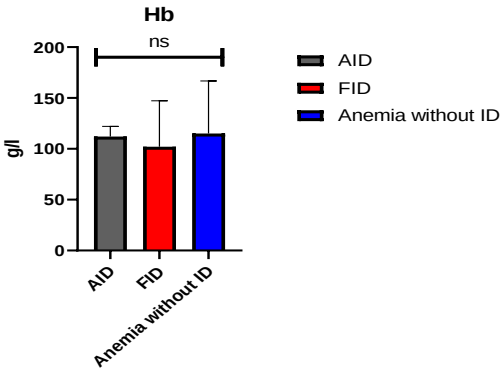

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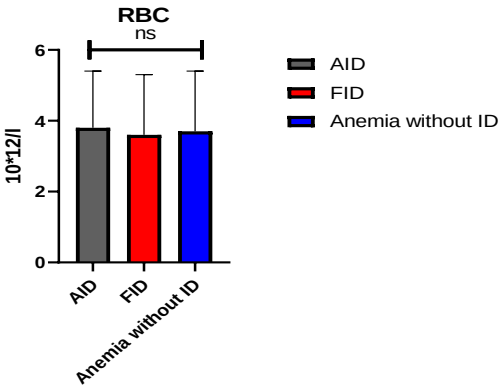

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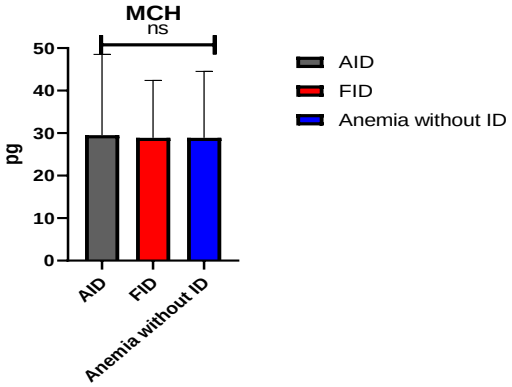

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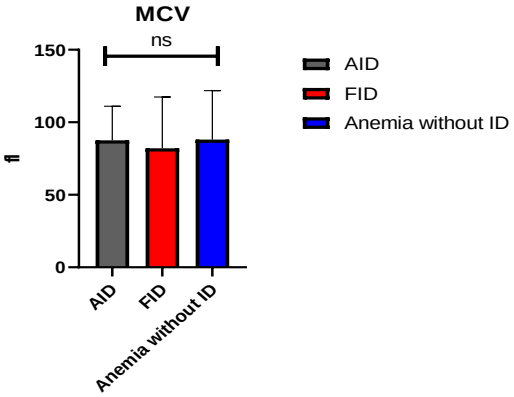

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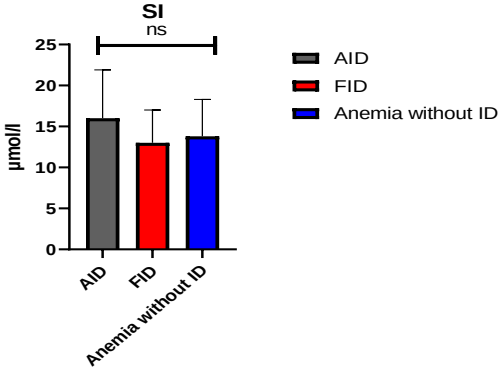

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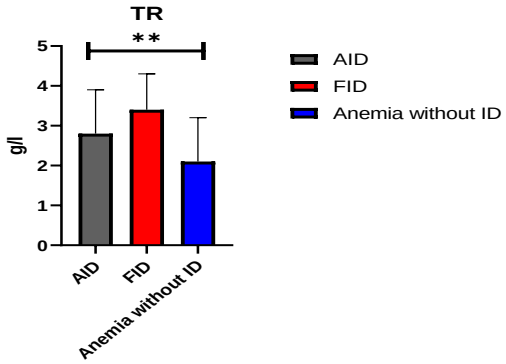

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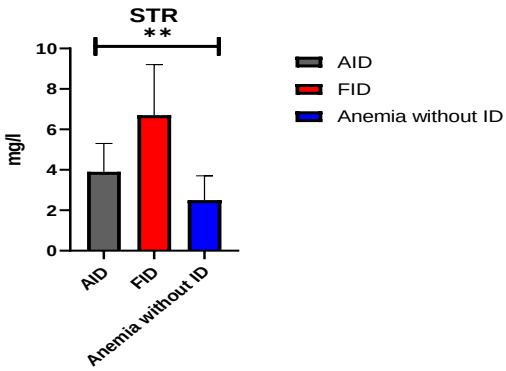

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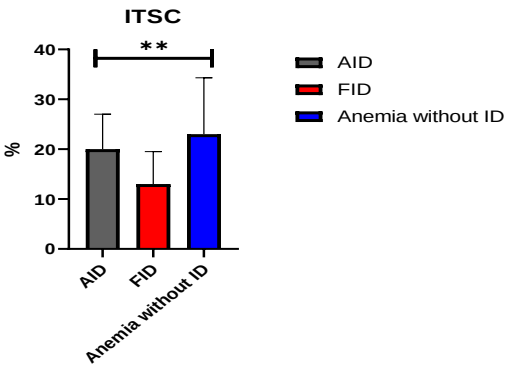

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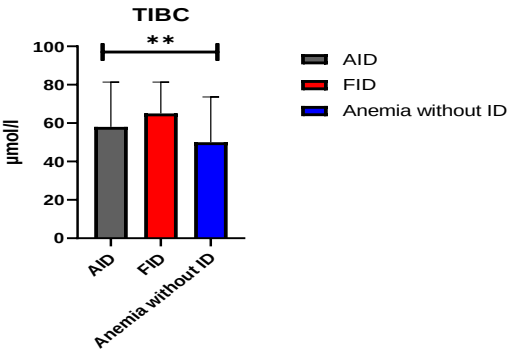

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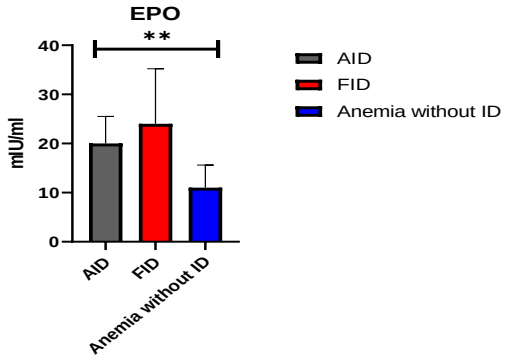

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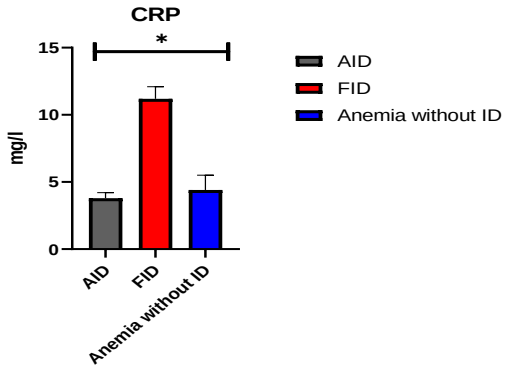

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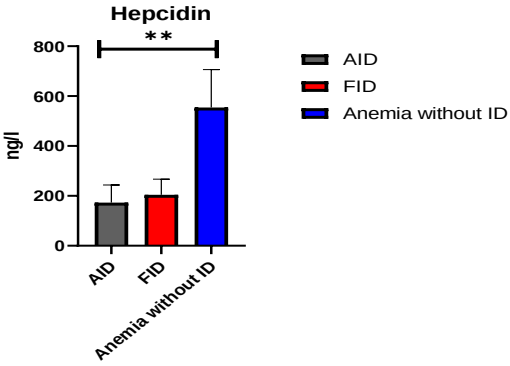

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Figure 1. Indicators of iron metabolism depending on the variant of anemia and ID.

Note: data was presented as Mean ± SD. AID — absolute iron deficiency, IA — iron deficiency, ITSC - Iron transferrin saturation coefficient, TIBC — total serum iron-binding capacity, STR — soluble transferrin receptors, SI — serum iron, CRP — C-reactive protein, TR — transferrin, MCH – mean content of hemoglobin in erythrocytes, FID — functional iron deficiency, SF — serum ferritin, EPO — erythropoietin, Hb — hemoglobin, RBC — Red blood cells, NT-proBNP — N-terminal fragment of probrain natriuretic peptide, MCV: Mean Corpuscular Volume. n.s: not significant, *p significant if <0.05, **p highly significant if <0.001.

Given the fact that statistically significant differences in **(Figure 1)** are presented only for indicators that had a nonparametric distribution, at the second stage of the analysis, post-hoc pairwise

comparisons of these indicators were carried out using the Mann-Whitney test. Since comparisons were made in 3 groups, taking into account the "multiple comparisons effect", a new critical significance level "*P*" was determined: 0.05/3=0.017 **(Table 4)**. In the AID subgroup, CRP and hepcidin values were minimal, indicating a minor role in inflammation; in the FID subgroup, iron transferrin saturation coefficient values were minimal, but TR, STR, TIBC, and EPO values were maximal, indicating a high need for iron and activation of hematopoiesis. A minimum of EPO and a maximum of hepcidin were found in the subgroup with anemia without ID, identifying these individuals as a group with the usual anemia of chronic illnesses.

Table 4. Post hoc comparisons of iron metabolism indicators among subgroups of AID, FID, and anemia without ID

Index	P-value		
	AID FID (n=50)	FID-without ID (n=50)	Anemia-without ID (n=50)
TR (g/l)	0.6	0.03	0.002
STR (mg/l)	0.05	0.002	0.2
Iron transferrin saturation coefficient (%)	0.08	0.002	0.02
TIBC (μmol/l)	0.8	0.008	0.003
EPO (mIU/ml)	0.04	0.004	0.2
CRP (mg/l)	0.08	0.9	0.004

Note: critical significance level p<0.017. AID — absolute iron deficiency, ID — iron deficiency, TIBC — total serum iron-binding capacity, STR — soluble transferrin receptors, CRP — C-reactive protein, TR — transferrin, FID — functional iron deficiency, EPO – erythropoietin.

The official literature has long discussed the close relationship between anemia and CHF, and its negative impact on the outcomes and course of CHF. It is still a debatable issue about the primary etiological factor of this problem and the methods for its solution [35]. However, the most important factor is currently assigned to the factor of ID, which, in addition to impaired hematopoiesis, leads to a decrease in the performance of the heart muscle [36, 37]. Thus, the problem of anemia and ID in CHF requires the development and implementation of diagnostic and therapeutic measures, especially since a pronounced positive clinical effect of successful correction of anemia in this category of patients has been proven [38-40]. To the best of our knowledge, this was the first study to evaluate the characteristics of iron metabolism markers in patients with CHF and anemia in Jordan.

Our findings, which were consistent with those of other investigations, demonstrated that anemia and a rise in its intensity might raise the risk of secondary, chronic conditions brought on by CHF and lead to an adverse prognosis for the condition [41-43].

Iron deficiency anemia is an extreme stage of ID, so it is completely wrong to interpret iron deficiency syndromes as iron deficiency anemia. For example, many domestic publications indicated the detection of ID anemia in patients with CHF and anemia [19, 44]; in turn, foreign colleagues interpreted such changes as ID — this is the right decision, which is confirmed by the latest accepted clinical recommendations for CHF [45, 46]. ID is a common cause of anemia and the factors that lead to the development of iron deficiency erythropoiesis are different and are called iron deficiency syndromes. There are AID, FID, and iron deposition as a manifestation of anemia of chronic diseases. They are characterized by common similar parameters in terms of erythrocyte and SI morphology: hypo-normochromic, micro-normocytic character of anemia, and low level of SI, so these parameters should never be used to confirm one or another variant of iron deficiency syndromes [35]. However, an obvious difference was found in the indicators of iron metabolism (SF, ITSC, TIBC, STR), which are necessary for differential diagnosis of syndromes and the issue of methods for further treatment of patients.

In the patients examined in this work, normochromic, normocytic anemia was revealed with EPO indicators, as a factor in the adequacy of erythropoiesis, 16 (9-24) IU/l, the most important regulator of iron metabolism, hepcidin - 173 (76-485) ng/l, CRP - 17 (5-46) mg/l, which characterized this variant of anemia as anemia of chronic disease, and the content of FS was 168 (75-352) μg/l, and ITSC - 18 (11-30), which indicated a significant the role of ID in this group.

In a related investigation by Spazzafumo *et al*. (2021) [47], they discovered a negative association between Hb and CRP, indicating that anemia may be a sign of inflammation in older people. The dysregulation of proinflammatory cytokines, especially interleukin-6, which might also negatively impact hematopoiesis by either blocking the generation of erythropoietin (EPO) or by interfacing with EPO receptors, is also substantially associated with aging, according to the latest researches [48, 49]. In a research similar to ours, Morici *et al*. found that older patients with CVD and anemia in the previous 24 months had a greater mortality risk than those with anemia in general [49, 50].

No data were obtained on the effect of CHF functional class on the parameters of erythrocytes, iron metabolism, erythropoiesis, and inflammation markers.

The number of patients with AID was 33.3%, with FID – 33.3%, with anemia without FD – 33.3%. Moreover, AIDS and FID were characterized by significant disorders of iron metabolism, and anemia without ID is a typical anemia of chronic diseases. Thus, about 66.7% of patients with anemia and CHF require the appointment of iron preparations.

The data obtained could make it possible to single out a separate group of patients with SF <30 μg/l according to the signs most similar to ID anemia. Other forms of iron deficiency syndromes with SI <30 μg/l met the criteria for anemia of chronic disease with or without ID (extremely high levels of not only hepcidin but also CRP and EPO).

Limitations

One limitation of our study was the absence of information on concurrent erythropoietin treatment or blood transfusions. Also, we lacked follow-up data regarding patients with anemia and

inflammation; this information would undoubtedly be very intriguing. To validate these results, larger clinical investigations with prospective designs are necessary.

Conclusion

In patients with CHF, anemia was normochromic, and normocytic, characterized by a high content of CRP, hepcidin, and inadequate production of EPO.

Patients with AID and FID did not differ in the main parameters of iron metabolism and in the aggregate account for 66.7% ($p = 0.02$) of the total group; these patients require the appointment of iron preparations.

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Conflict of interest: None

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Ethics statement: Informed consent was obtained from all subjects involved in the study.

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