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Iron deficiency in Russia heart failure patients. Observational cross-sectional multicenter study

Aim	To evaluate the prevalence of iron deficiency (ID) in Russian patients with heart failure (HF).
Material and methods	Iron metabolism variables were studied in 498 (198 women, 300 men) patients with HF. Data were evaluated at admission for HF (97%) or during an outpatient visit (3%). ID was determined according to the European Society of Cardiology Guidelines.
Results	83.1% of patients had ID; only 43.5% of patients with ID had anemia. Patients with ID were older: 70.0 [63.0;79.0] vs. 66.0 years [57.0;75.2] (p=0.009). The number of patients with ID increased in parallel with the increase in HF functional class (FC). Among patients with ID, fewer people were past or current alcohol users (p=0.002), and a greater number of patients had atrial higher fibrillation (60.1 vs. 45.2%, p=0.016). A multiple logistic regression showed that more severe HF (HF FC) was associated with a higher incidence of ID detection, whereas past alcohol use was associated with less pronounced ID. An increase in N-terminal pro-brain natriuretic peptide (NT-proBNP) by 100 pg/ml was associated with an increased likelihood of ID (odds ratio, 1.006, 95% confidence interval: 1.002–1.011, p=0.0152).
Conclusion	The incidence rate of HF patients is high in the Russian Federation (83.1%). Only 43.5% of these patients had anemia. The prevalence of ID in the study population increased with increases in HF FC and NT-proBNP.
Keywords	Heart failure; iron deficienc; anemia
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Introduction

Iron deficiency (ID) with or without anemia has been commonly associated with heart failure (HF). There is a well-established link between ID and numerous clinical signs and complications in HF patients, such as decreased functional ability and quality of life [1, 2], increased risk of hospitalization [3], and death in HF patients with reduced left ventricular (LV) ejection fraction (HFrEF) [4]. This connection is evident regardless of the presence of anemia. Currently, in Russia, internationally accepted principles of ID diagnosis are not included in the government standards of laboratory tests for patients with HF.

Moreover, most general practitioners are not cognizant of the presence of ID in patients with HF unless the patient is diagnosed with anemia. However, reduced hemoglobin can be viewed as the final step of a process beginning with the gradual depletion of iron stores, so even if chronic HF patients are not anemic, ID may be present. To our knowledge, there are no available data regarding the prevalence of ID among Russian HF patients. Thus, the aim of the study was to evaluate the prevalence of iron deficiency among such patients.

Material and methods

Study population

This observational, cross-sectional trial was organized by the Russian Society of Specialists in Heart Failure. Study investigators were specialists in HF management, i.e., cardiologists and geriatricians, at 13 clinical centers throughout Russia. Inclusion criteria were adult patients with pre-existing or new-onset HF, regardless of LV ejection fraction (LVEF), who were seen at the ambulatory clinic (3%) or were admitted to the hospitals of participating centers (97%) during the enrolment period. Exclusion criteria: age <18 yrs; red blood cell (or other blood components) transfusions or erythropoietin therapy within three mos prior to enrollment; iron, vitamin B12, or folate supplements to treat anemia within three mos prior to enrollment; known malignant, hematological, or other active neoplasia; immunosuppressive therapy, chemotherapy, or radiotherapy within three mos prior to enrollment; pregnancy or lactation.

HF was defined according to the 2016 European Society of Cardiology (ESC) guidelines [5] and based on typical symptoms, and signs of HF accompanied with elevated N-terminal pro-brain natriuretic peptide (NT-proBNP) ≥125 pg/l and any LVEF.

The study protocol was conducted in accordance with the Declaration of Helsinki and the Guidelines on Good Clinical Practice and was approved by the local ethics committee of each center.

Blood collection

The central laboratory of each center was used to collect, analyze, and report the results of the following parameters: ferritin, transferrin saturation, iron, NT-proBNP. Hemoglobin and complete blood count were measured in local laboratories. Using the World Health Organization criteria, anemia was defined as hemoglobin <12.0 g/dl in women and <13.0 g/dl in men [6]. The definition adopted by the ESC was used for ID, i.e., ferritin <100 μg/l or transferrin saturation (TSAT) <20% if ferritin 100–299 μg/l [5].

Statistical analysis

Numbers and percentages are reported for categorical variables, and the chi-square test was used to analyze these variables. For continuous variables, medians with 25th -75th quartiles are reported. Wilcoxon test was used to analyze continuous variables, and multiple logistic regression was used to identify variables associated with an ID diagnosis.

Results

From September 2020 to July 2021, 510 HF patients in 13 centers were screened, and 97.6% (498) were analyzed for iron status (Figure 1). Patient characteristics are shown in Table 1.

97.0% (483) of the HF patients were enrolled during hospitalization, and 3.0% (15) were enrolled at outpatient visits. ID was present in 83.1% (414) of the patients and absent in 16.9% (84). However, only 43.5% (180) of the patients with ID also had anemia. Among the 84 patients without ID, 25.0% (21) had anemia. The distribution of patients with ID and anemia is shown in Figure 2. Only 4.2% (21) of all patients had anemia without ID, 36.1% (180) had ID and anemia, 47.0% (234) had ID without anemia, and 12.7% (63) had neither ID nor anemia.

There was no difference in ID prevalence depending on HF type (Table 1), but the number of patients with ID increased with increasing NYHA (p=0.003) and with N-terminal pro-b-type natriuretic peptide (NT-proBNP) (p<0.001).

Patients with ID were older 70.0 [63.0;79.0] yrs vs 66.0 [57.0;75.2] yrs (p=0.009). Among patients with ID, there were fewer patients with a history of past or present heavy alcohol consumption (p=0.002), and more had atrial fibrillation (AF) (60.1% vs. 45.2%, p=0.016). Clinical and laboratory measurements at admission are summarized in Table 1.

As a higher prevalence of ID could be due to the fact that older patients could have both ID and AF, we performed a multiple logistic regression analysis that included AF, gender, age, and interaction between AF and age. This model confirmed an interaction between age and AF, and it showed that AF is not an independent predictor of ID.

To exclude the possibility that alcohol consumption could be due to a higher prevalence of excessive alcohol drinking in men, we examined another model that included age, past or present heavy alcohol consumption, gender, and their interaction. This model did not show an interaction between gender and alcohol consumption, but it showed that past but not current alcohol consumption is associated with a lower rate of ID.

A third model included age, sex, alcohol consumption, and NYHA. The model showed that NYHA IV vs. NYHA I was associated with a higher rate of ID (odds ratio 5.6, 95% CI 1.51–21.63, p=0.01) and that past heavy alcohol consumption was associated with a lower prevalence of ID (odds ratio 0.38, 95% CI 0.18–0.81, p=0.01). When NYHA was changed to NT-proBNP in the model, it showed that an increase of NT-proBNP by 100 pg/ml was associated with increased odds of ID (odds ratio 1.006, 95% CI 1.002–1.011, p=0.0152).

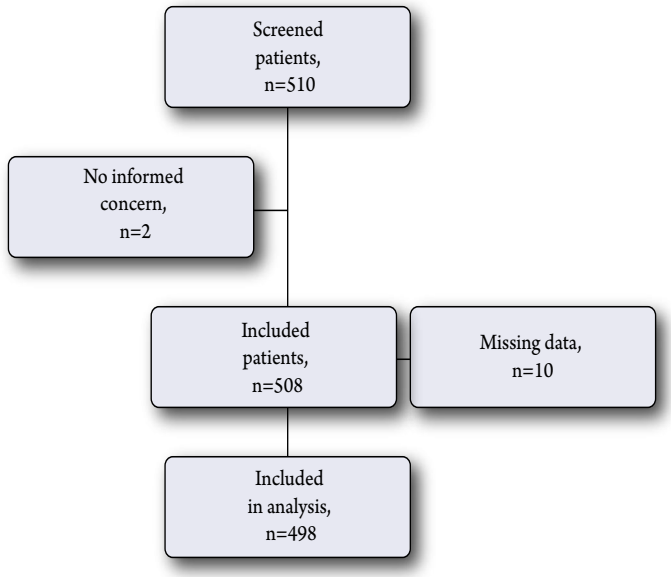
Discussion

The results of this study show that ID has a very high prevalence in Russian patients with HF, even among nonanemic patients. This study is, to our knowledge, the first assessment of ID in a large multicenter cohort of Russian HF patients. Previous a single-center studies showed a similar prevalence of ID in HF patients [7].

International works showed that 30–69% ambulatory and 60–85% hospitalized HF patients had ID [8], the number of ID is increased with increasing in NYHA and NTproBNP and that a high number of patients had ID without anemia [9].

In recent years, a number of studies have shown that correcting ID with intravenous iron supplementation in patients with chronic HF may improve LV function and quality of life [10–12]. This fact and the confirmed high prevalence of ID in Russia highlight the importance of ID screening and correction.

Figure 1. Patient inclusion flowchart



Conclusion

Rates of ID among hospitalized HF patients in the Russian Federation are high (83.1%). Only 43.5% of these patients were anemic. The number of ID is increasing with increasing in NYHA and NTproBNP.

Etics

Our study complies with the Declaration of Helsinki. Research protocol was approved by ethics committees in each centres. Informed consent has been obtained from the subjects.

Limitations

Some of the centers that participated in the trial were specialized centers for HF, and the ID and anemia

Figure 2. Distribution of patients depending on the presence anemia and ID

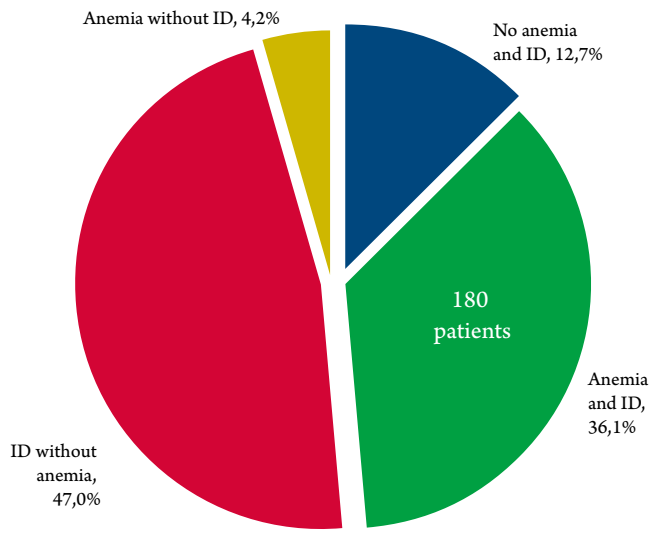


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Table 1. Patient characteristics

Variable	All, n=498	ID, n=414	No ID, n=84	p, ID vs No ID
Age	69.0 [61.0;79.0]	70.0 [63.0;79.0]	66.0 [57.0;75.2]	0.009
Body mass index, kg/m^2	30.3 [26.0;35.0]	30.7 [26.1;35.2]	29.1 [25.4;33.1]	0.061
Male gender	300 (60.2%)	240 (58.0%)	60 (71.4%)	0.030
AF	287 (57.6%)	249 (60.1%)	8 (45.2%)	0.016
Excessive alcohol consumption				0.002
Present	36 (7.23%)	27 (6.52%)	9 (10.7%)	–
Past	40 (8.03%)	26 (6.28%)	14 (16.7%)	–
Never	422 (84.7%)	361 (87.2%)	61 (72.6%)	–
Current heavy alcohol consumption	36 (7.23%)	27 (6.52%)	9 (10.7%)	0.262
Surgery	35 (7.03%)	25 (6.04%)	10 (11.9%)	0.092
DM	157 (31.5%)	134 (32.4%)	23 (27.4%)	0.442
Hypothyroidism	19 (3.82%)	17 (4.11%)	2 (2.38%)	0.534
Hyperthyroidism	3 (0.60%)	2 (0.48%)	1 (1.19%)	1.000
Type of CHF:				0.745
HFpEF	202 (40.6%)	165 (39.9%)	37 (44.0%)	–
HFrEF	213 (42.8%)	180 (43.5%)	33 (39.3%)	–
HFmrEF	83 (16.7%)	69 (16.7%)	14 (16.7%)	–
EF, %	45.0 [32.0;55.0]	45.0 [32.0;55.0]	46.0 [31.8;60.0]	0.197
Hemoglobin, g/dl				0.003
TSAT, %	19 (3.82%)	12 (2.90%)	7 (8.33%)	–
Ferritin, ng/ml	142 (28.5%)	110 (26.6%)	32 (38.1%)	–
Iron, ng/ml	261 (52.4%)	222 (53.6%)	39 (46.4%)	–
Transferin, mg/ml	76 (15.3%)	70 (16.9%)	6 (7.14%)	–
Anemia	3231 [995;7723]	3744 [1219;8446]	1402 [378;3544]	<0.001
Erythrocytes, 10^6/ µl	13.1 [11.6;14.4]	12.9 [11.4;14.3]	13.8 [12.7;15.9]	<0.001
Leukocytes, 10^9/l	13.8 [8.18;22.4]	12.1 [7.10;17.5]	28.0 [21.2;35.2]	<0.001
MCH, pg/cell	67.3 [35.5;129]	52.7 [30.0;90.8]	182 [139;324]	<0.001
MCV, fl	9.10 [5.56;14.3]	8.30 [5.12;12.1]	16.3 [11.0;20.6]	<0.001
NT-proBNP pg/ml	2.71 [2.29;3.17]	2.82 [2.40;3.25]	2.19 [1.94;2.58]	<0.001
NYHA:	201 (40.4%)	180 (43.5%)	21 (25.0%)	0.002
I	4.47 [4.00;4.91]	4.46 [3.99;4.89]	4.47 [4.10;5.07]	0.232
II	7.43 [6.22;9.10]	7.43 [6.20;9.05]	7.53 [6.54;9.22]	0.628
III	29.2 [26.9;30.9]	28.9 [26.7;30.5]	30.5 [29.4;32.0]	<0.001
IV	89.3 [83.9;94.1]	88.4 [83.0;93.4]	91.9 [89.0;97.4]	<0.001
6-min walking test (m)	252 [175;329]	250 [170;320]	299 [210;358]	<0.001

Data are number and percentage, or median with 25th;75th quartile, or mean±SD. AF, atrial fibrillation; DM, diabetes mellites; CHF, congestive heart failure; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HFmrEF, heart failure with midrange ejection fraction; EF, ejection fraction; TSAT, transferrin saturation; MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; NT-proBNP, N-terminal pro b-type natriuretic peptide; NYHA, New York Heart Association; I, II, III, IV, NYHA HF classes.

prevalence could somewhat differ from that in a primary care setting.

Since there were few ambulatory patients in the study, it was impossible to investigate separately ambulatory patients with HF.

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REFERENCES

1. Ezekowitz JA, McAlister FA, Armstrong PW. Anemia is common in heart failure and is associated with poor outcomes: insights from a cohort of 12 065 patients with new-onset heart failure. Circulation. 2003;107(2):223–5. DOI: 10.1161/01.CIR.0000052622.51963.FC

2. Mozaffarian D, Nye R, Levy WC. Anemia predicts mortality in severe heart failure. Journal of the American College of Cardiology. 2003;41(11):1933–9. DOI: 10.1016/S0735-1097(03)00425-X
3. Felker GM, Gattis WA, Leimberger JD, Adams KF, Cuffe MS, Gheorghiade M et al. Usefulness of anemia as a predictor of death and rehospitalization in patients with decompensated heart failure. The American Journal of Cardiology. 2003;92(5):625–8. DOI: 10.1016/S0002-9149(03)00740-9
4. Fitzsimons S, Yeo TJ, Ling LH, Sim D, Leong KTG, Yeo PSD et al. Impact of change in iron status over time on clinical outcomes in heart failure according to ejection fraction phenotype. ESC Heart Failure. 2021;8(6):4572–83. DOI: 10.1002/ehf2.13617
5. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. European Heart Journal. 2016;37(27):2129–200. DOI: 10.1093/eurheartj/ehw128
6. Tereshchenko S.N., Galyavich A.S., Uskach T.M., Ageev F.T., Arutyunov G.P., Begrambekova Yu.L. et al. 2020 Clinical practice guidelines for Chronic heart failure. Russian Journal of Cardiology. 2020;25(11):311–74. [Russian: Терещенко С.Н. Галявич А.С., Ускач Т.М., Агеев Ф.Т., Арутюнов Г.П., Беграмбекова Ю.Л. и др. Хроническая сердечная недостаточность. Клинические рекомендации 2020. Российский кардиологический журнал. 2020;25(11):311-74]. DOI: 10.15829/1560-4071-2020-4083
7. World Health Organization. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity. Av. at: https://apps.who.int/iris/bitstream/handle/10665/85839/WHO_NMH_NHD_MNM_11.1_eng.pdf?sequence=22&isAllowed=y.
8. Smirnova M.P., Chizhov P.A., Baranov A.A., Ivanova Yu.I., Medvedeva T.V., Pegashova M.A. Iron deficiency associations in patients with chronic heart failure. The Bulletin of Contemporary Clinical Medicine. 2021;14(4):27–34. [Russian: Смирнова М.П., Чижов П.А., Баранов А.А., Иванова Ю.И., Медведева Т.В., Пегашова М.А. Ассоциации дефицита железа у пациентов с хронической сердечной недостаточностью. Вестник современной клинической медицины. 2021;14(4):27-34]. DOI: 10.20969/VSKM.2021.14(4).27-34
9. Rocha BML, Cunha GJL, Menezes Falcão LF. The Burden of Iron Deficiency in Heart Failure. Journal of the American College of Cardiology. 2018;71(7):782–93. DOI: 10.1016/j.jacc.2017.12.027
10. Klip IjT, Comin-Colet J, Voors AA, Ponikowski P, Enjuanes C, Banasiak W et al. Iron deficiency in chronic heart failure: An international pooled analysis. American Heart Journal. 2013;165(4):575-582.e3. DOI: 10.1016/j.ahj.2013.01.017
11. Okonko DO, Grzeslo A, Witkowski T, Mandal AKJ, Slater RM, Roughton M et al. Effect of Intravenous Iron Sucrose on Exercise Tolerance in Anemic and Nonanemic Patients with Symptomatic Chronic Heart Failure and Iron Deficiency. Journal of the American College of Cardiology. 2008;51(2):103–12. DOI: 10.1016/j.jacc.2007.09.036
12. Ponikowski P, van Veldhuisen DJ, Comin-Colet J, Ertl G, Komajda M, Mareev V et al. Beneficial effects of long-term intravenous iron therapy with ferric carboxymaltose in patients with symptomatic heart failure and iron deficiency. European Heart Journal. 2015;36(11):657–68. DOI: 10.1093/eurheartj/ehu385
13. Anker SD, Comin Colet J, Filippatos G, Willenheimer R, Dickstein K, Drexler H et al. Ferric Carboxymaltose in Patients with Heart Failure and Iron Deficiency. New England Journal of Medicine. 2009;361(25):2436–48. DOI: 10.1056/NEJMoa0908355

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