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Iron deficiency in patients with heart failure and a higher incidence of stroke

Niedobór żelaza u pacjentów z niewydolnością serca a większa częstość udarów mózgu

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Abstract

Introduction. Iron deficiency (ID) is a common comorbidity in heart failure (HF), associated with a worse prognosis. According to European Society of Cardiology 2021 guidelines referring to chronic and acute HF, ID should be actively looked for in HF patients. It was found out that i.v. iron supplementation decreases the risk of hospitalisation in patients with heart failure with reduced ejection fraction (HFrEF). This study aimed to assess the significance of ID for the population with heart failure, especially with preserved ejection fraction (HFpEF).

Material and methods. The study was based on a retrospective analysis of 150 patients (69 women and 81 men) with heart failure (HFpEF = 44.67%; n = 67) treated between 2018 and 2021 in the Department of Non-invasive Cardiology, Medical University of Łódź. The analysis was performed related to ID and EF < 50 vs. ≥ 50% using Statistica 13.1PL (StatSoft, Tulsa, USA).

Results. Significant differences between HF patients with and without ID were observed not only in red blood cell parameters [haemoglobin (Hb), haematocrit (Ht), mean corpuscular volume, mean corpuscular haemoglobin concentration and red cell distribution width (RDW)] or other laboratory test results (urine acid, sodium ions) but also in 6 minute walking test (6MWT) (250.98 ± 101.55 vs. 292.52 ± 82.74; p = 0.041) and stroke/transient ischemic attack (TIA) history (19.77% vs. 4.68%; p = 0.015). Therefore, there was no significant difference in ferritin level, transferrin saturation or ID frequency between patients with EF < 50% and EF > 50%. Spearman's rank correlation analysis revealed negative correlation between number of hospitalisations due to HF in last 12 months and red blood cell count (r = –0.193; p = 0.018), Hb (r = –0.244; p = 0.003), Ht (r = –0.227; p = 0.005) and 6MWT (r = –0.224; p = 0.032), but positive correlation between number of hospitalisations due to HF in last 12 months and RDW (r = 0.238; p = 0.003). The regression analysis showed that the number of hospitalizations due to HF was dependent on N-terminal pro-B-type natriuretic peptide (b = 0.263) and RDW (b = 0.346).

Conclusions. Iron deficiency not only affects the results of 6MWT but also is associated with a higher incidence of TIA/stroke in the population suffering from HF. Thus, ID diagnosis and treatment should be considered among patients with HF, both in HFrEF and in HFpEF.

Key words: heart failure, iron deficiency, repeated hospitalisations, stroke, TIA

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Introduction

Optimal conventional therapy of heart failure (HF) remains insufficient to improve the quality of life of many patients with comorbidities. As consequence, they are susceptible to repeated hospitalisations [1]. Iron deficiency (ID) is one such comorbidity and affects approximately 55% of patients with HF irrespective of the range of left ventricular ejection fraction (LVEF) or the coexisting anaemia [2]. It is well known that ID contributes to worsening mitochondrial dysfunction, already present in HF, and promotes the metabolic shift from fatty acids to glucose use. Consequently, myocardial ID can cause progressive left ventricular remodelling and can lead to a decrease in exercise capacity [3]. Furthermore, there is a hypothesis that ID may play a key pathophysiological role in the progression of chronic HF as it enhances the activity of the sympathetic nervous system [4]. According to European Society of Cardiology (ESC) 2021 guidelines [2], all HF patients should be periodically screened for the presence of anaemia and ID by using full blood count, serum ferritin and transferrin saturation (TSAT) measurement. It was found out that i.v. iron decreases the risk of hospitalisation in patients with HF with reduced ejection fraction (HFrEF) [2]. Although the impact of ID on HF with preserved ejection fraction (HFpEF) was also confirmed, further investigation is still needed [2, 5]. This study aimed to assess the significance of ID for the population with HF, especially with HFpEF.

Material and methods

The study was approved by the Bioethical Commission of Medical University (MU) of Łódź, the resolution number RNN/25/22/KE dated 8 February 2022. The retrospective analysis included 150 patients (69 women and 81 men) with heart failure (HFpEF = 44.67%; n = 67) treated between 2018 and 2021 in the Department of Non-invasive Cardiology, MU of Łódź. The average patient's age was 72 ± 10.55 years. Collected data included a standard set of diagnostic tests, such as electrocardiogram, echocardiography, 6 minute walking test (6MWT) and blood tests. The information about patients' body mass index, HF aetiology, number of recurrent HF hospitalizations and concomitant diseases or conditions were also scored. The diagnosis of HFrEF, HFpEF and ID were established using the ESC 2021 guidelines criteria [2].

Patients were analysed related to ID and EF < 50 vs. ≥ 50% using appropriate statistical tests. The normality of distribution for continuous variables was tested using the Shapiro-Wilk test. To compare continuous variables, the Mann-Whitney U test or Student's t-test were used, as applicable. Continuous variables were presented as mean ± standard deviation or together with the interquartile range as applicable. Nominal variables were tested using the Chi-square test, with Yates correction where needed. Statistically significant nominal variables were expressed as percentages.

To assess which variables were associated with hospitalizations due to HF in one year, univariable analysis using Spearman's correlation coefficient and multivariable logistic regression using the backward stepwise method was performed. The correlation was evaluated using the R coefficient and the degree of change in the dependent variable was assessed with beta coefficients. A p-value of < 0.05 was statistically significant. Statistical analysis was performed using Statistica 13.1PL (StatSoft, Tulsa, USA).

Results

Iron deficiency was diagnosed in 86 (57.33%) patients, including 40 (59.7%) HFpEF patients. Therefore, numerous comorbidities were noticed — among others arterial hypertension (86%; n = 129), type 2 diabetes (38%; n = 57), gastroduodenal ulcer disease (11.33%; n = 17), chronic obstructive pulmonary disease (11.33%; n = 17) and cancer history (13.33%; n = 20).

Clinical variables in relation to iron status are summarized in Table 1. Significant differences between HF patients with and without ID were observed not only in red blood cell parameters or other laboratory test results (urine acid, sodium ions) but also in 6MWT and stroke/transient ischemic attack (TIA) history (Table 1).

However no significant differences in iron status between patients with EF < 50% and EF > 50% were found (serum iron: 12.40 µg/dL vs. 11.46 µg/dL; p = 0.224; ferritin: 161.96 µg/L vs. 135.47 µg/L; p = 0.288; TSAT: 21.94% vs. 20.37%; p = 0.523).

Spearman's rank correlation analysis revealed a negative correlation between the number of hospitalizations due to HF in the last 12 months and red blood cell count, Hb, Ht and 6MWT (Table 2), and a positive correlation between the number of hospitalisations due to HF in the last 12 months and red cell distribution width (RDW) (Table 2). Associations between HF stage (lower echocardiographic parameters such as EF and tricuspid annular plane systolic excursion or elevated troponin and NT-proBNP levels) and repeated HF hospitalizations were also found (Table 2).

The regression analysis revealed the independent variables for HF hospitalization in the 12 last months were NT-proBNP and RDW but not ID (Table 3). Both parameters were positively correlated with the number of hospitalizations (b = 0.263 and b = 0.346, respectively). The generated model explained 67% of the variance in the outcome variable (r = 0.670; p < 0.005).

Table 1. Patients' clinical variables according to iron status

Clinical variable	Non-ID patients	ID patients	p-value
Laboratory test results			
WBC [10 × 3/μL]*	7.29 (SD: 1.83)	7.47 (SD: 2.29)	0.615
RBC [10 × 6/μL]*	4.42 (SD: 0.63)	4.36 (SD: 0.61)	0.549
Hb [g/dL]*	13.70 (SD: 2.11)	12.59 (SD: 1.89)	**0.0009**
Ht [%]*	40.29 (SD: 5.71)	38.289 (SD: 5.49)	**0.031**
MCV [fL]	91.28 (IQR: 88–94)	88.19 (IQR: 84–93)	**0.0009**
MCHC [g/dL]*	33.96 (SD: 1.18)	32.81 (SD: 1.37)	**< 0.0001**
PLT [10 × 3/μL]	214.11 (IQR: 167–235)	215.51 (IQR: 169–251)	0.262
RDW [%]	13.81 (IQR:12.85–14.35)	15.34 (IQR:13.70–16.80)	**< 0.0001**
PCT [%]	0.235 (IQR: 0.19–0.26)	0.238 (IQR: 0.20–0.27)	0.222
PDW [fL]	13.67 (IQR: 11.80–15.20)	13.53 (IQR: 11.90–15.00)	0.918
Serum iron [μg/dL]	15.10 (IQR: 10.80–16.00)	9.83 (IQR: 6.90–12.35)	**0.010**
Ferritin [μg/L]	272.73 (IQR: 130.60–344.45)	58.89 (IQR: 31.20–74.80)	**< 0.0001**
TSAT [%]	26.85 (IQR: 22.60–28.10)	15.55 (IQR: 12.00–19.20)	**0.0002**
Glucose [mmol/L]	6.88 (IQR: 5.23–6.73)	6.44 (IQR: 5.25–6.82)	0.958
Creatinine [μmol/L]	106.39 (IQR: 83.00–122.10)	111.04 (IQR: 73.20–123.00)	0.800
Urea [mmol/L]	9.42 (IQR: 6.44–11.46)	8.39 (IQR: 5.94–10.16)	0.108
Urine acid [μmol/L]	466.03 (IQR: 360.80–575.50)	418.23 (IQR: 340.80–478.60)	**0.036**
eGFR [mL/min/1.73 m^2]	58.41 (IQR: 46.10–69.80)	56.11 (IQR: 41.30–72.60)	0.276
Bilirubin [μmol/L]	15.88 (IQR: 11.50–16.30)	16.28 (IQR: 9.20–21.50)	0.925
Na+ [mmol/L]	138.50 (IQR: 137.80–140.10)	139.59 (IQR: 138.40–141.30)	**0.014**
K+ [mmol/L]*	4.39 (SD: 0.504)	4.35 (SD: 0.544)	0.709
TC [mmol/L]	4.45 (IQR: 3.44–5.17)	4.09 (IQR: 3.29–4.58)	0.097
LDL [mmol/L]	2.47 (IQR: 1.57–3.24)	2.23 (IQR: 1.60–2.61)	0.299
HDL [mmol/L]	1.33 (IQR: 1.08–1.53)	1.25 (IQR: 1.02–1.39)	0.287
Triglycerides [mmol/L]	1.53 (IQR: 0.95–1.68)	1.32 (IQR: 0.85–1.53)	0.278
hs-TnT [ng/L]	26.95 (IQR:11.0–38.0)	43.17 (IQR: 13.0–37.0)	0.364
NT-proBNP [pg/mL]	3177.17 (IQR: 508.15–3108.0)	3248.25 (IQR: 448.0–3030.0)	0.689
ECG parameters			
HR [bpm]	75.20 (IQR: 64.50–81.00)	73.34 (IQR: 62.0–78.00)	0.442
QRS width [ms]*	153.31 (SD: 28.19)	137.56 (SD: 24.37)	0.174
BP values			
SBP	119.51 (IQR: 110.0–130.0)	122.62 (IQR: 110.0–135.50)	0.427
DBP*	74.22 (SD: 12.07)	70.14 (SD: 9.60)	0.079
Echocardiographic parameters			
LVEF [%]	45.16 (IQR: 30.50–58.00)	46.55 (IQR: 38.00–56.00)	0.593
LVD [mm]	53.68 (IQR: 46.00–60.00)	53.07 (IQR: 47.00–58.00)	0.769
IVSD [mm]	11.51 (IQR: 10.00–13.00)	12.33 (IQR: 10.50–14.00)	0.105
PWD [mm]	10.86 (IQR: 10.00–11.00)	10.89 (IQR: 9.00–12.00)	0.424
LAV [mL]	115.79 (IQR: 73.00–126.00)	101.92 (IQR: 74.00–123.00)	0.931
TAPSE [mm]	20.22 (IQR: 17.00–24.00)	19.72 (IQR: 16.00–22.00)	0.419
PASP [mm Hg]	41.35 (IQR: 30.00–48.00)	44.35 (IQR: 33.00–50.00)	0.359
Test results			
6MWT (m)*	292.52 (SD: 82.74)	250.98 (SD: 101.55)	0.041
Hospitalizations and comorbidities			
Number of repeated HF hospitalizations	0.92 (SD: 0.97)	0.88 (SD: 0.70)	0.927
Number of comorbidities	6.69 (IQR: 5.00–8.00)	7.69 (IQR: 6.00–9.00)	**0.016**
Stroke/TIA history [%]	4.68	19.77	**0.015**

All statistically significant values ($p < 0.05$) are provided in bold; *Variables normally distributed; 6MWT — 6 minute walking test; BP — blood pressure; DBP — diastolic blood pressure; ECG — electrocardiography; eGFR — estimated glomerular filtration rate; Hb — haemoglobin; HDL — high density lipoprotein; HR — heart rate; hs-TnT — high sensitivity troponin T; Ht — haematocrit; ID — iron deficiency; IQR — interquartile range; IVSD — intraventricular septum end-diastolic diameter; K+ — potassium ions; LAV — left atrium volume; LVD — left ventricular end-diastolic diameter; LVEF — left ventricular ejection fraction; LDL — low density lipoprotein; MCHC — mean corpuscular haemoglobin concentration; MCV — mean corpuscular volume; Na+ — sodium ions; NT-proBNP — N-terminal pro-B-type natriuretic peptide; PASP — pulmonary arterial systolic pressure; PCT — plateletcrit; PDW — platelet distribution width; PLT — platelet count; PWD — posterior wall end-diastolic diameter; RBC — red blood cell count; RDW — red cell distribution width; SBP — systolic blood pressure; SD — standard deviation; TAPSE — tricuspid annular plane systolic excursion; TC — total cholesterol; TIA — transient ischemic attack; TSAT — transferrin saturation; WBC — white blood cell count

Table 2. Spearman's rank correlation analysing the interaction between different variables and HF hospitalisations in the last 12 months

Pairs of variables	N	r Spearman	p-value
BMI & HF hospitalisations in the last 12 months	121	–0.206	0.024
NYHA class & HF hospitalisations in the last 12 months	118	0.394	< 0.0001
RBC & HF hospitalisations in the last 12 months	150	–0.193	0.018
Hb & HF hospitalisations in the last 12 months	150	–0.244	0.003
Ht & HF hospitalisations in the last 12 months	150	–0.227	0.005
RDW & HF hospitalisations in the last 12 months	150	0.238	0.003
hsTnT & HF hospitalisations in the last 12 months	144	0.209	0.012
NT-proBNP & HF hospitalisations in the last 12 months	150	0.329	< 0.0001
RDW & HF hospitalisations in the last 12 months	150	0.238	0.003
hsTnT & HF hospitalisations in the last 12 months	144	0.209	0.012
NT-proBNP & HF hospitalisations in the last 12 months	150	0.329	< 0.0001
LVEF & HF hospitalisations in the last 12 months	150	–0.215	0.008
TAPSE & HF hospitalisations in the last 12 months	143	–0.191	0.022
6MWT & HF hospitalisations in the last 12 months	91	–0.224	0.032

6MWT — 6 minute walking test; BMI — body mass index; Hb — haemoglobin; hs-TnT — high sensitivity troponin T; Ht — haematocrit; LVEF — left ventricular ejection fraction; NT-proBNP — N-terminal pro-B-type natriuretic peptide; NYHA — New York Heart Association; RBC — red blood cell count; RDW — red cell distribution width; TAPSE — tricuspid annular plane systolic excursion

Table 3. Multivariable regression analysis using the backward method for HF hospitalisation

Variable	B	p-value
NT-proBNP [pg/mL]	0.263	0.023
RDW [%]	0.346	0.002

HF — heart failure; NT-proBNP — N-terminal pro-B-type natriuretic peptide; RDW — red cell distribution width

Discussion

The present study showed that in patients hospitalized for HF those with ID had more comorbidities than those without ID. Furthermore, ID diagnosis was associated with a higher prevalence of a stroke/TIA in the study population. According to the authors' knowledge, this crucial result in research on ID in HF was observed for the first time.

According to the ESC 2021 guidelines [2], ID in patients in HF is defined as either serum ferritin concentration < 100 ng/mL or 100–299 ng/mL with TSAT < 20%. The most common reasons for ID in HF patients are reduced iron intake, reduced iron absorption, increased iron loss, which might be an effect of malignancy or gastritis/ulceration, and finally impaired iron release [14]. The diagnosis of ID does not require any specialist equipment and can be performed in any clinical centre. This is a significant feature that makes ID diagnosis widespread. However, in Poland similar to other countries, ID is recognized too rarely.

As in Beale et al. [5], the prevalence of ID in HFpEF is higher than in patients with EF < 50%. It may suggest a higher overall incidence of ID in HFpEF. Hence, the high prevalence of ID emphasizes the importance of performing iron measurements in patients with HFpEF and HFrEF alike.

Previously, the association between ID and cerebrovascular diseases was mostly reported in children and in relation to co-existing anaemia [6]. Nowadays, ID anaemia (IDA) is thought to be an etiological factor for stroke in the paediatric population [7]. However, Tang et al. [8] identified the connection between certain factors such as ID or IDA and ischemic stroke (IS) in the general population. This conclusion was based on transferrin's ability to enhance thrombin and restrain the inactivation of coagulation proteases by antithrombin. Analogically, Shovlin et al. [9] noticed probable stroke pathogenesis as increased platelet aggregation responses due to ID. Thus, low serum iron levels were proposed to double age-adjusted stroke risk. Potaczek et al. [10] highlighted that ID, independently of anaemia, may be a risk factor for recurrent venous thromboembolism. Moreover, Dubyk et al. [7] suggested that IDA and possibly sub-clinical ID may cause TIA and IS including in patients with cardiac diseases.

Subsequently, ID in the present population was associated with impaired exercise tolerance, which was indicated by a lower 6MWT result. It is consistent with previous research and was proved by Jankowska et al. [11] and confirmed in patients with HFpEF by Bekfani et al. [12].

The increased RDW level as a significant marker of long-term mortality in patients admitted to the hospital with acute HF is also worth emphasizing [15]. Therefore, the positive correlation between the number of hospitalizations due to HF in the last 12 months and RDW from the present study strengthens the abovementioned conclusion.

This biomarker is an effective indicator of the worsening and prognosis of HF [13].

The positive correlation between NT-proBNP level and the number of hospitalizations in the last 12 months is consistent with data which emphasize the role and high accuracy of natriuretic peptides in stratifying risk of the hospitalization due to HF [16].

Study limitations

There are several limitations of this study.

First, most studies regarding stroke history in HF patients were focused on IDA impact and not on sub-clinical ID. In consequence, it was not possible to precisely compare the results of this study with previous research.

Subsequently, the size of this study group was rather small, and the diagnosis of ID preceding cerebrovascular accident was not always confirmed. Therefore, further research in this field is needed.

Moreover, the design is that of a single clinical department, retrospective study, with potential selection bias; however, each patient admitted to the authors' department was screened regarding ID. This leads to the conclusion that results from other clinical centres are necessary.

Conclusions

The present study shows the importance of ID as a comorbidity in HF.

The most important finding from this study is a higher incidence of TIA/stroke in patients with ID. Therefore, ID screening and effective treatment of this condition are crucial for patients with HF.

Conflict of interest

None declared.

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Streszczenie

Wstęp. Niedobór żelaza (ID) jest częstym zaburzeniem współistniejącym z niewydolnością serca (HF), związanym z gorszym rokowaniem. Zgodnie z wytycznymi Europejskiego Towarzystwa Kardiolgicznego z 2021 roku dotyczącymi przewlekłej i ostrej HF, należy aktywnie poszukiwać ID u pacjentów z HF. Stwierdzono, że dożylna suplementacja żelaza zmniejsza ryzyko hospitalizacji u pacjentów z niewydolnością serca z obniżoną frakcją wyrzutową (HFrEF). Celem pracy była ocena znaczenia ID w populacji chorych z HF, zwłaszcza z zachowaną frakcją wyrzutową (HFpEF).

Materiał i metody. Badanie oparto na retrospektywnej analizie 150 pacjentów (69 kobiet i 81 mężczyzn) z niewydolnością serca (HFpEF = 44,67%; n = 67) leczonych w latach 2018–2021 w Zakładzie Kardiologii Nieinwazyjnej Uniwersytetu Medycznego w Łodzi. Analizę przeprowadzono pod względem obecności ID oraz EF < 50 *vs.* ≥ 50%, przy użyciu programu Statistica 13.1PL (StatSoft, Tulsa, USA).

Wyniki. Istotne różnice między pacjentami z HF z ID i bez ID obserwowano nie tylko w zakresie parametrów czerwonokrwinkowych (Hb, Ht, MCV, MCHC i RDW) czy wyników innych badań laboratoryjnych (kwas moczowy, jony sodowe), ale także w zakresie testu 6-minutowego marszu (6MWT) (250,98 ± 101,55 *vs.* 292,52 ± 82,74; p = 0,041) oraz dodatniego wywiadu w kierunku udaru mózgu/przejściowego napadu niedokrwiennego (TIA) (19,77% *vs.* 4,68%; p = 0,015). Nie stwierdzono jednak istotnych różnic w poziomie ferrytyny, saturacji transferryny czy częstości występowania ID pomiędzy pacjentami z EF < 50% i EF > 50%. Analiza korelacji rang Spearmana wykazała ujemną korelację pomiędzy liczbą hospitalizacji z powodu HF w ciągu ostatnich 12 miesięcy a liczbą krwinek czerwonych (r = –0,193; p = 0,018), Hb (r = –0,244; p = 0,003), Ht (r = –0,227; p = 0,005) i 6MWT (r = –0,224; p = 0,032), natomiast dodatnią korelację pomiędzy liczbą hospitalizacji z powodu HF w ciągu ostatnich 12 miesięcy a wskaźnikiem zmienności objętości krwinek czerwnych (RDW) (r = 0,238; p = 0,003). Analiza regresji wykazała, że liczba hospitalizacji z powodu HF była zależna od N-końcowego mózgowego peptydu natriuretycznego (b = 0,263) i RDW (b = 0,346).

Wnioski. Niedobór żelaza nie tylko wpływa na wynik 6MWT, ale również wiąże się z większą częstością występowania TIA/udaru mózgu w populacji chorych z HF. Dlatego też należy rozważyć diagnostykę i leczenie ID wśród pacjentów z HF, zarówno w HFrEF, jak i w HFpEF.

Słowa kluczowe: niewydolność serca, niedobór żelaza, powtarzające się hospitalizacje, udar mózgu, TIA

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References

1. Maggioni AP, Dahlström U, Filippatos G, et al. Heart Failure Association of the European Society of Cardiology (HFA). EURObservational Research Programme: regional differences and 1-year follow-up results of the Heart Failure Pilot Survey (ESC-HF Pilot). Eur J Heart Fail. 2013; 15(7): 808–817, doi: 10.1093/eurjhf/hft050, indexed in Pubmed: 23537547.
2. McDonagh TA, Metra M, Adamo M, et al. ESC Scientific Document Group. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021; 42(36): 3599–3726, doi: 10.1093/eurheartj/ehab368, indexed in Pubmed: 34447992.
3. Nikolaou M, Chrysohoou C, Georgilas TA, et al. Hellenic Iron Consensus Group. Management of iron deficiency in chronic heart failure: Practical considerations for clinical use and future directions. Eur J Intern Med. 2019; 65: 17–25, doi: 10.1016/j.ejim.2019.05.011, indexed in Pubmed: 31109847.
4. Moliner P, Enjuanes C, Tajes M, et al. Association between norepinephrine levels and abnormal iron status in patients with chronic heart failure: is iron deficiency more than a comorbidity? J Am Heart Assoc. 2019; 8(4): e010887, doi: 10.1161/JAHA.118.010887, indexed in Pubmed: 30760082.
5. Beale AL, Warren JL, Roberts N, et al. Iron deficiency in heart failure with preserved ejection fraction: a systematic review and meta-analysis. Open Heart. 2019; 6(1): e001012, doi: 10.1136/openhrt-2019-001012, indexed in Pubmed: 31168385.
6. Kinoshita Y, Taniura S, Shishido H, et al. Cerebral venous sinus thrombosis associated with iron deficiency: two case reports. Neurol Med Chir (Tokyo). 2006; 46(12): 589–593, doi: 10.2176/nmc.46.589, indexed in Pubmed: 17185884.
7. Dubyk MD, Card RT, Whiting SJ, et al. Iron deficiency anemia prevalence at first stroke or transient ischemic attack. Can J Neurol Sci. 2012; 39(2): 189–195, doi: 10.1017/s0317167100013214, indexed in Pubmed: 22343152.
8. Tang X, Fang M, Cheng R, et al. Iron-deficiency and estrogen are associated with ischemic stroke by up-regulating transferrin to induce hypercoagulability. Circ Res. 2020; 127(5): 651–663, doi: 10.1161/CIRCRESAHA.119.316453, indexed in Pubmed: 32450779.
9. Shovlin CL, Chamali B, Santhirapala V, et al. Ischaemic strokes in patients with pulmonary arteriovenous malformations and hereditary hemorrhagic telangiectasia: associations with iron deficiency and platelets. PLoS One. 2014; 9(2): e88812, doi: 10.1371/journal.pone.0088812, indexed in Pubmed: 24586400.
10. Potaczek DP, Jankowska EA, Wypasek E, et al. Iron deficiency: a novel risk factor of recurrence in patients after unprovoked venous thromboembolism. Pol Arch Med Wewn. 2016; 126(3): 159–165, doi: 10.20452/pamw.3311, indexed in Pubmed: 26942727.
11. Jankowska EA, Rozentryt P, Witkowska A, et al. Iron deficiency predicts impaired exercise capacity in patients with systolic chronic heart failure. J Card Fail. 2011; 17(11): 899–906, doi: 10.1016/j.cardfail.2011.08.003, indexed in Pubmed: 22041326.
12. Bekfani T, Pellicori P, Morris D, et al. Iron deficiency in patients with heart failure with preserved ejection fraction and its association with reduced exercise capacity, muscle strength and quality of life. Clin Res Cardiol. 2019; 108(2): 203–211, doi: 10.1007/s00392-018-1344-x, indexed in Pubmed: 30051186.
13. Lippi G, Turcato G, Cervellin G, et al. Red blood cell distribution width in heart failure: A narrative review. World J Cardiol. 2018; 10(2): 6–14, doi: 10.4330/wjc.v10.i2.6, indexed in Pubmed: 29487727.
14. Magrì D, De Martino F, Moscucci F, et al. Anemia and iron deficiency in heart failure: clinical and prognostic role. Heart Fail Clin. 2019; 15(3): 359–369, doi: 10.1016/j.hfc.2019.02.005, indexed in Pubmed: 31079694.
15. Melchio R, Rinaldi G, Testa E, et al. Red cell distribution width predicts mid-term prognosis in patients hospitalized with acute heart failure: the RDW in Acute Heart Failure (RE-AHF) study. Intern Emerg Med. 2019; 14(2): 239–247, doi: 10.1007/s11739-018-1958-z, indexed in Pubmed: 30276661.
16. Mueller C, McDonald K, de Boer RA, et al. Heart Failure Association of the European Society of Cardiology. Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. Eur J Heart Fail. 2019; 21(6): 715–731, doi: 10.1002/ejhf.1494, indexed in Pubmed: 31222929.
17. Wang XY, Zhang F, Zhang C, et al. The biomarkers for acute myocardial infarction and heart failure. Biomed Res Int. 2020; 2020: 2018035, doi: 10.1155/2020/2018035, indexed in Pubmed: 32016113.
18. Magnussen C, Blankenberg S. Biomarkers for heart failure: small molecules with high clinical relevance. J Intern Med. 2018; 283(6): 530–543, doi: 10.1111/joim.12756, indexed in Pubmed: 29682806.