Original article

UDC: 616.12-008:616.155.194
doi: 10.5633/amm.2024.0408

ANEMIA AS A COMMON COMORBIDITY AND PROGNOSTIC MARKER IN HEART FAILURE

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Heart failure (HF) is a clinical syndrome characterized by the inability of the heart to pump the amount of blood necessary to meet the body's needs for oxygen and energy substances in proportion to physical activity, provided that the venous blood flow to the heart is preserved.

The frequency of HF and left ventricular dysfunction increases with the age of patients. It is considered that the diagnosis of heart failure is the most common discharge diagnosis at the age of 65. Comorbidities are very important in HF patients for several reasons. Chronic anemia is very often associated with HF (up to 55% of patients). The aim of the work was to assess the presence of anemia in patients with HF and its impact on the prognosis of these patients.

The total number of subjects was 201. Anemia was more common in women than in men and was equally prevalent in systolic and diastolic HF, which is also consistent with previous reports. However, anemia was not more common in elderly HF patients. Patients with New York Heart Association (NYHA) class IV HF were significantly more likely to have anemia than those with NYHA class I or II, which is consistent with previous reports. In patients with HF, there is a significant frequency of anemia as non-cardiac comorbidity. The presence of anemia significantly impacts the hospital and post-hospital course. Therapy should be started even with subclinical anemia or with reduced iron depots even though the hemoglobin is still within the reference values because this improves the prognosis of our patients.

Acta Medica Medianae 2024;63(4):70–80.

Key words: *heart failure, comorbidities, anemia, prognosis*

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Introduction

Heart failure (HF) is a clinical syndrome characterized by the heart's inability to pump the amount of blood necessary to meet the body's needs for oxygen and energy in proportion to physical activity, provided that the venous blood flow to the heart is preserved (1).

The frequency of HF and left ventricular dysfunction increases with the age of patients. It is considered that the diagnosis of HF is the most common discharge diagnosis at the age of 65. It is estimated that 23 million people worldwide suffer from HF. New, modern methods of treatment in cardiology, primarily in coronary disease, reduce patient mortality and a large number of patients with chronic HF are recruited from the group of survivors (1). The mortality of HF patients is high and ranges from 15% to 60% per year. Patients with New York Heart Association (NYHA) class III/IV have a mortality of 50% compared to patients with NYHA class II/III where the two-year mortality is 25%. The prognosis is much more serious in older patients and men (2, 3).

In recent years, HF has become one of the biggest health and social problems in the field of cardiovascular pathology and one of the most common causes of hospitalization in the world. A special problem is the socioeconomic importance of HF, due to frequent hospitalizations and a greater number of medications that are used for a long time (4).

Comorbidities are very important in HF patients for several reasons. They can directly affect the therapy of patients with HF in the sense

of preventing the use of certain medications, medications used in the therapy of comorbidities can worsen HF, and drugs used in HF and comorbidities can show an interaction (beta-blockers in HF and beta-agonists in chronic obstructive pulmonary disease) (5).

Many comorbidities are associated with poor clinical status, which further aggravates HF, i.e., they are associated with a worse prognosis (diabetes mellitus) (5). Due to the possible improvement of the clinical status of HF, sometimes the treatment should be focused primarily on the treatment of comorbidities (anemia).

We should not ignore the cost of treating these patients, which is higher due to associated diseases, more frequent and longer hospitalizations, and the greater number of medications used (6). Comorbidities can be cardiac and extracardiac. Cardiac comorbidities can be causes of HF, but they can be present and associated with other primary causes. The most common are arterial hypertension (HTA), coronary disease, and valvular insufficiency (5). The most common noncardiac comorbidities in HF are anemia, diabetes mellitus, renal failure, obstructive lung disease, depression and infection, and cognitive dysfunction (7). Chronic anemia is very often associated with HF (up to 55% of patients). Anemia is defined as a state of decreased hemoglobin concentration < 12g/dl in women or < 13g/dl in men. It is more common in hospitalized HF patients, women, the elderly, and in patients with renal impairment. Anemia is associated with many symptoms, poor functional status and represents a high risk for hospitalized HF patients because it increases mortality (8). Anemia in these patients is associated with increased left ventricular mass. There is an increase in markers of inflammation and biohumoral parameters N terminal pro-BNP and C reactive protein. A systematic follow-up of more than 150,000 patients with HF and anemia showed the presence of an increased risk of death. Forty-eight percent of anemic patients died within 6 months of HF diagnosis compared to 29.5% of non-anemic patients (7). The etiology of anemia in HF is multifactorial. Additional factors that worsen anemia are the already mentioned elderly population and renal failure, but also hemodilution, increased circulation of pro-inflammatory cytokines (IL6, TNF-α), reduced bone marrow function, and therapy with aspirin and ACE inhibitors (2). Repeated hospitalizations due to decompensation and death are directly correlated with hemoglobin concentration. Probable mechanisms of deterioration are expansion of intravascular volume, increase in neurohumoral activity and worsening of myocardial ischemia. Absolute or relative deficiency of iron and/or erythropoietin is the leading factor in the pathophysiology of anemia in these patients, especially when a certain degree of renal insufficiency is present. Nanas et al. found that 73% of patients with HF and anemia had decreased iron levels on bone marrow aspiration (9).

Anemia therapy should be directed towards the causative factor, but even in the case of anemia of unknown etiology, intravenous iron and erythropoietin are used (10). Anemia improvement correlates with a reduction in HF symptoms, an increase in exercise tolerance, and an improvement in heart muscle condition.

Aim

The work aimed to assess the presence of anemia in patients with heart failure and its impact on the prognosis of these patients.

Patients and Methods

The study included patients who were treated at the Intensive Care Unit of the Clinic for Cardiovascular Diseases (CVD), University Clinical Center (UKC) Niš. They were hospitalized for signs of HF. The total number of patients was 201. During the processing of the patients, detailed anamnestic data were taken. In case of impossibility of cooperation with the patient, data were obtained heteroanamnestically from the closest family members. The examination included: the most important complaints, the time sequence of the occurrence of certain complaints; duration of the underlying disease that led to HF; way of treating HF; the presence of risk factors for heart diseases (smoking, arterial hypertension, family burden); frequency of hospitalizations, present comorbidities; previous illnesses; and medications used so far.

The clinical examination included the observation of HF signs: tachycardia, arrhythmias, crackles over the lungs, weakened breathing over the lung bases; the presence of peripheral edema, hepatomegaly; the presence of III or IV tones over the heart; swollen neck veins; clinical signs of anemia, hyperthyroidism or myxedema. The classification of heart failure used was NYHA classification. The ECG was performed on a twelve-channel ECG (Scheler). Heart rate, possible ischemic changes, and occurrence of acute myocardial infarction were monitored along with the presence of rhythm disorders such as atrial fibrillation, extrasystoles, and conduction disorders. Upon admission to the Clinic for CVD of UKC Niš, blood was taken for laboratory analysis at the Central Biochemical Laboratory and the Hematology Clinic of UKC Niš. The following values were determined: general laboratory analyses including glucose, urea, creatinine, total cholesterol, HDL and LDL fractions, triglycerides, sodium, potassium, Acidum uricum, transaminases, total proteins as well as cardiac markers of myocardial damage troponin I and CKMB. In the case of a negative finding and suspected acute coronary syndrome, the analyses were repeated after 6 hours; Markers of risk

factors: markers of inflammation (C-reactive protein, albumins), markers of coagulation (fibrinogen), markers of thrombosis (D dimer), markers of ischemia and remodeling of the left ventricle (BNP), thyroid hormones (T3, T4, TSH); Complete blood count: the total number of leukocytes, erythrocytes, hemoglobin, hematocrit and platelet count were determined. The blood test was done at the Hematology Clinic of UKC Niš. Each patient underwent a transthoracic echocardiographic examination on a General Electric Vivid 4 ultrasound machine. The techniques of one-dimensional examination, two-dimensional examination and Doppler technique from standard sections were used. The size of the left and right heart cavities and their volumes were assessed. The systolic and diastolic function of the left ventricle was evaluated as well as the function of the valvular apparatus. Disorders of regional contractility were monitored, and pericardial effusion was observed. Further, the possible presence of additional echoes in the cavities (dense spontaneous echoes, thrombi) or on the valvular apparatus (vegetation) was observed. A radiological examination of the lungs was performed in patients for possible evidence of an inflammatory process on the lung parenchyma (in patients with clinical signs of lung infection) and for the evidence and evolution of the presence of fluid in the pleural space. In addition, 24 Holter ECGs were performed in patients to monitor the presence of significant arrhythmias (paroxysmal atrial fibrillation, multifocal VES and ventricular tachycardia). We followed changes in the ST segment in terms of subendocardial ischemia, especially asymptomatic ones. An ultrasound examination of the abdomen was performed in patients to possibly prove the presence of free fluid in the abdomen (ascites) and to monitor the state of the parenchymatous organs (liver, gall bladder, kidneys). For a more precise diagnosis of comorbidities, examinations by doctors of other specialties were included: pulmonologists, neurologists and psychiatrists, hematologists, gastroenterologists and surgeons.

Statistical Analysis

Data were processed using standard descriptive statistical methods including mean value, standard deviation, percentage representation, and median. Pearson's linear correlation coefficient was used to determine the relationship. Statistical processing was done with Excel 7.0 and SPSS version 17 in the Windows XP environment, and the results are presented tabularly and graphically.

Results

A total of 201 patients with acute decompensation of chronic heart failure were included in the research. Among the patients, 60.7% were male, and 39.3% were female. The average age of patients was 71.55 ± 10.354 years. The average duration of heart failure and the average length of hospital treatment are given in Table 1.

On admission, 55 patients (27.4%) had NYHA class II, NYHA class III was the most frequent, i.e., it was present in 108 patients (53.7%), while 38 patients (18.9%) had NYHA class IV. There were no patients with NYHA class I, i.e., they were not included in the research (Figure 1).

There were 70 patients (34.8%) without peripheral edema on admission, 83 (41.3%) with peripheral edema, and 48 (23.9%) who had effusions along with edema, which is presented in Table 2.

Table 1. Baseline patients' characteristics at hospital admission

	X min	X max	$\bar{x}$	SD
Age (years)	40	90	71.55	10.354
Duration of heart failure (years)	0	3	1.69	1.129
Duration of hospitalization (years)	0	9	4.98	2.233

Table 2. Clinical presentation on hospital admission

	No.	%
0	70	34.8
1	83	41.3
2	48	23.9
Total	201	100.0

0—without edema and effusion, 1—peripheral edema, 2—pleural/pericardial effusion

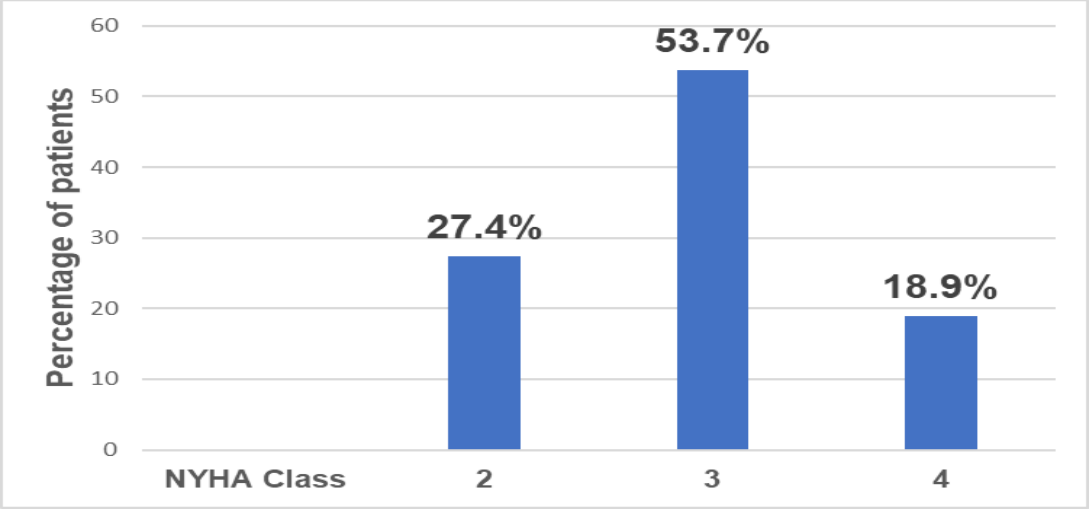

Figure 1. NYHA class on admission

Among the examined patients, 67 (33.3%) had HF with a preserved ejection fraction (Table 3).

Laboratory parameters on admission to the hospital are given in Table 4 (min, max, mean value and standard deviation). Table 5 shows the basic echocardiographic parameters examined on the patient's admission.

Of the cardiac comorbidities, arterial hypertension and atrial fibrillation were present in a high percentage. Among the non-cardiological comorbidities, diabetes, chronic renal failure, acute infections, anemia, chronic obstructive pulmonary disease (COPD), depression, cerebrovascular insult (CVI), hypothyroidism, hyperthyroidism, alcoholism and hematological diseases were monitored. The so-called "other comorbidities" were represented in a small percentage (up to 0.5%) and included the following associated diseases: oncological diseases of various localizations, sleep apnea, systemic connective tissue diseases, duodenal ulcer, psoriasis, osteoarthrosis and prostate adenoma (Table 6).

Of the examined patients, who were followed up for 1 year, 42.8% did not survive. 20 (10%) patients died during hospitalization, 26 (12.9%) patients died within 6 months of hospital discharge, and 40 (19.9%) patients died within 6–12 months after hospital discharge.

The largest number of patients who died (total, intra-hospital and in the period from 6 to 12 months) had three comorbidities, while the largest number of those patients who died within the period up to six months after discharge from the hospital had 2 comorbidities.

Table 3. Type of heart failure

HF with preserved LVEF	No.	%
No	134	66.7
Yes	67	33.3
Total	201	100.0

HF heart failure, LVEF—left ventricle ejection fraction

Table 4. Laboratory parameters on hospital admission

	X min	X max	$\bar{x}$	± SD
BNP	149.00	7714.30	1554.1426	1243.39835
TnI	0	12.2	12.5	10.0.827
Er	2	7	4.16	.867
Hb	65	197	122.77	23.189
Hct	17	55	36.58	7.742
Le	0	24	12.34	5.184
Tr	84	488	277.88	102.297
Blood glucose	2	28	8.77	4.924
Creatinine	53	665	152.18	87.602
Urea	3	617	15.72	45.508
Uric acid	195	921	471.07	137.794
Sodium	123	148	137.41	3.886
Potassium	3	7	4.46	.701
HOL	2	9	4.64	1.494
HDL	1	2	1.10	.306
LDL	1	6	2.93	1.091
TG	0	7	1.57	.929
AST	12	798	71.54	86.975
ALT	5	568	58.89	71.751
Albumin	22	49	33.75	5.096
D-dimer	95	5200	461.61	567.162
CRP	1	435	40.72	59.759
Fib	1	13	6.25	2.707
Hs CRP	11	83	53.95	37.781

BNP—brain or B-type natriuretic peptide, TnI—troponin I, Er—red blood cells, Hb—hemoglobin, Hct—hematocrit, Le—leukocyets, Tr—platelets, HOL—total cholesterol, HDL high density lipoprotein cholesterol, LDL—low density lipoprotein cholesterol, TG—triglycerides, AST—aspartate aminotransferase, ALT—Alanine aminotransferase, CRP—C reactive protein, Fib—fibrinogen

Table 5. Baseline echo parameters

	X min	X max	$\bar{x}$	± SD
EF (%)	11	79	37.40	13.743
ESD (mm)	37	88	61.37	9.007
EDD (mm)	20	74	48.11	10.019
SPDK (mmHg)	19	78	46.83	13.750

EF—left ventricular ejection fraction, ESD end systolic diameter of left ventricle, EDD end-systolic diameter of left ventricle, SPDK systolic pressure in right ventricle

Table 6. Comorbidities

	No.	%
Arterial hypertension	162	80.6
Diabetes mellitus	110	54.7
Atrial fibrillation	95	47.3
Chronic renal failure	87	43.3
Acute infection	66	32.8
Anemia	53	26.4
COPD	48	23.9
Depression	20	10
Hypothyreosis	16	8
Stroke	15	7.5
Hyperthyreosis	15	7.5.
Alcoholism	11	5.5
Other comorbidities	4	2
Hematological comorbidities	3	1.5

Discussion

A total of 201 patients with acute decompensation of chronic heart failure were included in our observational study. The majority of respondents were men (60.7%), with an average age of 71.55 years. The highest percentage of patients had Killip class II (patients with the acute coronary syndrome) on admission and peripheral edema (lower leg edema), and belonged to NYHA functional class III. Our results are consistent with those obtained by Rudiger et al. In a multicenter study on the clinical presentation of patients with acute heart failure as well as their one-year prognosis and factors affecting it, the average age of the patients was 73 years and 56% of the study sample was male. A slightly higher percentage of patients with

pulmonary edema (29.4%) in our study compared to 13% (from the aforementioned work by Rudiger et al.) can be explained by the fact that our research was conducted in the intensive care unit where patients with more severe forms of heart failure receive treatment and did not include all patients who were hospitalized with this diagnosis (11). Three percent of the patients were in cardiogenic shock, i.e. with seriously compromised hemodynamics, which is again in line with previous reports on the clinical presentation of patients with acute cardiac decompensation, which ranges from less than 1% in Euro-HF I to 7.7% in the Italian Survey study, while one of the largest registries of patients with acute heart failure, ADHERE, also reported rate of 3% (12–14). The average length of treatment lasted 2.43 days, which is in line with the length of treatment in intensive care units in Europe and America, which ranges from 2.6 days in the ADHERE registry including 105,388 patients to 7.6 days in the EFICA study performed on 599 subjects (14–16). Our subjects suffered from heart failure for an average of 1.69 years and were hospitalized due to worsening of the underlying disease. As the presumed root cause of heart failure, the following were found in almost the same percentage: coronary disease, dilated cardiomyopathy, hypertension and, with a slightly lower frequency, valvular disease. In a meta-analysis of 31 studies that included patients with heart failure, Tavazzi found that in 15–17% of patients with acute HF, arterial hypertension is an etiological factor, similarly, in our country this percentage is 18.4% (13). In a meta-analysis, Bui et al. conducted in subjects in North America, about 50% of patients had coronary disease as the main etiological factor (17). Tavazzi et al. state that coronary disease as an etiological factor of HF is mentioned with a significant difference in different studies ranging from 29% to 52%, while in our patients it was found in 29.9% of respondents (18). The same authors in their meta-analysis state that dilated cardiomyopathy is the most common cause of HF after coronary heart disease, which aligns with the results obtained in our study, where it was present in 27.9% of cases. In addition, the frequency of valvular disease decreases significantly in developed countries, whereas in our research, it was the cause of HF in 18.4% of patients (13, 17). This is in line with the results of the recently conducted EFICA study, where dilated cardiomyopathy and hypertension were reported in 15% of subjects, and valvular disease in 21% as the main cause of heart failure (15). One-third of our patients (33.3%) had heart failure with preserved ejection fraction. Large prospective European national registries indicate a high frequency of heart failure with preserved ejection fraction in hospitalized patients ranging from 46% to 51%. This type of heart failure is more common in elderly women who have been suffering from heart failure for a long time (18–22). In most Western European countries, the frequency of heart failure with a preserved ejection fraction is increasing, while in our country a greater number of patients have the type of heart failure with a reduced ejection fraction (23). It is assumed that this is a consequence of the high percentage of patients with coronary disease due to exposure to specific socioeconomic risk factors, but also due to less engagement in primary prevention (18, 21, 24).

The average value of arterial blood pressure on admission to the hospital was 134/80 mmHg, which corresponds to reports in previous studies in patients with acute HF (25–27). Patients were mildly tachycardic with an average heart rate of 97/min which is consistent with reports from other studies where heart rates ranged from 75/min in the Euro-HF I study (including 11,327 subjects) to 97/min in the Italian Survey study conducted on 2,807 patients (12, 13).

Of the laboratory parameters on admission, our subjects had significantly elevated BNP and D dimer values, which is consistent with biohumoral disorders in patients with acute HF. Natriuretic peptides type A and type B (BNP) play a significant role in the pathogenesis of heart failure with effects on the kidneys, heart and blood vessels. Today, the measurement of natriuretic peptides is of great importance for diagnosis and prognosis in patients with acute HF (28, 29). The largest percentage of our respondents have three and two comorbidities, respectively, which is in line with the majority of studies investigating this area (5, 6). The most common comorbidities are arterial hypertension, atrial fibrillation and diabetes mellitus. A significantly smaller percentage of respondents (1.5%) had no comorbidities, that is, they had as many as 6 associated comorbidities (30). During the one-year follow-up, 42.8% of patients did not survive, 10% of patients died during hospitalization, 12.9% of patients died within 6 months of discharge from the hospital, while 19.9% of patients died in the period from 6 to 12 months after discharge from the hospital. The obtained results are consistent with the results from the studies in which in-hospital mortality was monitored, among which the largest are the MAGGIC and EFICA studies (11, 15, 20). In the EFICA study, one-year mortality in patients treated in the Intensive Care Unit was slightly higher than in the non-implantation study (49%). The reason is probably the higher NYHA class in their patients (NYHA III/IV) (15).

We found a statistically significant association between the duration of hospital treatment and, therefore, the cost of treatment in patients with a greater number of comorbidities. This indicates the importance of comorbidity on the prognosis and mortality of patients with heart failure, but also the significant financial costs to society as a whole (31).

Iron deficiency is the main cause of anemia. Despite this known cause, there are a number of questions regarding the best choice of therapy. Commonly used drugs are ferrous sulfate, ferrous gluconate, or ferrous fumarate. These forms of iron (dionic) are more soluble than the ferric form,

with twice the absorption capacity (32, 33). Approximately 30–40% of patients with chronic HF had anemia (34). If iron deficiency in chronic HF is defined as a serum ferritin level < 100 mg/L, together with a transferrin saturation level < 20%, approximately 24% of all patients with chronic HF (e.g. about 40% of non-anemic patients) have iron deficiency (35). There are several possible reasons for iron deficiency in patients with chronic HF. Some patients with chronic HF are anemic not because their RBC mass is low, but because their plasma volume is high, which is described as hemodilution (36). The proteinuria often encountered in chronic HF can cause urinary loss of erythropoietin, as well as transferrin loss, which can lead to iron deficiency anemia (37). Anemia may be part of a chronic inflammatory process. Some studies suggest that about 60% of patients with chronic HF may have anemia of the aforementioned type, characterized by low iron levels and iron-binding capacity, but elevated ferritin levels (38). The disadvantage of ferritin is that it is an acute phase reactant and its level can be elevated during inflammation. The precise limit for defining anemia in CHF was mostly arbitrary in previous research. According to the World Health Organization (WHO), anemia is defined as hemoglobin concentrations < 13 g/dL for men or < 12 g/dL for women, but some authors use more conservative definitions. The prevalence and severity of anemia increase during the progression of chronic HF (37). Some studies have shown the importance of correcting anemia in patients with chronic HF. Treatment strategies include administration of erythropoietin, iron supplementation, or both (39). Most of these studies were conducted using intravenous formulations, but few observations were made with oral formulations of iron. Anemia is an independent prognostic factor for morbidity and mortality in patients with chronic HF. Previous studies have shown a beneficial effect of anemia therapy in patients with chronic HF. The prevalence of anemia in our patients is in accordance with previously published data (40). Anemia was more common in women than in men and was equally prevalent in systolic and diastolic HF, which is also consistent with previous reports (41). However, anemia was not more common in elderly HF patients. Patients with NYHA class IV were significantly more likely to have anemia than those with NYHA class I or II, which is consistent with previous reports (39). Anemia is a comorbidity that should be treated in HF patients. Potential beneficial effects of this treatment are improved oxygen delivery to tissues and inhibition of cardiomyocyte apoptosis due to ischemia, slowing of harmful left ventricular remodeling, improved exercise tolerance, and improved quality of life (42). It should be noted that the use of oral iron therapy is often associated with gastrointestinal side effects (20–30%), and a long duration of therapy is necessary to replenish iron stores. These side effects lead to poor therapeutic adherence. This is the main reason for switching to parenteral therapy. Regardless of whether iron deficiency is absolute or relative in HF, it appears to be a comorbidity per se (39). In a recent study of 459 anemic and iron-deficient patients, all prognostic markers were improved by supplementation (43). This finding also indicates that iron deficiency is a significant comorbidity in SI, even without anemia. The prognostic markers examined in these patients were variations in maximum oxygen consumption assessed by ergospirometry, NYHA class, BNP levels, quality of life questionnaires (Kansas City and EQ5D), LVEF, rehospitalization and HF mortality (43).

Conclusion

In patients with heart failure, there is a significant frequency of anemia as non-cardiac comorbidity. The presence of anemia has a significant impact on the hospital and post-hospital course. Therapy should be started even with subclinical anemia or with reduced iron depots even though the hemoglobin is still within the reference values because this improves the prognosis of HF patients.

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Originalni rad

UDC: 616.12-008:616.155.194
doi: 10.5633/amm.2024.0408

ANEMIJA KAO ČEST KOMORBIDITET I PROGNOSTIČKI MARKER U SRČANOJ SLABOSTI

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Srčana insuficijencija (SI) je klinički sindrom koji karakteriše nesposobnost srca da ispumpa količinu krvi neophodnu za zadovoljenje potreba organizma za kiseonikom i energetskim materijama srazmerno fizičkoj aktivnosti, pod uslovom da je dotok krvi kroz vene na srcu očuvan.

Učestalost srčane insuficijencije i disfunkcije leve komore raste sa starošću bolesnika. Smatra se da je dijagnoza srčane insuficijencije najčešća otpusna dijagnoza nakon 65. godine. Komorbiditeti su veoma važni kod bolesnika sa srčanom insuficijencijom iz nekoliko razloga. Hronična anemija veoma je često udružena sa srčanom insuficijencijom (javlja se kod čak 55% bolesnika). Cilj ovog rada bilo je sagledavanje prisustva anemije kod bolesnika sa srčanom insuficijencijom i uticaja koji anemija ima na prognozu pomenute bolesti.

U studiju je bio uključen 201 ispitanik. Anemija je bila češća kod žena nego kod muškaraca i bila je podjednako zastupljena u sistolnom i dijastolnom SI-ju; to je u skladu sa prethodno zabeleženim rezultatima. Međutim, anemija nije bila češća kod starijih bolesnika sa SI-jem. Bolesnici sa klasom IV Njujorške asocijacije za srce (engl. *New York Heart Association* – NYHA) imali su anemiju značajno češće od onih sa NYHA klasom I ili II, što odgovara stanju zabeleženom u ranijim saopštenjima. Kod bolesnika sa srčanom insuficijencijom uočena je značajna učestalost anemije kao nekardijalnog komorbiditeta. Prisustvo anemije ima važan uticaj na hospitalni i posthospitalni tok lečenja. Terapiju treba započeti čak i ako je posredi supklinička anemija, tj. ako su depoi gvožda sniženi iako je hemoglobin i dalje u okviru referentnih vrednosti, budući da to poboljšava prognozu bolesti kod osoba sa srčanom insuficijencijom.

Acta Medica Medianae 2024; 63(4):70–80.

***Ključne reči**: srčana slabost, komorbiditeti, anemija, prognoza*