Original article

doi:10.5633/amm.2024.0408

Anemia as a Common Comorbidity and Prognostic Marker in Heart Failure

Snežana Ćirić Zdravković[1,2], Goran Koraćević[1,2], Dragana Stanojević[1], Boris Djindjić[1,2], Svetlana Petrović Nagorni[1], Ivan Ngorni[3], Miloš Nagorni[4], Jelena Perišić[1]

[1]University Clinical Centar Niš, Clinic for Cardiovascular diseases, Niš, Serbia

[2]University of Niš, Faculty of Medicine, Niš, Serbia

[3]University Clinical Centar Niš, Clinic for Gastroenterology, Niš, Serbia

[4]University Clinical Centar Niš, Clinic for Orthopedics, Niš, Serbia Klinika za ortopediju

Contact:

Snežana Ćirić Zdravković

81 dr Zoran Đinđić Blvd., 18000 Niš, Serbia

E-mail: sczdravkovic@yahoo.com

AMM Paper Accepted

Heart failure 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 e 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 in the age of 65. Comorbidities are very important in HF patients for several reasons. Chronic anemia is very often associated with heart failure (HF) (up to 55% of patients). The aim of the work is to assess the presence of anemia in patients with HF and their 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 NYHA class IV 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 a 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 our patients.

Key words: heart failure, comorbidities, anemia, prognosis

AMM Paper Accepted

Original article

doi:10.5633/amm.2024.0408

Anemija kao čest komorbiditet i prognostički marker u srčanoj slabosti

Snežana Ćirić Zdravković[1,2], Goran Koraćević[1,2], Dragana Stanojević[1], Boris Djindjić[1,2], Svetlana Petrović Nagorni[1], Ivan Ngorni[3], Miloš Nagorni[4], Jelena Perišić[1]

[1]Univerzitetski klinički centar Niš, Klinika za kardiovaskularne bolesti, Niš, Srbija

[2]Univerzitet u Nišu, Medicinski fakultet, Niš, Srbija

[1]Univerzitetski klinički centar Niš, Klinika za gastroenterologiju, Niš, Srbija

Klinika za ortopediju UKC Niš

AMM Paper Accepted

Srčana insuficijencija je klinički sindrom koji se karakteriše nesposobnošću srca da ispumpa količinu krvi koja je neophodna za zadovoljenje potreba organizma za kiseonikom i energetskim materijama srazmerno fizičkoj aktivnosti, pod uslovom da je venski dotok krvi ka srcu očuvan.

Učestalost srčane insuficijencije i disfunkcije leve komore raste sa starošću pacijenata. Smatra se da je dijagnoza srčane insuficijencije najčešća otpusna dijagnoza u životnom dobu nakon 65 godine. Komorbiditeti su veoma važni kod pacijenata sa srčanom insuficijencijom iz više razloga. Hronična anemija je veoma često udružena sa srčanom insuficijencijom (do 55% pacijenata). Cilj rada je sagledavanje prisustva anemije u pacijenata sa srčanom insuficijencijom i njen uticaj na prognozu ovih bolesnika.

Ukupan broj ispitanika bio je 201. Anemija je bila češće zastupljena kod žena nego kod muškaraca i imala je podjenaku zastupljenost kod sistolne i dijastolne SI što je takođe u skladu sa prethodnim izveštajima. Međutim, anemija nije bila češća kod starijih pacijenata sa SI. Pacijenti sa NYHA klasom IV su značajno češće imali anemiju od onih sa NYHA klasom I ili II, što je u skladu sa ranijim saopštenjima. Kod bolesnika sa srčanom insuficijencijom postoji značajna učestalost anemije kao

nekardijalnog komorbiditeta. Prisustvo anemije ima značajan uticaj na hospitalni i posthospitalni tok. Terapiju treba započeti čak i kod subkliničke anemije odnosno kod sniženih depoa gvožđa iako je hemoglobin još uvek u okviru referentnih vrednosti jer to poboljšava prognozu naših bolesnika.

Ključne reči: srčana slabost, komorbiditeti, anemija, prognoza

AMM Paper Accepted

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 in 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 15-60% per year. Patients with New York Heart Association class (NYHA) 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 in 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, valvular insufficiency (5). The most common noncardiac comorbidities in HF are: anemia, diabetes mellitus, renal failure, obstructive lung disease,

AMM Paper Accepted

depression and infection, 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. 48% 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 worse 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, 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 erythropoetin 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 erythropoetin are used (10). Anemia improvement correlates with a reduction in HF symptoms, an increase in exercise tolerance, and an improvement in heart muscle condition.

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

Patients and methods. The study included patients who were treated at the Clinic for Cardiovascular diseases of the Clinical Center (KC) in Niš, Intensive Care Unit. They were hospitalized due to manifest 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

AMM Paper Accepted

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; 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; presence of peripheral edema, hepatomegaly; presence of III or IV tones over the heart; swollen neck veins; clinical signs of anemia, hyperthyroidism or myxedema. Classification of heart failure was NYHA classification. The ECG was performed on a twelve-channel ECG (Scheler). Heart rate, possible ischemic changes, occurrence of acute myocardial infarction were monitored; presence of rhythm disorders - atrial fibrillation, extrasystoles, conduction disorders. Upon admission to the CVD Clinic of KC Nis, blood was taken for laboratory analysis at the Central Biochemical Laboratory and the Hematology Clinic of UKC Nis. The following were determined: General laboratory analyses: values of glucose, urea, creatinine, total cholesterol, HDL and LDL fractions, triglycerides, sodium, potassium, acidum uricum, transaminases, total proteins; Cardiac markers of myocardial damage: troponin I and CKMB. In the case of a negative finding and suspected acute coronary syndrome, the analyzes 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 KC Nis. 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 evaluated. The systolic and diastolic function of the left ventricle was evaluated, the function of the valvular apparatus was evaluated, disorders of regional contractility were monitored, pericardial effusion was observed and monitored, 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)

AMM Paper Accepted

and for the evidence and evolution of the presence of fluid in the pleural space. 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 in order to possibly prove the presence of free fluid in the abdomen (ascites), in order 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 (mean value, standard deviation, percentage representation, 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 will be presented tabularly and graphically.

RESULTS

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. Average age of patients 71.55±10.354 years. The average duration of heart failure and the average length of hospital treatment are given in Table 1.

AMM Paper Accepted

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

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

AMM Paper Accepted

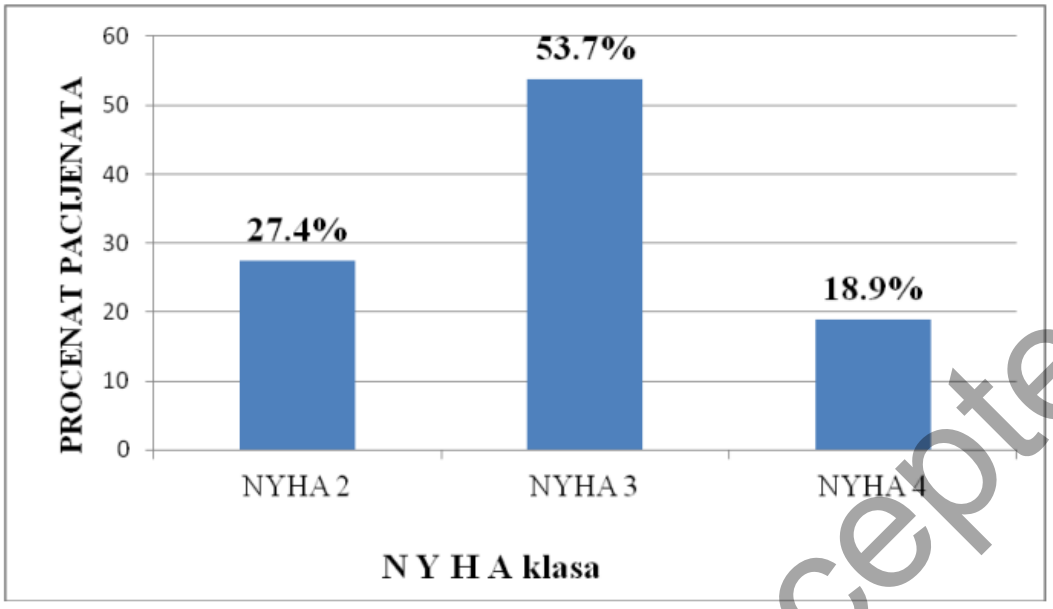

Figure 1. NYHA class at admission

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.

AMM Paper Accepted

Table 2. Clinical presentation at hospital admission

	N	%
0	70	34.8
1	83	41.3
2	48	23.9
Total	201	100.0

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

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 at the patient's admission.

AMM Paper Accepted

Table 3. Type of heart failure

HF with peresrved LVEF	N	%
No	134	66.7
Yes	67	33.3
Total	201	100.0

Table 4. Laboratory parameters at 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

AMM Paper Accepted

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

AMM Paper Accepted

Na	123	148	137.41	3.886
K	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

AMM Paper Accepted

CRP	1	435	40.72	59.759
Fib	1	13	6.25	2.707
hs CRP	11	83	53.95	37.781

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

AMM Paper Accepted

Of the cardiac comorbidities, we observed arterial hypertension and atrial fibrillation, which were represented 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" included associated diseases that were represented in a small percentage (up to 0.5%), namely: oncological diseases of various

localizations, sleep apnea, systemic connective tissue diseases, duodenal ulcer, psoriasis, osteoarthrosis and prostate adenoma (Table 6).

Table 6. Comorbidities

	N	%
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

AMM Paper Accepted

Of the examined patients, who were followed up for 1 year, 42.8% did not survive. 20 (10%) patients died during hospitalisation, 26 (12.9%) patients died within 6 months of hospital discharge, 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 the 6th to the 12th month) had three comorbidities, while the largest number of those patients who died within the period up to the sixth month after discharge from the hospital had 2 comorbidities.

DISCUSSION. In our observational study were included 201 patients with acute decompensation of chronic heart failure. The majority of respondents were men (60.7%), with an

average age of 71.55 years. The highest percentage of patients had Killip class 2 (patients with 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 their multicenter study on the clinical presentation of patients with acute heart failure, one-year prognosis and factors affecting it, and the average age of the patients was 73 years and 56% of the studied sample was male. A slightly higher percentage of patients with pulmonary oedema (29.4%) in our study compared to 13% (from the afore mentioned 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 are cared for and does not include all patients who are hospitalized with this diagnosis (11). Three percent of the patients were in cardiogenic shock, ie. 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 in one from the largest registries of patients with acute heart failure - ADHERE was also 3% (12,13,14). 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 105388 patients to 7.6 days in the EFICA study performed on 599 subjects (14,15, 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 heart failure is mentioned with a significant difference in different studies: 29% - 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 is in accordance with the results obtained in our study - 27.9%, while the frequency of valvular disease decreases significantly in developed countries and in our research it was cause of heart failure in 18.4% of patients. (13,17).

AMM Paper Accepted

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). A 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%-51%. This type of heart failure is more common in elderly women who have been suffering from heart failure for a long time. (18,19,20,21,22). 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 heart failure (25,26,27). 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 2807 patients (12,13).

Of the laboratory parameters at 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 one year of follow-up, 42.8% did not survive, 10% of patients died during hospitalisation, 12.9% of patients died within 6 months of discharge from the hospital, while 19.9% of patients died in the period from the 6 to 12 month after discharge from the hospital. The obtained results are in accordance with the results from the studies in which in-hospital mortality was monitored, among which the largest are the MAGGIC and EFICA studies (20,11,15). In the

AMM Paper Accepted

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 of 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 (eg. 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, as determined 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

AMM Paper Accepted

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 that were 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 a 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 our patients.

AMM Paper Accepted

REFERENCES

1. Ostojić M, Dobrić M. Srčana insuficijencija i principi terapije. U: Kažić T, Ostojić M. Klinička kardiovaskularna farmakologija. Integra, Beograd.2009; 495-524.

2. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bòhm M, Dickstein K, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail 2012;14:803-869.

3. Chen J, Normand SL, Wang Y, Krumholz HM. National and regional trends in heart failure hospitalization and mortality rates for Medicare beneficiaries**:**1998-2008. JAMA 2011;306:1669-1678.

4. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. Heart 2007;93:1137-1146.

5. Japp A, Newby D. Comorbidities associated with chronic heart failure. In: Kaerney M. Chronic Heart Failure, Oxford Cardiology Library. Oxford 2008;10:99-107.

6. Mogensen UM, Ersboll M, Andersen M, Anderson C, Hassager C, Torp-Pedersen C, et al. Clinical characteristics and major comorbidities in heart failure patients more than 85 years of age compared with younger age groups. Eur J of Heart Failure 2011;13:1216-1223.

7. Dahlstrőm U. Frequent non-cardiac comorbidities in patients with chronic heart failure. The Eur J of Heart Failure 2000;7:309-316.

8. Petrovic D, Ilić B, Marinković D, Nikolić Lj. Anemija i hronična srčana insuficijencija, značaj i indikacije za lečenje. Balneoclimatologia 2011;35:51-60.

9. Westenbrink BD,Voors AA,Van Veldhuisen DJ. Is anemia in chronic heart failurecaused by iron deficiency. JACC 2007;49:2301-2302.

AMM Paper Accepted

10. Anker SD, Comin CJ, Filippatos G, Willenheimer R, Dickstein K, Drexier H, et al. Ferric carboxymaltose in patients with heart failure and iron deficiency. N Engl J Med 2009;361:2436-2448.

11. Rudiger A, Harjola VP, Muller A, Saila P, Nieminen M. Acute Heart Failure: Clinical presentation, one-year mortality and prognostic factors. Eur J Heart Fail 2005;7:662-670.

12. Komajda M, Follath F, Swedberg K, Cleland J, Aquilar JC, Cohen-Solal A, et al. Study Group on Diagnosis of the Working Group on Heart Failure of the European Society of Cardiology. The EuroHeart Failure Survey programme--a survey on the quality of care among patients with heart failure in Europe. Part 2: treatment. Eur Heart J 2003;24:464-474.

13. Tavazzi L, Maggioni AP, Lucci D, Cacciatore G, Ansalone G, Oliva F, et al. Italian survey on Acute Heart Failure Investigators. Nationwide survey on acute heart failure in cardiology ward series in Italy. Eur Heart J 2006;27:1207-1215.

14. Fonarow GC. ADHERE Scientific Advisory Committee. The Acute Decompensated Heart Failure National Registry (ADHERE): opportunities to improve care of patients hospitalized with acute decompensated heart failure. Rev Cardiovasc Med 2003;4(suppl 7):S21-S30.

15. Zannad F, Mebazaa A, Juillière Y, Cohen-Solal A, Guize L. Clinical profile, contemporary management and one year mortality in patients with severe acute heart failure syndromes: The EFICA study. European Journal of Heart Failure 2006;8:697-705.

16. Dur O, Cowie M. Acute heart failure in the intensive care unit:epidemiology. Crit Care Med 2008:36(suppl): S3-S8.

17. Bui AL, Horwich TB, Fonarow GC. Epidemiology and risk profile of heart failure. Nat Rev Cardiol.2011;80:30-41.

18. Tavazzi L. Towards a more precise definition of heart failure aetiology. Eur Heart J.2001;22:192-195.

AMM Paper Accepted

19. McMurray JJ. Clinical practice. Systolic heart failure. N Engl J Med 2010;362:228-238.

20. Meta–analysis Global Group in Chronic Heart Failure (MAGGIC). The survival of patients with heart failure with preserved or reduced left ventricular ejection fraction: an individual patient data meta-analysis. Eur J Heart Fail 2011;10:254-268.

21. Lam C, Donal E, Kraigher-Krainer E, Vasan RS. Epidemiology and clinical course of heart failure with preserved ejection fraction. Eur J Heart Fail.2011;13;18-28.

22. Curtis LH, Greiner MA,Bradley G, Hammill BG, Judith M,Kramer MD. Early and long-term outcomes of heart failure in elderly persons. 2001-2005. Arch Intern Med.2008;168:2481-2488.

23. Mendez G, Cowie M. The epidemiological features of heart failure in developing countries: a review of the literature. Int J Cardiol.2001;80:213-219.

24. Foxx KF, Cowie MR, Wood DA, Coats AJS, Gibbs JSP, Underwood RM. Coronary artery disease as the cause of incident heart failure in the population. Eur Heart J.2001;22:228-236.

25. Desai RV, Banacchi M, Ahmed MI, Mujib M, Aban I, Love TE, et al. Impact of baseline systolic blood pressure on long-term outcomes in patients with advanced chronic systolic heart failure (insights from the BEST trial). Am J Cardiol 2010;106:221-227.

26. Raphael CE, Whinnett ZI, Davies JE, Fontana M, Ferenczi EA, Manisty CH et al. Quantifying the paradoxical effect of higher systolic blood pressure on mortality in chronic heart failure. Heart.2009;95:56-62.

27. Haider AW, Larson MG, Franklin SS, Levy D for the Framingham Heart study. Systolic blood pressure, diastolic blood pressure and pulse pressure as predictors of risk for congestive heart failure in the Framingham Heart Study. Ann Intern Med.2003;138:10-16.

AMM Paper Accepted

28. Gheorghiade M, Filippatos GS, Felker GM. Diagnosis and management of acute heart failure syndromes.520-523. In:Braunwald˙s Heart Disease. A Textbook of cardiovascular medicine, ninth edition. Saunders Elsevier, Philadelphia, 2012,517-539.

29. Alehagen U, Dahlstrom U, Lindahl TL. Elevated D-dimer level is an independent risk factor for cardiovascular death in outpatients with symptoms compatible with heart failure. Thromb Haemost 2004;92:1250-1258.

30. Azevedo A, Bettencourt P, Dias P, Abren-Lima C, Hence HW, Barros H. Population based study in the prevalence of the stages of heart failure. Heart 2006;92:1161-1163.

31. Bogaev RC. Cost considerations in the treatment of heart failure. Tex Heart Inst J 2010;37:557-558.

32. Rafie M, Rahmani H, Sadr M, et al. Prevalence and treatment of iron deficiency anemia in patients with chronic heart failure. J Clin Exp Cardiolog 2012; 3: 8.

33. Brittenham GM. Pathophysiology of iron homeostasis. In: Hoffman R, Benz EJ and Silberstein LE (eds) Hematology: basic principles and practice. 6th ed. Philadelphia: Elsevier Saunders, 2013, pp.427–436.

34. Brise H and Hallberg L. Absorbability of different iron compounds. Acta Med Scand Suppl 1962; 376: 23–37

35. Silverberg DS, Dov Wexler D and Schwartz D. Is correction of iron deficiency a new addition to the treatment of the heart failure? Int J Mol Sci 2015; 16: 14056–14074.

36. Androne AS, Hryniewicz K, Hudaihed A, et al. Relation of unrecognized hypervolemia in chronic heart failure to clinical status, hemodynamics, and patient outcomes. Am J Cardiol 2004; 93: 1254–1259.

37. Silverberg D, Wexler D and Iaina A. The importance of anemia and its correction in the management of severe congestive heart failure. Eur J Heart Fail 2002; 4: 681–686.

38. Windram JD, Loh PH, Rigby AS, et al. Relationship of high-sensitivity C-reactive protein to prognosis and other prognostic markers in outpatients with heart failure. Am Heart J 2007; 153: 1048–1055.

39. Kaldara-Papatheodorou EE, John V, Terrovitis JV, et al. Anemia in heart failure. Should we supplement iron in patients with chronic heart failure? Pol Arch Med Wewn 2010; 120: 354–360.

AMM Paper Accepted

40. Anand IS. Anemia and chronic heart failure implications and treatment options. J Am Coll Cardiol 2008; 52: 501–511.

41. Stamos TD and Silver MA. Management of anemia in heart failure. Curr Opin Cardiol 2010; 25: 148–154

42. Shah R and Agarwal AK. Anemia associated with chronic heart failure: current concepts. Clin Interv Aging 2013; 8: 111–122.

43. Beck-da-Silva L, Rohde LE, Pereira-Barretto AC, et al. Rationale and design of the IRON-HF study: a randomized trial to assess the effects of iron supplementation in heart failure patients with anemia. J Card Fail 2007; 13: 14–17.

AMM Paper Accepted