

Parameters of iron metabolism in acutely decompensated heart failure patients

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UNIVERSITY OF SPLIT



**UNIVERSITY OF SPLIT
SCHOOL OF MEDICINE**

FILIP MARUŠIĆ

**PARAMETERS OF IRON METABOLISM IN ACUTELY
DECOMPENSATED HEART FAILURE PATIENTS**

Diploma thesis

Academic year: 2018/2019

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Assist. Prof. Joško Božić, MD, PhD

Split, July 2019

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TABLE OF CONTENTS

1. INTRODUCTION	1
1.1. Etiology of heart failure	2
1. 2. Epidemiology	2
1.3. Pathophysiology.....	4
1.4. Classification.....	4
1.5. Heart failure and its clinical presentation	5
1.6. Diagnosis.....	5
1.7. Management.....	6
1.8. Prognosis.....	8
1.9. Iron metabolism physiology	9
1.9.1. Markers of iron deficiency	10
1.9.2. Iron role in disease	10
1.9.3 Iron in heart failure	11
1.9.4. Therapeutic options of iron deficiency in heart failure.....	12
2. OBJECTIVES	14
3. SUBJECTS AND METHODS	17
3.1. Subjects	18
3.2. Definitions.....	18
3.3. Procedures.....	18
3.4. Laboratory analysis	19
3.5. Statistical analysis	19
4. RESULTS	20
5. DISCUSSION	28
6. CONCLUSION.....	32
7. REFERENCES	34
8. SUMMARY	39
9. CROATIAN SUMMARY	41
10. CURRICULUM VITAE.....	43

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1. INTRODUCTION

1.1. Etiology of heart failure

Heart failure is a cardiac condition with multifactorial etiologies. Conditions altering the function or the actual structure of the left ventricle can eventually lead to patients developing heart failure. As heart failures most basic classification is based on the function of the heart into either depressed ejection fraction, preserved ejection fraction and high output states we can attribute causative etiologies to each of these functional groups (1).

Coronary artery disease is the predominant cause of heart failure in both men and women in industrialized countries and accounts for up to 75% of cases. It mainly leads to depressed ejection fraction heart failure but also hypertension is a contributing cause in nearly 75% of patients, other examples include chronic pressure or volume overload, chronic lung disease and non-ischemic dilated cardiomyopathy. However, one should remember that in depressed ejection fraction heart failure up to 30% of the patients will not have a known exact etiology (1).

Preserved ejection fraction heart failure is mainly caused by pathological hypertrophies such as primary hypertrophic cardiomyopathies. Other causes are endomyocardial disorders and process of aging (1).

High-output state heart failure is mainly related to metabolic disorders such as thyrotoxicosis, nutritional disorders like beriberi disease or states of excessive blood flow requirements such as chronic anemia (1).

Although it is possible to divide etiologies of heart failure based on functional type of heart failure one should remember that there is significant overlap of the etiologies especially between groups of depressed and preserved ejection fraction (1).

Furthermore, in developing countries there is significantly different underlying etiologies as for example in Africa and Asia rheumatic heart disease is still a major cause of heart failure most probably due to lack of antibiotic therapy (1).

1. 2. Epidemiology

Heart failure affects more than 20 million people worldwide, in the developed countries overall prevalence is around 2% and the prevalence is of exponential pattern rising with age (1).

Among higher income nations heart failure is the most common diagnosis in hospitalized patients aged over 65 and represents nearly two percent of all hospital admissions (2,3). Hospitalizations due to heart failure are predicted to increase by more than 50% by 2035, primarily due to an overall aging population. The average general practitioner in the United Kingdom will care for 30 patients with heart failure annually and will diagnose an addition of 10 patients with heart failure annually (4).

In a study from 2014 an estimation of 108 billion USD was spent on heart failure globally in 2012 of which 60% was direct medical costs (5). Eighty-six percent of this global expenditure was from higher income regions which only make up for 18% of the global population (Figure 1). Considering the predicted increase of hospitalizations due to heart failure we can estimate that the global expenditure will also increase over time. In Europe the estimation is an increase of cost due to cardiovascular disease from 102 billion euro in 2014 to 122 billion Euro by 2020 (6). In the USA as of 2011 estimated lifetime cost of heart failure per individual patient was 110,000 /year with more than three-fourths of this consumed by in-hospital care (7).

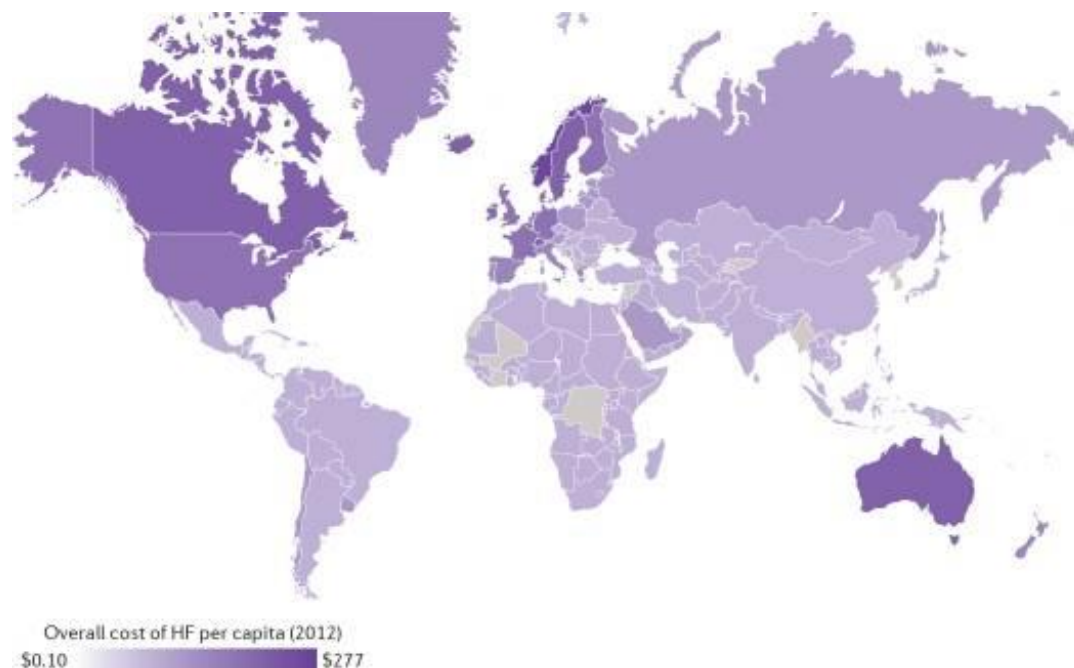


Figure 1. Costs of heart failure globally.

Source: Egan BM, Li J, Hutchison FN, Ferdinand KC. Hypertension in the United States, 1999 to 2012: Progress Toward Healthy People 2020 goals. *Circulation*. 2014;130:1692–99.

1.3. Pathophysiology

Diseases of heart muscle were documented widely by R. Virchow in the famous publication *Die cellular pathologie* in mid-19th century. Virchow defined non-valvular heart disease as chronic myocarditis but with time terminology and classification has drastically evolved and heart failure is today best described as “a syndrome due to functional and structural changes in myocardium leading to impaired ventricular filling or impaired ejection of blood”. Reduced left ventricular myocardial function is the most common cause of heart failure but causes can also be dysfunction of endocardium, myocardium, pericardium, heart valves or great vessels by their own or in combination.

Most important changes causing heart failure are ischemia, increased hemodynamic overload and ventricular remodeling (8). The underlying pathogenesis involves activation of immune regulatory and inflammatory responses which are not yet fully understood. Proposed theories suggest that excessive neuroendocrine activation leads to activation of neuro-hormones and pro-inflammatory cytokines following an initial cardiac insult leading to heart failure (9-11).

1.4. Classification

Heart failure is mainly classified into left ventricular, right ventricular or bi-ventricular heart failure and is further classified into acute or chronic depending on time of onset and duration. However, in the clinic the main classification is based upon the function of the heart, mainly heart failure with reduced ejection fraction (HFrEF), heart failure with preserved ejection fraction (HFpEF) or heart failure with mid-range ejection fraction (HFmrEF) (12). Reduced ejection fraction is defined as ejection fraction equal to or less than 40%, preserved ejection fraction is defined as ejection fraction more than or equal to 50% and HFmrEF is defined as ejection fraction of 40-49% (13).

Heart failure can be further classified based on function into high output failure and low output failure. High output failure is the least common and is characterized by increased resting cardiac index of greater than 2, 5-4L/min/m² in combination with low systemic vascular resistance. Causes of high output heart failure include among others anemia.

Low output heart failure is more common and a typical cause is myocardial infarction (14).

Also there is the functional classification of The New York heart association (NYHA) which defines four classes of the heart failure patient as (14):

- Class I: Heart failure does not cause limitations to physical activity; ordinary physical activity does not cause symptoms
- Class II: Heart failure causes slight limitations to physical activity; the patients are comfortable at rest, but ordinary physical activity results in heart failure symptoms
- Class III: Heart failure causes marked limitations of physical activity; the patients are comfortable at rest, but less than ordinary activity causes symptoms of heart failure
- Class IV: Heart failure patients are unable to carry on any physical activity without heart failure symptoms or have symptoms when at rest

1.5. Heart failure and its clinical presentation

Symptoms of heart failure include orthopnea, dyspnea, paroxysmal nocturnal dyspnea, fatigue and weakness etc. Dyspnea has sensitivity of up to 100% although specificity of only 17-34% whereas paroxysmal nocturnal dyspnea has sensitivity of 39-41% with specificity nearly 85%. Symptoms more associated with right sided heart failure include edema, abdominal distention and right hypochondrial pain (15,16).

In earlier stages of heart failure signs are lacking due to various compensatory mechanism however, later signs include tachycardia (99% specificity and 7% sensitivity); pedal edema (93% specificity and 10% sensitivity); increased jugular venous pressure (JVP) (specificity of 92% and sensitivity of 39%), abnormal lung sounds (crackles) (specificity of 78% and sensitivity of 60%); S3 gallop (specificity of 99% and sensitivity of 13%) (17,18).

The most common form of heart failure accounting for hospitalization is acute decompensated heart failure which accounts for roughly 80% of hospitalizations related to heart failure. Common causes of acute decompensated heart failure are non-adherence to medication, acute coronary syndrome and exacerbation of chronic obstructive pulmonary disease (19).

1.6. Diagnosis

In the process of evaluating if a patient has heart failure a variety of parameters are used. Determine existence of clinical symptoms by physical examination and the use of blood

tests to assess metabolic profile of serum electrolytes, glucose levels, fasting lipid profile, thyroid status. Other more specific laboratory tests used to assess heart failure are brain natriuretic peptide (BNP) with 70% sensitivity and 99% specificity, N-terminal proBNP (NT-proBNP) with 99% sensitivity and 85% specificity (20).

The neuro-hormone proBNP is secreted into the ventricles in response to volume expansion and pressure overload and breaks down into active BNP and inert NT-proBNP. Both BNP and NT-proBNP are significant in the use of diagnosing and assessing prognosis of heart failure (34). Patient at admission with BNP of more than 200 pg/mL compared to a patient with less than 200 pg/mL is associated with a 9% or 2% mortality rate respectively (21).

Some diagnostic options other than blood tests and physical examination include classic chest x-ray, computerized tomography (CT), magnetic resonance imaging (MRI) and trans-thoracic echocardiography (TEE). CT and MRI both provide detailed view of cardiac structure but both are of limited accuracy in patients with elevated heart rates. TEE is an important diagnostic tool used to assess among other ventricular function, calculate ejection fraction, wall thickness, size and function of heart valves. TEE should also be considered as an important tool in the follow up controls of patients with heart failure with altering symptoms (22).

1.7. Management

The management of patients with heart failure is guided based on pre-determined goals and also depend on whether the patient is an in-hospital patient or out-hospital patient. Major goals include improving prognosis and reducing mortality, alleviating symptoms and reverse or slow down cardiac dysfunction. In addition to previously stated goals for in-hospital patient goals also include reducing length of stay and readmission, prevent organ damage and manage co-morbidities contributing to poor prognosis (23).

Current recommendations by American college of cardiology, heart failure society of America and European society of cardiology include (23):

In-patient management of heart failure (23)

- Monitor oxygen if $\text{PaO}_2 < 60\%$ or $\text{SaO}_2 < 90\%$
- In cases with respiratory distress provide nasal intermittent positive pressure ventilation to avoid subsequent intubation

- Following pharmacological agents should be used depending on precipitating factors and symptoms/signs of congestion
 - Diuretic (to reduce edema), salt restriction (to reduce fluid retention)
 - Angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) (for neurohormonal modification, vasodilatation and LVEF improvement)
 - B-blocker for improved survival, arrhythmic prevention and control of ventricular rate
 - Aldosterone antagonist, for additional diuresis, symptom control, increased survival
 - Digoxin which in certain cases lead to increased cardiac output and improvement of symptoms
 - Anticoagulant therapy if possible to decrease thromboembolism risk
 - Inotropic agents for improved perfusion of organs by increasing cardiac output

Hemodynamic invasive monitoring is recommended for all patients with NYHA class III heart failure and above with respiratory distress, symptomatic hypotension, decreased perfusion, reduced renal function and cardiogenic shock. The first implantable wireless hemodynamic monitoring system approved by the FDA called CardioMEMS sensor showed a 30% reduction in hospitalization for patients with NYHA class III heart failure (23).

Discharge criteria for acute decompensated heart failure patients include (23)

- Exacerbating factors under control and assessed
- Optimized volume status
- Successful transition to oral diuretic therapy with discontinued IV vasodilator and inotropic therapy for minimum of 24 hours
- Oral therapy for heart failure including ACEi and B-blocker has been established with stable clinical status
- Education for family and patient completed with discharge instructions
- LVEF documented
- Smoking cessation counseling initiated
- Visit for follow up scheduled for 7-10 days
- Out-patient management of heart failure

- Individualized education and counseling
- Early attention to signs and symptoms of fluid overload
- Emphasis on behavioral strategies to increase adherence
- Medical therapy optimization
- Follow up after hospital discharge or after periods of instability
- Increased access to healthcare services
- Assistance with social and financial concerns

As science progresses newer alternatives of therapies emerge and today there is a new field of clinical trials targeting rejuvenation of the heart. Cardiac rejuvenation therapy so far mainly consists of gene therapy and stem cell transplantation (23).

Preclinical studies show possible benefits on infused stem cells especially during acute injury of the heart due to inflammatory cytokines guiding the stem cells to injured tissue by chemotaxis in contrary once cardiac remodeling has already taken place the stem cells may not have proper guidance to the injured sites (23).

One of many possible applications of gene therapy is targeting angiogenic proteins like fibroblast growth factor and vascular endothelial growth factor with aim of leading to improved angiogenesis and subsequent collateral vessel formation and perfusion of cardiac cells. Another genetic group of interest are genes (SERCA2a) affecting calcium channels and myocardial contractility which are also implicated in cardiac remodeling (23).

1.8. Prognosis

The five-year mortality rate for heart failure was reviewed to be approximately 50%, which is significantly higher than that of some cancers (24). Age adjusted rate for heart failure related mortality between 2000 and 2014 in the USA declined from 105.4 to 84.0 per 100,000 populations, furthermore the percentage of in-hospital heart failure related deaths declined from 42,6% to 30% in the same time interval. Prognosis of cardiac conditions such as acute coronary syndrome and valvular disorders has improved over the past decade however the prevalence of heart failure has increased probably due to an overall increase in population age and population body mass index (BMI) (25).

As an indicator of prediction of mortality and morbidity in heart failure the primary test of use has been the exercise intolerance test characterized by reduction in peak $\text{VO}_2/\text{VO}_2 \text{ max}$

capacity (VO₂ max is the maximum intake of oxygen despite an increase in exercise intensity). Other independent predictors of mortality are higher age, creatinine levels (serum >2.72 mg/dL), systolic blood pressure <115 mmHg, ejection fraction of left ventricle <45%, dyspnea at rest, lack of chronic B-blocker therapy, male sex and lower hemoglobin levels (26).

The S₂PLiT-UG score has shown value in predicting the 1-year all-cause mortality after hospitalization for an acute heart failure event. Three-hundred patients with acute heart failure were analyzed through 7 variables independently associated with all-cause mortality during 1-year follow-up. The seven independent risk factors include estimated glomerular filtration rate (GFR) 40-60; estimated GFR <40 ml/min/1.73m²; uric acid >450 µmol/L; left-ventricular ejection fraction <45%; sodium <136 mmol/L; systolic blood pressure <115 mmHg; and a positive history of previous heart failure-related decompensation event(s). The score divided patients into three risk categories: low (0-2 points), intermediate (3 points) and high (4-6 points) (27).

1.9. Iron metabolism physiology

Approximately 4 grams of iron of which 2.5 grams is within erythrocytes and 1 gram in hepatic and splenic macrophages is stored within humans. The rest of iron is distributed in a variety of proteins. Transferrin which makes up the mobile part of iron compartment consists of only approximately 3 mg of iron. Intake of iron per day is about 10-20mg on average. Roughly 20% of iron intake is absorbed by our intestines mainly in duodenum and the proximal jejunum. Normally humans lose about 1-2 mg of iron per day from our body however there are states of physiologic stress where iron loss is somewhat increased as for example during menstruation in women (28,29).

Viewing iron homeostasis, we can divide iron traffic into two systems, one related with iron absorption and its transport between tissues (systemic iron metabolism) and the other related to transport of iron between cell organelles (intracellular iron metabolism). Systemic iron metabolism is mainly regulated by hepcidin and ferroportin. Iron can be exported by cells through ferroportin which in turn is regulated inversely by hepcidin (28,29).

Hepcidin is a 25 amino acid peptide hormone produced mainly by hepatocytes which blocks export of iron from hepatocytes, macrophages and enterocytes by binding to ferroportin and induce its internalization. Elevated levels of hepcidin inhibit intestinal absorption of iron at the level of enterocytes. During inflammatory response or in case of abundant intracellular iron stores hepcidin will be elevated leading to internalization and subsequent lysosomal degradation of ferroportin whereas in times of increased iron requirements (elevated

erythropoiesis) or low iron stores hepcidin levels are low and expression of ferroportin is increased allowing for export of iron through blood by transferrin.

Transferrin usually has about 20-40% of binding sites occupied by iron and the saturation of transferrin (TSAT) can be used as an indicator of iron overload. Within cells iron is stored in the form of ferritin, one ferritin molecule can contain about 4500 iron atom. In this way cells regulate iron hemostasis (28,29).

In the past bone marrow examinations were carried out to evaluate iron stores, this has largely been replaced by blood measuring of ferritin although bone marrow examination remains as golden standard (29). This is just one parameter of iron metabolism among many others established with modern science, as mentioned above with markers as ferritin, transferrin, hepcidin and ferroportin we have gained a much clearer view of iron metabolism but also realization of a much more complex relationship then expected (30).

1.9.1. Markers of iron deficiency

As previously mentioned the most important markers of iron deficiency are serum ferritin and TSAT, additionally soluble transferrin receptor is a useful parameter if aiming for monitoring erythropoietic status and prediction of response of iron therapy (31). Increased soluble transferrin receptor indicates cells expressing increased need of iron uptake. Other parameters typically seen in anemia and iron deficiency is a decrease in red cell distribution width and lower mean corpuscular volume especially in absolute iron deficiency (32).

One important role of iron is in erythropoiesis mainly being incorporated into erythroblasts and reticulocytes. Restricted delivery to erythron can be an indication of iron restricted erythropoiesis and is possible to detect in blood by reticulocyte hemoglobin of <28 pg. More importantly reticulocyte hemoglobin can be used to follow response to iron therapy since reticulocytes only are present in blood for 1-2 days they typically increase in 2-4 days after successful intravenous iron therapy (29).

1.9.2. Iron role in disease

As an element iron is necessary due to its capability of not only transporting oxygen but also it plays a role in cell growth and proliferation. Iron deficiency can occur due to a reduction of dietary intake, excessive blood loss and many other however during chronic illness the main pathogenesis behind iron deficiency is immobilization of iron due to chronic inflammation leading to functional iron deficiency. Ferritin which as previously mentioned is

a marker of stored iron in cells can also be used as an inflammatory marker due to increase of stored iron during inflammation, the opposite can be said for transferrin which is a negative acute phase reactant meaning transferrin levels will decrease during times of inflammation (31).

In general, the two major elements requiring iron are haem and Fe-S clusters. The presence of Fe-S- cluster determines function of aconitase which is an essential enzyme in citrate cycle which catalyzes reaction from citrate into aconitate. Iron regulatory protein (IRP1) binds Fe-S clusters and acts as cytosolic aconitase which means that at times of low cellular iron, IRP1 will lose aconitase activity due to reduction in Fe-S synthesis. A reduction in aconitase activity due to reduced Fe-S cluster synthesis will in turn lead to reduced production of ATP in citrate cycle and result in reduced exercise capacity and increased fatigue (33).

1.9.3 Iron in heart failure

In heart failure one of many comorbidities is iron deficiency which also shows an increase in prevalence as disease progresses, this pattern can be seen by simply comparing prevalence of iron deficiency in different stages of NYHA classification heart failure. Furthermore, iron deficiency is an independent risk factor for heart failure mortality (34).

Basic division into functional and absolute iron deficiency is essential from practical standpoint. A functional deficiency of iron indicates presence of iron in the human body but inability of mobilization and hence inability to fulfill its function. An absolute deficiency means that iron stores are actually depleted in the human body. Generally speaking, in heart failure patients functional iron deficiency may be present at serum ferritin level <300 microgram/L with TSAT <20% whereas absolute iron deficiency in heart failure patient may be present at ferritin level <100 microgram/L. Around every-other patient with heart failure has either absolute or functional iron deficiency (31).

Theoretically the main reason of reduced iron intake in heart failure would be a consequence of malfunctioning transport system in enterocytes due to decreased ferroportin expression as result of elevated levels of hepcidin due to chronic inflammation. However, the relationships are much more complex, in study with animals comparing groups with iron deficiency alone and iron deficiency along with heart failure the group with both heart failure and iron deficiency showed reduced expression of iron transport proteins in duodenum compared to the group with iron deficiency without heart failure (29).

Furthermore, in clinical setting the levels of hepcidin did not correlate with levels of pro-inflammatory activation evident by circulating IL-6 (29). This indicates that heart failure itself has an impact on iron metabolism and the classic explanation of iron trapping during inflammatory state is not explanation enough for the metabolic changes.

Furthermore, iron deficiency naturally often goes together with anemia but does not necessarily have to be so and many of the symptoms of iron deficiency are explained by presence of anemia but as mentioned above iron itself plays important role in muscle functioning and exercise capacity.

In stable systolic heart failure patients iron deficiency was associated with a reduction in peak oxygen consumption to exercise, this was compared between iron deficient and iron repleted subjects and seen separately in anemics and non-anemics (35).

In experimental studies with iron deficiency, rats would develop sympathetic activation and subsequent increase in cardiac output, left ventricular hypertrophy and eventually left ventricular dilation which can conclude that in experimental models anemia and iron deficiency lead to unfavorable changes in the myocardium (36,37).

These new discoveries are reasons why during recent years' therapeutic options with iron replacement by oral or intravenous route have emerged (36,37).

1.9.4. Therapeutic options of iron deficiency in heart failure

Oral iron salts such as iron sulphate and iron succinate have been used to treat iron deficiency however due to common side effects of oral iron preparations and various drug interaction intravenous (IV) iron therapy is nowadays more advocated for. IV iron agents contain iron dextran, iron gluconate, iron sucrose or ferric carboxymaltos, with their carbohydrate portion acting as protective envelope to prevent toxic reactions. Some side effects due to this carbohydrate envelope have been reported, especially anaphylactic reactions in particular to iron dextran. All of these IV iron agents contain the same core but of varied size and differ mainly by surrounding carbohydrate (31).

The ferric iron in heart failure II (FERRIC-HF) trial where 16 weeks of iron sucrose therapy was used showed an improvement in symptoms and exercise capacity in patients with heart failure and iron deficiency furthermore their benefits were even more evident in anemic patients (38). In the ferinject assessment in patients with iron deficiency and chronic heart failure (FAIR-HF) study 459 patients with chronic heart failure NYHA class II or III, anemic and non-anemic with iron deficiency were given ferric carboxymaltose (ferinject) or placebo

for 24 weeks and improvement of life was similar in both anemic and non-anemic group, there was also improvement on patients NYHA class and there was no increase in side effects in treated vs. non-treated group during the 6 months' observation. This indicates that iron deficiency should be treated independent of anemia and is a significant co-morbidity in chronic heart failure (39).

According to current guidelines all heart failure patients should be screened for iron deficiency and anemia. Symptomatic patients in NYHA class II-IV could benefit from iron supplementation preferably by intravenous route (evident level C) (40).

2. OBJECTIVES

Aims:

1. To evaluate number of patients with acute decompensated heart failure that have anemia and/or iron deficiency.
2. To compare laboratory data and clinical parameters between patients with acute decompensated heart failure when divided in groups in regards to anemic and iron status.

Hypothesis:

1. Most of patients with acute decompensated heart failure will have anemia and/or iron deficiency.
2. There will be no differences in laboratory or clinical data parameters between groups.

3. SUBJECTS AND METHODS

3.1. Subjects

This was a clinical cross-sectional study, conducted between January 2018 and January 2019, that included a total of 60 consecutive patients with acute decompensation of chronic heart failure at Department of Cardiology of the University Hospital of Split. The study protocol was approved by the Ethics Committee of the University Hospital of Split. All medical procedures were done in accordance with the Declaration of Helsinki and its latest revision. Inclusion criteria were: patients with NYHA functional class II-IV and diagnosis of heart failure based on the ESC guidelines for the diagnosis and treatment of heart failure, both genders. Exclusion criteria were: patients younger than 35 years of age and adults older than 90 years of age, *cor pulmonale*, primary renal or hepatic disease, active malignant and/or infectious disease, systemic autoimmune disease, hemorrhagic diathesis or significant coagulopathy, systemic immunological and/or immunosuppressive disorder and/or positive recent history of immunosuppressive/cancer/anemia chemotherapeutic drug use.

3.2. Definitions

Iron deficiency was defined with ferritin levels <100 ng/mL and iron $8 < \mu\text{mol/L}$ for women and $11 < \mu\text{mol/L}$ for men. Anemia was defined as hemoglobin values of <119 g/L and <138 g/L for women and men, respectively. Patients were considered to have arterial hypertension if they were previously diagnosed with hypertension and taking prescribed medications for the condition. Patients who had total cholesterol ≥ 5.0 mmol/L and/or low-density lipoprotein cholesterol ≥ 3.0 mmol/L levels or were treated with lipid-lowering medications were considered to have dyslipidemia. Cut-off values for diabetes mellitus were ≥ 7.0 mmol/L for fasting glucose and $\geq 6.5\%$ for glycated hemoglobin (HbA1c) and/or treatment with antidiabetic medications or insulin agents. Obesity was defined at BMI ≥ 30 kg/m².

3.3. Procedures

Upon patient's arrival to hospital systolic and diastolic blood pressure was measured on patients seated with supported back and arm at heart level. Blood pressure was measured 3 times on both arms and the average value was used. Moreover, detailed anamnestic and clinical data was taken from medical records. Data of previous hospitalizations due to heart failure was provided from the protocol of the department of Cardiology.

3.4. Laboratory analysis

Venous blood sampling was performed within 24 hours of admission. All laboratory analyses were performed in the Department of Medical Laboratory diagnostics of University Hospital Split. Chemiluminescent Microparticle Immunoassay (CMIA) was used for the quantitative determination of ferritin in human serum (Abbott ARCHITECT ci16200 analyzer, Abbott, Chicago, IL, USA). For serum iron spectrophotometry with ferrous chromogen was used. Complete blood count was determined using standard flow-cytometry-based hematologic analyses (ADVIA 2120i, Siemens Healthcare, Erlangen, Germany). Other parameters were analyzed by using standard laboratory methods and procedures.

3.5. Statistical analysis

Data analysis was performed using MedCalc Statistical Software (version 17.9.4, Ostend, Belgium). Patients were divided in groups according to iron status and whether they had anemia. Kolmogorov-Smirnov test was used to test normality of distribution for continuous variables. One-way ANOVA was used for analysis of laboratory and clinical variables between groups of patients. Data are presented as whole number and proportion or as mean \pm standard deviation (SD). Descriptive statistics was used for analysis of patient characteristics when appropriate. P-values <0.05 were considered statistically significant.

4. RESULTS

This study included 60 patients with acute decompensated heart failure of which 30 patients had non-ischemic heart disease and 30 patients were with ischemic heart disease. Twenty-eight of the patients were men and 32 patients were women.

The included patients differed in their anemic and iron status, as presented in Table 1. Nine patients (15%) had anemia with iron deficiency, 12 patients (20%) were iron deficient without anemia, 13 patients (21.7%) were anemic without iron deficiency while the rest of the patients had neither anemia nor iron deficiency (43.4%). Figure 2 and Figure 3 shows distribution of the participants in concordance with NYHA classification and S₂PLiT UG risk category group, most of the patients where in NYHA class 3 and in low risk S₂PLiT category.

Table 1. Patients divided into groups by iron and anemic status.

Patients	N (%)
No anemia and no iron deficiency	26 (43.3)
Anemia with iron deficiency	9 (15.0)
Iron deficiency without anemia	12 (20.0)
Anemia without iron deficiency	13 (21.7)

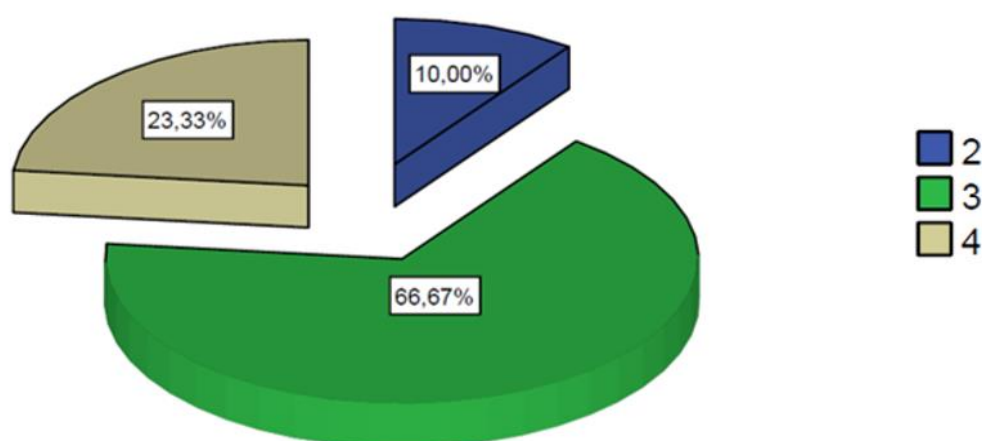


Figure 2. Representation of population divided into groups by NYHA classification.

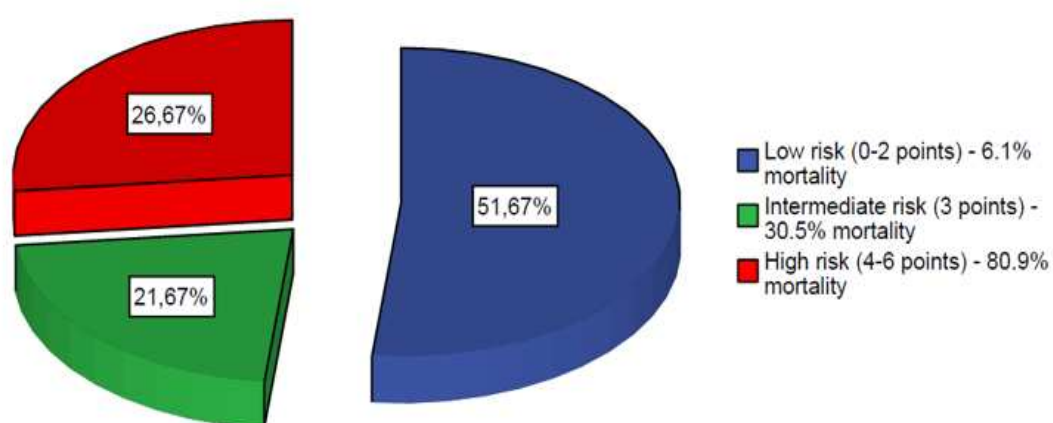


Figure 3. Representation of population when divided into S₂PLiT UG risk categories.

Study participants had different types of heart failure, most of the patients (48.3%) had reduced ejection fraction type of heart failure followed by preserved ejection fraction type of heart failure (31.7%) and the least common heart failure was mid-range ejection fraction type (20.0%) (Table 2).

Table 2. Number of patients in each functional class of heart failure.

Patients	N (%)
HFrEF	29 (48.3)
HFmrEF	12 (20.0)
HFpEF	19 (31.7)
Total	60 (100.0)

HFrEF – Heart failure with reduced ejection fraction; HFmrEF – Heart failure with mid-range ejection fraction; HFpEF – Heart failure with mid-range ejection fraction

In Table 3 patient's pharmacological therapies are shown. The majority of patients were using ACEi/ARBs, B-blockers, diuretic and anticoagulants.

Table 3. Pharmacotherapy of included patients.

Therapy	N (%)
ACEi or ARB	44 (73.3)
B-blocker	54 (90.0)
Statin	24 (40.0)
Allopurinol	14 (23.3)
MRA	27 (45.0)
Digoxin	12 (20.0)
Aspirin	22 (36.1)
Calcium-channel blocker	8 (13.3)
Angiotensin-receptor neprilysin inhibitor	13 (21.7)
Loop or thiazide diuretic	56 (93.3)
Anticoagulants	34 (56.7)

ACEi – Angiotensin converting enzyme inhibitor; ARB – Angiotensin receptor blocker; MRA – Mineralocorticoid receptor antagonist

In Table 4 comorbidities and conditions of the patients can be found, a majority of patients had arterial hypertension (98.3%), hyperuricemia (86.7%), dyslipidemias (73.3%) and/or atrial fibrillation (60.0%).

Table 4. Patients comorbidities and conditions.

Comorbidities	N (%)
Arterial hypertension	59 (98.3)
Dyslipidemia	44 (73.3)
Hyperuricemia	52 (86.7)
Obesity (BMI>30)	24 (40.0)
Diabetes mellitus	26 (43.3)
Past TIA or stroke	5 (8.3)
Atrial fibrillation	26 (60.0)
History of cardiac interventions	24 (40.0)

BMI – Body mass index; TIA – Transient ischemic attack

Comparison of baseline characteristics within subgroups regarding anemic and iron status is presented in Table 5. Patients with anemia and iron deficiency had significantly lower diastolic blood pressure than the other subgroups ($P=0.010$). There was no significant difference between groups in other variables.

Table 5. Baseline characteristics within each subgroup.

Variable	No anemia and no iron deficiency (n=26)	Anemia with iron deficiency (n=9)	Iron deficiency without anemia (n=12)	Anemia without iron deficiency (n=13)	P- value
Age (years)	70.0±9.1	77.8±7.9	73.8±6.8	68.3±10.0	0.057
BMI (kg/m ²)	30.4±3.9	28.8±2.3	30.1±4.7	29.9±4.3	0.829
SBP (mmHg)	138.9±26.1	120.6±13.1	133.3±19.8	137.7±28.4	0.086
DBP (mmHg)	83.1±10.1	70.0±12.5	75.8±8.2	86.2±17.5	0.010
Heart rate (bpm)	100.4±34.7	86.2±34.0	90.5±21.4	83.3±18.7	0.317
LVEF (%)	38.0±15.4	47.7±17.8	39.3±14.3	44.2±14.5	0.346
Previous HF- RHW1Year	0.6±0.9	0.9±0.9	0.6±1.4	0,8±0,8	0.870
NT-proBNP (pg/mL)	6374.1±6037.7	6525.8±6037.7	8640.3±7794.5	6367.2±5056.2	0.743

Data are presented as mean ± standard deviation

* One-way ANOVA test

BMI – Body mass index; SBP – Systolic blood pressure; DBP – Diastolic blood pressure; LVEF – Left ventricular ejection fraction; RHW1Year - Related hospitalizations within one year

As groups are defined based on iron and anemic status there was significant differences between the groups in laboratory testing in terms of hemoglobin, RDW, hematocrit, erythrocyte, ferritin, and serum iron levels. However, there was no significant difference in platelet count between the groups ($P=0.440$) (Table 6).

Table 6. Hematologic laboratory parameters of the red blood cell line.

	No anemia and no iron deficiency (n=26)	Anemia with iron deficiency (n=9)	Iron deficiency without anemia (n=12)	Anemia without iron deficiency (n=13)	P-value
Hemoglobin (g/L)	145.2±12.3	115.0±11.4	139.7±10.8	112.8±12.4	<0.001
Ferritin (ng/mL)	262.6±145.1	46.4±20.2	63.1±20.2	263.8±196.6	<0.001
Serum iron (μmol/L)	15.7±6.2	7.2±5.4	10.7±4.5	9.9±6.6	<0.001
RDW (%)	14.2±1.5	17.4±2.5	15.4±1.8	16.1±3.0	<0.001
RBC (x10 ¹² /L)	4.8±0.4	4.4±0.9	4.7±0.4	3.7±0.3	<0.001
Hematocrit (L/L)	0.44±0.04	0.37±0.04	0.34±0.04	0.34±0.04	<0.001
PLT (x10 ⁹ /L)	196.4±54.0	205.7±64.8	196.8±55.9	230.8±76.8	0.440

Data are presented as mean ± standard deviation

*One-way ANOVA test

RDW – Red blood cell distribution width; RBC – Red blood cells; PLT - Platelet

Variables of renal function (Table 7) differed significantly in levels of creatinine and urea. Anemic patients without iron deficiency had significantly higher levels of creatinine (P=0.020) and urea (P=0.001) when compared to other subgroups. However, there was no significant difference in levels of eGFR or stage of chronic kidney disease (CKD).

Table 7. Variables of renal function within subgroups.

	No anemia and no iron deficiency (n=26)	Anemia with iron deficiency (n=9)	Iron deficiency without anemia (n=12)	Anemia without iron deficiency (n=13)	P- value
Creatinine($\mu\text{mol/L}$)	104.3 \pm 36.3	108.6 \pm 50.7	124.8 \pm 57.2	163.5 \pm 81.5	0.020
Urea(mmol/L)	9.0 \pm 3.0	10.8 \pm 4.3	12.7 \pm 6.4	15.4 \pm 5.7	0.001
eGFR	60.5 \pm 22.5	52.8 \pm 24.5	50.4 \pm 22.5	42.7 \pm 21.3	0.140
CKD Stage	2.5 \pm 0.86	2.8 \pm 0.9	2.8 \pm 1.0	3.2 \pm 0.7	0.091

Data are presented as mean \pm standard deviation

*One-way ANOVA test

eGFR – Estimated glomerular filtration rate; CKD – Chronic kidney disease

In terms of electrolyte status there was no significant difference between the groups as shown in Table 8.

Table 8. Electrolyte status within groups

	No anemia and no iron deficiency (n=26)	Anemia with iron deficiency (n=9)	Iron deficiency without anemia (n=12)	Anemia without iron deficiency (n=13)	P-value
Na ⁺ (mmol/L)	139.2 \pm 4.0	139.9 \pm 3.9	139.1 \pm 3.0	138.5 \pm 1.6	0.813
K ⁺ (mmol/L)	4.1 \pm 0.5	4.2 \pm 0.5	4.2 \pm 0.4	4.3 \pm 0.4	0.556
Ca ²⁺ (mmol/L)	2.4 \pm 0.1	2.2 \pm 0.4	2.3 \pm 0.1	2.2 \pm 0.1	0.178
Mg ²⁺ (mmol/L)	0.9 \pm 0.1	0.8 \pm 0.1	0.8 \pm 0.2	0.8 \pm 0.1	0.490
Ch ⁻ (mmol/L)	100.9 \pm 5.7	101.7 \pm 5.9	100.8 \pm 6.2	102.8 \pm 4.4	0.788

Data are presented as mean \pm standard deviation

*One-way ANOVA test

There was a significant difference in levels of gamma-glutamyltransferase (GGT) between groups, where the highest level was noted in anemic patient without iron deficiency if

compared to other subgroups (P=0.048). In other liver and coagulation tests there was no significant differences as seen in Table 9.

Table 9. Parameters of liver function and coagulation tests.

	No anemia and no iron deficiency (n=26)	Anemia with iron deficiency (n=9)	Iron deficiency without anemia (n=12)	Anemia without iron deficiency (n=13)	P-value
Total bilirubin ($\mu\text{mol/L}$)	22.0 \pm 12.3	18.8 \pm 9.2	25.4 \pm 9.7	18.4 \pm 8.8	0.429
AST (U/L)	34.1 \pm 18.1	165.1 \pm 351.8	37.5 \pm 42.2	36.8 \pm 22.8	0.087
ALT (U/L)	39.4 \pm 26.6	115.6 \pm 199.0	35.6 \pm 33.3	53.1 \pm 61.3	0.120
ALP (U/L)	89.1 \pm 35.6	103.0 \pm 64.6	93.6 \pm 36.0	109.4 \pm 29.2	0.618
GGT (U/L)	94.6 \pm 71.9	45.2 \pm 41.8	64.1 \pm 49.8	103.9 \pm 58.7	0.048
D-dimer (mg/L)	2.2 \pm 1.4	1.4 \pm 0.5	0.6 \pm 0.4	2.4 \pm 2.0	0.163
PT-INR	1.5 \pm 0.6	1.5 \pm 0.4	1.4 \pm 0.6	1.7 \pm 0.9	0.687
aPTT	27.6 \pm 6.4	26.4 \pm 6.0	29.9 \pm 4.5	28.2 \pm 5.7	0.653

Data are presented as mean \pm standard deviation

*One-way ANOVA test

PT-INR - Prothrombin time – international normalized ratio; aPTT - Activated thromboplastin time; AST - Aspartate aminotransferase; ALT = alanine aminotransferase; ALP - alkaline phosphatase; GGT - Gammaglutamyltransferase

5. DISCUSSION

In this study the majority of patients had anemia and/or iron deficiency. Anemia without iron deficiency (22% of sample or 59% of anemic patients) was more prevalent than anemia with iron deficiency (15% of total population or 41% of anemic patients) similar results were found in a study by Darlington *et al* (41). However, in their study the patients had chronic heart failure and were not in phase of acute decompensated heart failure.

Both our study and Darlington's study had relatively small sample populations, if comparing our results with the French study by Cohen S *et al* that had a more than 10-fold larger sample population (42) there was a drastic difference where they showed prevalence of iron deficiency to be above fifty percent no matter if patients had anemia or not in patients with acute decompensated heart failure. One of possible explanations for such difference is different cut of values for iron deficiency and anemia.

In this study, it is shown that diastolic blood pressure is lowest in patients with iron deficiency and anemia when compared to other subgroups. Furthermore, in non-anemic iron deficient patients diastolic blood pressure is lower than in groups without anemia or iron deficiency which suggest iron deficiency itself could lead to lower levels of diastolic blood pressure.

It is known that lower levels of hemoglobin lead to decreased oxygen supply to peripheral tissues and due to these hypoxemic conditions local vasodilatory agents are released. This in turn leads to peripheral vasodilation and decreased peripheral vascular resistance which results in decreased diastolic blood pressure and could be the explanation to why patients in this study with the lowest levels of hemoglobin also had the lowest diastolic blood pressure. However, these mechanisms have only taken into account the role of hemoglobin and oxygen transport. The role of iron deficiency itself and its impact on blood pressure is not well studied.

In a study by Nair *et al.* (43) where severity of anemia was compared to diastolic blood pressure the conclusion was made that increased severity of anemia is inversely proportional to diastolic blood pressure. Our study would further amplify this hypothesis since diastolic blood pressure was lower in the group with both anemia and iron deficiency compared to iron deficiency alone. However, our study also suggests that iron deficiency itself could be related to lower diastolic blood pressure even in absence of anemia as the group of iron deficient patients without anemia had lower diastolic blood pressure then the patients with neither anemia nor iron deficiency.

We did not find a correlation of iron deficiency in terms of systolic blood pressure which should be expected as by the study of Hegde *et al.* which suggests iron deficiency leads to a cardiomyopathy mainly affecting the left ventricle of the heart and systolic functioning (44).

There was no statistically significant difference between iron deficiency and anemic subgroups of parameters such as heart rate, LVEF or previous heart failure related hospitalizations within the last year.

Furthermore, in laboratory testing as expected and by definition there was significant difference between groups in terms of ferritin, hemoglobin, Serum Iron, Hematocrit but there was no significant difference in terms of platelet count ($P=0.440$), the same was shown in Darlington's study.

In Darlington's study a healthy control group was used and significantly higher levels of creatinine were found in the group of patients with chronic heart failure, we did not use a control group in this study however we found that patients with the highest levels of urea and creatinine were recorded in anemic patient without iron deficiency which suggests a correlation between anemia and/or iron deficiency and renal function tests (41).

All patients included in this study had elevated Body mass index and BMI is an independent risk factor for developing iron deficiency, however we did not find any difference between BMI and level of iron deficiency between groups ($P=0.829$).

A study by Huang *et al.* proved a positive correlation between elevated BMI and increased risk of iron deficiency however the study was done in adolescents and showed varied results depending on whether iron deficiency was defined by serum iron levels or plasma ferritin levels (45).

In another study published by Khan *et al.* it was proposed that in people with BMI >25 ferritin could be used as a marker of inflammation rather than iron deficiency. In the study ferritin was higher in patients with higher BMI whereas transferrin was lowest in groups of higher BMI, ferritin had a positive correlation with both BMI and CRP indicating in obese population ferritin is a marker of inflammation in obese people rather than a marker of iron deficiency where complete iron profiling would be required to make conclusion of iron deficiency (46).

There were several limitations of this study, the relatively small sample size of 60 patients of which all patients were from the same hospital and department leading to a less varied collection of data not representing all patients with acute heart failure.

Since this study is of observational nature some degree of selection bias cannot be excluded. Furthermore, there was no data on how many patients on total were hospitalized during the enrolment period meaning some patients could have been excluded from the study which could potentially lead to different results. Some measurements such as blood pressure in this study were only recorded at admission and not recorded throughout the hospital stay which could have given a different result.

This study might not have included certain parameters affecting iron metabolism which could have led to different conclusions and interpretation of results. There was also great difficulty in comparing results between studies since different studies might use different cut of values for defining states of anemia and iron deficiency. Further research is necessary and future studies should include a larger sample population and more laboratory work-up in order to draw conclusions regarding the role of iron in patients with acute decompensated heart failure.

6. CONCLUSION

1. The majority of patients hospitalized due to acute decompensated heart failure have anemia and/or iron deficiency.
2. Most common type of anemia in patient with acute decompensated heart failure is anemia without iron deficiency.
3. Patients with iron deficiency and anemia have the lowest diastolic blood pressure when compared to other groups.
4. Increased levels of urea and creatinine was observed in patients with anemia and/or iron deficiency compared to patients without anemia or iron deficiency.

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8. SUMMARY

Objectives: The aim of the study was to compare how many patients with acute decompensated heart failure have iron deficiency or anemia and laboratory data between patients with acute decompensated heart failure when divided in groups based on iron and anemic status.

Material and methods: This was a clinical, cross-sectional study, conducted between January 2018 and January 2019, that included a total of 60 consecutive patients with acute decompensation of chronic heart failure at Department of Cardiology of the University Hospital of Split. Upon patient's arrival to hospital systolic and diastolic blood pressure was measured. Venous blood sampling was performed within 24 hours of admission. Chemiluminescent Microparticle Immunoassay was used for quantitative determination of ferritin. For serum iron spectrophotometry with ferrous chromogen was used. Complete blood count was determined using standard flow-cytometry-based hematologic analysis.

Results: In this study the majority of patients had anemia and/or iron deficiency. Anemia without iron deficiency (22% of sample or 59% of anemic patients) was more prevalent than anemia with iron deficiency (15% of total population or 41% of anemic patients). There was significant difference in DBP between the groups with the lowest DBP observed in patients with anemia and iron deficiency ($P=0.010$). In patients with acute decompensated heart failure and anemia or iron deficiency higher levels of urea ($P=0.031$) and creatinine ($P=0.020$) were observed than in other subgroups. There was no significant difference in biochemical tests between groups.

Conclusion: A significant number of patients hospitalized due to acute decompensated heart failure have anemia and/or iron deficiency. Diastolic blood pressure was lowest in patients with anemia and iron deficiency compared to other groups. Further research is necessary to draw any conclusions.

9. CROATIAN SUMMARY

Naslov: Parametri metabolizma željeza u pacijenata s akutno dekompenziranim srčanim zatajenjem.

Ciljevi: Cilj ovog istraživanja je ispitati koliki broj pacijenata s akutno dekompenziranim srčanim zatajenjem boluje od anemije ili manjka željeza te usporediti laboratorijske nalaze između različitih skupina pacijenata podijeljenih prema statusu željeza i anemije.

Materijali i metode: Presječno istraživanje je provedeno u periodu od siječnja 2018. do siječnja 2019, a uključivalo je 60 pacijenata s akutnom dekompenzacijom kroničnog srčanog zatajenja na Odjelu za kardiologiju Kliničkog bolničkog centra Split. Pacijentima je nakon prijema na odjel izmjeren sistolički i dijastolički krvni tlak. Uzorak venske krvi uzet je 24 sata nakon prijema. Kemiluminiscentna imunokemijska tehnologija korištena je za kvantitativno određivanje feritina u serumu. Spektrofotometrijska metoda s feren kromogenom korištena je za željezo u serumu. Kompletna krvna slika određena je protočnom citometrijom.

Rezultati: U ovom istraživanju većina je pacijenata imala anemiju i/ili manjak željeza. Anemija bez manjka željeza (22 % svih pacijenata, 59% pacijenata s anemijom) bila je učestalija od anemije s manjkom željeza (15 % svih pacijenata, 49% pacijenata s anemijom). Uočena je značajna razlika u vrijednostima dijastoličkog krvnog tlaka između skupina pacijenata, a najmanje vrijednosti bile su u skupini pacijenata s anemijom i manjkom željeza ($P=0,010$). U pacijenata s akutno dekompenziranim zatajenjem srca i anemijom ili nedostatkom željeza uočene su više serumske koncentracije ureje ($P=0,031$) i kreatinina ($P=0,020$) nego kod ostalih ispitanika. Nije pronađena značajna razlika između skupina u vrijednostima biokemijskih testova.

Zaključak: Značajan udio pacijenata koji su hospitalizirani zbog akutno dekompenziranog srčanog zatajenja imaju anemiju i/ili manjak željeza. Vrijednosti dijastoličkog krvnog tlaka značajno su bile niže u pacijenata s anemijom i/ili manjkom željeza u usporedbi s pacijentima koji nisu bili anemični niti su imali manjak željeza. Daljnja istraživanja su potrebna kako bi se mogli donositi zaključci.

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