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Chronic heart failure phenotypes in prevalent patients treated with hemodialysis – a single-center experience

Фенотипови хроничне срчане инсуфицијенције код болесника лечених хемодијализом – искуство једног центра

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SUMMARY

Introduction/Objective Heart failure (HF) is the main cause of morbidity and mortality of hemodialysis (HD) patients. The aim of this cross-sectional, single center, study was to examine: 1. frequency and characteristics of HF phenotypes in prevalent HD patients, 2. association of HF with traditional and non-traditional risk factors for cardiovascular diseases.

Methods We included all 96 maintenance HD patients from Special Hospital for Internal Diseases, Lazarevac, Serbia, and determined the prevalence of HF with preserved ejection fraction- HFpEF (per the 2016 criteria of the European Society of Cardiology) and HF with reduced and moderately reduced EF- HFrEF +HFmrEF- together in a group HFrEF (EF < 50%) using standardized post-HD transthoracic echocardiography. Clinical, routine laboratory and volume status parameters (by bioimpedance spectroscopy) was assessed.

Results 63 /96 examined patients (65.6%) had HF, among them 42 had HFpEF (66.7%), and 21 had HFrEF (33.3%). HFrEF was more common in older males, with diabetic nephropathy as underlying kidney disease (DN), with a longer dialysis vintage and in those with a previous history of ischemic heart disease. HFpEF was more common in males, with lower HD quality (kT/V) and higher pre-dialytic systolic blood pressure. In multivariable regression analysis, HFrEF was associated with DN, hypervolemia (positively) and triglyceride (negatively), while HFpEF was associated negatively with hemoglobin, iron and triglyceride.

Conclusion In order to control patients on maintenance HD with HF, in addition to appropriate drug therapy, it is advice to control of volemia and maintaining triglyceride, hemoglobin and iron concentration approximately within normal limits.

Keywords: heart failure; hemodialysis; associated factors

САЖЕТАК

Увод/Циљ Срчана инсуфицијенција (СИ) је главни узрок морбидитета и морталитета болесника лечених хемодијализом (ХД). Циљ ове студије пресека спроведене у једном центру био је да испита: 1) учесталост и карактеристике фенотипова СИ код ХД пацијената; 2) повезаност СИ са традиционалним и нетрадиционалним факторима ризика за кардиоваскуларне болести.

Методе Укључили смо свих 96 болесника лечених ХД у Специјалној болници за интерне болести, Лазаревац, Србија, и утврдили преваленцију СИ са очуваном ејекционом фракцијом (*EF*) – *SIpEF* (по критеријумима Европског кардиолошког друштва из 2016) и СИ са смањеном и умерено смањеном *EF* – *SIrEF* + *SImrEF* – заједно у групи *SIrEF* (*EF* < 50%) применом стандардизоване пост-ХД трансторакалне ехокардиографије. Процењивани су клинички, рутински лабораторијски и параметри запреминског статуса (биоимпедансном спектроскопијом).

Резултати Шездесет три од 96 испитаних болесника (65,6%) имало је СИ, од тога 42 *SIpEF* (66,7%), а 21 *SIrEF* (33,3%). *SIrEF* је била чешћа код старијих мушкараца, са дијабетичком нефропатијом (ДН) као основном болешћу бубрега, са дужим периодом дијализе и код оних са претходном исхемијском болешћу срца. *SIpEF* је била чешћа код мушкараца, са нижим квалитетом ХД (*kT/V*) и вишим предијализним систолним крвним притиском. У мултиваријантној регресионој анализи, *SIrEF* је била повезана са ДН, хиперволемијом (позитивно) и триглицеридима (негативно), док је *SIpEF* била повезана негативно са хемоглобином, гвожђем и триглицеридима.

Закључак У циљу контроле пацијената лечених ХД са СИ, поред одговарајуће терапије лековима, саветује се контрола волемије и одржавање концентрације триглицерида, хемоглобина и гвожђа приближно у границама нормале.

Кључне речи: срчана инсуфицијенција; хемодијализа; придружени фактори

INTRODUCTION

Patients on hemodialysis (HD) are at a higher risk of developing cardiovascular disease (CVD), which is a leading cause of death and accounts for approximately 30%–35% of all-

cause mortality among patients on HD [1]. Besides coronary artery disease (CAD), heart failure (HF) is the most common CVD in HD patients [2]. It is known that one third of patients have HF at the initiation of HD, and 25% of patients develop HF *de novo* during dialysis treatment [2].

Patients treated with HD have an increased risk of HF. In addition to the traditional (age, hypertension, diabetes, and dyslipidemia), many non-traditional factors mostly related to chronic kidney disease and dialysis itself are involved in the development of CVD and HF (volume load, hypertrophy and impaired left ventricular function (systolic and diastolic), valvular defects, AV fistula, anemia, mineral metabolism disorders, oxidative stress, inflammation) [2].

Three types of HF in general population are recognized: HF with preserved ejection fraction (EF), known as diastolic HF, HF with reduced EF known as systolic HF, and HF with moderately reduced EF [3]. Their clinical presentation and risk factors are similar, but the approach to treatment and response to treatment is different. Having in mind that HF is a poor predictor of HD patient outcome [1, 4], timely identification of HF risk factors, and clinical presentation would be helpful in prevention and management of those patients [5].

In order to contribute to the timely diagnosis of HF in HD patients, we conducted this study aiming to define: 1. frequency and characteristics of left ventricular function in prevalent patients treated with chronic HD, 2. association of HF with traditional and non-traditional risk factors for CVD.

METHODS

Patients

The study population consisted of 96 maintenance HD patients treated at the Special Hospital for Internal Diseases, Lazarevac, Serbia. Only the patients older than 18 who spent more than six months on HD were included. They were all asymptomatic for chest pain and had no history of acute coronary syndrome in the past three months. Exclusion criteria was the inability of the patients to provide. According to the criteria of the American and European

Society of Cardiology [5] and based on signs and/or symptoms of heart failure, and left ventricular function indicators obtained by transthoracic echocardiography, patients were divided into groups: 1. with HF and reduced - EF-rEF (EF< 40%), plus moderately reduced HFmrEF (EF = 40–50%)- 21 patients, 2. with HF and preserved EF- HFpEF (EF ≥ 50%)- 42 patients and 3. without overt HF - 33 patients.

The participants were monitored from January 2020 to the end of September 2020. The approval of the local ethics committee was obtained (number110/21.1.2020) and written informed consent was obtained from all the participants.

The study variables were as follows:

1. Demografic data: age, gender, renal disease, comorbidities (coronary artery disease, hypertension, diabetes mellitus, dyslipidemia, and peripheral obstructive arterial disease), residual diuresis, and body mass index (BMI) including history of coronary artery disease defined as prior revascularization (through angioplasty or coronary artery bypass). Also, each patient was physically examined and questioned for signs and/ or symptoms of HF including edema of the lower extremities, (exertional) dyspnea graded by the New York Heart Association criteria (NYHA I-IV) and paroxysmal nocturnal dyspnea/orthopnea [6].

2. Dialytic data: duration of dialysis session (four hours three times a week), dialysis vintage, dialysis membrane (low and high flow polysulphone membrane), single pool Kt/V [7], interdialytic weight gain, dialysis access, and systolic and diastolic blood pressure before HD session, volume status checked by bioimpedance spectroscopy, using the device Body Composition Monitor (BCM) manufactured by Fresenius Medical Care.

3. Laboratory data: urea, creatinine, markers of anemia, lipid fraction, lipoprotein subfraction, biomarkers of mineral bone disorder were determined by routine laboratory analyzes at the respective dialysis session.

4. Transthoracic echocardiography characteristics: left ventricular function, right ventricular function, pulmonary hypertension, diastolic dysfunction, pericardial effusion, and valvular heart disease. All echocardiographic measurements were performed by two experienced echocardiographers (cardiologists) who were blinded to the clinical status of the patients. Intra-observer variability was 4%.

To avoid the effect of volume load, all echocardiographic data were collected on dialysis days when the HD was done [8]. Atrial volume and ejection fraction (EF) were assessed using the modified Simpson biplane method [9]. LV mass was calculated using the Devereux formula and normalized by body surface area (LV mass index [LVMI]). Relative wall thickness (RWT) was calculated as 2 times PW divided by the LV diastolic diameter. Early and late diastolic peak filling velocities E and A waves were measured at the mitral leaflet tips. The early (e') and late (a') diastolic velocities at septal and lateral corner of mitral annulus were assessed with pulse-wave Tissue Doppler from a standard apical 4-chamber view [9].

Statistical analyses

The SPSS software (version 25.0) and R software (version 3.6.1) were used in the statistical analyses. Continuous variates with normal distribution were presented as mean ± SD and compared using the Student's t-test. Variables without normal distribution data were presented as median with interquartile ranges and compared using the Mann-Whitney U test. Categorical data were presented as the number of cases and percentages and compared using the χ2 test. Multivariable logistic regression model including all significantly different characteristics in the univariate logistic regression models (at a significance level of 0.05) as well as those predictors that are known to affect the dependent variable, was used to determine the independent association with HF. Two-sided P-values <0.05 were considered significant.

Data availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

RESULTS

Baseline characteristics

The baseline data on studied patients are presented in Table 1. Out of 96 examined patients 63 (65.6%) had HF, among them 42 patients had HFpEF (66.7%), and 21 patients had

HFrEF (33.3%). These groups compared with the control group consisted of 33 patients with no HF. The average patients' age in all three groups was higher than 60 years, but patients with HF were significantly older than patients without HF. Also, there were predominantly males in the groups with HF. In the previous history, a significantly smaller number of patients with HFpEF had myocardial infarction-IM and coronary artery bypass grafting (CABG) compared to the other two groups of patients. ACEi, calcium channel antagonists and beta blockers were most often used antihypertensive drugs in combination, or less often alone. Only beta-blockers were used in the smallest number of patients in group 3 compared to the other two groups of patients (data on treatment is not presented). Insignificantly but a slightly larger number of patients in group 1 were treated with statins. No difference was found among groups regarding underlying kidney disease, co-morbidities, BMI and smoking habit.

Data on HD characteristics, predialysis blood pressure, and NYHA are showed in Table 2. Patients with HF had lower kT/V, higher predialysis systolic pressure, and OH than patients without HF. Dialysis lasted the longest in group 1 patients. The most common access for HD was arteriovenous fistula in all three studied groups (data not presented). The mean value of OH / ECW measured by bioimpedance and indicating hyperhydration was highest in patients of group 1, in which 60% of patients had OH / ECW > 15%, which is higher than in the other two groups. No difference was found in NYHA classes groups between the examined patients with and without HF.

Laboratory analyses and echocardiographic parameters

The lowest serum concentration of hemoglobin, iron and TG was observed in groups with HF and HFpEF who additionally had the lowest iPTH concentration (Table 3). Also, almost half of the patients from groups 1 and 2 had TG below lower laboratory limit. Patients from group 1 had the lowest total cholesterol and LDL-C. The HDL / LDL ratio as an indicator of atherosclerosis risk in all three groups was within normal and similar in almost all three groups. Other laboratory analyses were similar. Unhealthy lean body mass was found in all studied patients (data not shown).

Echocardiographic findings are presented in Table 4. Several echocardiographic parameters distinguished both the HF groups from that without HF, as these patients had larger left ventricular, left atrial diameters and mass index, as well as E/e′ (Table 4).

Predictors of heart failure

The likelihood of HF (all HF, HFrEF, HFpEF) in comparison to no HF in prevalent hemodialysis patients is presented in Figure 1.

In multivariable regression analysis, HF was associated with patients' age, urea volume distribution and use of beta blockers, but HFrEF was associated with diabetic nephropathy and hypervolemia (positively) and triglyceride (negatively), while HFpEF was associated negatively with hemoglobin, iron and triglyceride.

DISCUSSION

Presence and risk factors of HF in patients on maintenance hemodialysis were analyzed in this single- center study. The key findings are the following: 1. 65.6% of all studied HD patients fulfilled the diagnostic criteria for HF, among them 66.7% had HFpEF, and 33.3% of patients had HFrEF. 2. No differences in patients' symptoms in different HF phenotypes were observed. 3. HF and both HF phenotypes share some clinical and biochemical contributing factors.

The frequency of HF in our group of patients is similar to that described by other authors [10, 11, 12]. Atlanger et al. reported on the prevalence of HF of up to 70% patients among 105 maintenance HD, of whom 81% had HFpEF and 19 % had HFrEF [10]. In the USA registry data, it was estimated that 44% of HD patients have HF: 10% with HFpEF, 13% with HFrEF [11]. Wang et al. found a slightly lower incidence of HF in 220 patients treated with PD, which was expected for this type of dialysis. The authors found that 86 (39.1%) patients had HF, of which 47 (54.7%) had a HFpEF and 39 (45.3%) had HFrEF [12].

The clinical diagnosis of HF is usually started on the identification of accompanying symptoms. In dialysis patients it is not easy to identify which symptoms originate from HF and which from ESKD and HD *per se*. Typical HF symptoms, such as paroxysmal nocturnal dyspnea, orthopnea, dyspnea, fatigue, ascites, and lower legs edema, may be intermittent. These symptoms are difficult to distinguish from periodic fluid retention, and chronic renal anemia, so the development of structural heart abnormalities may remain unrecognized in patients with ESKD treated with dialysis. Even the symptoms reported by patients (and according to NYHA criteria) are not completely reliable for the diagnosis of HF that was in

line with previous studies [10, 13, 14]. The presented results have shown that the majority of our patients had no or mild HF symptoms, i.e., more than 80% of patients with HFpEF and about 60% of patients with HFrEF had no or mild heart problems (NYHA classes 1 and 2). Furthermore, tests and biomarkers used to diagnose CVD and HF in the general population, including Framingham risk model cannot be performed and reliably interpreted in the dialysis population [15, 16]. However, patients with dialysis-dependent HF should undergo the same evaluation as patients with non−dialysis-dependent HF. K/DOQI guideline was recommended to perform a detailed echocardiographic and cardiac examination of all patients who start dialysis and then every three years during the treatment to monitor functional and structural changes in the myocardium even if they are asymptomatic and without overt cardiovascular disease [17, 18].

Many studies have been conducted to evaluate the factors associated with chronic HF related to dialysis, but the findings have been inconsistent. The association of among several traditional risk factors, such as age, diabetes, BMI, blood pressure, serum cholesterol, and mortality and HF have been previously reported [12, 19, 20].

Similarly to the aforementioned studies, we have found that HF phenotypes share some of the contributing factors based on demographic and clinical information. HFrEF was more common in older males, with diabetic nephropathy as underlying kidney disease and in those with a previous history of ischemic heart disease, with a longer dialysis vintage. On the other side, HFpEF was more common in males, with lower kT/V and higher pre-dialytic systolic blood pressure. Of these, only patients' age, diabetic nephropathy, and use of beta-blocker have been independently associated with HF, which is in accordance with previous data in dialysis patients [12, 19, 20].

Present results showed that HF and both HF phenotypes were associated negatively with triglyceride, meaning that the lower triglyceride, the more likely HF is to be present. This finding is in accordance with the earlier study conducted in non-CKD populations with HF. Namely, chronic HF can lead to a catabolic state and cachexia in advanced cases with reduced appetite, malabsorption, and reduced anabolic steroids levels with consequent low cholesterol and triglyceride level. At the molecular level, inflammation, endotoxins accumulation, adrenergic activation, oxidative stress, and tissue injury develop during chronic HF [21]. Also, HF might alter both the production and the storage of triglycerides true liver ischemia. Therefore, low triglyceride is not the cause of HF, but a sign of a disturbed state in the body.

The volume of urea distribution and the OH / ECW ratio as indicators of hypervolemia were selected as predictors of HF and HFrEF in our studied patients. The higher the OH / ECW ratio, the more likely a patient is to have HFrEF. Repeated water retention between dialysis contributes to the development of LVH and both types of HF in dialysis patients [12, 22, 23]. Thus, the control of hypervolemia by ultrafiltration during HD is the mainstay of treatment in the prevention of CV instability [17, 22, 24]. On the other hand, there is evidence that excessive ultrafiltration can adversely affect the hemodynamic stability of the cardiovascular system and trigger a range of inflammatory reactions in patients and thus affect the development of HF [20], suggesting that continuous volume status assessment in dialysis patients is necessary.

Hemoglobin concentration is an independent contributing factor for the development of HF and HFpEF in our analysis, with a negative sign. This is in line with literature data that anemia in CKD patients and those treated with dialysis is a strong predictor of HF [1, 2, 25]. Stable and almost normal Hb, especially after the introduction of erythropoietin stimulating agents, made it possible to maintain a good oxygen supply to the tissues, which had a protective effect especially on cardiomyocytes and coronary microvascular dysfunction [26].

In addition, iron concentration was selected as independent contributing factor of HFpEF in our study. For each reduction of iron per unit of measure, the probability that a patient will have HFpEF increases by 1.23 times. There is growing evidence that iron treatment has a beneficial effect in the non-CKD population with HF. The explanation lies in the fact that high metabolic needs in cardiomyocytes depend on iron [26]. When observing dialysis patients, maintaining iron balance was important not only for treating anemia, but also for reducing the number of hospitalizations due to HF and nonfatal myocardial infarction [27].

Some limitations of the current study need to be mentioned. This study was cross-sectional and therefore does not provide information on when HF developed. For the same reason, it was not possible to draw conclusions about causality, but about the association of HF and various examined factors.

CONCLUSION

Our cross-sectional study showed that more than half of the patients on maintenance hemodialysis met the criteria for HF. As it is not easy to distinguish common HF symptoms

from intermittent complications that accompany HD, it is recommended that a complete CV investigation be performed in accordance with the KDIGO guidelines. In addition to immutable factors such as patients age and sex and DN, HF should be sought in patients with recurrent hyperhydration, who have poorer parameters of HD adequacy, with lower TG, iron, and anemia.

Conflict of interest: None declared.

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Table 1. Baseline characteristics of examined patients

Characteristics	Group 1 HFrEF + HFmrEF	Group 2 HFpEF	Group 3 No HF	p
Number of patients	21	42	33	
Sex, m/f*	16 (76.2) / 5 (23.8)	32 (76.2) / 10 (23.8)	15 (45.5) / 18 (54.5)	f - (1 + 2):3 = 0.003 1:3 = 0.04 2:3 = 0.008
Age, years[1]	69 ± 1.88	68.62 ± 2.07	63.60 ± 1.67	1:3 = 0.042
Kidney diseases*: DN Nscl Others	8 (38.1) 6 (28.6) 7 (33.3)	10 (23.8) 19 (45.3) 13 (30.9)	4 (12.1) 14 (42.4) 15 (45.5)	NS
BMI	25.6 (19.2)	24.7 (5.9)	24.5 (6.5)	NS
Smoking*	6 (28.6)	9 (21.4)	7 (21.2)	NS
Comorbidities*: Hypertension CVI PVD Diabetes Malignancies HOBD	13 (61.9%) 1 2 1 1 2	19 (45%) 2 - 3 2 5	16 (48.5%) 2 1 3 1 2	
Coronary heart disease*: IM	7	1	4	1:2 = 0.0013
PCI	1	0	1	
CABG	5	1	3	1:2 = 0.013

Nscl – nephroangiosclerosis; DN – diabetic nephropathy; BMI – body mass index; CVI – cardiovascular insult; PVD – peripheral vascular disease; COPB – chronic obstructive pulmonary disease; IM – myocardial infarction; PCI – percutaneous coronary intervention; CABG – coronary artery bypass grafting;

[1]mean ± SD or median (IQR);

*frequency (%)

Table 2. Data on hemodialysis duration, kT/V, volemia, and pre-dialysis blood pressure

Parameter	Group 1 HFrEF+HFmrEF	Group 2 HFpEF	Group 3 No HF	p
HD duration, months[1]	57 (227)	31.50 (143)	36 (58.5)	1:2 = 0.027
kT/V	1.08 ± 0.06	1.07 ± 0.04	1.22 ± 0.05	(1+2):3 = 0.036 2:3 = 0.042
Interdialytic weight gain, kg*	3.41 ± 0.33	3.02 ± 0.17	2.83 ± 0.18	NS
Pre-dialysis BP*: Systolic, mmHg	149.04 ± 5.30	151.38 ± 3.49	141.09 ± 3.26	(1 + 2):3 = 0.044 1:3 = 0.029 2:3 = 0.039
Diastolic, mmHg	71.38 ± 2.92	74.88 ± 1.9	75.15 ± 2.03	
NYHA class, No. I II III	4 (19%) 11 (52.4%) 6 (28.6%)	8 (19.05%) 26 (61.9%) 8 (19.05%)	9 (27.3%) 20 (60.6%) 4 (12.1%)	NS
OH	3.2 (5.93)	2.9 (3.8)	2.1 (1.8)	1:3 = 0.005 2:3 = 0.035
ECW %	19.8 (21.83)	16.7 (16.8)	11.8 (10.9)	NS
OH / ECW	18.63 ± 2.59	16.55 ± 2.11	12.69 ± 1.43	1:2 = 0.035
OH / ECW > 15%	12/20 (60%)	13/39 (33.33%)	9/30 (30%)	1:2 = 0.05 1:3 = 0.045
Water load	37.74 ± 7.01	36.7 (12.3)	33.1 (6.43)	2:3 = 0.04
Volume of urea distribution	35.5 (7.33)	34.4 (11.6)	30.45 (5.67)	1:3 = 0.036 2:3 = 0.031
ECW/ ICW	1.15 ± 0.04	1.09 ± 0.03	1.03 ± 0.03	1:3 = 0.013

NYHA – New York Heart Association classification of heart failure; OH – overhydration;

ECW – extracellular water; ICW – intracellular water;

*mean ± SD. median (IQR)

Table 3. Laboratory analyses

Analysis	Group 1 HFrEF+HFmrEF	Group 2 HFpEF	Group 3 No HF	p
Hemoglobin, g/l	103.78 ± 4.73	97.94 ± 2.87	113.1 ± 3.7	(1+2):3 = 0.002; 2:3 = 0.001
Sodium, mmol/l	137.9 ± 0.44	139 ± 4.0	139.4 ± 0.43	1:3 = 0.014
Potassium, mmol/l	5.48 ± 0.18	5.3 (0.6)	5.3 ± 0.16	NS
Calcium, mmol/l	2.14 ± 0.05	2.15 (0.28)	2.18 ± 0.04	NS
Phosphate, mmol/l	1.36 ± 0.09	1.45 ± 0.09	1.53 ± 0.08	NS
Ferritin, ng/ml	438.78 ± 16.09	405 (119)	395 (135)	NS
Iron, μmol/l	15.03 ± 1.1	13.01 ± 2.5	15.48 ± 0.72	(1 + 2):3 = 0.03; 1:3 = 0.004 2:3 = 0.002
iPTH, pg/ml	463.3 (662.3)	189.5 (239.5)	340.5 (795.47)	2:3 = 0.05
Total cholesterol, mmol/l	3.88 (1.87)	4.16 (1.38)	4.72 (0.18)	1:3 = 0.017
TG, mmol/l	1.2 (1.06)	1.31(0.8)	2.07 (1.57)	(1 + 2):3 = 0.001; 1:3 = 0.013 2:3 = 0.002
< 1.35, No. (%)	10 (47.6)	19 (45.2)	7 (22.5)	
> 1.7, No. (%)	8 (38.1)	12 (28.6)		
HDL-C, mmol/l	1.47 (0.68)	1.18 (0.93)	1.14 (0.64)	NS
LDL-C, mmol/l	1.7 (1.25)	2.41(0.84)	2.42 (0.96)	1:2 = 0.05
HDL/LDL	1.87 ± 0.26	2.05 ± 0.13	2.19 ± 0.15	NS

PTH – parathyroid hormone; TG – triglyceride; HDL-C – high-density lipoprotein cholesterol

particles; LDL-C – low-density lipoprotein cholesterol particles

Table 4. Echocardiographic parameters

Parameters	Group 1 HFrEF+HFmrEF	Group 2 HFpEF	Group 3 No HF	p
EF, %	43 (7)	57.7 ± 0.9	59.7 ± 6.2	1:2. 1:3=0.0001
EDD, cm	5.85 ± 0.11	5.55 ± 0.1	4.75 ± 0.08	1:3=0.0001
				2:3=0.0001
ESD, cm	4.39 ± 0.13	3.73 ± 0.1	3.1 (0.35)	1:2. 2:3. 1:3= 0.0001
IVs	1.1 (0.25)	1.1 (0.2)	1.0 (0.1)	1:2:3. p= 0.000
Posterior wall, cm	1.1 (0.20)	1.1 (0.2)	0.9 (0.2)	1:2:3. p= 0.019
LVM index	145.86 ± 6.6	133.1 ± 4.7	90 (23)	1:3. 2:3 p= 0.0001
LA	4.3 ± 0.1	4.24 ± 0.1	3.63 ± 0.6	1:2. 2:3. p=0.0001
LAVi	59.2 ± 3.9	53 (21.3)	29 (11.6)	1:3. 2:3. p=0.0001
E/ A index	0.6 (0.73)	0.64 (0.28)	0.80 (0.26)	1:3. 2:3. p=0.001–0.021
e', cm/s	6 (2.25)	6 (1)	11.54 ± 0.3	1:3. 2:3. p= 0.000
≥ 8*	14 (66.6%)	0	31 (93.9%)	
E/e'	10.36 ± 1.1	10.87 ± 0.7	5.46 ± 0.3	1:3. 2:3. p= 0.000
≥ 8*	14 (66.6%)	34 (80.9%)	4 (12%)	

EF – ejection fraction; EDD – left ventricular end diastolic diameter; ESD – left ventricular end systolic diameter; LAVi – left atrial volume index; LVMi – left ventricular mass index; LA – left atrial; E – early mitral valve flow velocity; A – late mitral valve flow velocity; E/A – ratio of early to late mitral valve flow velocity; e' – early diastolic wave; E/e′ – ratio of early mitral valve flow velocity to early tissue Doppler lengthening velocity;

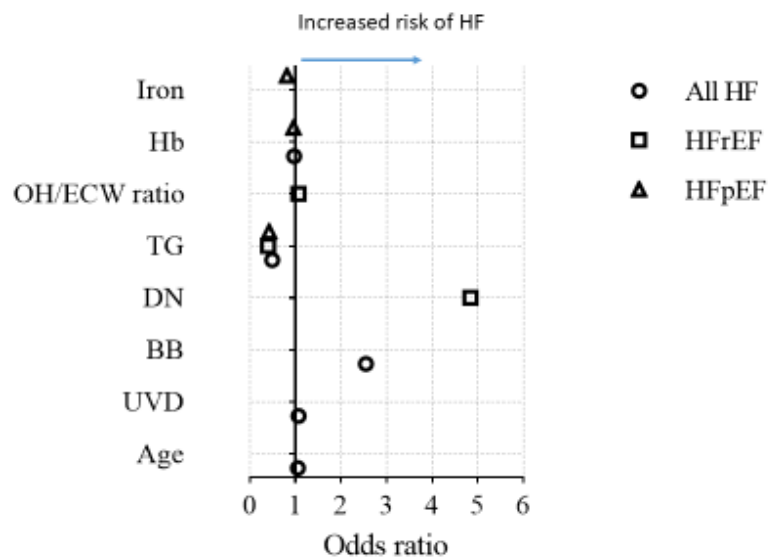*number of patients; mean ± SEM; M(IQR)

Figure 1. Multivariate prediction model of each contributing factor for heart failure (HF), HFrEF or HFpEF *vs*. no HF;

Hb – hemoglobin; TG – triglyceride; DN – diabetic nephropathy; BB – beta blocker; UVD – urea volume distribution