Renal Dysfunction - a Possible Marker of Severity of Heart Failure

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Heart failure (HF) and renal dysfunction are frequent associated in the same patient. The purpose of our study was to assess the prevalence of renal dysfunction and the clinical status in admitted patients for decompensated HF. Material and Methods. 397 patients succesively hospitalized for decompensated HF, NYHA III or IV functional class, with left ventricular ejection fraction (LVEF) ≤ 45% were included in the study. Renal dysfunction was defined by glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2. The mean GFR in patients with HF was 63.89 ± 21.5 mL/min/1.73 m^2 .The prevalence of renal dysfunction was 49.6%. Patients with GFR < 60 mL/min/1.73m^2, compared with those with preserved renal function were significantly more frequent older (75.37 ± 6.84 vs. 71.33 ± 8.08 years; p <0.001), females (53,8% vs. 43.5%; p = 0.04), had a significantly higher prevalence of diabetes mellitus (50.2% vs. 28.5%; p <0.001), atrial fibrillation (53.8% vs 46.2%, p = 0.04) and anemia (47.7% vs. 29.5% ; p <0.001). Also, patients with renal dysfunction had more severe HF than those without renal dysfunction (NYHA class IV: 65% vs 45%, p <0.001, clinical congestion: 78.2% vs 68%, p = 0.02, LVEF <35%: 47.21% vs ≥ 35%, p <0.001). Renal dysfunction can be considered an additional marker of severe cardiac dysfunction along with NYHA IV class and low LVEF. The presence of both renal dysfunction and anemia could represent prognostic markers in HF patients with reduced LVEF.

Keywords: renal dysfunction, heart failure, anemia

Renal dysfunction is a common complication of both chronic and acute heart failure and may contribute to the progression of the disease. In patients with cardiac dysfunction, renal impairment may be chronic (chronic kidney disease) or may occur during chronic heart failure decompensation (acute renal injury) and sometimes it is difficult to assess the acute or chronic character of renal dysfunction. Causes of renal dysfunction in patients with heart failure are various. In addition to common pathogenic mechanisms such as neurohormonal activation, decreased renal perfusion, oxidative stress and inflammation, an important etiological factor is medical treatment of heart failure (high dose of diuretics, angiotensin converting enzyme inhibitors, angiotensin receptor blockers) which may contribute to renal dysfunction [1-6]. Also, both chronic kidney disease and chronic heart failure can cause anemia. From a pathophysiological point of view, heart failure can cause renal dysfunction by decreasing renal plasma flow and, on the other hand, renal impairment is associated with a decrease in endogenous erythropoietin (EPO) levels with the occurrence of anemia which in turn causes increased heart work by completing a vicious circle. This association was named by Silverberg et al. cardio-renal-anemia syndrome (CRAS) [7].

The purpose of this study was to determine the prevalence and clinical profile associated with the presence of renal dysfunction in admitted patients for decompensation of heart failure.

Experimental part

Material and method. In our study, 397 patients were successively hospitalized at the Department of Cardiology of the Filantropia Clinical Hospital of Craiova for the decompensation of chronic heart failure. The inclusion criteria in the study were as follows: age 18 years, NYHA III or IV functional class, HF diagnosed at least 1 year prior to study entry, left ventricular ejection fraction (LVEF) ≤ 45% in echocardiographic evaluation. We excluded patients with left ventricular ejection fraction over 45%, heart failure at first presentation in a previously undiagnosed or heart failure diagnose for less than 1 year. Renal function was evaluated by estimating the glomerular filtration rate (GFR) using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula using serum creatinine and demographic variables - age, gender and race and adjusting GFR to body surface area [8]. We defined the presence of renal dysfunction by GFR values < 60 mL/min/1.73m^2. Anemia was defined using WHO criteria by hemoglobin (Hb) values <12g/dL in women and <13g/dL in men [9]. Taking into account the erythrocyte parameters we divided the patients with anemia into four groups: normocytic normochromic anemia defined as mean corpuscular volume (MCV) 80-98 fl and mean corpuscular hemoglobin (MCH) ≥ 27 pg, normocytic hypochromic anemia (MCV 80-98 fl and MCH <27 pg), microcytic hypochromic anemia (MCV <80 fl and MCH <27 pg) and macrocytic anemia (MCV> 98 fl). Clinical congestion was defined by the presence of ≥ 1 physical sign of hypervolemia (orthopnoea, peripheral oedema, rales, third heart sound, and jugular venous distension, hepatomegaly, hepato-jugular reflux) and ≥ 1 symptom due to hypervolemia (dyspnoea and orthopnoea, paroxysmal nocturnal dyspnea). All patients confirmed their participation in the study by signing an informed consent form.

Statistical analysis

Continuous type variables were expressed as mean ± standard deviation and category variables as percent (%). To investigate the existence of statistically significant differences between the different variables, groups or categories within the same variable, the t-student test and

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the Mann-Whitney test were performed to compare the meanings between two distinct categories within the same continuous variable with parametric and nonparametric distribution respectively; the ANOVA Analysis of Variation and the Kruskal-Wallis test for comparing the averages of three or more groups within the same continuous variable with parametric and non-parametric distribution and the chi-square test (chi^2) and the Fisher test were used to compare at least two groups within the category variables (contingency tables). To evaluate the existence of a correlation between the different variables we used the Pearson correlations for the continuum and Spearman variables for the categorical ones. A p value <0.05 was considered statistically significant. All statistical analyses were conducted using SPSS software, version 22.0 (SPSS for Windows 22.0, Chicago, IL, USA).

Results and discussions

The mean serum creatinine was 1.10 ± 0.4 mg/dL, with limits between 0.46 and 3.97 mg/dL. 11.3% (45/397) of the patients included in the study have serum creatinine > 1.5 mg / dL. The mean estimate GFR was 63.89 ± 21.5 mL/min/1.73m^2 with limits between 11 and 116 mL/min/1.73m^2. Depending on the degree of renal impairment, the distribution of patients was as follows: 2.5% (10/397) had GFR <30 mL/min/1.73m^2, 18.6% (74/397) had GFR 30-45 mL/min/1.73m^2, 28.5% (113/397) had GFR 45-59 mL/min/1.73m^2, 37% (147/397) had GFR 60-90 mL/min/1.73m^{2}and 13.3% (53/397) had GFR> 90 mL/min/1.73m^2 (fig. 1). The mean GFR was 68.43±21.04 mL/min/1.73 m^2 in men, respectively 59.08 ± 21.06 mL/min/1.73m^2 in women (p <0.001). The characteristics of the patients included in our study based on the presence or absence of renal dysfunction are presented in table 1. 49.6% (197/397) of the 397 patients studied had GFR <60 mL/min/1.73m^2.

Table 1 shows that renal dysfunction (GFR <60 mL/min/1.73m^2) was more common in females compared with those with normal renal function (53.8% vs. 43.5%, p = 0.04). The risk of renal dysfunction in women was 1.23 fold higher than in men (CI 95% 1.01-1.31).

Although the ischemic etiology of heart failure has more frequently associated with impaired renal function (46.7% vs 43.5%, p>0.05), smoking is not only one of the most important risk factor for lung cancer [10], COPD and asthma [11,12] but also for hypoxemia [13] and coronary artery disease, being more commonly encountered in patients without renal dysfunction (42.5% vs. 37.1%, p>0.05). Patients with low GFR (<60 mL/min/1.73m^2) compared with those without renal dysfunction had a higher prevalence of HTN (67% vs. 60.5%, p>0.05), diabetes mellitus (50.2% vs. 28.5%, p <0.001) and COPD (19.8% vs. 18.5%, p>0.05). The risk of renal impairment was 1.76 times higher in diabetic than in non-diabetic patients (CI 95% 1.36-2.28). The presence of HTN and COPD was not significantly influencing the risk of renal dysfunction (RR 1.0 CI 95% 0.95-1.28 respective RR 1.07 CI 95% 0.98-1.16). Atrial fibrillation was also more common in patients with impaired renal function compared to those with GFR ≥ 60 mL/min/1.73m^2 (53.8% vs 46.2%; p = 0.04). Patients with severe symptoms (NYHA IV class) had significantly lower GFR compared to those with mild symptoms (NYHA III class) (59.43 ± 20.49 mL/min/1.73m^2 versus 69. 31 ± 21.59 mL/min/1.73m^2, p = 0.004, fig. 2), and on the other hand, severe symptoms were significantly higher in patients with renal dysfunction versus those without renal dysfunction (65% vs 45%, p <0.001). Also,

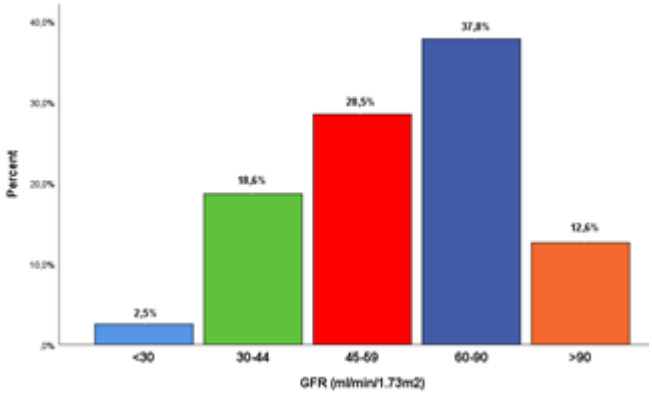

Fig. 1. Distribution of patients by glomerular filtration rate (Abreviation: GFR= glomerular filtration rate)

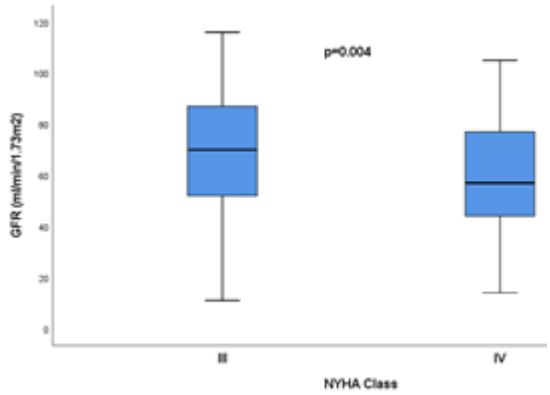

Fig. 2. Mean value of glomerular filtration rate depending on the functional NYHA class (Abreviation: GFR= glomerular filtration rate, NYHA=New York Heart Association)

Parameters analyzed	HF with renal dysfunction (n=197)	HF without renal dysfunction (n=200)	p
Age, mean ± SD (years)	75.37±6.84	71.33±8.08	**<0.001**
Female gender,% (n)	53.8% (106)	43.5% (87)	**0.04**
Ischemic etiology,% (n)	46.7% (92)	43.5% (87)	**NS**
HTN, % (n)	67% (132)	60.5% (121)	**NS**
Diabetes mellitus, % (n)	50.25% (99)	28.5% (57)	**<0.001**
COPD, % (n)	19.8% (39)	18.5% (37)	**NS**
Atrial fibrillation, % (n)	53.85% (126)	46.15% (108)	**0.04**
Smoking, % (n)	37.06% (73)	42.5% (85)	**NS**
NYHA IV, % (n)	65% (128)	45% (90)	**<0.001**
Clinical congestion, % (n)	78.17% (154)	68% (136)	**0.02**
LVEF < 35%, % (n)	47.21% (93)	30% (60)	**<0.001**
Anemia, % (n)	47.72% (94)	29.5% (59)	**<0.001**

Abbreviations: n = number of patients, SD = standard deviation, HF = heart failure, HTN = hypertension, COPD = chronic obstructive pulmonary disease, NYHA = New York Heart Association, LVEF = left ventricular ejection fraction

Table 1
CHARACTERISTICS OF PATIENTS BASED ON THE PRESENCE / ABSENCE OF RENAL DYSFUNCTION

patients with severe NYHA IV class heart failure had a 1.44-fold greater risk of renal dysfunction than those with mild symptomology, NYHA III class (CI 95% 1.20-1.73).

Clinical congestion was present in 78.2% of patients with renal dysfunction compared to 68% of those without renal impairment (p = 0.02), mean GFR being significantly lower in the presence of clinical congestion compared with no congestion (62.04 ± 21.27 mL/min/1.73m^2 versus 68.87 ± 21.57 mL/min/1.73m^2, p = 0.005). Mean GFR in patients with LVEF <35% was significantly lower compared to patients with LVEF ≥ 35% (57.41 ± 20.5 ml/min/1.73m^{2}vs. 67.95 ± 21.21 mL/min/1.73m^2, p<0.001). Severe impairment of cardiac function (LVEF <35%) was associated with a 1.57-fold greater risk of association with renal dysfunction compared to those with LVEF ≥35% (CI 95% 1.21 -2.03) and was present in 47.21% of patients with renal dysfunction and 30% of those without renal dysfunction (p <0.001). Also, patients with atrial fibrillation had lower GFR compared to those without atrial fibrillation (61.85 ± 21.48 mL/min/1.73m^{2}vs 66.8 ± 21.34 mL/min/1.73m^2, p = 0.024). The mean Hb in patients with renal dysfunction was significantly lower compared to those without renal dysfunction (12.58 ± 1.84 g/dL vs. 13.44 ± 1.83 g/dL, p<0.001). Pearson correlation analysis demonstrated that there is a direct and statistically significant correlation between GFR and hemoglobin (r = 0.359, p<0.001). However, GFR is a poor predictor of hemoglobin (R^2 = 0.123, beta = 0.031, p<0.001, fig. 3).

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The prevalence of anemia in patients with renal dysfunction was significantly higher compared to those without renal dysfunction (47.7% vs 29.5%, p <0.001). Patients with renal dysfunction have a 1.45-fold greater risk of having anemia compared to those without renal dysfunction (CI 95% 1.20-1.76). In fact, the mean GFR in patients with anemia was significantly lower than those without anemia (56.5 ± 20.09 mL/min/1.73m^2 versus 68.52 ± 21.15 mL/min/1.73m^2, p <0.001). Anemia was 2 times more frequent (CI95% 1.48-2.71) in patients with renal dysfunction and diabetes compare to patients with renal dysfunction without diabetes (30.6% - 30/98 patients respective 64.6% - 64/99 patients, p<0.001). On the other hand, the prevalence of anemia in diabetic patients was 54.5% (85/156 patients). Anemia was present in 36.8% (21/57 patients) of diabetic patients without renal impairment, 1.52 times (CI95% 1.17-1.99) less than in the diabetic patients with renal dysfunction (64.6% - 64/99 patients) (p=0.001, fig. 4).

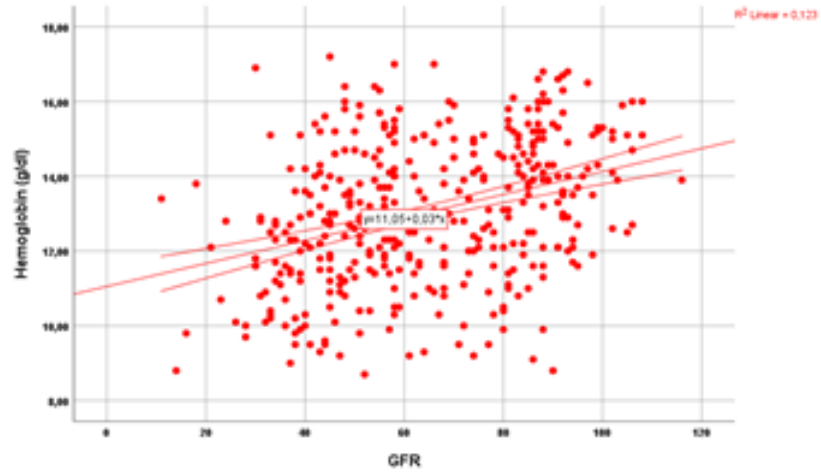

Fig. 3. Correlation between hemoglobin and glomerular filtration rate (GFR)
(Abreviation: GFR= glomerular filtration rate)

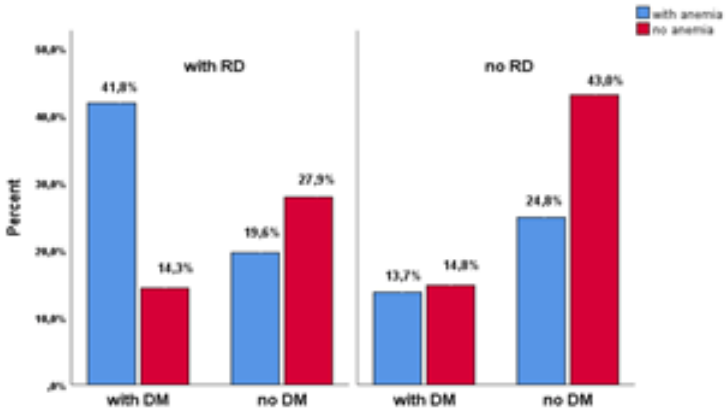

Fig. 4. Distribution of patients with heart failure depending on the presence of renal dysfunction, diabetes mellitus and anemia
(Abreviation: DM=diabetes mellitus, RD=renal dysfunction)

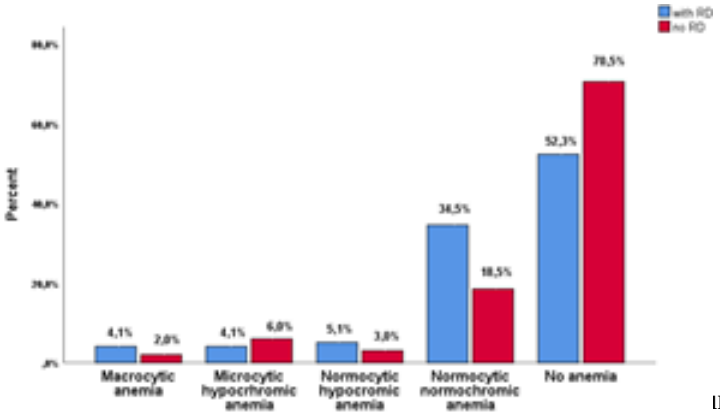

Fig. 5. Distribution of the morphological type of anemia depending on the presence/absence of renal dysfunction (Abreviation: RD=renal dysfunction)

23.7% (94/397) of patients had cardio-renal-anemia syndrome. The presence of CRAS correlated with the presence of HTN ($r = 0.223$, $p<0.001$) and diabetes mellitus ($r = 0.328$, $p <0.001$) as well as the more severe clinical picture of cardiac insufficiency such as LVEF <35% ($r = 0.277$, $p <0.001$), congestion ($r = 0.231$, $p<0.001$) and NYHA IV class ($r = 0.338$, $p<0.001$). Regarding the distribution of morphological types of anemia in patients with or without renal dysfunction, we found that in patients with renal dysfunction normocytic normochromic anemia was present in 34.5% (68/197) of cases, normocytic hypochromic anemia at 5.1% (10/197) of patients, and the microcytic hypochromic and macrocittic anemia were present in equal proportions of 4.1% (8/197) of patients. On the other hand, in patients with heart failure and normal renal function the morphological types of anemia were: normocytic normochromic anemia in 18.5% (37/200) of patients, microcytic hypochromic anemia in 6% (12/200 patients), normocytic hypochromic anemia in 3% (6/200 patients) and macrocittic anemia in 2% (4/200 patients, fig. 5).

Nearly half (49.6%) of the patients with chronic heart failure included in our study, hospitalized for cardiac failure decompensation had at least moderate renal impairment, evaluated by GFR<60mL/min/1.73m^2. It is thus confirmed that renal dysfunction has a high prevalence in patients with severe heart failure, data from the literature suggesting an estimated prevalence of renal dysfunction in patients with heart failure between 30% and 54% and increase cardiovascular risk and reduces the quality of life [14-21]. Conversely, cardiac disease is a very common comorbidity not only in patients with COPD [22] but also in cases with chronic kidney disease (CKD). Foley et al. showing that 39.9% of patients with CKD had heart failure at baseline, and another 30.7% developed heart failure in the following year after CKD diagnosis [23]. Depending on the severity of renal dysfunction, only 2.5% of our patients had severe renal dysfunction (GFR<30mL/min/1.73m^2). Renal function was within normal range (GFR>90mL/min/1.73m^2) in 13.35% of patients. In a meta-analysis of 16 studies, Smith et al. showed that 63% of patients with HF had a degree of renal impairment, and 29% had severe renal impairment [24]. The proportion of patients with GFR<30mL/min/1.73 m^2 in our study was much lower (2.5%) than the one found in the quoted study, 29% [24]. This may suggest that the prevalence of renal dysfunction has been underestimated, because patients with severe renal dysfunction mainly addressed to nephrology and not to cardiology clinics. These data support the fact that association of renal function impairment in patients with compromised cardiac function is frequent, therefore awareness of its consequences and preservation of renal function should be important for every clinician treating patients with heart failure.

Reduction of GFR reflects often a worsening of renal ınction in patients with decompensated heart failure and was associated with a higher prevalence of comorbidities such as diabetes mellitus, HTN, COPD and atrial fibrillation. These results are similar to the results of other studies that suggested a higher prevalence of cardiovascular risk factors in patients with a more severe reduction in renal function [17,25,26]. Also, both the significantly lower mean GFR and the higher prevalence of renal dysfunction were associated with female gender, advanced age, and a more severe cardiac status of patients with heart failure studied, characterized by a higher NYHA functional class, presence of clinical congestion in a larger number of patients, and lower LVEF. Our analysis confirms the results of other studies suggesting that renal function may be an additional marker of poor cardiac function along with LVEF and the NYHA functional class [14, 27, 28]. Also, evaluation of renal function may reflect hemodynamic status of patients through the presence of clinical congestion and requires the adaptation of the therapeutic regimen of cardiac insufficiency to achieve the maximum therapeutic benefit. The high prevalence of anemia in these patients with decompensated heart failure (38.54% - 153/397 patients), according to the data already published [29], could be associated with hypervolemia clinically assessed by the presence of congestion, present in a larger proportion in patients who have associated GFR<60mL/min/1.73m^2 (by hemodilution). Our study demonstrated the existence of statistically significant direct correlations between GFR and hemoglobin ($p <0.001$). The hemoglobin value is decreasing progressively with decreased renal function, and mean GFR was significantly lower in patients with heart failure and anemia compared to those without anemia. Wexler et al. showed there was a significant inverse relationship between serum creatinine and hemoglobin [15]. Renal dysfunction is a common comorbidity in diabetes, heart failure, is a strong independent predictor of an increased risk of anemia [30] and even death [31]. The data from the literature [32-36] and our results suggest that the presence of renal dysfunction in patients with heart failure is associated with a more severe clinical picture as well as the presence of anemia. Anemia is, on the one hand, a *marker* of more severe impairment of renal or cardiac function and, on the other hand, a *mediator* of direct damage to them. In our group, 23.7% of patients had cardio-renal-anemia syndrome, similar to literature data [32]. Anemia was more common in patients with heart failure and renal dysfunction, suggesting that renal impairment may additionally contribute to the development of anemia in heart failure. The existence of statistically significant correlations between GFR and hemoglobin, the association of renal dysfunction with a more severe cardiac status and the higher prevalence of anemia in patients with renal dysfunction may suggest the existence of common pathological pathways between impaired cardiac and renal

function, and anemia (eg as HF worsens, GFR decreases and anemia may get worse). It was observed that in chronic kidney disease without heart failure, moderate and severe renal impairment (defined by GFR<60 mL/min/1.73m^2) is associated with a linear decrease in hemoglobin relative to GFR reduction [36]. The main cause of anemia in chronic kidney disease is the reduction in erytropoetin (EPO) production and consequently the decrease in erythrocyte production in the bone marrow and hence the decrease in serum hemoglobin levels. Heart failure can cause renal dysfunction by lowering cardiac output, decreasing renal plasma flow, and renal vasoconstriction, resulting in chronic renal ischemia, increased EPO production in proportion to the severity of heart failure but less in relation to the degree of anemia suggesting a blocked production [37-40]. Relative EPO deficiency and EPO resistance are also two pathological phenomena present in chronic anemic patients with kidney disease and in those with heart failure [39-44]. Advanced age and the presence of diabetes are known risk factors for both heart failure and renal dysfunction. It is known that diabetes mellitus promotes anemia at the early stages of renal dysfunction [45]. In our study, patients with renal dysfunction had more frequent diabetes compared to those without renal dysfunction and anemia was 2 times more common in diabetic patients with renal dysfunction and heart failure compared to those with heart failure and preserved renal function. After the studies of Botnariu et al [46] both fasting glycaemia and HbA1c significantly correlated with cardiovascular risk scores in non-diabetic persons and could explain the high prevalence of renal dysfunction in our study. Normocytic normochromic anemia was the most common type of anemia seen in the patients in our study, regardless of the presence or absence of renal dysfunction. The proportion of patients with normocytic normochromic anemia was significantly higher in the presence of renal dysfunction compared to its absence, suggesting that chronic inflammation plays an important role in patients with chronic heart failure, the presence of renal dysfunction influencing hemoglobin synthesis in patients with chronic heart failure.

Study limits

Renal function was evaluated by the CKD-EPI equation. In patients with heart failure, GFR may be overestimated. Serum creatinine level depends of muscle mass, and patients with severe heart failure, included in our study, may have less well-defined muscle mass. Albuminuria, an important marker of renal lesion, especially in patients with GFR>60 mL/min/1.73m^2, has not been determined. In addition, our study is a cross-sectional observational study and does not provide data on patient prognosis.

Conclusions

The prevalence of kidney dysfunction and anemia in patients admitted for decompensation of heart failure is high. Also, renal function can be used as a marker of severe cardiac dysfunction associated with the presence of diabetes mellitus, more severe clinical status and the presence of anemia. Therefore, the presence of both renal dysfunction and anemia allow patients with severe heart failure to be identified and could have prognostic implications.

References

1.RONCO, C., CULLOUGH, P., ANKER S.D., ANAND, I., ASPROMONTE, N., BAGSHAW, S.M., BELLOMO, R., BERL, T., BOBEK, I., CRUZ, D.N. DALIENTO, L., DAVENPORT, A., HAAPIO, M., HILLEGE, H., HOUSE, A.A., KATZ,N., MAISEL,A., MANKAD,S., ZANCO, P., MEBAZAA, A., PALAZZUOLI, A., RONCO, F., SHAW, A., SHEINFELD, G., SONI,S., VESCOVO, G., ZAMPERETTI,N., PONIKOWSKI, P., Acute Dialysis Quality Initiative (ADQI) consensus group. Cardio-renal syndromes: report from the consensus conference of the Acute Dialysis Quality Initiative. Eur Heart J, **31**, 2010, p. 703

2.BERL, T., HENDRICH, H., Kidney-Heart interactions: epidemiology, pathogenesis and treatment. Clin. J. Am. Sos Nephrology, **1**, 2006, p. 8

3.ELLISON, D.H., Diuretic therapy and resistance in congestive heart failure. Cardiology, **96**, 2001, p. 132

4.SUN, W.K., REISER, I.W., CHON, S.Y., – Risk Factors for acute renal insufficiency induced by diuretics in patients with congestive heart failure. Am. J. Kidney Dis, **47**, 2006, p. 798

5.DICKSTEIN, K., COHEN-SOTAL, A., FILIPPATOS, G., MCMURRAY, J.J., PONIKOWSKI , P., POOLE-WILSON, P.A., STROMBERG, A., VAN VELDHUISEN, D.J., ATAR, D., HOES, A.W., KEREN, A., MEBAZAA, A., NIEMINEN, M., PRIORI, S.G., SWEDBERG, K., ESC guideline for the diagnosis and treatment of acute and cronic heart failure 2008: The Task Force for the diagnosis and treatment of acute and cronic heart failure of the European Society of Cardiology. Eur. J. Heart Fail, **10**, 2008, p. 933

6.GOIDESCU, C.M., FARCAS, A.D., ANTON, F.P., VIDA SIMITI, L.A., The pattern of ventricular remodeling influences the level of oxidative stress in heart failure patients. Rev Chim (Bucharest), **68**, no 7, 2017, p. 1506

7.SILVERBERG, D.S., WEXLER, D., SHEPS, D., BLUM, M., KEREN, G., BARUCH, R., SCHWARTZ, D., YACHNIN, T., STEINBRUCH, S., SHAPIRA, I., LANIADO, S., IAINA, A., The effect of correction of mild anemia in severe, resistant congestive heart failure using subcutaneous erythropoietin and intravenous iron: a randomized controlled study. J Am Coll Cardiol, **37**, 2001, p. 1775

8.LEVEY, A.S., STEVENS, L.A., SCHMID, C.H., ZHANG, Y.L., CASTRO, A.F. 3RD., FELDMAN, H.I., KUSEK, J.W., EGGERS, P., VAN LENTE, F., GREENE, T., CORESH, J., A new equation to estimate glomerular filtration rate. Ann Intern Med., **150**, No. 9, 2009, p. 604

9.*** WORLD HEALTH ORGANIZATION. Nutritional Anemia: Report of a WHO Scientific Group. Tech Rep Ser., **405**, 1968, p. 1

10.GORON, M., MAN, M., BONDOR C., ARGHIR O. Risk Factors in the Etiology of Lung Cancer. Conference: International Conference on Oncology Location Univ Cambridge, Cambridge , EnglandDate 23-25 Feb, 2010, Recent Advances In Clinical Medicine. Book Series: Recent Advances in Biology and Biomedicine, p. 207

11.MIHAILOV, C., JIMBOREAN, G., RASCU, A, ARGHIR, O.C. The Impact of Tobacco Smoke Exposure On Asthma COPD-Like Patients. J Environ Prot Ecol, **17**, No.4, 2016, p. 1523

12.VOICU, G, BECHIR, A., ARGHIR, O.C. Chemical Air Polution and the Prevalence of Respiratory Disorders and Diseases. J Environ Prot Ecol, **13**, No.3, 2012, p. 1357

13.OTELEA, M.R., TRENCHEA, M, ARGHIR, O.C., VELESCU, L., DANTES E, BECHIR, E.S., ELSAAFIN, M., RASCU, A., Glycosylated Hemoglobin and the Severity of Sleep Obstructive Apnea, Rev. Chim. (Bucharest), **69**, no.1, 2018, p. 282

14.AL-AHMAD, A., RAND, W.M., MANJUNATH, G., KONSTAM, M.A., SALEM, D.N., LEVEY, A.S., SARNAK, M.J., Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. J Am Coll Cardiol., **38**, No. 4, 2001, p. 955

15.WEXLER, D., SILVERBERG, D., SHEPS, D., BLUM, M., KEREN, G., IAINA, A., SCHWARTZ, D., Prevalence of anemia in patients admitted to hospital with a primary diagnosis of congestive heart failure. Int J Cardiol., **96**, No.1, 2004, p. 79

16.YANCY, C.W., LOPATIN, M., STEVENSON, L.W., DE MARCO, T., FONAROW, G.C., Clinical presentation, management, and in-hospital outcomes of patients admitted with acute decompensated heart failure with preserved systolic function: a report from the Acute Decompensated Heart Failure National Registry (ADHERE) Database. J Am Coll Cardiol., **47**, No.1, 2006, p. 76
17.LOFMAN, I., SZUMMER, K., HAGERMAN, I., DAHLSTRÖM, U., LUND, L.H., JERNBERG, T., Prevalence and prognostic impact of kidney disease on heart failure patients. Open Heart., **3**, No.1, 2016:e000324
18.METRA, M., COTTER, G., GHEORGHIADE, M., METRA, M., TRAVER, B., COOK, T., CAMPIA, U., AMBROSY, A., BURNETT, J.C. JR., GRINFELD, L., MAGGIONI, A.P., SWEDBERG, K., UDELSON, J.E., ZANNAD, F., KONSTAM, M.A., GHEORGHIADE, M., The role of the kidney in heart failure. Eur Heart J, **33**, 2012, p. 2135
19.BLAIR, J.E, PANG, P.S., SCHRIER, R.W., ET AL., Changes in renal function during hospitalization and soon after discharge in patients admitted for worsening heart failure in the placebo group of the EVEREST trial. Eur Heart J, **32**, 2011, p. 2563
20.DE SILVA, R., RIGBY, A.S., WITTE, K.K., NIKITIN, N.P., TIN, L., GOODE, K., BHANDARI, S., CLARK, A.L., CLELAND, J.G., Anemia, renal dysfunction, and their interaction in patients with chronic heart failure. Am J Cardiol., **98**, No.3,2006, p. 391
21.PLESOIANU, C.A., ANDRIESCU, G., SALARU, D., ARSENESCU GEORGESCU, C., The Relationship Between Biochemical Variables and the Quality of Life in Patients with Chronic Heart Failure, Rev. Chim. (Bucharest), **68**, no.10, 2017, p2452.
22.SALEH, A., LOPEZ-CAMPOS, J.L., HARTL, S., POZO-RODRIQUES, F., ROBERTS, M., European COPD Audit team. The Effect of Incidental Consolidation on Management and Outcomes in COPD Exacerbations: Data from the European COPD Audit, PLOS ONE, **10**, No.7, 2015, e0134004
23.FOLEY, R.N., MURRAY, A.M., LI, S., HERZOG, C.A., MCBEAN, A.M., EGGERS, P.W., COLLIN,S A.J., Chronic kidney disease and the risk for cardiovascular disease, renal replacement, and death in the United States Medicare population, 1998 to 1999. J Am Soc Nephrol, **16**, 2005, p. 489
24.SMITH, G.L., LICHTMAN, J.H., BRACKEN, M.B., SHLIPAK, M.G., PHILLIPS, C.O., DICAPUA , P., KRUMHOLZ, H.M., Renal impairment and outcomes in heart failure. J Am Coll Cardiol, **47**, 2006, p. 1987
25.KRUMHOLZ, H.M., CHEN, Y.T., WANG, Y., VACCARINO, V., RADFORD, M.J., HORWITZ, R.I., Predictors of readmission among elderly survivors of admission with heart failure. Am Heart J., **139**, 2000, p. 72
26.COWIE, M.R., KOMAJDA, M., MURRAY THOMAS,T., UNDERWOOD, J., TICHO, B., Prevalence and impact of worsening renal function in patients hospitalized with decompensated heart failure: results of the prospective outcomes study in heart failure (POSH). Eur Heart J., **27**, No.10, 2006, p. 1216
27. GO, A.S., CHERTOW, G.M., FAN, D., MCCULLOCH, C.E., HSU, C.Y., Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med, **351**, 2004, p. 1296
28.HILLEGE, H.L., NITSCH, D., PFEFFER, M.A., SWEDBERG, K., MCMURRAY, J.J., YUSUF, S., GRANGER, C.B., MICHELSON, E.L., OSTERGREN, J., CORNEL, J.H., DE ZEEUW, D., POCOCK, S., VAN VELDHUISEN, D.J., Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. Circulation , **113**, 2006, p. 671
29.ZAHARIE, M., CARSTEA, D., CARSTEA, A.P., ZAHARIE, S.I., Prevalence of Erythrocyte Changes in Patients with Heart Failure, Current Health Sciences Journal, **43**, No.3, 2017, p. 263
30.TANG, Y.D., KATZ, S.D., Anemia in chronic heart failure: prevalence, etiology, clinical correlates, and treatment options. Circulation. **113**, No.20, 2006, p2454.
31.MAN, M.A., ARGHIR, O.C., MAN, S., STREBA, C.T., OLTEANU M., NITU M. Fatal Paradoxical Cryptic Miliary Tuberculosis and Immune Reconstitution Disease in a Young Non- HIV Immunocompromised Male Patient- Case Report with Autopsy Findings. Rom J Morphol Embryol. **55**, No.2, 2014, p. 453
32.SCRUTINIO, D., PASSANTINO, A., SANTORO, D., CATANZARO, R., The cardiorenal anaemia syndrome in systolic heart failure: prevalence, clinical correlates, and long-term survival, European Journal of Heart Failure, **13**, 2011, p. 61
33.SILVERBERG, D.S., WEXLER, D., IAINA, A., STEINBRICH, S., WOLLMAN, Y., SCHWARTZ, D., Anemia, chronic renal disease and congestive heart failure-the cardio renal anemia syndrome: the need for cooperation between cardiologists and nephrologists. Int Urol Nephrol, **38**, 2006, p. 295
34. BONGARTZ, L.G., CRAMER, M.J., DOEVENDANS, P.A., JOLES, J.A., BRAAM, B., The severe cardiorenal syndrome: 'Guyton revisited'. Eur Heart J, **26**, 2005, p. 11
35.VAN DER MEER, P., VAN VELDHUISEN, D.J., Anaemia and renal dysfunction in chronic heart failure. Heart, **95**, 2009, p. 1808
36.IVERSEN, P.O., WOLDBAEK, P.R., TONNESSEN, T., CHRISTENSEN, G., Decreased hematopoiesis in bone marrow of mice with congestive heart failure. Am J Physiol Regul Integr Comp Physiol, **282**, No.1, 2002, p. 166
37.OPASICH, C., CAZZOLA, M., SCELSI, L., DE FEO, S., BOSIMINI, E., LAGIOIA, R., FEBO, O., FERRARI, R., FUCILI, A., MORATTI, R., TRAMARIN, R., TAVAZZI, L., Blunted erythropoietin production and defective iron supply for erythropoiesis as major causes of anaemia in patients with chronic heart failure. Eur Heart J, **26**, 2005, p. 2232
38.VOLPE, M., TRITTO, C., TESTA, U., RAO, M.A., MARTUCCI, R., MIRANTE, A., ENEA, I., RUSSO, R., RUBATTU, S., CONDORELLI, G.L., Blood levels of erythropoietin in congestive heart failure and correlation with clinical, hemodynamic, and hormonal profiles. Am J Cardiol, **74**, 1994, p. 468
39.VAN DER MEER ,P., VOORS, A.A., LIPSIC, E., SMILDE, T.D., VAN GILST, W.H., VAN VELDHUISEN, D.J., Prognostic value of plasma erythropoietin on mortality in patients with chronic heart failure. J Am Coll Cardiol, **44**, 2004, p. 63
40.VOLPE, M., TRITTO, C., TESTA, U., RAO, M.A., MARTUCCI, R., MIRANTE, A., ENEA, I., RUSSO, R., RUBATTU, S., CONDORELLI, G.L., Blood levels of erythropoietin in congestive heart failure and correlation with clinical, hemodynamic, and hormonal profiles. Am J Cardiol, **74**, 1994, p. 468
41.GEORGE, J., PATAL, S., WEXLER, D., ABASHIDZE, A., SHMILOVICH, H., BARAK, T., SHEPS, D., KEREN, G., Circulating erythropoietin levels and prognosis in patients with congestive heart failure: comparison with neurohormonal and inflammatory markers. Arch Intern Med., **165**, 2005, p. 1304
42.CARO, J., BROWN, S., MILLER, O., MURRAY, T., ERSLEV, A.J., Erythropoietin levels in uremic nephric and anephric patients. J Lab Clin Med, **93**, 1979, p. 449
43.FEHR, T., AMMANN, P., GARZONI, D., KORTE, W., FIERZ, W., RICKLI, H., WÜTHRICH, R.P., Interpretation of erythropoietin levels in patients with various degrees of renal insufficiency and anemia. Kidney Int, **66**, 2004, p. 1206
44.MASON-GARCIA, M., BECKMAN, B.S., BROOKINS, J.W., POWELL J.S., LANHAM, W., BLAISDELL S., KEAY L., LI, S-C., FISHER J.W., Development of a new radioimmunoassay for erythropoietin using recombinant erythropoietin. Kidney Int, **38**, 1990, p. 969
45.KDOQI. II., Clinical practice guidelines and clinical practice recommendations for anemia in chronic kidney disease in adults. Am J Kidney Dis, **47**, Suppl. 3, 2006, pS16
46.BOTNARIU G., FORNA N., POPA A., POPESCU R., ONOFRIESCU A., CIOLOCA D., LACATUSU C., MIHAI B., Correlation of Glycemic Control Parameters in Non-Diabetic Persons with Cardiovascular Risk Scores - Results from a Cross-Sectional Study, Rev. Chim. (Bucharest), **68**, no.1, 2017, p. 108

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