ORIGINAL ARTICLE

Prevalence of renal changes in patients with heart failure with mid-range and reduced ejection fraction

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Abstract: Introduction – The prevalence of cardio-renal impairment is continuingly increasing leading to high morbidity and mortality. **Study aim –** To assess renal impairment prevalence in patients with heart failure with mid-range and reduced ejection fraction. **Materials and methods –** The retrospective study included 194 patients with heart failure (HF) with mid-range and reduced ejection fraction (EF) hospitalized in the Cardiology Unit of Municipal Clinical Hospital „Sfanta Treime" during January 2014 – December 2015 period. **Results –** 113 subjects out of 194 assessed patients had HF with mid-range EF (40-49%) and 81 subjects had HF with reduced EF (<40%). An estimated glomerular filtration rate (eGFR) ≤60 mL/min/1.73m^2 was recorded in 27.31% cases, while proteinuria was present in 54.72% cases in patients with reduced eGFR comparing to 67.38% in those with an eGFR ≥60mL/min/1.73m^2. **Conclusions –** Study results confirm that renal impairment prevalence in heart failure is rather high whether we focus on eGFR or proteinuria.
Keywords: heart failure, cardio-renal, kidney disease

Rezumat: Introducere – Prevalența afectării cardio-renale este în continuă creștere și este însoțită de mortalitate și morbiditate înaltă. **Scopul studiului –** Aprecierea prevalenței afectarii renale la pacienți cu insuficiență cardiacă și fracție de ejecție redusă și intermediară. **Material și metode –** Studiul retrospectiv a inclus 194 de pacienți cu insuficiență cardiacă cronică (ICC) cu fracție de ejecție (FE) redusă și intermediară, spitalizați în perioada ianuarie 2014-decembrie 2015 în Clinica Cardiologie, SCM „Sfânta Treime". **Rezultate –** Au fost evaluați 194 de pacienți: 113 subiecți cu ICC cu FE intermediară - 40-49%; și 81 de subiecți cu ICC cu FE redusă <40%. Rata estimativă a filtrării glomerulare (RFGe) - ≤60 mL/min/1,73m^2 a fost înregistrată în 27,31%. Prezența proteinuriei a fost constatată în 54,72% cazuri dintre pacienții cu RFG diminuată comparativ cu 67,38% dintre cei cu RFGe ≥60mL/min/1,73m^2. **Concluzii –** Rezultatele studiului confirmă că prevalența afectării renale în insuficiența cardiacă este destul de înaltă, fie că ne concentrăm atenția asupra RFGe sau a proteinuriei.
Cuvinte cheie: insuficiență cardiacă, afectare cardio-renală, boală renală

INTRODUCTION

The prevalence of cardiac and renal comorbidity is steadily increasing. Approximately 5% of emergency hospitalizations are due to heart failure, 20% of these patients presenting with renal impairment[4]. Renal impairment is the most common comorbidity in HF. On the other hand, cardiovascular mortality (CV) in patients with chronic kidney disease (CKD) reaches 40 %[5]. In any context, cardiovascular impairment (combined heart and renal dysfunction) has high mortality and morbidity.

Cardio-renal syndrome (CRS), in the absence of a generally accepted definition, was previously seen as renal dysfunction secondary to chronic cardiac dysfunction (eg. HF). This definition failed to explain the multitude of situations where cardiac and renal dysfunctions coexist. In 2008, Ronco et al. proposed dividing the syndrome into five types, classification recommended in the report of the 2009 Acute Dialysis Quality Initiative (ADQI) Consensus Conference[5], in order to emphasize the different pathogenetic pathways of CRS and to define primary or secondary organic dysfunction.

The consensus group defines CRS as "heart or kidney disorder in which acute or chronic dysfunction in an organ can lead to acute or chronic dysfunction in

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the other". This type of expression was chosen in order to explain the bidirectional nature and character of the disorder.

EPIDEMIOLOGY

Kidney impairment in patients with primary cardiac disease (chronic CRS, type 2). Multiple observational studies describe the coexistence of chronic heart failure (CHF) and chronic kidney disease (CKD), however study inclusion is usually based on the presence of one disease (eg. CHF), studying further the prevalence of the other (eg. CKD)[2,3,5]. A meta-analytical study on the interrelation between heart failure and renal disorder reported a 63% prevalence of mild and 20% moderate renal impairment. In addition, a 7% increase rate in mortality was observed for each decrease in eGFR by 10 ml/min 2,5. In the DIG trial, that assessed 7788 ambulatory patients with congestive heart failure, Campbell et al. found an eGFR < 60 ml/min/1.73 m^2 in 45% of cases 1. Another study, focusing on ambulatory patients with congestive heart failure, found that 39% of patients with NYHA IV CHF and 31% of NYHA III CHF patients had severe renal dysfunction (creatinine clearance < 30ml/min)[2]. Bhatia et al. described a 45% incidence of decreased estimated glomerular filtration rate in patients with congestive heart failure with left ventricular ejection fraction impairment[1].

Cardiac impairment in patients with primary renal disease (RCS, type 4). The incidence depends on CKD severity and population risk. In the HEMO study, Cheung et al. found an 80% incidence of cardiac disease in patients with end-stage kidney disease 2. In the same study. a 3.7-year follow-up revealed a 39.8% rate of CV-based readmission to hospital (39.4% of them – CV related death). CV mortality in patients with CKD is 10-20 times higher compared to those with no CKD[5]. The NHANES study (17061 subjects) describes a prevalence of 4.5% (eGFR ≥ 90 ml/min/1.73m^2); 7.9% (eGFR 70-89 ml/min/1.73m^2); 12.9% (eGFR < 70 ml/min/1.73m^2). In the USRDS study of 1,091 201 subjects, Foley et al. describes an incidence of 4-7/100 patients/year for acute myocardial infarction and 31-52/100 patients/year for chronic heart disease[1,2].

The mere coexistence of cardiac and renal disease may confirm the presence of CKD; however, it is not sufficient to establish its type. According to the 11th ADQI Consensus Conference Working Group (2013), in order to confirm CKD diagnosis (except type 5) the following criteria are necessary: 1) coexistence of renal and cardiac disease in the patient; 2) temporary causality (eg. documented or assumed onset of heart failure precedes the onset of renal involvement); and 3) pathophysiological plausibility (eg. manifestation and degree of renal involvement can be explained by existing cardiac disorder)[2].

Study aim: To assess renal involvement (cardiorenal syndrome type 2/4) prevalence in patients with chronic heart failure with mid-range and reduced ejection fraction.

Materials and methods: The retrospective study included 194 HF patients with mid-range and reduced EF (as defined in the 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure) hospitalized in the Cardiology Unit of Municipal Clinical Hospital „Sfanta Treime" during January 2014 – December 2015 period. We examined the following data: age, gender, disease duration, echocardiographic data and markers of renal function.

Results and discussions: As an initial research step, we estimated the prevalence of cardiorenal syndrome in patients with mid-range and reduced ejection fraction heart failure. For this purpose, a preliminary retrospective study was carried out by examining medical reports of patients with CHF, LVEF ≤ 49%, hospitalized in the Cardiology Unit of the same hospital in the period of time mentioned above.

The mere coexistence of cardiac and renal disease may confirm the presence of CKD; however, it is not sufficient to establish its type. Given the retrospective analysis limited information, when the primary disorder cannot be assessed, we used the term CRS type 2/4[1].

The data provided above denote a male predominance in the study with a 3:2 M to F ratio, and a predominance of urban residence – 82.99% of cases.

Subsequently, we wanted to present the complex study group in terms of HF onset features presented in Table 2.

Data presented in the table show that patients' age at the time of research varied widely, ranging from 37 to 89 years, with a mean age of 66.56 years. We

Table 1. General characteristics of patients included in the research

Assessed parameters	Absolute number	(%)
Patients with HF	196	100
Gender		
• female	78	40.21
• male	116	59.79
Residence:		
• Rural	33	17.01
• Urban	161	82.99

Table 2. General characteristics of HF variables		
Assessed parameters	**Mean value ± SD**	**Max. value – min. value**
Age at time of study research, years	66.56± 10.23	37- 89
Age at disease onset, years	54.97±11.06	6- 86
Mean disease duration, years	11.56±8.80	0-50

noted heterogeneity for disease onset, the onset age ranging from 6 to 86 years, while disease duration ranged from 0 to 50, with a mean of 11.56 years. Next, we categorized patients by age according to HF onset.

According to Figure 1, the age with a higher HF incidence rate ranged between 50 and 60 years (40.72%). Concomitantly, increased prevalence was reported between 41-50 years with 22.16% patients, and between 61-70 years with 20.1% patients. Onset of heart failure by the age of 40 was seen in 8.76% of cases, and only 16 patients (8.25%) had the disease onset after 70 years.

Assessing HF according to NYHA functional classification, 20.60% patients had NYHA II HF, 59.80% NYHA II HF and 19.60% patients had NYHA IV HF. Over the past year, 15.5% of subjects required hospitalization while 12.4% of subjects reported weight changes.

When studying patients' past medical history, we found that 11.9% of subjects suffered from stroke, 39.7% of patients had AMI, sudden death in relatives was described by one patient only. Comorbidities were as follows: arterial hypertension in 84% cases, atrial fibrillation in 60.80% cases, diabetes mellitus in 26.30% cases, ischemic heard disease in 78.9% cases, rheumatic valve disease in 6.7% of subjects. 16.00%

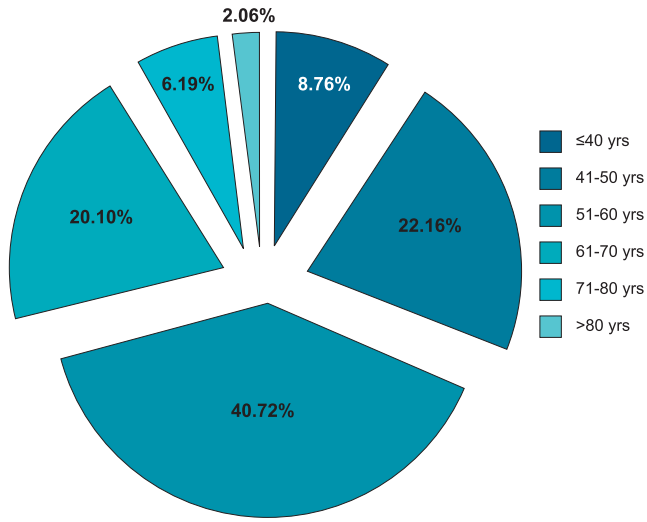

Figure 1. Age categories, according to HF onset (%).

of study group patients were employed while 23.20% were unemployed, 3.60% had registered disability and 56.70% were retired.

We performed a retrospective analysis of renal impairment prevalence in these patients. Of the 194 patients in the initial study group, 141 (72.68%) patients had increased or within normal range CKD-EPI GFR – 85.65 ± 14.60 ml/min/1.73m^2 ($p < 0.0001$), while 53 (27.31%) patients had decreased CKD-EPI GFR – 46.04 ± 12.99 ml/min/1.73 m^2 (CI 35.1-44.12, $p < 0.0001$). Using MDRD equation to assess GFR, we obtained a mean value of 85.42 ± 19.97 ml/min/1.73 m^2 for the group with no CKD and 45.43 ± 12.48 ml/min/1.73 m^2 (CI 34.19-45.78; $p < 0.0001$) for the other subjects. The results are shown in Table 3.

Table 3. General characteristics of renal impairment variables in HF			
	CKD	**No CKD**	**p**
Assessed parameters	Mean value ± SD	Mean value ± SD	
Patients, absolute No (%)	53 (27.31%)	141(72.68%)	
Gender ratio, F:M, %	56.6 : 43.39	65.96 : 34.04	
Research age, yrs	71.94±8.57	64.53±10.10	<0.0001
CVD duration, yrs	13.61± 8.33	11.17±9.55	0.1027
CVD onset age, yrs	58.33±10.87	53.36±11.80	<0.0001
Previous stroke, absolute No (%)	11 (20.8%)	12 (8.5%)	
Previous MI, absolute No (%)	20 (37.7%)	57 (40.4%)	
Diabetes, absolute No (%)	18 (34%)	33 (23.4%)	
Diabetes duration, yrs	7.05±0.97	3.48±0.39	< 0.05
Hypertension, absolute No (%)	45 (84.9%)	118 (83.7%)	
LVEF, %	41.68±5.11	49.00±6.84	0.0022
Serum creatinine, mg/dL	1.53±1.05	0.86±0.18	<0.0001
GFR CKD-EPI, ml/min/1.73m^2	46.04±12.99	85.65±14.60	<0.0001
GFR MDRD, ml/min/1.73m^2	45.43±12.48	85.42±19.97	<0.0001
Proteinuria, g/l	0.16±0.32	0.09±0.14	0.0258

According to the presented data, patients with CKD had a more advanced mean age – 71.94 ± 8.57 years, compared to the mean age of 64.53 ± 10.10 years (p <0.0001) of patients with no CKD. In addition, patients with renal impairment age had a longer CVD duration – 13.61 ± 8.33 ani (p = 0.1) and a more advanced CVD onset age – 58.33 ± 10.87 years (CI 55.34-61.33; p <0.0001) compared to the rest of the study group – 11.17 ± 9.55 years and 53.36 ± 11.80 years, respectively. According to gender distribution, males prevailed in both groups at a rate of 56.6% in the renal impairment group compared to 65.96% in the no CKD group.

In patients with CKD, proteinuria was present in 54.72% cases with a mean level of 0.16 ± 0.32 g/l (p = 0.0258) compared to 67.38% in those with eGFR ≥60mL/min/1.73m^2 with a mean proteinuria level of 0.09 ± 0.14 g/24h.

Table 4 presents patients' distribution according to the degree of renal and cardiac impairment. As a result of renal parameters assessment, patients were divided into 5 groups depending on the CKD-EPI GFR according to KDOQI recommended stages of CKD (G1> 90 ml/min/1.73m^2; G2 = 60-89 ml/min/1.73m^2; G3a = 45-59 ml/min/1.73m^2; G3b = 30-44 ml/min/1.73m^2; G4 = 15-29 ml/min/1.73m^2; G5 <15 ml/min/1.73m^2) and depending on albuminuria level (A1 < 30 mg/g; A2 = 30-300 mg/g; A3 > 300 mg/g). Analyzing the formed groups, we noted an increased prevalence for G1A1 – 23 (11.9%); G1A2 – 51 (26.3%); G2A1 – 28 (14.4%) and G2A2 – 49 (25.3%), corresponding to KDOQI CKD stages I-II. A lower prevalence was recorded for more severe forms of renal impairment: G3aA1 – 10 (5.2%); G3aA3 – 5 (2.6%); G3bA1 – 7 (3.6%); G3bA2 – 3 (1.5%); G4A1 – 2 (1.0%); G4A2 – 4 (2.1%); G5A3 – 1 (0.5%), corresponding to KDOQI CKD stages III-V, and also for normal or increased GFR cases with high levels of proteinuria: G2A3 – 8 (4.1%); G1A3 – 3 (1.5%) (Chi-squared – 18.63; p = 0.77). The data are similar to those obtained by Tan et al., who reported a 20% prevalence of renal impairment in a cohort of patients with low LVEF (LVEF < 40% in over 78% of cases) and a mean age of 61.6 years 6. Ronco C. and Cruz D. reported a 63% prevalence of mild renal impairment and a 20% prevalence of moderate renal impairment in patients with heart failure with no LVEF categorization (1). Dig and Bhatia et al. trial found an eGFR < 60 ml/min/1.73m^2 in 45% cases of patients with congestive heart failure with left ventricular ejection fraction impairment[2,5]. The increased prevalence was also described by Lofman, who analyzed a cohort of 47.716 patients from the Swedish Heart Failure Registry and found a 51% rate of GFR < 60 ml/min/1.73 m^2 and 11% rate of GFR < 30 ml/min/1.73 m^2 [7].

Gender distribution shows an increased prevalence of mild CKD forms (G1-G2) among men (62.96%), advanced renal impairment forms being more prevalent among women (56.25%).

Subsequently, we evaluated the distribution of patients with different degrees of renal impairment depending on the severity of cardiac involvement (II-IV NYHA functional classes). NYHA III HF predominated in mild renal impairment forms (G1-G2), while NYHA II and IV HF had a similar distribution in this group. The severe renal impairment group did not present any distribution patterns.

Table 4. Distribution of patients according to CKD stages and proteinuria, 2012 KDIGO classification.

CKD classification	Absolute total number (%)	HF, NYHA functional class			Gender distribution, absolute number	
	194	II	III	IV	M	F
G1A1	23 (11.9%)	4	15	4	14	9
G1A2	51 (26.3%)	12	29	10	32	19
G1A3	3 (1.5%)	0	2	1	1	2
G2A1	28 (14.4%)	5	18	5	13	15
G2A2	49 (25.3%)	12	28	9	35	14
G2A3	8 (4.1%)	1	5	2	7	1
G3aA1	10 (5.2%)	3	7	0	6	4
G3aA3	5 (2.6%)	0	3	2	5	0
G3bA1	7 (3.6%)	1	6	0	2	5
G3bA2	3 (1.5%)	1	1	1	1	2
G4A1	2 (1.0%)	0	1	1	0	2
G4A2	4 (2.1%)	1	1	2	0	4
G5A3	1 (0.5%)	0	0	1	0	1
Chi-squared		18.632			25.948	
Statistic significance		p = 0.7713			p = 0.0109	

Diabetes was found in 34% in patients with renal impairment and 23.4% in the control group (p> 0.05). According to the 2018 *European Society of Cardiology* data, 30-40% of the heart failure patients, regardless of LVEF, have diabetes. In the OPTIMIZE-HF study, the prevalence of diabetes was 42% in a cohort of 43,000 reduced ejection fraction HF subjects. (10) The Swedish IC registry data reported the diabetes rate in 21% in patients with renal function and 26-36% in those with reduced GFR. (8) The CHART study described diabetes in 17.1% for HF patients with GFR> 60ml / min / m^2 and 21.9% - 28.1% for HF patients with GFR <60ml / min / m^2. (9) The mean duration of diabetes was 7.05 ± 0.97 years for SCR and 3.48 ± 0.39 years (for those without SCR (<0.05)).

Thus, in the present study diabetes is not an significant independent risk factor for cardio-renal syndrome (RR = 1.44, p> 0.05); and may be explained by the short duration of diabetes, according to the literature data, in the natural course of diabetes, the risk of nephropathy is increased after 5 years. Bruno describes the occurrence of diabetic nephropathy at a duration of type 2 diabetes of 11.8 ± 7.8 years in subjects with normo-albuminuria and 10.0 ± 6.3 years in those with microalbuminuria.

We continued our research by analyzing other risk factors. The hypertensions prevalence was 84.9% in the study group and 83.7% in the control group (p = 0.37). Thus, we cannot consider hypertension as risk factor for cardio-renal syndrome (RR = 1.07, p> 0.05). 20.8% patients from the control group and 8.5% of the control group had previous stroke; while history of myocardial infarction was reported by 37.7% patients with reduced GFR and 40.4% of those with preserved kidney function.

Heart ultrasound is one of the diagnostic markers of cardiac damage and serves as a criterion for HF evolution and severity. In our study, we performed and assessed a total of 194 echocardiographic examinations. Upon reviewing the results, patients with renal impairment had a significantly lower LVEF – 41.68 ± 5.11% compared to 49.00 ± 6.84% (p = 0.0022) in those with no GFR decrease. In order to confirm the effect of low LVEF on CKD onset, we stratified patients based on LVEF according to the definition of heart failure: mid-range EF HF (HFmrEF) and reduced EF HF (HFrEF). We identified 126 subjects with HFmrEF (LVEF 40-49%) and 81 subjects with HFrEF (LVEF <40%).

The mean age of patients with HFmrEF was 67.89 years. Among them, 49.6% were men. CVD duration was 12.68 years. GFR according to CKD-EPI formula was 72.37 mL/min/1.73m^2, while renal impairment with an eGFR < 60 mL/min/1.73m^2 was recorded in 30.15% cases (p = 0.5344). GFR calculated by MDRD formula was 72.41 mL/min/1.73m^2, while moderate renal impairment with an eGFR < 60 mL/min/1.73m^2 was recorded in 32.53% cases. Mean proteinuria level was 0.08 g/24h with a proteinuria prevalence of 62.8% in patients with HFmrEF and GFR ≥ 60 mL/min/1.73m^2, and 78.57% in those with GFR < 60 mL/min/1.73m^2.

The mean age of patients with HFrEF was 64.69 years, 74.07% of them being men. CVD duration was 10.65 years. GFR according to CKD-EPI formula was 79.4 mL/min/1.73m^2, with a decreased GFR being recorded in 22.55% cases (p = 0.5344). GFR calculated by MDRD formula was 78.35 mL/min/1.73m^2, renal impairment being diagnosed in 25% cases. Average proteinuria level was 0.15 g/24h. The prevalence of proteinuria was 77.8% in patients with HFrEF and normal or slightly increased GFR, and 100% in those with an eGFR < 60 mL/min/1.73m^2.

Next, we searched for correlations between HF degree, EF level and renal impairment degree, and tried to appreciate the diagnostic value of these parameters in CKD development. Correlation analysis results are shown in Figure 2.

HF gravity did not correlate with renal impairment degree (r – 0.04, p = 0.55). NYHA I HF had a sensitivity of 24.5 and specificity of 80.9 (p = 0.72). For LVEF, sensitivity was 92.5 while specificity 22 (criterion > 35, p = 0.0.49). AUC (area under curve) is the measure of a test performance. In order to have a reasonable performance, a test should have an AUC above 0.5. In our study, we got an AUC of 0.515 for HF and 0.529 for LVEF, represented graphically by secondary obtained diagonals, proving that LVEF level and HF degree are random tests for CKD diagnosis.

CONCLUSIONS

The results of our study confirm that renal impairment prevalence in patients with heart failure is quite high, whether we focus on eGFR or proteinuria. Both proteinuria and glomerular filtration rate are easy to assess and therefore should be investigated in all patients with heart failure in order to stratify their risk and manage them more efficiently.

Multiple studies have proven that renal impairment has an essential role in HF pathogenesis and evolution of, being an independent prognostic factor. However, to date, possibilities of establishing the exact origin

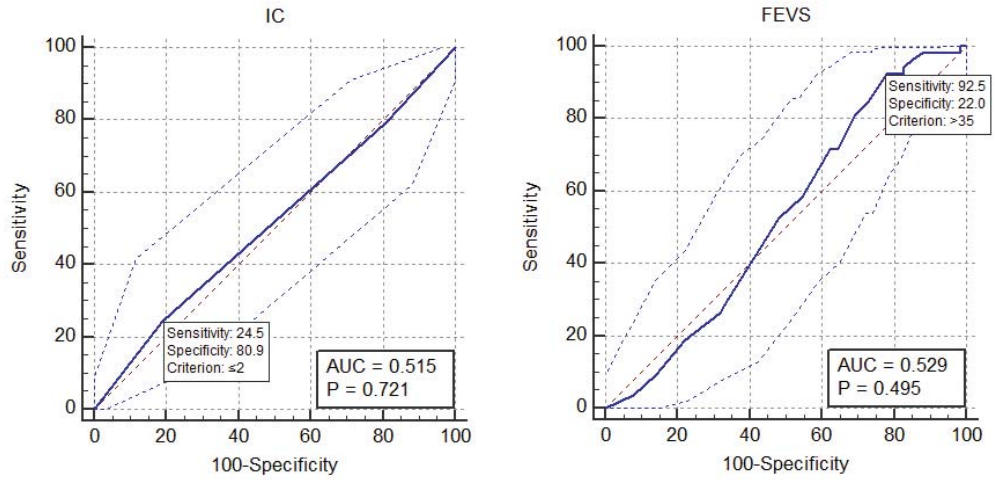

Figure 1. ROC curves for HF, EF in CKD diagnosis.

and timing of renal changes onset in heart failure are limited. Moreover, there are no clear criteria that differentiate a reversible, transient, renal dysfunction from a significant irreversible one.

Conflict of interest: none declared.

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