REVIEW ARTICLE

Cardiorenal Syndrome Type 2: A Strong Prognostic Factor of Survival

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Abstract

Background: Renal failure is common in patients with chronic heart failure, with a prevalence ranging from 20 % to 57% worldwide. It is associated with a poor prognosis and a high risk of readmission.

Objectives: The purpose of our study is to show the epidemiological, clinical, paraclinical and therapeutic features of Moroccan patients with chronic heart failure who had developed a chronic renal failure. The endpoints were cardiac death and any cause of hospitalization.

Methods: 563 patients followed for chronic heart failure at the heart failure unit in the Department of Cardiology of the University Hospital Ibn Rushd of Casablanca in Morocco, between July 30, 2012 and July 30, 2016 were assessed. Patients were divided into two groups according to the presence or absence of cardiorenal syndrome.

Results: Compared to patients who had no cardiorenal syndrome, patients with cardiorenal syndrome tended to be more aged, hypertensive and diabetic. Clinically more patients were at dyspnea stage III or IV. Biologically their hemoglobin was lower and their blood uric acid level was higher. Regarding echocardiography, their ejection fraction of the left ventricle was lower, with more of systolic dysfunction of the right ventricle and pulmonary hypertension in the CRS group, with a higher risk of readmission ($p < 0.0001$). The mortality was significantly higher in the group CRS ($p < 0.0001$).

Conclusion: The deterioration of renal function in chronic renal failure is associated with poor prognosis, including a high risk of rehospitalization, cardiovascular events and death. Patients who are elderly, diabetic, with a low left ventricular ejection fraction and pulmonary hypertension are the most concerned. (Int J Cardiovasc Sci. 2017;30(5):425-432)

Keywords: Cardio-Renal Syndrome; Heart Failure; Renal Insufficiency, Chronic / mortality, Renal Insufficiency, Chronic / prognosis, Patient Readmission.

Introduction

Renal failure is common in patients with chronic heart failure, with a prevalence ranging from 20 % to 57% worldwide. It is associated with a poor prognosis and a high risk of readmission.[1]

There is a complex relationship between heart and kidney in patients with heart failure, and the exact pathophysiological mechanisms of this association remain unclear.[2] Important pathophysiological triggers of renal disease progression include chronic increases in renal venous pressure, maladaptive activation of the renin-angiotensin –aldosterone axis and the sympathetic nervous system, as well as a chronic inflammatory state.[3]

The purpose of our study was to show epidemiological, clinical, paraclinical and therapeutic features of Moroccan patients with chronic heart failure who had developed chronic renal failure.

Methods

We conducted a monocentric, cross-sectional study on 563 patients attending the Unit of Heart Failure of

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DOI: 10.5935/2359-4802.20170072

Manuscript received October 22, 2016, revised manuscript November 04, 2016, accepted February 24, 2017

the Department of Cardiology of the University Hospital Ibn Rushd of Casablanca in Morocco, during the 3-year period between July 30, 2012 and July 30, 2016.

The Unit of Heart failure is a day hospital attended only by stable patients, who are checked up every 3 or 6 months. Our patients were clinically stable and were followed up for the occurrence of cardiac events. The endpoints were cardiac death and any hospitalization due to worsening heart failure with or without an aggravation of renal function, acute coronary syndrome and severe arrhythmia. The mean follow up was 681 ± 105 days. Follow-up and events were adjudicated using medical consultations each three months and/or phone calls.

Patients were divided into two groups depending on whether they have developed a cardiorenal syndrome (CRS) or not.

Diagnosis of CRS type 2 was established based on Kidney Disease: Improving Global Outcomes (KDIGO)/ Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines: albuminuria and/or GFR < 60 mL/in/1,73 m², or a sustained decrease in GFR > 5ml/min/1,73 m²/year or > 10 ml/min/1,73 m²/5 years or sustained increase in albuminuria, along with documented or suspected appearance of congestive heart failure before the onset or progression of chronic kidney disease, and association of the event or degree of kidney disease with underlying heart disease.

Regarding echographic findings, a left ventricle was considered dilated when its diameter diastolic was above 57 mm in men and 53mm in women. The left atrium was considered dilated when its surface was greater than 15cm² or diameter greater than 35 mm. The right ventricle was considered in systolic dysfunction if TAPSE (tricuspid annular plane systolic excursion) was less than 16mm, S-wave longitudinal velocity using DTI (Doppler tissue imaging) was less than 11.5 cm/s, or the fractional shortening was less than 30%. We defined pulmonary hypertension as any value of systolic pulmonary artery pressure, measured by the flow of tricuspid insufficiency greater than 40 mmHg.

The echocardiography was performed one month after starting treatment.

Baseline characteristics were the data recorded during the first consultation at the Heart Failure Unit. We included all patients who developed CRS at any time of the follow-up, even if it was at the first consultation.

Among the causes of readmission we selected patients who were admitted to emergency care for acute coronary syndrome, congestive heart failure or severe arrhythmia. We defined severe arrhythmia as any atrial or ventricular arrhythmia causing hemodynamic instability or requiring drug treatment.

We excluded all patients with renal failure secondary to another etiology including other CRSs, patients who did not meet the definition of CRS type 2, and hemodialysis patients.

Statistical analysis

Results are presented as the mean ± SD for continuous variables and as numbers and percentages for categorical variables. If data were not normally distributed, the Mann-Whitney U test was used. Baseline characteristics of patients in the two groups specified above were compared using the chi-square test for dichotomous variables and paired student's t-test for continuous variables. A p value < 0.05 was considered statistically significant. Significant variables selected in the univariate analysis were entered into the multivariable analysis. The cardiac event-free survival rates were calculated using the Kaplan-Meier analysis. All analyses were performed using SPSS statistical package, version 17.0(SPSS Inc, Chicago, IL).

Results

Clinical findings

Among the 563 patients analyzed, 46.5 %(262 patients) had CRS type 2.

The mean age was significantly higher in the group CRS (67 years vs. 61). By dividing patients into four age brackets, CRS was more common in patients over 70 years (Figure 1).

Higher frequency of male was observed in both groups, 53.1% in the CRS group and 60.1% in the group without CRS, but the difference was not statistically significant (p = 0.105).

Concerning the risk factors, the percentage of patients with hypertension and diabetes was significantly higher in the CRS group compared to the group without CRS (55.3% and 42%, respectively, in the CRS group vs. 39.5% and 26.6%, respectively, in the group without CRS, p < 0.0001). Among hypertensive patients, the proportion of those with uncontrolled hypertension was significantly higher in the CRS group (16.8% vs. 9.3%).

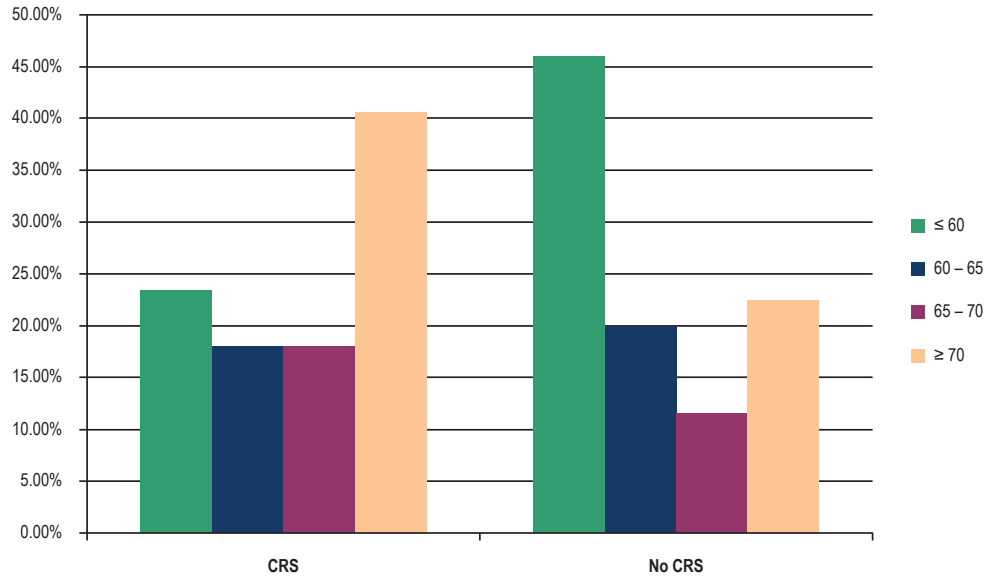

Figure 1 – *distribution of patients with and without cardio-renal by age.*

No difference between the two groups was observed for other risk factors.

Clinically, New York Heart Association class III and IV was reported in 25.6% in the CRS vs. 13.3% in the group without CRS ($p < 0.0001$). Mean heart rate was slightly higher in the group CRS ($p = 0.453$).

Higher, but not significant proportion of patients with atrial fibrillation was observed in the CRS group (17.2% vs. 13%).

Table 1 summarizes all these features.

Biological findings

The mean serum levels of sodium, calcium, and hemoglobin were significantly lower in the CRS group (139.1, 91.4 and 12.3, respectively) than in the group without CRS (140.1, 93.5 and 13.05, respectively).

Inversely, mean levels of serum potassium, uric acid and C-reactive protein (CRP) were significantly higher in the CRS group (4.8, 71.4 and 24.6, respectively) than in the group without CRS (4.5, 53.3 and 11.5, respectively).

Echographic findings

Mean ejection fraction (EF), left atrial dimensions and deceleration time of mitral flow were significantly lower in the group with CRS cardiorenal syndrome (33.50%, 43.6 and 137.70 , respectively) than in the group without CRS (37.57%, 39.96, and 161.59, respectively). Systolic right ventricular function was impaired in 19.1 % of patients with CRS, and only 12% in the group without CRS ($p = 0.025$). Compared with the group without CRS, 56.5% of the patients who developed CRS had a pulmonary hypertension ($p < 0.0001$) (Table 1).

Therapy

Mean ejection fraction (EF) and deceleration time of mitral flow were significantly lower in the group with CRS (33.50% and 137.70 ms, respectively) than in the group without CRS (37.57% and 161.59 ms, respectively). Left atrial area was significantly higher in the group with CRS (21.73 cm^2 vs. 18.95 cm^2). Systolic right ventricular function was impaired in 19.1% of patients with CRS, and only 12% in the group without CRS ($p = 0.025$). Compared with the group without CRS, 56.5% of the patients who developed CRS had a pulmonary hypertension ($p < 0.0001$) (Table 1).

The multivariate analysis showed that age, hypertension, diabetes, low ejection fraction, pulmonary hypertension, left atrium diameter, time of deceleration of mitral flow, anemia, high CRP and hyperuricemia are independents risks factors of CRS.

Table 1 – Baseline characteristics by the presence or absence of cardiorenal syndrome

n = 563	CARDIORENAL SYNDROME		p value	Multivariate analyses
	NO n = 301 (53,5%)	YES n = 262 (46,5%)		
Age (years)	61.45 ± 12.60	67.53 ± 10.80	‹0.0001	‹0.0001
Male	181(60.1%)	139(53.1%)	0.105	0.274
Smokers	111(36.9%)	77(29.4%)	0.073	0.182
Hypertension	113(39.5%)	145(55.3%)	< 0.0001	< 0.0001
Balanced	91(30.2%)	101(38.5%)		
Unbalanced	28(9.3%)	44(16.8%)		
Diabetes	80(26.6%)	110(42%)	< 0.0001	< 0.0001
Hyperlipidemia	43(14.3%)	48(18.3%)	0.208	0.329
Dyspnea stage III or IV	40(13.3%)	67(25.5%)	< 0.0001	
Heart rate	68.58 ± 12.59	69.42 ± 14.03	0.453	
BMI (kg/m²)	25.407 ± 3.70	25.474 ± 3.54	0.848	0.395
Atrial fibrillation	39(13%)	45(17.2%)	0.192	0.804
Etiologies				
IHD	202(67.1%)	179(68.3%)	0.096	NS
DCM	58(19.3%)	63(24%)		
Valve disease	8(2.7%)	6(2.3%)		
Others	33(11%)	14(5,3%)		
Echographic parameters				
LVDd (mm)	57.71 ± 11.51	59.11 ± 8.01	0.1	NS
LVDs (mm)	44.23 ± 9.45	46.79 ± 9.46	0.001	0.085
LVEF (%)	37.57 ± 7.50	33.50 ± 8.52	< 0.0001	< 0.0001
DcT (msec)	161.59 ± 47.45	137.70 ± 50.62	< 0.0001	< 0.0001
Area of the left atrium (cm²)	18.95 ± 6.25	21.73 ± 6.82	< 0.0001	< 0.0001
RV dysfunction	36(12%)	50(19.1%)	0.025	0.168
Pulmonary hypertension	64(21.3%)	148(56.5%)	< 0.0001	< 0.0001
Biological parameters				
Hemoglobin	13.05 ± 1.52	12.34 ± 1.75	< 0.0001	< 0.0001
BUN (mg/l)	0.36 ± 0.11	0.67 ± 0.36	< 0.0001	NS
Serum creatinine (mg/l)	9.51 ± 1.85	16.84 ± 8.72	< 0.0001	
Serum sodium	140.1 ± 3.8	139.4 ± 4.2	0.044	
Serum potassium	4.53 ± 0.50	4.83 ± 0.64	< 0.0001	
Serum calcium	93.56 ± 4.98	91.447 ± 4.84	< 0.0001	0.758
CRP	11.51 ± 18.22	24.65 ± 40.65	0.037	0.135
Uric acid	53.33 ± 14.52	71.47 ± 19.53	< 0.0001	< 0.0001

Continuation

Medication			
β-blocker	287(95,3%)	237(90.5%)	0.030
ACE inhibitor or ARB	298(99%)	257(98.1%)	0.482
CCB	39(13%)	55(21%)	0.013
Antiplatelet agents	249(82.7%)	234(89.3%)	0.029
Statin	248(82.4%)	234(89.3%)	0.022
Spironolactone	135(44.9%)	138(52.7%)	0.076
Readmission	16(5.30%)	78(30.20%)	< 0.0001
Mortality	6(2%)	34(13%)	< 0.0001

BMI: body mass index; IHD: ischemic heart disease; DCM: dilated cardiomyopathy; LVDd: left ventricular end-diastolic diameter; LVDs: left ventricular end-systolic volume; LVEF: left ventricular ejection fraction; DcT: deceleration time; RV: right ventricular; BUN: blood nitrogen urea; CRP: C reactive protein; ACE: angiotensin-converting enzyme; ARB: angiotensin-receptor blocker; CCB: calcium channel blocker.

Readmission

Readmission for congestive heart failure, severe arrhythmia or acute coronary event was more frequent in the group CRS, observed in 30.2% of patients vs. 5.3% ($p < 0.0001$) (Table 1).

Mortality and cardiac events

The mortality was significantly higher in the group CRS 13% vs. 2% in the group without CRS. Patients with CRS had higher rates of cardiac death and re-hospitalization due to worsening heart failure than those without CRS. This was also clearly demonstrated by Kaplan-Meier analysis (Figure 1).

Discussion

The major finding in our study was that, compared with patients without CRS, patients with CRS tended to be older, hypertensive and diabetic. Clinically, higher percentage of patients had dyspnea stage III or IV. Biologically, patients with CRS had lower hemoglobin and higher blood uric acid. Regarding echocardiographic findings, these patients also showed lower left ventricular EF, with higher prevalence of right ventricular and pulmonary hypertension, and higher risk of readmission.

The CRS is characterized by chronic abnormalities in cardiac function leading to kidney injury or dysfunction.[4]

Worsening cardiac performance in heart failure results in renal hypoperfusion, with subsequent activation of the renin-angiotensin-aldosterone pathway and the sympathetic nervous system, which can further impair renal function. Chronic kidney disease and consequent uremia can lead to abnormal regulation of myocyte calcium homeostasis and contractile function, increased sympathetic activity, endothelial dysfunction, microvessel dysfunction and accelerated atherosclerosis.[5,6]

Pre-existing chronic renal failure is found in 45% of chronic heart failure patients, and is associated with a higher risk of hospitalization and death[7]. This percentage is consistent with that of our series (46.5 % of patients with CRS).

Deterioration of renal function increases with age. In our study, patients with CRS were relatively older than patients with normal renal function. In all the studies that have been conducted, advanced age was a factor associated with the occurrence of the CRS. In the study by Lu et al.,[8] mean age of patients with CRS was 77 ± 8 years.

In our study, diabetes and uncontrolled hypertension were the major risk factors found in patients with CRS. It has been suggested an interplay of diabetes and/or hypertension- induced and heart failure-associated renal injury with a related and mutually perpetuating pathophysiology, as it was demonstrated in the model of Kishimoto et al.[9]

Anemia is associated with high mortality in all patients with heart failure and reflects an advanced state of the disease. Also, it is particularly considered as an

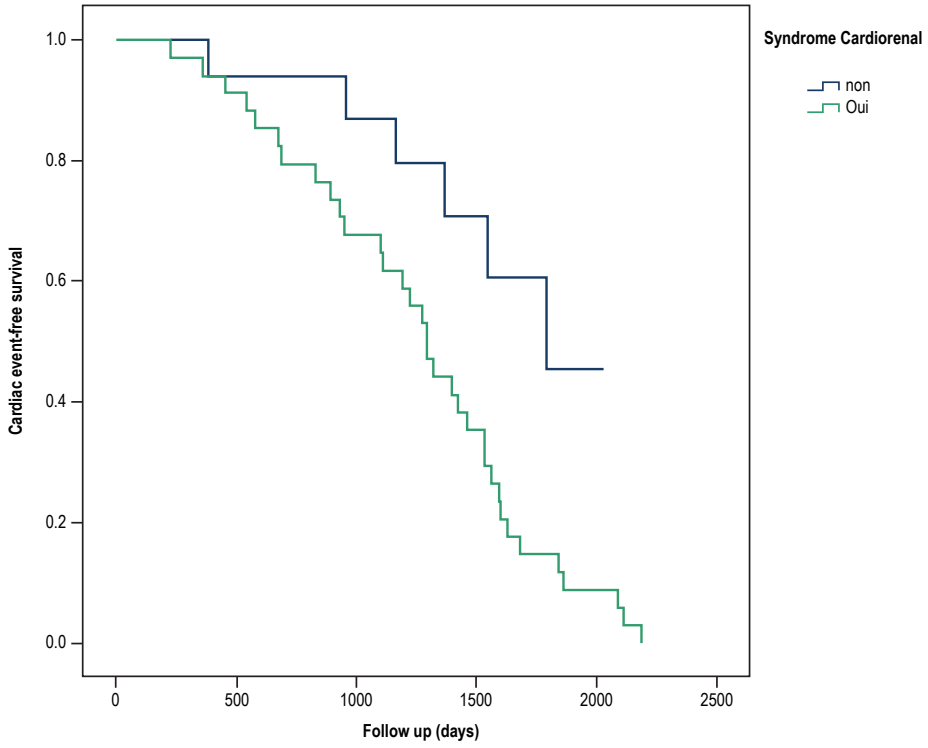

Figure 2 – *Kaplan-Meier cardiac event-free survival analysis in patients with and without cardiorenal syndrome*

independent risk factor of morbidity and mortality in all CRSs.[10] Sato et al.[11] reported that peak VO2, B-type natriuretic peptide levels, anemia and uric acid levels were independent prognostic factors of type 2 CRS[11]. Anemia, chronic heart failure and chronic kidney disease are capable of causing or worsening each other, forming a vicious circle.[12] Recently, a new term has been used – cardiorenal anemia syndrome. In all studies on heart failure, the average hemoglobin level was lower in the group with chronic renal failure, which was associated with a risk of re-hospitalization and higher mortality rates. Lu et al.[8] had reported a 4-year death rate of 51% in patients with cardiorenal anemia syndrome vs. 26% in those without the syndrome. Age and serum potassium were the predictive factors cardiorenal anemia syndrome progression among patients with heart failure.[13] More recently, it has been shown that anemia is common in diabetes mellitus, with chronic kidney disease and functional erythropoietin deficiency hypothesized as major contributing factors.[14]

Recent progresses in the treatment of anemia in heart failure have focused on the use of erythropoiesis-stimulating agents and intravenous iron transfusion. A recent meta-analysis involving more than 11 studies concluded that erythropoiesis-stimulating agents help improve symptoms, reduce hospitalization, and mortality.[15]

In our study, patients with CRS were less likely to be treated with beta-blocker, and more likely to receive loop diuretics and calcium channel blockers. This is explained by a higher rate of congestive heart failure, difficulties in the control of blood pressure and symptoms, and diuretic resistance. The cause of diuretic resistance is multifactorial: inadequate dosing of diuretic, increased sodium intake, delayed intestinal absorption of drugs, decreased diuretic tubular secretion, renal underperfusion and use of non-steroidal anti-inflammatory drugs.[16]

Our study had some limitations. This is an observational study and reflects the data from patients only from a single center, which is not representative of the Moroccan population. Some patients were not included, such as hemodialysis patients, who have a worse prognosis, to not create an ambiguity between all types of CRS. For this reason, a cause-consequence relationship has not been clearly established.

Conclusion

Deterioration of renal function in chronic renal failure is associated with poor prognosis, including a high risk of rehospitalization, cardiovascular events and death. More attention should be paid to elderly, diabetic patients, with a very low left ventricular EF or pulmonary hypertension.

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