

## Original Paper

# Prevalence and Clinical Features of Patients with the Cardiorenal Syndrome Admitted to an Internal Medicine Ward

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## Key Words

Cardiorenal syndrome · Infections · Chronic heart failure · Heart failure · Chronic kidney disease

## Abstract

**Background:** Many patients admitted to a Department of Internal Medicine have different degrees of heart and kidney dysfunction. Mortality, morbidity and cost of care greatly increase when cardiac and renal diseases coexist. **Methods:** A retrospective cohort study was conducted on 1,087 patients admitted from December 2009 to December 2012 to evaluate the prevalence of the cardiorenal syndrome (CRS) and clinical features. **Results:** Out of 1,087 patients discharged from our unit during the study period, 190 (17.5%) were diagnosed as having CRS and classified into five types. CRS was more common in males (68.9%). CRS type 1 was associated with higher age ( $79.9 \pm 8.9$  years) and accounted for 61.5% of all deaths ( $p < 0.001$ ), representing a risk factor for mortality (OR 4.23, 95% CI 1.8–10). Congestive heart failure was significantly different among the five CRS types ( $p < 0.0001$ ) with a greater frequency in type 1 patients. Infectious diseases were more frequent in CRS types 1, 3 and 5 ( $p < 0.05$ ). Pneumonia presented a statistically higher frequency in CRS types 1 and 5 compared to other classes ( $p < 0.01$ ), and community-acquired infections were statistically more frequent in CRS types 1 and 5 ( $p < 0.05$ ). The distribution of community-acquired pneumonia was different among the classes ( $p < 0.01$ ) with a higher frequency in CRS types 1, 3 and 5. **Conclusion:** CRS is a condition that is more frequently observed in the clinical practice. The identification of predisposing trigger factors, such as infectious diseases, particularly in the elderly, plays a key role in reducing morbidity and mortality. An early recognition can be useful to optimize therapy, encourage a multidisciplinary approach and prevent complications.

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## Introduction

A large number of patients admitted to hospital, especially to a Department of Internal Medicine, have different degrees of heart and kidney dysfunction. Primary disorders of one of these two organs can cause dysfunction to the other, determining the pathophysiological basis for the cardiorenal syndrome (CRS) (table 1). Moreover, mortality, morbidity and cost of care greatly increase when cardiac and renal diseases coexist [1].

Although it was defined and classified several years ago [2, 3], only in 2008 was this syndrome unanimously accepted in a consensus conference by experts in nephrology, critical care, cardiac surgery and cardiology, under the auspices of the Acute Dialysis Quality Initiative (ADQI) [4].

The aim of the study was to identify patients with CRS admitted to a Department of Internal Medicine in order to encode this syndrome and assess its impact in clinical practice.

## Materials and Methods

### Patients

A retrospective cohort study was conducted on 1,087 patients admitted to a Department of Internal Medicine from December 2009 to December 2012. A diagnosis of CRS was made in 190 patients according to the recommendations of the ADQI [4].

We analyzed history, anthropometric, clinical, biochemical and treatment characteristics, and the patients were classified according to the five types of CRS. Heart failure (HF) was diagnosed by the European Society of Cardiology criteria [5]. Thus, the degree of cardiac dysfunction was defined as mild, moderate or severe, where mild was used for patients presenting no significant limitations due to dyspnea or fatigue, severe for patients who are markedly symptomatic and need frequent medical attention, and moderate for the remaining patient cohort.

Acute kidney injury (AKI) was classified into three stages of severity based on serum creatinine (sCr) and urine output criteria, as proposed by the Acute Kidney Injury Network (AKIN) criteria [6]:

Stage 1: sCr increase of  $\geq 0.3$  mg/dl ( $\geq 26.5$   $\mu$ mol/l) or increase to  $\geq 150$ –200% (1.5- to 2-fold) from baseline (urine output  $< 0.5$  ml/kg/h for 6 h).

Stage 2: sCr increase of  $> 2$ - to 3-fold from baseline (urine output of  $< 0.5$  ml/kg/h for 12 h).

Stage 3: sCr increase of  $> 3$ -fold from the baseline, or sCr of  $\geq 4.0$  mg/dl ( $\geq 354$   $\mu$ mol/l) with an acute increase of at least 0.5 mg/dl (44  $\mu$ mol/l), or need for renal replacement therapy (urine output of  $< 0.3$  ml/kg/h for 24 h), or anuria for 12 h, or need for renal replacement therapy.

Chronic kidney disease (CKD) was diagnosed according to K-DOQI guidelines [7]. Renal function was evaluated by the estimated glomerular filtration rate (GFR) using two different formulas in relation to the different population of patients:

- The Modification of the Diet in Renal Disease (MDRD) equation:  $186 \times (\text{sCr level in mg/dl})^{-1.154} \times (\text{age in years})^{-0.203}$ . The product of this formula is multiplied by a correction factor of 0.742 for women and 1.21 for African-Americans [8].
- The CKD-EPI equation: expressed as a single equation:  $\text{GFR} = 141 \times \min(\text{sCr}/k, 1)^\alpha \times \max(\text{sCr}/k, 1)^{1-\alpha}$ , where  $k$  is 0.7 for females and 0.9 for males,  $\alpha$  is  $-0.329$  for females and  $-0.411$  for males,  $\min$  indicates the minimum of  $\text{sCr}/k$  or 1, and  $\max$  indicates the maximum of  $\text{sCr}/k$  or 1 [9, 10].

### Clinical and Laboratory Data Collection

Personal data and clinical course were collected daily on the single patient's case history, including age, sex, height, weight and hospital length-of-stay (LOS). Clinical data included primary diagnoses, comorbidities such as diabetes mellitus, hypertension, CKD, history of cerebrovascular accidents, myocardial infarction, coronary revascularization, chronic obstructive pulmonary disease (COPD) or smoking.

sCr and blood urea nitrogen values were recorded at admission, during hospitalization and discharge. We also recorded serum sodium, potassium, phosphorus, calcium, uric acid, hemoglobin, erythrocyte sedimentation rate and C-reactive protein at admission, during hospitalization and discharge. Hemodynamic

**Table 1.** Definition of the five subtypes of CRS

CRS	Definition
CRS type 1	Acute worsening of heart function leading to AKI
CRS type 2	Chronic abnormalities in heart function leading to progressive CKD
CRS type 3	Acute worsening of kidney function leading to acute heart dysfunction
CRS type 4	CKD leading to chronic heart disease
CRS type 5	Cardiac and renal dysfunction due to acute or chronic systemic disorders

**Table 2.** Distribution of patients, sex and age in the five types of CRS

	Total group	CRS type 1	CRS type 2	CRS type 3	CRS type 4	CRS type 5
Patients	190 (100)	61 (32.1)	30 (15.8)	15 (7.9)	11 (5.8)	73 (38.4)
Males	131 (68.9)	42 (32.1)	22 (16.8)	8 (6.1)	8 (6.1)	51 (38.9)
Females	59 (31.1)	19 (32.2)	8 (13.5)	7 (11.9)	3 (5.1)	22 (37.3)
Age, years	77.7 ± 9.8	79.90 ± 8.9	77.53 ± 9.1	72.53 ± 12.2	66.55 ± 6.7	76.23 ± 9.3

Values are presented as n (%) or as mean ± SD.

parameters (systolic and diastolic blood pressure and heart rate), echocardiography findings, chest X-ray and medications were also recorded.

The study was approved by the Ethical Board of the Sapienza University of Rome.

#### Statistical Analysis

All results are expressed as mean ± standard deviation. Commercial software (SPSS version 20.0) was used for statistical analysis. The coefficients of skewness and kurtosis were used to evaluate normal distribution of data. Multivariate analysis was applied for the estimation of the relationship of clinical features. The  $\chi^2$  test or Fisher's exact test, as appropriate, was used to compare categorical variables. Odds ratio (OR) and 95% confidence intervals (95% CI) are reported. p values <0.05 were considered significant.

## Results

Out of 1,087 patients discharged from our unit during the study period, 190 (17.5%) were diagnosed with CRS. Distribution of classes, sex and age in the five types of CRS are summarized in table 2.

The 190 evaluated patients were divided into five types of CRS: 61 patients had clinical signs compatible with a diagnosis of CRS type 1 (32.1%); 30 patients had CRS type 2 (15.8%); 15 patients had CRS type 3 (7.9%); 11 patients had CRS type 4 (5.8%), and 73 patients had CRS type 5 (38.4%). CRS was more common in males (68.9% of patients). In the single classes, the data was constant.

Age was significantly different among the five CRS types ( $p < 0.001$ ). The mean age was  $77.7 \pm 9.8$  years, with a higher mean age ( $79.9 \pm 8.9$  years) in patients with CRS type 1. Mortality was evaluated considering the days of hospitalization. In our study, 13.6% of patients (26 of 190) died in hospital with a mean of 18.8 days, and mortality was significantly different in CRS type 1 compared to other classes ( $p = 0.006$ ). CRS type 1 reported 61.5% (16/26) of all deaths ( $p < 0.001$ ) resulting in a risk factor for mortality (OR 4.23, 95% CI 1.8–10). Furthermore, table 3 describes OR for mortality in each CRS type.

**Table 3.** OR for mortality in each CRS type

	Mortality, n	OR	95% CI
CRS type 1	16/61	2.25	1.1–4.5
CRS type 2	1/30	0.21	0.02–1.6
CRS type 3	3/15	1.57	0.41–5.96
CRS type 4	1/11	0.63	0.07–5.1
CRS type 5	5/73	0.44	0.17–1.25

**Table 4.** Renal function in the five types of CRS

	CRS type 1	CRS type 2	CRS type 3	CRS type 4	CRS type 5	p
Creatinine	1.89±1.51	1.79±0.50	3.98±2.36	4.33±2.70	2.56±1.68	<0.0001
GFR <sub>CKD-EPI</sub> , ml/min/1.73 m <sup>2</sup>	40.75±19.19	36.77±12.92	21.33±18.45	21.82±17.04	29.68±15.23	<0.0001
GFR <sub>MDRD</sub> , ml/min/1.73 m <sup>2</sup>	42.75±21.31	37.73±12.57	21.73±18.08	22.09±16.60	30.64±15.10	<0.0001

**Table 5.** Infectious diseases in the five types of CRS

Infectious diseases	Total	CRS type 1	CRS type 2	CRS type 3	CRS type 4	CRS type 5
Total	103 (100)	37 (35.9)	9 (8.7)	11 (10.7)	8 (7.8)	38 (36.9)
Community-acquired infections	66 (64)					
Pneumonia	36 (54.5)	18 (50)	2 (5.5)	6 (16.6)	3 (8.3)	7 (19.4)
Urinary tract infections	25 (37.9)	5 (20)	4 (16)	2 (8)	2 (8)	12 (48)
Other	5 (7.6)	0 (0)	0 (0)	1 (20)	0 (0)	4 (80)
Nosocomial-acquired infections	37 (36)					
Pneumonia	13 (35.1)	7 (53.8)	2 (15.4)	1 (7.7)	1 (0)	3 (23.1)
Urinary tract infections	23 (62.2)	6 (26.1)	1 (4.3)	1 (4.3)	3 (13)	12 (52.2)
Other	1 (2.7)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)

Values are presented as n (%).

General LOS was  $17.9 \pm 17.4$  days and CRS type 5 LOS was higher ( $20.7 \pm 23.8$  days), but it was not significant ( $p = 0.51$ ).

Evaluation of renal function in the five types of CRS is shown in table 4. The worst renal function was recorded in CRS types 3 and 4. Smoking history ( $p = 0.89$ ), diabetes mellitus ( $p = 0.45$ ), hypertension ( $p = 0.27$ ), ischemic heart disease ( $p = 0.1$ ) and COPD ( $p = 0.21$ ) are not significant risk factors for the onset of CRS.

CKD was significantly different among the five CRS types ( $p < 0.0001$ ) with the highest prevalence in CRS type 3 (53.3%, 8 of 15 patients). AKI was significantly different among the five CRS types ( $p < 0.0001$ ) with the highest prevalence in CRS types 1, 3 and 5. HF was significantly different among the five CRS types ( $p < 0.0001$ ) with the highest prevalence in CRS type 1. Moreover, the degree of cardiac dysfunction of the studied population was distributed as follows: mild 15%, moderate 48.5% and severe 36%. We also checked the possible presence of trigger factors.

Infective features are summarized in table 5. The infectious diseases were significantly different among the five CRS types ( $p < 0.05$ ). When comparing the group of CRS types 1, 3 and 5 (149 patients) with the group of CRS types 2 and 4 (41 patients), it was possible to high-

light that in the first group, 86 patients (58%) presented an infectious disease compared to only 17 patients (41%) in the second group ( $p < 0.05$ ). Among all infections, pneumonia demonstrated a statistically higher frequency in the CRS types 1 and 5 classes, compared to others ( $p < 0.01$ ) and, in particular, 25 of 61 (41%) patients with CRS type 1 and 10 of 73 (14%) patients with CRS type 5 have developed pneumonia. Urinary tract infections and other infectious diseases did not show significant differences in the CRS classes ( $p = 0.11$ ).

Analyzing the distribution between community-acquired and nosocomial infections, community-acquired infections were statistically more frequent in CRS types 1 and 5 ( $p < 0.05$ ), 23 of 61 cases in CRS type 1 and 23 of 73 cases in CRS type 5.

In the CRS classes, the distribution of community-acquired pneumonia (CAP) is significantly different ( $p < 0.01$ ). CRS types 1, 3 and 5 presented the higher frequency of CAP (50, 16.6 and 19.4% of patients, respectively), while urinary tract infections and other infectious diseases showed no correlation ( $p = 0.11$ ).

The analysis revealed no significant difference in the distribution of nosocomial infections ( $p = 0.53$ ).

## Discussion

There are no epidemiological data regarding prevalence and incidence of CRS in a medical ward. Some observational studies evaluated the development of AKI in association with acute decompensated HF and acute coronary syndrome. These studies were performed retrospectively or as secondary and/or post hoc analyses from large registry databases, therefore they present some limitations [11, 12]. Thus, we will refer to heterogeneous data from the available literature.

CRS is a condition which is more frequently observed in the clinical practice. Consequently, renal insufficiency occurs in at least one third of patients with acute and chronic HF, and, conversely, most of the patients suffering from renal failure develop a heart disease.

In both acute and chronic pathological conditions, a careful evaluation of possible interactions between heart and kidney dysfunction is important because of practical implications, not only for the detection and an early diagnosis, but also for an optimization of management.

Unfavorable effects of volume overload and cardiopulmonary and venous congestion are well known in the course of CRS, but correction of volume overload in the setting of HF is complicated. Nevertheless, the use of a diuretic therapy was the mainstay in reducing the volume overload. Unfortunately, diuretic resistance, particularly in advanced stages of CRS, is often frequent [13]. In these cases, an aggressive therapy is required to achieve effective diuresis such as continuous infusions of loop diuretics, or combinations of loop and thiazides [14] able to maximize decongestion and minimize the worsening of renal function. Therefore, an early diagnosis of CRS may prevent this complication.

The complexity of the syndrome requires a multidisciplinary approach involving cardiologists, nephrologists and critical care physicians to reduce mortality and morbidity. The early biomarkers (able to recognize the onset of cardiac and/or renal damage) and the identification of predisposing and/or trigger factors (playing a key role to reduce morbidity and mortality) could improve prognosis through an effective therapeutic approach.

In our study, CRS type 1 is the class with the highest rate of morbidity and mortality. CRS types 3 and 4 were the least frequent, perhaps because the majority of patients with renal diseases were admitted to the specific Department of Nephrology.

CRS type 1 was found to be a risk factor for death possibly due to severity of HF as well as the higher age. CKD was a risk factor particularly in CRS type 3. Moreover, AKI was found

in CRS type 5 as well as in CRS types 1 and 3. CRS type 5 is also the most frequent class in our cohort, probably due to many clinical situations in which both organs are targeted simultaneously by systemic illnesses (such as sepsis, vasculitis, autoimmune diseases, etc.), either acute or chronic, which are very often present in internal medicine wards [15]. Consequently, infectious diseases were more often present in CRS type 5. Probably, the infections have been a trigger for the onset of CRS, and in our study, they were significantly different among the five CRS types, being more numerous in CRS types 1, 3 and 5.

CRS is characterized by multiple factors and its pathophysiology is very complex. Besides hemodynamic interactions, many other components are involved in the pathophysiology of CRS. Inflammatory pathways and immune-mediated mechanism seem to play a central role in organ crosstalk and may be fundamental to distant organ damage. In fact, both heart and renal failure can promote inflammatory and oxidative pathways [14]. For this reason, infections may have played a role in the CRS-triggered immune/inflammatory response in patients with comorbidities. Nonetheless, future studies need to evaluate the elements of this complex pathophysiology.

In our study, community-acquired infections correlate with onset of CRS, probably because the drugs were not administered based on GFR, hydration status, age of patients and other comorbidities. The patients were often treated only for the infectious disease, and not considering comorbidity and the risk of developing a heart and renal injury. Among all infections, pneumonia demonstrated a statistically higher frequency in the classes 1 and 5, compared to other types, while urinary tract infections did not show significant differences in the CRS classes. The distribution between community-acquired and nosocomial infections showed that community-acquired infections were statistically more frequent, particularly in CRS types 1 and 5 ( $p < 0.05$ ).

In the CRS classes, the distribution of CAP was different ( $p < 0.01$ ) with greater frequency in CRS types 1, 3 and 5 as compared to other infectious diseases. Considering the classes, we can observe that CAP is more frequent during acute CRS types 1 and 3. In addition, CRS type 5 can also have an acute onset, especially considering the pathologies that are part of it, including sepsis. The majority of CAP patients (about 80%) are treated as outpatients with a single-drug therapy. The remaining 20% of patients requires hospitalization and a different management [16]. It was shown that about 10% of the admitted patients with CAP have positive blood cultures (60% are infected with *Streptococcus pneumoniae*) [17]. Moreover, the most common cause of death in patients with CAP is *S. pneumoniae*, accounting for about two thirds of all cases, probably due to an aging population, an increasing number of immunocompromised patients and comorbidity conditions (COPD, HF, etc.) [16].

Our study has some limitations related to its retrospective design. Firstly, we did not consider that patients could change CRS subtypes during the course of the disease. Secondly, the patient's clinical condition or a change of therapy may influence the transition from one class to another. Thirdly, pneumonia has been classified as either community- or hospital-acquired, although health care-associated pneumonia has been recently proposed as a new category of respiratory infection [18].

However, our aim was to assess prevalence and clinical features of CRS in a cohort of patients not otherwise classified as CRS. We believe that an early recognition of this syndrome (especially in a Department of Internal Medicine) can help to optimize therapy, recognize trigger factors, encourage a multidisciplinary approach and reduce the high risks associated with the elderly.

Further clinical trials should be focused on reliable epidemiological data, helpful diagnostic tools and effective therapeutic options to allow a better understanding of the causal events and the possible therapeutic strategies.

## Disclosure Statement

The authors have no conflicts of interest to disclose.

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