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Prognostic Factors in Cardiorenal Syndrome Type 1: Retrospective Observational and Analytical Study

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Abstract

Introduction: Type 1 cardiorenal syndrome (CRS 1) is characterized by acute impairment of cardiac function leading to acute renal dysfunction. CRS1 is present in 25% of patients admitted for heart failure. The objective of our study is to analyze the epidemiological, clinical, therapeutic profile and the risk and prognostic factors of these patients. **Materials and Methods:** We identified 120 patients with cardiorenal syndrome (CRS) over a one-year period to determine the prevalence and risk factors for developing CRS 1. We analyzed the clinical, biological, and evolutionary profiles of patients with CRS 1 and determined the risk factors for the occurrence of acute kidney injury (AKI) as well as the mortality factors in these patients. **Résultats:** The average age of our patients with CRS1 is 58 ± 9 years, with a sex ratio of 1.4. The average eGFR of our patients is 35 ± 6.5 ml/min/1.73m^2. Diabetes was found in 17% of our patients and hypertension in 14%. The etiology of cardiac impairment is predominantly acute coronary syndrome (ACS), followed by rhythm disorders. Renally, all our patients have acute kidney injury (AKI), with 86% having functional acute renal failure and 14% having acute tubular necrosis. Therapeutically, 50% of our patients are on diuretics, 42% receive beta-blocker treatment, and RAAS blockers are used in 29% of cases. Renal replacement therapy (RRT) sessions were required in 13.8% of cases. In univariate analysis, male gender, tachyarrhythmia, and hypertension are associated with the early onset of acute kidney injury (AKI). The use of diuretics, anemia, and low left ventricular ejection fraction (LVEF) are linked to a higher risk of developing CRS 1 (p = 0.021, p = 0.037, p = 0.010 respectively).

In multivariate analysis, advanced age is significantly associated with increased mortality risk in CRS 1 patients (p = 0.030), while beta-blocker use is considered a protective factor (p = 0.014). **Conclusion:** Our study identifies several key factors associated with outcomes in type 1 CRS. Male gender, tachyarrhythmia, and hypertension are linked to early-onset AKI. The use of diuretics and the presence of anemia increase the risk of developing CRS1. Advanced age is significantly associated with higher mortality rates. Conversely, the use of beta-blockers appears to be protective in this patient population.

Keywords

Acute Kidney Injury, Type 1 Cardiorenal Syndrome, Acute Heart Failure, Diuretics

1. Introduction

Type 1 cardiorenal syndrome (CRS 1) refers to acute kidney injury induced by an acute deterioration of cardiac function. Worsening renal function is a powerful and independent predictor of poor prognosis.

Acute heart failure (AHF), characterized by an acute or subacute worsening of heart failure (HF) symptoms and signs, is a clinical and public health problem with high morbidity, mortality, and economic burden. AHF generally coexists with many complications, among which renal dysfunction is the most common, with a prevalence of approximately 25% to 40% [1] [2].

Hemodynamic mechanisms play an important role in the pathogenesis of CRS1. Primarily, low cardiac output leads to renal hypoperfusion, resulting in initially functional acute kidney injury, which subsequently progresses to acute tubular necrosis. This reduction in renal perfusion is associated with renal congestion, explaining the renal damage and subsequent loss of function.

Several studies have shown that renal insufficiency is an independent prognostic factor for the occurrence of multiple adverse events, notably cardiovascular mortality and increased length of hospitalization for AHF. The management of CRS 1 is a challenge for both nephrologists and cardiologists [3] [4].

The objective of our study is to analyze the clinical, biological, and evolutionary profiles of patients with CRS 1, to determine the risk factors for the onset of AKI, the factors influencing the progression to chronic kidney disease (CKD), and the mortality factors in these patients.

2. Material and Methods

2.1. Study Population

Our study was conducted in the nephrology and cardiology departments of Ibn Sina University Hospital in Rabat over a one-year period. Among the 120 patients with any type of CRS, we studied those with CRS 1. We included all pa-

tients who are over 30 years old. We excluded patients with obstructive renal insufficiency.

Epidemiological, anamnestic, clinical, biological, radiological, and therapeutic data were obtained from the patients' medical records. All biological and radiological tests were performed at the biology and radiology centers of Ibn Sina University Hospital.

2.2. Definitions

CRS 1 is defined as any acute cardiac failure leading to acute kidney injury. The different types of CRS are defined according to the classification by Ronco and colleagues (Table 1).

Table 1. Classification of Cardiorenal Syndrome (according to Ronco *et al.*) [5].

Type	Description
CRS 1	Acute Cardiorenal Syndrome: Acute cardiac failure leading to acute kidney injury.
CRS 2	Chronic Cardiorenal Syndrome: Chronic cardiac dysfunction leading to chronic kidney disease.
CRS 3	Acute Renocardiac Syndrome: Acute kidney injury leading to acute cardiac dysfunction.
CRS 4	Chronic Renocardiac Syndrome: Chronic kidney disease leading to chronic cardiac dysfunction.
CRS 5	Secondary Cardiorenal Syndrome: Systemic conditions causing both cardiac and renal dysfunction.

Acute kidney injury (AKI) is defined according to the KDIGO 2012 classification for AKI [6].

Chronic kidney disease (CKD) is defined by an estimated glomerular filtration rate (eGFR) of less than 60 ml/min/1.73m^2 for more than three months (KDIGO 2012 classification). The eGFR is calculated using the Modification of Diet in Renal Disease (MDRD) equation [7].

The diagnosis of heart failure is based on clinical signs of heart failure combined with elevated biomarkers and/or systolic or diastolic dysfunction on echocardiography, according to the 2021 recommendations of the European Society of Cardiology (ESC) [8].

A long duration of hospitalization is defined as a hospital stay exceeding ten days. We followed our patients for three months after discharge from the hospital.

2.3. Collected Parameters

We collected epidemiological data including the prevalence of CRS 1, gender, and age of our patients. We documented their comorbidities such as diabetes, hypertension, ischemic heart disease, and arrhythmias.

Biological assessments included evaluating the severity of renal insufficiency through serum creatinine levels and estimated glomerular filtration rate (eGFR), as well as cardiac involvement assessed by troponin and B-type natriuretic peptide (BNP) levels.

Renal ultrasound was performed for all patients to rule out obstructive causes of renal insufficiency and assess kidney size. Cardiac ultrasound was also conducted for all patients to detect signs of overload by assessing inferior vena cava diameter and filling pressures, signs of global or segmental hypokinesia, and to evaluate left ventricular ejection fraction (LVEF).

Regarding therapy, we documented the medications taken by our patients including renin-angiotensin-aldosterone system (RAAS) blockers, diuretics, and beta-blockers. We also recorded patients who underwent renal replacement therapy (RRT).

2.4. Criteria for Assessment

The evolution of our patients is characterized by either definitive healing, indicated by clinical and biological improvement with complete recovery of renal function, or progression to chronic kidney disease (CKD), or death either during hospitalization or within one month after discharge.

2.5. Statistical Analysis

All statistical calculations were performed using the Jamovi software. Quantitative variables are presented as means ± standard deviation, medians with interquartile ranges, or proportions, as appropriate. Continuous variables are compared using Student's t-test or Mann-Whitney U test. Qualitative variables are expressed as percentages and compared using the chi-square test or Fisher's exact test. A p-value less than 0.05 is considered statistically significant. We employed logistic regression in both univariate and multivariate analyses to determine prognostic factors.

3. Results

3.1. Characteristics of Patients with CRS 1

Among the 120 patients enrolled with any type of CRS, 36 had CRS 1, representing a prevalence of 30%. The average age of our patients was 58 ± 9 years, ranging from 39 to 75 years, with a sex ratio of 1.4 (male to female). The average eGFR of our patients was 35 ± 6.5 ml/min·1.73m^2.

Ischemic heart disease was observed in 80% of our patients, while arrhythmic heart disease was present in 25% of cases. Diabetes mellitus was found in 17% of our patients, and hypertension was present in 14% of cases.

We admitted 20 patients with CKD stage 1 to the intensive care units. **Table 2** summarizes the clinical, biological, therapeutic, and evolutionary characteristics of patients with CRS 1.

Table 2. Characteristics of patients with CRS 1.

	Type 1 CRS n = 36 (30%)
Median age	58 ± 9
Sex ratio(M/F)	1.4
LVEF	63%
Medical History	
Dyspnea stage III of VI (NYHA)	19 (52.8%)
High Blood Pressure	6 (16.7%)
Diabetes	5 (13.8%)
Ischemic Heart Disease	29 (80.5%)
Rhythmic Heart Disease	9 (25%)
Hemoglobin (g/dL)	9.7 ± 2.3
Creatinine (mg/L)	20 ± 7.2
GFR (ml/min/1.73m^2)	35 ± 6.5
Treatment	
ACE/ARB	10 (27.8%)
Beta-blocker	15 (41.7%)
Diuretic	18 (50%)
Vasoactive drugs	4 (11.1%)
Evolution	
Resorting to hemodialysis	5 (13.8%)
In-hospital mortality	6 (16.7%)

GFR = Glomerular Filtration Rate; LVEF = Left Ventricular Ejection Fraction; ACE = Angiotensin-Converting Enzyme inhibitor; ARB = Angiotensin II Receptor Blocker.

3.2. Risk Factors for the Occurrence of CRS 1

Diuretics are the first-line treatment for patients experiencing heart failure exacerbation. Among our patients with type 1 CRS, diuretics are used in 50% of cases. In univariate analysis, several parameters were studied to identify risk factors for the occurrence of type 1 CRS. Those found to be statistically significant are the maintenance of high doses of diuretics, anemia, and low LVEF (Left Ventricular Ejection Fraction) (OR = 3.189, p = 0.021; OR = 2.521, p = 0.037; OR = 1.734, p = 0.010 respectively) (Table 3).

3.3. Risk Factors for Early Onset of AKI

We studied certain parameters to identify those associated with the onset of AKI, and found that male gender, tachycardia, and hypertension are risk factors for early onset of AKI (Table 4).

Table 3. Risk factors for the occurrence of CRS 1.

	OR	IC 95%		p
		lower	higher	
Advanced age	2.157	1.951	2.985	0.543
Male gender	3.875	2.346	4.172	0.628
High Blood Pressure	1.652	1.324	1.782	0.071
Contrast agent injection	2.874	4.651	5.823	0.437
Maintenance of high-dose diuretics	3.189	2.893	4.323	**0.021**
Anemia	2.521	2.361	2.981	**0.037**
Impaired LVEF	1.734	1.498	1.832	**0.010**

LVEF: Left Ventricular Ejection Fraction.

Table 4. Risk factors for early onset of AKI.

	OR	IC 95%		p
		lower	higher	
Advanced age	1.936	2.892	3.172	0.172
Ischemic heart disease	2.734	3.194	3.764	0.642
Anemia	1.395	1.934	2.742	0.462
Male gender	4.183	1.017	5.659	**0.048**
Tachycardia	1.341	1.122	1.765	**0.008**
High blood pressure	3.739	2.273	4.215	**0.031**

3.4. Risk Factors for Progression to CKD

We analyzed certain patient data to identify factors associated with poor renal prognosis, and found that anemia and the need for RRT sessions are risk factors for progression to CKD, while male gender and hypertension are not significantly associated with CKD (Table 5).

Table 5. Risk factors for progression to CKD.

	OR	IC 95%		p
		lower	higher	
Hypertension	1.894	1.518	2.134	0.880
Anemia	3.715	3.521	4.182	**0.041**
RRT	2.134	2.105	2.567	**0.031**
Male gender	2.167	2.097	2.481	0.781

RRT: Renal Replacement Therapy.

3.5. Risk Factors for Mortality in Patients with CRS 1

We conducted a multivariate analysis of patient parameters to identify risk factors for mortality in type 1 CRS patients. We found that advanced age is significantly associated with death (OR = 2.134, p = 0.030), while the use of beta-blockers is considered a protective factor (OR = 0.219, p = 0.014). The use of diuretics and dialysis sessions is not correlated with mortality (Table 6).

Table 6. Risk factors for mortality in patients with CRS 1.

	OR	IC 95%		p
		lower	higher	
Advanced age	2.134	1.985	2.678	**0.030**
Use of beta-blockers	0.219	0.142	0.542	**0.014**
Use of diuretics	1.583	1.452	1.852	0.657
RRT	1.937	1.153	2.021	0.783

RRT: Renal Replacement Therapy.

4. Discussion

4.1. Epidemiology

CRS 1 occurs in 25% - 35% of patients admitted for heart failure decompensation, with its incidence varying based on criteria used for AKI diagnosis and the etiology responsible for cardiac dysfunction. Thirteen percent of patients with acute coronary syndrome and impaired cardiac function present with CRS [9]-[11].

In our study, the prevalence of type 1 CRS is 30%. This aligns with the study by Cowie *et al.*, and with Nohria *et al.*, where the prevalence of CRS 1 is respectively 29% and 29.5%. While in the study by Gottlieb *et al.*, the prevalence is 39%, and in the study by Lorgeart *et al.*, it is 37%.

The etiology of cardiac involvement is predominantly acute coronary syndrome followed by arrhythmias. Decompensations of heart failure and cardiogenic shock are also observed in our patients.

Several studies have shown that the onset of acute kidney injury is early in hospitalized heart failure patients, with forty percent developing renal dysfunction within 3 days of hospital admission [10]. In our study, 42% of our patients developed AKI within four days of hospitalization, consistent with literature findings.

4.2. Pathophysiology

The pathophysiological mechanisms through which acute cardiac dysfunction leads to impaired renal function are complex and multifaceted. These mechanisms can be categorized into hemodynamic and non-hemodynamic mechanisms.

Hemodynamic mechanisms play a crucial role in the pathogenesis of type 1

cardio-renal syndrome. Firstly, reduced renal perfusion pressure due to decreased cardiac output leads to renal hypoperfusion, resulting in initially functional acute kidney injury (AKI) that can progress to acute tubular necrosis. This reduction in renal perfusion is associated with increased venous congestion (renal congestion), which decreases oxygen delivery, thereby causing renal impairment and loss of function [5].

Simultaneously, non-hemodynamic mechanisms come into play, including activation of the sympathetic nervous system, activation of the renin-angiotensin-aldosterone system (RAAS), hormonal responses (natriuretic factors), and an inflammatory response involving cytokine production and free radical formation. Additionally, iatrogenic mechanisms contribute to understanding the pathophysiological pathways. Certain pharmacological treatments can induce renal toxicity (antibiotics, iodinated contrast agents, diuretics) and/or alter renal vasomotricity. Metformin, widely used for type 2 diabetes treatment, can lead to lactic acidosis upon accumulation, potentially contributing to negative inotropic effects [5].

4.3. Prognostic Factors

A Chinese study focusing on elderly subjects with CRS 1 showed that malnutrition, chronic kidney disease, heart failure, and high-dose diuretic use contribute to CRS 1 [12]. Zehra Eren *et al.* reported that advanced age, history of hypertension, chronic kidney disease, and anemia are significantly associated with AKI in patients with acute coronary syndrome (ACS) [13]. Valério Verdiani also demonstrated that elderly individuals with heart failure and a history of renal insufficiency are at higher risk of developing AKI [14].

In our study, however, it is predominantly male gender, tachycardia, and hypertension that are associated with early onset AKI in patients with acute coronary artery syndrome. In multivariate analysis, we found that diuretic use, anemia, and left ventricular ejection fraction (LVEF) are high-risk factors for CRS 1.

Some studies have shown that beta-blockers and diuretics are protective factors against type 1 CRS, while other studies indicate that high-dose and long-term diuretic use are independent risk factors for type 1 CRS.

In our study, we found that only the use of beta-blockers was associated with a protective effect, while the use of high-dose and long-term diuretics was identified as a risk factor for the occurrence of CRS 1. These results underscore the increased vulnerability of elderly patients to diuretics, emphasizing the need for careful monitoring of fluid balance and urine output in elderly individuals with heart failure. Additionally, higher estimated glomerular filtration rate (eGFR) and serum albumin levels emerged as protective factors in our patient cohort [13].

Regarding mortality, our study diverges from some findings in the literature. While renal replacement therapy (RRT) has been identified as an independent risk factor for mortality in type 1 CRS patients in other studies [14], we did not

find this association in our investigation. The mortality rate among patients with type 1 CRS in our study was 16.7%, which falls within the range reported in the literature (5.5% to 18.2%) [15]. This underscores the variability in outcomes and risk factors across different patient populations and settings.

5. Limitations

The study might be limited by the relatively small number of included patients, which can limit statistical power to detect significant associations. Selection bias could be a possibility, as the data were collected from medical records across different units.

6. Conclusion

Our study identifies several key factors associated with outcomes in type 1 CRS. Male gender, tachyarrhythmia, and hypertension are linked to early-onset AKI. The use of diuretics and the presence of anemia increase the risk of developing CRS 1. Advanced age is significantly associated with higher mortality rates. Conversely, the use of beta-blockers appears to be protective in this patient population. These findings underscore the importance of targeted management strategies to mitigate risks and optimize outcomes in patients with type 1 CRS.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Abbreviations

ACS:	Acute Coronary Syndrome
AHF:	Acute Heart Failure
AKI:	Acute Kidney Injury
ATN:	Acute Tubular Necrosis
CKD:	chronic Kidney Disease
CRS:	Cardiorenal Syndrome
CRS1:	Type 1 Cardiorenal Syndrome
eGFR:	estimated Glomerular Filtration Rate
GFR:	Glomerular Filtration Rate
HF:	Heart Failure
HTA:	Hypertension
LVEF:	Left Ventricular Ejection Fraction
RAAS:	Renin-Angiotensin-Aldosterone System
RRT:	Renal Replacement Therapy