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Clinical Profile and Outcomes of Acute and Chronic Type 5 Cardiorenal Syndrome

Mariam El Galiou[1], Samia El Hilali[2], Naima Ouzeddoun[1], Tarik Bouattar[1], Nawal Doghmi[3], Laila Lahlou[2], Loubna Benamar[1]

[1]Nephrology-Dialysis-Renal Transplantation Department, Ibn Sina University Hospital, Mohamed V University, Rabat, Morocco
[2]Department of Cardiology B, Ibn Sina University Hospital, Mohamed V University, Rabat, Morocco
[3]Laboratory of Biostatistics, Clinical Research and Epidemiology, Department of Public Health, Mohamed V University, Rabat, Morocco
Email: mariam6.9595@gmail.com

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Abstract

Introduction: Type 5 cardio-renal syndrome (CRS) is characterized by the combination of renal failure and heart failure secondary to an acute or chronic systemic disease. The most common situation of acute systemic involvement responsible for type 5 CRS is sepsis. The objective of our study is to determine the epidemiological, clinical, and therapeutic profile of patients with acute and chronic type 5 CRS and to identify the prognostic factors associated with type 5 CRS. **Materials and Methods:** This is a descriptive and analytical study conducted between the nephrology and cardiology departments of the Ibn Sina University Hospital in Rabat. Over a period of one year, we identified 120 patients with CRS. We studied and analyzed patients with type 5 CRS (46%). Two groups of patients with type 5 CRS were defined and compared to analyze the epidemiological, clinical, and therapeutic profile of each group. Group 1 included patients with acute type 5 CRS, and Group 2 included patients with chronic type 5 CRS. We also investigated the risk factors for mortality associated with type 5 CRS. **Results:** Among the 120 patients with CRS, those with type 5 CRS represent 46%. Chronic type 5 CRS is significantly associated with diabetes, hypertension, and chronic kidney disease (CKD). AL amyloidosis was found in two of our patients with chronic type 5 CRS. Acute type 5 CRS was found in 20% of our patients, with severe sepsis being the predominant etiology in 72% of cases, followed by systemic lupus erythematosus in 28% of cases. The use of renal replacement therapy (RRT) was indicated in 45.5% of patients in Group 1, while mortality occurred in 36.4% of these patients. In univariate and multivariate analysis, we found that the risk factors for mortality associated with type 5 CRS are prolonged stays in the cardiac intensive care unit (CICU), the use of RRT, and acute type 5 CRS ($p = 0.015$, $p = 0.031$, $p = 0.04$). **Conclusion:** In our study,

the prevalence of type 5 CRS is 46%. The etiology of acute type 5 CRS is dominated by sepsis, whereas chronic type 5 CRS is dominated by diabetes and hypertension. The risk factors for mortality associated with type 5 CRS are primarily; acute type 5 CRS, prolonged stays in CICU, and the use of RRT.

Subject Areas

Nephrology

Keywords

Type 5 Cardiorenal Syndrome, Sepsis, Systemic Disease, Acute Kidney Injury, Diabetes

1. Introduction

Type 5 CRS is characterized by an acute or chronic systemic disease that leads to simultaneous cardiac and renal dysfunction. Examples of this can be found in sepsis, systemic lupus amyloidosis, diabetes mellitus, and sarcoidosis. The coexistence of aggravating conditions, such as diabetes and/or hypertension, can worsen the severity of the involvement of both organs. The pathophysiological characteristics of the disease have not yet been well defined, but it has its own current epidemiological logic.

Epidemiological data concerning type 5 CRS are rare and insufficient given the large number of etiologies that can potentially be responsible for this disorder. The main etiologies of type 5 CRS are summarized in **Table 1**. Furthermore, the bidirectional interactions between cardiac and renal dysfunction make it difficult to analyze the scarce data in the literature. Sepsis in its most severe form is the major cause of type 5 CRS. It is a common problem with an increasing incidence in recent years among intensive care patients, and there is a stable but significant mortality rate of around 25% - 30% [1]. It is clearly established that in septic patients, the onset and/or worsening of renal failure worsens the prognosis and is an independent factor of excess mortality. The same characteristics are found regarding heart failure in septic intensive care patients [2] [3].

The objective of our study is to determine the epidemiological, clinical, etiological, and therapeutic profile of patients with acute and chronic type 5 CRS and to identify the prognostic factors associated with type 5 CRS.

2. Definitions

- Acute kidney injury (AKI) is defined according to the KDIGO 2012 classification of AKI [4]. Chronic kidney disease (CKD) is defined by an estimated glomerular filtration rate (eGFR) of less than 60 ml/min/1.73m^2 (KDIGO 2012 classification) [5]. The eGFR is calculated using the Modification of Diet in Renal Disease (MDRD) equation [5].

Table 1. Causes of type 5 CRS [1].

Acute systemic diseases	Chronic systemic diseases
Severe sepsis/septic shock	**Hypertension**
Specific infections	**Diabète**
HIV	
Malaria	
Leptospirosis	
Hepatitis C	
Toxic causes	**Primary/secondary amyloidosis**
Cocaine	
Heroin	
Calcium channel blocker	
Anticancer chemotherapy	
Systemic diseases	**Multiple myeloma**
Systemic lupus erythematosus	
Scleroderma	
Antiphospholipid syndrome	
Microangiopathy	
TTP/HUS	
Pregnancy	Sarcoidosis
Malignant hypertension	Cirrhosis
Hemorrhagic shock	Primary/secondary pulmonary arterial hypertension
Vasculitis	
Cancer (lymphoma, leukemia++)	

HIV: Human Immunodeficiency Virus, TTP: Thrombotic Thrombocytopenic Purpura, HUS: Hemolytic Uremic Syndrome.

- The diagnosis of heart failure is based on clinical signs of heart failure associated with elevated biomarkers and/or systolic or diastolic dysfunction on echocardiography (according to the European Society of Cardiology (ESC) 2021 recommendations) [6].
- The definition of acute/chronic type 5 CRS corresponds to any acute/chronic systemic disease leading to simultaneous acute/chronic renal and cardiac involvement.

3. Studied Population and Data Sources

This is a retrospective, descriptive, and analytical study conducted over a one-year period from June 2020 to June 2021, between the nephrology and car-

diology departments of the Ibn Sina University Hospital in Rabat. We identified 120 patients with CRS hospitalized in the cardiology department, focusing our study and analysis on patients with type 5 CRS.

We defined two groups of patients based on the type of type 5 CRS: acute or chronic. We excluded from our study other types of CRS (1, 2, 4), patients with end-stage chronic kidney disease stage 5 defined by an eGFR ≤ 15 ml/min (KDIGO 2012 classification), chronic hemodialysis patients, and patients with obstructive renal failure.

We compared the two groups to analyze their epidemiological, clinical, and therapeutic profiles, and the risk factors for mortality associated with type 5 CRS.

Epidemiological, anamnestic, clinical, biological, radiological, and therapeutic data were obtained from the patient's medical records. All biological and radiological assessments were conducted at the biology and radiology centers of the Ibn Sina University Hospital.

4. Statistical Analysis

All statistical calculations were performed using Jamovi software. Quantitative variables were presented as means ± standard deviation, medians with interquartile ranges, or proportions, as appropriate. Continuous variables were compared using the Student's t-test or the Mann-Whitney U test. Qualitative variables were expressed as percentages and compared using the chi-squared test or Fisher's exact test. A p-value of less than 0.05 was considered statistically significant. To identify risk factors, we used univariate and multivariate logistic regression.

5. Results

Over the course of one year, among 120 patients with CRS, 55 (46%) had type 5 CRS. Their average age was 55 years with a sex ratio of 0.96. We noted chronic type 5 CRS in 44 (80%) and acute type 5 CRS in 11 (20%). (Figure 1)

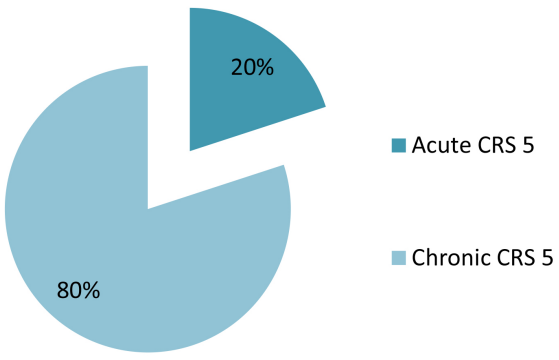

Figure 1. Types of CRS 5.

Table 2 summarizes the characteristics of the two groups of patients.

Table 2. Characteristics of patients with type 5 CRS.

	Acute CRS 5 n = 11 (20%)	Chronic CRS 5 n = 44 (80%)
Age	51 ± 11.6	63 ± 8.1
Male gender (%)	7 (64%)	27 (61.4%)
Sex Ratio	0.83	1.58
Creatinine Level	28 ± 8	39 ± 7.1
GFR (ml/min/1.73m^2)	21 ± 5.1	18 ± 8.4
Acute Renal Failure (ARF)	11 (100%)	-
Chronic Kidney Disease (CKD)	-	38 (86%)
CICU	11 (100%)	2 (4.5%)
History		
Hypertension	2 (18.2%)	39 (88%)
Diabetes	3 (27.3%)	21 (47.7%)
Ischemic heart disease	7 (64%)	17 (38%)
Rhythmic heart disease	2 (18.2%)	11 (25%)
Treatment		
Diuretics	7 (63.6%)	39 (88.6%)
Vasoactive drugs	10 (100%)	-
Use of crystalloid solutions	11 (100%)	-
Results		
Hemodialysis	5 (45.5%)	2 (4.5%)
Mortality	4 (36.4%)	2 (4.5%)

GFR: Glomerular Filtration Rate, CICU: Cardiac Intensive Care Unit.

Etiologies of Type 5 CRS

In our study, sepsis is the predominant cause of acute type 5 CRS. Pneumonia is the main cause of infection in our patients, followed by urinary tract infections, and then infective endocarditis. Some of our patients may have more than one source of infection. Systemic lupus erythematosus is found in 28% of cases. (Table 3)

Table 3. Causes of acute type 5 CRS in our patients.

	n = 11	20%
Sepsis	8	72.7%
Urinary infection	6	54.5%
Pneumonia	7	63.6%
Infective Endocarditis	3	27.3%
Systemic lupus	3	27.3%

Chronic Type 5 CRS

The causes responsible for chronic type 5 CRS in our patients are predominantly hypertension in 88% of cases, followed by diabetes in 47.7% of cases. AL amyloidosis is found in 5% of patients. (See Table 4)

Table 4. Causes of chronic type 5 CRS in our patients.

	n = 44	80%
Hypertension	39	88%
Diabetes	21	47.7%
Amyloidosis AL	2	5%

Renal Findings

AKI is found in all our patients with acute type 5 CRS. Functional AKI is observed in 18% of cases, while organic involvement is found in 82% of our patients, of whom 55% have acute tubular necrosis (ATN) and 27% have glomerular involvement secondary to lupus nephritis.

Among our patients with chronic type 5 CRS, 86% have CKD, of whom 88% have hypertensive nephropathy and 47.7% have diabetic nephropathy. Two of our patients have AL amyloidosis secondary to myeloma.

Cardiac Findings

Forty percent of our patients are hospitalized for chest pain, 31% for arrhythmias, and 29% for exacerbation of heart failure.

Cardiac ultrasound performed on our patients shows hypokinesia in 65% of cases, followed by left ventricular hypertrophy in 33% of cases. Preserved left ventricular ejection fraction (LVEF) with impaired systolic blood pressure is found in 62%, while impaired LVEF is found in 48% of our patients. Lupus cardiomyopathy presents in our patients as myocarditis, hypokinesia, and left ventricular dysfunction. AL amyloidosis is suggested by septal hypertrophy with a bright appearance and late subendocardial enhancement on cardiac MRI.

Therapeutic Approach

All our patients with acute type 5 CRS required fluid resuscitation with crystalloid solutions, as well as the use of vasoactive drugs. Diuretics are used in 89% of our patients with chronic type 5 CRS compared to 64% with acute type 5 CRS. The use of renal replacement therapy (RRT) sessions is indicated in 46% of patients with acute type 5 CRS, while only 4.5% of patients with chronic type 5 CRS required hemodialysis sessions.

Risk Factors for Mortality

In univariate and multivariate analysis, we found that the risk factors for mortality associated with type 5 CRS are prolonged stays in the cardiac intensive care units (CICUs), the use of RRT, and acute type 5 CRS ($p = 0.015$, $p = 0.031$, $p = 0.04$). (See Table 5)

Table 5. Univariate and multivariate analysis determining the risk factors for mortality in patients with type 5 CRS.

	Univariate analysis		Multivariate analysis	
	OR (IC 95%)	p	OR (IC 95%)	p
Acute CRS 5	2.1 (1.7 - 2.9)	**0.01**	1.9 (1.2 - 3.1)	**0.04**
Age	1.3 (1.1 - 1.7)	0.73	1.4 (1.2 - 1.8)	0.59
Male gender	1.2 (1.0 - 2.2)	0.52	1.1 (1.0 - 1.5)	0.62
Septic shock	2.7 (1.6 - 3.1)	0.02	1.7 (1.2 - 1.4)	0.049
Hypertension	1.9 (1.5 - 2.7)	0.69	2.3 (1.9 - 3.4)	0.71
Diabetes	1.4 (1.1 - 3.1)	0.57	1.6 (1.0 - 2.8)	0.66
Prolonged hospitalization in CICU	3.8 (3.2 - 4.4)	**0.035**	3.6 (2.9 - 4.8)	**0.015**
Use of RRT	2.9 (2.5 - 3.4)	**0.026**	2.7 (2.3 - 3.1)	**0.031**

6. Discussion

Epidemiological data concerning type 5 CRS are rare and insufficient given the large number of potential etiologies responsible for this disorder. Moreover, the bidirectional interactions between cardiac and renal dysfunction make it difficult to analyze the limited existing data [1].

Inflammation and microvascular alterations form the basis of the pathogenesis of kidney and cardiovascular involvement during sepsis (acute type 5 CRS), leading to alterations in cell ultrastructure and organ dysfunction [6] [7]. AKI is a common complication in patients with sepsis and leads to a poor prognosis, occurring in 20% of critically ill patients and in 51% of patients with septic shock [8]. In our patients, AKI is present in 20% of those with type 5 CRS.

Experimental studies on septic AKI have reported contradictory results [9]. On one hand, some studies have shown that total renal blood flow (RBF) decreases after the induction of sepsis or endotoxemia, leading to acute tubular necrosis (ATN), reduced glomerular filtration, and severe AKI [10] [11]. In our study, ATN secondary to septic shock was found in 64% of patients with acute type 5 CRS, while functional AKI was observed in 36% of cases.

A meta-analysis of 160 experimental studies on sepsis revealed preserved or increased RBF in about 30% of these studies [12]. The Changes in intra-renal hemodynamics also play a role in the pathogenesis of septic AKI. Non-hemodynamic renal injuries are mediated by various inflammatory mediators such as cytokines, arachidonate metabolites, and vasoactive and thrombogenic agents. These different mediators are involved in the pathogenesis of organ dysfunction in sepsis [13]. Among various mediators, tumor necrosis factor appears to play the predominant role in septic AKI [14].

The cardiovascular system is also frequently involved in sepsis and is always affected by septic shock. Cardiovascular dysfunction in sepsis is associated with a

significantly increased mortality rate of 70% - 90%, compared to 20% in patients without cardiovascular impairment [15]. Many mediators and pathways have been implicated in the pathogenesis of septic myocardial depression, but the precise etiopathogenesis remains unclear [16]. Echocardiographic studies have shown impaired left ventricular systolic and diastolic function in septic patients [2]. In our patients, impaired LVEF was found in 48% of cases.

Many other studies have confirmed decreased contractility and impaired myocardial compliance in sepsis [17]. Global or segmental hypokinesia is found in 65% of our patients with type 5 CRS, consistent with the literature. Septic cardiac dysfunction is multifactorial. Similar to septic AKI, ischemia and inflammatory mediators are the main culprits. Global myocardial ischemia was initially postulated as the main mechanism of cardiac dysfunction, but it was later shown that septic patients had high coronary blood flow and decreased oxygen difference between the coronary artery and coronary sinus [18].

Other experiments have suggested the possibility of myocardial hypoxia caused by alterations in coronary blood flow. In patients with underlying coronary artery disease, myocardial ischemia is exacerbated [19]. Inflammatory mediators also play a key role in the pathogenesis of cardiac dysfunction. Tumor necrosis factor and interleukin-1 are the main culprits [20].

The mortality rate for sepsis-induced AKI is high, around 70%, while the mortality rate for AKI alone is 40% - 45% [21]. Although the presence of multiple organ dysfunction and other comorbidities contributes to the high mortality rate, AKI independently increases morbidity and mortality [22]. The mortality rate of our patients is 36%, which is lower than reported in the literature.

7. 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.

8. Conclusion

In conclusion, in our study, the prevalence of type 5 CRS is 46%. The etiology of acute type 5 CRS is dominated by sepsis, whereas chronic type 5 CRS is dominated by diabetes and hypertension. The risk factors for mortality associated with type 5 CRS are primarily acute type 5 CRS, prolonged stays in CICU, and the use of RRT.

Conflicts of Interest

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

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