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Original Article

ORIGINAL ARTICLE

Multidisciplinary approach to patients with heart failure and kidney disease: preliminary experience of an integrated cardiorenal unit

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ABSTRACT

Background. Cardiorenal programs have emerged to improve the management of cardiorenal disease (CRD). Evidence about the benefits of these programs is still scarce. This work aims to evaluate the performance of a novel cardiorenal program and describe the clinical profile and outcomes of patients with CRD.

Methods. We conducted a retrospective observational study of patients with CRD attended in a cardiorenal unit (CRU) from February 2021 to February 2022. Demographics and laboratory tests were collected and events (all-cause death and cardiovascular hospitalizations) were evaluated. Optimization of comorbidities and protective therapies was also assessed.

Results. Eighty-two patients were included, with a mean age of 76.8 years [standard deviation (SD) 8.5] and 72% were men. A total of 58.5% ($n = 47$) had left ventricular ejection fraction <50%. The mean follow-up was 11 months (SD 4.0). Almost 54% of the patients ($n = 44$) required hospitalization, 30.5% for heart failure (HF) decompensation. Total hospitalizations significantly decreased after CRU inclusion: 0.70 versus 0.45 admissions/year ($P < .02$). Global mortality was 17.1% ($n = 14$). The percentage of patients with HF with reduced ejection fraction on quadruple therapy increased by 20%, and up to 60% of the patients were on three drugs. A total of 39% of the patients with HF and preserved ejection fraction started treatment with sodium–glucose co-transporter inhibitors. Hyperkalaemia required the use of potassium binders in 12.2% of the patients and treatment of secondary hyperparathyroidism was started in 42.7% and renal anaemia in 23.2%. Renal replacement therapy was initiated in 10% of the patients ($n = 8$).

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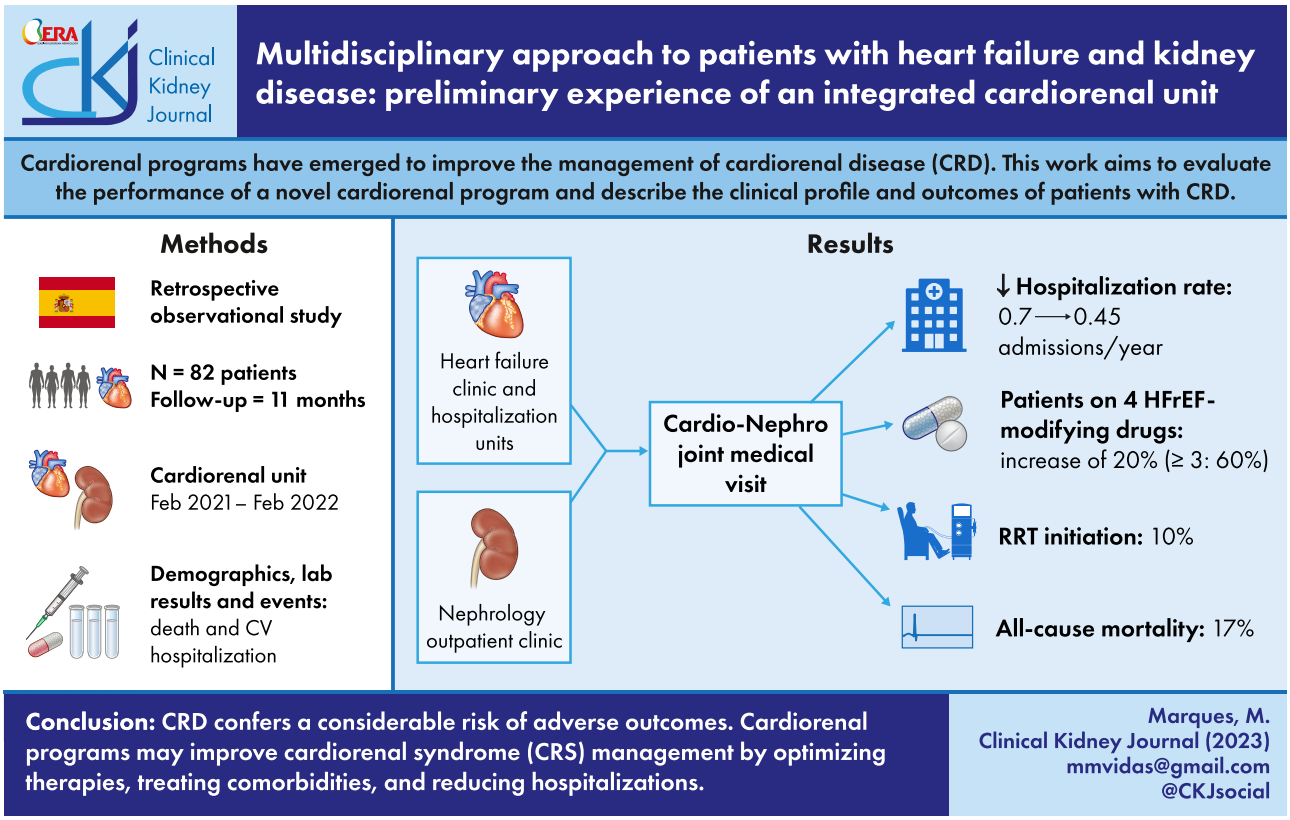
Conclusion. CRD confers a considerable risk of adverse outcomes. Cardiorenal programs may improve cardiorenal syndrome management by optimizing therapies, treating comorbidities and reducing hospitalizations.

LAY SUMMARY

This article describes the structure and the initial achievements of a recently created multidisciplinary unit focused on the management of cardiorenal patients with a high degree of complexity. Eighty-two patients were included in this analysis, with a mean follow-up of 11 months. Low estimated glomerular filtration rate, diuretic resistance or inexplicable worsening of renal failure were the main reasons for referral. This unit's main achievements were optimizing cardio- and nephroprotective therapies, managing diuretic resistance, treating chronic kidney disease comorbidities and planification of renal replacement therapy when indicated. This combined approach has led to significant benefits in terms of hospitalization rates and stability in renal function, with a low rate of patients initiating dialysis.

GRAPHICAL ABSTRACT



Keywords: cardiorenal syndrome, cardiorenal units, chronic kidney disease, heart failure, therapy optimization

INTRODUCTION

Chronic kidney disease (CKD) is one of the most prevalent comorbidities in patients with heart failure (HF): up to 50% of chronic heart failure (CHF) patients develop CKD to some degree [1]. In addition, concomitant heart and kidney disease encompass a bidirectional relationship associated with a high burden of comorbidities that worsens prognosis [2, 3] and may complicate the implementation of therapies, with a significant impact on prognosis [4].

In 2008, Ronco *et al.* [5] defined and categorized this correlation under the term cardiorenal syndrome (CRS), differentiating five types. Type 1 CRS reflects an abrupt worsening of cardiac function leading to acute kidney injury, type 2 CRS comprises chronic abnormalities in cardiac function causing progressive CKD, type 3 CRS consists of an abrupt worsening of renal function causing acute cardiac dysfunction, type 4 CRS describes a state of CKD contributing to decreased cardiac function, cardiac hypertrophy and/or an increased risk of adverse cardiovascular events and type 5 CRS reflects a systemic condition (e.g. sepsis) causing both cardiac and renal dysfunction [5]. Despite the close relationship between heart and kidney diseases, the follow-up of most of these patients is fragmented, being CRS types 1 and

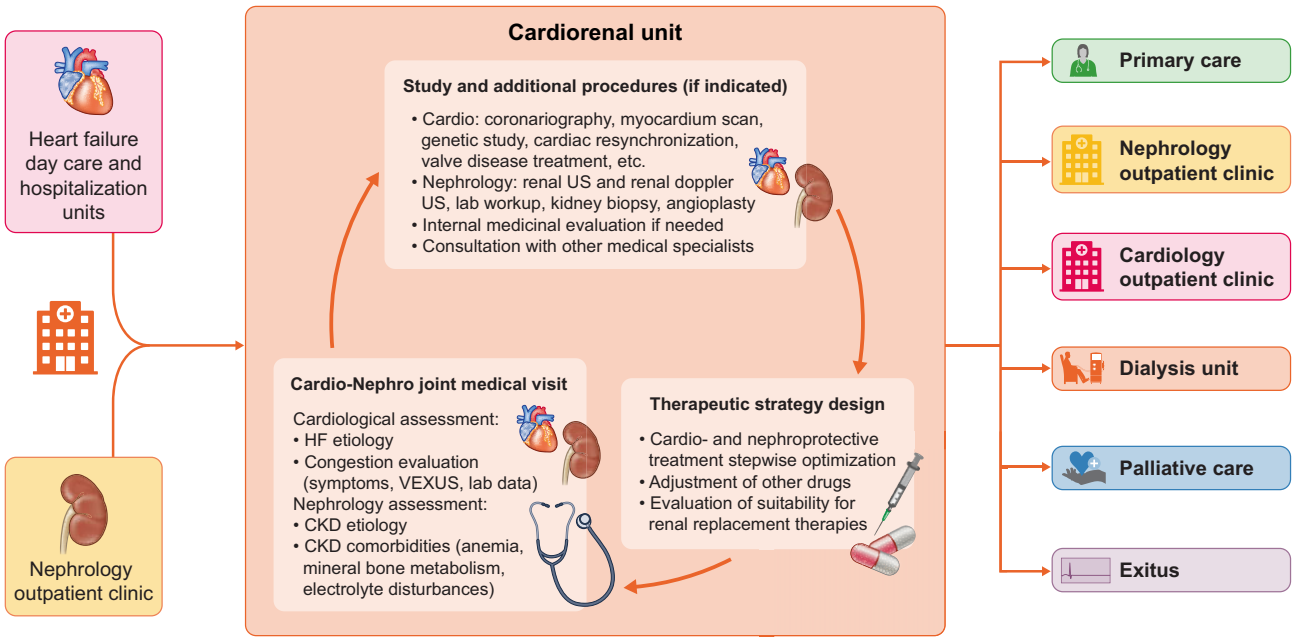


Figure 1: Flowchart of the CRU process with a general description of patient transitions.

2 managed by cardiologists and CRS types 3 and 4 managed by nephrologists [6].

In 2021, the Spanish working groups on cardiorenal disease (CRD) developed a consensus guideline that contains all the requisites needed to ensure the proper development of coordinated and multidisciplinary cardiorenal units (CRUs) [7] with the goal of improving the management of patients with CRS. However, evidence about the benefits of these programs is still scarce [8–11]. In February 2021, Hospital Universitario Puerta de Hierro (HUPH), Madrid, Spain, developed a new CRU. This article aims to describe this unit's structure and performance and analyse patients' characteristics and outcomes.

MATERIALS AND METHODS

The CRU was built on a pre-existing outpatient heart failure clinic, incorporating two nephrologists in a team composed of cardiologists, internal medicine doctors and specialized nurses (Fig. 1). We retrospectively analysed all patients admitted from February 2021 to February 2022. Follow-up time was defined as the time between inclusion in the program and July 2022, with the exception of death or loss to follow-up. Individualized follow-up and care transitions were planned according to the patient's needs.

Demographics, comorbidities and laboratory tests were collected at baseline and during the follow-up [laboratory tests included estimated glomerular filtration rate (eGFR), urine albumin:creatinine ratio (UACR) and haematological tests]. The cause of CKD was determined by referring to the electronic medical records or following the Kidney Disease: Improving Global Outcomes 2012 guidelines for newly diagnosed patients [12].

Mortality and hospitalization events were analysed. Hospitalization rates were compared pre- and post-inclusion in the program. Optimization of cardio- and nephroprotective therapies and treatment of comorbidities, including initiation of renal replacement therapy (RRT) during follow-up, was also assessed.

The Ethics Committee of HUPH reviewed and approved the study (PI 91/23).

Inclusion criteria were CHF, defined according to current European guidelines [13], and any of the following: CKD stage 4 A1–A3 and stage 3b A2–A3 [eGFR by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation <30 ml/min/1.73 m^2 or eGFR 30–44 ml/min/1.73 m^2 and UACR >30 mg/g] [14]; diuretic resistance, defined as the persistence of congestion despite treatment with 80 mg of furosemide [15, 16] and worsening of renal function of unknown aetiology not attributable to depletive therapy.

Exclusion criteria were kidney or heart transplant patients or patients on dialysis at the moment of CRU admission.

The primary endpoint of the study was to analyse the clinical impact of a multidisciplinary approach on CRS patients. Clinical profiles and therapeutic interventions were analysed; renal outcomes were assessed by changes in eGFR and UACR between baseline and the final visit. eGFR slope and the incidence of initiation of RRT were also explored. Finally, we assessed mortality, hospital admissions and changes in hospitalization rates pre- and post-CRU inclusion.

Statistical analysis

Quantitative variables with normal distribution are expressed as mean and standard deviation (SD), otherwise they are expressed as median and interquartile range (IQR). Categorical variables are expressed as percentages.

Student's *t*-test for paired samples, the sign test to equality of matched pairs and chi-squared or rank tests were used to compare groups according to variable characteristics. Hospitalization rates were estimated monthly by dividing the number of events by the total follow-up time.

Cox regression models were used to evaluate the hazard ratio for composite outcomes (death or cardiovascular admission). Models were examined using a uni- and

multivariate analysis in a stepwise backward analysis with *P*-values of 0.10 and 0.20. Variables with *P*-values <0.1 on univariate analysis were considered for inclusion in the multivariate model; others were selected based on prior knowledge/biological plausibility, independent of the *P*-value. The variables age, sex, diabetes mellitus, HF ejection fraction, alcohol or tobacco consumption, furosemide dose, N-terminal pro-brain natriuretic peptide (NT-proBNP), eGFR and transferrin saturation index (TSI) were analysed. A variable was considered confounding when a change >10% was generated in the full model. eGFR slopes were estimated by linear mixed models, using several measurements of eGFR (at baseline, 6 months, 12 months and the last visit).

Data processing and analysis were performed using Stata version 14 (StataCorp, College Station, TX, USA). *P*-values <.05 were considered statistically significant.

RESULTS

Patients' characteristics

After a mean follow-up of 11 months (SD 4.0), 82 patients were included [mean age 76.8 years (SD 8.5), 72% males]. The baseline characteristics of the 82 patients included are summarized in Table 1.

The clinical profile of our cohort represents a high-risk population with advanced age, low eGFR, a high need for diuretics and a significant burden of comorbidities, including a very high prevalence of atrial fibrillation. Almost half of the patients [45% ($n = 37$)] had a left ventricular ejection fraction (LVEF) ≤40%. Fourteen patients (17%) presented HF with mildly reduced ejection fraction (41–49%). The aetiology of CHF is shown in Table 1. Remarkably, ischaemic and valvular heart disease were responsible for HF in >50% of the patients. In fact, a high percentage of tricuspid regurgitation (71%) and echocardiographic signs of pulmonary hypertension (49%) were found (Table 1).

The median furosemide dose was 85 mg (IQR 40–160); 69.5% ($n = 57$) of the patients took >80 mg of furosemide and 34% of them needed thiazides (33%) and acetazolamide (13%) to avoid fluid overload.

A careful review of the electronic medical records revealed that 63 patients (76.8%) had CKD before HF debut and could be considered type 4 CRS according to Ronco's classification. Diabetes mellitus and vascular/nephroangiosclerosis were the most frequent renal diagnoses. The remaining 19 patients met the criteria of type 2 CRD.

Table 1: Demographic characteristics of patients (N = 82) and lab data (congestion indicators or quality indicators of HF) in the CRU

Variables	Values
Demographics and medical history	
Age (years), mean (SD)	76.8 (8.5)
Male, *n* (%)	59 (72)
Smoker/former smoker, *n* (%)	2 (2.4)/46 (56.1)
Alcohol abuse/previous alcohol abuse, *n* (%)	6 (7.3)/9 (11.0)
Diabetes mellitus, *n* (%)	44 (53.7)
Dyslipidaemia, *n* (%)	48 (58.5)
Hypertension, *n* (%)	74 (90.2)
Ischaemic cardiomyopathy, *n* (%)	35 (42.7)
Pulmonary hypertension, *n* (%)	40 (48.8)
Atrial fibrillation, *n* (%)	64 (78)
LVEF, *n* (%)	
≥50	31 (37.8)
41–49	14 (17.1)
≤40	37 (45.1)
HF aetiology, *n* (%)	
Ischaemic aetiology	25 (30.4)
Valvular heart disease	20 (24.4)
Idiopathic dilated cardiomyopathy	10 (12.1)
Hypertensive cardiomyopathy	7 (8.5)
Amyloidosis	4 (4.8)
Idiopathic HFpEF	4 (4.8)
Tachymiocardiopathy	3 (3.6)
Enolic dilated cardiomyopathy	3 (3.6)
Other	6 (7.3)
CKD aetiology, *n* (%)	
Diabetic	34 (41.5)
Vascular/nephroangiosclerosis	11 (13.4)
Cardiorenal disease syndrome type 2	19 (23.1)
Other	18 (22.0)
Laboratory data	
eGFR (ml/min/1.73 m^2), mean (SD)	32.5 (12.3)
Ferritin (mg/dl), median (IQR)	168 (79–387)
TSI (%),mean (SD)	17 (20.8%)
NT-proBNP (pg/ml), median (IQR)	2714 (1560–6378)
Albuminuria (UACR) (mg/dl), median (IQR)	14.2 (0–47.6)
Baseline treatment	
Diuretic, *n* (%)	79 (96.3)
Furosemide (mg), median (IQR)	85 (40–160)
Combination diuretic therapy, *n* (%)	28 (34)
SGLT2i, *n* (%)	21 (25.6)
ACEi/ARB, *n* (%)	14 (17.1)
Sacubitril–valsartan, *n* (%)	29 (35.4)
MRA, *n* (%)	5 (6.1)
Beta-blocker, *n* (%)	58 (70.7)

ACEi: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; LVEF: left ventricular ejection failure; MRA: mineralocorticoid receptor antagonist.

CRU process

The main reason for referral according to renal disease status was an eGFR <30 ml/min/1.73 m^2 (48.8%), FG ≤60 and diuretic resistance (31.7%), worsening of renal function with eGFR ≤60 ml/min/1.73 m^2 (14.6%) and other causes (4.6%).

Three patients were diagnosed with renal arterial stenosis after a complete workup for diagnosis of kidney disease. Percutaneous transluminal renal angioplasty with stent placement was successfully performed in all three patients.

The number of visits to the unit ranged from one to four. A total of 27 patients (33%) were discharged from the CRU: 17 to the outpatient clinic, 8 initiated RRT, 1 was transferred to another centre and 1 was lost the follow-up.

Therapeutic interventions

Fig. 2 shows the implementation of cardio- and nephroprotective therapies along the CRU process in heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF) patients. The optimization rate, considered as the percentage of HFrEF patients who were in the four pharmacological groups with proven cardio- and nephroprotective effects, was increased by 20%, but almost 60% of the patients had at least three drugs. In HFpEF patients, optimization, considered as the percentage of sodium–glucose co-transporter-2 inhibitor (SGLT2i) use, was 39% by the end of follow-up. The limitations to therapy optimization were symptomatic hypotension, low eGFR,

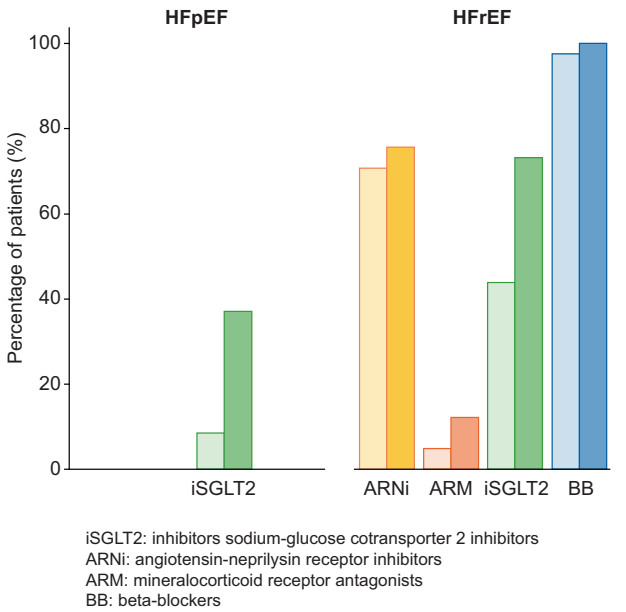


Figure 2: Cardio- and nephroprotective therapies (percentage of patients) at CRU inclusion (left bar) and at the end of follow-up (right bar) according to heart failure ejection fraction.

gastrointestinal side effects or active severe genital or urinary tract infection. Adjustments on diuretic therapy were the most common intervention, with 83.0% in HFrEF and 84.9% in HFpEF patients.

Several pharmacological therapies directed against CKD comorbidities were initiated in the CRU process. Hyperkalaemia required the use of potassium binders (patiromer or zirconium cyclosilicate) in 12.2% of the patients. Treatment with any hyperparathyroidism therapy was started in 42.7% of patients. Iron repletion improved, with 54.9% of patients having a TSI >20% at the end of follow-up. Erythropoietin-stimulating agents were started in 23.2% of patients.

RRT initiation

One of the main goals of our unit is to anticipate the indication for RRT while the patient is in a steady state, although the initiation of RRT is not immediately necessary. Twenty-one patients were considered for RRT because of low eGFR or diuretic resistance. Eight of them were excluded. Haemodynamic intolerance excluded haemodialysis (HD) as a RRT in all of them. Also, peritoneal dialysis (PD) was not considered due to comorbidities such as previous major abdominal surgery ($n = 7$) or inability of the patient to adhere to RRT ($n = 1$). RRT was initiated in 9.8% of patients ($n = 8$), six on PD and 2 on HD. A total of 14% of patients who met the criteria of diuretic resistance started dialysis. The other five patients were optimized without the need for RRT.

Outcomes

The mean eGFR and UACR did not show significant changes (Fig. 3). The mean monthly slope had as a decrease of 0.12 ml/min/1.73 m^2 [95% confidence interval (CI) −0.15–0.39], which is equivalent to an annual rate of 1.72 ml/min/1.73 m^2 (95% CI −2.28–5.72) (Fig. 4). Additional laboratory data assessing congestion and iron status are shown in Table 1.

Forty-four patients (53.7%) required hospitalization, 30.5% for HF decompensation. Some patients suffered several hospital admissions: the mean number of admissions was 1.4 (range 1–4) for HF and 1.8 (1–5) for any other cause.

Seven patients were referred to the CRU after their first HF hospital admission. In the remaining 75, the pre- and post-CRU HF hospitalization rate significantly decreased: 0.70 versus 0.45 admissions/year ($P < .018$). Reducing the follow-up period to 6 months before and after CRU admission showed an even more significant reduction in hospitalization rate: 0.09 versus 0.04 admissions/month ($P = .002$).

Global mortality during the total follow-up period was 17.1% (14 patients). The causes of death were cardiovascular ($n = 9$), coronavirus disease 2019 ($n = 2$), cancer ($n = 1$) and multiple organ failure ($n = 2$).

After multivariant adjustment, the most important variables associated with a composited event (death or cardiovascular hospitalization) were age, alcohol abuse, NT-proBNP levels, basal furosemide dose and treatment with angiotensin-converting enzyme inhibitors at baseline (Table 2).

DISCUSSION

Even though scientific statements support the need for a dedicated cardiorenal multidisciplinary team approach, specific cardiorenal care models are still scarce [17]. In a recent study conducted in Spain, only 10% of specialized HF clinics had a specific cardiorenal clinical program and only 30% had established protocols among cardiologists and nephrologists [18]. Along the same line, only a few experiences of a combined cardiorenal approach have been reported [8–11].

In this work, we show that a cardiorenal program is useful to improve renal diagnosis and outcomes of CRD patients, optimize cardio- and nephroprotective therapy in highly complex patients, provide complete CRD-associated comorbidities treatment and define mid- and long-term therapeutic strategies.

The clinical profile of our cohort of patients consists of an elderly population with a high prevalence of risk factors and comorbidities who show some characteristics of advanced HF. In addition, HF aetiology in our population differs from the current aetiologies of cardiac dysfunction. Remarkably, we found that ischaemic and valvular heart disease were responsible for HF in >50% of the patients. This finding may show different clinical profiles of patients with CRD, i.e. patients with a high burden of risk factors and ischaemic disease and patients with valvular disease and diuretic resistance.

Over the last decade, several drugs have shown cardio- and nephroprotective effects in patients with either HF or CKD. SGLT2is, mineral receptor antagonists and renin–angiotensin system inhibitors and angiotensin receptor–neprilysin inhibitors, along with beta-blockers and depletive therapy, have become the pillars of HFrEF therapy [19]. At the same time, SGLT2is are the only pharmacological group with proven prognostic benefit in HFpEF [20]. However, clinical trials have usually excluded patients with severe CKD. Also, as these drugs may induce an initial eGFR decline, clinicians often struggle to initiate or up-titrate these therapies, as any deterioration in kidney function is often perceived as deleterious [21]. In fact, the presence of kidney disease is one of the main reasons for ineffective drug implementation in HF patients [22]. Our experience illustrates how cardiorenal programs facilitate the optimization of disease-modifying therapy, offering a structured and personalized follow-up that helps solve drug-related adverse effects.

Diuretic resistance is another common problem in patients with CRD. Indeed, refractory congestion was the leading cause of referral to our unit. A total of 25% of the patients were

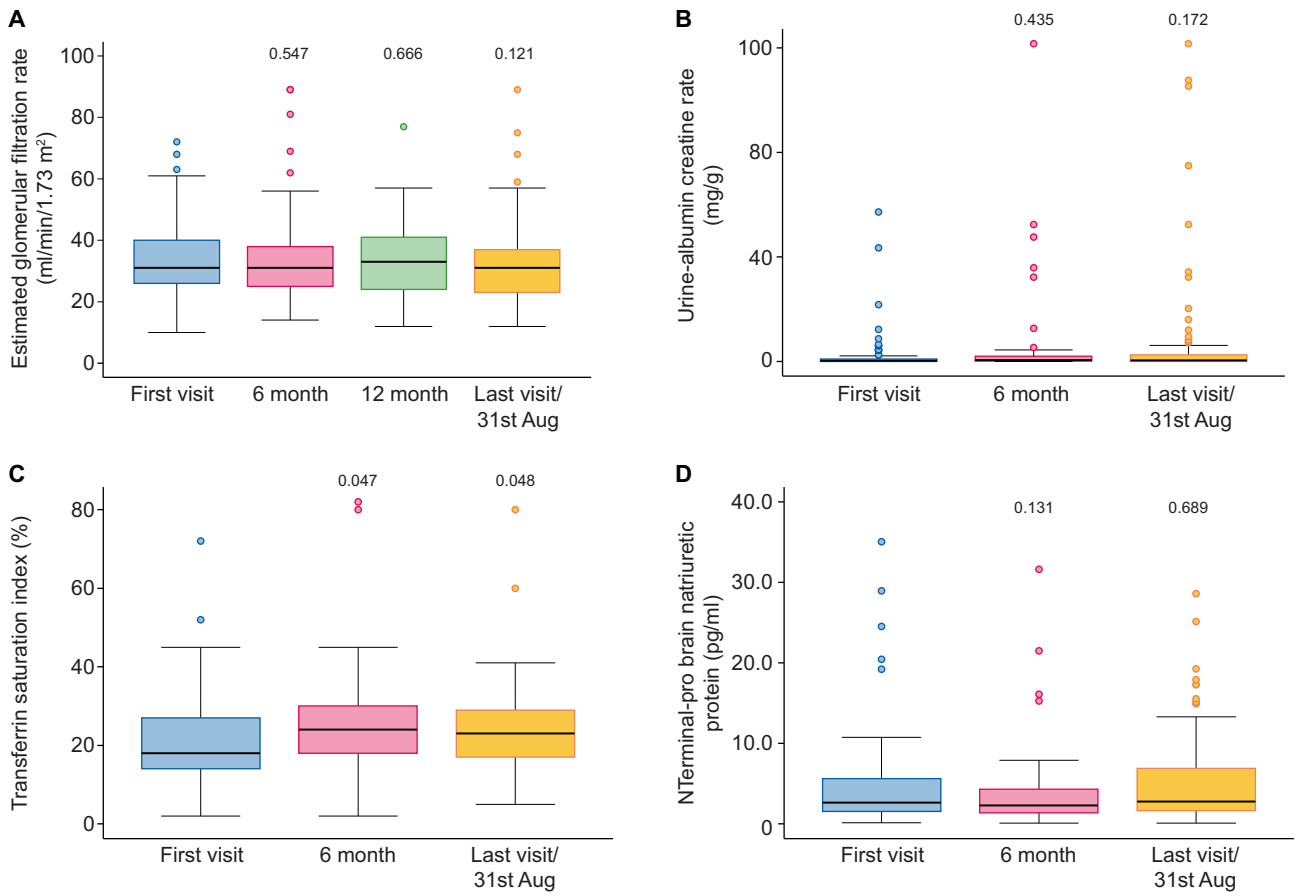


Figure 3: Evolution of **(A)** eGFR (estimated by the CKD-EPI formula), **(B)** UACR, **(C)** TSI and **(D)** NT-proBNP.

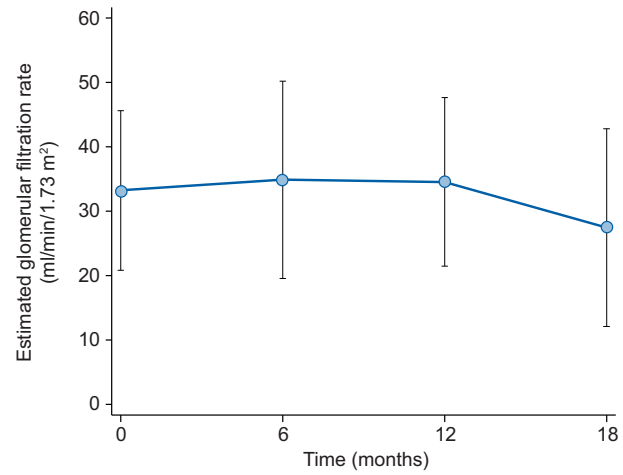


Figure 4: Trajectory of eGFR during the follow-up.

considered for RRT and 9.8% began any type of dialysis. Combined cardiologist and nephrologist management allowed a tailored adjustment of depletive therapy that solved a high proportion of diuretic resistance. Adjustments to diuretic therapy were the most common intervention, and the presence of accessible outpatient care led by specialized nurses allowed the ambulatory management of non-severe HF decompensations.

The use of dialysis to treat diuretic resistance or advanced CKD in CRS is well established in the literature. Still, there is no evidence-based guideline to support the use of a specific type of RRT, time for initiating RRT or even the benefit of initiating RRT versus conservative therapy in CRS [23]. In CHF, PD has been classically preferred [24], however, it requires some planning (catheter placement, healing and patient training) and CRS patients have frequent decompensation episodes that interfere with this process. In our CRU, RRT was planned pre-emptively. This novel approach allows evaluating the RRT indication in a steady state and facilitates the decision-making process in case of hospitalization.

A systematic approach to the specific CKD comorbidities of patients with CRD is mandatory for holistic management of the disease. Optimization therapy in patients with anaemia, with 40% of the patients receiving intravenous iron therapy and 23% erythropoietin-stimulating agents, led to an improvement in the management of CKD-associated anaemia. Also, assessment of mineral and bone disorders is often overlooked in the cardiology clinic. In our series, 42% of patients had to initiate secondary hyperparathyroidism treatment.

This comprehensive and coordinated clinical approach aims to improve patient outcomes and quality of life. Randomized trials evaluating the benefits of these models of care are ethically difficult to conduct. Assessing outcomes before and after the intervention is one way to evaluate the performance of the CRU.

Patients with CRD have a high risk of hospitalization and death [2, 3]. Previous data from cardiorenal patients report

Table 2: Cox regression for combined event (death or cardiovascular admission)

	Univariate			Multivariate		
Variables	HR	P-value	95% CI	HR	P-value	95% CI
Age	1.04	0.104	0.99–1.09	1.08	0.014	1.01–1.14
Male	0.9	0.778	0.43–1.89			
HFrEF	1.26	0.533	0.61–2.59			
Alcohol abuse	1.56	0.306	0.67–3.63	3.49	0.012	1.32–9.26
Smoking	0.96	0.902	0.47–1.95			
TSI	0.98	0.242	0.95–1.01			
NT-proBNP levels	1.00	<0.001	1.00–1.00	1.00	0.002	1.00–1.00
eGFR	0.97	0.046	0.94–1.00			
Basal furosemide dose	1.01	<0.001	1.00–1.02	1.01	<0.001	1.00–1.02
Hypertension	1.86	0.395	0.44–7.82			
Diabetes mellitus	1.11	0.758	0.56–2.22			
SGLT2i at baseline	0.49	0.052	0.24–1.01			
ARNI at baseline	0.57	0.305	0.2–1.66			
Beta-blockers at baseline	0.62	0.203	0.3–1.29			
ACEi at baseline	0.96	0.938	0.37–2.5	3.0	0.047	1.01–8.83
MRA at baseline	1.56	0.547	0.37–6.6			

ARNI: angiotensin receptor–neprilysin inhibitor; ACEi: angiotensin-converting enzyme inhibitor; HR: hazard ratio; MRA: mineralocorticoid receptor antagonist.

hospitalization rates similar to ours [25]. However, to the best of our knowledge, this is the first experience that shows a significant decrease in the rate of hospitalizations after the inclusion in a cardiorenal program.

Finally, termination of CRU process by referral of stable CRS patients to conventional cardiology and the nephrology outpatient clinics has allowed the maintenance of specialized management of CRS patients according to pre-specified strategies and shown the sustainability of the model.

LIMITATIONS

Our study has several limitations that need to be highlighted: the present study is observational in nature and, consequently, is exposed to different types of bias and residual confounding; our cohort consisted of 82 patients from one academic institution, so our findings may not be generalizable to the broader cardiorenal population; referral to the CRU was restricted to selected patients, so our results may not be reproducible; the lack of a control group is an important limitation, however, the absence of reported results of units similar to ours justify the relevance of this article; given the retrospective nature of the study, some parameters of interest have not been collected; and there is an absence of specific criteria to define in-hospital diuretic resistance. Although we preliminarily established a published definition of the need for 80 mg of furosemide, patients referred to our unit for refractory congestion were on high doses of loop diuretic and combination therapy. Finally, hospitalization rates were estimated before and after the intervention, so we cannot rule out that something other than the intervention may have contributed to the decrease in hospitalizations.

CONCLUSIONS

CRD confers a high risk of adverse outcomes. Multidisciplinary cardiorenal programs may improve CRS management by optimizing cardio- and nephroprotective therapies, managing HF and CKD comorbidities, including planification of RRT when required, and reducing hospitalizations.

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DATA AVAILABILITY STATEMENT

The data underlying this article will be shared upon reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest related to this article. The results presented in this article have not been published previously in whole or part, except in abstract format.

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