# La importancia primordial de la disfunción renal en el pronóstico de la insuficiencia cardíaca - Resultados del estudio REFERENCE

## *The Paramount Importance of Renal Dysfunction in Heart Failure Prognosis - Results from the REFERENCE study*

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## ABSTRACT

**Aims:** In heart failure patients renal dysfunction represents impaired tissue perfusion. We investigated the association of customarily used renal function parameters with short-term prognosis in patients admitted with acute decompensated heart failure in class III or IV of New York Heart Association.

**Material and Methods:** Univariate Cox proportional hazard model was used to assess the relationship between variables and outcomes. Survival curves were designed using the Kaplan-Meier method.

**Results:** We followed 65 patients for a median of 13.7 (Q1-Q3 6.7-18.9) months. Variables associated with an increased risk for short-term rehospitalization were baseline urea (HR: 1.098, 95% CI: 1.022-1.179, P-value=0.01), admission urea (HR: 1.048, 95% CI: 1.013-1.084, P-value=0.006), baseline creatinine (HR: 1.111, 95% CI: 1.004-1.229, P-value=0.041), admission creatinine (HR: 1.047, 95% CI: 1.005-1.092, P-value=0.027) and admission glomerular filtration rate <30 mL/min (HR: 3.535, 95% CI: 1.467-8.518, P-value=0.005).

Increased risk for short-term mortality was associated with baseline urea (HR: 1.145, 95% CI: 1.032-1.270, P-value=0.010), admission urea (HR: 1.076, 95% CI: 1.021-1.135, P-value=0.006), baseline creatinine (HR: 1.157, 95% CI: 1.009-1.328, P value=0.037), admission creatinine (HR: 1.127, 95% CI: 1.055-1.204, P-value<0.001) and admission glomerular filtration rate <30 mL/min (HR: 9.791, 95% CI: 2.855-33.580, P-value<0.001).

Variables associated with an increased risk for end of follow-up mortality were admission urea (HR: 1.056, 95% CI: 1.019-1.094, P-value=0.003), admission creatinine (HR: 1.104, 95% CI: 1.054-1.156, P- value<0.001) and admission glomerular filtration rate <30 mL/min (HR: 3.906, 95% CI: 1.7208.871, P- value=0.001).

**Conclusion:** Renal dysfunction was a reliable predictor of worse prognosis as several parameters correlated with short-term prognosis.

**Keywords:** Heart failure; Renal dysfunction; Cardiorenal syndrome; Prognosis.

## RESUMEN

**Introducción:** En la insuficiencia cardíaca, la disfunción renal representa hipoperfusión tisular. Investigamos la asociación entre parámetros utilizados cotidianamente y el pronóstico precoz de enfermos ingresados por insuficiencia cardíaca descompensada en clase III o IV de la New York Heart Association.

**Material y métodos:** Aplicamos el modelo de riesgo proporcional de Univariante Cox y curvas de supervivencia de Kaplan-Meier.

**Resultados:** La mediana de seguimiento de los 65 enfermos fue de 13.7 (Q1-Q3 6.7-18.9) meses. Se correlacionaron con el reingreso precoz la urea basal (HR: 1.098, 95% CI: 1.022-1.179, P-value=0.01), la urea al ingreso (HR: 1.048, 95% CI: 1.013-1.084, P-value=0.006), la creatinina basal (HR: 1.111, 95% CI: 1.004-1.229, P-value=0.041), creatinina al ingreso (HR: 1.047, 95% CI: 1.005-1.092, P-value=0.027) y la tasa de filtración glomerular <30 mL/min al ingreso <30 mL/min (HR: 3.535, 95% CI: 1.467-8.518, P-value=0.005).

El riesgo de mortalidad precoz se correlacionó con la urea basal (HR: 1.145, 95% CI: 1.032-1.270, P-value=0.010), la urea al ingreso (HR: 1.076, 95% CI: 1.021-1.135, P-value=0.006), la creatinina basal (HR: 1.157, 95% CI: 1.009-1.328, P value=0.037), creatinina al ingreso (HR: 1.127, 95% CI: 1.055-1.204, P-value<0.001) y la tasa de filtración glomerular <30 mL/min al ingreso <30 mL/min (HR: 9.791, 95% CI: 2.855-33.580, P-value<0.001).

Se correlacionarón con la mortalidad al final del seguimiento la urea al ingreso (HR: 1.056, 95% CI: 1.019-1.094, P-value=0.003), la creatinina al ingreso (HR: 1.104, 95% CI: 1.054-1.156, P- value<0.001) y la tasa de filtración glomerular <30 mL/min al ingreso (HR: 3.906, 95% CI: 1.7208.871, P- value=0.001).

**Conclusiones:** La disfunción renal fue un predictor de peor pronóstico precoz.

**Palabras clave:** Insuficiencia cardíaca; Disfunción renal; Síndrome cardiorrenal; Pronóstico.

## INTRODUCTION

Despite the diagnostic advances and guideline tailored management, surprisingly, heart failure (HF) short-term prognosis has failed to improve.[1]

Furthermore, HF is the main cause of hospital admissions in Europe and in the United States of America.[2]

The conjunction of its poor short-term prognosis (particularly in the first three months after hospital discharge)[3,4] and extremely high prevalence results in a tremendous social and economic burden.

Heart failure and chronic kidney disease (CKD) are frequently concomitant conditions as they affect an elder population that suffers from multiple pathologies.[5]

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As the incidence and prevalence of HF and CKD are escalating[5], it is of utmost importance to risk stratify such patients.

It is postulated that these conditions aggravate one another in a cyclic fashion causing an increased risk of hospitalization, rehospitalization and death.[6,7]

Renal failure is pointed as a relevant prognosticator in patients suffering from HF[8], as it is believed to be a marker of impaired tissue perfusion.[9]

Hallmark studies[10,11] have established renal dysfunction as a marker of adverse outcome and therefore a crucial topic in Acute Decompensated Heart Failure (ADHF) management.

Bearing this in mind, we assessed the impact of renal dysfunction in HF short-term rehospitalization, short-term mortality and end of follow-up mortality throughout the evaluation of quotidian parameters in order to yield data to risk stratification.

## MATERIAL AND METHODS

### Study design and population

The pREdictors oF Early REadmission iN Chronic hEart failure (REFERENCE) study was an observational prospective cohort, single-center study.

Patients were enrolled consecutively for a period of 12 months from an Internal Medicine ward of a tertiary care academic hospital.

Inclusion criteria were age ≥18 years old and hospitalization due to ADHF in class III or IV of the New York Heart Association (NYHA).

Exclusion criteria were:

1. In-hospital death in the first hospitalization.
2. Hospital discharge against medical advice.
3. Chronic kidney disease patients with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m2 [calculated with the Modification of Diet in Renal Disease (MDRD) score] or under renal replacement therapy.
4. Moderate or severe hepatic impairment (calculated with the Child-Pugh score).
5. Active neoplasm with or without metastasis.

Written informed consent was required for the recruitment. The study was approved by an Institutional Review Board (Academic Medical Center Ethics Committee) and was conducted in light of the Declaration of Helsinki and the Oviedo Convention.

### Protocol and definitions

The diagnosis of HF followed the European Society of Cardiology (ESC) guidelines.[12]

Patient assessment was based on a protocol that included clinical history, physical examination, 12-lead electrocardiogram (ECG), thoracic X-ray, blood sampling for laboratory tests, transthoracic Doppler echocardiography and therapeutic data. A postero-anterior thoracic X-ray was performed with conventional equipment.

A 12-lead ECG was executed using a 3-channel device and its interpretation was based on the American Heart Association Electrocardiography and Arrhythmias Committee criteria.[13]

All echocardiograms M mode, two-dimensional and Doppler were performed by a skilled operator. Echocardiographic values were determined based on the American Society of Echocardiography[14] using a Hitachi Aloka alfa 6 Medical device with a 2.5 MHz transducer.

Biochemical parameters were measured using plasma samples.

Subgroup analysis was performed in accordance to left ventricular ejection fraction (LVEF) following the ESC guidelines.[12]

Glomerular filtration rate was estimated applying the MDRD formula.[15]

Chronic kidney disease was defined according to the Kidney Disease: Improving Global Outcomes (KDIGO) standards[5] and the diagnosis was based on clinical records consultation.

Cardiorenal syndrome type I was defined as an acute worsening of cardiac function leading to acute kidney injury (defined by an increase in serum creatinine of ≥0.3 mg/dL) in accordance to the 7th Acute Disease Quality Initiative Consensus Conference.[16]

### Outcomes

The studied outcomes were short-term rehospitalization, short-term all-cause mortality and end of follow-up all-cause mortality. Short-term rehospitalization was defined as rehospitalization within 90 days of hospital discharge. Short-term mortality was defined as death occurring within 90 days after hospital discharge. End of follow-up mortality was defined as death that occurred during the whole study period.

### Statistical analysis

Categorical variables were summarized by relative and absolute frequencies and compared using the chi-squared test or Fisher's Exact test, as applicable.

Continuous variables were summarized by mean, standard deviation, median, first and third quartiles (Q1-Q3). Shapiro-Wilk test was used to assess the normality of continuous variables. Comparisons between patients with or without an event of interest were performed using the t-test or Wilcoxon Rank test, as applicable. Short-term rehospitalization, short-term mortality and end of follow-up mortality were considered as stratification variables.

A survival analysis was performed for the events of interest including short-term rehospitalization, short-term mortality and end of follow-up mortality. For each endpoint, Kaplan-Meier survival estimates were calculated and plotted for each categorical variable. Log-rank tests were used to compare survival probabilities in each of the considered variables.

A univariate Cox proportional hazards model was fitted to the data to obtain hazards ratio (HR) and 95% Confidence Interval (CI) for each variable. The proportional hazards assumption was tested using Schoenfeld residuals. All analyses were conducted at an overall significance level of 5%. No adjustments for multiplicity were performed.

## RESULTS

In total, 70 patients were recruited, of which 5 were excluded as they were diagnosed with active neoplasm. The remaining 65 participants were followed for a median (Q1-Q3) of 13.7 (6.7-18.9) months.

The mean (SD) age of the study population was 79.2 (10.8) years, 56.9% were female and the mean (SD) LVEF was 50.4 (19.1)%.

A 90-day post-discharge readmission percentage of 33.8% was documented and the 90-day mortality was 18.5%. By the end of follow-up 40% of the patients had died.

Chronic kidney disease was a prevalent prior (52.3%) and the majority (53.8%) of the patients developed Cardiorenal Syndrome (CRS).

The median baseline eGFR of the population study was 57.8 mL/min and median admission eGFR was 47.9 mL/min.

As for urea, the median baseline value was 47 mg/dL and the median admission value was 64 mg/dL.

The median baseline creatinine was 1 mg/dL and 1.3 mg/dL for median admission values.

Baseline characteristics are shown in Table 1.

Chronic kidney disease was more prevalent in patients with short-term mortality compared to those who survived the first 90 days post-discharge (P-value=0.024).

The incidence of CRS was more than twice as superior in the short-term mortality group compared to those who survived that period of time (P-value=0.004), likewise those who died during follow-up suffered more frequently from CRS (P-value=0.011).

Descriptive analysis regarding CKD and CRS is presented in Table 2 and baseline analysis regarding LVEF by outcome is represented in Table 3.

### Short-term rehospitalization

The hazard for short-term rehospitalization increased 9.8% per 5 mg/dL increment of baseline urea (HR: 1.098, 95% CI: 1.022-1.179, P-value=0.01) and 4.8% per 5 mg/dL increment of admission urea (HR: 1.048, 95% CI: 1.013-1.084, P-value=0.006).

An association between elevated baseline creatinine and short-term readmission was acknowledged (HR: 1.111, 95% CI: 1.004-1.229, P-value=0.041), the risk augmented 11.1% per 0.1 mg/dL increment of creatinine. Regarding admission creatinine, the risk for short-term readmission augmented 4.7% per 0.1 mg/dL increment of creatinine (HR: 1.047, 95% CI: 1.005-1.092, P-value=0.027).

Short-term readmission hazard increased 3.5 times for patients with admission eGFR <30 mL/min (HR: 3.535, 95% CI: 1.467-8.518, P-value=0.005).

Figure 1 represents Kaplan Meier survival curves regarding short-term rehospitalization and admission eGFR <30 mL/min.

Table 1. Baseline characteristics

| *CHARACTERISTICS* | *PATIENTS (N=65)* |
|---|---|
| Age, mean (SD) | 79.2 ± 10.8 |
| Female Gender, n (%) | 37 (56.9) |
| Hypertension, n (%) | 58 (89.2) |
| Type 2 Diabetes, n (%) | 25 (38.5) |
| Dyslipidemia, n (%) | 41 (63.1) |
| Obesity, n (%) | 17 (26.2) |
| Atrial Fibrillation, n (%) | 28 (43.1) |
| Family History of CVD, n (%) | 31 (47.7) |
| Ischemic Heart Disease, n (%) | 22 (33.8) |
| Anemia, n (%) | 38 (58.5) |
| Iron deficiency, n (%) | 30 (46.2) |
| Chronic Kidney Disease, n (%) | 34 (52.3) |
| eGFR (Baseline), median | 57.8 (43.8 - 82.2) |
| eGFR (Admission), median | 47.9 (33.2 - 68.1) |
| Urea (Baseline), median | 47.0 (35 - 76) |
| Urea (Admission), median | 64.0 (38 - 97) |
| Creatinine (Baseline), median | 1.0 (0.8 - 1.4) |
| Creatinine (Admission), median | 1.3 (1.0 - 1.8) |
| Cardiorenal Syndrome, n (%) | 35 (53.8) |
| LVEF, mean (SD) | 50.38 ± 19.07 |
| NYHA class III, n (%) | 43 (66.2) |
| ACE Inhibitor, n (%) | 43 (66.2) |
| Beta Blocker, n (%) | 38 (58.5) |
| Mineralocorticoid Receptor Antagonists, n (%) | 19 (29.2) |
| Angiotensin II Receptor Blocker, n (%) | 11 (16.9) |
| Loop Diuretic, n (%) | 54 (83.1) |
| Digoxin, n (%) | 8 (12.3) |

Values are median (IQR), n (%), or mean ± SD.
IQR: interquartile range and minimum/maximum.
SD: standard deviation.
CVD: cardiovascular disease.
eGFR: estimated glomerular filtration rate.
LVEF: left ventricular ejection fraction.
NYHA: New York Heart Association.
ACE: Angiotensin-Converting-Enzyme.

### Short-term mortality

With reference to short-term mortality both baseline and admission urea were predictors of risk (HR: 1.145, 95% CI: 1.032-1.270, P-value=0.010, determining a 14.5% additional risk per increments of 5 mg/dL and HR: 1.076, 95% CI: 1.021-1.135, P-value=0.006, implicating a 7.6% increased risk per increments of 5 mg/dL, respectively).

As for baseline creatinine for each 0.1 mg/dL increment the risk for short-term mortality augmented 15.7% (HR: 1.157, 95% CI: 1.009-1.328, P value=0.037), for the same amount of increase of admission creatinine the risk augmented 12.7% (HR: 1.127, 95% CI: 1.055-1.204, P-value<0.001) for the population study.

Table 2. Descriptive analysis regarding Chronic Kidney Disease and Cardiorenal Syndrome

| Characteristics | Short-term rehospitalization | | Short-term mortality | | End of follow-up mortality | |
|---|---|---|---|---|---|---|
| | No (N = 43) | Yes (N = 22) | No (N = 54) | Yes (N = 11) | No (N = 38) | Yes (N = 27) |
| Chronic kidney disease, n (%) | 20 (46.5) [43] | 14 (63.6) [22] | 25 (46.3) [54] | 9 (81.8) [11] * | 19 (50.0) [38] | 15 (55.6) [27] |
| Cardiorenal syndrome, n (%) | 21 (48.8) [43] | 14 (63.6) [22] | 25 (46.3) [54] | 11 (100.0) [11] *** | 16 (42.1) [38] | 19 (70.4) [27]* |

N, number of subjects included in the study; [n], number of subjects with the characteristic.
*p*-value: * < 0.05; ** < 0.01; *** < 0.001

Subgroup analysis showed that for short-term mortality, regarding heart failure with reduced ejection fraction (HFrEF) patients, the risk augmented 15.1% per 0.1 mg/dL increment of admission creatinine (HR: 1.151, 95% CI: 1.010-1.311, P- value=0.034).

Baseline comparison of subjects by short-term mortality status regarding admission creatinine is depicted in Figure 2.

Admission eGFR <30 mL/min increased the likelihood of short-term mortality 9.8 times in the entire population study (HR: 9.791, 95% CI: 2.855-33.580, P-value<0.001) and the risk rose up to 14.8 times in the HFrEF subgroup (HR: 14.783, 95% CI: 1.267-172.493, P-value=0.032).

Kaplan-Meier survival curves were performed to compare patients with and without CRS. As illustrated in Figure 3, the rate of short-term mortality was significantly higher for patients admitted with CRS (P-value=0.0013).

### End of follow-up mortality

On the subject of end of follow-up mortality, admission urea elevated the hazard 5.6% per increments of 5 mg/dL (HR: 1.056, 95% CI: 1.019-1.094, P-value=0.003) in the total population study and in the HFrEF subgroup the risk increased 10.5 % (HR: 1.105, 95% CI: 1.037-1.177, P value=0.002).

In the HFrEF, end of follow-up mortality risk increased 13.2% per increments of 5 mg/dL of baseline urea (HR: 1.132, 95% CI: 1.004-1.276, P value=0.042).

With regard to admission creatinine, end of follow-up mortality risk raised 10.4% per increments of 0.1 mg/dL (HR: 1.104, 95% CI: 1.054-1.156, P-value<0.001) in the general population study, whereas in the subgroup of heart failure with preserved ejection fraction (HFpEF) the risk for this end-point was inferior, as it augmented only 8% (HR: 1.080, 95% CI: 1.007-1.159, P-value=0.032) and in the HFrEF subgroup the risk was greatest, since it increased 14.8% (HR: 1.148, 95% CI: 1.051-1.253, P-value=0.002).

Higher admission eGFR decreased end of follow-up mortality hazard approximately 20% per increments of 10 mL/min (HR: 0.788, 95% CI: 0.649-0.957, P-value=0.016) in the general population study. As for the HFrEF subgroup end of follow-up mortality risk diminished 41% per increments of 10 mL/min of admission eGFR (HR: 0.590, 95% CI: 0.365-0.953, P-value=0.031).

Admission eGFR <30 mL/min increased end of follow-up mortality risk 3.9 times (HR: 3.906, 95% CI: 1.7208.871, P- value=0.001) in the general population study, 3.6 times (HR: 3.640, 95% CI: 1.073-12.351, P-value=0.038) in the subgroup of HFpEF and in the HFrEF subgroup a 13 fold augmented risk was verified (HR: 13.387, 95% CI: 2.356-76.075, P value=0.003).

Presenting with CRS determined a 2.6 fold increased risk of end of follow-up mortality in the general population study (HR: 2.582, CI: 1.120-5.950, P-value=0.026) and, as anticipated, the hazard for this outcome was superior for the HFrEF subgroup (HR: 8.567, 95% CI: 1.034-70.981, P-value=0.046).

## DISCUSSION

The association of advanced age, multiple recent HF hospitalizations and CKD, which is common in the HF population, represents a subset of patients expected to evolve with a worse prognosis.[17]

Heart failure and CKD frequently overlap. In fact, the prevalence of HF rises in parallel with the severity of advanced kidney disease, which is elucidative of this bidirectional interrelation.[18]

Cardiorenal syndrome is the paradigm of the indissociable binomium failing heart-renal malfunction.[9] In the particular case of CRS type 1, the deficient forward flow results in prerenal hypoperfusion.[9]

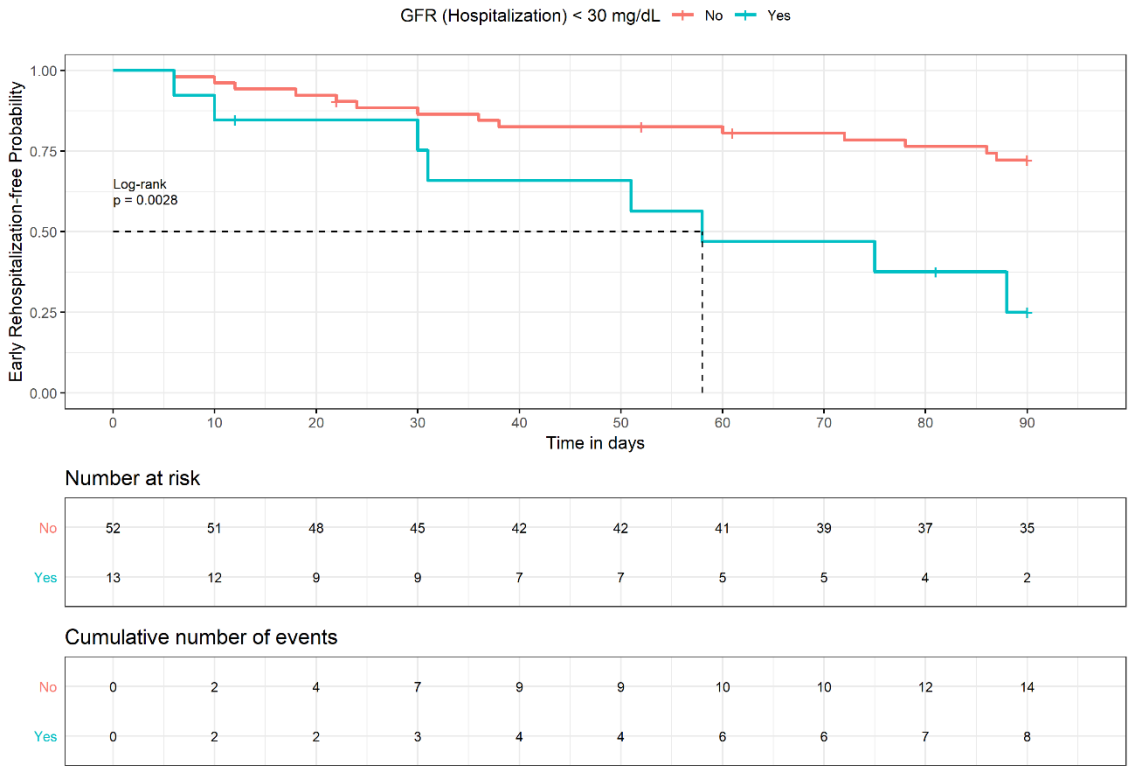
Nevertheless, renal venous congestion and compromised renal autoregulation due to neurohormonal activation also intervene in this frequent ADHF complication.[19]

It is estimated that one third of ADHF patients develop CRS,[20] which portends an adverse prognosis as even discrete decreases in kidney function determine a significant increase in mortality.[10]

The CKD clinical background (hypotension, low GFR, hyperkalemia) leads to the underutilization of HF evidence-based therapy, further compromising the unfavorable outcome.[21]

Renal dysfunction is an indicator of inadequate tissue perfusion which is a cardinal characteristic of the HF syndrome. It is believed that it aggravates congestion and neurohormonal activation, which are well established predictors of poor prognosis in HF.[22,23]

Figure 1. Short-term rehospitalization - Kaplan Meier: Admission eGFR <30 mL/min




The significant burden of comorbidities, namely diabetes, obesity, anemia and iron deficiency are additional risk factors in the pathophysiology of HF in CKD.[5]

Since renal injury plays an important role in the pathogenesis, progression, decompensation and complications of HF, markers of renal dysfunction may be used as clinical risk prediction tools.[10]

The presence of CKD and impaired GFR at admission are predictors of increased rehospitalization and mortality rates in ADHF patients. Importantly, the ESC Heart Failure Long-Term Registry verified that CKD was a predictor of impaired outcome in ADHF in all LVEF groups.[24]

A large scale study performed in the United States of America based on the Nationwide Readmission Database correlated renal failure with short-term HF readmissions.[8]

The PREDICE study, performed in Spain, acknowledged that the severity of renal dysfunction at admission was an independent predictor of increased mortality risk during the first year of follow-up.[25]

The high rates of short-term readmission and mortality documented in our investigation are consistent with other trials[3,4]; remarkably, the risk was further increased in those with renal dysfunction.

Considerable increase of the risk of the proposed outcomes due to marginal decreases in renal function was indeed a relevant finding.

The verified rate of CRS, higher than that reported in some series,[20] makes proof of the severity of the HF cases encompassed by us.

Figure 2. Baseline comparison of subjects by short-term mortality status: Admission creatinine

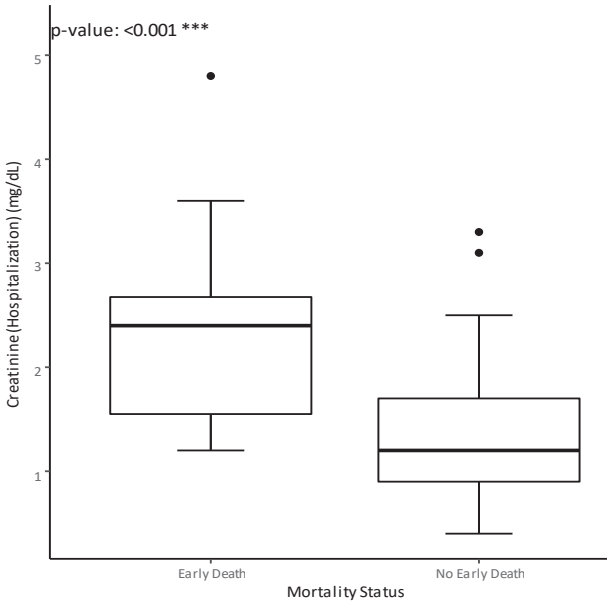


Table 3. Baseline analysis regarding LVEF by outcome

| SHORT-TERM REHOSPITALIZATION | HFREF | | HFMREF | | HFPEF | |
|---|---|---|---|---|---|---|
| Characteristics (n=65) | No | Yes | No | Yes | No | Yes |
| Cardiorenal syndrome (n, %) | 6 (9.7) | 4 (6.5) | 6 (9.7) | 2 (3.2) | 9 (14.5) | 7 (11.3) |
| Ureia (Admission), mg/dL | | | | | | |
| Mean (SD) | 73.10 (51.2) | 122.14 (69.6) | 60.56 (29.9) | 95.75 (85.6) | 60.50 (40.1) | 76.70 (40.1) |
| Median (Min; Max) | 55.50 (29.00; 203.00) | 97.00 (33.00; 244.00) | 50.00 (25.00; 107.00) | 67.50 (30.00; 218.00) | 50.00 (13.00; 187.00) | 70.00 (16.00; 129.00) |
| Ureia (Baseline), mg/dL | | | | | | |
| Mean (SD) | 49.70 (29.3) | 78.43 (26.0) | 49.33 (23.9) | 61.50 (19.1) | 50.91 (25.4) | 59.40 (24.9) |
| Median (Min; Max) | 42.50 (21.00; 119.00) | 78.00 (33.00; 116.00) | 39.00 (25.00; 100.00) | 61.50 (44.00; 79.00) | 47.00 (13.00; 109.00) | 60.50 (25.00; 97.00) |
| Creatinine (Admission), mg/dL | | | | | | |
| Mean (SD) | 1.60 (0.7) | 2.39 (1.4) | 1.41 (0.4) | 1.48 (0.8) | 1.27 (0.7) | 1.59 (0.7) |
| Median (Min; Max) | 1.50 (0.70; 3.10) | 1.70 (1.10; 4.80) | 1.30 (1.00; 2.30) | 1.30 (0.80; 2.50) | 1.10 (0.40; 3.30) | 1.45 (0.60; 2.90) |
| Creatinine (Baseline), mg/dL | | | | | | |
| Mean (SD) | 1.14 (0.4) | 1.36 (0.3) | 1.13 (0.4) | 1.07 (0.4) | 1.00 (0.3) | 1.29 (0.4) |
| Median (Min; Max) | 1.00 (0.70; 1.90) | 1.40 (1.00; 1.70) | 1.00 (0.75; 2.00) | 1.05 (0.70; 1.50) | 1.00 (0.40; 1.50) | 1.30 (0.70; 2.10) |
| GFR (Admission) mL/min | | | | | | |
| Mean (SD) | 49.61 (20.5) | 36.20 (21.3) | 53.56 (16.2) | 56.96 (40.4) | 59.97 (33.7) | 44.83 (24.8) |
| Median (Min; Max) | 56.09 (15.37; 83.55) | 41.02 (12.44; 73.33) | 56.17 (29.86; 83.08) | 51.66 (19.36; 105.16) | 57.94 (14.05; 168.21) | 36.47 (20.24; 100.28) |
| GFR (Baseline), mL/min | | | | | | |
| Mean (SD) | 71.47 (32.4) | 53.92 (15.8) | 69.54 (19.8) | 68.44 (40.3) | 67.53 (29.2) | 56.44 (21.0) |
| Median (Min; Max) | 69.36 (37.72; 116.85) | 51.57 (33.31; 75.66) | 76.42 (35.08; 98.37) | 58.17 (34.75; 122.68) | 60.91 (34.52; 168.21) | 52.39 (24.75; 84.94) |

| SHORT-TERM MORTALITY | HFREF | | HFMREF | | HFPEF | |
|---|---|---|---|---|---|---|
| Characteristics (n=65) | No | Yes | No | Yes | No | Yes |
| Cardiorenal syndrome (n, %) | 6 (9.7) | 3 (4.9) | 5 (8.1) | 2 (3.2) | 13 (21.0) | 3 (4.9) |
| Ureia (Admission), mg/dL | | | | | | |
| Mean (SD) | 75.69 (46.2) | 142.00 (97.4) | 52.70 (26.4) | 91.50 (21.9) | 63.50 (41.0) | 84.33 (42.1) |
| Median (Min; Max) | 74.00 (29.00; 203.00) | 132.00 (50.00; 244.00) | 43.00 (25.00; 101.00) | 91.50 (76.00; 107.00) | 53.50 (13.00; 187.00) | 76.00 (47.00; 130.00) |
| Ureia (Baseline), mg/dL | | | | | | |
| Mean (SD) | 56.85 (29.4) | 78.33 (42.0) | 43.70 (14.4) | 87.00 (18.4) | 51.43 (25.3) | 71.67 (25.0) |
| Median (Min; Max) | 45.00 (21.00; 119.00) | 86.00 (33.00; 116.00) | 41.50 (25.00; 77.00) | 87.00 (74.00; 100.00) | 45.50 (13.00; 109.00) | 71.00 (47.00; 97.00) |

| SHORT-TERM MORTALITY | HFREF | | HFMREF | | HFPEF | |
|---|---|---|---|---|---|---|
| Characteristics (n=65) | No | Yes | No | Yes | No | Yes |
| Creatinine (Admission), mg/dL | | | | | | |
| Mean (SD) | 1.56 (0.6) | 2.93 (1.7) | 1.26 (0.4) | 1.75 (0.8) | 1.29 (0.7) | 2.00 (0.6) |
| Median (Min; Max) | 1.60 (0.70; 3.10) | 2.60 (1.40; 4.80) | 1.20 (0.80; 1.90) | 1.75 (1.20; 2.30) | 1.15 (0.40; 3.30) | 2.00 (1.40; 2.60) |
| Creatinine (Baseline), mg/dL | | | | | | |
| Mean (SD) | 1.17 (0.4) | 1.33 (0.3) | 1.04 (0.3) | 1.38 (0.9) | 1.05 (0.4) | 1.27 (0.2) |
| Median (Min; Max) | 1.00 (0.70; 1.90) | 1.40 (1.00; 1.60) | 1.00 (0.70; 1.50) | 1.38 (0.75; 2.00) | 1.00 (0.40; 2.10) | 1.20 (1.10; 1.50) |
| GFR (Admission), mL/min | | | | | | |
| Mean (SD) | 49.53 (19.3) | 29.06 (23.3) | 61.55 (22.6) | 37.52 (10.8) | 59.04 (31.9) | 27.06 (10.0) |
| Median (Min; Max) | 45.38 (15.37; 83.55) | 19.02 (12.44; 55.72) | 57.62 (28.16; 105.16) | 37.52 (29.86; 45.17) | 56.75 (14.05; 168.21) | 24.88 (18.30; 37.99) |
| GFR (Baseline), mL/min | | | | | | |
| Mean (SD) | 67.80 (29.1) | 55.68 (24.7) | 74.56 (25.1) | 56.38 (30.1) | 67.31 (27.3) | 43.18 (8.0) |
| Median (Min; Max) | 56.56 (37.72; 116.85) | 51.57 (33.31; 82.15) | 75.78 (34.75; 122.68) | 56.38 (35.08; 77.69) | 64.67 (24.75; 168.21) | 44.86 (34.52; 50.17) |

| END OF FOLLOWUP MORTALITY | HFREF | | HFMREF | | HFPEF | |
|---|---|---|---|---|---|---|
| Characteristics (n=65) | No | Yes | No | Yes | No | Yes |
| Cardiorenal syndrome (n, %) | 3 (4.9) | 7 (11.3) | 4 (6.5) | 4 (6.5) | 10 (16.2) | 7 (11.3) |
| Ureia (Admission), mg/dL | | | | | | |
| Mean (SD) | 55.89 (25.0) | 135.38 (66.4) | 75.00 (67.0) | 67.17 (32.9) | 64.10 (38.4) | 73.83 (47.2) |
| Median (Min; Max) | 54.00 (29.00; 101.00) | 114.50 (50.00; 244.00) | 42.00 (30.00; 218.00) | 63.00 (25.00; 107.00) | 56.00 (13.00; 134.00) | 65.50 (18.00; 187.00) |
| Ureia (Baseline), mg/dL | | | | | | |
| Mean (SD) | 47.11 (17.0) | 77.75 (35.6) | 51.29 (18.8) | 55.17 (27.9) | 54.33 (28.5) | 57.00 (24.3) |
| Median (Min; Max) | 43.00 (29.00; 78.00) | 82.00 (21.00; 119.00) | 46.00 (35.00; 79.00) | 49.50 (25.00; 100.00) | 47.00 (13.00; 111.00) | 55.00 (18.00; 97.00) |
| Creatinine (Admission), mg/dL | | | | | | |
| Mean (SD) | 1.36 (0.5) | 2.56 (1.2) | 1.43 (0.6) | 1.43 (0.6) | 1.20 (0.5) | 1.68 (0.9) |
| Median (Min; Max) | 1.20 (0.70; 2.10) | 2.15 (1.40; 4.80) | 1.30 (0.80; 2.50) | 1.30 (0.80; 2.30) | 1.20 (0.40; 2.50) | 1.50 (0.70; 3.30) |
| Creatinine (Baseline), mg/dL | | | | | | |
| Mean (SD) | 1.13 (0.4) | 1.34 (0.3) | 1.06 (0.3) | 1.18 (0.5) | 1.05 (0.4) | 1.17 (0.3) |
| Median (Min; Max) | 1.00 (0.70; 1.90) | 1.40 (0.90; 1.70) | 1.00 (0.70; 1.50) | 1.00 (0.75; 2.00) | 1.00 (0.40; 2.10) | 1.15 (0.70; 1.50) |

| END OF FOLLOWUP MORTALITY | HFREF | | HFMREF | | HFPEF | |
|---|---|---|---|---|---|---|
| Characteristics (n=65) | No | Yes | No | Yes | No | Yes |
| GFR (Admission), mL/min | | | | | | |
| Mean (SD) | 53.76 (19.1) | 33.20 (19.1) | 54.64 (28.1) | 54.56 (21.4) | 60.23 (34.2) | 44.59 (23.8) |
| Median (Min; Max) | 56.45 (30.15; 83.55) | 30.02 (12.44; 59.88) | 56.17 (19.36; 105.16) | 51.64 (29.86; 83.08) | 54.75 (20.24; 168.21) | 39.04 (14.05; 86.70) |
| GFR (Baseline), mL/min | | | | | | |
| Mean (SD) | 67.46 (28.1) | 60.63 (28.5) | 71.31 (31.2) | 66.74 (20.4) | 68.22 (30.7) | 54.86 (16.7) |
| Median (Min; Max) | 56.56 (37.72; 116.85) | 47.67 (33.31; 116.32) | 68.63 (34.75; 122.68) | 76.42 (35.08; 83.08) | 58.26 (24.75; 168.21) | 52.41 (34.52; 86.70) |

Values are median (IQR), n (%), or mean ± SD.
IQR: interquartile range and minimum/maximum,
SD: standard deviation

HFrEF- heart failure with reduced ejection fraction,
HFmrE- heart failure with mildly reduced ejection fraction,
HFpEF- heart failure with preserved ejection fraction

GFR: glomerular filtration rate.

Our study demonstrates that patients with impaired renal function face a worse prognosis as various renal function parameters correlated with precocious readmission and all-cause mortality.

Based on our results one can infer that abnormal baseline values of urea and creatinine (which can represent CKD, i.e. kidney damage) determined a greater risk for the studied outcomes than altered admission values (which could represent, merely, transient worsening kidney function). For instance, subgroup analysis corroborated this assumption given that in the HFrEF subgroup end of follow-up mortality risk was greater with elevated baseline urea than with elevated admission urea.

As anticipated, for admission eGFR <30 mL/min the risk for end of follow-up mortality was inferior in the subgroup of HFpEF comparing to that of the general population and the risk for this end-point was also inferior considering admission creatinine for the given groups.

Subgroup analysis confirmed a plausible worse outcome for short-term mortality in HFrEF patients, compared to general population study for similar increments of creatinine and admission eGFR <30 mL/min.

Coherently, end of follow-up mortality risk was greatest, regarding admission creatinine and admission eGFR <30 ml/min, in the HFrEF subgroup (HR=1.148 and HR=13.387, respectively).

We emphasize that HFrEF patients benefited more from the increase in admission eGFR than the general population study in what matters to end of follow-up survival. This finding suggests that HFrEF is a vulnerable subgroup in which renal function has a significant impact on prognosis.

Chronic kidney disease was an important clinical prior as it correlated with short-term mortality (present in 45.3% of survivors versus 83.3% of the decedents) and CRS was found to be a strong predictor of both short and long-term mortality. Once again, the end of follow-up mortality risk related to CRS was greatest in the HFrEF subgroup.

Our results also consubstantiate the premise that the first 90 days post discharge represents a period of greatest risk as mortality hazard declined along the follow-up (e.g. the short-term mortality risk for admission eGFR< 30 mL/min was HR: 9.791 Vs end of follow-up mortality HR: 3.906).

Due to the reduced sample size multivariable analysis was not executed. Besides, our research was a single-center study which may hinder the extrapolation of our results.

Notwithstanding, we believe that the fact that several renal function parameters, customarily used in general practice, correlated with the aimed end-points adds valuable real-world data regarding HF prognosis.

Moreover we analyzed short-term readmission and mortality, which may provide information to the understanding of these hard end-points, a crucial subject for the improvement of HF prognosis.

## CONCLUSIONS

We acknowledged that routinely used indices of renal function can reliably estimate short-term prognosis as several parameters correlated with the proposed end-points.

These easily available tools may aid clinical decision making as patients identified as high risk profile may benefit from more intensive treatment for ADHF and stricter surveillance.

Renal dysfunction was a predictor of HF short-term rehospitalization and all-cause mortality. Interestingly, the mortality risk peaked at the first 3 months after hospital discharge and declined during follow-up.

**CONFLICTS OF INTEREST AND SOURCE OF FUNDING**
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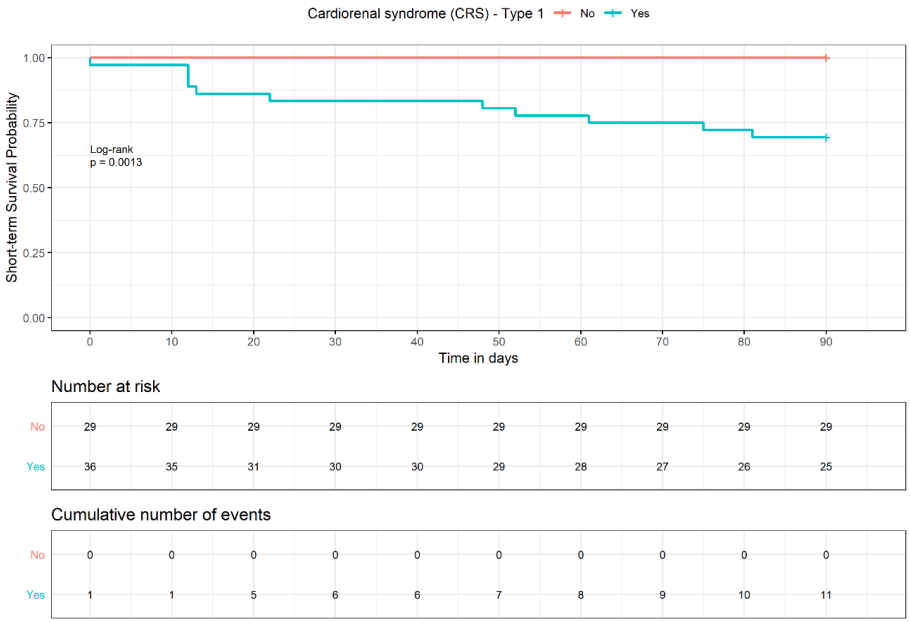
Figure 3. Short-term mortality - Kaplan Meier: Cardiorenal Syndrome Type 1

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