Prognostic Significance of Creatinine Clearance in Patients With Heart Failure and Normal Serum Creatinine

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Kidney failure is an important prognostic factor in patients with heart failure. Renal function is usually evaluated by measuring the serum creatinine level. However, a normal creatinine level can mask established kidney failure. We investigated the prognostic significance of the estimated creatinine clearance (Cockcroft formula) in 235 patients with heart failure and a normal serum creatinine level. The 2-year mortality rate was significantly higher in patients who had established kidney disease (ie, a creatinine clearance <60 mL/min) than in those who did not (35.1% vs 10.1%, *P*<.001). Even when only patients without established kidney failure were analyzed, the creatinine clearance had prognostic significance (rate ≥ 90 mL/min, mortality 3.2%; rate 89–60 mL/min, mortality 13.9%; *P*=.02). On Cox regression analysis, which included age, sex, heart failure etiology, left ventricular ejection fraction, diabetes, and hypertension, the creatinine clearance remained an independent predictor of mortality.

Key words: *Heart failure. Kidney failure. Creatinine.*

Significado pronóstico del aclaramiento de creatinina en pacientes con insuficiencia cardiaca y creatinina sérica normal

La insuficiencia renal es un importante factor pronóstico en pacientes con insuficiencia cardiaca. Para valorar la función renal se suelen utilizar las cifras de creatinina sérica. Sin embargo, cifras normales pueden ocultar una insuficiencia renal establecida. Hemos evaluado el significado pronóstico del aclaramiento de creatinina estimado (Cockcroft) en 235 pacientes con insuficiencia cardiaca y cifras de creatinina normales. Los pacientes con insuficiencia renal establecida (aclaramiento < 60 ml/min) tuvieron una mortalidad a 2 años muy superior a la de aquellos sin ella (el 35,1 y el 10,1%; p < 0,001). Incluso al analizar exclusivamente a los pacientes sin insuficiencia renal establecida, el aclaramiento de creatinina demostró tener significación pronóstica (≥ 90 ml/min, mortalidad del 3,2%; 89-60 ml/min, mortalidad del 13,9%; p = 0,02). En el análisis de regresión de Cox en el que se incluyeron además edad, sexo, etiología de la insuficiencia cardiaca, clase funcional, fracción de eyección de ventrículo izquierdo, diabetes e hipertensión, el aclaramiento de creatinina permaneció como predictor independiente de mortalidad.

Palabras clave: *Insuficiencia cardiaca. Insuficiencia renal. Creatinina. Aclaramiento de creatinina. Supervivencia.*

INTRODUCTION

Kidney failure (KF) is an important prognostic factor in patients with heart failure.[1] It has even been considered a more conclusive predictor than parameters such as ejection fraction or functional class.[2] Renal function is usually estimated by measuring serum creatinine levels. However, normal levels of serum creatinine can mask different degrees of KF[3] when renal function is determined by another method, such as creatinine clearance (CrC).

In a general analysis of patients attending our heart failure unit, we found CrC had predictive significance for 2-year mortality.[4] In the present study, our objective was to determine the prevalence of established KF and analyze the relationship between CrC and 2-year mortality in patients with normal creatinine levels.

METHODS

Of 423 patients admitted to our heart failure unit from August 2001 through April 2004 for whom we had CrC

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ABBREVIATIONS
CrC: creatinine clearance
KF: kidney failure

data for their first visit and 2-year follow-up data, we selected those with initial serum creatinine levels that were considered normal (<1.3 mg/dL in men and <1.1 mg/dL in women).[3] The study group consisted of 235 patients. We used estimated CrC calculated with the Cockcroft formula[5]: [140–age (years)]×weight (kg)/[72×plasma creatinine concentration (mg/dL)], adjusted for gender (×0.85 in women). Although an indirect measure of glomerular filtration, the Cockcroft formula is recommended in clinical practice guidelines to classify chronic renal disease (Kidney Disease Outcomes Quality Initiative Chronic Kidney Disease Classification [K/DOQI CKD]).[6,7]

Established KF was defined as CrC <60 mL/min. Patients without established KF were divided into 2 subgroups by CrC values: ≥90 mL/min and 89-60 mL/min (National Kidney Foundation classification groups 1 and 2).

Statistical analysis was with SPSS® 11.0 for Windows. To test differences between variables we used χ^2 for categorical variables and Student's *t* test or the Kruskal-Wallis test for continuous variables, depending on whether or not they had a normal distribution. A $P<.05$ was consedered significant. We obtained Kaplan-Meier survival curves and conducted Cox multiple regression analysis to identify factors independently associated with mortality. In the Cox model, we introduced, CrC (as a continuous variable and later as a variable within the 3 subgroups), age, gender, heart failure etiology, New York Heart Association functional class, ejection fraction and presence of diabetes, and high blood pressure. For these analyses, we used CrC measured at first visit without considering possible clinical course during follow-up.

The study fulfilled Spanish personal data protection law requirements in line with World Medical Association Declaration of Helsinki international recommendations on clinical research.

RESULTS

Demographic characteristics of the 235 patients analyzed are in Table 1. Data distinguish between presence and absence of established KF according to CrC. Prevalence of established KF was 24.2%. At 2-year follow-up, mortality was 16.1%; significantly higher (35.1%) in patients with established KF than in patients without established KF (10.1%) ($P<.001$). Creatinine clearance had a statistically significant relation with 2-year mortality (survivors, 82.5 [36.4] mL/min; deceased, 58.8 [22.9] mL/min; P<.001). In contrast, creatinine levels were similar in both groups: survivors, 1.05 (0.15) mg/dL; deceased, 1.04 (0.15) mL/min ($P=.97$).

Kaplan-Meier survival curves calculated as a function of presence or absence of established KF clearly diverged early (Figure 1). On dividing patients without established KF into 2 subgroups according to CrC, 63 (26.8%) patients had CrC ≥90 mL/min and 115 (49%) had CrC

TABLE 1. **Demographic and Clinical Characteristics**[a]

	Total (n=235)	CrC <60 mL/min (n=57)	CrC ≥60 mL/min (n=178)	*P*
Men	185 (78.7%)	34 (59.6%)	151 (84.8%)	<.001
Age, mean (SD), years	62.9 (11.4)	73.5 (6.3)	59.6 (10.6)	<.001
Etiology				.004
Ischemic heart disease	133 (56.6%)	27 (47.4%)	106 (59.6%)	
Dilated cardiomyopathy	29 (12.3%)	10 (17.5%)	19 (10.7%)	
Hypertensive heart disease	17 (7.2%)	6 (10,5%)	11 (6,2%)	
Alcohol-induced cardiomyopathy	20 (8.5%)	0 (0%)	20 (11.2%)	
Adriamycin-induced cardiomyopathy	2 (0.9%)	1 (1.8%)	1 (0.6%)	
Valvular disease	19 (8.1%)	8 (14%)	11 (6.2%)	
Other	15 (6.4%)	5 (8.8%)	10 (5.6%)	
Clinical course of heart failure, median, months	20	20	20.5	.36
NYHA functional class				.003
I	14 (6%)	2 (3.5%)	12 (6.7%)	
II	124 (52.7%)	22 (38.6%)	102 (57.3%)	
III	89 (37.9%)	29 (50.9%)	64 (37.7%)	
IV	8 (3.4%)	4 (7%)	4 (2.2%)	
LVEF, mean (SD), %	32.3% (12.1)	33.8% (14.2)	31.8% (11.4)	.57
Diabetes	85 (36.2%)	26 (45.6%)	59 (33.1%)	.08
High blood pressure	108 (46%)	32 (56.1%)	76 (42.7%)	.07

[a]CrC indicates creatinine clearance; SD, standard deviation; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

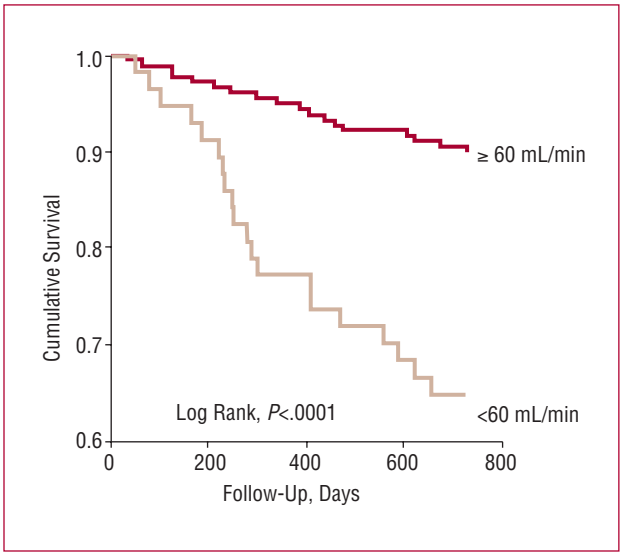

Figure 1. Kaplan-Meier survival curves as a function of presence of kidney failure.

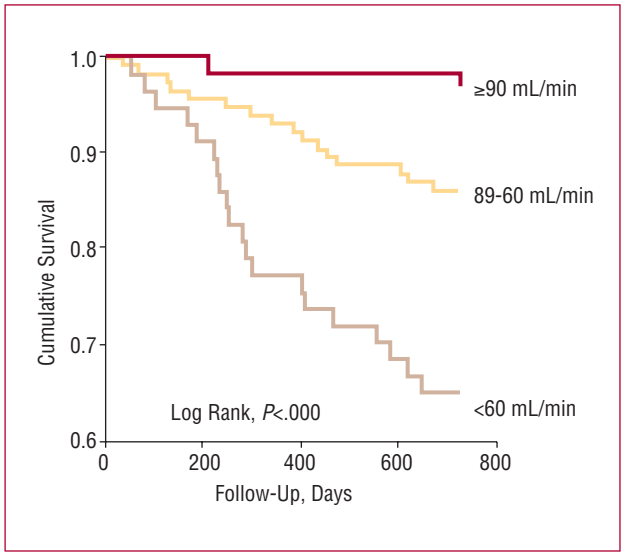

Figure. 2. Kaplan-Meier survival curves as a function of Creatinine clearance (CrC) ≥90 mL/min, 89-60 mL/min, and <60 mL/min.

89-60 mL/min. At 2-year follow-up, mortality was 3.2% and 13.9%, respectively (*P*=.02). Figure 2 shows Kaplan-Meier survival curves for these 2 subgroups, together with that for patients with established KF.

Cox multiple regression analysis of CrC as a continuous variable found it remained an independent prognostic factor (Table 2). On repeating Cox analysis with CrC as a function of the 3 subgroups and not a continuous variable, the hazard ratio was 2.1 (1.2-4.1); *P*=.01.

DISCUSSION

The relationship between KF and heart failure is complex. Renal dysfunction in heart failure can be a consequence of the latter, although KF can also cause heart failure. The coexistence of risk factors and generalized cardiovascular disease can cause primary damage to both organs. This interrelationship is considered reciprocal and bidirectional, and the term "cardiorenal failure" has even been proposed to define the combined failure of both organs.[8]

TABLE 2. **Cox Multiple Regression Analysis**[a]

	Cox HR	95% CI	*P*
Age	1.02	0.97-1.07	.39
Gender	1.19	0.57-2.46	.64
Etiology	1.14	0.97-1.33	.09
NYHA class	2.06	1.25-3.40	.004
LVEF	0.98	0.96-1.01	.26
Diabetes	1.57	0.79-3.12	.19
High blood pressure	0.79	0.39-1.57	.50
CrC	0.97	0.95-0.99	.03

[a]CrC indicates creatinine clearance; LVEF, left ventricular ejection fraction; HR, hazard ratio; CI, confidence interval.

Prevalence of KF depends on the criteria used to define it. In patients with heart failure, prevalence varies with the series and generally exceeds 40% when analyzed using CrC.[9-11] As Fernández-Fresnedo et al have already shown,[3] levels of creatinine considered normal can mask a population of patients with established KF. In fact, a reduction of glomerular filtration close to 60% is needed for KF to appear in serum creatinine levels.[12] In our series, in patients with normal creatinine levels, prevalence of established KF, defined as CrC <60 mL/min, was 24.2% and entailed a much worse prognosis at 2-year follow-up. Even in patients with slightly diminished CrC (National Kidney Foundation classification group 2) mortality was greater than in those with normal CrC. This contrasts with the DIG study results,[13] which reported similar mortality rates in patients with CrC 86-64 mL/min and in those with CrC >86 mL/min (18% and 21%). However, in our series creatinine levels were similar in survivors and in patients who died.

In the population studied, patients with established KF clearly presented a very different clinical profile to that of patients without established KF (Table 1). However, CrC maintained a statistically significant relationship with 2-year mortality in the Cox regression analysis model that included the aforementioned distinctive clinical parameters.

Our study clearly reflects the prognostic significance of CrC in patients with normal creatinine levels. To stratify prognosis correctly, we could justifiably analyze renal function using CrC at initial cardiologic examination of patients with heart failure.

However, we should point to a limitation of our study: the Cockcroft formula is an indirect measure used to calculate CrC. As all formulas used, it adjusts better to low CrC. More precise analysis of CrC ≥60 mL/min

requires isotopic glomerular filtration. Although other formulas to estimate CrC exist, the Cockcroft formula is accepted in international clinical practice guidelines with level of evidence A.

To conclude, in our series we found that determining renal function through CrC, estimated using the Cockcroft formula, proved to have significant prognostic value in patients with heart failure and normal serum creatinine levels. Even slight alterations of CrC have shown prognostic significance when compared with normal CrC.

REFERENCES

1. Smith GL, Leichtman JH, Bracken MB, Shlipak MG, Phillips CO, DiCapua P, et al. Renal impairment and outcomes in heart failure. Systematic Review and Meta-Analysis. J Am Coll Cardiol. 2006;47:1987-96.
2. de Santo NG, Cirillo M, Perna A, Pollastro RM, Frangiosa A, di Stazio E, et al. The kidney in heart failure. Semin Nephrol. 2005; 25:404-7.
3. Fernández-Fresnedo G, de Francisco ALM, Rodrigo E, Piñero C, Herraez I, Ruiz JC, et al. Insuficiencia renal "oculta" por valoración de la función renal mediante la creatinina sérica. Nefrología. 2002; 22:144-51.
4. Zamora E, Lupón J, Urrutia A, González B, Díez C, Altimir S, et al. Creatinine clearance calculated by Cockcroft's formula: a highly predictive prognostic factor for two years mortality in heart failure patients. Eur Heart J. 2006;27 (Abstract Suppl): 54.
5. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31-41.
6. National Kidney Foundation: K/DOQI Clinical Practice Guidelines to define chronic kidney disease: Evaluation, classification and stratification. Am J Kidney Dis. 2002;39:S1-266.
7. NKF Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. Ann Intern Med. 2003; 139:137-47.
8. Caramelo C, Gil P. Insuficiencia combinada cardiorrenal: una clave evolutiva y terapéutica en el fallo cardíaco. Rev Esp Cardiol. 2006;59:87-90.
9. Gregorian-Shamagian L, Varela-Román A, Pedreira-Pérez M, Gómez-Otero I, Virgós-Lamela A, González-Juanatey JR. La insuficiencia renal es un predictor independiente de la mortalidad en pacientes hospitalizados por insuficiencia cardíaca y se asocia con un peor perfil de riesgo cardiovascular. Rev Esp Cardiol. 2006;59:99-108.
10. de Silva R, Nikitin NP, Witte KK, Rigby AS, Goode K, Bhandari S, et al. Incidence of renal dysfunction over 6 months in patients with chronic heart failure due to left ventricular systolic dysfunction: contributing factors and relationship to prognosis. Eur Heart J. 2006;27:569-81.
11. McAlister FA, Ezekowitz J, Tonelli M, Armstrong PW. Renal insufficiency and heart failure. Prognostic and therapeutic implications from a prospective cohort study. Circulation. 2004;109:1004-9.
12. Kassirer JP. Clinical evaluation of kidney function-glomerular function. N Engl J Med 1971;285:385-9.
13. Mahon NG, Blackstone EH, Francis GS, Starling RC 3rd, Young JB, Lauer MS. The prognostic value of estimated creatinine clearance alongside functional capacity in ambulatory patients with chronic congestive heart failure. J Am Coll Cardiol. 2002;40:1106-13.