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.

INTRODUCTION

Kidney failure (KF) is an important prognostic factor in patients with heart failure. It has even been considered a more conclusive predictor than parameters such as ejection fraction or functional class. Renal function is usually estimated by measuring serum creatinine levels. However, normal levels of serum creatinine can mask different degrees of KF 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. 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...
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\(^5\): \[\frac{140 - \text{age (years)} \times \text{weight (kg)}}{72 \times \text{plasma creatinine concentration (mg/dL)}}\], 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 considered 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 \(\geq\) 90 mL/min and 115 (49%) had CrC

![Table 1](http://www.revespcardiol.org)
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

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

![Figure 1. Kaplan-Meier survival curves as a function of presence of kidney failure.](image1)

![Figure 2. Kaplan-Meier survival curves as a function of Creatinine clearance (CrC) ≥90 mL/min, 89-60 mL/min, and <60 mL/min.](image2)

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**TABLE 2. Cox Multiple Regression Analysis**

<table>
<thead>
<tr>
<th></th>
<th>Cox HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.02</td>
<td>0.97-1.07</td>
<td>.39</td>
</tr>
<tr>
<td>Gender</td>
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<td>0.57-2.46</td>
<td>.64</td>
</tr>
<tr>
<td>Etiology</td>
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<td>0.97-1.33</td>
<td>.09</td>
</tr>
<tr>
<td>NYHA class</td>
<td>2.06</td>
<td>1.25-3.40</td>
<td>.004</td>
</tr>
<tr>
<td>LVEF</td>
<td>0.98</td>
<td>0.96-1.01</td>
<td>.26</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.57</td>
<td>0.79-3.12</td>
<td>.19</td>
</tr>
<tr>
<td>High blood pressure</td>
<td>0.79</td>
<td>0.39-1.57</td>
<td>.50</td>
</tr>
<tr>
<td>CrC</td>
<td>0.97</td>
<td>0.95-0.99</td>
<td>.03</td>
</tr>
</tbody>
</table>

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


