Estimated creatinine clearance: a determinant prognostic factor in heart failure

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Elisabet Zamora, Josep Lupón, Agustín Urrutia, Beatriz González, Dolors Mas, Crisanto Díez, Salvador Altimir, Ramon Coll, and Vicente Valle

Unitat d'Insuficiència Cardíaca. Hospital Universitari Germans Trias i Pujol. Departament de Medicina. Universitat Autònoma de Barcelona. Badalona. Barcelona. España.

BACKGROUND AND OBJECTIVE: **Patients with heart failure and overt kidney failure (KF) have poor prognosis. Even mild degrees of kidney dysfunction might have prognostic value. The aim was to assess whether creatinine clearance values estimated with Cockroft formula correlated with survival at 2 years of follow-up in an outpatient heart failure unit population.**
PATIENTS AND METHOD: **423 patients (72% men), with a mean (standard deviation) age of 65.5 (11) years, were studied. Etiology of heart failure was mainly ischemic heart disease (59.6%). Mean left ventricle ejection fraction was 32.3% (13.3%). Patients were grouped according to stages of chronic kidney disease: ≥ 90 ml/min; 89-60 ml/min; 59-30 ml/min; 29-15 ml/min, and < 15 ml/min or on dialysis. KF was defined as creatinine clearance < 60 ml/min.**
RESULTS: **Prevalence of KF was 52%. Mortality at 2 years was 3.2% in patients with creatinine clearance ≥ 90 ml/min; 13.7% between 89-60 ml/min; 23.7% between 59-30 ml/min; 51% between 29-15 ml/min and 80% in patients with creatinine clearance < 15 ml/min or on dialysis (p < 0.001). Mortality was 30.4% in patients with KF and 10.3% in those without it (p < 0.001).**
CONCLUSIONS: **Creatinine clearance values estimated by Cockroft formula had a highly predictive prognostic value in patients with heart failure. Even mild degrees of kidney function impairment showed higher mortality than normal kidney function values.**

Key words: Heart failure. Kidney failure. Creatinine clearance. Survival.

Aclaramiento estimado de creatinina: un factor pronóstico determinante en la insuficiencia cardíaca

FUNDAMENTO Y OBJETIVO: **Los pacientes con insuficiencia cardíaca e insuficiencia renal (IR) establecida tienen peor pronóstico. Incluso grados leves de disfunción renal pueden tener significado pronóstico. El objetivo del estudio ha sido evaluar si los valores de aclaramiento de creatinina estimados mediante la fórmula de Cockroft se relacionan con la supervivencia a los 2 años de seguimiento en pacientes ambulatorios de una unidad de insuficiencia cardíaca.**
PACIENTES Y MÉTODO: **Se estudió a 423 pacientes (un 72% varones) con una edad media (desviación estándar) de 65,5 (11) años. La etiología de la insuficiencia cardíaca fue principalmente la cardiopatía isquémica (59,6%). La fracción de eyección media del ventrículo izquierdo era del 32,3% (13,3%). Se dividió a los pacientes de acuerdo con los estadios de IR crónica (≥ 90; 89-60; 59-30; 29-15, y < 15 ml/min o en diálisis). Se consideró que había IR establecida cuando el aclaramiento de creatinina era inferior a 60 ml/min.**
RESULTADOS: **La prevalencia de IR fue del 52%. La mortalidad a los 2 años fue del 3,2% en el grupo con aclaramiento de creatinina ≥ 90 ml/min; del 13,7% en el de 89-60 ml/min; del 23,7% en el de 59-30 ml/min; del 51% en el de 29-15 ml/min, y del 80% en pacientes con aclaramiento de creatinina < 15 ml/min o en diálisis (p < 0,001). La mortalidad fue del 30,4% en pacientes con IR y del 10,3% en aquellos sin la enfermedad (p < 0,001).**
CONCLUSIONES: **Los valores de aclaramiento de creatinina estimados por la fórmula de Cockroft mostraron un alto valor pronóstico predictivo en pacientes con insuficiencia cardíaca. Incluso los pacientes con un grado leve de disfunción renal presentaron una mortalidad más elevada que aquellos con valores normales de función renal.**

Palabras clave: Insuficiencia cardíaca. Insuficiencia renal. Aclaramiento de creatinina. Supervivencia.

Correspondence: Dr. J. Lupón.
Unitat d'Insuficiència Cardíaca. Hospital Universitari Germans Trias i Pujol.
Ctra. de Canyet, s/n. 08916 Badalona. Barcelona. España.
E-mail: jlupon.germanstrias@gencat.cat

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Kidney dysfunction, considered to be one of the main cardiovascular risk factors[1], plays an important role in the overall prognosis of cardiovascular diseases[2-4] and is common in heart failure (HF) patients. Numerous studies have shown worse prognosis in HF patients with advanced kidney failure (KF), which has even been considered a more precise predictor of mortality than other important parameters such as ejection fraction or functional class according to the New York Heart Association (NYHA) classification[5].

The aim of the present study was to assess, among other clinical parameters, the prevalence of KF and to analyze renal function in relation to mortality at 2 years in patients at our HF outpatient unit. To this end, we used creatinine clearance (CrC) estimated by the Cockcroft formula[6], a universally-accepted indirect measurement of glomerular filtration used in clinical guidelines for the classification of chronic kidney disease (Kidney Disease Outcomes Quality Initiative Chronic Kidney Disease Classification [K/DOQI CKD])[7].

Patients and method

Of the 441 patients who had been admitted to our HF Unit between August 2001 and April 2004, 423 of those for whom CrC was available at the first visit and whose *status vitae* at 2 years of follow-up was known were analyzed. Patients had been referred mainly from the Departments of Cardiology and Internal Medicine and, to a lesser degree, from the Emergency Room, other units of the centre or from cardiologists of the referral area of our hospital. The inclusion criterion to the Unit was HF as the patient's principal diagnosis.

Serum creatinine level was analyzed with the CREA method of the Dimension® Clinical Chemistry System, using a modification of the Jaffe kinetics reaction described by Larsen[8] using picrate as reactant.

Together with other demographic, clinical, echocardiographic and analytic data, kidney function was analyzed at the first Unit appointment using CrC estimation in milliliters per minute, according to the Cockroft formula [(140-age (years)] × weight (kilograms)/[72 × serum creatinine level (mg/dl)] adjusted by sex (× 0.85 in women)[6]. CrC was used owing to its greater precision in assessing renal function status. Once obtained, the relationship between CrC and survival at 2 years of follow-up was evaluated. KF was considered to be CrC below 60 ml/min. Furthermore, 5 subgroups of patients were analyzed according to their clearance, following the stages defined in the clinical guidelines of the National Kidney Foundation: ≥ 90 ml/min, 89-60 ml/min, 59-30 ml/min, 29-15 ml/min and < 15 ml/min or on dialysis.

TABLE 1

Demographic and clinical characteristics

Number of patients	423
Men/women	306/117
Age (years)[a]	65.5 (11)
Etiology	
Ischemic heart disease	252 (59.5%)
Dilated cardiomyopathy	44 (10.4%)
Hypertension	40 (9.5%)
Alcoholic cardiomyopathy	24 (5.7%)
Adryamicin cardiomyopathy	6 (1.4%)
Valvular disease	27 (6.4%)
Other	30 (7.1%)
Time (months) of heart failure symptoms[b]	24 (0-288)
NYHA functional class	
I	17 (4.0%)
II	202 (47.8%)
III	188 (44.4%)
IV	16 (3.8%)
LVEF[a] (%)	32.3 (13.3)
LVEF ⩾ 45%	64 (15.1%)
Diabetes	171 (40.4%)
Hypertension	235 (55.6%)
Creatinine clearance (ml/min)	
⩾ 90	64 (15.1%)
89-60	139 (32.9%)
59-30	177 (41.8%)
29-15	33 (7.8%)
< 15 or on dialysis	10 (2.4)
Kidney failure (creatinine clearance < 60 ml/min)	220 (52%)
Serum creatinine ⩽ 1.3 mg/dl	81 (36.8%/220)
Serum creatinine > 2.5 mg/dl	22 (10%/220)

LVEF: left ventricle ejection fraction; NYHA: New York Heart Association. [a]Mean (standard deviation); [b]median (range).

The study met the criteria of the personal data protection law and the international recommendations for clinical research of the Declaration of Helsinki of the World Medical Association.

Statistical analysis

The statistical package SPSS® 11.0 for Windows was used for statistical analysis. The relationship between CrC as a continuous variable and mortality at 2 years was analyzed by the Kruskal-Wallis test after verifying that CrC did not have a normal distribution. Chi-square test was used to analyze the relationship between mortality at 2 years and the different KF stages of the National Kidney Foundation and also the presence of KF, defined as CrC < 60 ml/min. Inter-group comparisons were made with chi-square test for categorical variables, and Student's t-test or Kruskal-Wallis test for continuous variables according to whether there was a normal distribution or not. A «p» value less than 0.05 was considered significant. Kaplan-Meier survival curves with log-rank statistical test were also performed and Cox regression was used to calculate the hazard ratio (HR). In order to estimate the adjusted mortality risk (HR), a Cox multiple regression analysis (conditional backward step) was performed including demographic variables, medical history parameters and treatments (age, sex, HF etiology, NYHA functional class, hypertension, diabetes, left ventricular function, plasma hemoglobin levels, serum sodium levels and use of angiotensin-converting enzyme inhibitors [ACEI] or angiotensin II receptor blockers, beta-blockers, spironolactone and statins).

Results

Of the 441 patients admitted to the HF Unit between August 2001 and April 2004, CrC at the first visit and survival at 2 years of follow-up were available in 423. Demographic characteristics of patients are shown in table 1. Some of the clinical features and the main treatment received by patients of each of the 5 KF stages are described in tables 2 and 3.

KF prevalence in our patients was 52%. Overall mortality during follow-up at 2 years was 20.7%. CrC bore a statistically-significant relationship with mortality at 2 years (surviving patients: 69.01 [34.9] ml/min; deceased patients: 44.18 [23.4] ml/min; p < 0.001). Each increase in CrC of 1 ml/min decreased mortality by 3.2% (HR_{Cox} = 0.968; 95% confidence interval [CI], 0.958-0.978). Mortality was 3.2% in patients with CrC ⩾ 90 ml/min, 13.7% in those with CrC between 89 and 60 ml/min, 23.7% in those with CrC between 59 and 30 ml/min, 51% in those with CrC between 29 and 15 ml/min, and 80% in those with CrC < 15 ml/min or on dialysis (p < 0.001). Mortality at 2 years was 30.4% in patients with KF and 10.3% in those without KF (p < 0.001). Causes of death are shown in table 4. No statistically significant differences were observed among causes of death between patients with and without KF (p = 0.09). Nevertheless, a trend of more deaths due to non-cardiovascular cause and sudden death and fewer deaths due to HF progression was observed in patients with KF.

Differences in mortality were statistically significant for each National Kidney Foundation stage with respect to the correlative stage (p = 0.022 between stages I and II; p = 0.025 between stages II and III, and p = 0.001 between stages III and IV), with the exception of stages IV and V, probably due to the low number of patients. Kaplan-Meier survival curves diverged significantly early from the beginning of the follow-up (figs. 1 and 2).

In the Cox multiple regression analysis, CrC as a continuous variable (HR_{Cox} = 0.98; 95% CI, 0.97-0.99), and National Kidney Foundation CrC stages (HR_{Cox} = 1.71; 95% CI, 1.32-2.21) remained statistically significantly associated with 2-year mortality (tables 5 and 6).

Discussion

Although the causes of the relationship between KF and HF are not well defined, kidney dysfunction in HF may be a consequence of the hemodynamic changes produced in the syndrome and, on occasions, be related to certain drugs used in the treatment of HF, some of which exert known deleterious effects on kidney function such as diuretics or, in specific patients, ACEI.

KF may also be a cause of HF either due to diastolic dysfunction secondary to left ventricle hypertrophy caused by the volume overload implicit in KF, or to the coexistence of cardiovascular risk factors such as arterial hypertension. On the other hand, the presence of KF may also be secondary to primary organic involvement of renal function in the context of generalized cardiovascular disease. The coexistence of multiple cardiovascular risk factors as precipitators or triggering factors of both syndromes is accompanied by physiopathologic changes such as abnormalities in the fibrinolysis system, accelerated vascular calcification, endothelial dysfunction and hyperhomocystinemia[9]. Other situations including the increase in circulating cytokines or presence of anemia, also contribute to

TABLE 2

Clinical characteristics according to creatinine clearance

	Creatinine clearance (ml/min)					p
	⩾ 90 (n = 64)	89-60 (n = 139)	59-30 (n = 177)	29-15 (n = 33)	< 15 or on dialysis (n = 10)	
Age (years)*	53.0 (8.5)	62.5 (10)	70.5 (10.6)	75.1 (8.1)	68.1 (14.5)	< 0.001
Men (%)	92.1	79.8	62.7	57.5	60	< 0.001
Ischemic etiology (%)	53.1	63.3	59.3	57.6	60	0.472
Diabetes (%)	21.8	39.5	48.6	30.3	60	0.002
Hypertension (%)	45.3	43.8	67.2	51.5	90	< 0.001
LVEF (%)	32.0 (9.3)	30.9 (13)	32.8 (14.1)	35.3 (15)	35.1 (18.5)	0.621
SBP (mmHg)*	120.7 (19.5)	123.4 (21.7)	126.0 (20.3)	127.3 (18.2)	124.0 (32.8)	0.479
DBP (mmHg)*	73.1 (12.8)	69.9 (11.3)	69.0 (10.7)	68.2 (9.7)	67.0 (15.6)	0.191
Plasma hemoglobin (g/dl)*	14.0 (1.4)	13.3 (1.8)	12.5 (1.6)	11.6 (1.7)	11.8 (1.6)	< 0.001
Serum urea (mg/dl)*	65.5 (41.7)	60.6 (31.2)	69.8 (39.4)	102.1 (84.3)	112.4 (58.2)	< 0.001
Serum sodium (mg/dl)*	139.0 (2.5)	138.1 (3.1)	138.5 (3.6)	138.3 (3.9)	137.8 (4.0)	0.757

DBP: diastolic blood pressure; LVEF: left ventricle ejection fraction; SBP: systolic blood pressure. *Mean (standard deviation).

this potentiation[10,11]. As observed by numerous authors, anemia also correlates closely with HF and KF; it remains for future studies to analyze whether the therapies used to correct it (erythropoietin and iron therapy) may modify the prognosis of HF.

This inter-relationship between HF and KF is considered to be reciprocal and bidirectional and the term «cardio-renal syndrome» has even been proposed to define the combined failure of both organs[2,12]. Although the definition of this term implies the joint and generally severe failure of both systems, it covers a very wide range of possible combinations in their severity, form of presentation and evolution.

The prevalence of KF among patients with HF varies according to series[2,13,14], but generally exceeds 50%. An example of this can be observed in a recent study[15] in a cohort of 754 patients with HF in which 56% had CrC below 60 ml/min. In our series, the prevalence of KF considered as CrC below 60 ml/min was 52%. In a recent meta-analysis[16] the prevalence of renal impairment assessed by different methods was quite similar in outpatients (51%). It is noteworthy that a significant proportion of patients with KF (36.8%) had serum creatinine levels considered normal (≤ 1.3 mg/dl). This evidence would warrant the assessment of kidney function using CrC since apparently normal serum creatinine values may mask an incipient KF. A reduction in glomerular filtration close to 60% is necessary for KF measured by serum creatinine to be evident[17].

The high prevalence of KF among patients with HF would justify the analysis of kidney function to stratify the prognosis within the initial cardiologic assessment of this syndrome. On the other hand, it should be analyzed whether differences should exist in the treatment and follow-up of patients with both HF and KF. Without doubt, the regulatory capacity of volemia and the hydroelectrolytic balance is clearly diminished in patients with HF who also present advanced KF. This would warrant adjusting some of the HF treatments to optimize their effect and reduce potentially dangerous side effects such as hyperpotassemia.

The relationship between HF and KF not only includes patients with HF due to systolic dysfunction, but also those with HF and preserved systolic function. In the previously-described study[15] of 754 patients, 57% had left ventricle ejection fraction ≥ 35%. During the mean follow-up of 2.5 years, mortality was 37% with an increase of 1% per each ml/min of lower CrC. In our study, mortality decreased 3.2% for each ml/min of increase in CrC, and, even when adjusted by numerous demographic variables, medical history parameters and treatments, CrC remained statistically significantly associated with 2-year mortality (HR_{Cox} = 0.98; 95% CI, 0.97-0.99). In the above mentioned study[15], renal function was significantly related to survival both in patients with systolic and those with diastolic dysfunction. Our study also included patients with preserved systolic function, although not in significantly sufficient numbers to be analyzed (only 15.1% of the patients had left ventricle ejection fraction ≥ 45%).

In our work, the relationship between CrC and 2-year mortality was also assessed according to the stratified National Kidney Foundation classification; an increase in mortality for each of the stages analyzed was notable, even in those with slight CrC deterioration. Other studies had already observed this effect of increased mortality even in non-advanced degrees of KF. One example is the work of Dries el al[18], who evaluated the prognostic implication of moderate KF defined as CrC below 60 ml/min, in symptomatic and asymptomatic patients with systolic dysfunction, in a retrospective analysis of the SOLVD study (Studies Of Left Ventricular Dysfunction trials). In multivariate analysis, moderate KF was associated with an increased risk of death from all causes, particularly due to an increase in mortality from HF progression. However, conflicting results have been found on the severity of renal impairment that actually increases risk in patients with HF[16]. In our study we found an increase in mortality even in patients with slight CrC deterioration (between 89 and 60 ml/min) compared with those with CrC ≥ 90 ml/min. This was not observed in the DIG study where mortality was quite similar in patients with CrC between 86 and 64 ml/min (18%) and those with CrC > 86 ml/min (21%)[19].

Although a worse evolution of KF patients has been demonstrated in different cardiovascular diseases[20-24], particularly ischemic heart disease[25-28], evidence of this relationship among patients with HF is less clear, mainly due to the fact that the majority of large studies in HF exclude patients with KF, besides other confounding factors such as presence of anemia, common in KF, which is in itself a factor of worse evolution[10]. A subanalysis of the CHARM study[29] evaluated the significance of KF in the prognosis of patients with symptomatic chronic HF. Although all patients with serum creatinine > 3 mg/dl were excluded, the reduction in glomerular filtration and left ventricular ejection fraction during a mean follow-up of 34.4 months proved to be the independent factors of worse evolution, once adjusted for the main confounding clinical factors, both in patients with depressed systolic function and those with preserved systolic function.

A further example of the role of KF as a prognostic factor of mortality in HF patients is the study by Gregorian-Shamagian et al[30], who underlined the importance of KF in the evolution of 552 hospitalized HF patients, both those with systolic and those with diastolic dysfunction. Patients with CrC < 30 ml/min, considered severe KF although they also had a worse cardiovascular risk profile, had clearly lower survival than the other

TABLE 3

Treatments according to creatinine clearance

	Creatinine clearance (ml/min)					p
	⩾ 90 (n = 64)	89-60 (n = 139)	59-30 (n = 177)	29-15 (n = 33)	< 15 or on dialysis (n = 10)	
Beta-blockers	90.6%	71.2%	65.5%	48.5%	40%	< 0.001
ACEI or ARB	98.4%	93.5%	85.3%	60.6%	30%	< 0.001
Spironolactone	32.8%	25.2%	36.7%	30.3%	10%	0.796
Digoxin	26.6%	21.6%	28.2%	27.3%	30%	0.472
Statins	60.8%	63.3%	51.4%	36.4%	20%	0.004
Loop diuretics	64.1%	75.5%	90.4%	81.8%	50%	< 0.001

ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers.

TABLE 4

Causes of death

	Total deaths (n = 88)	With KF (n = 67)	Without KF (n = 21)
Sudden death	30 (34.1%)	24 (35.8%)	6 (28.5%)
Heart failure	22 (25%)	13 (19.4%)	9 (42.8%)
AMI	3 (3.4%)	2 (3%)	1 (4.8%)
Stroke	1 (1.1%)	0	1 (4.8%)
Other CV	4 (4.6%)	3 (4.5%)	1 (4.8%)
Procedures	5 (5.7%)	5 (7.5%)	0
Non-CV	23 (26.1%)	20 (29.8%)	3 (14.3%)

AMI: acute myocardial infarction; CV: cardiovascular; KF: kidney failure.

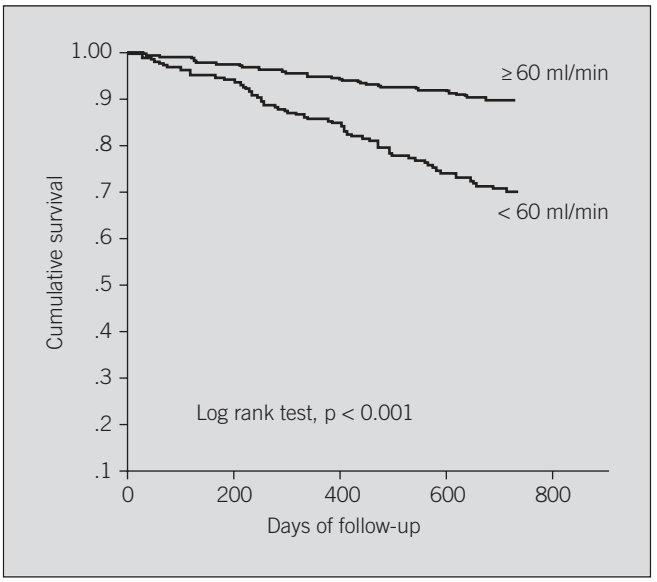

Fig. 1. Kaplan-Meier survival curves according to the presence of kidney failure (creatinine clearance < 60 ml/min).

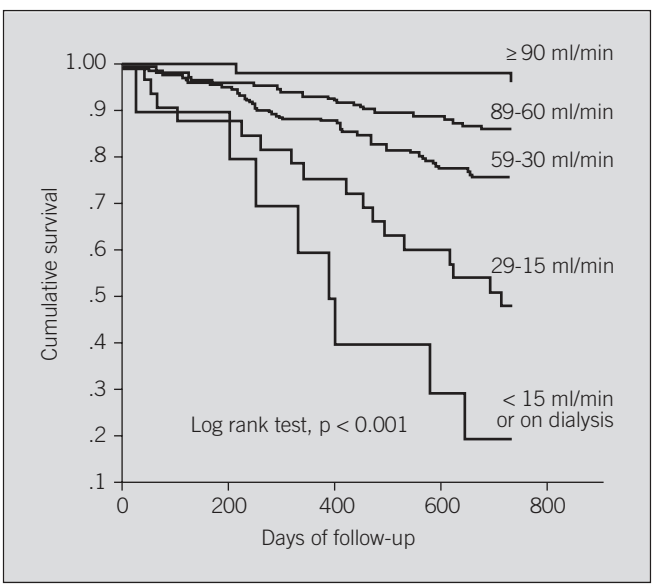

Fig. 2. Kaplan-Meier survival curves according to creatinine clearance stages of the National Kidney Foundation.

TABLE 5

Cox multiple regression analysis (conditional backward step), including creatinine clearance as continuous variable

	HR_{Cox}	95% CI
LVEF	0.97	0.96-0.99
NYHA functional class	2.1	1.42-3.12
Betablockers (no)	2.57	1.53-4.31
Statins (no)	2.39	1.39-4.13
Creatinine clearance	0.98	0.97-0.99
Hemoglobin	0.87	0.75-1.02
Age, sex, diabetes, hypertension, etiology, sodium, spironolactone, ACEI or ARB	NS	

ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers; CI: confidence interval; HR: hazard ratio; LVEF: left ventricle ejection fraction; NYHA: New York Heart Association.

TABLE 6

Cox multiple regression analysis (conditional backward step), including National Kidney Foundation (NKF) creatinine clearance stages

	HR_{Cox}	95% CI
LVEF	0.97	0.96-0.99
NYHA functional class	2.2	1.50-3.29
Betablockers (no)	2.38	1.42-3.98
Statins (no)	2.22	1.30-3.8
NKF creatinine clearance stages	1.74	1.34-2.25
Age, sex, hemoglobin, diabetes, hypertension, etiology, sodium, spironolactone, ACEI or ARB	NS	

ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers; CI: confidence interval; HR: hazard ratio; LVEF: left ventricle ejection fraction; NYHA: New York Heart Association.

groups, regardless of their systolic function. This relationship was independent of other risk factors that could increase mortality. Unlike our series, in the study of Gregorian-Shamagian et al[30] patients with CrC > 60 ml/min were considered as one group, and the effect of slight degree (CrC between 89 and 60 ml/min) of KF on survival was not approached.

In the present study, despite the fact that patients with more advanced degrees of KF had a worse clinical profile, were older, with diabetes and hypertension, had more anemia and received fewer betablockers and ACEI or angiotensin II receptor blockers, CrC proved to be an independent prognostic factor of mortality in the multivariate regression analysis; even after adjustment by numerous variables a 1.7 fold increase in 2-year mortality for each of the stages of National Kidney Foundation classification was observed.

All currently available data, although the majority stem from cross-sectional studies, suggest that KF is a potent risk factor which determines worse evolution in HF patients, even more so than other factors considered classic. Its high prevalence calls the attention of all professionals involved, both specialists (nephrologists or cardiologists) and primary health-care physicians, with a view to improving its diagnosis, treatment and evolution of both syndromes.

This study has some limitations. Calculation of CrC by the Cockroft formula is an indirect measurement that does not require 24-h urine collection and is thus a readily orientative calculation of patients' renal function. The Cockroft formula, like all those used, is adjusted better to low CrC. Isotopic glomerular filtration should be used if a more exact analysis of patients with CrC ⩾ 60 ml/min is sought. Data on the presence of microalbuminuria, an acknowledged cardiovascular risk factor, were not available in our patients. Although MDRD equation could also be used, in our population survival curves were not so clearly discriminated using this other formula.

Although our study cohort was a general HF population, treated at a specific, multidisciplinary HF Unit of a tertiary hospital, they remained patients selected from the total of HF patients. The majority was referred from the Cardiology Department, ischemic heart disease was the cause of their HF, they were relatively young and the percentage of women was low, which could suggest that the results obtained may not necessarily be comparable to the total HF population.

In conclusion, assessment of kidney function by estimated CrC using the Cockroft formula proved to be a significant prognostic factor in our patients with HF. Even CrC values considered normal or only slightly impaired showed a correlation with mortality. When KF was present, mortality at 2 years in these patients was 3 times higher than that of patients without KF. Furthermore, CrC is an easy and simple-to-obtain parameter that could be included in the initial evaluation of patients with HF.

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