ORIGINAL ARTICLE

CME

Cystatin C as Marker of Cardiorenal Syndrome and Poor Prognosis in Patients Hospitalized with Acute Heart Failure and Normal Renal Function

Cistatina C como predictor de síndrome cardiorrenal y mal pronóstico en pacientes internados por insuficiencia cardíaca aguda y función renal normal

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ABSTRACT

Background: The development of renal dysfunction in patients hospitalized for acute heart failure is known as cardiorenal syndrome type 1 (CRS). Worsening renal function (WRF) during hospitalization is associated with poor prognosis. Cystatin C has emerged as an alternative renal function marker to creatinine.
Objective: The aim of this study was to demonstrate the usefulness of cystatin C as predictor of WRF and prognostic factor in patients with acute heart failure and normal renal function assessed by creatinine level on admission.
Methods: A prospective, observational study was performed on consecutive patients with acute heart failure and normal renal function defined as serum creatinine <1.3 mg/dL on admission. Cystatin C was measured on admission. The primary endpoint was WRF, and secondary endpoints were in-hospital mortality, total mortality and rehospitalization for heart failure.
Results: A total of 166 patients were included in the study. Median age was 85 years (IQR 77.7- 89 years). The incidence of WRF was 29.7%, with in-hospital mortality of 3.1% and total mortality of 24.4%. Median follow-up was 193 days. Serum cystatin C was significantly higher in patients who developed WRF (1.72±0.58 mg/dL vs. 1.51±0.41 mg/dL, p=0.03) and in patients who died during follow up (1.76±0.49 vs. 1.51±0.46, p=0.004). Multivariate analysis showed that cystatin C was an independent predictor of mortality (OR 3.03, 95% CI 1.22-7.47) and WRF (OR 2.38, 95% CI 1.02-5.5). The optimal cystatin C cutoff point was 1.6 mg/dL, with 61.22% sensitivity and 60.34% specificity for the development of WRF, and 61.54% sensitivity and 61.98% specificity for total mortality.
Conclusions: Cystatin C on admission is a predictor of in-hospital WRF and increased mortality in this population hospitalized with acute heart failure and preserved renal function.

Key words: Acute heart failure – Cardiorenal syndrome – Cystatin C

RESUMEN

Introducción: El desarrollo de disfunción renal en el contexto de una falla cardíaca aguda se conoce como síndrome cardiorrenal (SCR) tipo 1. El empeoramiento de la función renal (EFR) durante la internación es un predictor de mal pronóstico. La cistatina C ha surgido como un marcador de función renal alternativo a la creatinina.
Objetivo: Demostrar la utilidad clínica de la cistatina C como predictor de EFR y factor pronóstico en pacientes con insuficiencia cardíaca aguda y sin disfunción renal evaluada por creatinina al ingreso.
Material y métodos: Se llevó a cabo un estudio observacional, prospectivo, de pacientes consecutivos con diagnóstico de insuficiencia cardíaca aguda y sin disfunción renal, definida como un valor de creatinina <1,3 mg/dl al ingreso. Se realizó un dosaje de cistatina C al ingreso. El punto final primario fue EFR y los secundarios fueron mortalidad hospitalaria, mortalidad total y reinternación por insuficiencia cardíaca.
Resultados: Se incluyeron 166 pacientes con una mediana de edad de 85 años (IIC 77,7-89). La incidencia de EFR fue del 29,7%, con una mortalidad hospitalaria del 3,1% y una mortalidad total del 24,4%. La mediana de seguimiento fue de 193 días. El valor de cistatina C fue significativamente mayor en los pacientes que desarrollaron EFR (1,72 ± 0,58 mg/dl vs. 1,51 ± 0,41 mg/dl; p = 0,03) y en los pacientes que murieron en el seguimiento (1,76 ± 0,49 mg/dl vs. 1,51 ± 0,46 mg/dl; p = 0,004). La cistatina C resultó un predictor independiente de mortalidad (OR 3,03, IC 95% 1,22-7,47) y de EFR (OR 2,38, IC 95% 1,02-5,5) en el análisis multivariado. Se halló un punto de corte óptimo de 1,6 mg/dl de cistatina, con una sensibilidad del 61,22% y una especificidad del 60,34% para el desarrollo de EFR y del 61,54% y 61,98%, respectivamente, para mortalidad total.
Conclusión: El valor de cistatina C al ingreso es predictor de desarrollo de EFR durante la internación y de mayor mortalidad en esta población con insuficiencia cardíaca aguda y función renal conservada al ingreso.

Palabras clave: Insuficiencia cardíaca - Síndrome cardiorrenal - Cistatina C

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Abbreviations

WRF	Worsening renal function	**CRS**	Cardiorenal syndrome
IQR	Interquartile range	**GFR**	Glomerular filtration rate

INTRODUCTION

Heart failure is a condition with high morbidity and mortality in which a great proportion of patients requiring hospitalization also present different degrees of renal dysfunction. (1, 2) The interaction between cardiac and renal dysfunction is known as cardiorenal syndrome (CRS). (3, 4) In this context, the condition produced by acute heart failure triggering renal dysfunction is known as CRS type 1. (5)

The pathophysiology of this phenomenon is complex and greatly depends on the clinical context. Its main causes are altered renal perfusion pressure (drop in renal perfusion pressure due to low blood flow and/or increased central venous pressure) and neurohumoral disorders. (6, 7) Worsening renal function (WRF) during hospitalization for acute heart failure is present in 21% to 45% of patients (8-11) and has been shown to be a poor prognostic factor, (2, 8, 12-14) with longer hospital stay and higher in-hospital and at follow-up mortality. Age >80 years, glomerular filtration rate (GFR) <60 ml/min and hypotension on admission are independent predictors of WRF. (8)

The diagnosis of CRS is not easy due to the different presentation forms and pathophysiological variants. Serum creatinine levels are used in clinical practice to estimate GFR; however, they present some limitations, as creatinine synthesis depends on muscle mass, and serum levels may remain normal in different situations as older age, chronic diseases, malnutrition or free water excess. Therefore, despite an established renal failure, in many occasions CRS diagnosis is delayed by 24-48 h. (15)

As a consequence of these shortcomings, the last years have seen the emergence of new biomarkers with the ability to detect earlier decreases in GFR. Cystatin C is a 13 kDa endogenous protein, constantly produced in nuclear cells of the body. It is filtered by the glomerulus, reabsorbed at the tubular level and completely metabolized. Its serum levels do not depend on muscle mass, age, race, liver disease or infections. (16) Different from creatinine, changes in GFR are verified faster and more accurately with serum cystatin C concentration, (15) turning it into an early marker of renal failure in patients with acute heart failure. Both serum cystatin C concentration on admission as its increase during hospitalization have been shown to have prognostic value in different studies. (14, 17-20) However, the populations evaluated presented a wide range of renal function on admission, as only hemodialysis and/or severe renal failure patients were excluded. (20-23) Thus, it is unknown whether cystatin C could preserve its prognostic value in patients with normal renal function on admission, according to their serum creatinine level.

Early WRF diagnosis would allow adjusting medical treatment, from an increase in diuretic doses, prevention or delayed use of nephrotoxic drugs, to a potential early ultrafiltration.

The aim of this study was to demonstrate the clinical usefulness of cystatin C as WRF predictor and as prognostic factor in patients with acute heart failure and normal renal function on admission, defined as serum creatinine <1.3 mg/dL.

METHODS

An observational, prospective study was conducted in consecutive patients admitted with diagnosis of acute heart failure to a high complexity hospital of the Autonomous City of Buenos Aires from January 2013 to December 2014. Patients were >18 years and without renal dysfunction on admission, defined as serum creatinine <1.3 mg/dL. Patients with severe valve disease in short-term surgical plan, who had received iodine contrast 2 days earlier or up to 5 days after admission, were coursing an acute coronary syndrome or were in the waiting list for heart transplantation were excluded from the study. Blood samples to asses cystatin C levels were withdrawn within the first 24 hours of admission. Worsening renal function was defined as an increase in admission creatinine of at least 0.3 mg/dL within the first five days of hospitalization. The primary endpoint was WRF and the secondary endpoints were in-hospital mortality, rehospitalization for acute heart failure and total mortality. Follow-up was performed through computerized clinical history and/or telephone contact.

Statistical analysis

Continuous variables are expressed as mean and standard deviation (SD) or median and interquartile range (IQR), according to normal or non-normal distribution. Categorical variables are expressed as percentages. Continuous variables were compared using Student's t test or the Wilcoxon Rank sum test according to their distribution. Categorical variables were analyzed using the chi-square test.

A ROC analysis was performed and the area under the curve was determined to assess cystatin C accuracy to discriminate patients developing events. The Younden index was used to establish cystatin C optimal cut-off point. A multivariate model was developed including variables showing significant statistical differences in the univariate analysis or which were considered clinically relevant. A Kaplan-Meier survival analysis was performed dividing the total population according to cystatin C optimal cut-off point in the ROC analysis. Both survival curves were compared using the Cox proportional hazard model. A p value <0.05 was considered as statistically significant. Stata 12.0 (Stata Statistical Software, version 12.0, Stata Corporation) was used to perform statistical analyses.

Ethical considerations

The protocol was approved by the Institutional Ethics Committee.

RESULTS

A total of 166 patients with median age of 85 years (IQR 77.7-89 years) were included in the study. Table 1 details the general population characteristics. The incidence of WRF was 29.7%, with in-hospital mortality of 3.1% and total mortality of 24.4%. Median follow-up was 193 days (IQR 62-314). Cystatin C levels on admission were significantly higher in patients developing WRF (1.72±0.58 mg/dL vs. 1.51±0.41 mg/dL, p=0.03) and in those who died during follow-up (1.76±0.49 mg/dL vs. 1.51±0.46 mg/dL, p=0.004) (Figure 1). No differences in cystatin C levels were found according to in-hospital mortality (1.69±0.41 mg/dL vs.1.57±0.48 mg/dL, p=0.58) or rehospitalization (1.6±0.5 mg/dL vs.1.47±0.4 mg/dL, p=0.58). Patients developing WRF presented slightly longer hospital stay (5, IQR 4-7.5 vs. 4, IQR 3-6, p=0.003) and a tendency to higher in-hospital mortality (6.1% vs. 1.76%, p=0.14) and total mortality (31.9 % vs. 21.4%, p=0.16), although without statistical differences. In the multivariate analysis, cystatin C was an independent predictor of mortality (OR 3.03, 95% CI 1.22-7.47) and WRF (OR 2.38, 95% CI 1.02-5.5) (Table 2). Serum creatinine levels on admission, that in the univariate analysis resulted predictor of WFR (OR 6.38, 95% CI 1.14-35.6), lost statistical significance in the multivariate analysis (OR 2.44 CI 0.35-16.7, p 0.36).

The ROC analysis of cystatin C on admission gave an area under the curve of 0.6 for WRF and 0.65 for mortality (Figure 2). An optimal cystatin C cut-off point of 1.6 mg/dL was found for both endpoints, with 61.54% sensitivity and 61.98% specificity for total mortality and 61.22% sensitivity and 60.34% specificity for WRF. In the survival analysis dividing the population according to cystatin C optimal cut-off point, higher mortality was observed in the group of patients with cystatin C on admission >1.6 mg/dL (RR 2.59, 95% CI 1.33-5.02; p=0.005) (Figure 3).

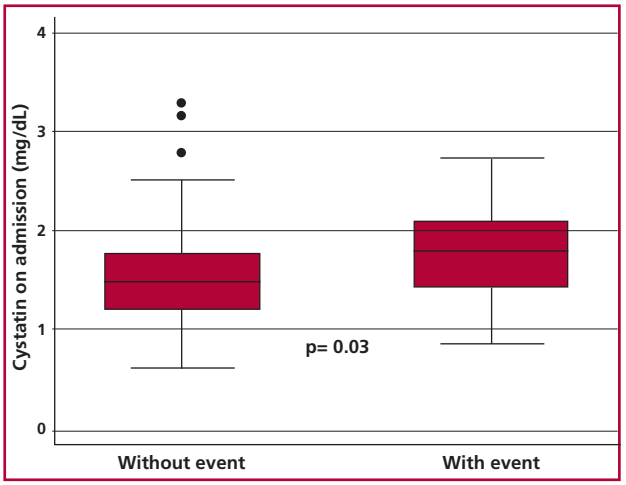

Fig. 1. Box plot of cystatin C concentration on admission according to mortality

Table 1. General population characteristics

	N=166
Age (years)	85 (77.7-89)
Male gender, %	29.5
History of HF, %	66.6
Coronary heart disease, %	21.7
Severe valve disease, %	30.9
EF<45%, %	34.4
Presentation form	
-APE/pulmonary congestion, %	42.8
-Water overload, %	53.6
-Low cardiac output, %	1.2
Betablockers, %	62.7
ACEI/ARB, %	55.6
Diuretics, %	47.6
Antialdosterone, %	12.7
Cystatin, (mg/dL)	1.57±0.47
Cr, (mg/dL)	0.9±0.2
GFR, (ml/min/m2)	66 (55.7-81)
ProBNP, (pg/dL)	6547 (1941.5-8331)
Hospital stay, (days)	6.8 (3-7)
Follow-up, (days)	193 (62-314)
WRF, %	29.7
In-hospital mortality, %	3.1
Rehospitalization for HF, %	27.8
Total mortality, %	24.4

EF: Ejection fraction. HF: Heart failure. APE: Acute pulmonary edema. ACEI: Angiotensin converting enzyme inhibitors. ARB: Angiotensin II receptor blockers. Cr : Creatinine. GFR: Glomerular filtration rate calculated by MDRD (Modification of diet in renal disease). WRF: Worsening renal function.

DISCUSSION

This is the first work evaluating the usefulness of cystatin C in patients diagnosed with acute heart failure

Table 2. Multivariate analysis for mortality and worsening renal function (WRF)

Mortality	OR	CI	p
Mortality			
Cystatin	3.02	1.22-7.47	0.01
Serum creatinine	0.52	0.06-4.5	0.55
Age	1.003	0.9-1.04	0.85
Ventricular function	0.87	0.62-1.23	0.62
WRF			
Cystatin C	2.38	1.02-5.53	0.04
Serum creatinine	2.44	0.35-16.7	0.36
Age	0.98	0.95-1.02	0.53
Ventricular function	1.09	0.91-1.3	0.33

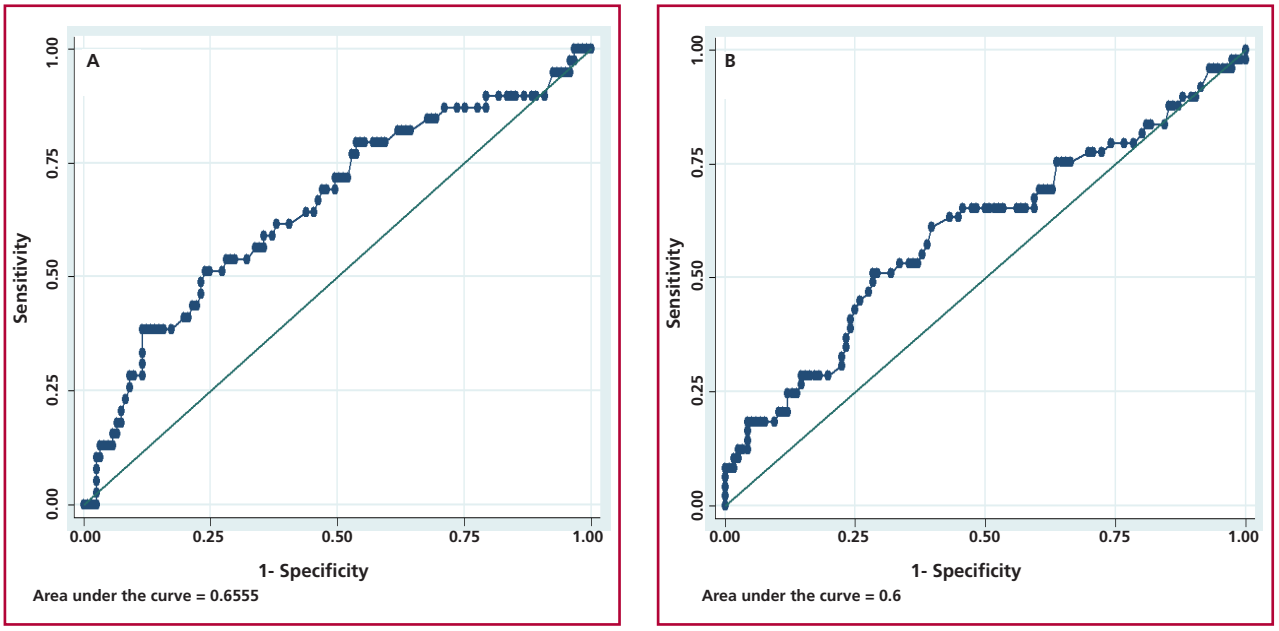

Fig. 2. Cystatin C ROC curve for mortality (A) and worsening renal function (B)

and preserved renal function. The most significant finding is that cystatin C maintained its prognostic value in patients without evident renal dysfunction according to their creatinine level on admission.

Serum creatinine level <1.3 mg/dL as criterion of normal renal function used in our study could have overestimated renal function (approximately 25% of patients had GFR <60 ml/min/1.73 m2). However, despite these limitations, creatinine is still widely used as a renal function parameter in the vast majority of centers of our country. In this sense, the contribution of equations using creatinine to estimate GFR (MDRD, CKD-EPI, etc.) in the context of acute renal failure is under continuous revision, as they were developed to follow-up patients with chronic kidney disease (24) and also because they tend to underestimate GFR with creatinine levels <1.5 mg/dL. (25)

Although in theory a patient with some degree of chronic kidney failure may develop CRS during hospitalization due to acute renal failure, (3-5) in general, the management of these patients is already adjusted to their previous renal disease (for example, higher diuretic doses, use of contrast, nephrotoxic drugs, etc.). Conversely, elevated cystatin C levels on admission in patients with an apparently normal renal function according to their serum creatinine level might help to adjust treatment and thus avoid or decrease the incidence of WRF.

Plasma urea has been shown to be a predictor of poor prognosis in patients with heart failure. (26) Its excretion is reduced in acute heart failure by activation of the renin-angiotensin-aldosterone system, the sympathetic nervous system and use of diuretics. Additionally, heart failure generates a hypercatabolic state that increases its production, so that plasma urea concentration does not depend only of renal function but reflects the neurohumoral system activation level and metabolic state. (27) Cystatin C would then be a exclusive marker of renal function.

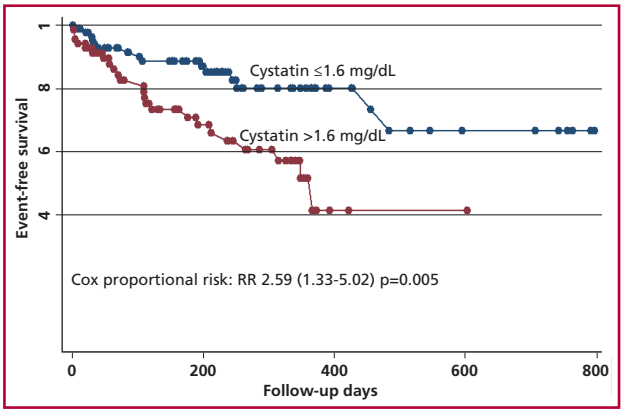

Fig. 3. Survival curve according to cystatin C level on admission

Different from Lassus et al.'s study, (17) WRF during hospitalization was not a predictor of greater in-hospital mortality in our population, and even though there is contradictory evidence on the ability of WRF as a prognostic marker, (9, 23, 28) this could have been related with the low number of deaths during hospitalization.

There is consensus in the literature concerning the use of 0.3 mg/dL increase in serum creatinine as WRF

criterion. (29) However, the time limit in which this increase should be verified was variable in different studies. (8, 10, 17, 30, 31) The time window of 5 days used in this analysis was chosen based on the average hospital stay for acute renal failure. (32) Longer time windows would have added difficult to adjust confounders (in-hospital infections, use of contrast, etc.) and shorter time windows would have decreased sensitivity. In this study we could not measure serial cystatin C levels. Worsening renal function defined as 0.3 mg/dL increase of cystatin C during hospitalization has been shown to have prognostic value (13) and could be a more sensitive marker of WRF than creatinine increase during hospitalization.

Age is an independent predictor of WRF (8) and also influences both serum creatinine levels as the equations used to estimate GFR based on this biomarker. (25) This is particularly important in elderly populations as the one included in our study (median age 85 years, IQR 77.7-89) and sets it apart from similar studies including patients with lower average age (52-75 years). (13, 18, 19, 22, 33, 34)

Limitations

A limitation of this study was the fact that it was a single center study performed in a high complexity hospital and referral center, so the population might not be representative of the whole range of patients admitted for acute heart failure. Similarly to other studies, a direct GFR measurement was not performed. Also, we did not measure serial cystatin C values to assess the prognostic value of WRF defined as an increase of cystatin C levels during hospitalization.

CONCLUSIONS

Cystatin C on admission was an independent predictor of WRF during hospitalization and of higher mortality in this population with acute heart failure and preserved renal function on admission.

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Conflicts of interest

None declared. (See author´s conflicts of interest forms in the web / Supplementary Material)

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