Prognostic Value of Cystatin C on Admission in Heart Failure With Preserved Ejection Fraction

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ABSTRACT

Background: Cystatin C has emerged as a new biomarker of renal function that has been found to predict adverse cardiovascular outcomes, especially heart failure (HF). Evidence of the usefulness of cystatin C in patients with heart failure with preserved ejection fraction (HFPEF) remains sparse. It is hypothesized that serum cystatin C levels in HFPEF has prognostic value.

Methods and Results: Cystatin C, urea nitrogen, creatinine, and N-terminal proBNP-type natriuretic peptide levels were measured on admission in 218 consecutive patients with HF and left ventricular ejection fraction >45%, as measured by Doppler echocardiography. The primary end point was all-cause mortality and/or readmission at 1 year. We determined the adjusted hazard ratio (HR) by Cox regression model. During the 1-year follow-up period, 70 patients (32.2%) died, and 126 patients (57.8%) died and/or required rehospitalization. Serum cystatin C levels by quartiles were associated with increased risk for adverse events. Kaplan-Meier survival curves showed significantly increased primary end point with each quartile of cystatin C (log rank <0.001). Patients in the highest quartile of cystatin C level were at increased adjusted risk for the primary end point (HR 3.40; 95% confidence interval [CI] 1.86−6.21; $P < .0001$) and all-cause mortality (HR 8.14; 95% CI 1.21−23.26; $P < .01$). Furthermore, high serum cystatin C levels were also associated with poor prognosis despite normal or mildly reduced renal function.

Conclusions: Serum cystatin C level on admission in patients with HFPEF is a strong and independent predictor of an unfavorable outcome. This relationship remains in patients without advanced renal dysfunction. (*J Cardiac Fail 2011;17:31−38*)

Key Words: Cystatin C, preserved ejection fraction, heart failure, creatinine, renal dysfunction.

Heart failure (HF) is one of the main health problems in developed countries because of its increasing prevalence. HF is characterized by repeat hospitalizations with heavy health burden and associated with a poor long-term prognosis. Additionally, patients with HF develop elevated mortality and suffer a reduction in quality of life.[1]

Heart failure with preserved ejection fraction (HFPEF) is more frequent than systolic ventricular dysfunction in hospitalized patients, and its prevalence and incidence are increasing.[2] Even though the HFPEF prognosis is as severe as systolic dysfunction, there is not enough evidence available to manage these patients effectively. Therapeutic advances in HF with depressed ejection fraction are not applied to HFPEF. Given that the mechanisms underlying HFPEF are still under debate, there is no evidence-based treatment for these patients, so it seems useful to identify prognostics factors while waiting for results of ongoing clinical trials.[3]

The association between renal dysfunction and increased mortality has been reported in patients with HF.[4] Cystatin C, a cysteine proteinase inhibitor, has emerged as a new biomarker of renal function.[5] A serum cystatin C−based equation has even been proposed to estimate glomerular filtration rate (GFR) in patients with chronic kidney disease.[6] Recent studies have revealed that cystatin C has a predictive and prognostic value in cardiovascular disease, especially coronary artery disease[7−9] and HF,[10−13] but its usefulness

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in patients with HFPEF is less well defined. Measurements of cystatin C improve early risk stratification compared with GFR in HF with normal to moderately impaired renal function.[14]

The primary aim of the present investigation was to examine the value of cystatin C as a predictor of poor prognosis in patients with HFPEF. We also evaluated the prognostic significance of cystatin C in patients with normal or mildly reduced renal function.

Materials and Methods

Study Design

We performed a prospective and observational study of patients with HFPEF who were admitted to the department of internal medicine of the Juan Ramón Jiménez Hospital (Huelva, Spain) between September 2007 and June 2008. All patients presenting with symptoms, signs, and diagnostic findings of HF, according to the current European Society of Cardiology guidelines,[15] were eligible, so we included patients with a new onset of heart failure and acute decompensation of chronic heart failure. Another inclusion criterion was serum level of N-terminal proB-type natriuretic peptide (NT-proBNP) $>2{,}000$ pg/mL. The patients were systematically characterized and clinical data on admission recorded in detail.

All patients underwent a 2-dimensional doppler-echocardiography during admission to estimate left ventricular ejection fraction (LVEF) by the biplane Simpson method. We assumed preserved ejection fraction with an LVEF $>$ 45%. Additionally, we measured transmitral flow velocity to assess patterns of left ventricular diastolic filling.[16]

Exclusion criteria were acute coronary syndrome, hemodynamically significant valvular heart disease, pulmonary embolism, ventricular arrhythmias, stage 5 chronic kidney disease (CKD), uncontrolled hyperthyroidism,[17] steroid treatment,[18] liver insufficiency, and life expectancy <1 year due to severe disease. Written informed consent was obtained from each patient at inclusion, and the protocol was approved by the Ethics Investigations Committee of our institution. Physicians, who were blinded to cystatin C level, independently selected the standard management, as recommended by contemporary guidelines.[15]

The primary end point was defined as the combination of mortality or readmissions by HF at 1 year. Electronic medical records from the hospital were reviewed to obtain mortality data and to determine whether patients were rehospitalized during the year after enrollment. Patients were also contacted by phone during the follow-up after discharge to obtain information on readmissions and mortality at other institutions.

Laboratory Measurements

Venous blood samples were drawn on admission. Samples for measuring serum cystatin C were centrifuged at 4°C for 15 minutes at 1000*g* and immediately stored at −80°C until assayed. All analytics determinations were performed in a central laboratory.

Serum cystatin C levels were measured by a particle-enhanced nephelometric immunoassay (N latex Cystatin C; Dade Behring Diagnostics, Marburg, Germany) on a BN II nephelometer. This is a latex-enhanced nephelometric immunoassay using rabbit polyclonal antibodies.[19] The interassay coefficient of variation (CV) was 2.3%−4.1%, and the intra-assay CV was 2.6%−3.3%. Kidney function was also assessed through serum creatinine levels, urea nitrogen levels, and a creatinine-based estimating equation. The GFR was estimated (eGFR) using the simplified Modification of Diet in Renal Disease (MDRD-4) equation: $\text{GFR} = 186 \times (\text{serum creatinine}^{-1.154}) \times (\text{age}^{-0.203}) \times 0.742$ (if female) $\times$ 1.21 (if black).[20] Impaired renal function was defined as eGFR <60 mL kg^{-1} 1.73 m^{-2}, consistent with stage ≥ 3 chronic kidney disease.[21] NT-proBNP was determined using the Elecsys proBNP II assay, an electrochemiluminescence immunoassay (Roche Diagnostics, Mannheim, Germany). The linear range of detection of this assay is 5-35,000 pg/mL. The inter-assay CV was 2.5%−5.8%, and the intra-assay CV was 1.2%−3.1%. High-sensitivity C-reactive protein (CRP) was determined by particle-enhanced inmunoturbidimetric assay on Roche automated clinical chemistry analyzers (detection range of 1−228 mg/L; (Roche Diagnostics, Mannheim, Germany)).

Data and Statistical Analysis

We tested several variables, including demographic characteristics such as age and gender, antecedents of hypertension, diabetes, hyperlipemia, obesity (body mass index >30 kg/m^2), coronary artery disease, hypertensive heart disease, cerebrovascular disease, peripheral arterial disease, atrial fibrillation, chronic obstructive pulmonary disease, and New York Heart Association basal status on admission.

Biochemical variables included markers of renal function (cystatin C, creatinine, urea, and eGFR), anemia (using the World Health Organization definition: hemoglobin <12 g/dL in women and <13 g/dL in men), hyponatremia (serum sodium <135 mmol/L), NT-proBNP, and CRP.

Continuous variables were tested for normal distribution using Kolmogorov-Smirnov test. Analysis of variance or Kruskal-Wallis test, according to whether or not distribution was normal, was used to test the equality of distributions in quartiles of cystatin C. Differences in proportions were judged by clinical chi-square analysis. Spearman correlation coefficient was used as a nonparametric measurement of association for correlations between plasma cystatin C and all clinical quantitative variables. Kaplan-Meier survival curves and the log-rank test were calculated from baseline to time of all-cause mortality and/or readmissions by quartile of cystatin C at 1-year follow-up. We calculated hazard ratios (HRs) derived from the Cox proportional hazard model to identify predictors of mortality and/or readmissions by heart failure at 1-year follow-up. The independent effect of variables on prognosis was calculated using stepwise Cox multivariable regression analysis (Wald), incorporating all variables with $P < .1$ in the univariate analysis.

Discrimination and calibration were also evaluated by the area under a receiver operating characteristic (ROC) curve (AUC) and by the Hosmer-Lemeshow goodness-of-fit test, respectively.

The increased discriminative value of the biomarkers was further examined with the method described by Pencina et al.[22] This method is based on the difference between two models in the individual estimated probability that a case subject will be categorized as a case subject. An increased probability that case subjects will be categorized as case subjects together with a decreased probability that control subjects will be categorized as case subjects implies better prediction ability, whereas the opposite implies worse prediction ability. Net reclassification improvement requires that there exist a priori meaningful risk categories. We have used 0 to 40%, 41% to 80% and >80% for the risk of the primary end point.

We also tested the hypotesis that patients without renal impairment (eGFR by MDRD-4 >60 mL kg^{-1} 1.73 m^{-2}) but with elevated cystatin C values would have a higher risk of mortality and/or readmissions compared with subjects with normal values of cystatin C. We assessed the clinical risks of serum cystatin C levels at the 1.23 mg/L cutoff (which was the cystatin C level that matches eGFR <60 mL kg^{-1} 1.73 m^{-22} using the cystatin C–based equation: $GFRcysC = 77.24 \times CystC^{-1.2623}$ (Dade Behring cystatin C calibration).[23]

Results are shown as mean ± SD, median (interquartile range [IQR]), numbers (%), and HR with 95% confidence interval (CI). Tests were two sided, and *P* values of <.05 were regarded to be statistical significant. All statistical analyses were performed using SPSS version 16.0 for windows (SPSS, Inc., Chicago, Illinois).

Results

Follow-Up Period

A total of 255 patients were eligible and offered to participate, and 22 patients declined. Of the 233 patients enrolled, eight patients had LVEF ≤45%, another six patients were withdrawn during the follow-up because they did not answer the phone, and one patient died of ventricular fibrillation during the first 24 hours. Consequently, 218 patients were included in the present study. During 1-year follow-up, the primary end point reached 57.8% (126 patients) and all-cause mortality at 1-year after admission was 32.2% (70 patients).

Baseline Characteristics of Populations

The distribution of baseline characteristics and laboratory parameters by cystatin quartiles are listed in Tables 1 and 2. The median of cystatin C concentration was 1.45 mg/L (IQR 1.12–2.06), the medians of serum creatinine and urea were 1.06 mg/dL (IQR 0.80–1.42) and 54.0 mg/dL (IQR 0.80–1.42), respectively, and the median eGFR by MDRD-4 was 61.36 mL kg^{-1} 1.73 m^{-2} (41.56–84.43). Only 24 patients (11%) had a LVEF between 50% - 46%.

Patients with higher cystatin C levels were older and had more frequent history of hypertension and diabetes mellitus. Overall mean in-hospital length of stay was 10.7 ± 8.7 days and increased slightly with higher quartile of cystatin C at admission.

Serum creatinine and NT-proBNP were higher in patients with elevated cystatin levels, whereas hemoglobin and eGFR by MDRD-4 were lower in these patients. Serum levels of cystatin C showed stronger correlations with creatinine ($\rho = 0.68$; $P < .001$), urea ($\rho = 0.66$; $P < .001$), and eGFR by MDRD-4 ($\rho = -0.72$; $P < .001$). However, the correlations with age ($\rho = 0.30$; $P < .001$), hemoglobin ($\rho = -0.32$; $P < .001$), and NT-proBNP ($\rho = 0.30$; $P < .001$) were very weak.

Prognostic Significance of Cystatin C

In the Kaplan-Meier survival curves, each quartile of cystatin C were associated with an incremental rate of

Table 1. Baseline Characteristics of Study Population According to Quartiles of Cystatin C

Variable	Overall (n = 218)	Cystatin C Quartile, mg/L: First (<1.12 mg/L) (n = 54)	Second (1.12–1.45 mg/L) (n = 55)	Third (1.46–2.06 mg/L) (n = 54)	Fourth (>2.06 mg/L) (n = 55)	*P* Value for Linear Trend
Demographics						
Age, y (mean ± SD)	75.6 ± 8.7	69.74 ± 10.1	76.95 ± 7.3	77.41 ± 7.52	78.24 ± 8.7	<.005
Female gender; n (%)	131 (60.1%)	30 (56.6%)	27 (48.2%)	39 (72.2%)	35 (63.6%)	.064
History, n (%)						
Hypertension	182 (83.5%)	36 (67.9%)	45 (80.4%)	50 (92.6%)	51 (92.7%)	.001
Diabetes mellitus	115 (52.8%)	21 (39.6%)	27 (48.2%)	32 (59.3%)	35 (63.6%)	.052
Obesity (BMI >30 kg/m^2)	93 (42.7%)	23 (43.4%)	25 (44.6%)	24 (44.4%)	21 (38.2%)	.891
Stroke	27 (12.4%)	5 (9.4%)	10 (17.9%)	5 (9.3%)	7 (12.7%)	.482
COPD	78 (35.8%)	15 (28.3%)	24 (42.9%)	19 (35.2%)	20 (36.4%)	.467
Peripheral arterial disease	23 (10.6%)	4 (7.5%)	8 (14.3%)	5 (9.5%)	6 (10.9%)	.701
Atrial fibrillation	133 (61.0%)	36 (67.9%)	29 (51.8%)	33 (61.1%)	35 (63.6%)	.360
Hypertensive heart disease	116 (53.2%)	28 (52.8%)	28 (50.0%)	27 (50.0%)	33 (60.0%)	.686
Coronary artery disease	41 (18.8%)	6 (11.3%)	12 (21.4%)	12 (22.2%)	11 (20.0%)	.409
NYHA functional class III-IV	86 (39.4%)	11 (20.8%)	20 (35.7%)	24 (44.4%)	31 (56.4%)	.002
Anemia*	114 (52.3%)	19 (35.8%)	23 (41.1%)	35 (64.8%)	37 (67.3%)	.001
Renal insufficiency†	104 (47.7%)	4 (7.5%)	12 (21.4%)	37 (68.5%)	51 (92.7%)	<.005
Length of stay (d)	10.70 ± 8.7	8.19 ± 4.8	10.45 ± 7.6	10.85 ± 7.3	13.42 ± 12.6	.020
Treatment at discharge, n (%)						
Loop diuretics	202 (92.7%)	49 (92.5%)	50 (89.3%)	48 (88.9%)	55 (100%)	.093
Beta-blockers	104 (47.7%)	28 (52.8%)	25 (44.6%)	21 (38.9%)	30 (54.5%)	.321
ACE inhibitors/ARBs	174 (79.8)	39 (73.6%)	47 (83.9%)	45 (83.3%)	43 (78.2%)	.499

ACE, angiotensin-converting enzyme; ARBs, angiotensin-receptor blockers; BMI, body mass index; COPD, chronic obstructive pulmonary disease; NYHA, New York Heart Association.

Groups were compared using chi-square, analysis of variance, or Kruskal-Wallis tests.

*Anemia was defined using the World Health Organization definition of hemoglobin <12.0 g/dL in women and <13.0 in men.

†Renal insufficiency was defined as glomerular filtration rate estimated by Modified Diet in Renal Disease 4 <60 mL kg^{-1} 1.73 m^{-2}.

Table 2. Laboratory Parameters and Outcomes According to Quartiles of Cystatin C

Laboratory Parameter	Overall (n = 218)	Cystatin C Quartile, mg/L				*P* Value for Linear Trend
		First (<1.12 mg/L) (n = 54)	Second (1.12−1.45 mg/L) (n = 55)	Third (1.46−2.06 mg/L) (n = 54)	Fourth (>2.06 mg/L) (n = 55)	
Cystatin C (mg/L)	1.45 (1.12−2.06)	0.93 (0.84−1.03)	1.28 (1.19−1.34)	1.65 (1.54−1.78)	2.63 (2.29−3.08)	<.0001
Hemoglobin (mg/dL)	12.0 ± 2.32	13.0 ± 2.4	12.4 ± 2.3	11.6 ± 2.1	11.0 ± 11.9	<.001
Serum creatinine (mg/dL)	1.06 (0.80−1.42)	0.76 (0.59−0.99)	0.91 (0.71−1.14)	1.17 (0.93−1.43)	1.79 (1.31−2.51)	<.005
Urea nitrogen (mg/dL)	54.0 (40−78)	39 (30−46)	47 (33.25−59)	62 (50−79.5)	93 (68-138)	<.0001
eGFR by MDRD-4 (mL min^{-1} 1.73 m^{-2})	61.36 (41.56−84.43)	88.47 (71.57−119.04)	76.31 (61.23−87.18)	52.81 (42.01−65.34)	32.95 (22.47−45.71)	<.001
Sodium (mg/dL)	137.3 ± 5.1	137.7 ± 4.7	137.6 ± 5.1	137.3 ± 5.2	136.6 ± 5.5	.780
NT-proBNP (pg/mL)	3606 (1824−7123)	2515 (1289−4571)	3724 (1777−6148)	3896 (1699−8513)	5578 (2752−17458)	<.001
High-sensitivity CRP (mg/L)	2.55 (0.9−5.7)	2.2 (0.6−5.2)	3.2 (1.0−6.7)	2.05 (0.8−4.6)	2.9 (1.1−6.8)	.459
Patterns of diastolic filling						.163
Relaxation abnormality	59 (27.1%)	11 (20.4%)	21 (38.2%)	17 (31.5%)	10 (8.2%)	
Pseudonormal filling	23 (10.6%)	5 (9.3%)	5 (9.1%)	4 (7.4%)	9 (16.4%)	
Restricted filling	3 (1.4%)	1 (1.9%)	1 (1.8%)	0	1 (1.8%)	
Monophasic	133 (61%)	37 (68.5%)	28 (50.9%)	33 (6.1%)	35 (63.6%)	
Outcomes at 1 year						
Combined end point	126 (57.8%)	17 (32.1%)	27 (48.2%)	37 (68.5%)	45 (81.8%)	<.0001
All-cause mortality	70 (32.2%)	4 (7.5%)	13 (23.2%)	21 (38.9%)	32 (58.2%)	<.0001

eGFR, estimation of glomerular filtration rate; MDRD-4, Modification of Diet in Renal Disease; NT-proBNP, N-terminal proB-type natriuretic peptide; CRP, C-reactive protein.
Data are expressed as mean ± SD or median (IQR). Groups were compared using analysis of variance or Kruskal-Wallis tests.

adverse clinical events (log rank <0.001; Fig. 1) and all-cause mortality (log rank <0.001) at 1-year follow-up.

Discrimination was also assessed by AUC for the primary end point: 0.734 (95% CI 0.66-0.80; $P < .001$). The largest AUC was obtained with cystatin C with the optimal cutoff value of 1.30 mg/L, sensitivity 75.6%, and specificity 68.3%. A comparison of the four ROC curves is showed in Figure 2.

In the univariate Cox regression analysis, all measures of kidney function and other variables presented in Table 3 were associated with higher risk for adverse clinical events. After adjusted multivariable stepwise Cox regression model, including all variables with $P < .1$ in the univariate analysis, the third (HR 2.54, 95% CI 1.41−4.57; $P = .002$) and fourth (HR 3.40, 95% CI 1.86−6.21; $P < .0001$) quartiles of cystatin C were significantly associated with increased primary end point risk compared with the lowest quartile. However, the second quartile (HR 1.39, 95% CI 0.75−2.59; $P = .290$) did not reach statistical significance. Serum creatinine, blood urea nitrogen, and eGFR by MDRD-4 were no longer significant. Hyponatremia (HR 1.61, 95% CI 1.11−2.32; $P = .011$) also reached statistically significant in multivariable regression analysis. Furthermore, the third and fourth quartiles of serum cystatin C were also associated with all-cause mortality at 1 year (HRs 2.34 ($P = .008$) and 8.14 ($P = .001$), respectively). Other variables included in multivariate stepwise Cox regression analysis by all-cause mortality alone are presented in Table 4.

The *P* value for the Hosmer-Lemeshow test indicated good calibration for the model with and without cystatin C ($P > .11$ for all comparisons).

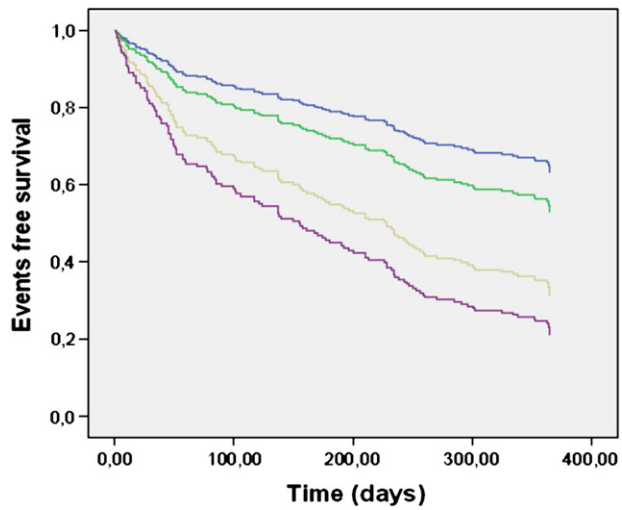

Fig. 1. Kaplan-Meier curves by quartiles of cystatin C. Primary end point at 1 year: 32.1% for first quartile (*upper line*, cystatin C < 1.12 mg/L), 48.2% for second quartile (*upper middle line*, cystatin C 1.12−1.45 mg/L), 68.5% for third quartile (*lower middle line*, cystatin C 1.46−2.06 mg/L), and 81.8% for fourth quartile (*lower line*, cystatin C >2.06 mg/L). Log rank $P < .001$.

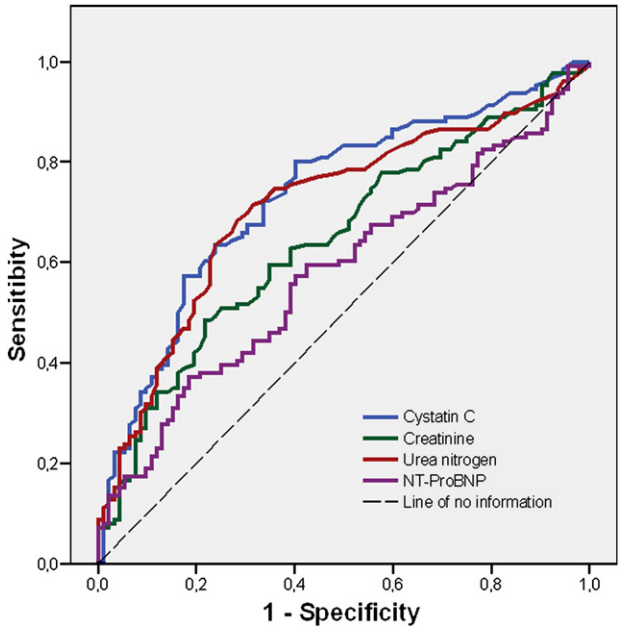

Fig. 2. Combined receiver-operating characteristic (ROC) curves for cystatin C, urea, creatinine, and N-terminal proB-type natriuretic peptide (NT-proBNP) for the primary end point. The ROC analysis for cystatin C showed an area under the curve (AUC) of 0.74 ($P < .001$). The ROC analysis for urea showed an AUC of 0.71 ($P < .001$). The ROC analysis for creatinine showed an AUC of 0.64 ($P < .001$). The ROC analysis for NT-proBNP showed an AUC of 0.58 ($P = .04$).

Reclassifications for patients with and without events are summarized in Table 5. For 12 patients who experienced events, reclassification improved using the model with cystatin C, and for 19 patients it became worse. Among the patients who did not experience events, 31 were reclassified into a lower risk category and 4 were reclassified into a higher risk category. The net improvement in reclassification was estimated to be 0.238 ($P < .001$).

Patients with eGFR >60 mL kg^{-1} 1.73 m^{-2} by MDRD-4 (without advanced renal impartment) and serum cystatin C levels >1.23 mg/L were also associated with significantly higher all-cause mortality and/or readmission at 1 year (log rank <0.001; Fig. 3). Again, the adjusted risk for primary outcome showed an HR of 3.30 (95% CI 1.89−5.78) for these patients.

Discussion

In this study, we have described for the first time the prognostic value of serum cystatin C levels as a predictor of adverse outcomes in patients with HFPEF. The predictive value of cystatin C has not been established previously in patients hospitalized for HFPEF. Recently, Naruse et al[14] demonstrated that serum cystatin C may be a stronger predictor of outcome than LVEF, but only 40% of the population experienced HFPEF. In fact, the medians of LVEF for all quartiles of cystatin C were <40% and the subgroup of patients with preserved ejection fraction was not analyzed as an independent group.

Because there is no consensus regarding the cutoff for preserved ejection fraction, we also established LVEF >45%. Current guidelines for diagnosis and treatment of heart failure require the presence of normal or mildly abnormal LVEF (≥45%−50%) for the diagnosis of HFPEF.[15] Recognizing the difficulties in the assessment of diastolic LV dysfunction, measurement of diastolic dysfunction was not required to make the diagnosis of HFPEF.[24] Therefore, our results may be put directly into clinical practice, because patients do not routinely undergo a measurement of diastolic LV dysfunction. On the other hand, we did not find any relationship between the different patterns of LV diastolic filling and outcomes. Although there are other works concerning the role of cystatin C in diastolic function, they do not have clinical end points.[25,26] With the failure of the recent clinical trials, the management of patients with HFPEF continues to be unclear. As a consequence, the guidelines are now focused on control of comorbidities and stratification risk.

Table 3. Univariate and Multivariate Predictors of 1-Year Primary End Point (All-Cause Mortality and Readmission)

	Univariate		Multivariate	
Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age (y)	1.02 (1.00−1.05)	.013	—	NS
Cystatin C (mg/L)		<.0001		<.0001
First quartile	1.0		1.0	
Second quartile	1.80 (0.98−3.31)	.057	1.39 (0.75−2.59)	.290
Third quartile	3.32 (1.86−5.91)	<.0005	2.54 (1.41−4.57)	.002
Fourth quartile	4.85 (2.76−8.51)	<.0001	3.40 (1.86−6.21)	<.0001
Creatinine (mg/dL)	1.70 (1.31−2.20)	<.001	—	NS
Urea nitrogen (mg/dL)	1.008 (1.005−1.011)	<.001		NS
eGFR by MDRD-4 (mL min^{-1} 1.73 m^{-2})	0.98 (0.98−0.99)	<.0001	—	NS
Hemoglobin (mg/dL)	0.91 (0.84−0.97)	.008	—	NS
NT-proBNP >3,606 (pg/mL)	1.62 (1.14−2.31)	.007	—	NS
Hyponatremia (Na^+ <135 mg/dL)	1.61 (1.12−2.32)	.009	1.61 (1.11−2.32)	.011
NYHA functional class (III-IV)	1.75 (1.23−2.48)	.002	—	NS

CI, confidence interval; HR, hazard ratio; other abbreviations as in Tables 1 and 2.
HR from stepwise Cox regression analysis. Variables with $P < .1$ on univariate analysis are shown and were included in the multivariable model.

Table 4. Univariate and Multivariate Predictors of 1-Year All-Cause Mortality

	Univariate		Multivariate	
Variable	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age (y)	1.07 (1.03−1.10)	.0005	1.06 (1.02−1.10)	.001
Cystatin C		<.0001		<.001
First quartile	1.0		1.0	
Second quartile	3.55 (1.15−10.89)	.027	2.45 (0.79−7.59)	.118
Third quartile	6.48 (2.22−18.89)	.001	4.34 (1.47−12.78)	.008
Fourth quartile	11.35 (4.01−32.14)	.0001	8.14 (1.21−23.26)	.001
Creatinine (mg/dL)	2.02 (1.48−2.75)	<.0001	—	NS
Urea nitrogen (mg/dL)	1.009 (1.005−1.012)	<.001		NS
eGFR by MDRD-4 (mL min^{-1} 1.73 m^{-22})	0.98 (0.97−0.99)	.0005	—	NS
Hemoglobin (mg/dL)	0.90 (0.82−0.99)	.42	—	NS
NT-proBNP >3,606 pg/mL	1.93 (1.18−3.13)	.008	—	NS
Hyponatremia (Na^+ <135 mg/dL)	1.81 (1.12−2.92)	.014	1.96 (1.21−3.20)	.006
NYHA functional class III-IV	1.77 (1.27−2.48)	.004	—	NS

Abbreviations as in Tables 1−3.
HR from Cox regression analysis. Variables with $P < .1$ on univariate analysis are shown and were included in multivariable model.

As expected, baseline characteristics of the population were concurrent with previous studies about epidemiology of HFPEF.[27,28] In accordance with this description, we can emphasize that the present population is similar to the patients typically hospitalized. In contrast, adverse events were slightly different to outcomes observed by Lassus et al.[11] They found 25.4% of all-cause mortality at 1-year follow-up. Although the baseline population was very similar, 50% of the patients had systolic dysfunction (LVEF <45%), which could be the reason for these differences.

Renal dysfunction, as defined by blood urea nitrogen, creatinine, eGFR, and so on, is one of the strongest risk factors for mortality in hospitalized and nonhospitalized HF patients.[4] Cystatin C is a new endogenous marker of renal function over a wide range of GFR. As a result, we found a stronger correlation with all measures of renal function by the Spearman rho correlation coefficient. It should be recommended for use as a reliable tool to assess renal dysfunction, especially in patients with normal creatinine levels.[29] Although we also found a correlation between hemoglobin and cystatin C, this was very weak. Anemia is usually associated with HF with or without renal impairment.

In the stepwise multivariate Cox regression model and in accordance with other publications, we noted a close relation between higher serum cystatin C levels and the incidence of all-cause mortality and/or readmissions. Although blood urea nitrogen is a simple test that seems to predict outcome better than creatinine in acute decompensated heart failure,[30] we also found cystatin C to be a stronger predictor of adverse events than urea, creatinine, and eGFR. Moreover, this relationship remained constant in patients with normal or mild impaired renal function (stages 1 and 2 of chronic kidney disease defined as eGFR >60 mL kg^{-1} 1.73 m^{-2}). These findings are also consistent with other studies.[7,11,14]

Despite the fact that many authors use the median of the cystatin C level, we preferred to categorize cystatin into quartiles, because normal ranges have not been well established in conditions other than renal failure. In fact, recent publications studied the usefulness of cystatin C by

Table 5. Reclassification Among Patients Who Experienced a Primary End Point and Those Who Did Not Experience a Primary End Point on Follow-Up

	Model with Cystatin C			
Model Without Cystatin C	<40% Risk	40%−80% Risk	>80% Risk	Total
Patients who experienced an event, n (%)				
<40% risk	7 (58.3)	5 (41.7)	0 (0.0)	12
40%−80% risk	13 (15.3)	65 (76.5)	7 (8.2)	85
>80% risk	0 (0.0)	6 (20.7)	23 (79.3)	29
Total	20	76	30	126
Patients who did not experience an event, n (%)				
<40% risk	17 (85.0)	3 (15.0)	0 (0.0)	20
40%−80% risk	29 (43.9)	36 (54.5)	1 (1.5)	66
>80% risk	0 (0.0)	2 (33.3)	4 (66.7)	6
Total	46	41	5	92

Established risk factors included age, GFR by MDRD-4 (mL kg^{-1} 1.73 m^{-2}), creatinine (mg/dL), urea nitrogen (mg/dL), hemoglobin (mg/dL), NT-proBNP > median, hyponatremia (Na^+ <135 mg/dL), and NYHA functional class III-IV. The net reclassification improvement was estimated to be 0.238 ($P < .001$).

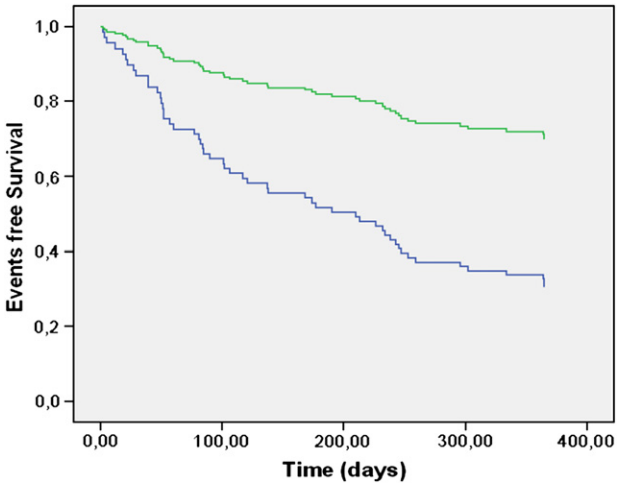

Fig. 3. Effect on survival and/or readmission of elevated cystatin C in patients without advance renal impairment (glomerular filtration rate estimated by Modified Diet in Renal Disease 4 >60 mL kg^{-1} 1.73 m^{-2}). Kaplan-Meier curves for patients with cystatin C <1.23 mg/L (*upper line*) and patients with cystatin C ≥1.23 mg/L (*lower line*). Mortality and/or readmission at 1 year 30.3% versus 68.8%. Log rank $P < .0001$.

quartiles[31] and tertiles[32] in acute HF. We did not find differences between the first and second quartiles of cystatin C in the adjusted model, but we demonstrated a strong prediction of outcomes, such that patients in the third quartile had a threefold adjusted risk for adverse events and in the highest quartile almost fivefold.

The prognostic value of hyponatremia, as one of the characteristics of a severely diseased population, was consistent with Tribouilloy et al,[2] who demonstrated the relation between mortality and hyponatremia in patients with HFPEF.

Serum cystatin C levels were also a stronger predictor of all-cause mortality than creatinine, urea, or eGFR. As a consequence, mortality increased specifically from the second quartile of cystatin C, because the adjusted model did not reach differences between first and second quartile. This finding could be used to stratify patients with HFPEF according to risk of death and may help to identify patients who need close management. This may also be an important strategy for focusing future clinical trials on this highest-risk population.

It is well known that patients with HF and renal dysfunction are at significantly higher risk of in-hospital mortality compared with patients without kidney disease, so increased mortality with higher serum cystatin C levels largely reflects the association with renal impairment. Nevertheless, the prognostic value of cystatin C may be dependent on mechanisms unrelated to renal function, so whether the usefulness of cystatin C reflects is solely due to its superior ability to detect small changes in GFR is not clear. In the present study, serum cystatin C levels >1.23 mg/L showed threefold adjusted risk for adverse outcome in patients without advanced renal impairment. In our opinion, cystatin C could have an independent mechanism of the renal dysfunction that contributes to increased risk, and it should be recommended to assess the risk stratification at the bedsides of patients with HFPEF.

Although Manzano-Fernández et al[32] found that each biomarker (cystatin C, NT-proBNP, and cardiac troponin T) provided independent and complementary prognostic information, we defend the highest prognostic power of cystatin C over NT-proBNP. We demonstrated improvement in the reclassification strategy with and without the new biomarker. We think cystatin C may have several advantages over NT-proBNP. Serum levels of NT-proBNP are usually very sensitive to congestion treatment, so they decrease quickly after diuretics therapy in the emergency department. Cystatin C levels could remain unchanged after initial treatment. Therefore, a sample of blood to measure cystatin C just before discharge could give important information to identify higher-risk patients. This issue should be evaluated in future studies. Furthermore, cystatin C levels also provide information of renal function despite normal levels of creatinine, urea, and eGFR by MDRD. Although NT-proBNP assay is cheaper than cystatin C assay, we need to perform only one determination of cystatin C, and HF patients usually undergo several measurements of NT-proBNP during hospitalization.

Unlike other studies, we excluded factors that might influence cystatin C levels, such as corticosteroid use[18] and thyroid dysfunction.[17] Although some authors believe that these factors do not contribute to the results, we do not totally agree.

Study Limitations

Limitations of our study are similar to those of any single-center prospective observational study. First, we cannot exclude residual or unmeasured confounding as a possible alternative explanation of our observational results, and a relatively small number of patients included in each group also made it difficult to detect firm conclusions. Second, owing to cystatin C being measured on admission, we do not know if serum cystatin C levels may change during the hospitalization. Third, we studied inpatients with high comorbidity, so the results should be analyzed under this special situation. Finally, we did not analyze cardiovascular mortality, and because we had evaluated a population with cardiac disease it would have been of interest to know it.

Conclusions

In the present study, we suggest that cystatin C is a strong and independent predictor of all-cause mortality and/or readmission in patients with acute heart failure with normal or mildly abnormal systolic LV function. Furthermore, cystatin C also identifies adverse outcomes without advance renal impairment (stages 1 and 2 CKD). Measurement of serum cystatin C may substantially improve the early assessment of heart failure with preserved or mildly reduced ejection fraction independent of renal function.

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Disclosures

None.

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