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Cystatin C Identifies Patients with Stable Chronic Heart Failure at Increased Risk for Adverse Cardiovascular Events

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Background—Renal function is a strong predictor of adverse events in heart failure. Current renal function measures are imperfect, and cystatin C (CysC) is promoted as a better marker of glomerular filtration rate. This study compares the prognostic use of CysC and derived glomerular filtration rate estimates with other measures of renal function in patients with chronic heart failure.

Methods and Results—We measured serum CysC levels in 823 patients with heart failure undergoing coronary angiography with follow-up of major adverse cardiovascular events (death, myocardial infarction, stroke). CysC levels strongly correlated with creatinine (r=0.73), blood urea nitrogen (r=0.70), and estimated glomerular filtration rate by the 4-variable modification of diet in renal disease equation (r=−0.62) (all P<0.001). However, the correlation was lower in estimated glomerular filtration rate ≥60 mL/min per 1.73 m^2. CysC-based measures significantly improved areas under the receiver operating characteristic curve for the prediction of major adverse cardiovascular events, especially in estimated glomerular filtration rate ≥60 mL/min per 1.73 m^2 (P<0.01). Net reclassification improvement was 22.2% (P<0.001) in this group. CysC remained an independent predictor of major adverse cardiovascular events (P<0.001) after adjustment for traditional risk factors and brain natriuretic peptide.

Conclusions—CysC is an independent predictor of adverse events in chronic heart failure. It adds prognostic value to creatinine, particularly in patients with preserved renal function.

Although risk prediction in individual patients with heart failure remains challenging, many factors have been shown to be predictive of adverse long-term outcomes. Renal dysfunction and elevated natriuretic peptides are among the strongest predictors.[1–3] Renal insufficiency has often been considered as a reduction in glomerular filtration rate (GFR) and is traditionally quantified based on serum creatinine (sCr) levels or equations that are derived from sCr measurements. However, the prognostic use of these sCr-based estimates in the chronic heart failure population remains inferior to GFR, directly quantified by ^{125}I-iothalamate clearance, suggesting that confounders exist.[4] Nevertheless, cardiovascular risk is believed to be significantly elevated below an estimated GFR of 60 mL/min per 1.73 m^2 based on these equations.[5]

In recent years, cystatin C (CysC) has emerged as a sensitive measure of renal function. CysC is a cysteine protease inhibitor produced by nearly all nucleated human cells at a fairly constant rate (housekeeping gene) and is subsequently circulated in the bloodstream. Compared with creatinine, levels of CysC are less influenced by age, sex, or race. Because of its low molecular weight (13 kDa), it is freely filtered and neither secreted from nor reabsorbed back into the bloodstream (although it is metabolized by the proximal tubular cells).[6] All these properties render CysC a potentially better estimate of GFR than sCr-based estimates. In the chronic kidney disease population, estimates of GFR have incorporated CysC as part of the new equations.[7] CysC has also proven to be a better predictor of mortality and cardiovascular events than sCr-based estimates in different populations studied (elderly, coronary heart disease, acute and chronic heart failure).[8–11]

Natriuretic peptides have found their way to everyday cardiology practice for diagnostic as well as prognostic purposes in patients with heart failure. Natriuretic peptides reflect myocardial stress and have proven to predict outcome after coronary syndromes, after hospitalization for acute heart failure, and in chronic heart failure.[2] Despite brain natriuretic peptide (BNP) levels being somewhat dependent on renal function, BNP and CysC potentially constitute a unique biomarker combination for risk prediction, particularly in the setting of relatively preserved renal function.

The aims of this study were as follows: (1) to examine the prognostic ability of CysC and derived equations, independent of BNP, (2) to examine its incremental value over traditional markers of renal function, and (3) to investigate risk

stratification by the combination of BNP and CysC in a chronic stable heart failure population undergoing cardiac evaluation.

Methods

Patient Population and Study Design

We evaluated 823 stable patients with a clinical history of heart failure undergoing elective coronary angiography as part of the GeneBank study. GeneBank was a large prospective study, conducted at the Cleveland Clinic between 2001 and 2006 (NCT 00590200) that established a well-characterized clinical repository with clinical and longitudinal outcomes. Inclusion criteria were age ≥18 years and planned coronary angiography. There were no specific exclusion criteria. All participants gave written informed consent approved by the Cleveland Clinic Institutional Review Board. At the time of cardiac catheterization, blood samples were collected, processed, and stored at −80°F until analyses.

Renal function was expressed as sCr, blood urea nitrogen levels, CysC, and estimated GFR by the 4-variable modification of diet in renal disease (MDRD) equation ($eGFR_{MDRD}=186\times sCr^{-1.154}\times age^{-0.203}\times[0.742$ if women$]\times[1.21$ if black$]$), the chronic kidney disease epidemiology collaboration equation for CysC ($eGFR_{CysC}=127.7\times CysC^{-1.17}\times age^{-0.13}\times[0.91$ if women$]\times[1.06$ if black$]$), or the $eGFR_{sCr+CysC}$ equation ($eGFR_{sCr+CysC}=177.6\times sCr^{-0.65}\times CysC^{-0.57}\times age^{-0.20}\times[0.82$ if women$]\times[1.11$ if black$]$). Preserved and impaired renal function were defined as $eGFR_{MDRD}$ ≥60 mL/min per 1.73 m^2 and $eGFR_{MDRD}$ <60 mL/min per 1.73 m^2, respectively.

The end point of this study was a composite of major adverse cardiovascular events (MACE), including all-cause mortality, nonfatal myocardial infarction (MI), and nonfatal cerebrovascular accident. Nonfatal events were defined as MI or cerebrovascular accident in patients who survived at least 48 hours after the onset of symptoms. These clinical outcomes were prospectively ascertained during the ensuing 3 years for all subjects after enrollment, adjudicated, and verified by source documentation.

CysC Assay

Plasma CysC level was determined with a particle-enhanced immunoturbidimetric immunoassay on the Architect ci8200 platform (Abbott Laboratories, Abbott Park, IL). Briefly, latex particles are coated with antihuman CysC antibody and agglutinated with CysC present in the patient's sample. The result is a change in absorbance, which is proportional to the amount of CysC present in the sample. The analytical range spans 0.05 mg/L to the highest calibration point. Intra- and interassay coefficients are 3.1% and 6%, respectively. BNP, high-sensitivity C-reactive protein (hsCRP), sCr, blood urea nitrogen, fasting blood glucose, and lipid profiles were all measured by clinically approved assays on the same platform. The intra- and interassay coefficients were, respectively, 0.9% and 0.8% for blood urea nitrogen, 1.7% and 1% for sCr, 2.6% and 3.5% for BNP, and 4% and 2.4% for hsCRP.

Statistical Analyses

Continuous variables were expressed as mean±SD if normally distributed or as median and interquartile range for non-normally distributed data. Categorical data were summarized as proportions and frequencies. Baseline characteristics between patients with preserved and decreased renal function were compared using the Student *t* test, the Wilcoxon rank-sum test, or the χ^2 test, as appropriate. The Spearman rank correlation method was used as a nonparametric measure of association for correlations between CysC and the different measures of renal function (sCr, blood urea nitrogen, eGFR equations). Areas under the receiver operating characteristic curves (C-statistics) for the prediction of MACE were compared between different measures of renal function, and net reclassification improvement was calculated. Univariate Cox proportional hazard models were used to evaluate the association of different measures of renal function along other variables with the composite outcome. Measures of renal function were entered as continuous variables (logarithmic transformed when non-normally distributed), categorized in quartiles. Because sCr levels differ substantially between sexes, sex-specific quartiles for sCr were used to equalize the distribution of men and women. Afterward, 2 types of multivariate Cox proportional hazard models were constructed: a shorter model, using one measure of renal function in combination with BNP, and a longer model, with a measure of renal function adjusted for all variables with $P<0.05$ in univariate analysis. The 3-year outcome was evaluated by Kaplan-Meier survival analyses, using the aforementioned quartiles. Differences between groups were evaluated with the log-rank test. Statistical significance was set at a 2-tailed $P<0.05$. All statistical analyses were performed using JMP Pro 9.0 (SAS Institute, Cary, NC). All authors had full access to all the data in the study and take responsibility for the integrity of data and accuracy of data analysis. All authors have read and agree to the article as written.

Results

Table 1 illustrates the baseline characteristics of our study population, which included 35% of subjects with left ventricular ejection fraction >50%. In our study cohort, 208 subjects (25%) had impaired renal function as defined by $eGFR_{MDRD}$ <60 mL/min per 1.73 m^2. Subjects with impaired renal function were likely older, women, with more comorbid conditions and higher median BNP levels (Table 1). CysC levels demonstrated a non-normal distribution (Figure 1), with a median level of 1.11 mg/L (interquartile range, 0.92–1.41 mg/L). As expected, CysC had a strong correlation with other markers of renal function. However, in the subgroup with preserved renal function, such correlations were less robust with non–CysC-based measures of renal function (online-only Data Supplement Table). There were no significant differences in baseline CysC levels between those with impaired versus preserved left ventricular ejection fraction.

During the 3-year follow-up period, the combined end point of MACE occurred in 201 (24%) patients, including 20% in the preserved renal function group (121 patients, 132 events: 80 deaths, 41 MI, and 11 cerebrovascular accidents) and 39% in the impaired renal function group (80 patients, 93 events: 62 deaths, 25 MI, and 6 cerebrovascular accidents). Areas under the receiver operating characteristic curves for CysC and CysC-based GFR estimations are significantly better than $eGFR_{MDRD}$, both in the total cohort and in the subgroup of patients with $eGFR_{MDRD}$ ≥60 mL/min per 1.73 m^2 but not in patients with $eGFR_{MDRD}$ <60 mL/min per 1.73 m^2 (Table 2). Nevertheless, in the $eGFR_{MDRD}$ ≥60 mL/min per 1.73 m^2 group, net reclassification improvement (compared with $eGFR_{MDRD}$) was 22.2% with CysC, 22.8% with $eGFR_{CysC}$, and 22.2% with $eGFR_{sCr+CysC}$ (all $P<0.001$). In univariate analysis, elevated levels of all renal measures were significantly associated with higher risks for the combined outcome in the overall cohort, both when entered as a continuous variable and when divided in quartiles (Table 3 and Figure 2). Age, body mass index, diabetes mellitus, coronary artery disease, hemoglobin, hsCRP, and BNP were also significantly associated with risk of future MACE in univariate analysis (data not shown). Increasing quartiles of CysC and decreasing quartiles for $eGFR_{CysC}$ demonstrated progressively higher risk of future MACE (Figure 3). In particular, by adjusting for age, sex, and race in the $eGFR_{CysC}$ equation, there was a better separation of patients with higher $eGFR_{CysC}$ values. However, in an analysis with covariate information (BNP, age, body mass index, history of coronary artery disease, history of diabetes mellitus, hemoglobin, and hsCRP), the difference in C-statistics was not significant anymore.

Table 1. Baseline Characteristics

	Total Cohort (n=823)	$eGFR_{MDRD}$ ≥60 mL/min per 1.73 m^2 (n=615)	$eGFR_{MDRD}$ <60 mL/min per 1.73 m^2 (n=208)	*P* Value*
Demographics				
Age, y	66±11	65±11	71±9	<0.0001
Male sex, %	60	64	48	<0.0001
BMI, kg/m^2	29.5±6.7	29.7±6.7	28.9±6.6	0.12
Comorbidities				
Diabetes mellitus, %	29	23	45	<0.0001
Hypertension, %	76	72	86	<0.0001
Hyperlipidemia, %	80	80	80	0.68
Current smoker, %	12	13	8	0.05
CAD, %	76	74	84	0.002
Echocardiographic data				
LVEF, %	35 (25–55)	35 (25–50)	40 (25–55)	0.10
Laboratory data				
Urea, mg/dL	21 (16–27)	19 (15–23)	35 (27–44)	<0.0001
Creatinine, mg/dL	0.94 (0.8–1.17)	0.87 (0.76–1.15)	1.41 (1.22–1.81)	<0.0001
Cystatin C, mg/dL	1.11 (0.92–1.41)	1.01 (0.88–1.18)	1.69 (1.42–2.13)	<0.0001
$eGFR_{MDRD}$, mL/min per 1.73 m^2	77 (60–93)	85 (72–97)	44 (36–53)	<0.0001
$eGFR_{CysC,}$ mL/min per 1. 73m^2	63 (47–80)	71 (58–84)	37 (30–46)	<0.0001
$eGFR_{sCr+CysC,}$ mL/min per 1.73 m^2	70 (53–86)	77 (66–90)	40 (32–48)	<0.0001
BNP, pg/mL	300 (118–675)	259 (106–540)	557 (220–1108)	<0.0001
Hemoglobin, g/dL	13.2±1.8	13.5±1.7	12.4±1.8	<0.0001
CRP, mg/dL	3.8 (1.6–9)	3.2 (1.4–7.8)	5.5 (2.6–14.1)	<0.0001
Medications				
ACE-I or ARB, %	68	68	66	0.49
β-blockers, %	67	67	66	0.67
Diuretic, %	58	53	72	<0.0001
Aspirin, %	62	62	63	0.80
Statin, %	59	60	57	0.36

eGFR indicates estimated glomerular filtration rate; BMI, body mass index; CAD, coronary artery disease; LVEF, left ventricular ejection fraction; CysC, cystatin C; sCr, serum creatinine; BNP, brain natriuretic peptide; CRP, C-reactive Protein; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker.
**P* value for difference between $eGFR_{MDRD}$ ≥60 mL/min per 1.73 m^2 and $eGFR_{MDRD}$ <60 mL/min per 1.73 m^2.

Figure 2 also demonstrates that, when looking at $eGFR_{MDRD}$, the risk of MACE seems to increase only when $eGFR_{MDRD}$ <60 mL/min per 1.73 m^2, in agreement with classic teaching. But when patients are stratified by CysC or derived equation, the risk of MACE seems to increase earlier and looks more like a continuum. Fifty-two percent (212/409 subjects) in the 2 higher CysC quartiles and 67% (415/617 subjects) in the 3 lower $eGFR_{CysC}$ quartiles had $eGFR_{MDRD}$ ≥60 mL/min per 1.73 m^2

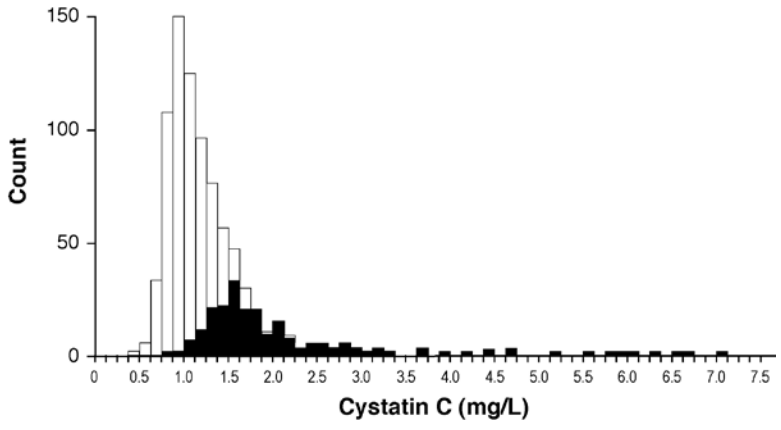


Figure 1. Histogram of serum cystatin C concentrations. Patients with $eGFR_{MDRD}$ <60 mL/min per 1.73 m^2 are projected in darker shade. eGFR indicates estimated glomerular filtration rate.

Table 2. AUC-ROC for Different Measures of Renal Function as Predictors of MACE

	AUC-ROC		
	Total Cohort (n=823)	eGFR ≥60 mL/min per 1.73 m^2 (n=615)	eGFR <60 mL/min per 1.73 m^2 (n=208)
$eGFR_{MDRD}$	0.615	0.529	0.550
CysC	0.648	0.600	0.586
	(*P*=0.07)	(*P*=0.006)	(*P*=0.18)
$eGFR_{CysC}$	0.652	0.603	0.589
	(*P*=0.01)	(*P*=0.001)	(*P*=0.18)
$eGFR_{sCr+CysC}$	0.641	0.581	0.573
	(*P*=0.02)	(*P*=0.02)	(*P*=0.25)

AUC-ROC indicates area under the curve-receiver operating characteristics; MACE, major adverse cardiovascular events; eGFR, estimated glomerular filtration rate; CysC, cystatin C; sCr, serum creatinine.

MACE=death, myocardial infarction, or stroke.

P values are for comparison with $eGFR_{MDRD}$.

and were not deemed to be at higher risk of MACE based on their $eGFR_{MDRD}$. However, CysC-based measurements showed they were at risk. This is particularly apparent when comparing different measures of renal function in those with $eGFR_{MDRD}$ ≥60 mL/min per 1.73 m^2, indicating a progressive increased risk for future MACE with increasing quartiles of CysC and decreasing quartiles of $eGFR_{CysC}$ (*P*=0.002 and 0.001, respectively) but not other measures (online-only Data Supplement Figure).

In different multivariate Cox proportional hazard models (each containing one measure of renal function), all renal function measures (except urea) were associated with higher risk of future MACE when adjusted for BNP (model 1) and other risk factors (model 2) (Table 3). Figure 4 depicts the additive value of CysC and BNP in overall risk prediction. Patients in the highest tertile of both variables had a 45% risk to experience death, MI, or stroke after 3 years compared with only 12% when both variables were in the lowest tertile (*P*<0.0001).

Discussion

There is a wealth of literature demonstrating the ability of CysC as a reliable and sensitive measure of renal dysfunction, and we and others have demonstrated the prognostic value of CysC in the setting of acute heart failure,[10,12–14] as well as in stable chronic heart failure.[9,15–17] However, the majority of studies have been limited to relatively small sample sizes that precluded adequately powered subgroup analyses with covariate adjustments to shed the light on how to best use this measure of renal function in the clinical setting. As the largest study looking at the clinical use of CysC in stable chronic heart failure using contemporary statistical methodologies, we observed that elevated CysC may identify a large number of patients at increased cardiovascular risk with what was previously labeled as preserved renal function ($eGFR_{MDRD}$ >60 mL/min per 1.73 m^2). Combining CysC with BNP provides excellent risk stratification, with an incidence of 12% of MACE at 3 years when both variables were in the lowest tertiles, versus an incidence of 45% of MACE at 3 years when both variables were in the highest tertiles. Taken together, our results imply that there is incremental prognostic value of CysC in patients with chronic stable heart failure, particularly in those with relatively preserved renal function based on creatinine-based estimates. This demonstrates that even in the setting of mild renal dysfunction there seems to be heightened risk for adverse cardiovascular outcomes.

Our findings corroborated prior studies[9,15] that suggested CysC may improve overall risk prediction in heart failure. The limitations of sCr's reciprocal relationship with GFR are well known, largely because of variable production (as a function of age, sex, muscle mass, and ethnicity), diet, and tubular secretion.[18] Creatinine-based equations try to correct for this by including determinants of muscle mass (age, weight, race, sex) in their formulas.[19] The equations were developed in patients with chronic kidney disease, where they are reasonably accurate.[20] It remains intriguing to see, in this and other studies,[21] that CysC is consistently better in risk prediction, whereas it is either equivalent or only slightly improves $eGFR_{MDRD}$ estimation.[7] We see 2 potential explanations for this observation.

Table 3. Uni- and Multivariate Cox Proportional Hazard Models for Different Renal Measures as Predictors of MACE

	Cox Proportional Hazard					
	Unadjusted		Model 1*		Model 2†	
Log-Transformed	Hazard Ratio†	*P* Value	Hazard Ratio†	*P* Value	Hazard Ratio‡	*P* Value
Urea	1.40 (1.22–1.59)	<0.0001	1.25 (1.09–1.42)	0.0016	1.14 (0.96–1.28)	0.17
Creatinine	1.34 (1.21–1.48)	<0.0001	1.22 (1.09–1.35)	0.0008	1.17 (1.03–1.32)	0.015
$eGFR_{MDRD}$	0.72 (0.65–0.80)	<0.0001	0.80 (0.72–0.90)	0.0002	0.85 (0.75–0.96)	0.012
Cystatin C	1.45 (1.30–1.60)	<0.0001	1.29 (1.15–1.44)	<0.0001	1.20 (1.05–1.36)	0.0085
$eGFR_{CysC}$	0.69 (0.62–0.77)	<0.0001	0.77 (0.68–0.87)	<0.0001	0.82 (0.73–0.94)	0.006
$eGFR_{sCr+CysC}$	0.70 (0.63–0.78)	<0.0001	0.78 (0.70–0.88)	<0.0001	0.83 (0.73–0.94)	0.006

MACE indicates major adverse cardiovascular events; eGFR, estimated glomerular filtration rate; CysC, cystatin C; sCr, serum creatinine; BNP, brain natriuretic peptide.

P value for log(BNP) <0.001 in every model.

*Model 1 is adjusted for log-transformed BNP.

†Model 2 is further adjusted for age, body mass index, history of coronary artery disease, history of diabetes mellitus, hemoglobin, and high-sensitivity C-reactive protein.

‡Hazard ratios are per 1 SD (urea 12.7, creatinine 0.89, $eGFR_{MDRD}$ 26.2, cystatin C 0.73, $eGFR_{CysC}$ 23.7, $eGFR_{sCr+CysC}$ 24.8).

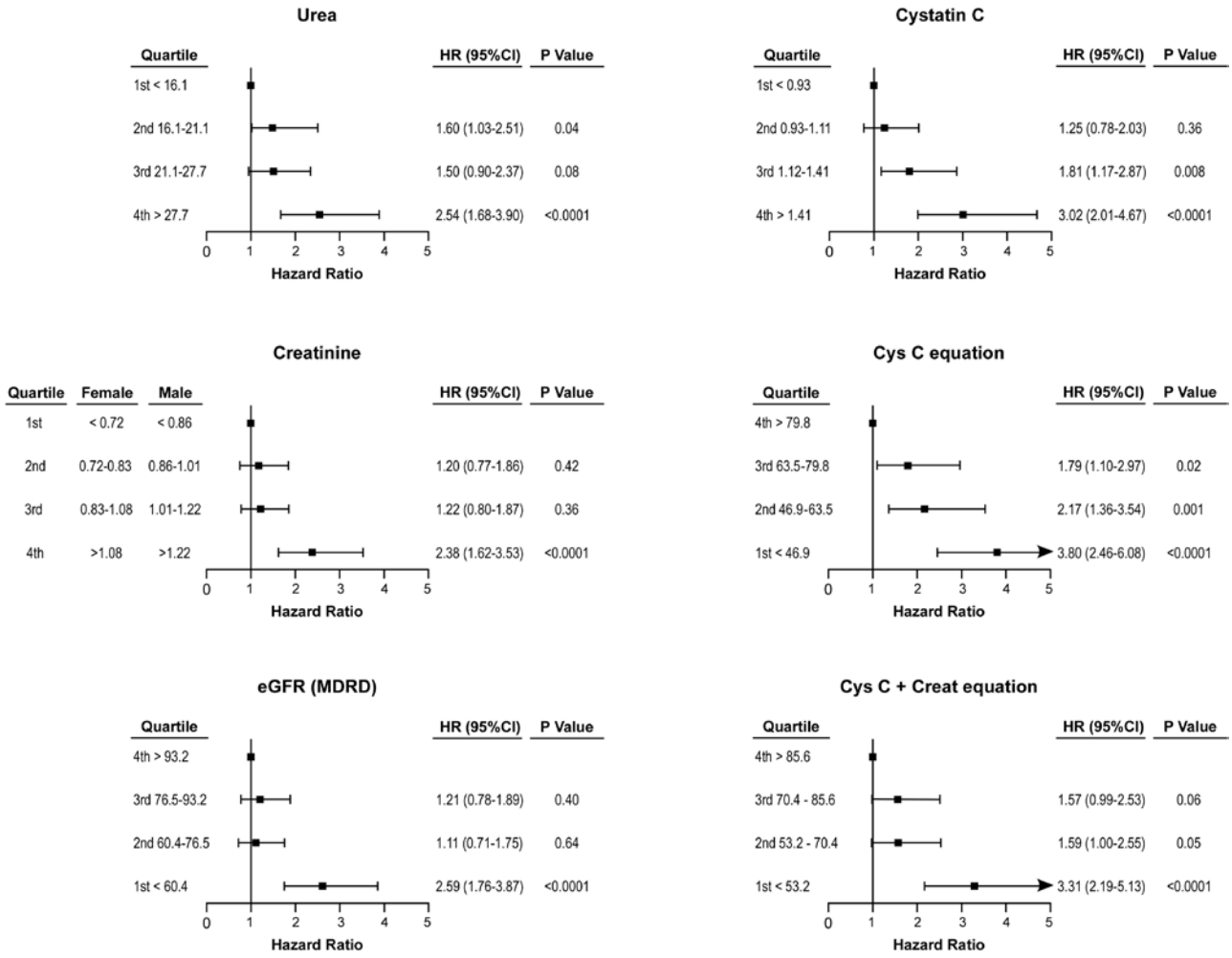
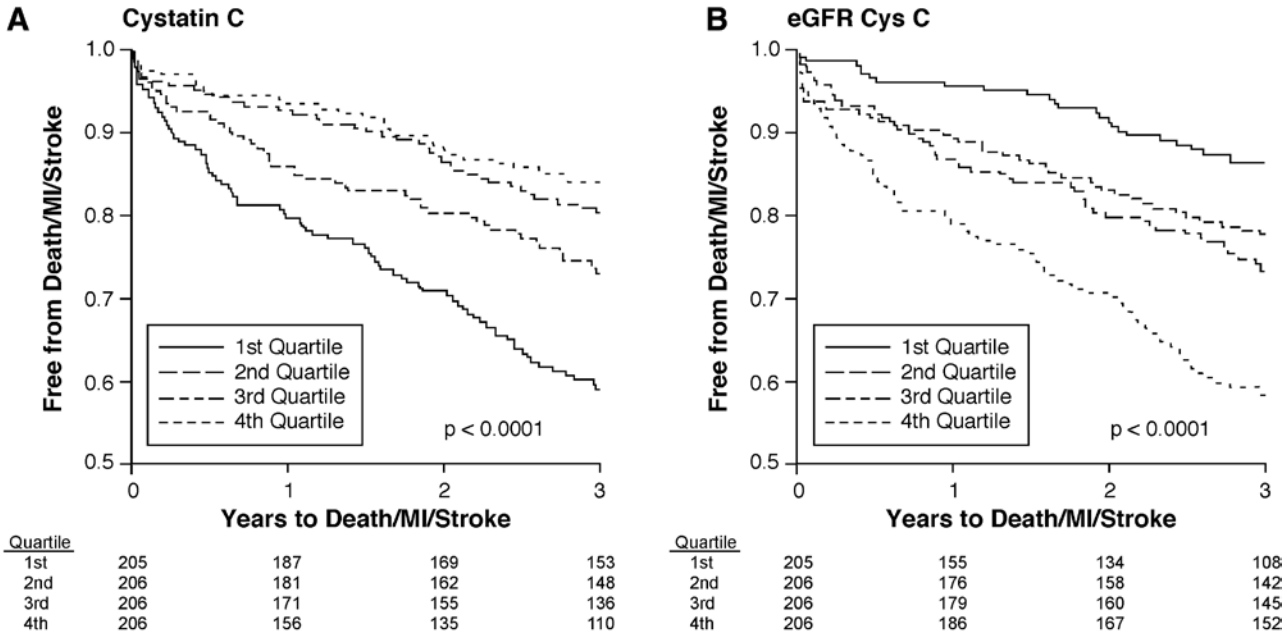


Figure 2. Forrest plots (unadjusted) for quartiles of different measures of renal function. Hazards ratio compared with reference for quartiles of urea, cystatin, creatinine (all in mg/dL), as well as estimated glomerular filtration rate (eGFR) equations (all in mL/min per 1.73 m²). CysC indicates cystatin C.

First, CysC and derived equations are significantly better than sCr-derived equations in estimating GFR in the nonchronic kidney disease population. This is well possible because in these nonchronic kidney disease populations (elderly, heart failure, coronary patients), mean GFR is higher, patients are older, and have more comorbidities. Current creatinine-based GFR equations tend to be less accurate in the higher GFR ranges as nicely demonstrated in the diabetic population and the heart failure population.[4,22,23] In addition, in the aforementioned settings, the dependence of creatinine on factors other than GFR (muscle mass, diet, and general health condition) becomes more and more important. These influences are not captured by correcting for age, sex, and race. A second possibility is that CysC represents other factors aside renal impairment. There is indeed some mechanistic evidence to suggest that CysC, being an inhibitor of cysteine proteases, may be intricately involved in the pathogenesis of atherosclerosis.[24] In addition, it has been shown that the levels of CysC can be influenced by inflammation, glucocorticoid use, and thyroid function.[25] All this may explain why the incremental prognostic value of CysC is mainly confined to those with relatively preserved renal function, whereas the role of measuring CysC in those with already impaired renal function as determined by sCr-based estimates is limited.

We have also applied for the first time the CysC-derived equation for estimating GFR in the heart failure population and found $eGFR_{CysC}$ to be reliably predictive of long-term outcomes (and potentially superior to $eGFR_{sCr+CysC}$). The observation that the $eGFR_{CysC}$ equation further improved risk prediction compared with CysC was unexpected. In fact, the correlation between CysC and $eGFR_{CysC}$ equation is very high (r=0.98), and the equation only reclassified 14% of patients in a different quartile. However, in addition to a play of chance, it remains possible that adjusting for age, sex, and race is important in this population. Interestingly, the addition of creatinine to the CysC-based equation ($eGFR_{sCr+CysC}$) weakened the prognostic ability again. This suggests that, once GFR is estimated on the base of CysC, any potential improvement of GFR estimation by adding sCr is outweighed by its association with muscle mass or general health condition.

One important observation from our study is the fact that one third of subjects in the subset with $eGFR_{MDRD}$ ≥60 mL/min per 1.73 m² (or up to one quarter of subjects in our entire study cohort) may demonstrate an elevated CysC level that



Quartile				
1st	205	187	169	153
2nd	206	181	162	148
3rd	206	171	155	136
4th	206	156	135	110

Quartile				
1st	205	155	134	108
2nd	206	176	158	142
3rd	206	179	160	145
4th	206	186	167	152

Figure 3. Kaplan-Meier curves for death/myocardial infarction (MI)/stroke according to quartiles of cystatin C (CysC) (**A**) and $eGFR_{CysC}$ (**B**). eGFR indicates estimated glomerular filtration rate.

is associated with heightened risk for future adverse cardiac events. This represents a relatively large population at risk. In this subgroup, CysC and CysC-derived equation were the only measures of renal function that stratified risk of adverse events. Taken together, the present data suggest that a decrease in GFR increases cardiovascular risk throughout its spectrum without a clear normal cut-off by sCr or sCr-based equations.

The current use of CysC in clinical practice is limited, despite its approval, clinical availability, and extensive nephrology and epidemiology literature to support its value. This is, in part, because no prior studies have relied on CysC as an inclusion criterion for treatment decisions, and limited therapeutic studies have provided analyses to test the differential impact of interventions in high versus low CysC subgroups. Nevertheless, the ability to identify a vulnerable population in a cohort of chronic stable heart failure is an opportunity to test therapeutic strategies that may potentially provide incremental benefit to existing therapies. Current clinical trials have used sCr-based cut-off values as exclusion criterion either because of therapeutic contraindications or to remove confounding because of concomitant end-organ dysfunction that may indirectly affect the demonstration of therapeutic efficacy. In contrast, natriuretic peptide-based cut-off values, identifying a more at-risk subpopulation, have been increasingly used in clinical studies to facilitate the successful demonstration of the benefits of drug therapy (such as eplerenone in mild heart failure).[26] At the other end of the spectrum, post hoc subgroup analysis has implied that lower rather than higher natriuretic peptide levels may demonstrate therapeutic benefits of statin therapy in ischemic cardiomyopathy.[27]

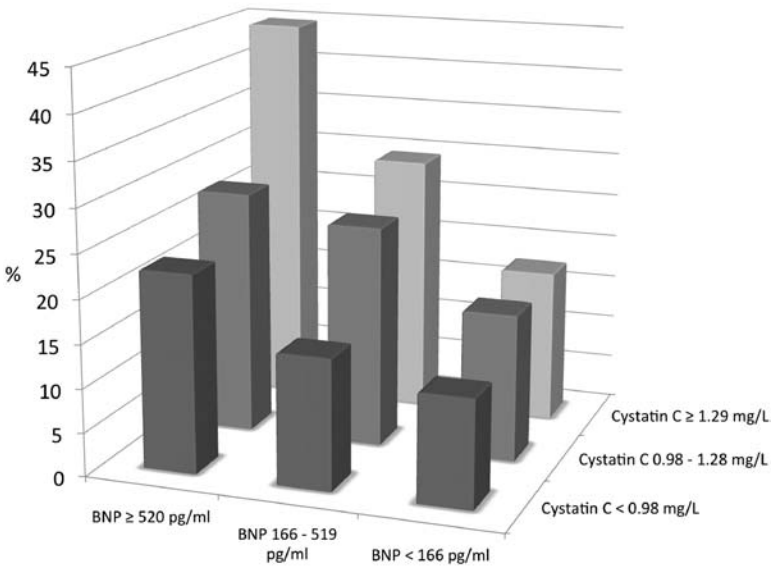


Figure 4. Risk stratification in patients with heart failure according to tertiles of cystatin C and brain natriuretic peptide (BNP). The risk of the combined outcome (death, myocardial infarction, stroke) increases from 12.3% in patients with both biomarkers in the lowest tertile to 44.8% in patients with both biomarkers in the highest tertile (P<0.0001).

Based on the interrelationship between CysC and BNP, it is conceivable to identify those with elevated natriuretic peptides and elevated CysC levels to test therapeutic strategies toward combined or separate targets in the setting of mild heart failure.

Study Limitations

The biggest limitation of this study is that there was no direct gold standard measurement of GFR (eg, inulin or ^{125}I-iothalamate clearance), yet recent reports of relationships between iothalamate-derived GFR measures and CysC or $eGFR_{MDRD}$ have been reported.[17] Consequently, it remains speculative to state that the CysC-derived equation may better reflect GFR in the heart failure population. Second, there was some degree of selection bias because the population studied included patients undergoing elective cardiac catheterization for symptom evaluation, and there were no prospective outcomes regarding heart failure hospitalizations. Furthermore, the particle-enhanced turbidimetric immunoassay used to determine CysC levels may have resulted in values that are 20% to 30% higher than in the common particle-enhanced nephelometric immunoassay method.[28] Similarly, the $eGFR_{CysC}$ equation was derived with CysC values determined by the nephelometric and not turbidimetric method, thus resulting in lower absolute $eGFR_{CysC}$ values. However, this should not alter the correlation of CysC or $eGFR_{CysC}$ with other measures of renal function, nor its risk predictive ability. Finally, we were not able to examine how CysC adds to other renal biomarkers (eg, neutrophil gelatinase-associated lipocalin) that reflect complementary renal processes (eg, tubular injury).

Conclusion

CysC is a strong predictor of adverse events in stable chronic heart failure, independent of traditional risk factors and BNP. CysC and its derived equation to eGFR add significant prognostic value to creatinine, predominantly in patients with relatively preserved renal function.

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Disclosures

Drs Dupont and Wu had no relationships to disclose. Dr Hazen reports being listed as coinventor on pending and issued patents held by the Cleveland Clinic relating to cardiovascular diagnostics. Dr Hazen reports having been paid as a consultant or speaker for the following companies: Abbott Diagnostics, BG Medicine Inc, Cleveland Heart Lab, Esperion, Lilly, Liposcience Inc, Merck & Co, Inc, and Pfizer Inc. Dr Hazen reports receiving research funds from Abbott, Cleveland Heart Lab, Liposcience Inc, and Pfizer Inc. Dr Hazen reports having the right to receive royalty payments for inventions or discoveries related to cardiovascular diagnostics or therapeutics from the companies shown below: Abbott Laboratories, Inc, Cleveland Heart Lab, Esperion, Frantz Biomarkers, LLC, Liposcience Inc, and Siemens. Dr Tang reports having received research grant support from Abbott Laboratories, Inc.

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