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Cystatin-C and mortality in elderly persons with heart failure

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Abstract

Objectives:

To evaluate cystatin-C, a novel measure of renal function, as a predictor of mortality in elderly persons with heart failure (HF), and to compare it with creatinine.

Background:

Renal function is an important prognostic factor in patients with HF, but creatinine levels, which in part reflect muscle mass, may be insensitive for detecting renal insufficiency.

Methods:

279 Cardiovascular Health Study participants with prevalent HF and measures of serum cystatin-C and creatinine were followed for mortality outcomes over a median of 6.5 years.

Results:

Median creatinine and cystatin-C levels were 1.05mg/dL and 1.26mg/L. Each SD increase in cystatin-C (0.35mg/L) was associated with a 31% greater adjusted mortality risk (95% CI: 20-43%; $p<0.001$); whereas each SD increase in creatinine (0.39mg/dL) was associated with a 17% greater adjusted mortality risk (95% CI: 1-36%; $p=0.04$). When both measures were combined in a single adjusted model, cystatin-C remained associated with elevated mortality risk (1.60; 1.32-1.94), whereas creatinine levels appeared associated with lower risk (0.73; 0.57-0.95).

Conclusions:

Cystatin-C is a stronger predictor of mortality than creatinine in elderly persons with HF. If confirmed in future study, this new marker of renal function could improve risk stratification in patients with HF.

Condensed Abstract

Cystatin-C, a novel measure of renal function, was evaluated as a predictor of mortality in elderly persons with heart failure (HF). 279 Cardiovascular Health Study participants with prevalent HF were followed for mortality outcomes. Each SD increase in cystatin-C (0.35mg/L) was associated with a 31% greater adjusted mortality risk (95% CI: 20-43%; $p<0.001$); whereas each SD increase in creatinine (0.39mg/dL) was associated with a 17% greater adjusted mortality risk (95% CI: 1-36%; $p=0.04$). Cystatin-C appears to be a stronger predictor of mortality than creatinine in elderly persons with HF.

Abbreviations

HF = Heart Failure

GFR = Glomerular Filtration Rate

CHS = Cardiovascular Health Study

MDRD = Modification of Diet in Renal Disease

MI = Myocardial Infarction

ACE = Angiotensin Converting-Enzyme

SD = Standard Deviation

Renal dysfunction is an important adverse prognostic factor in patients with heart failure (HF) (1-3). However, the standard clinical measures of renal function, serum creatinine and creatinine-based estimates of glomerular filtration rate (GFR), may be less correlated with actual GFR in the elderly (4). Cystatin-C, a novel serum measure of renal function (5), is a serine protease inhibitor that is released from all functioning cells. Although studies suggest that cystatin-C may better approximate GFR than creatinine (5-7), their associations with HF outcomes have not been compared. In this pilot study, we compared cystatin-C with creatinine and estimated GFR as mortality predictors in a cohort of elderly patients with HF.

METHODS

Participants

The Cardiovascular Health Study (CHS) is a community-based, longitudinal study of adults aged ≥ 65 years at entry. The objective of the study was to evaluate risk factors for the development and progression of cardiovascular disease (8). The original cohort of 5,201 study participants was recruited between 1989 and 1990, and an additional 687 African-Americans were recruited in 1992 and 1993. Follow-up interviews to identify potential clinical events were done semi-annually.

This study includes the 279 participants with prevalent HF at the 1992-93 visit of CHS. An expert panel adjudicated diagnoses of HF based on published criteria (9,10). The study design was approved by the Institutional Review Board at the University of Washington.

Predictors

Renal function:

Cystatin-C was measured from samples collected at the 1992-1993 visit and stored at -70°C, using a BNII nephelometer (Dade Behring Inc., Deerfield, IL) and a particle enhanced immunonephelometric assay (N Latex Cystatin-C) (11).

Serum creatinine was measured using the Kodak Ektachem 700 Analyzer (Eastman Kodak, Rochester, New York), a colorimetric method. We used the simplified MDRD equation to estimate GFR from serum creatinine.

Covariates:

Predictors used for adjustment included demographic characteristics (age, sex, race, and education level); past medical history [diabetes, hypertension, smoking status, alcohol intake, body mass index; myocardial infarction (MI) (prior to 1992-1993 visit), stroke, coronary revascularization procedure, claudication, and cancer (all prior to 1992-1993 visit); chronic obstructive pulmonary disease (from the 1989-90 visit)]; fibrinogen, C-reactive protein, lipid and hemoglobin levels from the 1992-93 visit; electrocardiogram findings (left ventricular hypertrophy and atrial fibrillation); and medication use (aspirin, diuretics, angiotensin converting-enzyme (ACE)-inhibitors, beta blockers, and calcium antagonists).

Outcome

The outcomes of interest was all-cause mortality. Follow-up began at the 1992-93 visit, and continued until June 30th, 2001.

Analysis

We compared participants with HF who survived to those who died during follow-up. To evaluate measures of renal function as predictors of mortality, cystatin-C and creatinine were evaluated as continuous variables per standard deviation. We used multivariate Cox proportional hazards models that were adjusted for all the above characteristics as candidate predictors. Covariates, whose entry into the model changed the coefficient of cystatin-C by 5% were retained and included in the final models for cystatin-C, creatinine, and estimated GFR. We also evaluated models that included both cystatin-C and creatinine. We did not evaluate estimated GFR as a continuous variable because of the implications of modeling ratios in regression analyses - in particular, problems with spurious correlations and the loss of scientific interpretation of the coefficient by adjusting for GFR (12).

We evaluated the association of quartiles of estimated GFR, cystatin-C, and creatinine as predictors of mortality. Creatinine quartiles were sex-specific to insure adequate representation of men and women within each. We determined the unadjusted and multivariate-adjusted risk for quartiles 2-4 compared with quartile 1. Multivariate analyses were done using the covariates selected for continuous variable analyses.

We compared adjusted mortality risk of participants with cystatin-C levels above and below the median after stratifying the cohort by the median creatinine and estimated GFR levels.

S-Plus (release 6.1, Insightful Inc, Seattle, WA) and SPSS statistical software (release 12.0.0, SPSS Inc, Chicago, IL) were used for the analyses.

RESULTS

During a median (range) follow-up time of 6.5 years (0.1-9.1), 182 (65%) died and the annual mortality risk was 11.1%. Characteristics associated with mortality include advanced age, male sex, reduced body mass index, and prior stroke (**Table 1**). Mean cystatin-C and creatinine levels were significantly higher and estimated GFR was lower among the participants who died during follow-up.

A one SD change in cystatin-C (0.34mg/L) was associated with mortality risk in unadjusted analyses, (1.31; 1.20-1.43), and this association was unchanged after multivariate adjustment (1.31; 1.17-1.47). A one SD change in creatinine (0.39mg/dL) was less strongly associated with mortality risk (1.23; 1.12-1.36), and the point estimate was attenuated somewhat by multivariate adjustment (1.17; 1.01-1.36). When both measures were combined in a single adjusted model, cystatin-C remained associated with elevated mortality risk (1.60; 1.32-1.94), whereas creatinine levels appeared associated with lower risk (0.73; 0.57-0.95). However, we cannot exclude colinearity as an explanation for this finding, as the correlation of the two measures was high ($r=0.80$).

After multivariate adjustment, the highest quartile of cystatin-C ($>1.55\text{mg/L}$) was associated with a two-fold mortality risk, whereas the lower three quartiles had similar risk (**Table 2**). Although the highest quartile of creatinine had elevated mortality risk in

unadjusted analysis, this association was not significant in adjusted analysis. After multivariate adjustment, the highest quartile of estimated GFR was associated with a 60% greater mortality risk than the lowest quartile (**Table 2**).

We evaluated the association of cystatin-C levels above and below the median (1.26mg/L) with mortality after stratifying by the median creatinine (1.05mg/dL) and estimated GFR levels (61ml/min/1.73m²) (**Figure 1**). Participants with cystatin-C levels above the median were at similarly elevated mortality risk, regardless of whether their creatinine or estimated GFR levels were above or below the median.

DISCUSSION

Cystatin-C was an independent predictor of mortality in elderly persons with HF. Persons with cystatin-C levels in the highest quartile ($>1.55\text{mg/L}$) had a two-fold adjusted mortality risk compared with those in the lowest quartile. Although creatinine levels were associated with mortality in a linear model, the association of cystatin-C with mortality was greater in magnitude, and persisted even after adjustment for creatinine. This novel measure of renal function could potentially improve the risk stratification of elderly patients with HF.

Prior studies have found that renal dysfunction, measured by creatinine or estimated GFR, is a strong predictor of mortality in the setting of HF (1-3). Because creatinine levels are influenced heavily by muscle mass, estimated GFR is recommended by the National Kidney Foundation as the appropriate renal function measure for clinicians (13). However, estimates of GFR may not be optimal in persons with normal creatinine levels (14). Cystatin-C may overcome some of the limitations of creatinine and estimated GFR, as it does not appear to be dependent on age, sex, or body mass.

This study has certain important limitations. The small sample size of participants with HF limited power to detect differences across the lower quartiles of each renal function measure, or to conduct subgroup analyses by sex and race. This is a sample of elderly subjects with heart failure, so we do not know whether cystatin-C would have advantages over creatinine in younger patients or those with different diagnoses. In addition, though we presume that the association of cystatin-C with mortality is caused by its correlation with GFR, we cannot exclude the

possibility that circulating cystatin-C levels have either directly harmful effects or reflect another pathological process distinct from renal function.

CONCLUSION

Independent of both creatinine and traditional risk factors, cystatin-C is a strong predictor of mortality in persons with HF. Further study will be needed to confirm this finding and to determine whether measurement of cystatin-C would have clinical benefits in the care of elderly patients with HF.

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Single copies of the article can be downloaded and printed only for the reader's personal research and study.

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REFERENCES

1. Al Ahmad A, Rand WM, Manjunath G, et al. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. *J Am Coll Cardiol* 2001;38:955-62.
2. Dries DL, Exner DV, Domanski MJ, Greenberg B, Stevenson LW. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. *J Am Coll Cardiol* 2000;35:681-9.
3. Shlipak MG, Smith GL, Rathore SS, Massie BM, Krumholz HM. Renal function, digoxin therapy and heart failure outcomes - evidence from the Digoxin Intervention Group Trial. *J Am Soc Nephrol* 2004;In press.
4. Lamb EJ, O'Riordan SE, Webb MC, Newman DJ. Serum cystatin C may be a better marker of renal impairment than creatinine. *J Am Geriatr Soc* 2003;51:1674; author reply 1674-5.
5. Fliser D, Ritz E. Serum cystatin C concentration as a marker of renal dysfunction in the elderly. *Am J Kidney Dis* 2001;37:79-83.
6. Newman DJ, Thakkar H, Edwards RG, et al. Serum cystatin C measured by automated immunoassay: a more sensitive marker of changes in GFR than serum creatinine. *Kidney Int* 1995;47:312-8.
7. Bokenkamp A, Domanetzki M, Zinck R, Schumann G, Byrd D, Brodehl J. Cystatin C--a new marker of glomerular filtration rate in children independent of age and height. *Pediatrics* 1998;101:875-81.
8. Fried LP, Borhani NO, Enright P, et al. The Cardiovascular Health Study: Design and rationale. *Ann Epidemiol* 1991;1:263-276.

9. Psaty BM, Kuller LH, Bild D, et al. Methods of assessing prevalent cardiovascular disease in the Cardiovascular Health Study. *Ann Epidemiol* 1995;5:270-7.
10. Gottdiener JS, McClelland RL, Marshall R, et al. Outcome of congestive heart failure in elderly persons: influence of left ventricular systolic function. The Cardiovascular Health Study. *Ann Intern Med* 2002;137:631-9.
11. Erlandsen EJ, Randers E, Kristensen JH. Evaluation of the Dade Behring N Latex Cystatin C assay on the Dade Behring Nephelometer II System. *Scand J Clin Lab Invest* 1999;59:1-8.
12. Kronmal RA. Spurious correlation and the fallacy of the ratio standard revisited. *J Royal Stat Soc A* 1993;156:379-392.
13. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Kidney Disease Outcome Quality Initiative. *Am J Kidney Dis* 2002;39:S1-246.
14. Verhave JC, Gansevoort RT, Hillege HL, De Zeeuw D, Curhan GC, De Jong PE. Drawbacks of the use of indirect estimates of renal function to evaluate the effect of risk factors on renal function. *J Am Soc Nephrol* 2004;15:1316-22.

Table 1: Baseline characteristics of participants with heart failure, by survival during follow-up

Characteristic	Alive (n=97)	Dead (n=182)	P-value
Age (years)	74 (5)	78 (6)	<0.0001
Male	37 (38%)	101 (56%)	0.01
African-American	22 (23%)	28 (15%)	0.13
High school graduate	63 (65%)	106 (58%)	0.45
Body Mass Index	29 (5)	27 (5)	<0.0001
Diabetes	25 (26%)	54 (30%)	0.49
Prior MI	40 (41%)	75 (41%)	1.00
Prior Stroke	8 (8%)	36 (20%)	0.01
Prior Revascularization	16 (17%)	17 (9%)	0.08
Cancer	14 (15%)	36 (22%)	0.19
Systolic Blood Pressure	136 (25)	136 (24)	0.96
Diastolic Blood Pressure	68 (13)	68 (14)	0.86
Total cholesterol (mg/dl)	203 (40)	195 (40)	0.12
LDL cholesterol (mg/dl)	122 (36)	118 (33)	0.34
HDL cholesterol (mg/dl)	49 (13)	49 (14)	0.91
CRP (mg/dl)	9.0 (16.8)	8.4 (13.3)	0.76
Hemoglobin	13.4 (1.5)	13.2 (1.7)	0.17
Atrial Fibrillation	7 (7%)	22 (12%)	0.20
Left Ventricular Hypertrophy	8 (8%)	13 (14%)	0.20
Cystatin-C (mg/l)	1.18 (0.29)	1.46 (0.53)	<0.0001
Creatinine (mg/dl)	1.03 (0.33)	1.24 (0.48)	<0.0001
Estimated GFR (ml/min/1.73 m ²)	70 (18)	62 (22)	0.001

CRP = C-reactive protein, GFR = Glomerular filtration rate, HDL = High density lipoprotein, LDL = Low density lipoprotein, MI = Myocardial infarction

Table 2: Quartiles of renal function and mortality risk in elderly patients with heart failure

	1 st Quartile	2 nd Quartile	3 rd Quartile	4 th Quartile
Cystatin-C				
Range	≤1.03	1.04-1.26	1.27-1.55	≥1.56
N	69	71	70	69
Annual Risk	7%	10%	12%	19%
Unadjusted HR	1.00	1.49 (0.94-2.37)	1.89 (1.21-2.96)	3.35 (2.17-5.17)
Adjusted HR	1.00	1.04 (0.64-1.70)	1.18 (0.70-1.99)	2.15 (1.30-3.54)
Creatinine				
Range in Women	0.45-0.75	0.85	0.95-1.05	1.15-4.05
Range in Men	0.75-0.95	1.05-1.25	1.35-1.45	1.55-3.05
N	77	70	54	78
Annual Risk	9%	11%	10%	16%
Unadjusted HR	1.00	1.32 (0.87-2.00)	1.19 (0.75-1.89)	2.01 (1.36-2.98)
Adjusted HR	1.00	0.97 (0.61-1.54)	1.01 (0.62-1.64)	1.38 (0.88-2.16)
Estimated GFR				
Range	>80.96	61.80-80.96	49.28-61.79	≤49.27
N	70	69	71	69
Annual Risk	7%	12%	10%	17%
Unadjusted HR	1.00	1.64 (1.05-2.55)	1.37 (0.87-2.14)	2.67 (1.75-4.09)
Adjusted HR	1.00	1.20 (0.74-1.95)	0.77 (0.47-1.26)	1.62 (1.01-2.59)

HR = Hazard ratio

Figure legend: Association of cystatin-C levels with mortality in elderly persons with heart failure, stratified by creatinine and estimated GFR levels. The figure displays annual mortality risk for participants with cystatin-C levels above (high) or below (low) the median of 1.26mg/L. The adjusted hazard ratios compare high versus low cystatin-C among subgroups of participants with high creatinine (above median of 1.05mg/dL) or low creatinine ($<1.05\text{mg/dL}$); and by high estimated GFR ($>61\text{ml/min/1.73m}^2$) or low estimated GFR ($<61\text{ml/min/1.73m}^2$).

Cr = Creatinine, eGFR = Estimated GFR, HR = Hazard ratio

Figure 1:

