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Biomarkers

Cystatin C and Long-Term Mortality Among Subjects With Normal Creatinine-Based Estimated Glomerular Filtration Rates

NHANES III (Third National Health and Nutrition Examination Survey)

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Objectives The objective was to test the association of cystatin C (Cys-C) with long-term mortality risk in the subjects with normal creatinine-based estimated glomerular filtration rates (eGFR).

Background Cys-C has been proposed as a sensitive indicator of renal dysfunction that is associated with cardiovascular events. The predictive value of Cys-C for mortality risk (both cardiovascular and noncardiovascular) and its utility among persons with normal kidney function remains unclear.

Methods The analysis included 2,990 subjects over 40 years of age with normal eGFR who participated in NHANES III (Third National Health and Nutrition Examination Survey). Normal eGFR was defined by Modification of Diet in Renal Disease (MDRD) equation ≥60 ml/min/1.73 m^2. Serum Cys-C was categorized as high, medium, or low. In 1 analysis, the high and low groups were the top and bottom 10%, and in the second analysis, they were the upper and lower thirds. All-cause and cause-specific mortality were obtained from the NHANES III–linked follow-up file through December 31, 2006. Multivariate Cox regression models were applied to assess the association of interest.

Results Within an average of 13.7 years follow-up, 488 cardiovascular and 719 noncardiovascular deaths occurred. When the first and last deciles were compared, the relative risks were all increased statistically as follows: all-cause, 4.36 (95% confidence interval [CI]: 2.52 to 7.82); cardiovascular, 7.44 (95% CI: 3.06 to 18.1); cancer, 2.45 (95% CI: 0.85 to 7.04); and noncardiovascular 3.15 (95% CI: 1.53 to 6.49) mortalities. Relative risks all moderated to lower values when the comparisons were expanded to include the upper and lower thirds. Similar associations were still present when Cys-C was modeled on a continuous scale, suggesting a linear relationship between Cys-C and mortality outcomes.

Conclusions Serum Cys-C is prognostic of long-term mortality in the subjects with relatively normal renal function, independent of MDRD eGFR and albuminuria. (J Am Coll Cardiol 2010;56:1930–6) © 2010 by the American College of Cardiology Foundation

Cystatin C (Cys-C) is a 13-kDa protein and member of the family of competitive lysosomal cysteine protease inhibitors. The continual synthesis of Cys-C in nucleated cells and its association with pre-clinical renal disease have prompted the use of Cys-C to estimate renal function. For instance, high serum Cys-C is reportedly predictive for all-cause mortality, cardiovascular disease, and the prognosis for congestive heart failure (1,2).

Cys-C is freely filtered by the glomerulus and has potential advantages over creatinine when estimating glomerular filtration rate (GFR) in that its production is not dependent on muscle mass. In addition, it is unaffected by age, fever, or exogenous agents (3). In comparison, serum

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creatinine, the primary tool for evaluation of kidney function in clinical practice, can be affected by extrarenal factors including age, body weight, nutritional status, ethnicity, and gender (4). In addition, it is insensitive to modest decreases in kidney function (5). As a result, Cys-C has been suggested as a more accurate estimate of GFR than creatinine-based equations and may also predict declining kidney function even when the GFR is actually near the normal range (6).

Although renal dysfunction appears to be the most plausible link between increased Cys-C and impaired cardiovascular outcomes, the predictive value of Cys-C for long-term mortality outcomes among populations with normal kidney function has not been studied extensively (7). In addition, whereas most studies on Cys-C focus on cardiovascular outcomes, it remains unclear whether elevated Cys-C is also associated with increased mortality of cancer and other noncardiovascular disorders. In the current study, cohort follow-up data were analyzed to test the hypothesis that Cys-C is associated with long-term mortality for all-cause, cardiovascular disease, cancer, and noncardiovascular death among subjects with normal creatinine-based GFR. The data were obtained from a large national dataset.

Methods

Study design and population. NHANES III (Third National Health and Nutrition Examination Survey) was conducted by the National Center for Health Statistics (NCHS) from 1988 to 1994 using a stratified, multistage, and cluster sampling design to obtain a representative sample of the noninstitutionalized civilian U.S. population. The NHANES III was reviewed and approved by the NCHS Institutional Review Board. Data collection included in-depth, in-person interviews, physical and physiological examinations, and laboratory tests. This study was restricted to 2,990 non-Hispanic Whites, non-Hispanic Blacks, and Mexican-American participants aged 40 years or older with normal kidney function, defined as Modification of Diet in Renal Disease (MDRD) estimated glomerular filtration rate (eGFR) ≥60 ml/min/1.73 m^2, and valid measurements of serum Cys-C (8). Serum Cys-C was measured in NHANES III in all participants age 60 years and in a 25% random sample of participants age 12 to 59 years. A sample weight variable for Cys-C was thus used to adjust for the unequal probabilities of selection to represent the U.S. population (9).

Measurements of serum Cys-C. Serum from fasting blood samples was stored at −70°C until analyzed. Cys-C was then measured using a particle-enhanced immunonephelometric assay (N Latex Cys-C, Dade Behring, Deerfield, Illinois) at the Cleveland Clinical Research Laboratory. Cys-C samples with this assay had a range of 0.23 to 7.25 mg/l (17.2 to 543.0 nmol/l) and an intra-assay imprecision of 2.0% to 3.0% coefficient of variation and an interassay imprecision of 3.2% to 4.4% coefficient of variation (10).

Abbreviations and Acronyms

AUC = area under the curve
Cys-C = cystatin C
eGFR = estimated glomerular filtration rate
GFR = glomerular filtration rate
ROC = receiver-operating characteristic
TG = triglyceride
UACR = urinary albumin-to-creatinine ratio

Baseline demographic and clinical factors. Data were collected by trained personnel according to standardized procedures (11). Information for age, sex, and smoking was self-reported. Current cigarette smoking was coded as a dichotomous "yes/no" variable. Hypertension was defined as an average systolic blood pressure ≥140 mm Hg, a diastolic blood pressure ≥90 mm Hg, a physician's diagnosis or the use of antihypertensive medication (12). Diabetes mellitus was assessed by self-reported diagnosis of diabetes, the use of diabetic medications (insulin or oral agents), a nonfasting plasma glucose ≥11.1 mmol/l (200 mg/dl), or a fasting plasma glucose ≥7 mmol/l (126 mg/dl). Serum triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, fibrinogen, uric acid, hemoglobin, blood urea nitrogen, C-reactive protein (CRP), urinary albumin, and creatinine were analyzed by laboratory methods reported elsewhere (13). Urinary albumin-to-creatinine ratios (UACR, in mg/mmol) were calculated accordingly (14,15). The GFR was calculated from MDRD (Modification of Diet in Renal Disease) study equation: (ml/min/1.73 m^2) = 175 × $(Scr)^{-1.154}$ × $(Age)^{-0.203}$ × (0.742 if female) × (1.210 if African American) (16). Serum creatinine was measured by means of the modified kinetic Jaffé reaction, followed by calibration using an enzymatic creatinine assay traceable to a gold-standard reference method as described previously (17).

Mortality follow-up. The underlying cause of death was coded using the International Classification of Diseases-10th Revision (ICD-10) (18). The association of Cys-C with long-term mortality was evaluated for deaths from all-cause, cardiovascular disease (ICD codes: I00 to I78), malignant neoplasm (ICD-10 codes: C00 to C97), and noncardiovascular mortality. Noncardiovascular mortality was defined as mortality cases not belonging to the category of cardiovascular causes. Length of follow-up for each participant was calculated as the time from the NHANES III examination date to the end of follow-up (date of death or December 31, 2006). Thus, those found alive were right-censored on the last date known alive or at the end of the study, and likewise those who died from other causes were also right-censored at the time of death for cause-specific analysis. Age-adjusted all-cause and cause-specific mortality rates (per 1,000 person-years) were calculated using direct standardization according to the 2000 U.S. standard population (19).

Statistical analysis. NHANES used a complex sampling design and a complex survey design, including nonresponse

and unequal sampling probabilities, and provided sampling weights for constructing national estimates. SUDAAN 9.03 (2004, Research Triangle Institute, Research Triangle Park, North Carolina) was used with the Taylor-series linearization to obtain unbiased standard errors for statistical estimates in all analyses. Demographic and clinical characteristics were compared across 3 categories of Cys-C level with analysis of variance (ANOVA) for continuous variables and the Cochran-Mantel-Haenszel chi-square test for categorical variables. Subjects were classified into the high (>90th percentile) (Cys-C >1.08 mg/l), medium (10th to 90th percentile) (Cys-C 0.7 to 1.08 mg/l), and low (<10th percentile) (Cys-C <0.7 mg/l) and also into tertiles (Cys-C <0.80, 0.80 to 0.93, and >0.93 mg/l). Time to event was first examined using the Kaplan-Meier product limit survival method, followed by univariate and multivariate Cox proportional hazard model with Efron method to calculate relative risk (RR), also known as the hazard ratios, to evaluate mortality risk associated with serum Cys-C for all-cause and cause-specific deaths. Potential confounding factors such as MDRD, UACR, and CRP were accordingly examined and adjusted in the models based on p values from univariate analyses (included when $p < 0.10$) and prior knowledge regarding the importance of risk factors. The level of significance was set at 0.05.

The receiver-operating characteristic (ROC) curves were used to assess the discriminative power of Cys-C as a continuous variable to differentiate the occurrence of all-cause mortality, cardiovascular mortality, cancer mortality, and noncardiovascular mortality. Area under curve (AUC) was calculated. The optimal cutoff point, defined as the least $(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2$ or the shortest distance from the left upper corner to the ROC curve, was reported.

Results

Baseline demographic and clinical variables are shown in Table 1. The sample of 2,990 participants was equivalent to an estimated U.S. population of 63,192,373 persons 40+ years of age after adjusting for sample weights. The overall mean (± SE) serum Cys-C of the study population was 0.89 ± 0.01 mg/l (5th to 95th percentile range 0.66 to 1.16 mg/l), with the average concentrations, respectively, for subjects in the high (highest decile, n = 577), medium (2nd to 9th decile, n = 2,199), and low (lowest decile, n = 214) groups were 1.19 ± 0.008 mg/l, 0.87 ± 0.004 mg/l, and 0.65 ± 0.005 mg/l (Fig. 1). Except fasting glucose, all demographic and clinical variables were statistically different across Cys-C categories ($p < 0.05$, ANOVA and chi-square tests for continuous and categorical outcomes, respectively). Overall, the participants in the high Cys-C group were more often older, male, and hypertensive. Likewise, CRP increased with Cys-C concentrations (Spearman's correlation: 0.092, $p < 0.001$). In addition, there was a significant but nonlinear relationship between Cys-C and UACR (Spearman's correlation: 0.164, $p < 0.001$, data not shown).

Within an average of 13.7 years of follow-up (range 0.5 to 18 years), 1,206, 487, 320, and 719 subjects died, respectively, from all-cause, cardiovascular, cancer, and noncar-

Table 1 Baseline Demographic and Clinical Characteristics of Participants* (n = 2,990)

Characteristics	Cystatin C <10th Percentile (<0.70 mg/l) (n = 214)	Cystatin C 10th–90th Percentile (0.70–1.08 mg/l) (n = 2,199)	Cystatin C >90th Percentile (>1.08 mg/l) (n = 577)
Males, %*	20.6 (5.02)	53.3 (1.96)	62.1 (3.82)
Microalbuminuria, %	12.2 (4.41)	10.6 (1.15)	22.3 (2.94)
Diabetes, %	14.7 (4.31)	6.77 (1.19)	11.3 (1.97)
Hypertension, %	25.0 (4.39)	39.9 (1.69)	51.9 (3.54)
Current smoking, %	20.4 (4.09)	24.8 (1.84)	35.5 (4.70)
Age, yrs	46.8 (0.73)	53.4 (0.56)	64.3 (1.17)
BMI, kg/m^2	25.0 (0.62)	27.4 (0.19)	28.0 (0.28)
Hemoglobin, g/dl	13.5 (0.19)	14.3 (0.07)	14.3 (0.07)
TG, mg/dl	117.7 (10.5)	170.0 (10.7)	184.8 (9.52)
HDL, mg/dl	58.5 (2.38)	50.0 (0.79)	44.9 (0.99)
Fibrinogen, mg/dl	310.1 (13.5)	295.5 (4.34)	322.8 (7.57)
C-reactive protein, mg/l	0.35 (0.03)	0.42 (0.03)	0.62 (0.06)
Uric acid, mg/dl	4.16 (0.13)	5.35 (0.06)	5.91 (0.09)
Fasting glucose, mg/dl	113.3 (8.09)	101.6 (1.90)	103.9 (2.83)
Blood urea nitrogen, mg/dl	12.3 (0.37)	14.2 (0.22)	16.0 (0.35)
Serum creatinine, mg/dl	0.92 (0.01)	1.03 (0.01)	1.08 (0.01)
eGFR, ml/min/1.73 m^2	79.4 (1.40)	73.5 (0.38)	68.6 (0.61)
UACR, mg/mmol	4.85 (2.59)	1.77 (0.20)	7.62 (3.29)

All demographic and clinical variables, except fasting glucose, are statistically different across cystatin C categories ($p < 0.05$). Data are expressed as either mean or percentage with standard error. *With adjustment for sample weight.

eGFR = glomerular filtration rate calculated from the Modification of Diet in Renal Disease (MDRD) study equation; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TG = triglyceride; UACR = urinary albumin-to creatinine ratio.

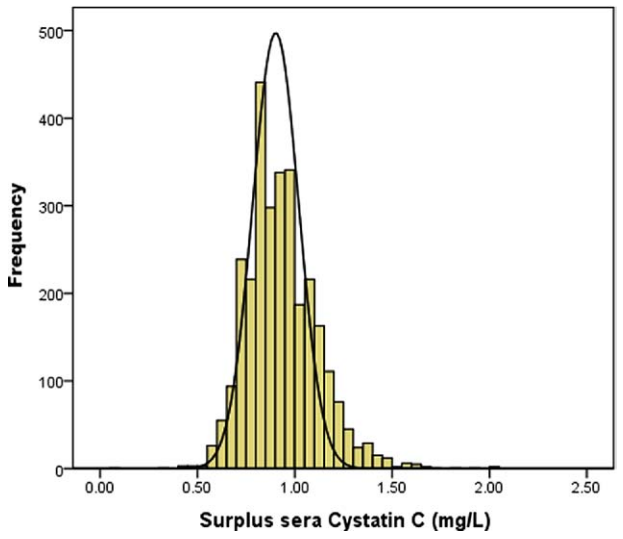

Figure 1 **Histogram of Serum Cys-C Concentrations**

The histogram shows the distribution of serum cystatin C (Cys-C) concentrations. Kolmogorov-Smirnov *Z*-test indicates a deviation from normal distribution ($p < 0.001$). The overall mean (± SE) serum Cys-C of the study population was 0.89 ± 0.01 mg/l (5th to 95th percentile range: 0.66 to 1.16 mg/l). **Solid curve** = the normality plot.

diovascular causes. This corresponds to age-adjusted mortality rates (year 2000 U.S. standard population) of 19.8, 7.7, 5.7, and 12.1 per 1,000 person-years in that order (data not shown). The results from Kaplan-Meier survival curves stratified by Cys-C categories for all-cause (Fig. 2A) and cause-specific mortality (Figs. 2B to 2D) showed that, when compared with persons with low Cys-C, those with medium or high levels of Cys-C concentrations were generally at higher risk for all-cause and cause-specific mortality. Similar results were obtained from univariate analyses (Table 2). For instance, the relative risks for all-cause mortality for high and medium Cys-C were 17.6 (95% CI: 10.1 to 30.9) and 5.64 (95% CI: 3.11 to 10.2), respectively, as compared with those with low levels of serum Cys-C. Despite the decrease in relative risks following adjustment for age, sex, diabetes mellitus, hypertension, smoking, CRP, UACR, and MDRD eGFR, the associations between Cys-C and mortality risk remained significant for all-cause, cardiovascular, and noncardiovascular disease but not for cancer (Table 2). Although an apparent increased risk of cancer mortality was still observed in individuals with high and medium Cys-C, the results did not attain statistical significance ($p = 0.18$). Similar trends were observed when the population was divided into tertiles based on serum Cys-C concentrations. The associations were statistically significant for all-cause and cause-specific mortalities in the univariate analyses but did not reach statistical significance after adjustment for covariates (Online Table 1).

Of the covariates examined in multivariate-adjusted analyses, age and current smoking were 2 leading risk factors for mortality. Excluding cancer, MDRD eGFR and UACR were important predictors of all-cause and cause-specific deaths ($p < 0.05$). Hypertension and CRP are likewise related to increased mortality risk, but are only significant in all-cause mortality and cancer death (hypertension only). Sex and diabetes were also significantly associated with all-cause and cardiovascular mortality ($p < 0.05$) (Table 2, Online Table 1).

The multivariate-adjusted relative risks by modeling mortality using log-transformed serum Cys-C concentrations on a continuous scale were significant for all-cause, 3.96 (95% CI: 2.17 to 7.23, $p < 0.001$), cardiovascular disease, 6.51 (95% CI: 1.96 to 21.6, $p = 0.003$), noncardiovascular disease, 2.77 (95% CI: 1.14 to 6.71, $p = 0.03$) but not for cancer, 2.26 (95% CI: 0.57 to 9.04, $p = 0.24$) (data not shown). The comparable findings suggested a dose-responsive relationship between Cys-C and mortality outcomes. ROC analysis showed that the AUC for all-cause mortality, cardiovascular mortality, cancer mortality, and noncardiovascular mortality were 0.72, 0.74, 0.64, and 0.67, respectively. The estimated optimal cutoff values of Cys-C were 0.95 mg/l for all-cause and cardiovascular mortality and 0.97 mg/l for cancer and noncardiovascular mortality (Online Fig. 1).

Discussion

The present study demonstrates that an elevated serum Cys-C concentration is associated with all-cause, cardiovascular, and noncardiovascular mortality adjusted for other risk factors (e.g., MDRD eGFR and albuminuria) in a general population with creatinine-based eGFR ≥60 ml/min/1.73 m^2. In general, the results support previous findings suggesting that Cys-C is linked to long-term all-cause and cardiovascular mortality independent of kidney function (20).

Although the mechanisms through which elevated Cys-C relates to long-term mortality remain undetermined, it is generally assumed that serum Cys-C reflects the balance of its primary physiological determinants: cellular generation, renal filtration, and subsequent renal degradation (9). Also, the generation of Cys-C by nucleated cells is constant, and the concentration is not influenced by age, sex, height, and body composition (21). An increased Cys-C concentration identifies early deviations in GFR and becomes a sensitive indicator of "pre-clinical" renal disease, which thus may be associated with adverse cardiovascular outcomes (6). In addition, inflammatory status, thyroid disease, serum CRP, and current smoking were all associated with Cys-C concentrations (22). Inflammatory cytokines associated with atherosclerosis may alter the relationship between lysosomal cathepsins and their endogenous inhibitors like Cys-C in favor of remodeling and atherogenesis (23). Elastolytic cysteine proteases and their inhibitors, including Cys-C, are suggested to be involved in the pathogenesis of atherosclerosis (24). This may explain in part the

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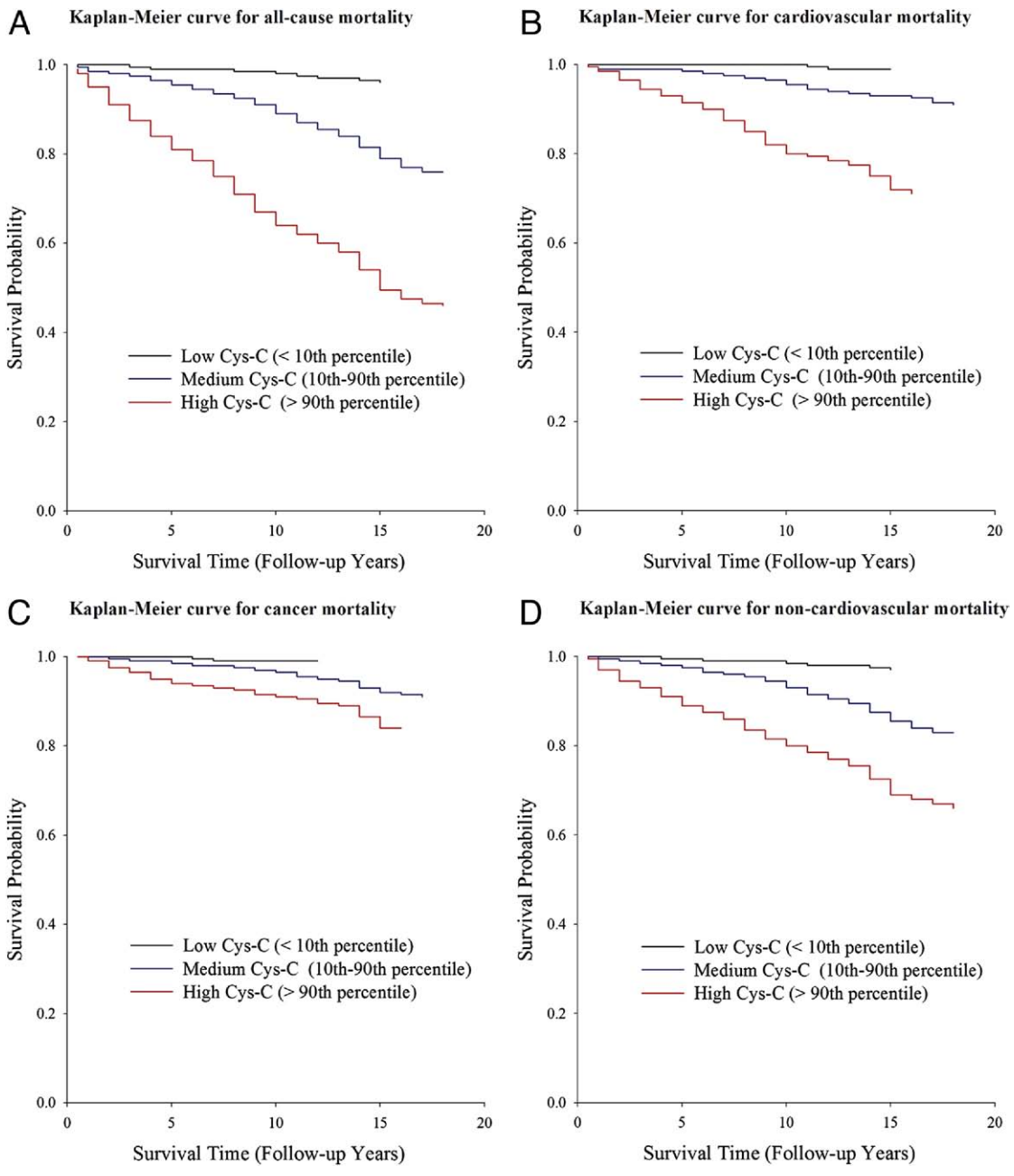

Figure 2 **Survival Curves for All-Cause and Cause-Specific Mortality**

Kaplan-Meier cumulative survival curves for risk for **(A)** all-cause, **(B)** cardiovascular disease, **(C)** cancer, and **(D)** noncardiovascular cause stratified by cystatin C (Cys-C) levels: high, >90th percentile; medium, 10th to 90th percentile; low, <10th percentile. **x-axis** indicates time (in years), **y-axis** indicates cumulative survival (%).

mechanism underlying the statistical link between Cys-C and cardiovascular outcomes in subjects with normal creatinine-based eGFR. Thus, increases in serum Cys-C may be sensitive harbingers of cardiovascular disease that are associated with inflammation (e.g., CRP) and atherosclerosis (25). Alternatively, the connection may be related to other pathophysiologic pathways that amplify the mortality risk independent of GFR (26).

Previous studies have demonstrated that Cys-C predicts all-cause mortality and cardiovascular events among elderly cohorts, subjects with chronic kidney disease, or patients with coronary heart disease (1,27,28). A recent study on 4,663 elderly persons (age >65 years) by Shlipak et al. (27) reported that higher Cys-C was associated with higher risk for cardiovascular events and mortality. The current study reinforces the prior findings that Cys-C is

Table 2 RR of All-Cause and Cause-Specific Mortality by 10th to 90th Percentiles of Cys-C Levels and Other Confounding Risk Factors

	All-Cause		Cardiovascular		Cancer		Noncardiovascular	
Predictor Variable	RR (95% CI)	p Value	RR (95% CI)	p Value	RR (95% CI)	p Value	RR (95% CI)	p Value
Univariate analysis								
Serum Cys-C level		<0.001		<0.001		<0.001		<0.001
>90th percentile	17.6 (10.1–30.9)		24.9 (11.2–55.3)		8.66 (3.94–19.1)		13.8 (7.10–26.7)	
10th–90th percentile	5.64 (3.11–10.2)		5.98 (2.68–13.4)		4.01 (1.70–9.44)		5.45 (2.76–10.7)	
<10th percentile	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Multivariate analysis								
Serum Cys-C level		<0.001		<0.001		0.18		0.006
>90th percentile	4.36 (2.52–7.82)		7.44 (3.06–18.1)		2.45 (0.85–7.04)		3.15 (1.53–6.49)	
10th–90th percentile	3.45 (2.04–5.82)		4.59 (1.99–10.6)		2.36 (0.95–5.88)		2.99 (1.57–5.72)	
<10th percentile	1.00 (reference)		1.00 (reference)		1.00 (reference)		1.00 (reference)	
Males	1.41 (1.06–1.89)	0.02	1.67 (1.11–2.56)	0.02	1.25 (0.72–2.13)	0.42	1.27 (0.93–1.72)	0.14
Diabetes, yes	1.35 (1.03–1.76)	0.03	1.72 (1.23–2.42)	0.002	0.95 (0.58–1.55)	0.82	1.12 (0.77–1.63)	0.56
Hypertension, yes	1.36 (1.04–1.78)	0.03	1.38 (0.96–1.98)	0.08	1.75 (1.15–2.65)	0.01	1.35 (0.99–1.83)	0.06
Current smoking, yes	2.00 (1.54–2.58)	<0.001	1.79 (1.19–2.71)	0.01	2.32 (1.34–4.02)	0.004	2.12 (1.47–3.06)	<0.001
CRP, mg/l*	1.13 (1.00–1.28)	0.04	1.12 (0.90–1.39)	0.30	1.09 (0.86–1.38)	0.45	1.14 (0.97–1.33)	0.10
UACR ratio, mg/mmol*	1.17 (1.10–1.25)	<0.001	1.21 (1.08–1.34)	0.001	1.04 (0.90–1.21)	0.59	1.14 (1.05–1.23)	0.002
Age, per yr	1.10 (1.09–1.11)	<0.001	1.11 (1.09–1.13)	<0.001	1.07 (1.04–1.09)	<0.001	1.09 (1.08–1.11)	<0.001
eGFR, ml/min/1.73 m^2*	4.25 (1.76–10.3)	0.002	9.51 (2.26–40.1)	0.003	1.04 (0.25–4.36)	0.96	2.50 (1.00–6.25)	0.05

*Log-transformed.
CI = confidence interval; CRP = C-reactive protein; Cys-C = cystatin C; RR = relative risk; other abbreviations as in Table 1.

associated with increased risk of all-cause and cardiovascular mortality among the elderly, and expands these findings to include noncardiovascular disorders in a younger (age >40 years) population with average age of 53 years and "clinically normal" kidney function. The ROC analysis by Astor et al. showed that Cys-C–based eGFR was predictive of all-cause and cardiovascular mortality, with an AUC of 0.80, in the general U.S. population with creatinine-based eGFR >15 ml/min/1.73 m^2 (29). In the current study, we used a simple dichotomized approach to assess the mortality risk associated with serum Cys-C concentrations and found that Cys-C could still predict increased mortality in the subjects with normal creatinine-based eGFR who were previously thought to belong to a low-risk group.

Increased risk of noncardiovascular illness may reflect associations between Cys-C and declining physical function mediated by inflammation (30). Such subjects with declining health might reasonably have additional comorbidities, such as aspiration pneumonia and bedsore, and therefore are prone to noncardiovascular mortality. Alternatively, high Cys-C may contribute to noncardiovascular mortality risks indirectly through cognitive impairments mediated by Cys-C–associated vascular disease (31).

Study limitations. There are some limitations in the current study. First, the selection of subjects used eGFRs based on single creatinine determinations. This potential concern is mitigated in part by the observation that repeated creatinine measurements in a subpopulation of 1,919 NHANES III subjects showed a reasonable agreement between the 2 measurements (32). Thus, errors in selection of subjects as "normal" seem unlikely to account for the better prognostic value of Cys-C. On the other hand, it is not unlikely that the association of interest could be confounded by other risk factors, such as thyroid disease, which may affect both Cys-C concentrations and mortality outcomes (33). Also, several single nucleotide polymorphisms have been associated with altered Cys-C concentrations (34). The current study, however, does support Cys-C concentrations as an indicator of increased risk of long-term mortality independent of residual renal function. Furthermore, a recent study showed that Cys-C was associated with an increased risk in the composite end point of death or rehospitalization in patients hospitalized for heart failure (35). However, the present analysis dealt with long-term survival. Thus, the association between Cys-C and the incidence of nonfatal cardiovascular events may have been missed.

Conclusions

This study has demonstrated that Cys-C, an alternative predictor of renal function, is significantly associated with all-cause, cardiovascular, and even noncardiovascular mortality in the general population with normal kidney function. Thus, Cys-C has a unique prognostic potential regarding long-term mortality. It remains to be elucidated as to whether some novel combination of measurements will provide even greater sensitivity and predictive power including perhaps for cancer.

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Key Words: cystatin C ■ glomerular filtration rate ■ nutrition survey ■ survival analysis.

APPENDIX

For a supplementary table and figure, please see the online version of this article.