Title

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Journal

Journal of renal nutrition : the official journal of the Council on Renal Nutrition of the National Kidney Foundation, 33(1)

ISSN

1051-2276

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Publication Date

2023

DOI

10.1053/j.jrn.2021.11.005

ORIGINAL RESEARCH

Serum Creatinine-to-Cystatin-C Ratio as a Potential Muscle Mass Surrogate and Racial Differences in Mortality

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Objectives: Serum creatinine–based estimated glomerular filtration rate equations and muscle mass are powerful markers of health and mortality risk. However, the serum creatinine-to-cystatin-C ratio may be a better indicator of health status. The objective of this study was to describe the relationship between creatinine-to-cystatin-C ratio and all-cause mortality when stratifying patients as per race and as per chronic kidney disease status.

Methods: This was a retrospective cohort study examining black and nonblack US veterans between October 2004 and September 2019, with baseline cystatin C and creatinine data from those not on dialysis during the study period. Veterans were divided into four creatinine-to-cystatin-C ratio groups: <0.75, 0.75-<1.00, 1.0-<1.25, and ≥1.25. The primary outcome of interest was all-cause mortality subsequent to the cystatin C laboratory measure.

Results: Among 22,316 US veterans, the mean (± standard deviation) age of the cohort was 67 ± 14 years, 5% were female, 82% were nonblack, and 18% were black. The proportion of black veterans increased across creatinine-to-cystatin-C ratio groups. In the fully adjusted model, compared with the reference (creatinine-to-cystatin-C ratio: 1.00-<1.25), a creatinine-to-cystatin-C ratio <0.75 had the highest mortality risk among both black and nonblack veterans (nonblack: hazard ratio [HR] [95% confidence interval {CI}]: 3.01 [2.78-3.26] and black: 4.17 [3.31-5.24]). A creatinine-to-cystatin-ratio ≥1.25 was associated with lower death risk than the referent in both groups (nonblack: HR [95% CI]: 0.89 [0.80-0.99] and black: HR [95% CI]: 0.55 [0.45-0.69]). However, there was a significant difference in the effect by race (Wald's *P*-value: <0.01).

Conclusions: Higher creatinine-to-cystatin-C ratios indicate better health status and are strongly associated with lower mortality risk regardless of the kidney function level, and the relation was similar for both black and nonblack veterans, but with different strengths of effect across racial groups. Thereby, use of a fixed race coefficient in estimating kidney function may be biased.

Keywords: Creatinine; Cystatin C; Creatinine-to-cystatin C ratio; Kidney disease; Race; Muscle mass

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Introduction

CYSTATIN C (CYSC) is a well-validated marker of renal function that is produced by virtually all nucleated cells and at a relatively constant rate.[1] Owing to its small size (13-kDa) and basic pH, CysC is freely filtered at the glomerulus and completely reabsorbed in the proximal tubules, catabolized, and not reabsorbed in the bloodstream (i.e., no re-entry into circulation).[2,3] Unlike

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Financial Disclosure: K.K.Z. is supported by K24-DK091419 as well as philanthropic grants from Mr. Harold Simmons, Mr. Louis Chang, Dr. Joseph Lee, and AVEO. K.K.Z. has received honoraria and/or support from Abbott, AbbVie, Alexion, Amgen, American Society of Nephrology, AstraZeneca, AVEO Oncology, Chugai, DaVita, Fresenius, Genentech, Haymarket Media, Hofstra Medical School, International Federation of Kidney Foundations, International Society of Hemodialysis, International Society of Renal Nutrition & Metabolism, Japanese Society of Dialysis Therapy, Hospira, Kabi, Keryx, Novartis, National Institutes of Health, National Kidney Foundation, OPKO, Pfizer, Relypsa, Resverlogix, Sandoz, Sanofi, Shire, Vifor, UpToDate, and ZSPharma. E.S. is supported by a career development award from the Office of Research and Development of the Department of Veterans Affairs (IK2-CX001266-01).

S.C., M.S., K.K.Z., and E.S. are employees of the VA. The interpretation and reporting of these data are the responsibility of the authors and in no way should be seen as official policy or interpretation of the Department of Veterans Affairs or the US government.

The data reported here have been supplied by the United States Renal Data System (USRDS). Support for Veterans Affairs/Center for Medicare and Medicaid Services data is provided by the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development, Veterans Affairs Information Resource Center (Project No. SDR 02-237 and 98-004).

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Published by Elsevier Inc. on behalf of the National Kidney Foundation, Inc.
1051-2276/$36.00
https://doi.org/10.1053/j.jrn.2021.11.005

creatinine (Cr), CysC is not secreted by the proximal renal tubules.[4] Importantly, CysC generation and release into the circulation are not dependent on muscle mass or other variables that affect Cr variability such as dietary meat intake.[5,6] Because of these features, CysC is believed to be a more accurate predictor than Cr of glomerular filtration rate (GFR) and several other clinical outcomes independent of muscle mass or other confounders.[7-9]

It has been previously reported that serum CysC and Cr levels differ significantly by race and ethnicity.[10,11] The higher level of kidney function in the black population compared with the nonblack population at the same average Cr levels has been well described and attributed to racial differences in muscle mass. Given this premise, the black population would be anticipated to have a higher Cr-to-CysC ratio (CrCyR) than the nonblack population. Because both Cr and CysC are similarly eliminated via glomerular filtration, and with Cr being more dependent on muscle mass than CysC, it was hypothesized that a CrCyR would be a valid marker of muscle mass independent of the level of kidney function.[12,13]

Based on this relationship, there has been increasing interest in studying the association between the CrCyR and patient outcomes, especially across race. Lower muscle mass is linked to a higher likelihood of several disease states such as heart failure, liver cirrhosis, and cancer, which are associated with poor clinical outcomes.[14-16] Thus, we investigated whether the CrCyR would allow us to evaluate prognosis as a health status indicator.

US veterans may suffer from higher rates of comorbidities and physical changes associated with reduced muscle mass, such as paraplegia and quadriplegia due to spinal cord injuries, amputations, muscular dystrophies, and other muscle disorders,[17] making them an important population to study. Consequently, there may be value in the adoption of this approach to screen and diagnose sarcopenia among veterans.[18] In addition, the projected demographic changes in the veteran population suggest the need for a tool that would predict mortality regardless of the race and kidney function level.[19]

Studies of non-US cohorts have shown that a higher CrCyR level is independently associated with all-cause mortality in critically ill patients,[12,13,20] but this finding has not been studied in the noncritically ill and stratified by racial groups in the United States. We elected to study a contemporary cohort of veterans and examined the hypothesis that CysC levels and the CrCyR had a prognostic significance for mortality among veterans across race and with or without chronic kidney disease (CKD).

Methods

Study Population and Data Source

We retrospectively examined data from a population of 25,030 US veterans with a CysC laboratory measurement between October 01, 2004 and September 30, 2019. Patients were excluded from the study if they were younger than 18 years of age (N = 5), if they were on dialysis (N = 1,088), if they did not have a Cr value measured on the same day as the CysC laboratory measurement (N = 1,309), if they had an outlier CysC measurement (N = 1), or if they had errors in follow-up time (N = 311). The final cohort consisted of 22,316 US veterans.

This study was reviewed by the VA Long Beach Healthcare System's Institutional Review Boards and deemed exempt from the written consent requirement as all analyses in this study used preexisting, deidentified data.

Demographic and Clinical Data

Baseline characteristics and demographics were obtained from a combination of three different data sources: dialysis information was obtained from United States Renal Data System, outcomes and comorbid information were extracted from the VA and Centers for Medicare and Medicaid databases using International Classification of Diseases (ICD)-9, ICD-10, and Current Procedural Terminology codes, and data on mortality were extracted from the VA Vital Status File.

Statistical Methods

Exposure Assessment

The exposure variables of interest were deciles of Cr and CysC as well as the CrCyR. Black and nonblack veterans were divided into four groups as per their CrCyR (≤0.75, 0.75-≤1.00, 1.00-≤1.25, or >1.25). The estimated GFR (eGFR) was calculated using the CKD Epidemiology Collaboration (CKD-EPI) Cr, CysC, and the combined Cr-CysC equation, the latter both with and without the component for race. Information on demographics and comorbidities was extracted and compared across the four CrCyR groups. Baseline information was reported using mean (± standard deviation [SD]) for age and eGFR, frequency and proportions (N [%]) for gender and comorbidities, and median (interquartile range) for the Charlson comorbidity index. Linear regression, the chi-squared test for trend, and Jonckheere-Terpstra trend test were used to compare differences in variables across the four CrCyR groups.

Outcome Assessment

The primary outcome used in this study was all-cause mortality that occurred after the CysC laboratory date. Follow-up time was calculated from the CysC laboratory date until the date of death, loss to follow-up, kidney transplant date, or the end of the study period (May 30, 2020), whichever occurred first. Proportional hazards assumptions were assessed using Kaplan-Meier curves. Cox proportional hazards models were used to compare the risk of all-cause mortality across deciles of Cr, deciles of CysC, and among the four CrCyR groups. Effect modification and interaction by race and CKD status on the association of the CrCyR with all-cause mortality were examined by

Wald's test for interaction and repeated analyses stratified by race (black and nonblack) and CKD status (eGFR <60 and eGFR ≥60 mL/min/1.73 m^2). After an unadjusted model, we adjusted for age, gender, race, eGFR calculated from the CKD-EPI Cr-CysC equation without the component for race, and comorbid myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatologic diseases, peptic ulcer disease, liver disease, diabetes, paralysis, cancer, and acquired immunodeficiency syndrome.

All analyses were conducted using SAS, version 9.4 (SAS Institute Inc., Cary, NC).

Results

Demographics and Comorbidities

Baseline characteristics were compared among all veterans across the four CrCyR groups. The mean ± SD age of the cohort was 67 ± 14 years. Age decreased with increasing CrCyR groups (for a CrCyR <0.75, the mean ± SD age was 70 ± 13 years, and for a CrCyr ≥1.25, the mean ± SD age was 58 ± 15 years). Overall, 5% of the cohort were female, 69% were white, 18% were black, and 6% were Hispanic. A lower proportion of women were noted with increasing CrCyR groups. The highest CrCyR category had the lowest proportions of white and Hispanic veterans and had substantially higher proportions of black veterans. Nearly all comorbidities decreased in prevalence with higher categories of the CrCyR. From the CKD-EPI equations, the mean ± SD eGFRcr was 63 ± 28, eGFRcysc was 60 ± 30, eGFRcre-cysc was 62 ± 30, and eGFRcre-cysc without using race was 61 ± 30 mL/min/1.73 m^2. Across increasing CrCyR groups, eGFR showed a U-shaped association when calculated using the combined Cr-Cys equation with and without race. However, eGFR showed an increasing trend across the CrCyR groups when calculated using the CysC equation, and a decreasing trend when calculated using the Cr equation (Table 1).

Deciles of Creatinine and Cystatin C with Mortality

When comparing deciles of Cr and CysC with mortality, Cox proportional hazards models showed a U-shaped association for increasing Cr with mortality. On the other hand, increasing CysC showed a linear association with mortality. Using the 5th decile as the reference and after adjusting for age, gender, race, and comorbidities, the first decile of CysC showed a lower risk in mortality, whereas the first decile of Cr showed a higher risk of mortality (hazard ratio [95% confidence interval]: 0.77 [0.67-0.89] for CysC and 2.25 [2.00-2.53] for Cr). Mortality risk increased incrementally with deciles of CysC, where the 10th decile showed a significantly higher risk than the reference decile (2.70 [2.44-2.98]). In contrast, although the first decile of Cr showed a significantly higher risk in mortality, the 2nd to the 7th deciles of Cr showed a null association, and the 8th, 9th, and 10th deciles had a significantly higher risk in mortality than the referent (1.23 [1.09-1.38], 1.57 [1.41-1.75], and 2.38 [2.14-2.66], for the 8th, 9th, and 10th Cr deciles, respectively) (Table 2 and Figure 1).

Mortality Risk Across Creatinine-to-cystatin C Ratio Groups

Among all veterans, using those with the CrCyR of 1.00-<1.25 as a reference, the CrCyR <0.75 was associated with higher risk for mortality (3.03 [2.81-3.27]), and CrCyR >1.25 was associated with substantially lower mortality risk (0.80 [0.73-0.88]), after adjustments for age, gender, race, comorbidities, and eGFR (Figure 2).

There was an incremental increase in the frequency of black veterans within each CrCyR category. Wald's test for interaction between race and the CrCyR was significant (*P*-value: <0.01), indicating that the associations vary across race group. After adjustments for age, gender, comorbidities, and eGFR, Cox proportional hazards models showed that black veterans with a CrCyR <0.75 had a higher risk (4.17 [3.31-5.24]) and those with a CrCyR ≥1.25 had a lower risk of mortality (0.55 [0.45-0.69]). This trend was similar among nonblack veterans where those with a CrCyR <0.75 had a higher risk (3.01 [2.78-3.26]) and those with a CrCyR ≥1.25 had a lower risk in mortality (0.89 [0.80-0.99]) than the reference (CrCyR: 1.0-<1.25) (Figure 3).

In addition to stratifying by race, survival analyses between CrCyR groups with all-cause mortality were repeated among subgroups of eGFR <60 and eGFR ≥60 mL/min/1.73 m^2. Associations were somewhat stronger among veterans with an eGFR ≥60 than those in veterans with an eGFR <60. In the adjusted model, those with an eGFR <60 and a CrCyR <0.75 had a higher mortality risk (1.72 [1.46-2.01]) and those with a CrCyR ≥1.25 had a lower mortality risk (0.92 [0.81-1.05]). Similarly, among those with an eGFR ≥60, those with a CrCyR <0.75 had a higher mortality risk (3.35 [3.06-3.65]) and those with a CrCyR ≥1.25 had a lower mortality risk (0.61 [0.53-0.70]) than the reference (Figure S1).

Discussion

Among a large, nationally representative cohort of veterans, we demonstrated that for both black and nonblack veterans, a CrCyR <0.75 had the highest mortality risk, whereas a CrCyR ≥1.25 had the lowest death risk compared with the reference independent of the kidney function level and race. We also found that the proportion of black veterans increased across the CrCyR and that a higher CrCyR was observed in blacks than in nonblacks, although there was wide variability in both racial groups of veterans. Although serum Cr is commonly used as a kidney filtration marker in mortality outcome studies adjusting for kidney function, our study showed that serum CysC has a much stronger and linear association with prognosis in US

Table 1. Baseline Characteristics As Per Creatinine-to-cystatin-C Ratio Category

		Creatinine-to-cystatin-C Ratio				
	Total	≤0.75	0.75-≤1.0	1.0-≤1.25	>1.25	
Variables	N = 22,316	N = 4,129	N = 7,680	N = 5,850	N = 4,657	*P*-value
Age (mean ± SD)	67 ± 14	70 ± 13	71 ± 12	68 ± 13	58 ± 15	<.0001
Female (N [%])	1,081 (5)	304 (7)	413 (5)	248 (4)	116 (2)	<.0001
Race/ethnicity (N [%])						
White	15,402 (69)	3,195 (77)	5,881 (77)	4,056 (69)	2,270 (49)	<.0001
Black	3,960 (18)	337 (8)	723 (9)	1,062 (18)	1,838 (39)	<.0001
Hispanic	1,356 (6)	184 (4)	446 (6)	379 (6)	347 (7)	<.0001
Other	2,375 (11)	439 (11)	842 (11)	614 (11)	480 (10)	.4010
Comorbidities (N [%])						
MI	1,400 (6)	359 (9)	554 (7)	330 (6)	157 (3)	<.0001
CHF	3,969 (18)	1,046 (25)	1,623 (21)	855 (15)	445 (10)	<.0001
PVD	2,820 (13)	746 (18)	1,120 (15)	657 (11)	297 (6)	<.0001
CVD	1,936 (9)	558 (14)	720 (9)	409 (7)	249 (5)	<.0001
Dementia	1,367 (6)	488 (12)	526 (7)	237 (4)	116 (2)	<.0001
CPD	4,397 (20)	1,329 (32)	1,740 (23)	883 (15)	445 (10)	<.0001
Rheum	408 (2)	128 (3)	164 (2)	74 (1)	42 (1)	<.0001
PUD	339 (2)	127 (3)	122 (2)	58 (1)	32 (1)	<.0001
Liver disease	1,633 (7)	499 (12)	628 (8)	334 (6)	172 (4)	<.0001
Diabetes	8,710 (39)	1,591 (39)	3,311 (43)	2,410 (41)	1,398 (30)	<.0001
Paralysis	3,637 (16)	1,746 (42)	1,217 (16)	494 (8)	180 (4)	<.0001
Cancer	3,510 (16)	889 (22)	1,332 (17)	802 (14)	487 (10)	<.0001
AIDS	439 (2)	42 (1)	123 (2)	116 (2)	158 (3)	<.0001
CCI (median [IQR])	3 (1,5)	4 (2,6)	3 (1,5)	2 (1,4)	2 (0,4)	<.0001
eGFR (Cr) (mean ± SD)	62.57 ± 28.45	82.77 ± 32.10	61.79 ± 26.14	55.71 ± 24.75	54.57 ± 24.15	<.0001
eGFR (CysC) (mean ± SD)	59.89 ± 30.13	51.30 ± 27.12	53.10 ± 25.80	60.29 ± 27.47	78.18 ± 34.34	<.0001
eGFR (Cr-CysC) (mean ± SD)	61.85 ± 29.98	68.95 ± 35.69	58.03 ± 27.92	58.47 ± 27.20	66.07 ± 29.43	.0329
eGFR (Cr-CysC no race) (mean ± SD)	60.94 ± 29.45	68.50 ± 35.38	57.58 ± 27.61	57.62 ± 26.71	63.98 ± 28.32	<.0001

AIDS, acquired immunodeficiency syndrome; CCI, Charlson comorbidity index; CHF, congestive heart failure; CPD, chronic pulmonary disease; CVD, cerebrovascular disease; eGFR, estimated glomerular filtration rate; eGFR (Cr), CKD-EPI creatinine equation; eGFR (CysC), CKD-EPI cystatin C equation; eGFR (Cr-CysC), CKD-EPI creatinine-cystatin C equation; eGFR (Cr-CysC no race), CKD-EPI creatinine-cystatin C equation without using race; IQR, interquartile range; MI, myocardial infarction; PUD, peptic ulcer disease; PVD, peripheral vascular disease; Rheum, rheumatologic disease; SD, standard deviation.

Units for eGFR are mL/min/1.73 m^2.

veterans as also shown in previous studies.[5,21] Moreover, we demonstrate that the CrCyR may be a good health status indicator as it isolates the role of muscle mass and muscle activity from kidney function. We have found that the CrCyR is associated with mortality in veterans regardless of the race or kidney function level and that this association persists after adjustment for age, gender, race, comorbidities, and eGFR.

Because clinical registries lack direct measurements of the GFR, comparisons of alternative eGFR methods must be conducted with prognosis as the most relevant outcome. Higher plasma concentrations of CysC are known to have stronger associations than Cr with clinical outcomes in cohort studies, but few studies have used real-world clinical data from an electronic health record.[22,23] Our findings provide additional evidence that CysC is a better marker of mortality risk than Cr using this clinical population of veterans, which supplements prior studies conducted on the general population.[21,24] This strong association between CysC and mortality was also validated in patients with or without acute kidney injury[22] and patients with or without CKD.[25] We believe that it is important that we have validated these findings in an unselected clinical population of veterans, who have a high prevalence of comorbidities.

The primary finding of this study is that the CrCyR represents a novel health status indicator as it represents the patient's muscle mass relative to their kidney function. Urinary creatinine excretion has been reported to be strongly associated with mortality.[26-29] This shows that low creatinine production is clinically important, but it is hard to distinguish serum Cr from kidney function. The main advantage of the CrCyR is that it separates two important prognostic dimensions: Cr production (through the ratio), and thus muscle mass, and eGFR (through CysC). This effectively splits the U-shape of Cr into its two components. A study by Purde et al. demonstrates the potential clinical use of cystatin-C-to-creatinine ratio (reciprocal of CrCyR), as a predictor of morbidity and mortality in older adults, and that an increase in this ratio indicates a change in GFR suggesting early-stage kidney dysfunction.[30]

Table 2. Cox Proportional Hazards Model Showing the Associations Between Creatinine and Cystatin C Deciles With All-cause Mortality in Unadjusted and Adjusted Models

					Unadjusted		Adjusted	
Cystatin C Deciles	N	Mortality	Cohort Years	Mortality Rate (95% CI)	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
1	1,977	284	6,523	44 (39-44)	0.52 (0.45-0.60)	<.0001	0.77 (0.67-0.89)	.0004
2	2,734	381	8,096	47 (43-52)	0.55 (0.48-0.63)	<.0001	0.71 (0.61-0.82)	<.0001
3	2,148	427	6,528	65 (59-72)	0.77 (0.68-0.87)	<.0001	0.87 (0.77-0.97)	.0164
4	2,107	474	6,278	76 (69-83)	0.88 (0.78-0.99)	.0477	0.90 (0.79-1.01)	.0818
5	2,176	568	6,715	85 (78-92)	Reference		Reference	
6	2,530	815	6,847	119 (111-127)	1.37 (1.23-1.53)	<.0001	1.07 (0.96-1.19)	.2470
7	1,821	716	4,829	148 (138-160)	1.71 (1.53-1.90)	<.0001	1.28 (1.15-1.42)	<.0001
8	2,365	1,102	5,210	212 (199-224)	2.34 (2.12-2.59)	<.0001	1.53 (1.38-1.69)	<.0001
9	2,223	1,202	3,977	302 (286-320)	3.19 (2.89-3.53)	<.0001	1.96 (1.77-2.17)	<.0001
10	2,235	1,359	2,708	502 (476-529)	4.86 (4.40-5.36)	<.0001	2.70 (2.44-2.98)	<.0001
Creatinine Deciles	N	Mortality	Cohort Years	Mortality Rate (95% CI)	Unadjusted		Adjusted	
					HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
1	2,251	1,032	4,571	226 (212-240)	2.38 (2.14-2.66)	<.0001	2.25 (2.00-2.53)	<.0001
2	1,817	486	5,181	94 (86-103)	1.06 (0.94-1.21)	.3521	1.11 (0.98-1.26)	.1100
3	2,634	624	8,190	76 (70-82)	0.88 (0.78-0.99)	.0351	0.93 (0.82-1.05)	.2207
4	2,218	519	6,984	74 (68-81)	0.86 (0.76-0.97)	.0156	0.92 (0.81-1.04)	.1723
5	1,788	468	5,355	87 (80-96)	Reference		Reference	
6	3,124	817	9,222	89 (83-95)	1.01 (0.90-1.13)	.8860	1.04 (0.93-1.17)	.4899
7	1,791	450	4,769	94 (86-104)	1.05 (0.92-1.19)	.5082	1.04 (0.91-1.18)	.5864
8	2,034	678	4,974	136 (126-147)	1.48 (1.31-1.66)	<.0001	1.23 (1.09-1.38)	.0006
9	2,457	1,107	5,216	212 (200-225)	2.23 (2.00-2.49)	<.0001	1.57 (1.41-1.75)	<.0001
10	2,202	1,147	3,249	353 (333-374)	3.41 (3.06-3.80)	<.0001	2.38 (2.14-2.66)	<.0001

CI, confidence interval; HR, hazard ratio.

Covariates in the adjusted model include age, gender, race, ethnicity, myocardial infarction (MI), congestive heart failure (CHF), peripheral vascular disease (PVD), dementia, cerebrovascular disease (CVD), chronic pulmonary disease (CPD), rheumatologic disease (Rheum), peptic ulcer disease (PUD), liver disease, cancer, diabetes, paralysis, acquired immunodeficiency syndrome (AIDS), and Charlson comorbidity index (CCI).

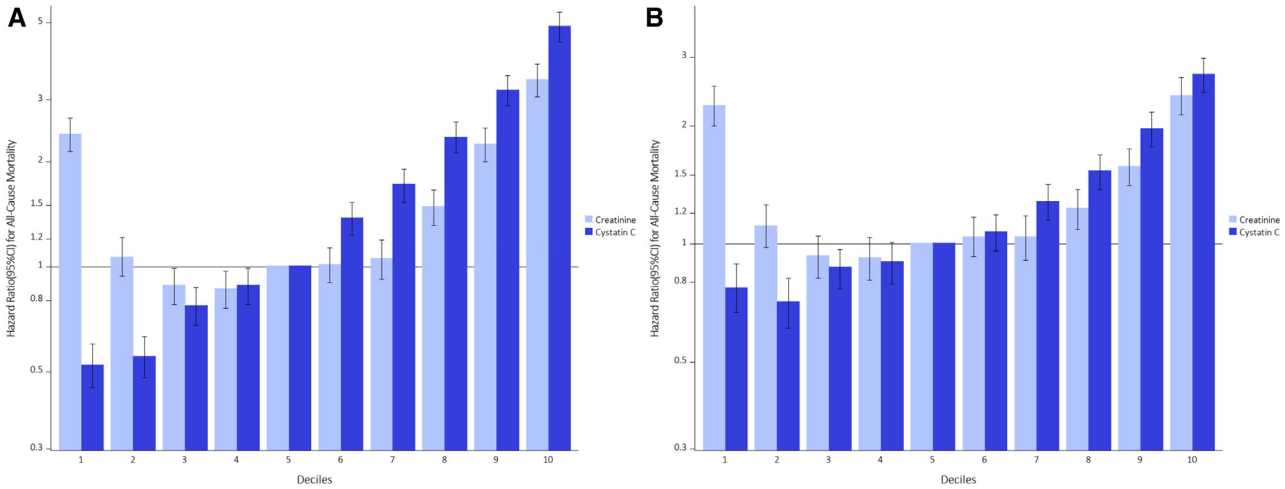

Figure 1. Cox proportional hazards models showing the association of creatinine and cystatin c deciles with all-cause mortality in (A) unadjusted and (B) adjusted models. CI, confidence interval.

In addition, a higher CrCyR could potentially be used as a simple proxy of higher muscle mass, which has been shown to be associated with decreased mortality.[31,32] The relationship between lower muscle mass and activity and mortality has been elucidated in patients with chronic obstructive pulmonary disease and critical illness.[31,32] Muscle mass can also serve as a proxy of malnutrition and impaired insulin signaling.[32] Two studies have already shown that the CrCyR is a surrogate for muscle mass evaluated by abdominal computed tomography scans and is strongly associated with short-term mortality in patients without kidney disease.[12,13] More recently, a retrospective study by Jung et al. revealed that the CrCyR is correlated with both short- and long-term mortality and that this association could be extended to patients with impaired kidney function (i.e., acute kidney injury), where the kinetics of Cr and CysC can be altered.[20] Unlike our study, which included both ambulatory and inpatients, these studies were conducted on critically ill patients, where it is likely that the CrCyR can be impacted by unpredictable renal or nonrenal factors (e.g., inflammation, infections, sepsis). Cr and CysC levels can also be affected by factors other than the GFR. CysC levels can be influenced by thyroid function abnormalities, steroid use, inflammation, and diabetes,[33] whereas Cr can be influenced by animal protein intake.[34,35] Therefore, nonrenal factors such as nutrition status and inflammation may impact the CrCyR. Our current results extend prior findings to highlight that measuring the CrCyR can help identify noncritically ill individuals with or without CKD who are at a higher risk of

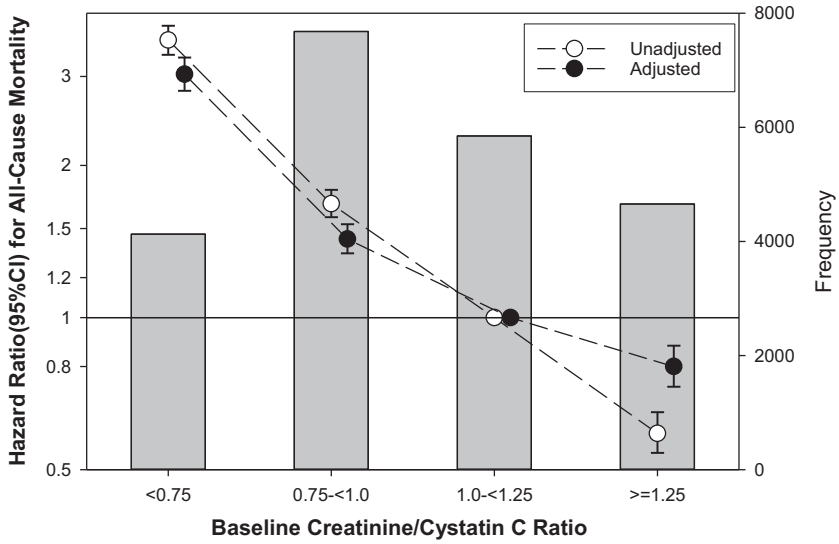

Figure 2. Unadjusted and adjusted Cox proportional hazards models showing the association of the creatinine-to-cystatin-C ratio category with all-cause mortality among all veterans. CI, confidence interval.

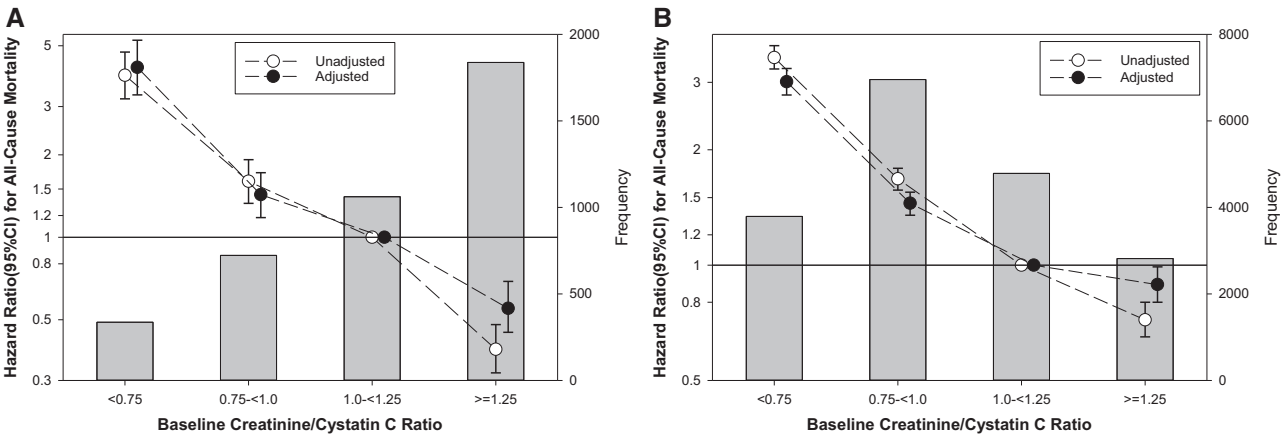

Figure 3. Unadjusted and adjusted Cox proportional hazards models showing the association of the creatinine-to-cystatin-C ratio category with all-cause mortality among (A) black and (B) nonblack veterans.

mortality and are in congruence with those by Lin et al, who report that a lower serum CrCyR is an independent indicator of mortality in nondialysis CKD patients.[36] This tool has also been validated as a surrogate for muscle mass in solid organ transplantation, amyotrophic lateral sclerosis, and lung cancer.[37-40]

Given that the CrCyR appears to serve as a surrogate of Cr generation, it is not surprising that black veterans were more likely to have a higher CrCyR (i.e., ≥ 1.25) than nonblack veterans. The mean ± SD CrCyR was 1.27 ± 0.45 and 0.99 ± 0.35 in blacks and nonblacks, respectively. A prior study found that black patients have approximately 5-8% higher levels of muscle mass than nonblack patients based on total body potassium assessment.[19,41] The reason for this finding is not clear but could be related to structural racism and more black persons having blue collar manual labor jobs leading to higher muscle mass.[42] Although this might appear to justify the use of a fixed ratio to represent the relative differences in Cr production between blacks and nonblack persons, there was actually wide variability in both groups. A very low CrCyR was observed in 8% of black veterans, and most both black and nonblack veterans had a normal CrCyR of approximately 1.0. However, the CrCyR varies widely across populations, between men and women and within black and nonblack veterans, and would also vary within individuals when their health status declines such as with disability or hospitalization.

Earlier studies reported that a higher CrCyR is associated with lower mortality in heterogeneous cohorts or homogenous South Korean cohorts of critically ill patients,[12,13,20] but this finding had not previously been validated in a noncritically ill large cohort and specific racial groups in the United States. To our knowledge, this study is the first to evaluate the effect of race on the association between the CrCyR and all-cause mortality. By subgrouping patients into black or nonblack, we were able to demonstrate that the CrCyR is strongly associated with mortality in both groups. Although a higher CrCyR was observed in more black veterans than nonblack veterans, both racial groups manifested better overall survival at a higher CrCyR regardless of the kidney function level.

Beyond the value of having a novel index of muscle activity and health status, our findings on the CrCyR have an additional important implication for GFR estimation. Namely, our findings demonstrate the inappropriateness of using a fixed coefficient to represent racial differences in Cr generation between blacks and nonblack persons at an individual level. Equations have used 21% or 16% as a fixed ratio that assumes each black person produces Cr at that ratio compared with a nonblack person,[43] implying race is a biologic construct which it is not (ecologic fallacy).[44] Our study in unselected patients demonstrates the wide variety of CrCyRs across both groups and shows how few black persons would have exactly a 16% higher Cr production than an average nonblack person. This inaccuracy (aggregation bias) can also be extended to age assumptions around Cr production as the CrCyR has a wide range of values within each stratum of age and to sex differences.

Strengths and Limitations

Strengths of this study include use of this large contemporary cohort of patients with available CysC with longitudinal follow-up and ability to adjust for a number of potential confounders. However, limitations should be noted for our analysis. Owing to the observational nature of the study design, we cannot completely eliminate residual confounding nor make causal inferences on the relationship. Moreover, we adjusted for only available confounders, yet we were unable to fully account for other potential confounders. Finally, the VA population is primarily composed of older white men, and thus, our

findings may not be generalizable to the general population, especially among women who only represent approximately 5% of this population.

Conclusion

Higher CrCyRs indicate better health status and are strongly associated with lower mortality risk regardless of the kidney function level. The broad range of CrCyRs among both black and nonblack veterans is consistent with the futility of predicting Cr production in GFR estimating equations. We demonstrate the promising role for this affordable, minimally invasive, and broadly applicable approach to identify patients at high risk for mortality. Future studies should evaluate whether a CrCyR can provide a more precise and accurate prediction of mortality than CysC alone across the range of eGFRs and in specific racial subgroups.

Practical Application

Prior studies on critically ill, non-US cohorts have reported that a higher serum CrCyR level is inversely associated with all-cause mortality. This finding has not been studied in particular race subgroups in the United States. In the largest cohort study to date, we show that the CrCyR is a muscle mass surrogate and survival predictor in both race groups of US veterans independent of the eGFR. Thus, the CrCysR may serve as a novel health status indicator, with a higher CrCyR indicating better health status and lower mortality risk. With the CrCysR not being consistently proportionally higher for blacks than for nonblacks, we infer that the use of a fixed race coefficient in estimating kidney function may be biased.

Credit Authorship Contribution Statement

John G. Rizk: Writing – original draft. **Elani Streja:** Writing – original draft, Formal analysis, data acquisition and processing. **Cachet Wenziger:** Writing – original draft, data acquisition and processing, Formal analysis. **Michael G. Shlipak:** Writing – original draft. **Keith C. Norris:** Writing – original draft. **Susan T. Crowley:** Writing – original draft. **Kamyar Kalantar-Zadeh:** Writing – original draft.

Acknowledgments

Preliminary findings were presented as a poster at the Society of Cachexia, Sarcopenia, and Wasting 2020 Virtual Conference.

Supplementary Data

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1053/j.jrn.2021.11.005.

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