

Cystatin C, mortality risk, & clinical triage in US adults: threshold values & hierarchical importance

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Introduction

- As chronic kidney disease is common and associated with adverse outcomes such as cardiovascular disease, end-stage kidney disease, and death, there is increasing interest in routine measurement of kidney function in community-dwelling adults, in much the same way that measurement of blood pressure, lipids, and body mass index is recommended.
- Cystatin C has several potentially attractive features as a measure of estimated glomerular filtration rate (eGFR), including stable production rates, free filtration by the glomerulus, no overall renal tubular effect on serum levels, and serum levels that are not heavily influenced by race, sex, or lean body-mass proportions.
- Regarding the issues of cystatin C levels, mortality, and clinical triage, several questions have yet to be addressed: should serum cystatin C, serum creatinine, eGFR-Creatinine, or urinary albumin-creatinine ratio (ACR) be used? In this nationally representative study, we used diagnostic test and classification tree methodology to assess the efficacy of cystatin C as a mortality discriminator among community-dwelling adults.

Methods

- NHANES III was a cross-sectional, multistage, stratified, clustered probability sampling of the non-institutionalized US civilian population undertaken between 1988-1991 and 1994. Cystatin C was assayed in stored serum samples from all male and female participants with standardized serum creatinine levels > 1.0 mg/dL and 1.2 mg/dL, respectively, and age ≥ 60 years. In addition, cystatin C was measured in a 25% random sample of participants without these characteristics. GFR values from cystatin C and creatinine were estimated with the CKD-EPI and Stevens formulas, respectively.
- Vital status for NHANES III participants was established through December 31, 2006.
- To identify mortality MaxSn+Sp levels for cystatin C, sensitivity (exposure among subjects who died) and specificity (non-exposure among subjects who survived) values were computed separately for cystatin C thresholds that varied in 0.01 mg/L increments between 0.6 and 2.0 mg/L.
- A similar procedure was used for serum creatinine, in the range 0.5 to 2.0 mg/L.
- For all other continuous variables, thresholds were moved in 1-unit increments.
- Because the discriminatory power of many variables might reflect correlations with other variables such as age, and (2) differ substantially in major population subsets, we constructed classification trees for death based on the highest MaxSn+Sp value when all variables were considered simultaneously.

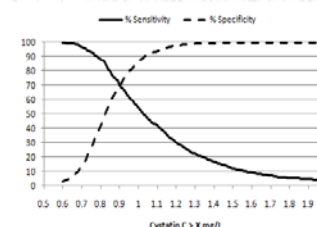
Results

- Mean age was 44.43 years. Mean cystatin C level was 0.90 mg/L, standardized serum creatinine 0.84 mg/dL, eGFR-Cystatin C 93.42 mL/min/1.73 m², and eGFR-Creatinine 99.54 mL/min/1.73 m².
- The death rate was 1.33%. Figure 1 shows sensitivity and specificity values for predicting death at different cystatin C thresholds. A threshold value of 0.94 mg/L exhibited the highest maximum combined value of sensitivity (Sn) and specificity (Sp) for predicting death (MaxSn+Sp, Sn 0.64/Sp 0.78).
- Because age exhibited the highest mortality discrimination, age ≤ 58 and > 58 years were the first two branches of the classification tree. Among continuous variables, only cystatin C and ACR were represented in the classification tree. Cystatin C was a primary discriminator in the subgroups that added up to 41% of the study population: age 42-58 years (23%), age 58-71 years with ACR ≤ 10 mg/g (9%), age 58-71 years with ACR > 10 mg/g (5%), and age 71-76 years (4%). ACR was a primary discriminator in the subgroup aged 58-71 years (14%).

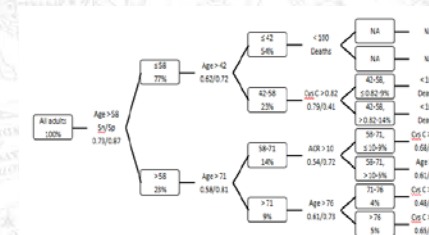
Baseline characteristics

	Mean or % (SE)	Median (IQR)
Cystatin C, mg/L	0.90 (0.01)	0.90 (0.01)
eGFR _{Cystatin C} , mL/min/1.73 m ²	93.42 (0.83)	93.42 (0.83)
Creatinine, mg/dL	0.84 (< 0.01)	0.84 (< 0.01)
eGFR _{Creatinine} , mL/min/1.73 m ²	99.54 (0.77)	99.54 (0.77)
Urinary albumin-creatinine ratio, mg/g	5.8 [3.5-10.6]	5.8 [3.5-10.6]
Age, years	44.43 (0.75)	44.43 (0.75)
Systolic blood pressure, mm Hg	122.5 (0.53)	122.5 (0.53)
Diastolic blood pressure, mm Hg	74.39 (0.3)	74.39 (0.3)
Body mass index, mm Hg	26.62 (0.17)	26.62 (0.17)
Total cholesterol, mg/dL	208.36 (1.3)	208.36 (1.3)
HDL-cholesterol, mg/dL	50.24 (0.38)	50.24 (0.38)
Women, %	52.3 (1.53)	52.3 (1.53)
White, %	76.46 (1.89)	76.46 (1.89)
African American, %	10.94 (0.92)	10.94 (0.92)
Hispanic, %	5.1 (0.54)	5.1 (0.54)
Other, %	7.51 (1.21)	7.51 (1.21)
Hypertension, %	23.89 (0.91)	23.89 (0.91)
Diabetes, %	4.98 (0.45)	4.98 (0.45)
Cardiovascular disease, %	4.79 (0.52)	4.79 (0.52)
Current smoker, %	28.87 (1.24)	28.87 (1.24)

Sensitivity & specificity of different cystatin C thresholds for predicting death



Mortality classification tree based on maximum sensitivity & specificity for predicting death



Mortality risk estimates from categories derived from classification tree analysis

Categories	Prevalence	Mean Age	Death Rate	OR, Death Unadjusted	OR, Death Age Adjusted
Age ≤ 42	34.1	31.2	2.0	1 (Reference)	1 (Reference)
Age > 42, ≤ 58, cystatin C ≤ 0.82	8.9	49.1	4.4	2.2 (1-4.3)	1.3 (0.7-2.7)
Age > 42, ≤ 58, cystatin C > 0.82	34.1	50.5	10.6	5.7 (3.3-8.8)	3.4 (1.8-6.2)
Age > 58, ≤ 71, ACR ≤ 10, cystatin C ≤ 0.91	4.6	64.2	11.7	6.3 (3.3-10.3)	2.6 (1.3-4.4)
Age > 58, ≤ 71, ACR ≤ 10, cystatin C > 0.91	4.1	65.1	20.7	10.3 (2-21.8)	7.9 (4.1-15.2)
Age > 58, ≤ 65, ACR > 10	2.6	62.4	32.3	21.6 (13.2-35.4)	9.5 (5.1-17.7)
Age > 65, ≤ 71, ACR > 10	2.6	68.5	61.2	36.7 (35.1-91.6)	21.1 (9.3-47.8)
Age 71-76, cystatin C ≤ 1.15	2.6	73.6	48.3	36.7 (23.5-67.3)	11.9 (6.3-21.7)
Age 71-76, cystatin C > 1.15	1.7	74.1	81.1	103.9 (60.4-178.1)	33.2 (13.7-80.6)
Age > 76, cystatin C ≤ 1.11	1.8	80.7	86.2	120.9 (71.4-204.6)	32.4 (10.7-98)
Age > 76, cystatin C > 1.11	2.9	82.4	140.1	508.5 (24.7-998.1)	130.5 (43.9-387.6)

Model P < 0.0001; Model P < 0.0001

ACR, albumin-creatinine ratio; OR, odds ratio

Units: age, years; albumin-creatinine ratio, mg/g; cystatin C, mg/L

Conclusions

- Limitations notwithstanding, this study has some attractive features. By design, the study is representative of the US population as a whole, at least between 1988 and 1994. Several commonly measured risk-stratification measures, such as body mass index, blood pressure, and cholesterol were routinely available. While further clarification is needed, this study suggests that measuring cystatin C may be useful for clinical triage in public health settings.