Optimal Threshold of Urinary Albumin-to-Creatinine Ratio (UACR) for Predicting Long-Term Cardiovascular and Noncardiovascular Mortality

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Research Article

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Abstract

Background Traditional cutoff values of urinary albumin-to-creatinine ratio (UACR) for predicting mortality have recently been challenged. In this study, we investigated the optimal threshold of UACR for predicting long-term cardiovascular and noncardiovascular mortality in the general population.

Methods Data for 25,302 adults were extracted from the National Health and Nutrition Examination Survey (2005–2014), with mortality status obtained by data matching with death certificates in the National Death Index until December 31, 2015. Receiver operating characteristic (ROC) curve analysis was performed to assess the predictive value of UACR for cardiovascular and noncardiovascular mortality. A Cox regression model was established to examine the association between UACR and cardiovascular and noncardiovascular mortality. X-tile was used to estimate the optimal cutoff of UACR.

Results The UACR had acceptable predictive value for both cardiovascular (area under the ROC curve [AUC]=0.769, 95% confidence interval [CI]: 0.711–0.828) and noncardiovascular (AUC=0.722, 95% CI: 0.681–0.764) mortality. Excellent linearity was observed between log-transformed UACR and cardiovascular and noncardiovascular mortality. The optimal cutoff values were 16 and 30 mg/g for predicting long-term cardiovascular and noncardiovascular mortality, respectively. The adjusted hazard ratios of cardiovascular and noncardiovascular mortality for the high-risk group were 2.55 (95% CI: 2.03–3.22, P<0.001) and 1.94 (95% CI: 1.72–2.18, P<0.001), respectively.

Conclusions Compared to the traditional cutoff value (30 mg/g), a UACR cutoff of 16 mg/g may be more sensitive for identifying patients at high risk for cardiovascular mortality in the general population.

Introduction

The urinary albumin-to-creatinine ratio (UACR) is a commonly used indicator of albuminuria and renal insufficiency[1, 2] that is associated with cardiovascular as well as all-cause mortality.[3, 4] Unlike other laboratory measures of albuminuria, UACR is unaffected by variations in the specific gravity of urine or 24-h urine collection. Additionally, timed specimens are not necessary for measurement, making it more suitable for general albuminuria screening.[5–8]

The Current Kidney Disease: Improving Global Outcomes (KDIGO) guidelines define albuminuria as UACR ≥30 mg/g, and persistent elevation of UACR ≥30 mg/g is regarded as a marker of chronic kidney disease that increases cardiovascular and noncardiovascular mortality risk in both specific populations such as patients with diabetes mellitus or hypertension and in the general population.[9–11] A number of studies have demonstrated the significance of a UACR that is slightly elevated but <30 mg/g in predicting cardiovascular and all-cause mortality.[4, 11, 12] However, various cutoff values of UACR were used in previous studies to assess the risk of cardiovascular mortality.[13–15] Moreover, the UACR cutoff for predicting long-term noncardiovascular mortality is unknown.

The aim of this study was to determine the optimal cutoff of UACR for predicting cardiovascular and noncardiovascular mortality in the general population based on analysis of National Health and Nutrition Examination Survey (NHANES) data.

Methods

Study population

Data from NHANES (2005–2014)[16]—a nationwide survey of the general population in the U.S. conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention—were analyzed in this study. The subjects were aged ≥18 years. Individuals who were <18 years old (n=20,670) or had missing questionnaire (n=1835), ACR (n=1710), or creatinine (n=1448) data were excluded, leaving 25,302 participants for the final analysis (Fig. 1). The survey protocol was approved by the Institutional Review Board of the Centers for Disease Control and Prevention. All participants had provided written, informed consent for the use of their data.

Baseline assessment

The questionnaires and examinations in NHANES were standardized. Covariates included sociodemographic information (age and ethnicity), body mass index, current smoking status, medical history (eg, hypertension, diabetes, stroke, emphysema, liver disease, malignant tumor, congestive heart disease, and coronary heart disease), hemoglobin, serum creatinine, and serum albumin. Demographic, health, and lifestyle information was obtained through questionnaires. All ethnicities were included. Estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation[17].

UACR measurement

A fluorescence immunoassay involving a solid-phase, noncompetitive, double-antibody reaction was used to measure urinary albumin in clinical samples. Urinary creatinine was determined with an enzymatic assay using the Cobas 6000 Analyzer (Roche Diagnostics, Basel, Switzerland). UACR was calculated as the ratio of urinary albumin to urinary creatinine.

Outcomes

The endpoints were long-term cardiovascular or noncardiovascular mortality. The mortality status of participants was obtained by data matching with death certificates in the National Death Index until December 31, 2015. Cardiovascular death was determined based on the International Classification of Diseases, 10th Edition, Clinical Modification System codes (I00–I09, I11, I13, I20–I51).

Statistical analysis

Baseline characteristics were expressed as a median with interquartile range (25th to 75th percentiles) for continuous variables and with categorical data expressed as n (%). Survival analysis was performed with standardized Kaplan–Meier curves and the log-rank test. Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for cardiovascular and noncardiovascular mortality. We used X-tile[18] to estimate the optimal cutoff for UACR, which was then used to divide the cohort into 2 groups according to long-term mortality risk (high vs low). Receiver operating characteristic (ROC) curve analysis was performed and the area under the ROC curve (AUC) was calculated.

The participants were divided in 2 groups according to KDIGO UACR (<30 or ≥30 mg/g) or the optimal cutoff generated by X-tile that differentiates between high and low cardiovascular risk; UACR was analyzed as a categorical variable in both cases. Additionally, unadjusted and adjusted Cox proportional hazard regression models were established for both cases. For the continuous model, a normal distribution was observed when UACR was log-transformed. All statistical analyses were performed using SPSS v25.0 (IBM, Armonk, NY, USA) and X-tile (Yale School of Medicine, New Haven, CT, USA), and $P<0.05$ was considered statistically significant.

Results

Baseline characteristics of the study population

The baseline characteristics of participants are summarized in Table 1. The analysis included 25,302 U.S. adults with an average age of 49.1±17.8 years; 51.3% were female. Overall, 7.5% of participants died during the survey with an average follow-up time of 5.7±2.8 years; 1.3% (n=420) died from cardiovascular causes and 6.1% (n=2020) from noncardiovascular causes.

Table 1
Baseline clinical characteristics of included patients.

Variables	Total (n=25302)
Age, years	49.1±17.8
Female gender, n (%)	14659 (51.3)
Ethnicity, n (%)	15715 (54.0)
Non-white	12745 (45.6)
White	
BMI	29.0±6.8
Current smoke, n (%)	6056 (21.2)
Hypertension, n (%)	10038 (34.8)
Diabetes mellitus, n (%)	3417 (11.7)
Stroke, n (%)	1109 (3.5)
Emphysema, n (%)	594 (2.0)
Liver disease, n (%)	1031 (3.6)
Malignant tumor, n (%)	2645 (9.0)
Congestive heart failure, n (%)	940 (3.0)
Coronary heart disease, n (%)	1135 (3.9)
Hemoglobin, g/L	14.1±1.5
eGFR(ml/min/1.73m^2)	93.9±23.4
Serum albumin, g/L	42.2±3.5
Follow-up time, years	5.7±2.8
Long-term mortality*, n (%)	2440 (7.5)
All-cause	420 (1.3)
Cardiovascular	2020 (6.1)
Non-cardiovascular	
Abbreviations: BMI, Body Mass Index;eGFR, estimated glomerular filtration rate	

UACR values for predicting survival

To explore the predictive value of UACR for cardiovascular and noncardiovascular mortality in the general population, we plotted an ROC curve for 1-year mortality. The AUCs for UACR were 0.769 (95% CI: 0.711–0.828; Fig. 2A) and 0.772 (95% CI: 0.681–0.764; Fig. 2B) for predicting cardiovascular and noncardiovascular mortality, respectively.

Optimal cutoff for UACR

Participants were divided into 2 groups based on KDIGO diagnostic criteria for albuminuria (UACR ≥30 mg/g). As shown by univariate and multivariate Cox proportional hazard regression (Table 3) and Kaplan–Meier survival curves (Fig. 3), individuals with UACR ≥30 mg/g had significantly higher risk of cardiovascular mortality (crude HR=5.32, 95% CI: 4.23–6.70, P<0.001; adjusted HR=2.24, 95% CI: 1.77–2.85, P<0.001) and noncardiovascular mortality (crude HR=4.12, 95% CI: 3.70–4.60,

P<0.001; adjusted HR=1.93, 95% CI: 1.72–2.17, P<0.001), even after adjusting for variables such as age, sex, renal insufficiency, and other diseases that could have influenced long-term mortality in univariate Cox regression analyses (Table 2). Additionally, univariate Cox regression analyses showed a significant correlation between UACR as a continuous variable and both cardiovascular and noncardiovascular death; excellent linearity was observed between log-transformed UACR and cardiovascular and noncardiovascular mortality (Figure 4 and Table 2). We used X-tile plots to determine the optimal cutoff value (16 mg/g), which divided subjects into 2 groups with high risk (UACR ≥16 mg/g) or low risk (UACR <16 mg/g) of long-term mortality. The HR for cardiovascular mortality in the high-risk group was 5.68 (95% CI: 4.54–7.11, P<0.001; Table 3), and the risk remained significant after adjustment. Compared to the low-risk group (UACR <16 mg/g), subjects with UACR ≥16 mg/g also had a higher risk of noncardiovascular mortality (HR=1.87, 95% CI: 1.67–2.08, P<0.001; Fig. 3 and Table 3). Interestingly, the optimal cutoff value (30 mg/g) for differentiating between subjects with high or low risk of noncardiovascular mortality determined from X-tile plots was very close to the current diagnostic cutoff for albuminuria (30 mg/g).

Table 2
Univariate Cox survival analysis for long-term mortality

Variables	Cardiovascular death			Non-cardiovascular death		
	HR	95%CI	P	HR	95%CI	P
Age	1.12	1.11-1.13	<0.001	1.08	1.08-1.09	<0.001
Female gender	0.47	0.38-0.59	<0.001	0.68	0.61-0.75	<0.001
White race	2.08	1.66-2.61	<0.001	1.69	1.53-1.87	<0.001
BMI	0.99	0.97-1.00	0.098	0.98	0.98-0.99	<0.001
Current smoke	0.88	0.67-1.15	0.339	0.89	0.79-1.01	0.079
Hypertension	3.98	3.18-4.99	<0.001	2.83	2.56-3.13	<0.001
Diabetes mellitus	3.70	2.91-4.71	<0.001	2.77	2.46-3.11	<0.001
Stroke	6.68	4.97-8.98	<0.001	4.78	4.11-5.55	<0.001
Emphysema	6.24	4.24-9.20	<0.001	5.85	4.92,6.97	<0.001
Liver disease	0.90	0.48-1.68	0.733	1.82	1.48-2.24	<0.001
Malignant tumor	3.14	2.41-4.09	<0.001	3.28	2.91-3.69	<0.001
Congestive heart failure	13.47	10.40-17.46	<0.001	5.60	4.79-6.54	<0.001
Coronary heart disease	8.26	6.33-10.77	<0.001	3.90	3.34-4.55	<0.001
Anemia (hemoglobin <90g/L)	2.98	1.97-4.52	<0.001	3.97	3.36-4.69	<0.001
eGFR<60mL/min/1.73 m^2	8.18	6.58-10.18	<0.001	6.16	5.56-6.83	<0.001
Hypoproteinemia (serum albumin < 40g/L)	1.83	1.12-2.98	0.016	1.95	1.57-2.41	<0.001
lnUACR	1.71	1.62-1.80	<0.001	1.55	1.51-1.6	<0.001

Abbreviations: BMI, Body Mass Index;eGFR, estimated glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio

Table 3
Adjusted HR and 95%CI of UACR categories for long-term mortality

Variables	UACR≥30mg/g				UACR≥16mg/g			
	Unadjusted		Adjusted*		Unadjusted		Adjusted*	
	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
Cardiovascular death	5.38(4.31-6.71)	<0.001	2.21(1.73-2.82)	<0.001	5.58(4.51-6.98)	<0.001	2.52(1.99-3.19)	<0.001
Non-cardiovascular death	4.20(3.78-4.66)	<0.001	1.94(1.72-2.18)	<0.001	3.68(3.32-4.08)	<0.001	1.86(1.67-2.07)	<0.001
Adjusted for age, sex, white race, BMI, hypertension, diabetes mellitus, stroke, emphysema, liver disease, malignant tumor, congestive heart failure, coronary heart disease, hemoglobin, eGFR(estimated glomerular filtration rate) and serum albumin.								
Abbreviations: UACR, urinary albumin-to-creatinine ratio								

Discussion

In this study we investigated the relationship between UACR and long-term cardiovascular and noncardiovascular mortality risk in the general population. Our results showed that the traditional UACR cutoff (30 mg/g) is suitable for predicting long-term noncardiovascular mortality risk in the community; however, setting the cutoff value at 16 mg/g may have greater sensitivity for identifying individuals with high cardiovascular mortality risk.

Albuminuria, which is often caused by increased glomerular permeability or impaired reabsorption by proximal tubule epithelial cells, is significantly associated with cardiovascular and noncardiovascular mortality.[19–21] However, a recent study of 31,413 U.S. adults showed that even a slightly elevated UACR that was still within the normal range (30 mg/g) was associated with a significantly higher cardiovascular mortality;[14] and a meta-analysis of albuminuria in the general population also found that individuals with UACR in the range of 10 to 29 mg/g had a higher risk of all-cause and cardiovascular mortality compared to those with a ratio of 5 mg/g.[7] These reports cast doubt on the suitability of the traditional UACR cutoff (30 mg/g) for long-term mortality prediction. However, previous studies did not explore optimal UACR cutoffs, and the values used to assess long-term cardiovascular mortality risk were inconsistent. In the Reasons for Geographic and Racial Differences in Stroke (REGARDS) trial, UACR was categorized as <10 mg/g, 10 to <30 mg/g, 30 to 300 mg/g, and >300 mg/g.[15] However, in the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) study that explored the association between baseline UACR and cardiorenal outcome, UACR was categorized as 0, >0 to <15, 15 to <30, 30 to <100, 100 to <300, and ≥300 mg/g.[13]

We observed a strong linear relationship between log-transformed UACR and cardiovascular mortality. This can be explained as follows. Firstly, inflammation and oxidative stress are known to be key pathophysiologic roles in atherosclerosis,[22] and recent studies have demonstrated a positive correlation between inflammatory and oxidative stress markers such as interleukin (IL)-2, IL-6, and superoxide dismutase and UACR.[23, 24] Therefore, low-grade inflammation in patients with increased UACR may contribute to atherosclerotic plaque development and progression, leading to late clinical complications. Secondly, elevated UACR was shown to be associated with left ventricular hypertrophy, which increases the risk of decompensated heart failure and ventricular arrhythmia; this in turn increases the risk of cardiovascular mortality 4 fold.[25] Thirdly, a previous study showed that elevated UACR was associated with higher levels of coagulation factors;[26] this increased the risk of thrombosis, which is among the most common causes of cardiovascular mortality.[27]

Based on the linearity between UACR and cardiovascular mortality, we explored the predictive value of different UACR cutoffs. We found that setting the cutoff at 16 mg/g instead of 30 mg/g was more advantageous for identifying individuals with higher cardiovascular mortality risk in the general population. This raises the question of why the cutoff value that differentiates high and low risk of cardiovascular mortality deviated to the left of 30 mg/g. One explanation is that increased urinary albumin excretion and cardiovascular disease development share a common pathologic mechanism—namely, endothelial dysfunction, which could increase glomerular permeability to macromolecules such as albumin and result in increased urinary albumin excretion.[20, 28, 29] Endothelial dysfunction also contributes to the development of coronary artery disease, heart failure, etc. Because of the close relationship between urinary albumin excretion and cardiovascular disease, cardiovascular mortality risk may be more sensitive to small increases in UACR. Additionally, in the cohort analyzed in this study, there was a high prevalence of hypertension and diabetes mellitus; in these patients, a slight increase in UACR may be a sign of target organ damage, which can significantly increase cardiovascular mortality.[30, 31]

The linearity observed between log-transformed UACR and noncardiovascular mortality has a few possible explanations. A longitudinal observational study conducted in Australia showed that in individuals with normoalbuminuria, UACR was significantly associated with glomerular hyperfiltration, which plays an important role in the induction of renal damage.[32] Individuals with glomerular hyperfiltration also have a higher risk of mortality from noncardiovascular causes such as infection or liver failure.[33] On the other hand, increased UACR was found be associated with increased cancer mortality,[34] which accounted for a large proportion of noncardiovascular death in our analysis. The UACR cutoff of 30 mg/g was ideal for predicting noncardiovascular mortality.

There were several limitations to this study that should be noted. Firstly, the UACR was calculated from a single, untimed urine collection, and therefore did not reflect changes in urinary albumin excretion over the course of the day.[35] Secondly, because of the retrospective study design, our findings should be interpreted with caution. Finally, although the models were adjusted for potential risk factors using multiple regression analysis techniques, there may have been some residual confounding factors.

Conclusion

In summary, compared to the traditional cutoff value (30 mg/g), a UACR cutoff of 16 mg/g may be more sensitive for identifying patients with high risk of cardiovascular mortality. Therefore, individuals with even slightly elevated UACR (16–30 mg/g) should be closely monitored to reduce the risk of death from a cardiovascular cause.

Declarations

Ethics approval and consent to participate: All NHANES study protocols survey protocol was approved by the Ethics Review Committee of NCHS of the Centers for Disease Control and Prevention. All participants had provided written, informed consent for the use of their data. All procedures in this study were conducted in accordance with all the relevant guidelines.

Consent for publication: Not applicable.

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Figures

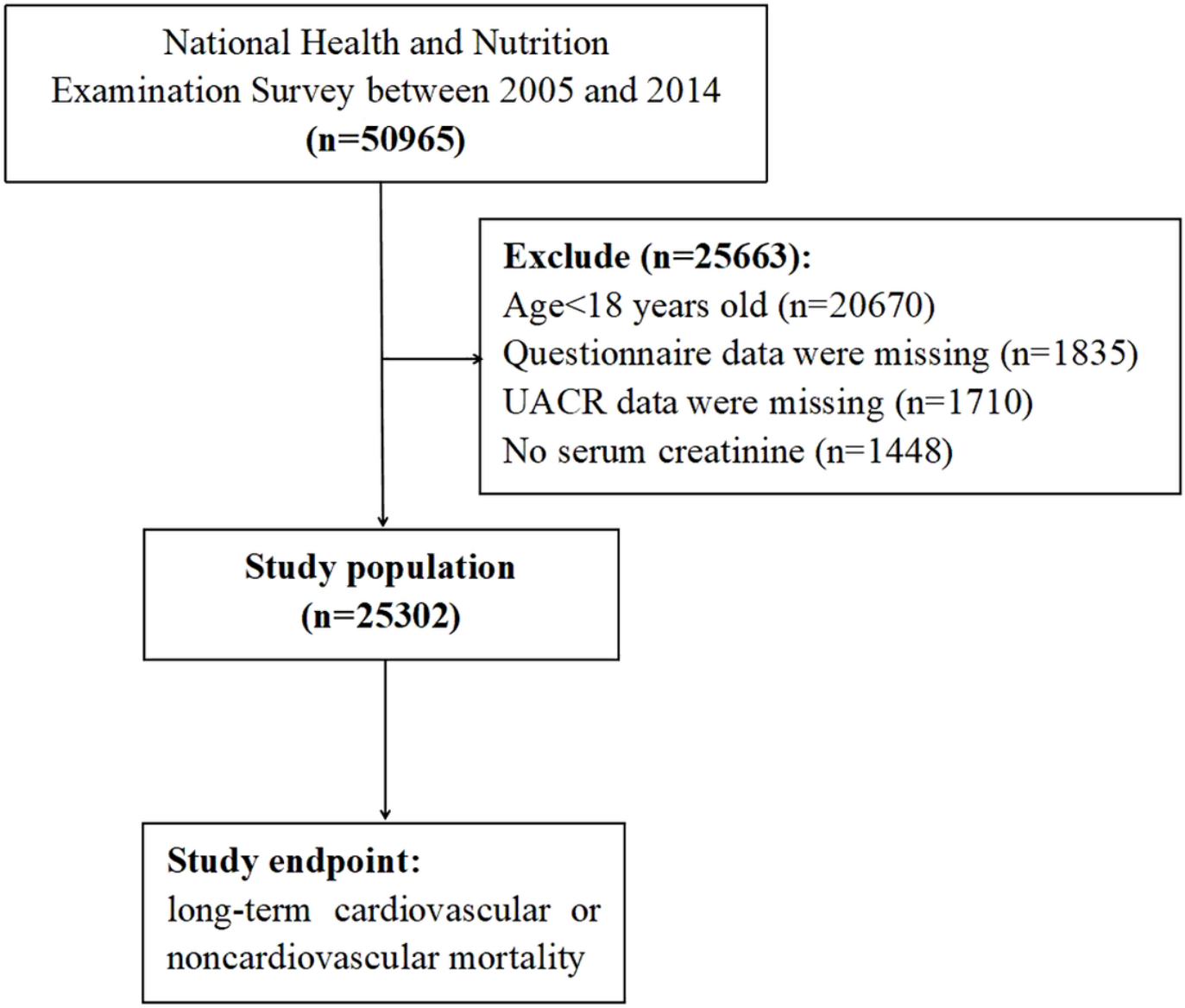

Figure 1

Flow diagram for the selection of the study population

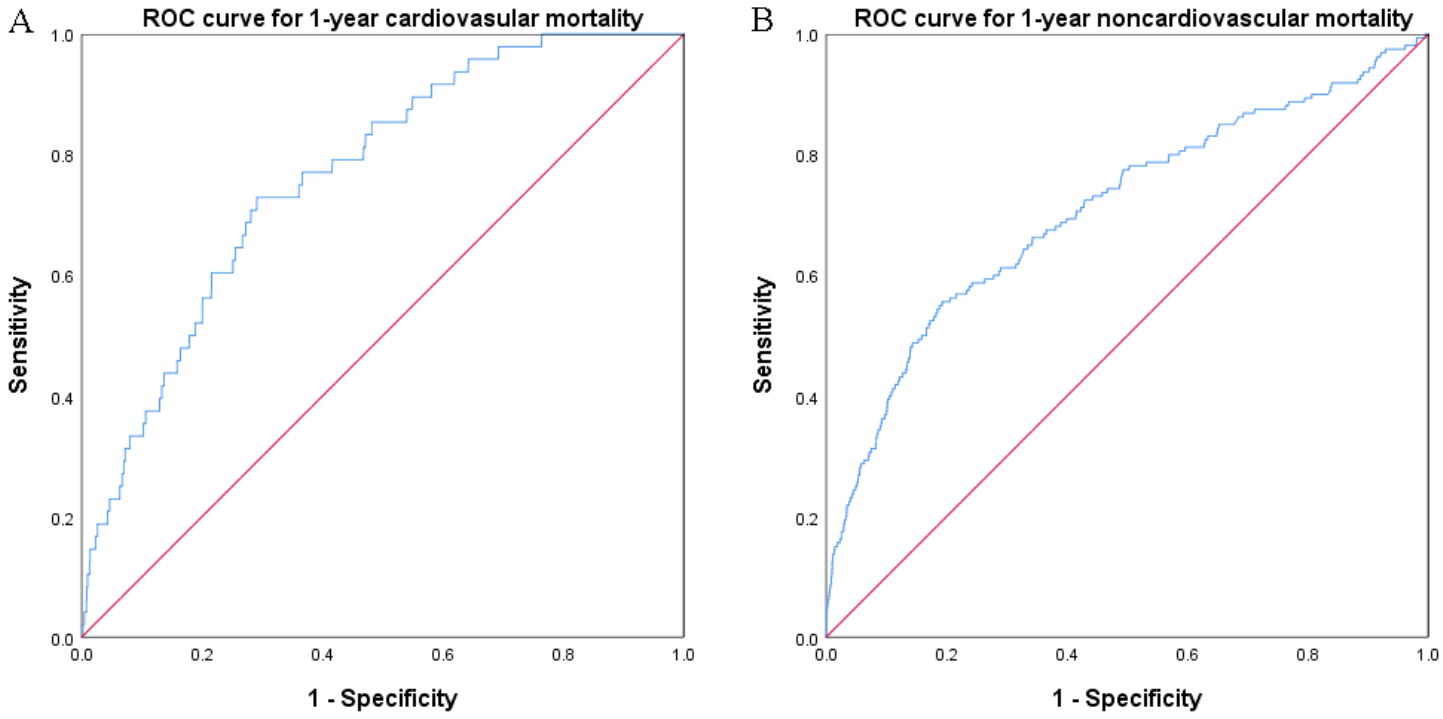

Figure 2

ROC curve analysis of UACR for predicting 1-year cardiovascular and noncardiovascular mortality

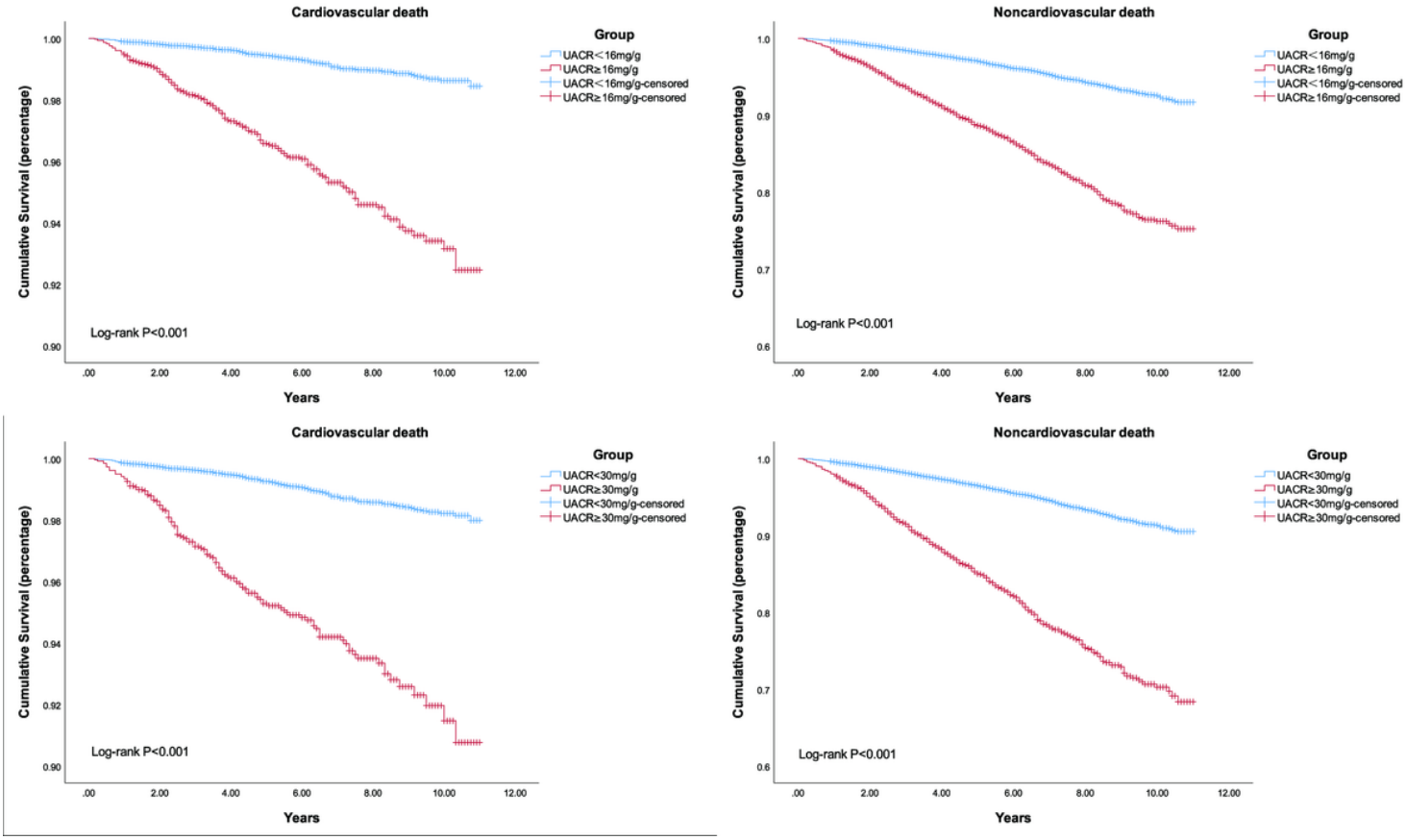

Figure 3

Kaplan–Meier curves of long-term cardiovascular and noncardiovascular mortality for different cutoff values of UACR

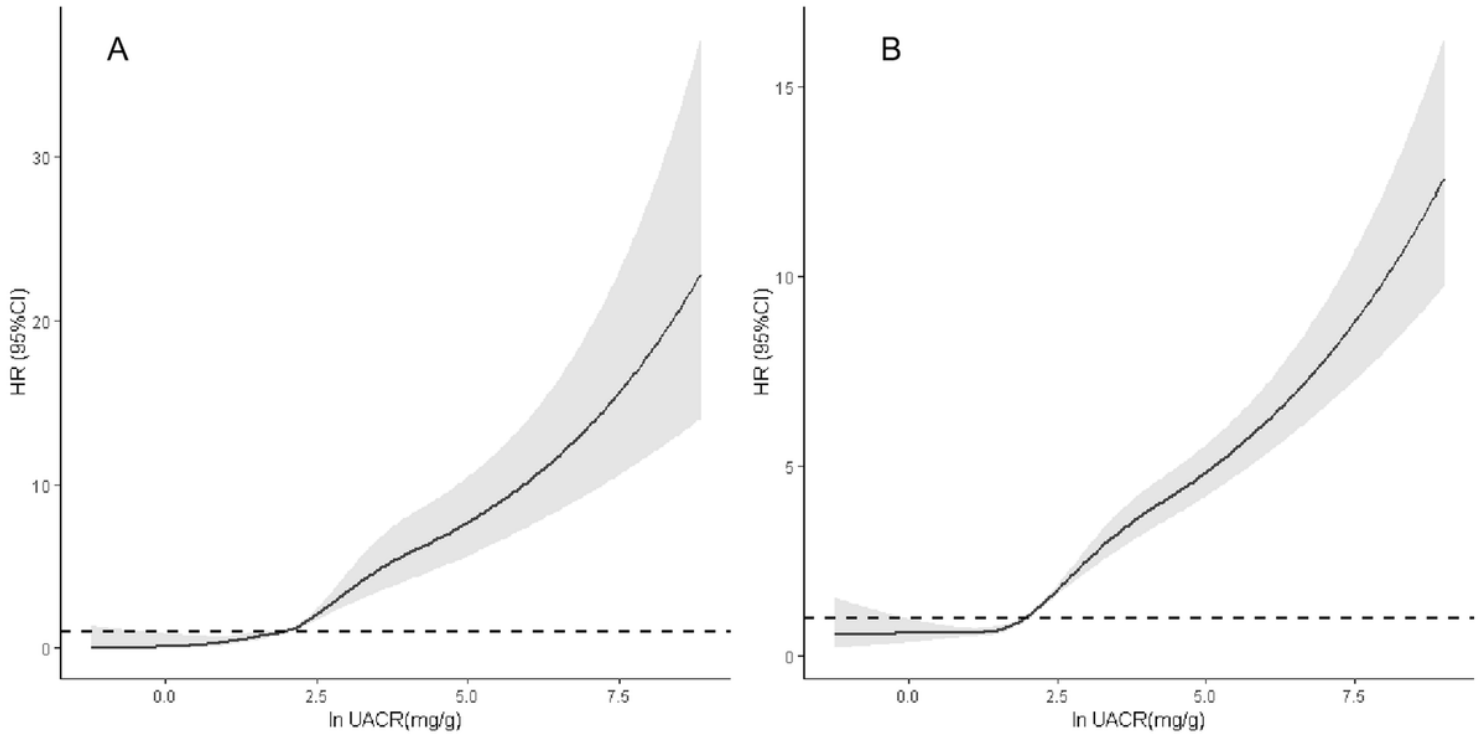

Figure 4

Effect of UACR on mortality. (A, B) Unadjusted effect of UACR on cardiovascular mortality (A) and noncardiovascular mortality (B) hazard function. Solid line shows the estimated relationship when the logarithm of the hazard ratio is modeled as linear function of ln(UACR). The shaded area shows the 95% confidence limits for a more general functional relationship, as estimated by P-splines.