Optimal threshold of urinary albumin-to-creatinine ratio (UACR) for predicting long-term cardiovascular and noncardiovascular mortality

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Abstract
Purpose 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 non-cardiovascular mortality in the general population.

Methods Data for 25,302 adults were extracted from the National Health and Nutrition Examination Survey (2005–2014). Receiver operating characteristic (ROC) curve analysis was performed to assess the predictive value of UACR for cardiovascular and non-cardiovascular mortality. A Cox regression model was established to examine the association between UACR and cardiovascular and non-cardiovascular mortality. X-tile was used to estimate the optimal cutoff of UACR.

Results The UACR had acceptable predictive value for both cardiovascular (AUC (95% CI) for 1-year, 3-year and 5-year mortality, respectively: 0.769 (0.711–0.828), 0.764 (0.722–0.805) and 0.763 (0.730–0.795)) and non-cardiovascular (AUC (95% CI) for 1-year, 3-year and 5-year mortality, respectively: 0.772 (0.681–0.764), 0.708 (0.686–0.731) and 0.708 (0.690–0.725)) mortality. The optimal cutoff values were 16 and 30 mg/g for predicting long-term cardiovascular and non-cardiovascular mortality, respectively. Both cutoffs of UACR had acceptable specificity (0.785–0.891) in predicting long-term mortality, while the new proposed cutoff (16 mg/g) had higher sensitivity. The adjusted hazard ratios of cardiovascular and non-cardiovascular mortality for the high-risk group were 2.50 (95% CI 1.96–3.18, \( P < 0.001 \)) and 1.92 (95% CI 1.70–2.17, \( P < 0.001 \)), 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.

Keywords Urinary albumin-to-creatinine ratio · Cardiovascular mortality · Non-cardiovascular mortality · X-tile · National health and nutrition examination survey
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 non-cardiovascular 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 UACR that is slightly elevated but < 30 mg/g in predicting cardiovascular and non-cardiovascular mortality [4, 11–13]. Moreover, a linear relationship between UACR levels within normal range and both cardiovascular and all-cause mortality has also been reported [7, 14, 15]. However, there was no agreement on the optimal cutoff of UACR to predict cardiovascular mortality and non-cardiovascular mortality, which result in various cutoff values of UACR were used in different studies [13, 15, 16].

The aim of this study was to determine the optimal cutoff of UACR for predicting cardiovascular and non-cardiovascular 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) [17]—a nationwide survey of the general population in the US 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.

UACR measurement

A fluorescence immunoassay involving a solid-phase, non-competitive, double-antibody reaction was used to measure urinary albumin in clinical samples. The lowest detect limit of this assay for urinary albumin measurement was 0.21 mg/L, and value below 0.21 mg/L was recorded as 0.21 mg/L. 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 non-cardiovascular 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 mean with standard deviation for normally distributed continuous variables. Median interquartile range (25–75th percentiles) for skewed distributed continuous variables and categorical data was 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 non-cardiovascular mortality. We used X-tile [19] 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). The X-tile worked by assessing all possible cutoffs of UACR by plotting Kaplan–Meier curves and log-rank test, and chose the most significant one as the best cutoff. Compared to the way of using Receiver operating characteristic (ROC) to determine the cutoff, the outcome in this method included both survival time and status while the outcome in ROC was only the survival status in a certain time point. ROC curve analysis was performed and the area under the ROC curve (AUC) was calculated.

The participants were divided into 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 risks. 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 US 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 non-cardiovascular causes.

| Variables                  | Total (n = 25302) |
|----------------------------|-------------------|
| Age, years                 | 49.1 ± 17.8       |
| Female gender, n (%)       | 14659 (51.3)      |
| Ethnicity, n (%)           |                   |
| Non-white                  | 15715 (54.0)      |
| White                      | 12745 (45.6)      |
| 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)        |
| Embryophyma, 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/1.73 m²)      | 93.9 ± 23.4       |
| Serum albumin, g/L         | 42.2 ± 3.5        |
| Follow-up time, years      | 5.7 ± 2.8         |
| Long-term mortality, n (%) |                   |
| All-cause                  | 2440 (7.5)        |
| Cardiovascular             | 420 (1.3)         |
| Non-cardiovascular         | 2020 (6.1)        |

BMI body mass index, eGFR estimated glomerular filtration rate

**UACR values for predicting survival**

To explore the predictive value of UACR for cardiovascular and non-cardiovascular mortality in the general population, we plotted ROC curves for 1-year, 3-year and 5-year mortality. The AUCs for UACR were 0.769 (95% CI 0.711–0.828), 0.764 (95% CI 0.722–0.805) and 0.763 (95% CI 0.730–0.795) for predicting 1-year, 3-year and 5-year cardiovascular mortality and were 0.772 (95% CI 0.681–0.764), 0.708 (95% CI 0.686–0.731) and 0.708 (95% CI 0.690–0.725) for predicting 1-year, 3-year and 5-year non-cardiovascular mortality, respectively (Fig. 2).

**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 5.38, 95% CI 4.31–6.71, P < 0.001; adjusted HR 2.14, 95% CI 1.66–2.76, P < 0.001) and non-cardiovascular mortality (crude HR 4.20, 95% CI 3.78–4.66, P < 0.001;
Fig. 2 ROC curve analysis of UACR for predicting 1-year, 3-year and 5-year cardiovascular and noncardiovascular mortality

Fig. 3 Kaplan–Meier curves of long-term cardiovascular and noncardiovascular mortality for different cutoff values of UACR
adjusted HR 1.92, 95% CI 1.70–2.17, \( P < 0.001 \), even after adjusting for variables which could have influenced long-term mortality in univariate Cox regression analyses (Table 2), such as age, sex, renal insufficiency, hypertension, diabetes mellitus, stroke, emphysema, malignant tumor, congestive heart failure, and coronary heart disease. Additionally, univariate Cox regression analyses showed a significant correlation between UACR as a continuous variable and both cardiovascular and non-cardiovascular death; excellent linearity was observed between log-transformed UACR and cardiovascular and non-cardiovascular mortality (Fig. 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

| Variables         | Cardiovascular death |     | Non-cardiovascular death |     |
|-------------------|----------------------|-----|--------------------------|-----|
|                   | HR       | 95% CI |    | HR       | 95% CI |    |
| 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 | 0.099 | 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 |
| Hemoglobin        | 0.88     | 0.82–0.94 | <0.001 | 0.83     | 0.81–0.86 | <0.001 |
| eGFR              | 0.95     | 0.95–0.96 | <0.001 | 0.96     | 0.96–0.96 | <0.001 |
| Serum albumin     | 0.92     | 0.90–0.94 | 0.016 | 0.91     | 0.90–0.92 | <0.001 |
| lnUACR            | 1.71     | 1.62–1.80 | <0.001 | 1.55     | 1.51–1.6  | <0.001 |

BMI body mass index, eGFR estimated glomerular filtration rate, UACR urinary albumin-to-creatinine ratio

Fig. 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

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high-risk group was 5.57 (95% CI 4.48–6.92, \(P < 0.001\); Table 3) and the risk remained significant after adjustment (adjusted HR 2.50, 95% CI 1.96–3.18, \(P < 0.001\); Table 3). Compared to the low-risk group (UACR < 16 mg/g), subjects with UACR ≥ 16 mg/g also had a higher risk of non-cardiovascular mortality (crude HR 3.78, 95% CI 3.43–4.18, \(P < 0.001\); adjusted HR 1.86, 95% CI 1.66–2.08, \(P < 0.001\); Fig. 3 and Table 3). The sensitivity and specificity of new proposed cutoff (16 mg/g) were 0.606 and 0.798, 0.620 and 0.792, 0.606 and 0.798 for 1-year, 3-year, and 5-year cardiovascular death, respectively. The sensitivity and specificity of traditional cutoff (30 mg/g) were 0.394 and 0.880, 0.382 and 0.886, 0.367 and 0.891 for 1-year, 3-year, and 5-year non-cardiovascular death, respectively. Both cutoffs of UACR had acceptable specificity, while the new proposed cutoff (16 mg/g) had higher sensitivity and Youden index (Supplementary table 1). Further subgroup analysis of UACR categories for long-term mortality (Table 4) showed that the new proposed cut-off of UACR (16 mg/g) was associated with both higher cardiovascular and non-cardiovascular mortality which was not affected by gender and comorbidities and had advantages on cardiovascular mortality prediction than traditional cut-off (30 mg/g) in male, female and people with chronic disease. Interestingly, the optimal cutoff value (30 mg/g) for differentiating between subjects with high or low risk of non-cardiovascular mortality determined from X-tile plots was very close to the current diagnostic cutoff for albuminuria (30 mg/g).

### Discussion

In this study, we investigated the relationship between UACR and long-term cardiovascular and non-cardiovascular mortality risk in the general population. Our results showed that the traditional UACR cutoff (30 mg/g) is suitable for predicting long-term non-cardiovascular mortality risk in

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

| Variables          | UACR ≥ 30 mg/g |                      | UACR ≥ 16 mg/g |                      |
|--------------------|----------------|----------------------|----------------|----------------------|
|                    | Unadjusted     | Adjusted*            | Unadjusted     | Adjusted*            |
|                    | HR (95% CI)    | \(P\)                | HR (95% CI)    | \(P\)                |
| Cardiovascular     |                |                      |                |                      |
| death              | 5.38 (4.31–6.71) | <0.001               | 2.14 (1.66–2.76) | <0.001               |
| Non-cardiovascular | 4.20 (3.78–4.66) | <0.001               | 1.92 (1.70–2.17) | <0.001               |

### Table 4  Subgroup analysis of UACR categories for long-term mortality

| Subgroup            | UACR ≥ 30 mg/g |                      | UACR ≥ 16 mg/g |                      |
|---------------------|----------------|----------------------|----------------|----------------------|
|                     | HR (95% CI)    | \(P\)                | HR (95% CI)    | \(P\)                |
| Gender              |                |                      |                |                      |
| Male                |                |                      |                |                      |
| Cardiovascular death| 4.89 (3.70–6.45) | <0.001               | 5.22 (4.00–6.80) | <0.001               |
| Non-cardiovascular  | 4.14 (3.60–4.76) | <0.001               | 4.13 (3.62–4.71) | <0.001               |
| Female              |                |                      |                |                      |
| Cardiovascular death| 6.66 (4.60–9.66) | <0.001               | 7.77 (5.23–11.54) | <0.001               |
| Non-cardiovascular  | 4.31 (3.67–5.06) | <0.001               | 3.62 (3.11–4.22) | <0.001               |
| Comorbidities       |                |                      |                |                      |
| With chronic disease|                |                      |                |                      |
| Cardiovascular death| 3.69 (2.92–4.67) | <0.001               | 4.14 (3.26–5.26) | <0.001               |
| Non-cardiovascular  | 3.03 (2.71–3.40) | <0.001               | 2.92 (2.62–3.27) | <0.001               |
| Without chronic disease |          |                      |                |                      |
| Cardiovascular death| 2.56 (1.09–6.05) | <0.001               | 2.50 (1.29–4.36) | 0.007                |
| Non-cardiovascular  | 2.04 (1.40–2.96) | <0.001               | 1.88 (1.42–2.50) | <0.001               |

\(UACR\) urinary albumin-to-creatinine ratio

*Adjusted for age, sex, white race, BMI, hypertension, diabetes mellitus, stroke, emphysema, liver disease, malignant tumor, congestive heart failure, coronary heart disease, current smoking, hemoglobin, eGFR (estimated glomerular filtration rate) and serum albumin

*Chronic disease includes hypertension, diabetes mellitus, stroke, emphysema, liver disease, malignant tumor, congestive heart failure, and coronary heart disease
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 non-cardiovascular mortality [20–22]. However, a recent study of 31,413 US 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 [15]; and a meta-analysis of albuminuria in the general population also found that individuals with UACR in the range of 10–29 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 < 100 mg/g, and > 300 mg/g [16]. However, in the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER) study that explored the association between baseline UACR and cardio-renal 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. First, inflammation and oxidative stress are known to be key pathophysiologic roles in atherosclerosis [23], 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 [24, 25]. Therefore, low-grade inflammation in patients with increased UACR may contribute to atherosclerotic plaque development and progression, leading to late clinical complications. Second, 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 fourfold [26]. Third, a previous study showed that elevated UACR was associated with higher levels of coagulation factors [27]; this increased the risk of thrombosis, which is among the most common causes of cardiovascular mortality [28].

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 [21, 29, 30]. 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 [31, 32].

The linearity observed between log-transformed UACR and non-cardiovascular 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 hyper-filtration, which plays an important role in the induction of renal damage [33]. Individuals with glomerular hyper-filtration also have a higher risk of mortality from non-cardiovascular causes such as infection or liver failure [34]. On the other hand, increased UACR was found to be associated with increased cancer mortality [35], which accounted for a large proportion of non-cardiovascular death in our analysis. The UACR cutoff of 30 mg/g was ideal for predicting non-cardiovascular mortality.

There were several limitations to this study that should be noted. First, 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 [36]. Second, due the retrospective study design, there might be recall bias in information collection. Therefore, our findings should be interpreted with caution.

Third, although the models were adjusted for potential risk factors using multiple regression analysis techniques, there may have been some residual confounding factors. Finally, this study was based on United States population, which might not be applicable for other populations. Thus, further confirmation in other population is necessary.

**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.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11255-023-03499-z.

Author contributions ZWY, WXH and YDQ contributed to the conception or design of the study. ZWY, YBF, JLH, BQF, GRZ contributed to the acquisition, analyses, and interpretation of data. ZWY, YBF, WXH drafted the manuscript. YDQ revised the manuscript critically. YDQ had all access to the data and is responsible for the overall content as guarantor. All authors contributed to refinement of the study protocol and approved the final manuscript.

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Data availability Data are from Centers for Disease Control and Prevention, National Center for Health Statistics. National health and nutrition examination survey data. Available at: https://www.cdc.gov/nchs/nhanes/

Declarations

Conflict of interest None.

Ethical approval All NHANES study protocols survey protocol was approved by the Ethics Review Committee of NCHS of the Centers for Disease Control and Prevention.

Consent to participate 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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