Association of Serum Uromodulin with Death, Cardiovascular Events, and Kidney Failure in CKD

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Abstract

Background and objectives Uromodulin is exclusively produced by tubular epithelial cells and released into urine and serum. Higher serum uromodulin has been associated with lower risk for kidney failure in Chinese patients with CKD and with lower risk for mortality in the elderly and in patients undergoing coronary angiography. We hypothesized that lower serum uromodulin is associated with mortality, cardiovascular events, and kidney failure in white patients with CKD.

Design, setting, participants, & measurements We measured serum uromodulin in 5143 participants enrolled in the German CKD (GCKD) study. The associations of baseline serum uromodulin with all-cause mortality, major adverse cardiovascular events (MACE; a composite of cardiovascular mortality, nonfatal myocardial infarction or stroke, or incident peripheral vascular disease), and kidney failure (dialysis or transplantation) were evaluated using multivariable Cox proportional hazard regression analyses in a cohort study design, adjusting for demographics, eGFR, albuminuria, cardiovascular risk factors, and medication.

Results The mean age of participants was 60±12 years, 60% were male. Mean serum uromodulin concentration was 98±60 ng/ml, eGFR was 49±18 ml/min per 1.73 m^2, and 78% had eGFR <60 ml/min per 1.73 m^2. Participants in lower serum uromodulin quartiles had lower eGFR and higher albuminuria, prevalence of diabetes, hypertension, coronary artery disease, and more frequent history of stroke at baseline. During a follow-up of 4 years, 335 participants died, 417 developed MACE, and 229 developed kidney failure. In multivariable analysis, the highest serum uromodulin quartile was associated with lower hazard for mortality (hazard ratio [HR], 0.57; 95% CI, 0.38 to 0.87), MACE (HR, 0.63; 95% CI, 0.45 to 0.90), and kidney failure (HR, 0.24; 95% CI, 0.10 to 0.55) compared with the lowest quartile.

Conclusions Higher serum uromodulin is independently associated with lower risk for mortality, cardiovascular events, and kidney failure in white patients with CKD.

Clinical Trial registry name and registration number Deutsches Register für Klinische Studien (DRKS; German national database of clinical studies), DRKS00003971.

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Introduction

CKD has a high prevalence and represents a great burden for health care systems (1–4). CKD is associated with a higher risk for mortality and cardiovascular disease (5,6). Patients with CKD are at risk of progressing to kidney failure, *i.e.*, of needing KRT. Kidney failure further increases health care costs and the risk for mortality and cardiovascular disease (3,4,7). Therefore, understanding the risk factors for mortality, cardiovascular disease, and kidney failure in patients with CKD is important.

Lower eGFRs and higher urinary albumin-creatinine ratio (ACR) are strongly associated with all-cause and cardiovascular mortality, progression of CKD, and kidney failure (8–10). However, both eGFR estimated from creatinine and ACR are influenced by parameters such as nutrition, muscle mass, and liver function. Furthermore, eGFR and ACR do not accurately represent the extent of tubular atrophy and interstitial fibrosis, but tubular atrophy is positively associated with CKD progression (11,12).

Uromodulin, also known as Tamm–Horsfall protein, is exclusively expressed in the cells of the ascending limb of the loop of Henle and secreted into the urine and, to a lower extent, into the circulation (13). Urinary uromodulin has been suggested as a proxy for tubular mass (14), whereas serum uromodulin is stronger correlated to eGFR (15,16). Although higher serum and urinary uromodulin have been associated with lower risk for mortality in elderly people and with lower risk for cardiovascular disease (16–18), neither serum nor

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urinary uromodulin have been well studied in patients with CKD. A recent study performed in Chinese patients with CKD detected an association of high serum uromodulin with lower risk for kidney failure, but not mortality nor cardiovascular disease (19). Given these heterogeneous findings, we observationally tested whether higher serum uromodulin values are associated with lower risk for mortality, major adverse cardiovascular events (MACE), and kidney failure in the German CKD (GCKD) cohort over a follow-up period of 4 years.

Materials and Methods

Study Participants and Study Design

The GCKD cohort is a prospective, observational, nationwide cohort study. Main inclusion criteria were an eGFR between 30 and 60 ml/min per 1.73 m^2 or overt proteinuria (urinary protein-creatinine ratio >500 m/g or equivalent) if eGFR was >60 ml/min per 1.73 m^2 (20). Exclusion criteria were solid organ or bone marrow transplantation, malignancy, advanced heart failure, legal attendance, or inability to provide informed consent.

A total of 5217 participants were enrolled between 2010 and 2012. All participants gave written informed consent for participation, and local institutional review boards approved the study methods. Serum uromodulin measurements were available in 5134 participants, and these data form the basis for this analysis. A small group of 84 participants (approximately 2%) were lost to follow-up after 4 years. Any recorded event occurring before loss to follow-up was included in the analysis. If there was no event, these participants were censored at the time loss to follow-up occurred.

Exposure

Serum samples were obtained at the baseline study visit and stored at −80°C until they were thawed. Serum uromodulin measurements were performed in singlicate at the Laboratory for Clinical Chemistry and Laboratory Medicine, University Hospital Greifswald, Germany, using a commercial ELISA (Euroimmun, Medizinische Labordiagnostika AG, Lübeck, Germany) as described previously based on the manufacturer's instructions (15). This assay is based on a colorimetric sandwich immunoassay using a polyclonal antibody against human uromodulin as the capture antibody and a biotinylated polyclonal antibody against human uromodulin as the detection antibody. Characteristics of the ELISA were as follows: intra-assay coefficient of variation, 1.8%–3.2%; interassay coefficient of variation, 6.6%–7.8%; mean linearity recovery, 97%; lower limit of detection, 2.0 ng/ml.

Outcomes

The outcomes analyzed were all-cause mortality; MACE as a composite of fatal cardiovascular event, nonfatal myocardial infarction, or nonfatal stroke and incident peripheral vascular disease; and incident kidney failure, a composite of incident dialysis or kidney transplantation. The GCKD cohort end point committee centrally adjudicated all outcomes.

Covariates

For the multivariable models, we used baseline data on sociodemographic variables (age, sex, body mass index), markers of kidney function (eGFR calculated using the CKD Epidemiology Collaboration equation (21), urinary ACR), cardiovascular risk factors (prevalent diabetes, defined by prescription of antidiabetic medication or hemoglobin A1c >6.5%), hypertension (defined by a mean of three BP measurements ≥140 mm Hg systolic or ≥90 mm Hg diastolic, or prescription of any antihypertensive drug), systolic BP, diastolic BP, HDL cholesterol, LDLcholesterol, C-reactive protein (CRP), serum phosphorus, pharmacologic therapy (lipid-lowering therapy, antihypertensive medication, diuretic therapy), and prevalent cardiovascular disease (defined by previous coronary, cerebrovascular, or peripheral vascular disease). All variables were selected based on their clinical relevance for the outcomes of interest.

Statistical Analyses

We describe the population overall and across serum uromodulin quartiles using means and SDs for continuous variables and number with percentages for binary and categoric variables. Multivariable Cox proportional hazard regression models were used to examine the association of serum uromodulin at baseline with all-cause mortality, MACE, and incident kidney failure during follow-up. We evaluated a series of nested models for all outcomes: (*1*) unadjusted, (*2*) adjusted for baseline demographic/clinical parameters (age, sex, body mass index; model 1), (*3*) model 1 with eGFR and ACR added (model 2), and (*4*) model 2 with diabetes, hypertension, prevalent cardiovascular disease, systolic BP, diastolic BP, HDL cholesterol, LDL cholesterol, CRP, serum phosphorus, and medication added (model 3). Restricted cubic splines were used to illustrate the individual hazard ratio (HR) of each participant in model 3. We further evaluated the influence of eGFR, ACR, and diabetes status on the associations of serum uromodulin with the outcomes mentioned above using interaction terms in the Cox regression models. In a secondary analysis, we examined the association of serum uromodulin with kidney failure and MACE in multivariable adjusted competing risk regression models using the Fine and Gray method (22), with mortality and/or kidney failure/MACE as the competing events. Estimates with P values <0.05 were considered statistically significant. The prevalence of missing data were very low in our cohort (<2% for all variables), and therefore no imputation methods were applied. To assess clinical utility in a predictive setting, we split the available data randomly in a training set and a test set (containing two thirds and one third of the patients, respectively) and fitted the aforementioned models to the training data. Discriminatory power was subsequently evaluated by estimating the concordance probability (C-index) from the test data. All analyses were conducted using R version 3.5.1 (R Core Team, Vienna, Austria). Estimates of the concordance probability were obtained using the methods implemented in the R add-on package pec.

Results

Population Characteristics

Mean age of the cohort (n=5143) was 60±12 years, 60% were male, serum uromodulin concentration was

98±60 ng/ml, eGFR was 49±18 ml/min per 1.73 m^2, and 78% had an eGFR <60 ml/min per 1.73 m^2 (Table 1). Individuals in the higher serum uromodulin quartile were more frequently female and had a nominally lower prevalence of diabetes and diabetic nephropathy, hypertension, coronary heart disease, and stroke (Table 1). They also less frequently received antihypertensive, diuretic, and lipid-lowering medication.

Serum Uromodulin and Outcomes

A total of 335 participants died during the median follow-up period of 4 years, with the lowest cumulative incidence rates in the highest serum uromodulin quartile (n=41, cumulative incidence per person year 0.6%; 95% CI, 0.4 to 0.9; Table 2). In univariable Cox regression analysis, each SD (*i.e.*, 60 ng/ml) higher serum uromodulin was associated with a 39% lower hazard (HR, 0.61; 95% CI, 0.52 to 0.71) of all-cause mortality (Table 3). Compared with the lowest serum uromodulin quartile, all other quartiles had a significantly lower HR for this end point. In multivariable analysis, each SD higher serum uromodulin was associated with a 20% lower hazard of mortality (HR, 0.80; 95% CI, 0.66 to 0.96); the two highest serum uromodulin quartiles had a significantly lower HR compared with the lowest quartile.

A total of 229 participants developed kidney failure, with the lowest cumulative incidence rates in the highest serum uromodulin quartile (n=8, cumulative incidence per person year 0.1%; 95% CI, 0.0 to 0.1; Table 2). In univariable analysis, each SD higher serum uromodulin was associated with a 70% lower hazard (HR, 0.30; 95% CI, 0.24 to 0.39) of kidney failure (Table 3). All quartiles had significantly lower HR compared with the lowest quartile. In multivariable analysis, each SD higher serum uromodulin was associated with a 39% lower hazard of kidney failure (HR, 0.61; 95% CI, 0.46 to 0.81); the two highest serum uromodulin quartiles had a significantly lower HR.

A total of 417 participants experienced MACE, with the lowest cumulative incidence rates in the highest serum uromodulin quartile (n=59, cumulative incidence per person year 3.2%; 95% CI, 2.7 to 3.9; Table 2). In univariable analysis, each SD higher serum uromodulin was associated with a 32% lower hazard of MACE (HR, 0.68; 95% CI, 0.60 to 0.77; Table 3). All quartiles had lower HR compared with the lowest quartile. In multivariable analysis, each SD higher serum uromodulin was borderline associated with MACE, having a 13% lower hazard of MACE (HR, 0.87; 95% CI, 0.77 to 1.02); the highest serum uromodulin quartile had a significantly lower HR compared with the lowest. In all multivariable analyses there was a linear association between the HR for the respective outcome and serum uromodulin, with lower HR at higher serum uromodulin concentrations (Figure 1).

When performing competing risk analyses with mortality as the competing risk, the quartile with the highest serum uromodulin concentrations still had a significantly lower hazard of kidney failure (subdistribution HR [SHR], 0.28; 95% CI, 0.13 to 0.60; Supplemental Table 1). For MACE, the group with the second highest serum uromodulin concentrations had 21% lower hazard (SHR, 0.79; 95% CI, 0.65 to 0.97), whereas the difference between the highest and the lowest quartile was only borderline significant (SHR for the highest quartile, 0.80; 95% CI, 0.64 to 1.01).

We further evaluated a potential interaction between serum uromodulin and eGFR, ACR, and diabetes status on the associations of serum uromodulin and mortality, kidney failure, and MACE. No significant interaction term was identified (P>0.05 for all outcomes, the lowest P=0.21 for all-cause mortality and the interaction with diabetes).

The predictive ability of the models showed a C-index of 0.744 for the univariable serum uromodulin model in regards to kidney failure within the first year; the C-index was lower in the adjusted model (0.706; Table 4). After 4 years of follow-up, the C-index for serum uromodulin in the univariable model for kidney failure was 0.575, lower than in the adjusted model (0.740). The C-index for the univariable serum uromodulin model was 0.675 and 0.573 for all-cause mortality after 1 and 4 years of follow-up, respectively. Adjustment resulted in nominally lower C-indices (0.646 and 0.555, respectively). The univariable serum uromodulin model showed the nominally lowest C-indices for MACE after 1 and 4 years of follow-up (0.567 and 0.528, respectively); multivariable adjustment led to a nominal increase (0.659 and 0.575, respectively).

Discussion

Our results show that higher serum uromodulin is associated with lower hazard for mortality, MACE, and incident kidney failure in a large European CKD cohort, independently from eGFR, ACR, and cardiovascular and CKD risk factors.

An association of serum uromodulin with all-cause and cardiovascular mortality, as well as cardiovascular events, has previously been reported in two studies of participants at high risk for cardiovascular disease (17,18). However, both studies only categorized serum uromodulin, which can be statistically problematic for various reasons (23). In addition, the results of both studies might be limited due to unmeasured confounding because analyses were not adjusted for ACR. In a more recent analysis, higher serum uromodulin was associated with lower risk for mortality in the Cardiovascular Health Study—an older, community-based cohort—independent of demographics, eGFR, ACR, and cardiovascular risk factors (24). Due to nonlinear association between serum uromodulin and the outcomes at both ends of the serum uromodulin range, the analysis was restricted to 95% of cohort participants. Our results show for the first time that the association between serum uromodulin and death is consistent over the whole range of serum uromodulin concentrations, also including serum uromodulin concentrations not previously covered in the Cardiovascular Health Study. However, comparison of the results should be done cautiously due to different cohort characteristics.

Another recent study evaluated the association of serum uromodulin with kidney failure in a large cohort of Chinese patients with CKD (19). This study did not find a significant association of serum uromodulin with mortality and cardiovascular disease, possibly due to limited statistical power. However, higher serum uromodulin was significantly associated with lower hazard for kidney failure

Table 1. Baseline characteristics of German CKD study participants, stratified by quartiles of serum uromodulin (*n*=5143)

Characteristics	Total Cohort (*n*=5143)	Quartile 1 (*n*=1286)	Quartile 2 (*n*=1287)	Quartile 3 (*n*=1285)	Quartile 4 (*n*=1285)	Missing Data (*n* [%])
Serum uromodulin range (ng/ml)	0.0–490.4	≤55.6	>55.6–83.4	>83.4–125.3	>125.3	
Demographics						
Age (yr)	60±12	61±12	61±11	60±12	58±13	1 (0)
Male	3088 (60)	833 (65)	824 (64)	766 (60)	665 (52)	0 (0)
Laboratory measures						
eGFR<60 ml/min per 1.73 m^2	4007 (78)	1185 (92)	1116 (87)	984 (77)	722 (56)	28 (0.5)
eGFR (ml/min per 1.73 m^2)	49±18	40±13	45±14	51±17	62±20	28 (0.5)
Albuminuria (ACR>30 mg/g Cr)	2987 (58)	867 (67)	793 (62)	720 (56)	607 (47)	83 (2)
ACR (mg/g Cr)	51 (10–389)	89 (15–603)	61 (13–426)	43 (9–350)	24 (7–250)	83 (2)
Hemoglobin (g/dl)	13.6±1.7	13.1±1.7	13.5±1.7	13.8±1.6	14.0±1.5	96 (2)
CRP (mg/dl)	2.3 (1.0–5.0)	3.0 (1.3–6.6)	2.5 (1–5.5)	2.2 (1–4.9)	1.7 (0.8–3.5)	27 (0.5)
HbA1c (%)	6.2±1.0	6.5±1.2	6.4±1.0	6.4±1.0	6.1±0.8	37 (0.7)
Total cholesterol (mg/dl)	211±53	206±54	207±53	214±50	218±52	33 (0.6)
LDL cholesterol (mg/dl)	118±43	112±44	115±44	121±42	125±44	38 (0.7)
HDL cholesterol (mg/dl)	52±18	48±17	50±17	53±18	57±19	37 (0.7)
Triglycerides (mg/dl)	113 (89–143)	182 (126–268)	177 (123–247)	161 (115–233)	155 (105–212)	38 (0.7)
Phosphate (mg/dl)	3.4±0.6	3.5±0.7	3.4±0.6	3.4±0.6	3.4±0.6	26 (0.5)
Uric acid (mg/dl)	7.2±1.9	7.8±2.1	7.4±1.9	7.2±1.7	6.4±1.7	26 (0.5)
Cardiovascular risk factors and prevalent cardiovascular disease						
Systolic BP (mm Hg)	140±20	140±21	141±21	140±20	138±20	32 (0.6)
Diastolic BP (mm Hg)	79±12	78±13	80±12	80±12	80±11	32 (0.6)
BMI (kg/m^2)	29.8±6.0	31.0±6.5	30.1±5.9	29.7±5.8	28.4±5.3	53 (1)
Diabetes	1830 (36)	575 (45)	490 (38)	465 (36)	300 (23)	0 (0)
Hypertension	4952 (96)	1268 (99)	1271 (99)	1239 (96)	1174 (91)	3 (0.1)
Coronary heart disease	1022 (20)	310 (24)	284 (22)	258 (20)	170 (13)	2 (0)
Stroke	497 (10)	151 (12)	143 (11)	118 (9)	85 (7)	2 (0)
Smoking history						15 (0.3)
Never	2101 (41)	467 (36)	494 (38)	546 (43)	594 (46)	
Former	2213 (43)	585 (46)	573 (45)	537 (42)	518 (40)	
Current	815 (16)	228 (18)	217 (17)	199 (16)	171 (13)	
Unknown	14 (0)	6 (0)	3 (0)	3 (0)	2 (0)	
Medication use						
ACE inhibitor	2434 (47)	639 (50)	609 (47)	624 (49)	562 (44)	0 (0)
Angiotensin-II receptor blocker	2142 (42)	583 (45)	563 (44)	533 (42)	463 (36)	0 (0)
Diuretic	3133 (61)	976 (76)	870 (68)	744 (58)	543 (42)	0 (0)
Lipid-lowering therapy	2624 (51)	734 (57)	709 (55)	632 (49)	549 (43)	0 (0)
β-Blocker	2822 (55)	828 (64)	773 (60)	678 (53)	543 (42)	0 (0)
Calcium-channel blocker	2036 (40)	605 (47)	565 (44)	488 (38)	378 (29)	0 (0)
Lifestyle factors						
Drinking						31 (0.6)
Light	4142 (81)	1003 (78)	1036 (81)	1062 (83)	1041 (81)	
Heavy	971 (19)	272 (21)	244 (19)	217 (17)	238 (19)	
Unknown	30 (0)	11 (0)	7 (0)	6 (0)	6 (0)	
Underlying kidney disease						0 (0)
Diabetes	1382 (27)	454 (35)	376 (29)	341 (27)	211 (16)	
Hypertension	2121 (41)	576 (45)	558 (43)	528 (41)	459 (36)	
Systemic disease	606 (12)	140 (11)	142 (11)	164 (13)	160 (13)	
GN	1171 (23)	288 (22)	278 (22)	274 (21)	331 (26)	
Interstitial nephropathy	437 (9)	94 (7)	111 (9)	115 (9)	117 (9)	
Hereditary	232 (5)	59 (5)	58 (5)	72 (6)	43 (3)	
Obstructive	374 (7)	79 (6)	103 (8)	88 (7)	104 (8)	
AKI	242 (5)	75 (6)	65 (5)	62 (5)	40 (3)	
Solitary kidney	324 (8)	92 (7)	69 (5)	76 (6)	87 (7)	
Miscellaneous	236 (5)	74 (6)	53 (4)	42 (3)	67 (5)	
Undetermined	319 (6)	71 (6)	72 (6)	82 (6)	94 (7)	

Continuous variables are presented as mean and SD or median and interquartile range, and categoric variables are presented in percentage of referring population, unless otherwise specified. ACR, albumin-creatinine ratio; CRP, C-reactive protein; HbA1c, hemoglobin A1c; BMI, body mass index; ACE, angiotensin-converting enzyme.

in a multivariable model, a finding that we could reproduce in our white cohort.

There are several possible explanations for the association of serum uromodulin with mortality and cardiovascular disease. Serum uromodulin has been shown to be associated with markers of systemic inflammation such as CRP, fibrinogen, and galectin-3 (17,25,26). Also, uromodulin appears to regulate systemic granulopoiesis with uromodulin

Table 2. Cumulative incidence rates for mortality, kidney failure, and major adverse cardiovascular events in the total cohort and by serum uromodulin quartiles

Event	Total Cohort (0.0–490.4 ng/ml)	Quartile 1 (≤55.6 ng/ml)	Quartile 2 (>55.6–83.4 ng/ml)	Quartile 3 (>83.4–125.3 ng/ml)	Quartile 4 (>125.3 ng/ml)
All-cause mortality					
Events, *n*	335	145	86	63	41
Incidence per person year, % (95% CI)	1.1 (0.8 to 1.4)	1.7 (1.2 to 2.3)	0.9 (0.6 to 1.4)	1.0 (0.7 to 1.4)	0.6 (0.4 to 0.9)
Kidney failure					
Events, *n*	229	122	64	35	8
Incidence per person year, % (95% CI)	0.4 (0.3 to 0.6)	0.9 (0.6 to 1.4)	0.4 (0.3 to 0.7)	0.2 (0.1 to 0.4)	0.1 (0.0 to 0.1)
MACE					
Events, *n*	417	152	115	91	59
Incidence per person year, % (95% CI)	4.8 (4.3 to 5.5)	6.7 (5.8 to 7.8)	5.5 (4.7 to 6.4)	4.0 (0.3 to 4.8)	3.2 (2.7 to 3.9)

MACE, major cardiovascular event—defined as a composite of fatal cardiovascular event, nonfatal myocardial infarction, nonfatal stroke, or incident peripheral vascular disease.

deficiency leading to systemic neutrophilia (27). Furthermore, circulating uromodulin ameliorates systemic oxidative damage (28). Therefore, reduced circulatory serum uromodulin concentrations might promote a proinflammatory milieu, which has been shown to be associated with mortality and cardiovascular disease (29,30). A recent study also demonstrated that higher serum uromodulin was associated with lower risk for progression of coronary artery calcification, suggesting that higher serum uromodulin might modulate arterial calcification (31).

For kidney failure, it has been shown that 24-hour urine uromodulin excretion correlates with tubular mass (14). Lower serum uromodulin could therefore also reflect tubular atrophy, which in turn has been shown to be associated with kidney failure and kidney function decline

Table 3. Associations of serum uromodulin with mortality, kidney failure, and major adverse cardiovascular events

Outcome	Events	Hazard Ratio (95% CI)			
		Univariable	Model 1[a]	Model 2[b]	Model 3[c]
All-cause mortality					
HR per SD higher serum uromodulin	335/5143	0.61 (0.52 to 0.71)	0.67 (0.57 to 0.78)	0.75 (0.63 to 0.89)	0.80 (0.66 to 0.96)
Quartile 1 (≤55.6 ng/ml)		1 (reference)	1 (reference)	1 (reference)	1 (reference)
Quartile 2 (>55.6–83.4 ng/ml)		0.63 (0.48 to 0.82)	0.69 (0.52 to 0.90)	0.76 (0.57 to 1.01)	0.80 (0.60 to 1.07)
Quartile 3 (>83.4–125.3 ng/ml)		0.48 (0.36 to 0.65)	0.53 (0.39 to 0.71)	0.62 (0.45 to 0.86)	0.70 (0.50 to 0.97)
Quartile 4 (>125.3 ng/ml)		0.31 (0.22 to 0.44)	0.40 (0.28 to 0.57)	0.50 (0.34 to 0.75)	0.57 (0.38 to 0.87)
Kidney failure					
HR per SD higher serum uromodulin	229/5143	0.30 (0.24 to 0.39)	0.31 (0.25 to 0.40)	0.61 (0.46 to 0.80)	0.61 (0.46 to 0.81)
Quartile 1 (≤55.6 ng/ml)		1 (reference)	1 (reference)	1 (reference)	1 (reference)
Quartile 2 (>55.6–83.4 ng/ml)		0.50 (0.37 to 0.68)	0.50 (0.37 to 0.68)	0.73 (0.53 to 0.99)	0.73 (0.52 to 1.01)
Quartile 3 (>83.4–125.3 ng/ml)		0.27 (0.19 to 0.40)	0.28 (0.19 to 0.42)	0.64 (0.43 to 0.96)	0.65 (0.43 to 0.99)
Quartile 4 (>125.3 ng/ml)		0.07 (0.03 to 0.14)	0.06 (0.03 to 0.13)	0.27 (0.12 to 0.59)	0.24 (0.10 to 0.55)
MACE					
HR per SD higher serum uromodulin	417/5143	0.68 (0.60 to 0.77)	0.74 (0.65 to 0.84)	0.80 (0.70 to 0.92)	0.87 (0.77 to 1.02)
Quartile 1 (≤55.6 ng/ml)		1 (reference)	1 (reference)	1 (reference)	1 (reference)
Quartile 2 (>55.6–83.4 ng/ml)		0.73 (0.57 to 0.93)	0.75 (0.59 to 0.96)	0.76 (0.59 to 0.99)	0.85 (0.66 to 1.11)
Quartile 3 (>83.4–125.3 ng/ml)		0.61 (0.47 to 0.79)	0.64 (0.49 to 0.83)	0.70 (0.53 to 0.93)	0.78 (0.58 to 1.03)
Quartile 4 (>125.3 ng/ml)		0.35 (0.26 to 0.48)	0.43 (0.32 to 0.59)	0.49 (0.35 to 0.69)	0.63 (0.45 to 0.90)

MACE, major cardiovascular event—defined as a composite of fatal cardiovascular event, nonfatal myocardial infarction, nonfatal stroke, or incident peripheral vascular disease; HR, hazard ratio.
[a]Adjusted for age, sex, and body mass index.
[b]Model 1 plus eGFR and urinary albumin-creatinine ratio.
[c]Model 2 plus prevalent cardiovascular disease, diabetes and hypertension at baseline, systolic BP, diastolic BP, serum high and LDL concentration, serum C-reactive protein and phosphorus concentration, prescription of diuretics, and lipid- and BP-lowering medication.

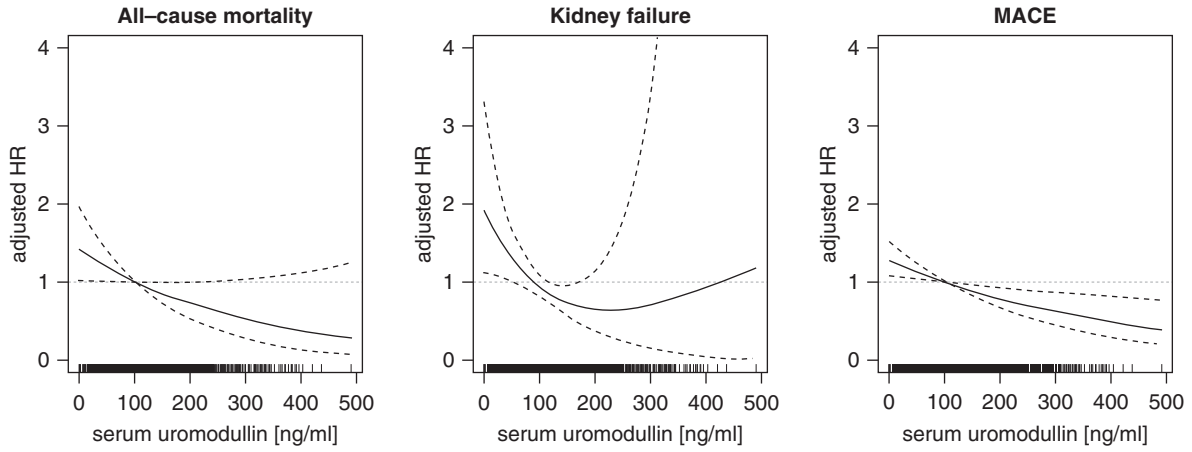

Figure 1. | Penalized splines demonstrating the adjusted association of serum uromodulin with all-cause mortality, kidney failure, and MACE (major adverse cardiovascular events, a composite of cardiovascular mortality, non-fatal myocardial infarction or stroke, or incident peripheral vascular disease). Serum uromodulin in ng/ml is shown on the *x* axis and the partial adjusted hazard ratio (HR) on the *y* axis. The solid black line indicates the partial HR; the two dotted lines around the black line indicate its 95% confidence interval. Ticks on the *x* axis represent individual participants.

(12,32). In addition, basic research supports that serum uromodulin counteracts inflammatory processes in the kidney interstitium: serum uromodulin influences tubular crosstalk by inhibiting proinflammatory signaling from proximal tubular cells, which can improve the recovery from AKI (33). Uromodulin knock-out mice showed more inflammation and tubular necrosis in a model of ischemia-reperfusion injury and incomplete recovery (34). This might also be explained by different proinflammatory toll-like receptor 4 expression based on local uromodulin concentrations (34). Furthermore, uromodulin modulates the IL-23/-17 axis and mononuclear phagocytic activity in the kidney parenchyma (27,35). In addition, a cytokine imbalance was described in uromodulin-deficient mice (36). Low serum uromodulin might therefore reflect a proinflammatory state in the kidney, which could facilitate progressive fibrosis and loss of kidney function. Also, AKI might lead to more severe, irreversible damage in the state of serum uromodulin deficiency. Further work is warranted to decipher the mechanism responsible for the protective effect of serum uromodulin, which could potentially result in strategies to improve outcomes.

Major strengths of this study are the large sample size, covering all CKD stages in a well characterized, ethnically homogenous cohort with standardized assessment of independent variables and outcomes. We were able to adjust for a large number of risk factors for cardiovascular disease and CKD progression, among them ACR, which enabled us to reduce the risk of potential unmeasured confounding.

Table 4. Concordance probability of different multivariable models including serum uromodulin to predict all-cause mortality, kidney failure, and major cardiovascular events

Outcome	Events	Univariable	Model 1[a]	Model 2[b]	Model 3[c]
All-cause mortality	335/5143				
Concordance probability for event within first year		0.674	0.622	0.605	0.646
Concordance probability for event within 4 years		0.573	0.589	0.582	0.555
Kidney failure	229/5143				
Concordance probability for event within first year		0.744	0.796	0.699	0.706
Concordance probability for event within 4 years		0.575	0.667	0.769	0.740
MACE	417/5143				
Concordance probability for event within first year		0.567	0.677	0.647	0.659
Concordance probability for event within 4 years		0.528	0.551	0.547	0.575

Concordance probability indicates the discriminatory power and predictive ability of statistical models for respective outcomes. It estimates the probability of concordance between predicted and observed outcomes. MACE, major cardiovascular event—defined as a composite of fatal cardiovascular event, nonfatal myocardial infarction, nonfatal stroke, or incident peripheral vascular disease.
[a]Adjusted for age, sex, and body mass index.
[b]Model 1 plus eGFR and urinary albumin-creatinine ratio.
[c]Model 2 plus prevalent cardiovascular disease, diabetes and hypertension at baseline, systolic BP, diastolic BP, serum high and LDL concentration, serum C-reactive protein and phosphorus concentration, prescription of diuretics, and lipid- and BP-lowering medication.

A concerning limitation in this study is that serum uromodulin was only measured once at baseline. Future studies need to evaluate whether changes in serum uromodulin concentrations are also associated with adverse outcomes. Furthermore, we did not assess biomarkers of tubular damage such as neutrophil gelatinase–associated lipocalin and compare its associations with serum uromodulin. However, we believe that there are currently no other serum markers of tubular function that have the same evidence base in terms of associations with the outcomes evaluated in this study. Last, we did not validate our findings in a second, independent cohort.

The findings of our study may have clinical implications. Given the fact that serum uromodulin is exclusively secreted in the tubular system and is independently associated with adverse outcomes, assessing tubular function by measuring serum uromodulin may guide medical treatment that affects the tubular system such as exposure to potentially tubulotoxic agents. In addition, low serum uromodulin concentrations may help to identify patients deserving more intensive care and optimization of cardiovascular risk factors.

In conclusion, we demonstrate that higher serum uromodulin is associated with lower risk for all-cause mortality and kidney failure, as well as borderline associated with lower risk for cardiovascular disease in a large white CKD cohort, independent from eGFR, ACR, and other cardiovascular and CKD risk factors. Therefore, serum uromodulin might be a promising complementary circulatory marker to assess the mortality and kidney risk, along with markers of glomerular function, in patients with CKD.

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Supplemental Material

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Supplemental Table 1. Associations of serum uromodulin with kidney failure and major adverse cardiovascular events (MACE) with mortality and/or kidney failure/MACE as the competing risks.

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Supplemental material:

Suppl. Table 1: Associations of serum uromodulin with kidney failure and major adverse cardiovascular events (MACE) with mortality and/or kidney failure/MACE as the competing risks

	Events	Univariable	Model 1[a]	Model 2[b]	Model 3[c]
Kidney failure					
Q1 (≤55.6)	229/5143	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Q2 (>55.6-83.4)		0.57 (0.42-0.77)	0.54 (0.40-0.73)	0.72 (0.52-1.00)	0.74 (0.53-1.02)
Q3 (>83.4-125.3)		0.35 (0.24-0.50)	0.34 (0.23-0.49)	0.68 (0.46-1.01)	0.72 (0.47-1.10)
Q4 (>125.3)		0.08 (0.04-0.17)	0.07 (0.03-0.14)	0.27 (0.12-0.60)	0.28 (0.13-0.60)
MACE					
Q1 (≤55.6)	417/5143	1 (ref.)	1 (ref.)	1 (ref.)	1 (ref.)
Q2 (>55.6-83.4)		0.90 (0.76-1.06)	0.95 (0.80-1.13)	0.92 (0.77-1.10)	0.96 (0.81-1.16)
Q3 (>83.4-125.3)		0.69 (0.58-0.83)	0.76 (0.63-0.92)	0.75 (0.62-0.92)	0.79 (0.65-0.97)
Q4 (>125.3)		0.57 (0.46-0.69)	0.69 (0.56-0.85)	0.69 (0.55-0.87)	0.80 (0.64-1.01)

Results are presented as subdistribution hazard ratios with 95%-confidence intervals given in parentheses. Major cardiovascular event (MACE) is defined as a composite of fatal cardiovascular event, non-fatal myocardial infarction or non-fatal stroke or incident peripheral vascular disease. Abbreviations: HR=hazard ratio; Q=quartile; eGFR=estimated glomerular filtration rate; uACR=urinary albumin/creatinine-ratio; RF=risk factors. Serum uromodulin ranges of each quartile presented in ng/ml.

[a] adjusted for age, sex, body-mass-index

[b] Model 1 + eGFR & uACR

[c] Model 2 + prevalent cardiovascular disease, diabetes and hypertension at baseline, systolic blood pressure, diastolic blood pressure, serum high and low density lipoprotein concentration, serum C-reactive protein and phosphorus concentration, prescription of diuretics, lipid and blood pressure lowering medication