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Original Article

Serum uric acid, protein intake and mortality in hemodialysis patients

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ABSTRACT

Background. The association between serum uric acid (SUA) and mortality has been conflicting among studies using hemodialysis (HD) patients. Given the close link between purine and protein in foods, we hypothesized that normalized protein catabolic rate (nPCR), a dietary protein intake surrogate, modifies the SUA–mortality association in the HD population.

Methods. We identified 4298 patients who initiated HD and had one or more SUA measurement in a contemporary cohort of HD patients over 5 years (1 January 2007–31 December 2011), and examined survival probability according to the first uric acid measurement, adjusting for dialysis vintage, case-mix and malnutrition–inflammation complex-related variables.

Results. Mean SUA concentration was 6.6 ± 1.8 mg/dL. There was a consistent association of higher SUA with better nutritional status and lower all-cause mortality irrespective of adjusted models ($P_{trend} < 0.001$). In the case-mix adjusted model, the highest SUA category (≥8.0 mg/dL) compared with the reference group (>6.0–7.0 mg/dL) showed no significant mortality risk [hazard ratio (HR) 0.90, 95% confidence interval (CI) 0.72–1.13], while the lowest category (<5.0 mg/dL) was associated with higher mortality (HR 1.42, 95% CI 1.16–1.72). The hypouricemia–mortality association was significantly modified by nPCR ($P_{interaction} = 0.001$). Mortality risk of low SUA (<5.0 mg/dL) persisted among patients with low nPCR (<0.9 g/kg/day; HR 1.73, 95% CI 1.42–2.10) but not with high nPCR (≥0.9 g/kg/day; HR 0.99, 95% CI 0.74–1.33).

Conclusions. SUA may be a nutritional marker in HD patients. Contrary to the general population, low but not high SUA is associated with higher all-cause mortality in HD patients, especially in those with low protein intake. Nutritional features of SUA warrant additional studies.

Keywords: chronic hemodialysis, hyperuricemia, nutrition, survival analysis, uric acid

INTRODUCTION

Uric acid is the end product of purine metabolism, and is considered overloaded in the human body when its serum concentration exceeds 6.8 or 7.0 mg/dL [1]. Hyperuricemia is often observed among obese individuals and patients with diabetes or hypertension, and has been associated with cardiovascular disease and mortality mainly in the general population [1, 2]. Uric acid may have both proinflammatory and antioxidant properties, and therefore its exact role in disease-mortality risk is not clear [3].

Several experimental and epidemiological studies have suggested that uric acid is a causal or independent risk factor in the progression of renal diseases [4–9]. Renal excretion is responsible for approximately 70% of uric acid clearance from the body in healthy individuals [10], and thus serum uric acid (SUA) concentration rises with the progression of chronic kidney disease (CKD). The rise in SUA in chronic renal failure is

substantially mitigated by marked reduction of its biosynthesis via downregulation xanthine oxidase and upregulation of its secretion by colonic epithelium [11, 12]. The CKD-induced upregulation of uric acid secretion by colonic epithelium is, in part, mediated by activation of angiotensin II receptor. This is based on the results of an earlier study that demonstrated a significant rise in urate secretion by colonic tissue in response to angiotensin II and its inhibition by the angiotensin receptor blocker, losartan [13]. Within the colon, the secreted uric acid is degraded by uricase-possessing bacteria whose population is greatly expanded in end-stage renal disease (ESRD) patients [14]. In addition to the CKD-induced changes in uric acid metabolism, dietary and pharmacological interventions as well as the nature and extent of dialysis treatments heavily modify SUA concentrations in the ESRD population.

There are conflicting data on the role of uric acid and its relation to cardiovascular events and all-cause mortality among patients with ESRD [15–24], which may be partly attributed to the differences in treatment modality [i.e., hemodialysis (HD) versus peritoneal dialysis] and protein intake among study populations. Indeed, protein-rich diets tend to contain large quantities of purines [25], and higher uric acid concentrations may represent better nutritional status in the ESRD population [18–23].

Therefore, we examined a 5-year cohort of incident HD patients treated in facilities operated by a large dialysis organization in the USA, hypothesizing that the association between uric acid concentrations and all-cause death varies according to normalized protein catabolic rate (nPCR), a protein intake surrogate, among ESRD patients receiving HD treatment.

MATERIALS AND METHODS

The parent study was approved by the Institutional Review Committee of the Los Angeles Biomedical Research Institute at Harbor-UCLA, the University of California Irvine Medical Center and the University of Washington as exempt from informed consent. The study proceeded in accordance with the Declaration of Helsinki.

Participants

We extracted, refined and examined electronic data from all incident dialysis patients who were age ≥18 years and received conventional HD treatment in facilities operated by a large dialysis organization in the USA from 1 January 2007 to 31 December 2011 [26]. Patients were followed until 31 December 2011, and the follow-up time was divided into patient-quarters (91-day periods from date of first dialysis). For each patient-quarter, patients were assigned the 'conventional HD' modality if they did not receive peritoneal dialysis, less-frequent in-center HD, home HD, frequent in-center HD or nocturnal in-center HD for >45 days within the patient-quarter. Data from dialysis facility electronic medical records were used to determine demographics and comorbidities. All routine blood and urine samples were shipped to a central laboratory (Deland, FL, USA) and analyzed within 24 h of collection. Results of laboratory tests, hemodynamic parameters and parenteral medications were summarized for each patient-quarter (91-day period).

We excluded patients who had ever been treated with less frequent HD, frequent HD, peritoneal dialysis, home HD or nocturnal in-center HD from this study. Out of 128 675 patients who were treated only with conventional HD during follow-up, we identified 4298 patients who survived the first 60 days and who had available data on SUA concentration during the follow-up (Supplementary Figure S1). The first patient-quarter with available SUA measurements in those 4298 HD patients was considered the baseline quarter.

Statistics

A comparison between included versus excluded HD patients, consisting of demographic, clinical and laboratory characteristics obtained during the patients' first 91 days of dialysis, was evaluated by standardized differences and is presented in the Supplementary Table S1 [27, 28]. In our analytical cohort, the primary exposure of interest, baseline SUA concentrations, was grouped into the five following categories: <5.0 mg/dL (16%); 5.0–6.0 mg/dL (referent, 21%); >6.0–7.0 mg/dL (24%); >7.0–8.0 mg/dL (19%); and >8.0 mg/dL (20%). Baseline demographic, clinical and laboratory characteristics were summarized as percentages, means ± standard deviation or median [interquartile range (IQR)] across uric acid categories. We evaluated the unadjusted association of these covariates with uric acid concentrations by a non-parametric trend test. We used logistic regression models to examine the cross-sectional association between patient characteristics and hyperuricemia defined as >7.0 mg/dL. The primary outcome of interest was defined as time to all-cause death. Survival estimates with the Kaplan–Meier method were used to illustrate differences in unadjusted all-cause mortality across five uric acid categories. Cox models were used to evaluate the association of uric acid concentrations with time to all-cause death. In all analyses including both survival and logistic regression models, we employed three-level hierarchical adjustments as follows:

(i) unadjusted model;
(ii) case-mix adjusted models that included age, race and ethnicity (Caucasian, African-American, Hispanic and the others), sex, insurance (Medicare, Medicaid and the others), the use of central venous catheter, single-pool Kt/V, comorbidities (congestive heart failure, hypertension, history of cancer, dyslipidemia, liver disease, diabetes and alcohol), body mass index (BMI) and dialysis vintage; and
(iii) fully adjusted models that included all covariates in the case-mix model plus 10 laboratory variables, that is, serum albumin, calcium, phosphorus, serum ferritin, intact parathyroid hormone (PTH), hemoglobin, bicarbonate, creatinine, iron saturation and nPCR.

Data on uric acid-lowering drugs were not available in the current database. We categorized dialysis vintage into four groups (≤6, >6–12, >12–24 and >24 months), serum ferritin into four groups (<150, 150–<300, 300–<600 and ≥600 ng/mL) and intact PTH into four groups (<150, 150–<300, 300–<600 and ≥600 pg/mL). Proportional hazards assumptions for the uric acid categories were tested using log-log against survival plots and Schoenfeld residuals. SUA concentrations were also

modeled as a continuous variable, and their relationship with all-cause death was estimated using restricted cubic spline functions, where knots were placed at the 5th, 35th, 65th and 95th percentiles. Associations of high (>8 mg/dL) and low (<5 mg/dL) uric acid concentrations with all-cause mortality (reference; 5–8 mg/dL) were also evaluated across *a priori* selected subgroups. Statistical significance of potential effect modification by these covariates was tested with the Wald test, after including the interaction term between a given variable and three uric acid categories.

Missing data for BMI (0.5%), albumin (1.0%), calcium (1.5%), ferritin (3.1%), hemoglobin (0.7%), phosphorus (0.9%), intact PTH (1.9%), bicarbonate (0.8%), creatinine (4.5%), spKt/V (3.5%) and nPCR (3.7%) were imputed by the median. Missing race (0.6%) was collapsed into 'the others' category. For all analyses, a two-tailed P-value <0.05 was considered statistically significant. All analyses were conducted using STATA version 13.1 (StataCorp, College Station, TX, USA).

RESULTS

Baseline demographic, clinical and laboratory characteristics

A total of 4298 HD patients had available data on SUA concentrations during their follow-up (Supplementary Figure S1), and were included in this study. These patients were less likely to use a central venous catheter as their vascular access type and more likely to be male compared with those excluded patients who did not have uric acid data. Included patients also tended to have higher prevalence of dyslipidemia, congestive heart failure and cardiovascular disease, and to have higher nPCR and higher serum albumin concentrations (absolute standardized difference >0.1, Supplementary Table S1). Their mean age was 63 ± 15 years, 39% were female, and median (IQR) uric acid concentration was 6.5 (5.4, 7.7) mg/dL. Additional baseline characteristics are shown in Table 1.

Predictors of high SUA concentrations

Covariates positively correlated with uric acid concentrations included BMI, nPCR, serum albumin and phosphorus. Variables associated with high uric acid concentrations were younger age, male sex, longer dialysis vintage, higher nPCR and higher serum concentrations of albumin, creatinine, phosphorus and intact PTH. Additional factors inversely associated with high uric acid concentrations included diabetes, history of cancer, dyslipidemia and serum ferritin concentrations (Table 1). After adjustment for case-mix and laboratory variables the relationship between diabetes, serum creatinine and serum phosphorus with high uric acid concentrations (i.e, ≥7.0 mg/dL) was attenuated; however, the relationship between other variables with high uric acid showed consistent associations across adjusted models (Table 2).

Uric acid concentrations and all-cause mortality

Among 4298 HD patients with uric acid measurements, 903 (21%) patients died during the follow-up [median 22 (IQR, 11 to 37) months] with an incidence of 10.1 [95% confidence interval (CI), 9.4–10.8] per 100 patient-years. There was a significant trend toward lower mortality risk across higher SUA concentrations (Figure 1), which was consistent across adjusted models (P_{trend} <0.001 for all). When compared with the reference category (>6.0–7.0 mg/dL), the lowest SUA category (<5.0 mg/dL) showed higher mortality risk in the unadjusted model [hazard ratio (HR) 1.67, 95% CI 1.38–2.03; Figure 2A]. This association was slightly attenuated with further adjustment for case-mix and laboratory variables, but remained significant; HR (95% CI) was 1.42 (1.16–1.72) and 1.35 (1.11–1.65) in the case-mix and fully adjusted models, respectively. In contrast, the highest category (>8 mg/dL) did not show increased mortality risk. These associations were confirmed across adjusted models in Cox regression analyses with restricted cubic splines where uric acid concentrations were modeled as a continuous variable (Figure 2B–D).

Effect modification of nPCR

The associations of low and high uric acid concentrations were consistent across the subgroups of age, sex, diabetes, race, BMI, albumin and the use of central venous catheter ($P_{interaction}$ > 0.1); when compared with the reference group (5–8 mg/dL), the mortality risk associated with hyperuricemia (>8 mg/dL) was not significant while hypouricemia (<5.0 mg/dL) was associated with high mortality risk in the case-mix adjusted model (Figure 3). However, the uric acid–mortality association was significantly modified by nPCR ($P_{interaction}$ = 0.005), and the mortality risk associated with hypouricemia was observed only among patients with low nPCR (<0.9 g/kg/day; HR 1.73, 95% CI 1.42–2.10) but not among those with high nPCR (≥0.9 g/kg/day; HR 0.99, 95% CI 0.74–1.33). Hyperuricemia was not associated with mortality in both nPCR groups.

DISCUSSION

In this study, using administrative data from a large dialysis organization in the USA, we found a relationship between high uric acid concentrations and better nutritional status among HD patients and demonstrated that hyperuricemia was not associated with all-cause mortality among HD patients, irrespective of adjusted models. Rather, hypouricemia showed higher mortality risk especially among patients with low nPCR, suggesting that SUA may be a nutritional marker that may provide additional information on mortality predictability.

The link between high uric acid concentrations and better nutritional status may be explained by diet. Nutritional parameters are closely associated with each other, and high uric acid concentrations have been linked to protein intake or high nPCR, greater BMI, and higher serum concentrations of albumin, creatinine and phosphorus [18–23]. The major source of uric acid is purine-rich foods such as meats, seafood and purine-rich vegetables, all of which also include high protein. This close link between purine and protein in foods can explain the reason why higher nPCR maintained a significant relationship with higher SUA concentrations even in the fully adjusted model, while many of the other nutritional parameters lost their

Table 1. Baseline demographic and clinical characteristics of 4298 HD patients

Variable	Uric acid (mg/dL)					P
	<5.0	5.0–6.0	>6.0–7.0	>7.0–8.0	>8.0	
N (%)	695 (16)	886 (21)	1052 (24)	801 (19)	864 (20)	
Age (years)	69 ± 13	67 ± 13	63 ± 14	61 ± 15	57 ± 15	<0.001
Female (%)	45	46	39	35	30	<0.001
Race (%)						
Non-Hispanic white	59	54	47	43	40	<0.001
Non-Hispanic black	26	27	32	31	31	0.012
Hispanic	10	12	13	16	15	<0.001
Other races	5	6	8	10	14	<0.001
Insurance (%)						
Medicare	63	56	54	52	47	<0.001
Medicaid	4	5	5	8	8	<0.001
Other	33	38	41	40	45	<0.001
Access type (%)						
Central venous catheter	46	48	46	50	57	<0.001
Comorbidities (%)						
Diabetes	63	59	60	57	55	0.001
Congestive heart failure	43	41	44	44	40	0.671
Hypertension	56	55	54	54	55	0.554
History of cancer	3	5	3	2	2	0.001
Dyslipidemia	34	34	36	30	27	0.001
Liver disease	1	2	1	1	1	0.306
Alcohol	0.29	0.11	0.19	0.37	0.46	0.259
Cardiovascular disease	33	34	30	31	29	0.039
BMI (kg/m^2)	28 ± 7	28 ± 7	29 ± 8	29 ± 7	29 ± 8	<0.001
Dialysis vintage (%)						<0.001
≤6 months	65	67	67	75	80	
>6–12 months	12	12	12	9	9	
>12–24 months	13	13	12	10	8	
>24 months	10	8	10	6	4	
Single-pool Kt/V	1.58 ± 0.30	1.59 ± 0.30	1.57 ± 0.33	1.52 ± 0.31	1.48 ± 0.33	<0.001
nPCR (g/kg/day)	0.85 (0.70, 1.02)	0.88 (0.74, 1.05)	0.90 (0.75, 1.09)	0.91 (0.75, 1.08)	0.90 (0.73, 1.10)	<0.001
Laboratory tests						
Hemoglobin (g/dL)	11.3 ± 1.1	11.4 ± 1.1	11.3 ± 1.1	11.3 ± 1.1	11.2 ± 1.2	0.027
Albumin (g/dL)	3.63 ± 0.44	3.69 ± 0.44	3.71 ± 0.45	3.72 ± 0.44	3.73 ± 0.43	<0.001
Creatinine (mg/dL)	6.0 ± 2.3	6.3 ± 2.4	6.8 ± 2.6	7.1 ± 2.7	7.4 ± 3.1	<0.001
Calcium (mg/dL)	9.1 ± 0.6	9.1 ± 0.5	9.0 ± 0.5	9.1 ± 0.5	9.0 ± 0.6	<0.001
Phosphorus (mg/dL)	4.7 ± 1.1	4.9 ± 1.1	5.1 ± 1.2	5.2 ± 1.2	5.4 ± 1.2	<0.001
Intact PTH (%)	256 (179, 383)	283 (188, 420)	299 (197, 456)	315 (213, 497)	332 (228, 508)	<0.001
Ferritin (%)	503 (308, 755)	450 (237, 708)	412 (236, 672)	369 (213, 633)	383 (218, 629)	<0.001
Bicarbonate (mEq/L)	24 ± 3	24 ± 3	23 ± 3	23 ± 3	23 ± 3	<0.001

Values are expressed as mean (standard deviation), median (IQR) or percentage, appropriately.
SI conversion factors: to convert hemoglobin to g/L, multiply by 10; albumin to g/L, multiply by 10; creatinine to μmol/L, multiply by 88.4; calcium to mmol/L, multiply by 0.25; phosphorus to mmol/L, multiply by 0.323; PTH to ng/L, multiply by 1.0; ferritin to pmol/L, multiply by 2.247; bicarbonate to mmol/L, multiply by 1.0.

significance. Hence, uric acid concentrations may reflect patient appetite or dietary protein intake, which may in part explain the relationship between higher uric acid concentrations and lower mortality [29].

The effect modification of nPCR on the association between SUA and mortality may indicate the importance of adequate protein intake, which has been associated with lower mortality in HD patients as well [30–36]. With a given amount of protein intake, purine content depends on the type of food; dairy products, eggs, nuts and fish are among low-purine protein sources. Hence, patients with high nPCR and lower uric acid might have consumed these types of foods more often while maintaining their protein intake. Uric acid-lowering drugs such as allopurinol, febuxostat and losartan, if given to patients, also lower SUA levels independent of protein intake. Our finding suggests that such patients consuming adequate protein intake may not have higher risk of mortality even if they have hypouricemia.

Meanwhile, the association of hypouricemia with high mortality among patients with low nPCR may be partly explained by residual kidney function (RKF), a strong survival predictor that plays important roles in solute clearance, uremic toxin removal, volume control and mineral metabolism [37–39]. Even at such low levels of RKF as observed in HD patients, its continuous nature results in large urea clearance from the body. Therefore, nPCR underestimates protein intake among patients with substantial RKF if renal urea clearance is not taken into account [40]. In contrast, SUA concentrations are maintained within only slightly higher levels among HD patients than in normal individuals while serum concentrations of urea nitrogen and creatinine increase several times over their normal ranges. The

Table 2. Likelihood of having SUA concentrations (≥7.0 mg/dL) in 4298 HD patients in the case-mix and fully adjusted models

Variable	Case-mix adjusted			Fully adjusted		
	OR	(95% CI)	P	OR	(95% CI)	P
Age (per 10 years)	0.74	(0.70–0.78)	<0.001	0.79	(0.74–0.83)	<0.001
Female (versus male)	0.67	(0.59–0.78)	<0.001	0.73	(0.63–0.85)	<0.001
Race						
Non-Hispanic white	Ref.			Ref.		
Non-Hispanic black	1.08	(0.92–1.27)	0.33	1.15	(0.97–1.37)	0.11
Hispanic	1.25	(1.02–1.54)	0.03	1.21	(0.98–1.50)	0.07
Other races	2.29	(1.81–2.90)	<0.001	2.19	(1.72–2.80)	<0.001
Insurance						
Medicare	Ref.			Ref.		
Medicaid	1.10	(0.83–1.46)	0.52	1.06	(0.79–1.41)	0.71
Other	0.96	(0.84–1.11)	0.58	0.95	(0.82–1.09)	0.47
Access type						
Central venous catheter	1.09	(0.94–1.25)	0.25	1.18	(1.02–1.37)	0.03
Comorbid conditions						
Diabetes	0.90	(0.78–1.03)	0.14	0.93	(0.80–1.07)	0.29
Congestive heart failure	1.01	(0.88–1.16)	0.85	1.02	(0.89–1.18)	0.74
Hypertension	1.12	(0.98–1.28)	0.11	1.13	(0.98–1.30)	0.08
History of cancer	0.58	(0.37–0.90)	0.02	0.57	(0.36–0.90)	0.02
Dyslipidemia	0.83	(0.72–0.96)	0.01	0.81	(0.70–0.94)	0.004
Liver disease	0.81	(0.44–1.47)	0.48	0.93	(0.50–1.71)	0.81
Alcohol	2.66	(0.79–8.97)	0.11	2.78	(0.83–9.34)	0.10
Cardiovascular disease	0.99	(0.86–1.15)	0.93	1.02	(0.88–1.18)	0.83
BMI (per 1 kg/m^2)	1.01	(1.00–1.02)	0.01	1.01	(1.00–1.02)	0.05
Dialysis vintage						
≤6 months	Ref.			Ref.		
>6–12 months	0.66	(0.52–0.82)	<0.001	0.60	(0.48–0.76)	<0.001
>12–24 months	0.66	(0.52–0.83)	<0.001	0.61	(0.48–0.77)	<0.001
>24 months	0.44	(0.33–0.58)	<0.001	0.42	(0.31–0.56)	<0.001
Single-pool Kt/V (per 0.1)	0.71	(0.56–0.89)	0.003	0.63	(0.48–0.82)	0.001
nPCR (per 0.1 g/kg/day)	1.10	(1.06–1.13)	<0.001	1.06	(1.02–1.09)	0.001
Laboratory tests						
Hemoglobin (per 1 g/dL)	0.99	(0.94–1.05)	0.82	0.97	(0.91–1.04)	0.43
Albumin (per 0.1 g/dL)	1.03	(1.02–1.05)	<0.001	1.02	(1.00–1.04)	0.03
Creatinine (per 0.1 mg/dL)	1.01	(1.00–1.01)	<0.001	1.00	(1.00–1.01)	0.38
Calcium (per 0.1 mg/dL)	0.98	(0.97–0.99)	0.002	0.99	(0.98–1.00)	0.18
Phosphorus (per 0.1 mg/dL)	1.02	(1.01–1.02)	<0.001	1.01	(1.00–1.01)	0.06
Intact PTH						
<150 pg/mL	1.01	(0.82–1.25)	0.90	1.08	(0.87–1.34)	0.48
150–<300 pg/mL	Ref.			Ref.		
300–<600 pg/mL	1.21	(1.03–1.41)	0.02	1.11	(0.95–1.30)	0.20
≥600 pg/mL	1.32	(1.07–1.63)	0.01	1.10	(0.88–1.38)	0.40
Iron saturation (per 1%)	0.99	(0.98–1.00)	0.001	0.99	(0.98–0.99)	<0.001
Ferritin						
<150 ng/mL	0.92	(0.74–1.14)	0.44	0.83	(0.66–1.04)	0.11
150–<300 ng/mL	1.03	(0.87–1.23)	0.70	1.00	(0.83–1.19)	0.96
300–<600 ng/mL	Ref.			Ref.		
≥600 ng/mL	0.94	(0.80–1.11)	0.46	0.99	(0.84–1.18)	0.94
Bicarbonate (per 1 mEq/L)	0.91	(0.88–0.93)	<0.001	0.92	(0.90–0.95)	<0.001

SI conversion factors: to convert hemoglobin to g/L, multiply by 10; albumin to g/L, multiply by 10; creatinine to μmol/L, multiply by 88.4; calcium to mmol/L, multiply by 0.25; phosphorus to mmol/L, multiply by 0.323; PTH to ng/L, multiply by 1.0; ferritin to pmol/L, multiply by 2.247; bicarbonate to mmol/L, multiply by 1.0.

mechanisms involved include enhanced gastrointestinal excretion of uric acid and decreased uric acid production due to reduced xanthine oxidase activity and expansion of the intestinal population of uricase-possessing bacteria [11–14]. Hence, SUA may be an alternative laboratory marker of nutrition intake to nPCR when patients have substantial RKF and when data on renal urea clearance is not available. In this case, patients with low nPCR and higher SUA, compared with those with low nPCR and lower SUA, might have had better RKF and greater dietary intake, both of which lead to lower mortality risk [30–34, 37, 38]. In addition, given that ESRD patients on HD are exposed to various oxidative stresses [41], the antioxidative property of uric acid [42] may play a role in achieving better survival among hyperuricemic HD patients with poor nutritional status.

There is no definite evidence regarding the treatment of asymptomatic hyperuricemia in either the general population or the ESRD population [1]. Our study and other studies have shown that the association between uric acid and mortality in

the HD population is reversed compared with the general population [17–20]. We acknowledge that these studies including ours did not examine the effect of intervention and thus may not indicate a causal relationship. Indeed, a previous small clinical trial showed that allopurinol decreased cardiovascular and hospitalization risk in non-dialysis dependent patients with CKD [43], but a recent small randomized clinical trial showed insignificant benefit of allopurinol on endothelial function [44]. Moreover, among patients with advanced CKD including ESRD, allopurinol may occasionally precipitate severe adverse events [2], and those drugs increasing urinary excretion of uric acid such as probenecid are usually ineffective. Febuxostat, a newer generation xanthine oxidase inhibitor that is metabolized by the liver, was approved by the US Food and Drug Administration in the middle of our study period, and its effects on clinical outcomes need to be examined in future clinical trials.

We acknowledge several limitations in this study. By nature of this being an observational study, we could not make definitive statements about the causal relationship between SUA and mortality as mentioned above. We are also not able to exclude the possibility of residual confounding and the presence of unmeasured confounders such as uric acid-lowering drugs including allopurinol, febuxostat and losartan. Selection bias may also be present in our study because patients needed to survive until their uric acid was measured. Information about the rationale for measuring first uric acid measurements is not available, and patients included in this study may have a higher likelihood of being treated with uric acid-lowering interventions. The previous international cohort study of HD patients showed a similar distribution of SUA in Europe to our study and also reported a low prevalence of allopurinol use in patients either with or without available SUA (5.8% versus 2.1%) [17], but the prevalence of uric acid-lowering drug is not well known among HD patients in the USA. There was also a small yet meaningful

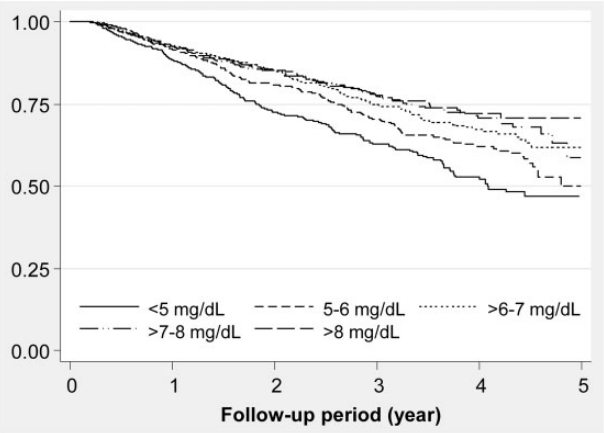

FIGURE 1: Kaplan–Meier survival estimates of 4298 HD patients according to SUA concentrations.

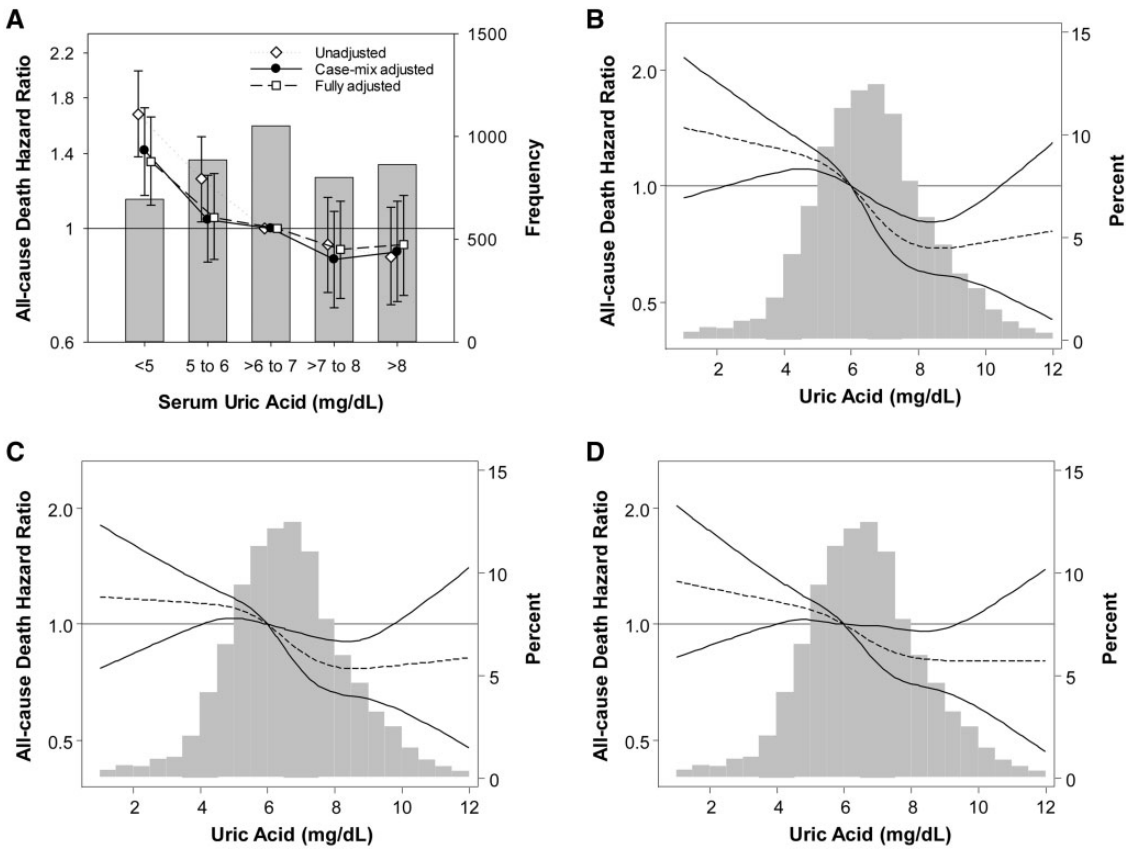

FIGURE 2: Frequency distributions and mortality risk according to SUA concentrations in 4298 HD patients: (**A**) stratified by five categories with three-level hierarchical adjusted models, (**B**) the unadjusted model with restricted cubic spline functions, (**C**) the case-mix adjusted model with restricted cubic spline functions and (**D**) the fully adjusted model with restricted cubic spline functions.

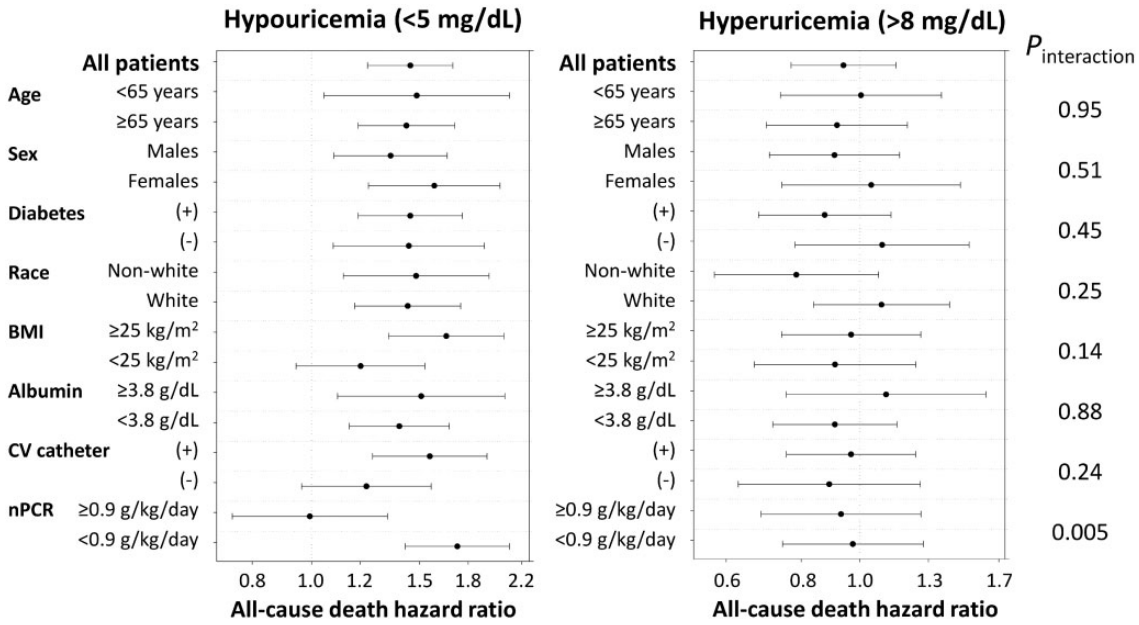

FIGURE 3: Subgroup analyses of the association of high (<5.0 mg/dL) and low (>8.0 mg/dL) uric acid concentrations (reference: 5–8 mg/dL) with all-cause mortality in the case-mix adjusted model. CV, central venous.

difference in nPCR and serum albumin favoring those included versus excluded patients. Nevertheless, the association of SUA with mortality was consistent between the present study and previous studies.

In conclusion, our study suggested that SUA concentrations may provide additional information about nutrition intake and demonstrated the association of hypouricemia, not hyperuricemia, with mortality when patients had low nPCR. The paradoxical relationship between SUA and all-cause mortality in the HD population warrants further research to understand the association of SUA with nutrition intake and to explore the optimal management of SUA.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

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AUTHORS' CONTRIBUTIONS

Study design: Y.O. and K.K.-Z. Study conduct: C.P., Y.O. and E.S. Data collection: K.K.-Z. Data analysis: C.P., Y.O., C.C. and E.S. Data interpretation: C.P., Y.O., N.D.V., C.P.K. and K.K.-Z. Drafting manuscript: C.P. and Y.O. Revising manuscript content: E.S., C.M.R., C.C., N.D.V, C.P.K. and K.K.-Z. Approving final version of manuscript: C.P., Y.O., E.S., C.M.R., C.C., N.D.V, C.P.K. and K.K.-Z. Y.O. takes responsibility for the integrity of the data analysis.

CONFLICT OF INTEREST STATEMENT

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