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Relationship between serum uric acid and mortality among hemodialysis patients: Retrospective analysis of Korean end-stage renal disease registry data

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Background: It is thought that hyperuricemia might lower the risk of mortality among hemodialysis patients, unlike in the general population, but the evidence is controversial. The aim of the current study was to evaluate the impact of serum uric acid level on the long-term clinical outcomes of hemodialysis patients in Korea.

Methods: Retrospective analysis was performed on data from the End-Stage Renal Disease Registry of the Korean Society of Nephrology. This included data for 7,333 patients (mean age, 61 ± 14 years; 61% male) who received hemodialysis from January 2001 through April 2015. Initial laboratory data were used in the analysis.

Results: The mean serum uric acid level in this study was 7.1 ± 1.7 mg/dL. Body mass index, normalized protein catabolic rate, albumin, and cholesterol were positively correlated with serum uric acid level after controlling for age and sex. After controlling for demographic data, comorbidities, and residual renal function, a higher uric acid level was independently associated with a significantly lower all-cause mortality (hazard ratio [HR], 0.90 per 1 mg/dL increase in uric acid level; 95% confidence interval [CI], 0.83–0.97; P = 0.008), but not cardiovascular mortality (HR, 0.90; 95% CI, 0.80–1.01; P = 0.078). Comparing uric acid levels in the highest and lowest quintiles, the HR for all-cause mortality was 0.65 (95% CI, 0.42–0.99; P = 0.046).

Conclusion: Hyperuricemia was strongly associated with a lower risk of all-cause mortality, but there seems to be no significant association between serum uric acid level and cardiovascular mortality among Korean hemodialysis patients with end-stage renal disease.

Keywords: Renal dialysis, Hyperuricemia, Mortality, Korea

Introduction

Uric acid is a product of the metabolic breakdown of purine nucleotides. A high uric acid concentration can result in gout and urolithiasis [1]. In the general population, hyperuricemia has been associated with increased risk of incident hypertension, congestive heart failure, metabolic syndrome, diabetes mellitus, obesity, atherosclerosis, and cardiovascular diseases [1–5]. Moreover, recent studies have suggested that elevated serum uric acid is a contributing risk factor for the development and progression of chronic kidney disease (CKD) [6–8]. The

detrimental effects of hyperuricemia are more complicated in patients with CKD or end-stage renal disease (ESRD), in whom serum uric acid concentration rises as CKD progresses and the excretion capacity of the kidneys decreases [9]. Interestingly, uric acid is also a nutritional marker and has antioxidant properties [10,11]. In fact, a previous study reported that serum uric acid has a J-shaped association with all-cause or cardiovascular mortality among patients in advanced stages of CKD [12,13]. Therefore, the association between serum uric acid level and mortality risk among hemodialysis patients is not straightforward.

Several studies have shown that elevated serum uric acid level increases the mortality risk among diabetic patients undergoing hemodialysis or peritoneal dialysis [14–17]. On the other hand, lower uric acid level has been associated with a higher risk of all-cause or cardiovascular mortality among hemodialysis patients [18–23]. Moreover, a recent study showed that a longitudinal increase in serum uric acid level over time is associated with lower all-cause or cardiovascular mortality in this clinical population [24]. Therefore, current evidence regarding the relationship between serum uric acid level and all-cause or cardiovascular mortality among patients with ESRD is conflicting. Specific data on the relationship between serum uric acid in Korean patients on maintenance hemodialysis are lacking. Therefore, the aim of the current study was to evaluate the association between serum uric acid level and all-cause or cardiovascular mortality through a retrospective analysis of a cohort of Korean patients with ESRD receiving hemodialysis treatment.

Methods

Study participants and data collection

We conducted a retrospective analysis of patient data from the Korean Society of Nephrology (KSN) registry, which is a nationwide database of the medical records of patients with ESRD, from January 2001 to April 2015. The ESRD registry committee of the KSN launched the official ESRD patient registry in 1985, and collected all registry data by mail until 1994, and subsequently through an internet program that opened in 2001 and was revised in 2013 (http://www.ksn.or.kr) [25]. As registry enrollment is voluntary, the ESRD registry covers only about two-thirds of all dialysis patients in Korea. Prospective cases for our analysis were outpatients ≥ 18-years-old who underwent maintenance hemodialysis between 2001 and 2015. Among the possible 42,791 cases identified, cases with insufficient data or for which uric acid was not measured were excluded. After screening, our analysis was based on the data of 7,333 cases.

Demographic and clinical data were collected at the time of study enrollment. Age, sex, body mass index, comorbidities, systolic and diastolic blood pressures, presence of residual renal function, duration of dialysis, hemodialysis adequacy (standard Kt/V), normalized protein catabolic rate (nPCR), and laboratory findings were recorded. The presence of residual renal function was defined when urine volume was measurable in maintenance hemodialysis patients. We used the Leypoldt equation for the standard Kt/V calculation [26]. All laboratory data were based on initial values entered in the KSN registry. Of note, the registry does not include data on uric acid-lowering drugs used.
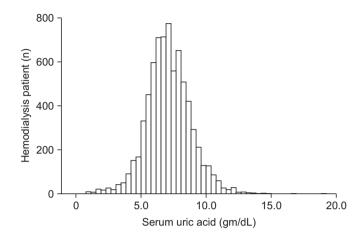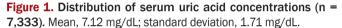
Clinical outcomes

The primary outcome measure was all-cause mortality, and the secondary outcome was cardiovascular mortality. Of note, there is a possibility of over-estimation of patient survival due to the voluntary nature of registration in the ESRD patient registry, with submission of death reports being easily missed.

Statistical analysis

Continuous variables are presented as a mean ± standard deviation or median with interquartile range, as appropriate. Categorical variables are presented as number with percentage. We compared the demographic characteristics and covariates using the Pearson chi-square test for categorical variables and one-way analysis of variance for continuous variables. Correlations between univariate variables and serum uric acid level were assessed using Pearson's correlation coefficients. Partial correlations were used to correct for age and sex. All independent variables in the multiple linear regression were tested for multicollinearity; if the variance inflation factor exceeded 10, the variable was considered to be collinear. Missing

data were replaced using multiple imputation analysis [27]. The resulting output was 5 complete datasets, with missing data imputed. Variables used in the multiple imputation model were body mass index, creatinine, albumin, phosphorus, and log transformed nPCR. A Cox proportional hazards analysis was performed to evaluate the independent association between serum uric acid level and long-term risk of death among patients undergoing maintenance hemodialysis and was presented as a hazard ratio (HR) and 95% confidence interval (95% CI). The proportional hazard assumption for the Cox model was tested using log minus log plots. The following variables were adjusted in the models: age, sex, body mass index, history of hypertension and diabetes mellitus, systolic and diastolic blood pressure, albumin, presence of residual renal function, and standard Kt/V. A Kaplan-Meier analysis was used to evaluate the change in survival between the quintiles of uric acid, and curves were compared using the log-rank test. All statistical tests were two-tailed, and $P < 0.05$ was considered significant. The analyses were performed using the Statistical Package for Social Sciences (SPSS®) software, version 21.0 (IBM Co., Armonk, NY, USA).

Figure 1. Distribution of serum uric acid concentrations (n = 7,333). Mean, 7.12 mg/dL; standard deviation, 1.71 mg/dL.

Table 1. Baseline clinical characteristics of the study population according to quintile of serum uric acid level

Variable	Serum uric acid level (mg/dL)					P value
	≤ 5.8 (n = 1,506)	5.9–6.6 (n = 1,365)	6.7–7.4 (n = 1,502)	7.5–8.4 (n = 1,528)	≥ 8.5 (n = 1,432)	
Age (yr)	64.5 ± 13.3	62.1 ± 13.2	61.3 ± 13.5	59.1 ± 13.6	58.0 ± 13.1	< 0.001
Male	827 (54.9)	794 (58.2)	885 (58.9)	976 (63.9)	989 (69.1)	< 0.001
SBP (mmHg)	141.5 ± 19.7	142.6 ± 19.6	141.9 ± 19.7	141.6 ± 19.1	142.0 ± 19.4	0.273
DBP (mmHg)	77.4 ± 12.0	78.0 ± 11.7	77.9 ± 11.8	78.8 ± 11.3	78.9 ± 11.9	0.002
Diabetes	822 (54.6)	722 (52.9)	774 (51.5)	745 (48.8)	616 (43.0)	< 0.001
Hypertension	280 (18.6)	286 (21.0)	324 (21.6)	313 (20.5)	327 (22.8)	0.017
Body mass index (kg/m²)	21.8 ± 15.4	22.0 ± 3.4	22.4 ± 4.8	23.0 ± 14.8	22.8 ± 5.3	0.009
Dialysis time/session (min)	235 ± 20	238 ± 19	237 ± 19	237 ± 17	236 ± 20	< 0.001
nPCR (g/kg/day)	0.92 ± 1.00	1.03 ± 1.20	1.22 ± 1.79	1.10 ± 1.46	1.32 ± 2.29	0.002
Standard Kt/V	2.11 ± 0.49	2.14 ± 0.39	2.12 ± 0.40	2.10 ± 0.36	2.07 ± 0.39	< 0.001
Hemodialysis duration (y)	2.80 ± 2.52	2.92 ± 2.53	3.00 ± 2.54	3.01 ± 2.59	2.87 ± 2.49	0.163
Presence of RRF	45 (3.0)	37 (2.7)	30 (2.0)	38 (2.5)	34 (2.4)	0.259
Hemoglobin (g/dL)	10.2 ± 1.2	10.3 ± 1.5	10.4 ± 1.2	10.4 ± 1.1	10.5 ± 1.2	< 0.001
Hematocrit (%)	31.2 ± 4.4	31.3 ± 3.9	31.6 ± 3.7	31.4 ± 3.8	31.4 ± 4.0	0.002
Albumin (g/dL)	3.7 ± 0.7	3.8 ± 0.6	3.8 ± 0.6	3.9 ± 0.5	3.9 ± 0.5	< 0.001
Calcium (mg/dL)	8.72 ± 0.90	8.67 ± 0.89	8.67 ± 0.86	8.67 ± 0.91	8.63 ± 0.89	0.074
Phosphorus (mg/dL)	4.1 ± 1.5	4.6 ± 1.4	4.9 ± 1.5	5.2 ± 1.7	5.5 ± 1.7	< 0.001
Baseline creatinine (mg/dL)	6.9 ± 3.0	7.8 ± 2.8	8.6 ± 2.9	9.3 ± 3.1	9.7 ± 3.6	< 0.001
Uric acid (mg/dL)	4.9 ± 1.0	6.3 ± 0.2	7.1 ± 0.2	7.9 ± 0.3	9.6 ± 1.1	< 0.001
PTH (pg/mL)	145 ± 155	180 ± 184	191 ± 213	208 ± 226	220 ± 203	< 0.001
Cholesterol (mg/dL)	142.8 ± 42.0	145.6 ± 40.5	144.6 ± 40.5	145.2 ± 39.5	144.7 ± 40.7	0.417
All-cause death	121 (8.0)	83 (6.1)	66 (4.4)	60 (3.9)	48 (3.4)	< 0.001
Cardiovascular death	45 (3.0)	40 (2.9)	27 (1.8)	26 (1.7)	20 (1.4)	< 0.001

Values are presented as mean ± standard deviation or number (%).

DBP, diastolic blood pressure; nPCR, normalized protein catabolic rate; PTH, parathyroid hormone; RRF, residual renal function; SBP, systolic blood pressure.

Results

Baseline demographic, clinical, and laboratory characteristics

Demographic and clinical data of our study group are presented in Supplementary table 1, with relevant data summarized as follows: mean age, 61 years; 61% male; 50% with diabetes; and mean baseline creatinine level of 8.5 ± 3.3 mg/dL. Compared to excluded cases (n = 35,438), included cases (7,333) tended to be male and to be older, as well as have a higher body mass index, nPCR (as a marker of daily protein intake), serum hemoglobin, albumin, calcium and cholesterol, prevalence of diabetes, and hypertension and lower hemodialysis duration and presence of residual renal function. Fig. 1 shows the distribution of serum uric acid in the study population, with the baseline serum uric acid level being approximately normally distributed, with a mean of 7.12 ± 1.71 mg/dL and a median (interquartile range) of 7.1 (6.1−8.1) mg/dL. Baseline characteristics of the study population were evaluated based on quintile of serum uric acid level (≤ 5.8, 5.9−6.6, 6.7−7.4, 7.5−8.4, and ≥ 8.5 mg/dL; Table 1). Compared to patients with serum uric acid level in the lowest quintile, patients with higher serum uric acid level were younger; tended to be male; had a higher prevalence of hypertension; had a higher body mass index, nPCR, hemoglobin, albumin, phosphorus, baseline creatinine, and parathyroid hormone (PTH); and had a lower prevalence of diabetes as well as a lower standard

Kt/V. The patients in the lowest and highest quintiles had a shorter dialysis time compared to patients in other quintiles.

Correlations between serum uric acid level and clinical variables

Serum uric acid was positively correlated with body mass index, nPCR, and levels of albumin, phosphorus,

Table 2. Significant correlations of several variables with serum uric acid level in the study population

| Variable | Serum uric acid level | | | |
| | Unadjusted | | Adjusted for age and sex | |
	r	P value	r	P value*
Age (yr)*	−0.166	< 0.001	−	−
Body mass index (kg/m²)	0.036	0.002	0.097	< 0.001
Dialysis time/session (min)	0.007	0.532	0.025	0.290
nPCR (g/kg/day)	0.069	0.001	0.069	0.004
Standard Kt/V	−0.045	< 0.001	−0.031	0.194
Hemodialysis duration (y)	0.017	0.167	0.017	0.477
Hemoglobin (g/dL)	0.066	< 0.001	0.040	0.089
Albumin (g/dL)	0.124	< 0.001	0.146	< 0.001
Calcium (mg/dL)	−0.034	0.004	−0.016	0.511
Phosphorus (mg/dL)	0.308	< 0.001	0.252	< 0.001
Baseline creatinine (mg/dL)	0.300	< 0.001	0.188	< 0.001
PTH (pg/mL)	0.130	< 0.001	0.084	< 0.001
Cholesterol (mg/dL)	0.013	0.266	0.032	0.184

nPCR, normalized protein catabolic rate; PTH, parathyroid hormone.

r = correlation coefficient.

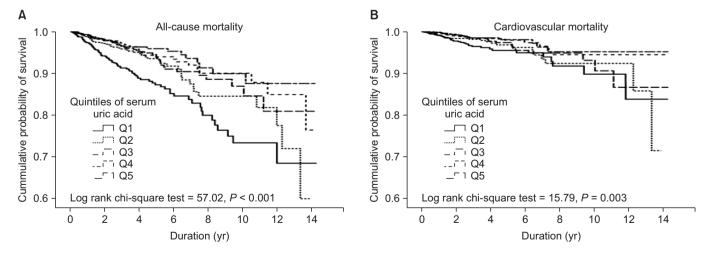*For adjusted values, partial correlations were used.

Figure 2. Kaplan-Meier survival curves for quintiles of serum uric acid level in patients undergoing maintenance hemodialysis and followed for up to 14 years. (A) All-cause mortality and (B) cardiovascular mortality. Q1 (≤ 5.8 mg/dL), Q2 (5.9−6.6 mg/dL), Q3 (6.7−7.4 mg/dL), Q4 (7.5−8.4 mg/dL), and Q5 (≥ 8.5 mg/dL).

creatinine, and PTH, in both unadjusted models and models adjusted for age and sex. However, standard Kt/V, hemoglobin, and calcium were not correlated with serum uric acid level after adjusting for age and sex (Table 2).

Effects of serum uric acid level on all-cause and cardiovascular mortality

Among the 7,333 cases included in our analysis, 378 (5.2%) all-cause deaths and 158 (2.2%) cardiovascular deaths were recorded over the follow-up period (Supplementary table 1), with higher mortality identified for the lower serum uric acid quintile (Table 1). Kaplan-Meier survival curves confirmed incremental increase in all-cause and cardiovascular mortality across the lower serum uric acid quintile (Fig. 2A, B).

Cox proportional hazards models were used to quantify the associations between serum uric acid level and all-cause and cardiovascular death (Table 3, 4). Based on the continuous linear model, a higher uric acid level was associated with lower all-cause and cardiovascular mortality in the unadjusted Cox proportional hazards model. Even after adjustment for potential confounders, the all-cause mortality HR was 0.90 (95% CI, 0.83−0.97; $P = 0.008$) for each 1 mg/mL increase in uric acid level. However, no significant association between serum uric acid level and cardiovascular death was observed after adjusting for confounding factors (HR, 0.90; 95% CI, 0.80−1.01; $P = 0.078$).

Multiple imputation analysis and sensitivity analyses

Analysis of imputed datasets (adjusted for missing uric acid level data) in the Cox proportional model yielded survival outcomes comparable to those calculated from the non-imputed data (Table 3, 4). For each 1 mg/dL increase in uric acid level, all-cause mortality HR was 0.92 (95% CI, 0.86−0.98; $P = 0.013$), whereas cardiovascular mortality HR was not significantly associated with serum uric acid level after adjustment for confounding factors (HR, 0.90; 95% CI, 0.81−1.00; $P = 0.057$).

We also performed sensitivity analyses to determine the robustness of the association between serum uric acid level and risk of death. All-cause mortality was significantly lower among cases above the serum uric acid (> 5.8 mg/dL) than below (≤ 5.8 mg/dL), after adjustment, with no between-group difference in cardiovascular mortality.

Table 3. Hazard ratio of all-cause mortality associated with continuous, dichotomous, and quintiles of serum uric acid level in unadjusted and multivariable-adjusted Cox proportional hazards models using multiple imputation

Variable	Non-imputed data					Multiple imputation (pooling)		
	Event	Unadjusted	P value	Multivariable adjusted*	P value	Events	Multivariable adjusted*	P value
All-cause mortality†	378/7,333 (5.2)	0.786 (0.734–0.841)	< 0.001	0.900 (0.834–0.973)	0.008	8,837/42,791 (20.7)	0.916 (0.855–0.982)	0.013
Binary uric acid level (mg/dL)								
B1 (≤5.8)	121/1,501 (8.1)	Reference		Reference		2,426/10,234 (23.7)	Reference	
B2 (>5.8)	257/5,822 (4.4)	0.430 (0.339–0.545)	< 0.001	0.662 (0.509–0.859)	0.002	6,411/32,557 (19.7)	0.662 (0.513–0.854)	0.002
Quintile of uric acid level (mg/dL)								
Q1 (≤5.8)	121/1,506 (8.0)	Reference		Reference		2,426/10,234 (23.7)	Reference	
Q2 (5.9–6.6)	83/1,365 (6.1)	0.560 (0.406–0.773)	< 0.001	0.685 (0.480–0.977)	0.037	1,675/7,789 (21.5)	0.715 (0.504–1.014)	0.060
Q3 (6.7–7.4)	66/1,502 (4.4)	0.447 (0.321–0.622)	< 0.001	0.646 (0.451–0.925)	0.017	1,559/7,790 (20.0)	0.627 (0.440–0.894)	0.010
Q4 (7.5–8.4)	60/1,528 (3.9)	0.390 (0.277–0.550)	< 0.001	0.667 (0.463–0.961)	0.030	1,559/8,164 (19.1)	0.661 (0.462–0.945)	0.023
Q5 (≥8.5)	48/1,432 (3.4)	0.336 (0.230–0.490)	< 0.001	0.648 (0.423–0.992)	0.046	1,618/8,814 (18.4)	0.636 (0.422–0.959)	0.031

Values are presented as number (%) of events or hazard ratio (95% confidence interval).

B, binary; Q, quintile.

*Models are adjusted for the factors of age, sex, body mass index, primary renal disease (history of hypertension and diabetes mellitus), systolic blood pressure, diastolic blood pressure, albumin, presence of residual renal function, and standard Kt/V; †Continuous per 1 mg/dL increase in uric acid.

Table 4. Hazard ratio of cardiovascular mortality associated with continuous, dichotomous, and quintiles of serum uric acid level in unadjusted and multivariable-adjusted Cox proportional hazards models using multiple imputation

Variable	Non-imputed data					Multiple imputation (pooling)		
	Event	Unadjusted	P value	Multivariable adjusted*	P value	Event	Multivariable adjusted*	P value
Cardiovascular mortality†	158/7,333 (2.2)	0.810 (0.729–0.900)	< 0.001	0.901 (0.802–1.012)	0.078	3,231/42,791 (7.6)	0.903 (0.813–1.003)	0.057
Binary of uric acid level (mg/dL)								
B1 (≤5.8)	45/1,501 (3.0)	Reference		Reference		860/10,234 (8.4)	Reference	
B2 (>5.8)	113/5,822 (1.9)	0.533 (0.365–0.777)	0.001	0.745 (0.498–1.115)	0.152	2,371/32,557 (7.3)	0.724 (0.491–1.067)	0.103
Quintile of uric acid level (mg/dL)								
Q1 (≤5.8)	45/1,506 (3.0)	Reference		Reference		860/10,234 (8.4)	Reference	
Q2 (5.9–6.6)	40/1,365 (2.9)	0.752 (0.463–1.222)	0.250	0.830 (0.489–1.407)	0.488	613/7,789 (7.9)	0.839 (0.495–1.421)	0.513
Q3 (6.7–7.4)	27/1,502 (1.8)	0.565 (0.340–0.940)	0.028	0.785 (0.466–1.324)	0.365	574/7,790 (7.4)	0.738 (0.440–1.240)	0.251
Q4 (7.5–8.4)	26/1,528 (1.7)	0.453 (0.264–0.777)	0.004	0.697 (0.401–1.213)	0.202	575/8,164 (7.0)	0.672 (0.388–1.165)	0.157
Q5 (≥8.5)	20/1,432 (1.4)	0.382 (0.211–0.693)	0.002	0.631 (0.328–1.212)	0.167	610/8,814 (6.9)	0.603 (0.317–1.145)	0.122

Values are presented as number (%) of events or hazard ratio (95% confidence interval).

B, binary; Q, quintile.

*Models are adjusted for the factors of age, sex, body mass index, primary renal disease (history of hypertension and diabetes mellitus), systolic blood pressure, diastolic blood pressure, albumin, presence of residual renal function, and standard Kt/V; †Continuous per 1 mg/dL increase in uric acid.

When participants were divided into quintiles of serum uric acid level, the HR for all-cause mortality among cases in the highest quintile (≥ 8.5 mg/dL) compared to the lowest quintile (≤ 5.8 mg/dL) was 0.65 (95% CI, 0.42−0.99; P = 0.046). Similarly, a graded effect of the level of serum uric acid on cardiovascular mortality was identified, but comparisons between the higher and lower quintiles were not statistically significant, even after adjustment or multiple imputation analysis. Furthermore, we performed an additional Cox proportional analysis according to quartile of serum uric acid level (≤ 6.0, 6.1−7.0, 7.1−8.0, and ≥ 8.1 mg/dL), as well as using the data since 2012 (Supplementary table 2, 3). The results were similar to that reported previously.

Discussion

Using data from the KSN registry of ESRD, we found that, among Korean hemodialysis patients, serum uric acid level was correlated with nutritional status indicators, such as body mass index, nPCR, and phosphorus. Moreover, higher uric acid level was associated with lower all-cause mortality in these patients, even after adjustment. However, hyperuricemia could not predict long-term cardiovascular mortality in this population.

Several studies have described an association between serum uric acid concentration and mortality among patients on maintenance hemodialysis or peritoneal dialysis [12−24]. Although most of these studies demonstrated that low serum uric acid concentration was independently associated with all-cause mortality among dialysis patients, the results remained controversial. A recent prospective observational study of 261 patients on maintenance hemodialysis reported that, for each 1 mg/dL increase in baseline serum uric acid level, the HR of both all-cause and cardiovascular death decreased by 45% [19]. Moreover, a large retrospective study identified that patients with serum uric acid level < 5.0 mg/dL at the initiation of hemodialysis were at a significantly higher risk of mortality compared to those with normal uric acid level [21]. In addition, in a multicenter prospective cohort of 1,738 Korean patients undergoing maintenance hemodialysis, a time-average uric acid level < 5.5 mg/dL was independently associated with all-cause mortality over a median follow-up of 44 months [22]. Similar to the results of previous studies, our results revealed that lower uric acid level was associated with a higher risk of

all-cause mortality among hemodialysis patients, after adjusting for various confounders. The HR of all-cause mortality was lowered by 0.9 for each 1 mg/dL increase in serum uric acid concentration.

The mechanism underlying the paradoxical association between serum uric acid level and all-cause mortality among dialysis patients has not been clearly elucidated and is multifactorial in nature. Several possible explanations could be proposed based on previous studies and our findings. First, serum uric acid level could be considered an indicator of nutritional status among patients on dialysis. In fact, serum uric acid level is significantly associated with handgrip strength, geriatric nutritional risk index, and malnutrition-inflammatory score, which are useful tools for monitoring nutritional status in hemodialysis patients [19]. In line with previous studies [18,19,21–23], we also found that high uric acid level was positively correlated with nutritional status indicators of body mass index, nPCR, and serum level of albumin, phosphorus, and creatinine. Level of nPCR is often used as a measure of daily protein intake among dialysis patients. A high protein diet can increase the protein-nitrogen balance and lead to increased serum albumin and muscle mass, with increased serum albumin being associated with lower mortality in patients on dialysis [28,29], while uric acid has been shown to have antioxidant and anti-inflammatory properties [10,30]. Indeed, a recent study showed a negative correlation between serum uric acid level and interleukin-6, a surrogate marker of inflammation, in hemodialysis patients [19]. Although further studies are needed to clarify the protective effect of serum uric acid on mortality, these properties of uric acid might have contributed to the lower mortality rate in our hemodialysis population.

Although low uric acid level might be associated with all-cause mortality in dialysis patients, it is important to clarify whether hyperuricemia *per se* is a risk factor for mortality. To date, three studies have suggested that a high uric acid concentration is an independent predictor of mortality, especially among patients receiving peritoneal dialysis [15–17]. Other studies have also revealed a J-shaped or U-shaped relationship between uric acid and mortality [21,22]. However, the Dialysis Outcomes and Practice Patterns Study (DOPPS) and a prospective observational study reported that higher uric acid level was associated with a lower risk of all-cause mortality among hemodialysis patients, in agreement with our study findings [18,19]. These inconsistent results, including our results, could be due to differences in dialysis settings, presence of residual renal function, sex-related differences, and length of follow-up periods. Therefore, further large, multicenter prospective trials with long-term follow-up are needed to confirm these findings.

The present study did not find an association between serum uric acid level and cardiovascular mortality, even after adjustment of the models. Similarly, a longitudinal cohort study on maintenance hemodialysis patients indicated that a longitudinal increase in serum uric acid level over time was correlated with better all-cause mortality but not cardiovascular mortality or first cardiovascular event [24]. The inconsistent trend in uric acid level according to cardiovascular mortality was more likely to be explained by its dual effects on cardiovascular outcomes in patients undergoing hemodialysis [17]. An abnormally high level of uric acid also contributes to the pathogenesis of cardiovascular disease via the induction of oxidative stress, activation of the renin-angiotensin system, and B-type natriuretic peptide, despite its antioxidant effects [31,32]. Although cardiovascular disease is the leading cause of mortality among patients with ESRD, all-cause mortality might be more influenced by the beneficial effects of uric acid in patients undergoing dialysis.

The limitations of the current study must be acknowledged. First, because of the retrospective design, a substantial number of patients with unavailable serum uric acid data were excluded from our cohort. Patients included in the analysis had lower all-cause and cardiovascular mortality compared to the excluded patients. Thus, selection bias might have affected the generalization of our findings to the maintenance hemodialysis population. Nevertheless, a multiple imputation model was used to estimate missing values, and similar results were obtained using the resulting dataset. Second, the rate of mortality in our cohort could have been underestimated because death reports are collected voluntarily, and the causes of death were extracted from patient records. Third, we could not exclude the possibility of residual confounding factors and the presence of unmeasured confounders, such as uric acid-lowering agents, despite our best efforts to adjust for significant confounding factors, including residual renal function that can influence serum uric acid level and standard Kt/V as a marker of

hemodialysis adequacy. Despite these limitations, the strength of our study is that it used data from a nationwide Korean ESRD registry with a large number of patients undergoing maintenance hemodialysis and long-term follow-up, up to 14 years.

In conclusion, our study demonstrated that higher serum uric acid level at the commencement of dialysis was strongly associated with a lower risk of all-cause mortality, except for cardiovascular mortality, in Korean patients undergoing hemodialysis. These findings suggest the need for simple laboratory tests to estimate serum uric acid level in order to identify disease prognosis and the requirement for nutritional interventions. Further studies are also needed to evaluate and determine the precise mechanisms behind our findings.

Conflicts of interest

All authors have no conflicts of interest to declare.

Acknowledgments

Supplementary materials

Futher detailes are presented in the online version of this article (available at https://doi.org/10.23876/j.krcp.2017.36.4.368).

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