Original Paper

Uric Acid in the Follow-Up Determines 30% Decline in Estimated GFR Over 2 Years: a Propensity Score Analysis

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Key Words

Uric acid • Time-averaged uric acid • 30% decline in eGFR • Propensity score analysis • Stratified Cox proportional hazards model • Propensity score matching

Abstract

Background/Aims: Higher level of serum uric acid (SUA) predicts early entry to dialysis in chronic kidney disease (CKD) patients. However, a short-term effect of SUA remains to be elucidated using a novel surrogate endpoint. **Methods:** Japanese CKD stage 3 to 4 patients were retrospectively examined (n= 701). The follow-up level of SUA was estimated as time-averaged uric acid (TA-UA). A propensity score for 6.0, 6.5 or 7.0 mg/dL of TA-UA was respectively calculated using baseline 23 covariates. The time-to-event analysis was performed for 30% decline in estimated GFR over 2 years. **Results:** Incidence rates over 2 years were 90 of 440 in men and 36 of 261 in women ($p = 0.03$). Despite the negative result of baseline SUA, stratified Cox regression on the quintiles of the estimated propensity score showed that higher TA-UA of the three thresholds were all significant (crude HR 2.10 to 2.44) even after adjusting for the confounders. Kaplan-Meier analysis after propensity score matching likewise showed worse survival in the patients with the higher TA-UA (HR 3.11 to 4.26). **Conclusion:** Higher SUA increases likelihood of reaching a surrogate endpoint over 2 years. Early intervention for SUA less than 6.0 mg/dL is recommended for slowing CKD progression.

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Introduction

Intervention for accelerating factors toward end-stage renal disease (ESRD) is the mainstay of stabilizing the progression of chronic kidney disease (CKD). For the daily

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clinical practice, we had better focus on the modifiable risk factors but not the demographic characteristics such as ethnicity, age, sex and original kidney disease. While hypertension and proteinuria are widely established as the first line risk factors, the second line risk factors may include anemia, hyperphosphatemia, metabolic acidosis as well as hyperuricemia. The incidence of hyperuricemia, however, is confounded with not only CKD but also metabolic syndrome and hypertension [1]. Since the impact of proteinuria is so enormous as to mask other risk factors, the classical risk analysis failed to draw consistent results. Hyperuricemia has been among such risk factors because preceding investigations showed the positive results whereas not in other observational studies as reviewed in the recent literature [2]. The independent significance of serum uric acid (SUA) was indeed abolished when adjusted for the existence of kidney dysfunction [3-6]. The inconsistency may also be attributed to the test cohorts which differed in the grades of CKD stages, the presence or absence of other CKD risk factors, and additional comorbidities such as diabetes. In addition, the selection of renal outcome also varied from the slight increase in serum creatinine to entering ESRD. Another important property that has long been overlooked is the time-varying nature of SUA in the clinical course of CKD.

To overcome these limitations we recently performed the propensity score analysis to mimic the randomized controlled trial (RCT), examining the causal effect of SUA on the incidence of ESRD [7]. The results revealed that lower levels of SUA may slow the progression to ESRD and that the target threshold appears to be below 6.5 mg/dL. The number needed to treat (NNT) was as low as 9, suggesting that one extra patient can be rescued from entering ESRD by maintaining SUA below 6.5 mg/dL in 9 CKD patients [7].

The urgent need to retard CKD progression is to define a novel surrogate endpoint of the renal outcome instead of classical doubling of serum creatinine and reaching ESRD. Very recently, 30% decline in estimated GFR (eGFR) over 2 years was advocated [8] and has been debated on its utility and limitations [5, 9, 10]. Since 30% decline can be reached earlier than ESRD, it has an obvious advantage to increase the incidence rate despite lower specificity in some clinical setting [9]. In the present study we were prompted to employ both the propensity score analysis and the novel surrogate endpoint to investigate the impact of SUA on CKD progression over as short a period as 2 years.

Materials and Methods

Study protocol and ethical statement

We used a retrospective Japanese CKD cohort of Teikyo University Hospital, Tokyo, Japan as already reported [5], which included the patients having two measurements of serum creatinine 2 years apart, and the observation periods were limited to 2 years. Inclusion criteria consisted of CKD stage 3 and 4 and age 20 to 84 years. On the other hand, patients with nephrotic syndrome, malignancy, obstructive nephropathy, acute kidney injury and gout were excluded. Total participants accounted for 701 patients with no censoring. The present study was approved by the institutional review board (IRB) in the Teikyo University Review Board #14-115 and was executed in accordance with the principle of the Helsinki Declaration. Written informed consent was waived after approval of IRB and the patient records and information was anonymized and de-identified prior to analysis.

Parameters analyzed

The demographic characteristics included age, body mass index (BMI), original kidney disease (diabetic nephropathy or not) and systolic blood pressure (SBP). Blood parameters included hemoglobin (Hb), white blood cell (WBC), platelet (Plt), albumin (Alb), uric acid (UA), sodium (Na), potassium (K), chlorine (Cl), Na-Cl (as a surrogate of HCO_3^-), albumin-corrected calcium (cCa), phosphorus (P), low-density lipoprotein cholesterol (LDL-C) and c-reactive protein (CRP). Urine parameters included spot urine proteinuria (expressed as gram per gram creatinine excretion; TPU/CrU) and spot urine hematuria by dipstick (expressed as an ordinal variable of 0, 1, 2, 3 corresponding to negative, $\pm$, 1+, 2+ or greater,

respectively; UB_score). Due to the distribution, CRP and proteinuria were converted to log-transformed values for analysis.

Blood was tested using hematology autoanalyzer (Sysmex XE-5000, Kobe, Japan) and blood chemistry parameters were measured by routine measurements using autoanalyzer (LABOSPECT 008, Hitachi High-Technologies Corporation, Tokyo, Japan). Creatinine concentration in serum and urine was measured by an enzymatic method. Assay of SUA was based on uricase method and urinary protein concentration was measured by pyrocatechol violet-metal complex assay method. Estimated GFR was calculated according to the equation for Japanese [11], and the grade of CKD was classified based on the Kidney Disease Outcomes Quality Initiative (K/DOQI) practice guidelines [12].

Use of antihypertensives including angiotensin converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB) (combined as RASi), diuretics, and UA-lowering drugs were recorded as yes (coded as 1) or no (coded as 0). Final 23 baseline covariates examined in the present study included age, sex, DMN, BMI, eGFR, SBP, Hb, WBC, Plt, Alb, UA, Na, K, Na-Cl, cCa, P, LDL-C, Log CRP, Log TPU/CrU, UB_score, use of RASi, use of diuretic and use of LUA, those of which were used for modeling the propensity score estimate.

A propensity score analysis

The time-varying values of SUA in the follow-up were averaged until reaching 30% decline in eGFR or 2 years (time-averaged UA; TA-UA). The target thresholds of TA-UA were set at 6.0, 6.5 and 7.0 mg/dL based on the clinical implication [7]. The probability to reach the threshold or above (defined as a propensity score) was determined by multivariate binary logistic regression using the aforementioned 23 baseline covariates. After estimating the propensity score, the participants whose propensity scores were non-overlapped between the higher and the lower groups of the test threshold, that is, outside the common support, were trimmed out and the remaining subsample was used for a propensity score analysis [13].

Stratified Cox regression model for the surrogate endpoint over 2 years

The subsample thus trimmed was stratified on the quintiles of overlapping propensity scores because the stratification on quintiles is able to remove 90% bias as demonstrated by the original work of Rosenbaum and Rubin [14] and the previous studies [7, 15, 16]. A stratified Cox regression model was first conducted to examine the significance of the univariate TA-UA for the surrogate endpoint over 2 years (Model 1). In addition to this crude hazard ratio (HR), the impact of sex was tested for the significance by incorporating the interaction term (Model 2). Cox regression model was further adjusted for the major confounders on the renal outcome, yielding adjusted HR (Model 3). The covariates used for adjustment were chosen based on our previous analysis and the standard Cox regression model in the present study; age, sex, diabetic nephropathy, eGFR, SBP, Alb, P, proteinuria and use of RASi [5]. The double adjustment in propensity score analysis is recommended to remove the residual imbalance especially when standardized difference > 0.1 [17].

Matching

Patients whose TA-UA was above or below the threshold (TA-UA 6.0, 6.5 and 7.0 mg/dL) were subjected to propensity score matching analysis using a 1:1 greedy method without replacement. The caliper size was first set at 0.25 times standard deviation of the propensity scores in the participants and gradually narrowed until reaching the standardized difference < 0.1 on most covariates, the value being proposed to meet the balance between treated and untreated groups [17-20]. The model assignment was estimated by c-statistics and the balance between two groups was checked by paired comparison tests and standardized differences of the 23 baseline covariates [21]. Moreover, the distribution of the propensity scores between higher and lower TA-UA groups after matching was visually confirmed by kernel density lines [22, 23]. Time-to-event survival analysis for 30% decline in eGFR over 2 years was examined by Kaplan-Meier analysis and the statistical significance was tested by stratified log-rank test for paired samples [20, 24].

Statistical analysis

Values for categorical variables are given as number (percentage) and values for continuous variables are given as mean ± standard deviation or median [interquartile range] depending on the distribution. Correlation of between parameters was analyzed by Pearson's correlation test and the slopes of the

regression lines were tested for the difference by ANCOVA. The c-statistics of the propensity score model was estimated by the area under the Receiver Operating Characteristic (ROC) curve for the threshold [19] and for its goodness-of-fit by Hosmer-Lemeshow test. Time-to-event survival analysis was conducted by Cox proportional hazards model for the event of reaching 30% decline in eGFR. Any covariate was tested for its proportional hazards assumption using both a time-dependent Cox regression model and a Schoenfeld residual plot. Goodness-of-fit of the proposed model by a stratified multivariate Cox regression was evaluated by Akaike information criterion (AIC) [25]. Statistical analyses were undertaken using SPSS statistics for Windows version 22 (IBM Corp, Armonk, NY, USA) and STATA version 14 (StataCorp LP, College Station, TX, USA). A *p* value less than 0.05 was considered statistically significant.

Results

Baseline characteristics and TA-UA in the follow-up

During 2 years of the follow-up, 90 out of 440 male patients and 36 out of 261 female patients reached renal endpoint (*p* = 0.03 by chi-square test), thus the total incidence rate was 96.0 per 1, 000 person-years (male 110.4 and female 72.3, *p* = 0.03). The number was 3.6-fold greater than the incidence rate of ESRD (26.5 per 1, 000 person-years) as published previously [7]. The values of baseline UA and TA-UA until reaching 30% decline in eGFR or over 2 years are normally distributed and the mean value of TA-UA was significantly increased from the baseline as depicted in Fig. 1 (6.46 ± 1.38 vs. 6.53 ± 1.27 mg/dL, *p* = 0.036 by paired *t* test). Of note is that the patients having TA-UA less than 6 mg/dL decreased and those having TA-UA between 6.5 and 8.0 mg/dL increased and that those with TA-UA greater than 8.0 mg/dL did not necessary increase. The relationships between baseline UA and TA-UA are drawn in Fig. 2, showing the positive correlation irrespective of the renal event (without event, *n* = 575, *r* = 0.743, *R*² 0.552, *p* < 0.001; with event, *n* = 126, *r* = 0.737, *R*² = 0.543, *p* < 0.001). The declined slope in the patients who occurred the renal event indicates that lower baseline UA tended to increase before reaching the renal endpoint (ANCOVA, *p* = 0.066).

Fig. 1. The distribution of baseline uric acid and time-averaged uric acid over 2 years. Histograms of serum uric acid (SUA) at the baseline (grey bars) and time-averaged UA until reaching 30% decline in eGFR or over 2 years (black bars) are depicted and overlaid with normal distribution curves as shown by grey line and black line, respectively. The mean of the values were significantly different by paired *t* test (6.46 ± 1.38 vs. 6.53 ± 1.27 mg/dL, *p* = 0.036 by paired *t* test).

The demographic characteristics and baseline values separated by the threshold of TA-UA are shown in Table 1a-c. The patients whose TA-UA ≥ 6.0 mg/dL showed the following characteristics compared with those < TA-UA 6.0 mg/dL; lower baseline eGFR, higher percentage of CKD stage 4, male preponderance, higher proportion of diabetic nephropathy, higher systolic blood pressure, higher white blood cells, lower serum albumin, higher baseline UA, higher serum K, more acidotic, more urinary protein excretion, more use of diuretics. The whole picture of the patients is basically concordant with more advanced CKD stage (Table 1a). The patients whose TA-UA ≥ 6.5 mg/dL showed the similar findings at baseline except for the following covariates; younger age, higher BMI, lower serum Na and higher degree of hematuria (Table 1b). The patients whose TA-UA ≥ 7.0 mg/dL likewise showed the consistent result further adding the followings; lower

Fig. 2. The relationship between baseline uric acid and time-averaged uric acid over 2 years with or without renal event. A regression line without event is $y = 0.68x + 2.06$, $r = 0.743$, $p < 0.001$, while that with event is $y = 0.51x + 4.00$, $r = 0.684$, $p < 0.001$. Slopes of two regression lines tended to differ by ANCOVA ($p = 0.066$), indicating the lower baseline SUA increased when the patient reached the renal event. Abbreviations: SUA, serum uric acid; ANCOVA, analysis of covariance.

hemoglobin, higher serum phosphorus and lower LDL-C (Table 1c). These changes simply reflect that CKD stage gradually progress as TA-UA increases.

Time-to-event analysis by standard Cox regression analysis using baseline values

Univariate standard Cox regression analysis showed that baseline SUA has a strong impact on the renal endpoint over 2 years (Table 2, Model 1; HR 1.30, 95% CI 1.15-1.47) but dismissed its impact after adjusting for other covariates (Table 2, Model 2; HR 1.04, 95% CI 0.91-1.19), indicating that the effect of baseline SUA is confounded by other stronger parameters such as proteinuria (Wald 50.76), higher serum phosphorus (14.93), the presence of diabetic nephropathy (11.27), lower eGFR (11.05), lower serum albumin (9.33), younger age (7.14), higher systolic blood pressure (5.05), acidosis (4.20) and use of RASi (3.90) in the descending order of Wald statistic (Table 2). This result was not contradictory with the previous reports in which ESRD was utilized as a renal endpoint [5, 7, 26]. Therefore, a propensity score analysis was instituted to remove the confounding as much as

Fig. 3. Kernel density plots of propensity scores between higher and lower TA-UA before and after matching. a) TA-UA 6.0 mg/dL before matching, b) TA-UA 6.5 mg/dL before matching, c) TA-UA 7.0 mg/dL before matching, d) TA-UA 6.0 mg/dL after matching, e) TA-UA 6.5 mg/dL after matching, f) TA-UA 7.0 mg/dL after matching. Abbreviation: TA-UA, time-averaged uric acid.

Table 1a. Baseline covariates balance before and after matching by TA-UA threshold 6.0 mg/dL. Note: Values for categorical variables are given as number (percentage); values for continuous variables are given as mean $\pm$ standard deviation or median [interquartile range]. For statistical analyses, CRP and TPU/CrU were log-transformed. Conversion factors for units: creatinine in mg/dL to $\mu\text{mol/L}$, $\times 88.4$; uric acid in mg/dL to $\mu\text{mol/L}$, $\times 59.48$. Abbreviations: TA-UA, time-averaged uric acid; eGFR, estimated glomerular filtration rate; DMN, diabetic nephropathy; BMI, body mass index; SBP, systolic blood pressure; Hb, hemoglobin; WBC, white blood cell; Plt, platelet; Alb, albumin; UA, uric acid; Na, sodium; K, potassium; Cl, chloride; cCa, albumin-corrected calcium; P, phosphorus; CRP, c reactive protein; LDL-C, low-density lipoprotein cholesterol; TPU/CrU, urine total protein divided by urine creatinine; UB_score, urine blood score; RASi, RAS inhibitor; LUA, lowering uric acid drugs. * Unpaired *t* test, chi square test as appropriate. † Paired *t* test, McNemar test, Wilcoxon test or Friedman test as appropriate

Characteristics	Before matching (n = 701)			After matching (n = 222)		
	TA-UA < 6.0 n=237	TA-UA $\geq$ 6.0 n=464	p value*	TA-UA < 6.0 n=111	TA-UA $\geq$ 6.0 n=111	p value†
TA-UA (mg/dL)	5.2 $\pm$ 0.6	7.2 $\pm$ 0.9	< 0.001	5.4 $\pm$ 0.5	6.6 $\pm$ 0.6	< 0.001
Age (y)	63 $\pm$ 13	62 $\pm$ 13	0.14	63 $\pm$ 13	65 $\pm$ 13	0.38
eGFR (mL/min/1.73m ²)	46 $\pm$ 11	40 $\pm$ 13	< 0.001	44 $\pm$ 12	44 $\pm$ 12	0.95
CKD stage (3a, 3b, 4) (%)	62, 27, 1	39, 33, 28	< 0.001	50, 36, 14	54, 32, 14	0.90
Male (%)	43	73	< 0.001	60	59	1.00
DMN (%)	17	25	0.017	18	17	1.00
BMI (kg/m ²)	24.1 $\pm$ 4.5	24.5 $\pm$ 4.3	0.24	24.4 $\pm$ 4.8	24.6 $\pm$ 4.0	0.71
SBP (mmHg)	135 $\pm$ 19	138 $\pm$ 20	0.021	133 $\pm$ 17	135 $\pm$ 17	0.54
Blood Parameters						
Hb (g/dL)	13.0 $\pm$ 1.7	12.9 $\pm$ 2.0	0.67	13.2 $\pm$ 1.8	13.1 $\pm$ 1.8	0.90
WBC ($\times 10^2/\mu\text{L}$)	62 $\pm$ 20	66 $\pm$ 21	0.018	63 $\pm$ 21	64 $\pm$ 20	0.75
Plt ($\times 10^4/\mu\text{L}$)	22.3 $\pm$ 6.9	21.7 $\pm$ 6.6	0.32	22.2 $\pm$ 6.3	22.1 $\pm$ 6.5	0.98
Alb (g/dL)	4.1 $\pm$ 0.4	3.9 $\pm$ 0.5	< 0.001	4.1 $\pm$ 0.3	4.1 $\pm$ 0.4	0.66
UA (mg/dL)	5.3 $\pm$ 1.0	7.0 $\pm$ 1.2	< 0.001	5.9 $\pm$ 0.9	6.0 $\pm$ 0.9	0.56
Na (mEq/L)	141.0 $\pm$ 2.5	140.7 $\pm$ 2.8	0.18	140.8 $\pm$ 2.3	140.6 $\pm$ 3.0	0.66
K (mEq/L)	4.4 $\pm$ 0.4	4.5 $\pm$ 0.5	< 0.001	4.5 $\pm$ 0.5	4.4 $\pm$ 0.5	0.17
Na-Cl (mEq/L)	36.0 $\pm$ 2.1	35.3 $\pm$ 2.4	< 0.001	36.0 $\pm$ 2.2	36.0 $\pm$ 2.4	0.89
cCa (mg/dL)	8.8 $\pm$ 0.4	8.9 $\pm$ 0.5	0.81	8.9 $\pm$ 0.4	8.8 $\pm$ 0.5	0.79
P (mg/dL)	3.4 $\pm$ 0.5	3.4 $\pm$ 0.5	0.94	3.3 $\pm$ 0.5	3.3 $\pm$ 0.5	0.87
CRP (mg/dL)	0.08[0.04-0.19]	0.09[0.05-0.20]	0.60	0.08[0.05-0.22]	0.09[0.05-0.20]	0.98
LDL-C (mg/dL)	113 $\pm$ 28	109 $\pm$ 31	0.09	114 $\pm$ 29	110 $\pm$ 30	0.28
Urine Parameters (spot)						
TPU/CrU (g/g Cr)	0.27[0.15-0.48]	0.60[0.20-1.34]	< 0.001	0.29[0.17-0.57]	0.28[0.15-0.68]	0.98
UB_score (0, 1, 2, 3) (%)	62, 18, 9, 11	55, 21, 9, 15	0.27	61, 19, 8, 12	67, 20, 4, 9	0.37
Drug use						
RASi (%)	54	56	0.52	57	57	1.00
Diuretic (%)	10	18	0.008	17	14	0.73
LUA (%)	25	32	0.07	36	33	0.80

possible.

A propensity score analysis

a) Trimming and stratification of the subsample of the CKD cohort. The distribution of the propensity score of the participants above and below the threshold of TA-UA was plotted by kernel density (Fig 3a-c), showing the marked differences in the likelihood of segregating patients into either group. The resulted numbers of the participants after trimming were reduced to 631, 513 and 525 in 6.0, 6.5 and 7.0 mg/dL of TA-UA, respectively. The subsample was divided on the quintiles of the propensity score and the distribution of the propensity score in low and high levels of TA-UA were shown in box-plots in the strata (Fig 4a-c), demonstrating the comparable distribution of the propensity scores despite the big

Table 1b. Baseline covariates balance before and after matching by TA-UA threshold 6.5 mg/dL. Note: Values for categorical variables are given as number (percentage); values for continuous variables are given as mean $\pm$ standard deviation or median [interquartile range]. For statistical analyses, CRP and TPU/CrU were log-transformed. Conversion factors for units: creatinine in mg/dL to μ mol/L, $\times$ 88.4; uric acid in mg/dL to μ mol/L, $\times$ 59.48. Abbreviations: TA-UA, time-averaged uric acid; eGFR, estimated glomerular filtration rate; DMN, diabetic nephropathy; BMI, body mass index; SBP, systolic blood pressure; Hb, hemoglobin; WBC, white blood cell; Plt, platelet; Alb, albumin; UA, uric acid; Na, sodium; K, potassium; Cl, chloride; cCa, albumin-corrected calcium; P, phosphorus; CRP, c reactive protein; LDL-C, low-density lipoprotein cholesterol; TPU/CrU, urine total protein divided by urine creatinine; UB_score, urine blood score; RASi, RAS inhibitor; LUA, lowering uric acid drugs. * Unpaired t test, chi square test as appropriate. † Paired t test, McNemar test, Wilcoxon test or Friedman test as appropriate

Characteristics	Before matching (n = 701)			After matching (n = 226)		
	TA-UA < 6.5 n=349	TA-UA $\geq$ 6.5 n=352	p value*	TA-UA < 6.5 n=113	TA-UA $\geq$ 6.5 n=113	p value†
TA-UA (mg/dL)	5.5 $\pm$ 0.7	7.5 $\pm$ 0.8	< 0.001	5.9 $\pm$ 0.5	7.2 $\pm$ 0.5	< 0.001
Age (y)	64 $\pm$ 13	61 $\pm$ 13	0.001	61 $\pm$ 14	62 $\pm$ 13	0.43
eGFR (mL/min/1.73m ²)	45 $\pm$ 12	39 $\pm$ 13	< 0.001	42 $\pm$ 12	43 $\pm$ 13	0.62
CKD stage (3a, 3b, 4) (%)	59, 27, 14	35, 36, 29	< 0.001	48, 32, 20	47, 36, 17	0.81
Male (%)	50	75	< 0.001	70	66	0.58
DMN (%)	18	28	0.002	20	22	0.87
BMI (kg/m ²)	24.0 $\pm$ 4.2	24.8 $\pm$ 4.5	0.017	24.3 $\pm$ 4.5	24.4 $\pm$ 4.1	0.93
SBP (mmHg)	135 $\pm$ 20	139 $\pm$ 20	0.012	137 $\pm$ 21	135 $\pm$ 18	0.39
Blood Parameters						
Hb (g/dL)	13.0 $\pm$ 1.7	12.9 $\pm$ 2.1	0.38	13.3 $\pm$ 1.7	13.3 $\pm$ 1.8	0.75
WBC ($\times 10^2/\mu$ L)	62 $\pm$ 20	67 $\pm$ 20	0.001	65 $\pm$ 24	64 $\pm$ 19	0.65
Plt ($\times 10^4/\mu$ L)	22.1 $\pm$ 6.7	21.8 $\pm$ 6.7	0.57	21.8 $\pm$ 6.3	21.3 $\pm$ 5.7	0.55
Alb (g/dL)	4.1 $\pm$ 0.4	3.9 $\pm$ 0.5	<0.001	4.0 $\pm$ 0.4	4.1 $\pm$ 0.4	0.53
UA (mg/dL)	5.6 $\pm$ 1.0	7.3 $\pm$ 1.2	<0.001	6.5 $\pm$ 0.9	6.6 $\pm$ 0.9	0.40
Na (mEq/L)	141.0 $\pm$ 2.5	140.5 $\pm$ 2.8	0.027	140.8 $\pm$ 2.4	141.2 $\pm$ 2.1	0.20
K (mEq/L)	4.4 $\pm$ 0.5	4.5 $\pm$ 0.5	<0.001	4.5 $\pm$ 0.5	4.5 $\pm$ 0.5	0.78
Na-Cl (mEq/L)	36.0 $\pm$ 2.2	35.1 $\pm$ 2.4	<0.001	35.9 $\pm$ 2.4	35.8 $\pm$ 2.5	0.79
cCa (mg/dL)	8.8 $\pm$ 0.5	8.9 $\pm$ 0.5	0.46	8.9 $\pm$ 0.4	8.8 $\pm$ 0.5	0.56
P (mg/dL)	3.3 $\pm$ 0.5	3.4 $\pm$ 0.5	0.08	3.3 $\pm$ 0.5	3.3 $\pm$ 0.4	0.90
CRP (mg/dL)	0.08[0.05-0.18]	0.10[0.05-0.22]	0.55	0.09[0.05-0.20]	0.10[0.05-0.22]	0.37
LDL-C (mg/dL)	113 $\pm$ 29	109 $\pm$ 31	0.08	115 $\pm$ 31	113 $\pm$ 29	0.60
Urine Parameters (spot)						
TPU/CrU (g/g Cr)	0.29[0.15-0.56]	0.77[0.25-1.64]	<0.001	0.36[0.18-0.88]	0.39[0.15-0.85]	0.89
UB_score (0, 1, 2, 3) (%)	62, 18, 9, 11	52, 22, 9, 17	0.036	61, 18, 10, 11	57, 18, 6, 19	0.39
Drug use						
RASi (%)	57	54	0.45	60	57	0.69
Diuretic (%)	12	19	0.012	18	18	1.00
LUA (%)	30	29	0.93	43	38	0.49

differences in overall appearance of the propensity scores (Fig 3a-c).

b) Stratified Cox regression analysis. The likelihood to reach the surrogate endpoint over 2 years was examined by a Cox regression analysis stratified on the quintiles of the propensity score for the TA-UA threshold. Crude HRs of the higher TA-UA were significant in all three thresholds (Table 3, Model 1). To evaluate the effect of sex on the renal outcome, the interaction term of TA-UA and sex was added to the model but without a significant result in any threshold (Table 3, Model 2), suggesting no modifiable effect of sex on the result. No decrease in AIC also confirmed no improvement of the Cox regression models. The Cox regression model was further adjusted for other outcome-associated baseline covariates including sex, age, diabetic nephropathy, eGFR, SBP, Alb, P, proteinuria and use of RASi [5].

Table 1c. Baseline covariates balance before and after matching by TA-UA threshold 7.0 mg/dL. Note: Values for categorical variables are given as number (percentage); values for continuous variables are given as mean $\pm$ standard deviation or median [interquartile range]. For statistical analyses, CRP and TPU/CrU were log-transformed. Conversion factors for units: creatinine in mg/dL to $\mu\text{mol/L}$, $\times 88.4$; uric acid in mg/dL to $\mu\text{mol/L}$, $\times 59.48$. Abbreviations: TA-UA, time-averaged uric acid; eGFR, estimated glomerular filtration rate; DMN, diabetic nephropathy; BMI, body mass index; SBP, systolic blood pressure; Hb, hemoglobin; WBC, white blood cell; Plt, platelet; Alb, albumin; UA, uric acid; Na, sodium; K, potassium; Cl, chloride; cCa, albumin-corrected calcium; P, phosphorus; CRP, c reactive protein; LDL-C, low-density lipoprotein cholesterol; TPU/CrU, urine total protein divided by urine creatinine; UB_score, urine blood score; RASi, RAS inhibitor; LUA, lowering uric acid drugs.* Unpaired t test, chi square test as appropriate.† Paired t test, McNemar test, Wilcoxon test or Friedman test as appropriate

Characteristics	Before matching (n = 701)			After matching (n = 268)		
	TA-UA < 7.0 n=454	TA-UA $\geq$ 7.0 n=247	p value*	TA-UA < 7.0 n=134	TA-UA $\geq$ 7.0 n=134	p value†
TA-UA (mg/dL)	5.8 $\pm$ 0.8	7.9 $\pm$ 0.7	< 0.001	6.4 $\pm$ 0.5	7.7 $\pm$ 0.5	< 0.001
Age (y)	63 $\pm$ 13	61 $\pm$ 13	0.13	61 $\pm$ 14	62 $\pm$ 12	0.31
Baseline eGFR (mL/min/1.73m ²)	44 $\pm$ 12	37 $\pm$ 13	< 0.001	41 $\pm$ 12	40 $\pm$ 13	0.58
CKD stage (3a, 3b, 4) (%)	55, 29, 16	31, 36, 33	< 0.001	44, 33, 23	40, 34, 26	0.67
Male (%)	55	77	< 0.001	71	73	0.79
DMN (%)	19	29	0.006	19	22	0.64
BMI (kg/m ²)	24.1 $\pm$ 4.1	25.1 $\pm$ 4.8	0.004	24.2 $\pm$ 4.3	24.1 $\pm$ 4.1	0.90
SBP (mmHg)	135 $\pm$ 20	140 $\pm$ 20	0.001	138 $\pm$ 21	139 $\pm$ 20	0.48
Blood Parameters						
Hb (g/dL)	13.0 $\pm$ 1.7	12.7 $\pm$ 2.2	0.035	13.1 $\pm$ 1.8	12.9 $\pm$ 2.1	0.40
WBC ($\times 10^2/\mu\text{L}$)	63 $\pm$ 20	67 $\pm$ 20	0.012	67 $\pm$ 23	67 $\pm$ 20	0.95
Plt ($\times 10^4/\mu\text{L}$)	22.1 $\pm$ 6.6	21.6 $\pm$ 6.9	0.33	22.1 $\pm$ 6.7	21.9 $\pm$ 7.0	0.82
Alb (g/dL)	4.0 $\pm$ 0.4	3.9 $\pm$ 0.5	< 0.001	3.9 $\pm$ 0.4	3.9 $\pm$ 0.5	0.82
UA (mg/dL)	5.9 $\pm$ 1.1	7.5 $\pm$ 1.2	< 0.001	6.9 $\pm$ 0.8	6.9 $\pm$ 0.9	0.98
Na (mEq/L)	140.9 $\pm$ 2.7	140.5 $\pm$ 2.7	0.09	140.9 $\pm$ 2.7	141.0 $\pm$ 2.3	0.63
K (mEq/L)	4.4 $\pm$ 0.5	4.6 $\pm$ 0.5	< 0.001	4.5 $\pm$ 0.6	4.5 $\pm$ 0.5	0.83
Na-Cl (mEq/L)	35.9 $\pm$ 2.2	34.9 $\pm$ 2.5	< 0.001	35.3 $\pm$ 2.1	35.3 $\pm$ 2.5	0.96
cCa (mg/dL)	8.8 $\pm$ 0.5	8.8 $\pm$ 0.5	0.96	8.9 $\pm$ 0.4	8.9 $\pm$ 0.5	0.45
P (mg/dL)	3.3 $\pm$ 0.5	3.4 $\pm$ 0.5	0.026	3.3 $\pm$ 0.5	3.4 $\pm$ 0.5	0.47
CRP (mg/dL)	0.08[0.05-0.18]	0.10[0.05-0.22]	0.82	0.08[0.05-0.24]	0.09[0.05-0.18]	0.41
LDL-C (mg/dL)	112 $\pm$ 30	107 $\pm$ 31	0.026	111 $\pm$ 32	110 $\pm$ 28	0.66
Urine Parameters (spot)						
TPU/CrU (g/g Cr)	0.29[0.15-0.56]	0.77[0.25-1.64]	< 0.001	0.65[0.27-1.33]	0.57[0.20-1.23]	0.33
UB_score (0, 1, 2, 3) (%)	62, 18, 8, 12	50, 23, 10, 17	0.020	59, 20, 10, 11	54, 22, 8, 16	0.19
Drug use						
RASi (%)	57	53	0.38	58	54	0.56
Diuretic (%)	14	19	0.06	17	17	1.00
LUA (%)	32	26	0.10	39	31	0.24

The residual imbalance, if existed, could be adjusted for these confounders by this double adjustment [17]. Adjusted HRs showed virtually the similar values as crude HRs, indicating that residual imbalance was minimum in three thresholds (Table 3, Model 3). The multivariate model of Cox regression clearly showed the markedly reduced AIC, suggesting the better goodness-of-fit of the model (Table 3). In addition to TA-UA, the statistical significance was commonly found in covariates such as younger age, diabetic nephropathy, decline in baseline eGFR, decreased serum albumin, elevated serum phosphorus, greater degree in proteinuria

Fig. 4. Box plots of propensity score on quintiles of propensity scores. a) TA-UA 6.0 mg/dL before matching, b) TA-UA 6.5 mg/dL before matching, c) TA-UA 7.0 mg/dL before matching. The propensity score in the same quantile are comparable, suggesting the confounding is equivalent between 2 groups of higher and lower TA-UA. Abbreviations: TA-UA, time-average uric acid; Q1-5, quantile 1 to 5 based on the quintiles of the propensity scores from 0 to 1.

Fig. 5. Standardized differences of baseline parameters before and after propensity score matching. a) TA-UA 6.0 mg/dL, b) TA-UA 6.5 mg/dL, c) TA-UA 7.0 mg/dL. Asterisks indicate the value > 0.1 after matching. Most covariates show the value < 0.1. Abbreviations: TA-UA, time-averaged uric acid; eGFR, estimated glomerular filtration rate; DMN, diabetic nephropathy; BMI, body mass index; SBP, systolic blood pressure; Hb, hemoglobin; WBC, white blood cells; Plt, platelet; Alb, serum albumin; UA, uric acid; cCa, albumin-corrected serum calcium; P, serum phosphorus; CRP, c reactive protein; LDL-C, LDL-cholesterol; log TPU/CrU, log transformed proteinuria in spot urine; UB_score, urine blood score; RASi, use of RAS inhibitor; LUA, lowering uric acid drug.

and non-use of RASi (Table 3, Model 3). Of note is that AIC dramatically decreased by 100 from the Model 1 using the univariate TA-UA.

c) Propensity score matching.

Following matching, all the baseline covariates were well balanced by pairwise statistics (Table 2a-c after matching). The kernel density of the propensity score after matching above and below the threshold of TA-UA showed virtually identical distribution (Fig 3d-f), showing the comparable confounding between 2 groups. Moreover, c-statistics estimated by the area under the ROC curve were all greater than 0.8, indicating the superb accuracy of the propensity score models (TA-UA 6.0, 6.5 and 7.0 md/dL, 0.902, 0.901 and 0.895, respectively). Hosmer Lemeshow test showed all $p > 0.05$, indicating the acceptable goodness-of-fit of the propensity score models (TA-UA 6.0, 6.5 and 7.0 md/dL, $p = 0.33$, $p = 0.12$ and $p = 0.69$, respectively). Standardized differences of the baseline parameter between

two groups after matching were less than 0.1 except for a few parameters such as age, sex, SBP, Na, K, LDL-C use of RASi and use of UA-lowering drug (Fig 5). Some of the covariates which may influence the renal event were doubly adjusted for to remove the residual imbalance [17].

Finally, matched two groups divided by the threshold of TA-UA were subjected to Kaplan-Meier analysis (Table 4), the survival curve of which are plotted in Fig 6a-c. The two survival curves in three different thresholds showed the statistical significance by the stratified log-rank test, consistent with the univariate result of Cox regression models, suggesting that lower level of SUA in the follow-up delayed reaching the 30% decline in eGFR over 2 years. The result strongly suggests the beneficial effect of lowering UA on slowing the progression of CKD and the target level of SUA may be less than 6.0 mg/dL.

Discussion

In the present study we performed time-to-event survival analysis for reaching 30% decline in eGFR over 2 years as a novel surrogate renal endpoint. The incidence rate was much greater than that of ESRD (3.6-fold), providing more statistical power to analyze but we failed to show the independent predictive effect of baseline SUA on the renal outcome. It is probably due to the presence of confounding and the time-varying nature of SUA in the clinical course. It was fortunate enough that the role of SUA was uncovered by implementing propensity score analysis. Since sex difference is noted by some reports where female subjects are predisposed to develop CKD, we tested for that hypothesis by incorporating interaction term of sex and SUA in the follow-up. The result, however, could not show the sex difference in the risk for surrogate endpoint. The inconsistent result is probably due to the fact that the previous studies used the participants for annual health examinations whose kidney function are within normal range [27, 28]. In contrast, we used the patients having advanced CKD stage greater than stage 3, thus eliminating sex difference in the effect of SUA as a CKD risk factor. But further investigation is necessary.

The renal outcome for clinical research in nephrology has been evaluated using composite endpoints of doubling of serum creatinine, entering ESRD or death which were originally established by Lewis et al [29]. Since then these three endpoints have held as gold standard for clinical trials including RENAAL and IDNT [30, 31]. These endpoints, however, may have several problems these days. Firstly, reaching these endpoint need many patients at risk and long observation period, thus requiring a huge amount of effort and cost to execute. Secondly, death does not seem an appropriate outcome measure because older age, the one of the most influential risk of death, is not a risk factor for CKD progression [5, 26, 32]. To confine the research purpose to examine the risk analysis for the CKD progression to ESRD, it has long been awaited that we determine an alternative endpoint. In order to solve these issues, percent decline in eGFR was investigated and 30% decline in eGFR over 2 years was advocated as a novel surrogate endpoint of renal outcome due in part to the highest population attributable risk [8]. We verified the usefulness of this endpoint using our Japanese CKD cohort [5].

Table 2. Standard Cox regression for 30% decline in eGFR over 2 years using baseline values; Abbreviations: UA, uric acid; DMN, diabetic nephropathy; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; Hb, hemoglobin; Alb, albumin; UA, uric acid; Na, sodium; K, potassium; Cl, chloride; P, phosphorus; TPU/CrU, urine total protein divided by urine creatinine; RASi, RAS inhibitor

Model	Parameter	Wald	HR	95% CI	p value
Model 1	UA	18.29	1.30	1.15-1.47	< 0.001
Model 2	UA	0.33	1.04	0.91-1.19	0.57
	Sex	3.30	1.50	0.97-2.31	0.07
	Age	7.14	0.98	0.97-0.99	0.008
	DMN	11.27	1.91	1.31-2.79	0.001
	Baseline eGFR	11.05	0.97	0.95-0.99	0.001
	SBP	5.05	1.01	1.00-1.02	0.025
	Hb	0.06	0.99	0.88-1.10	0.82
	Alb	9.33	0.50	0.33-0.78	0.002
	Na-Cl	4.20	0.91	0.84-0.99	0.041
	P	14.93	2.04	1.42-2.93	< 0.001
	log TPU/CrU	50.76	3.26	2.36-4.51	< 0.001
	RASi	3.90	0.69	0.48-0.99	0.048

Table 3. Stratified Cox regression with three thresholds of TA-UA for 30% decline in eGFR over 2 years after trimming; Model 1: Univariate (TA-UA). Model 2: Adjusted for Sex, Sex*TA-UA. Model 3: Adjusted for Sex, Age, DMN, Baseline eGFR, SBP, Alb, P, log TPU/CrU, RASi: AIC, Akaike information criterion; TA-UA, time-averaged uric acid; DMN, diabetic nephropathy; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; Alb, serum albumin; P, serum phosphorus; log TPU/CrU, log transformed proteinuria in spot urine; RASi, use of RAS inhibitor

Threshold of TA-UA	Model	Parameter	Wald	HR	95% CI	p value
6.0 mg/dL	Model 1	TA-UA	5.86	2.44	1.19-5.02	0.016
	Model 2	TA-UA	2.73	1.92	0.89-4.15	0.10
		Sex	7.56	0.05	0.01-0.42	0.006
		Sex*TA-UA	6.45	1.49	1.10-2.02	0.011
	Model 3	TA-UA	5.76	2.61	1.19-5.71	0.016
		Sex	0.47	1.18	0.73-1.90	0.49
		Age	5.02	0.98	0.97-1.00	0.025
		DMN	8.83	1.89	1.24-2.87	0.003
		Baseline eGFR	10.61	0.97	0.96-0.99	0.001
		SBP	2.71	1.01	0.99-1.02	0.10
		Alb	9.66	0.49	0.31-0.77	0.002
		P	13.54	2.09	1.41-3.09	<0.001
		log TPU/CrU	37.86	3.13	2.18-4.50	<0.001
		RASi	6.70	0.58	0.39-0.88	0.010
	Model 1	TA-UA	5.91	2.10	1.16-3.82	0.015
	Model 2	TA-UA	0.04	1.09	0.49-2.43	0.84
		Sex	6.03	0.28	0.10-0.78	0.014
		Sex*TA-UA	4.58	3.40	1.11-10.45	0.032
	Model 3	TA-UA	5.72	2.15	1.15-4.01	0.017
		Sex	0.98	1.28	0.79-2.07	0.32
6.5 mg/dL		Age	4.92	0.98	0.97-0.99	0.026
		DMN	12.48	2.17	1.41-3.32	<0.001
		Baseline eGFR	15.58	0.97	0.95-0.98	<0.001
		SBP	2.49	1.01	0.99-1.02	0.11
		Alb	6.27	0.57	0.36-0.88	0.012
		P	10.62	2.05	1.33-3.16	0.001
		log TPU/CrU	32.30	3.10	2.10-4.57	<0.001
		RASi	3.54	0.67	0.44-1.02	0.06
	Model 1	TA-UA	13.16	2.44	1.51-3.95	<0.001
	Model 2	TA-UA	5.98	2.01	1.15-3.52	0.015
		Sex	2.14	0.17	0.02-1.84	0.14
		Sex*TA-UA	1.75	1.25	0.90-1.72	0.19
	Model 3	TA-UA	12.24	2.38	1.47-3.88	<0.001
		Sex	0.62	1.21	0.75-1.94	0.43
		Age	6.93	0.98	0.96-0.99	0.008
		DMN	12.68	2.16	1.42-3.31	<0.001
		Baseline eGFR	17.63	0.96	0.95-0.98	<0.001
		SBP	1.65	1.01	0.99-1.02	0.20
		Alb	3.71	0.64	0.41-1.01	0.05
		P	11.82	2.08	1.37-3.15	0.001
		log TPU/CrU	37.86	3.26	2.24-4.76	<0.001
7.0 mg/dL		RASi	3.72	0.99	0.44-1.01	0.05

Although some arguments exist, it is expected that this surrogate endpoint will be widely used in the clinical trial and clinical practice [9, 10]. Given the higher incidence rate, the present study vividly demonstrated that the novel surrogate endpoint was taken advantage of increasing statistical power for the analysis as short as 2 years.

Given the robust results conducted by both the multivariate Cox regression analysis and Kaplan-Meier analysis adjusted for the propensity scores, the target SUA to delay CKD progression is thought as low as 6.0 mg/dL, the value of which is lower than 6.5 mg/dL found in the our preceding study using ESRD as renal endpoint [7]. The slight difference is attributed to using the surrogate endpoint in the present study rather using the hard endpoint, ESRD, in the previous study. In fact, the patients whose TA-UA was less than 6.0 mg/dL scarcely progressed to the renal endpoint. Lowering the target value of the modifiable risk factor entails subsequent issues such as health economic problem, polypharmacy and resultant drug-induced adverse effects. The susceptibility to hyperuricemia as a higher risk for CKD progression need to be determined to avoid these problems and an individualized total care including selection of the UA-lowering drug will be the next stage of the CKD research for an efficient use of healthcare resources.

The present finding is worth consideration in light of the deteriorating mechanism of the damaged kidney induced by a variety of risk factors because the value at baseline and the value in the follow-up may impose different impacts on the CKD. Moreover, a kind of legacy effect is recently hypothesized since the intervention for hyperglycemia or hypertension persists for a longer period of time after cessation of the treatment [33, 34]. The effect of SUA, however, seems instantaneous and not long-lasting given the fact that the baseline SUA did not affect the outcome and the value in the follow-up was intimately associated with the outcome. Number needed to treat was very small indicating the large impact of controlling SUA in the follow-up. Intervening high SUA at every visit can afford the beneficial effect on

Table 4. Time-to-event survival analysis after propensity score matching; Hosmer-Lemeshow test for goodness-of-fit of propensity score modeling was $p = 0.33$, $p = 0.12$, $p = 0.69$ for 6.0, 6.5 7.0 mg/dL of TA-UA, respectively. Abbreviations: TA-UA, time-averaged uric acid; HR, hazard ratio; ARR, Absolute risk reduction; NNT, number needed to treat

Threshold of TA-UA	Low group (N/Incident)	High group (N/Incident)	HR (95% CI)	p value (stratified log-rank)	ARR (95% CI)	NNT (95% CI)
6.0 mg/dL	111/4	111/16	4.26(1.77-10.23)	< 0.001	0.10 (0.02-0.18)	10.08 (5.59-51.17)
6.5 mg/dL	113/7	113/21	3.11(1.48-6.53)	< 0.001	0.13 (0.04-0.22)	7.54 (4.52-22.82)
7.0 mg/dL	134/14	134/42	3.30(1.95-5.57)	< 0.001	0.21 (0.11-0.31)	4.18 (3.24-9.14)

Fig. 6. Kaplan-Meier plots after the propensity score matching. a) TA-UA 6.0 mg/dL, b) TA-UA 6.5 mg/dL, c) TA-UA 7.0 mg/dL. The patients at risk are shown below and p values are computed by stratified log-rank test. No censoring occurred in the present study. Abbreviation: TA-UA, time-average uric acid.

slowing down the CKD progression and clinicians can realize the usefulness of the treatment. Fine tuning risk factors by foreseeing immediate future of the individual may be warranted in the real-world clinic.

We have to mention about limitations of the present study. The biggest problem is that the number of the participants was relatively small, which could be solved by taking advantage of using surrogate endpoint. With respect to propensity score analysis the inherent problems such as potential presence of unmeasured confounding, a possibility of misspecification of the propensity score model and the remaining imbalance should be remembered. Despite these limitations, we could clearly show the impact of SUA in the follow-up. The effect of SUA on the progression of CKD could be demonstrated only by implementing propensity score analysis because the impact is too small to overlook compared with other classical risk factors such as proteinuria, hypertension and precedent renal dysfunction. The target SUA may be considered below 6.0 mg/dL in both sexes, the value of which would be confirmed in the future by an ongoing randomized controlled trial in a double-blind manner [35].

Conclusion

We have demonstrated that SUA in the follow-up is independently associated with the risk of 30% decline in eGFR over 2 years. The level of SUA should be targeted below 6.0 mg/dL irrespective of sex.

Disclosure Statement

The authors have declared that no competing interests exist.

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