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Original Article

Hyperuricemia as a Predictive Marker for Progression of Nephrosclerosis: Clinical Assessment of Prognostic Factors in Biopsy-Proven Arterial/Arteriolar Nephrosclerosis

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***Aim*: The influence of serum urate on kidney disease is attracting attention, but the effects of uric acid (UA) on nephrosclerosis have not been elucidated.**
***Methods*: We reviewed data from 45 patients diagnosed with arterial/arteriolar nephrosclerosis. The renal outcomes of the arterial/arteriolar nephrosclerosis patients were assessed by performing logistic and Cox regression analyses. A Kaplan−Meier analysis was used to evaluate the impact of hyperuricemia (HU) on kidney survival. The renal outcomes of patients with and without HU were compared by using a propensity score-matched cohort.**
***Results*: The logistic regression models showed no significant differences in renal outcomes, according to baseline parameters or follow-up parameters, except the serum UA value and body mass index (BMI). Baseline serum UA level had the highest odds ratio (OR) for estimated glomerular filtration rate (eGFR) decline (OR, 1.86; 95% confidence interval (CI), 1.12 to 3.45), among the parameters assessed. In the multivariate Cox regression analysis, HU (UA ≥ 8.0 mg/dL) (P = 0.01) and BMI (P = 0.03) were significantly associated with a ≥ 50% eGFR decline or ESRD. The Kaplan−Meier analysis in the propensity score-matched cohort indicated that the renal survival rate of the group of arterial/arteriolar nephrosclerosis patients with HU was significantly lower than that of the group without HU (log rank, P = 0.03).**
***Conclusion*: The results of this study suggest that the baseline serum UA value can serve as a renal outcome predictor in arterial/arteriolar nephrosclerosis patients.**

Key words: Arterial/arteriolar sclerosis, Biopsy, Hyperuricemia, nephrosclerosis, Prognosis

Introduction

Chronic kidney disease (CKD) is affected by multiple risk factors for disease progression[1, 2], and it is extremely important to identify these factors. Various clinical factors have been identified as independent predictors of CKD progression[3, 4], including proteinuria[5, 6], elevated serum creatinine level[5], hypertension[7], smoking[8, 9], anemia[4, 5], sex[10], race[4], genetic disorders[11], diabetes[12], metabolic syndrome[13], overweight[14, 15], and obesity[15]. The impact of serum uric acid (UA) on renal prognosis in CKD patients has attracted recent attention[16].

Nephrosclerosis is a major cause of CKD and subsequent end-stage renal disease (ESRD)[17-19]. A previous study found that 32% of patients with biopsy-proven nephrosclerosis developed ESRD during a 13-year follow-up period[17]. However, not all of the risk factors for progression of nephrosclerosis to ESRD have been identified due to lack of biopsy evidence. Regardless of the underlying etiology of CKD, the clinical risk factors of CKD progression described above may have significant predictive power for the long-term outcome of nephrosclerosis. Nevertheless, it remains difficult to predict the renal outcome of individual nephrosclerosis patients. Clinically, understanding each renal prognostic factor of the different primary diseases associated with CKD is important to

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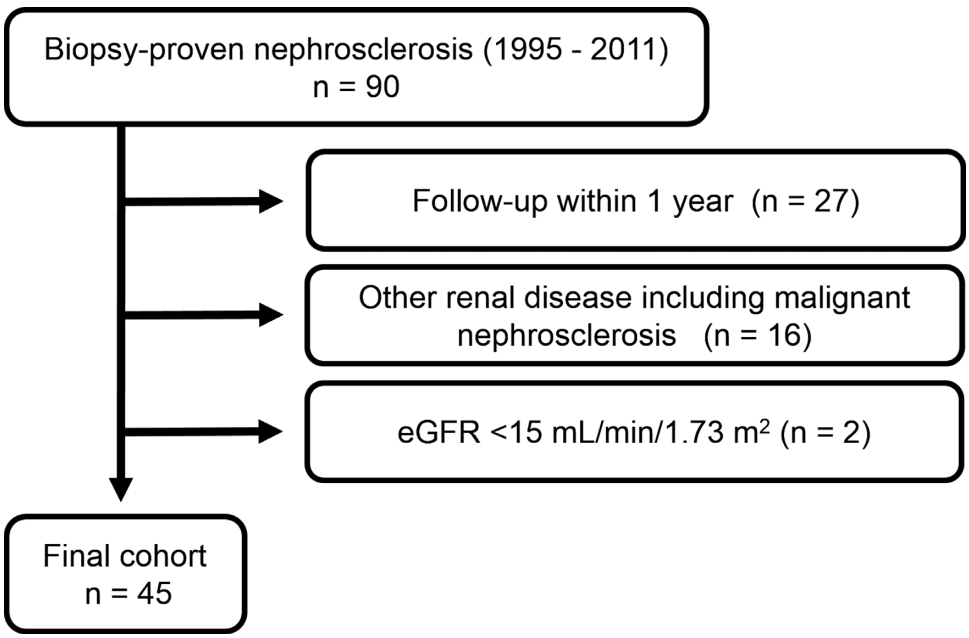

Fig. 1. Flow chart of patient selection.

The 45 patients who did not meet the entry criteria were excluded from the 90 patients screened, and the other 45 patients were deemed eligible to enter this study.

treat the individual patient meticulously. The aim of the present study was to identify clinical prognostic factors for kidney disease progression and to elucidate the predictive value of hyperuricemia (HU) in patients with biopsy-proven nephrosclerosis.

Materials and Methods

Patient Selection

We examined the cases of 90 patients diagnosed with nephrosclerosis by kidney biopsy at Tokyo Woman's Medical University Hospital between February 1995 and November 2011. All kidney tissue specimens were obtained by percutaneous needle biopsy. Nephrosclerosis was diagnosed on the basis of renal pathology showing sclerosis of renal arterioles and small arteries[20]. The inclusion criteria in the present study were: (1) duration of follow-up ≥ 1 year (which excluded 27 patients), (2) absence of any other renal disease, including malignant nephrosclerosis (which excluded 16 patients), and (3) estimated glomerular filtration rate (eGFR) ≥ 15 mL/min/1.73 m^2 (which excluded 2 patients). The remaining 45 patients who met these criteria were ultimately enrolled in the present study (**Fig. 1**). eGFR for patients was calculated as previously described[21].

The subjects' human rights and methods of protecting personal information were well considered. All the relevant and responsible staff adhered to the Helsinki Declaration (amended October 2013) and the Ethical Guidelines for Clinical Studies (revised July 31, 2008, referred to hereafter as the Clinical Studies Ethical Guidelines) in the execution of this study. This cohort study was approved by the Medical Ethics Committee of Tokyo Women's Medical University (#3667). Written informed consent for renal biopsy and use of clinical data at the time of the kidney biopsy, as well as subsequent histological data, was obtained from all patients.

Measurements of Covariates

The clinical parameters assessed at the time of the kidney biopsy (baseline) were as follows: age, gender, systolic blood pressure (SBP), diastolic blood pressure (DBP), body mass index (BMI), eGFR, serum creatinine, urea nitrogen, albumin, UA, total cholesterol (TC), LDL cholesterol (LDL-C), HDL cholesterol (HDL-C), triglyceride (TG) levels, and proteinuria (g/day). We also investigated concomitant drug use and comorbidities at the time of the kidney biopsy[22, 23]. The concomitant drugs were antihypertensive drugs, diuretics, and drugs for the treatment of hyperuricemia, dyslipidemia, and diabetes mellitus. Comorbidities are defined in the next section.

The clinical parameters assessed at the time of the 6-month follow-up examinations were as follows: SBP, DBP, BMI, eGFR, eGFR slope per year, and serum creatinine, albumin, UA, TC, LDL-C, HDL-

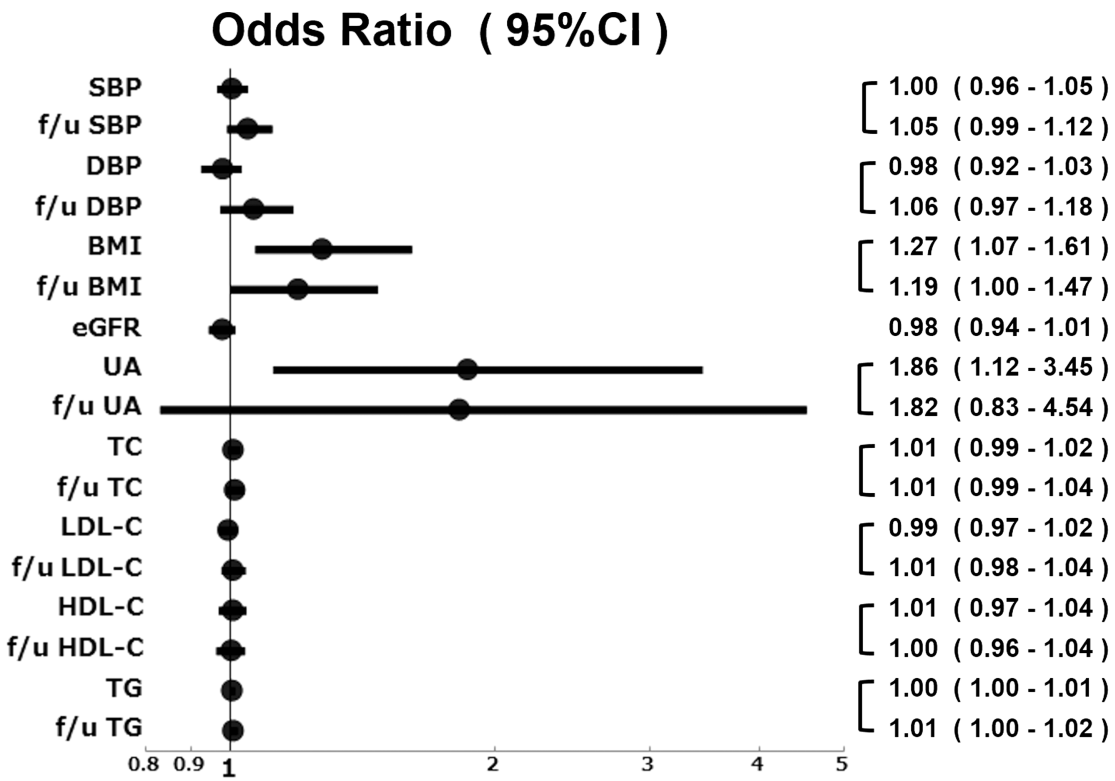

Fig. 2. Odds ratio for a decline in eGFR by ≥ 50% from baseline or end-stage renal disease during the follow-up examination period.

C, and TG levels.

Definition of Comorbidities

Hypertension: Being treated with an oral antihypertensive agent, SBP ≥ 140 mmHg, DBP ≥ 90 mmHg

Hyperuricemia (HU): Being treated with an oral antihyperuricemic agent, serum UA level ≥ 6.0 mg/dL, serum UA level ≥ 7.0 mg/dL, or serum UA level ≥ 8.0 mg/dL

Hypercholesterolemia: Being treated with an oral antidyslipidemic agent, serum TC level ≥ 220 mg/dL, or serum LDL level ≥ 140 mg/dL

Hypertriglyceridemia: Being treated with an oral antidyslipidemic agent or a serum TG level ≥ 150 mg/dL

Diabetes mellitus: Being treated with an antidiabetic agent or a history of diagnosis with diabetes mellitus

Outcome Evaluation (Endpoint)

The outcome variable of interest was kidney disease progression, defined as a ≥ 50% decline in eGFR from baseline (≥ 50% eGFR decline) or ESRD requiring dialysis.

Statistical Analysis

Continuous variables are reported as the mean ± SD, and categorical variables are reported as percentages, unless otherwise stated. We compared participant outcomes by performing an unpaired *t*-test, chi-square test, or Fisher's exact test. The patients whose renal outcome was a ≥ 50% eGFR decline or ESRD were assigned to the poor outcome group. The patients whose renal outcome was not a ≥ 50% eGFR decline or ESRD were assigned to the benign outcome group. Data are expressed as the mean ± standard deviation (SD). Logistic-regression models were prepared to estimate the risk of ≥ 50% eGFR decline or ESRD associated with baseline and follow-up parameters, including clinical and laboratory variables.

Our principal goal was to determine whether the baseline serum UA value is a prognostic indicator in nephrosclerosis patients. The optimal cut-off serum UA value for discriminating ≥ 50% eGFR decline or ESRD during follow-up examination was determined by performing receiver operating characteristic (ROC) analyses. Patients were divided into an HU group (i.e., a group of patients being treated with an oral antihyperuricemic agent or whose UA level was ≥ 8.0 mg/dL) and a non-HU group (i.e., a group of patients

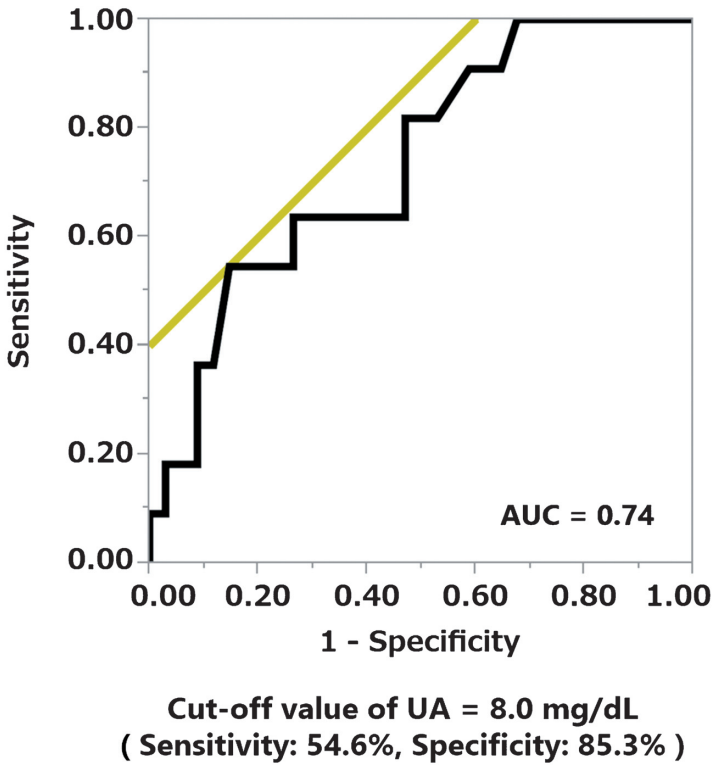

Fig. 3. Receiver operating characteristic analysis to identify the optimal serum uric acid cut-off value for predicting an eGFR decline by ≥50% from baseline or end-stage renal disease during the follow-up examination period.

being not treated with an oral administration antihyperuricemic agent or whose UA value was <8.0 mg/dL). We compared participant characteristics of the two groups using the unpaired *t*-test, chi-square test, or Fisher's exact test. Prognostic variables for renal outcome were assessed by the univariate and multivariate Cox proportional hazards method. We included covariates for age, sex, BMI, eGFR, urine protein, and comorbidities, including HU, at baseline in Cox proportional hazards models. Variables with *P*-values of less than 0.1 in the univariate model were included in the multivariate model. The renal outcome, which was a ≥50% eGFR decline or ESRD and interval estimates between the HU group and the non-HU group, was calculated by the Kaplan–Meier method and evaluated by the log-rank test.

To further assess whether the associations were consistent across clinically matched subgroups, we fit propensity score-matched models that included several potential modifying variables (age, sex, eGFR, SBP, and BMI) and performed subgroup analyses of the groups. The caliper-matching method was used with a maximum tolerance level of 0.2. The standardized differences were calculated to assess the appropriateness of matching. The 95% confidence intervals (CIs) were calculated. *P* values <0.05 were considered statistically significant. All statistical analyses were performed by using the JMP Pro ver.12.1.0 software program (SAS Institute, Cary, NC, USA).

Results

Patients

The 45 subjects consisted of 29 males and 16 females, and their mean age at the time of the kidney biopsy was 49.4±12.5 years (range 16–67 years). The mean SBP was 136.1±17.3 mmHg, DBP 83.4±14.6 mmHg, BMI 25.7±4.3 kg/m^2, proteinuria 0.8±0.8 g/day, and eGFR 54.6±21.0 mL/min/1.73 m^2 (**Supplemental Table 1**). The concomitant drug data showed that 38 were being treated with an antihypertensive agent, 14 with an antihyperuricemic agent, 16 with an antidyslipidemic agent, 22 with an antiplatelet agent, 2 with an antidiabetic agent, and 3 with a diuretic. The comorbidity data showed that 41 patients had hypertension; 18 had severe HU (UA ≥8 mg/dL or treatment with an antihyperuricemic agent); 25 had hypercholesterolemia; 24 had hypertriglyceride-

Table 1. Univariate and multivariate analysis of risk factors associated with ≥50% eGFR decline or ESRD (Total cohort $n=45$)

Variables	Univariate analysis		Multivariate analysis	
	Hazard Ratio (95% CI)	*P*-value	Hazard Ratio (95% CI)	*P*-value
Age (1 year increase)	1.04 (0.99−1.11)	0.2	−	−
Male (vs. female)	0.74 (0.21−2.93)	0.7	−	−
BMI (1 kg/m^2 increase)	1.22 (1.07−1.41)	0.003	1.30 (1.01−1.68)	0.03
eGFR (1 mL/min/1.73 m^2 increase)	0.98 (0.95−1.02)	0.3	−	−
U-Prot (1 g/day increase)	2.24 (1.19−4.10)	0.009	2.07 (0.85−5.75)	0.1
Hypertension (vs. no)	1.83 (0.32−35.5)	0.6	−	−
Hypercholesterolemia (vs. no)	6.68 (1.59−45.8)	0.02	2.42 (0.52−18.9)	0.3
Hypertriglyceridemia (vs. no)	2.50 (0.68−11.8)	0.2	−	−
Diabetes mellitus (vs. no)	1.04 (0.27−3.50)	1.0	−	−
Hyperuricemia (UA ≧8 mg/dL) (vs. no)	5.81 (1.57−27.6)	0.01	18.2 (2.68−278.8)	0.01

Abbreviation: CI=confidence interval; BMI, body mass index; eGFR, estimated glomerular filtration rate; U-Prot, urinary protein excretion; vs, versus

mia; and 10 had diabetes mellitus. The overall follow-up period was 6.8±4.5 years. The rate of progression as measured by eGFR slope was −2.6±3.1 mL/min/1.73 m^2/year, and 11 patients had reached the endpoint (≥50% eGFR decline or ESRD) during the follow-up period.

Comparison of the Clinical and Pathological Findings between Groups According to Renal Outcome

The results of the comparison of clinical and laboratory findings at the time of the kidney biopsy in the two groups according to renal outcome are summarized in **Supplemental Table 1**. The following values were significantly higher in the poor outcome group than in the benign outcome group: BMI (28.8±4.3 vs. 24.7±3.9 kg/m^2, $P=0.005$), UA (7.7±1.4 vs. 6.5±1.3 mg/dL, $P=0.02$), proteinuria (1.29±0.97 vs. 0.69±0.70 g/day, $P=0.03$), f/u BMI (27.6±3.6 vs. 25.0±3.8 kg/m^2, $P<0.05$), and eGFR slope (−5.4±2.6 vs. −1.8±2.8 mL/min/1.73 m^2/year, $P=0.0004$). There were no significant differences between the groups in any of the other parameters.

Baseline Parameters and Serum Uric Acid Cut-Off Value as an Indicator of Kidney Disease Progression

We assessed the baseline and follow-up parameters of the nephrosclerosis patients. The logistic regression models showed no significant differences between the groups in any of the baseline parameters and follow-up parameters except BMI and serum UA level (**Fig. 2**). The baseline serum UA value yielded the highest odds for a ≥50% eGFR decline or ESRD (OR, 1.86; 95% CI, 1.12 to 3.45). Based on these results, we decided to use baseline parameters to predict kidney disease progression. We performed ROC analyses to identify the optimal UA cut-off value for discriminating a ≥50% eGFR decline or ESRD during the follow-up examination. The results of the ROC analyses showed that the optimal UA cut-off value was 8.0 mg/dL (AUC=0.74, sensitivity=54.6%, specificity=85.3%, **Fig. 3**).

Hyperuricemia as a Prognostic Indicator in Nephrosclerosis Patients

To determine whether severe HU (UA ≥8.0 mg/dL) at the time of the renal biopsy was an independent predictor of a decline in renal function, we performed univariate and multivariate regression analyses based on the Cox hazard model for associations between the clinical findings and a ≥50% eGFR decline or ESRD during the follow-up (**Table 1**). The results showed that HU [Hazard Ratio (HR)=18.2, $P=0.01$] and BMI (HR=1.30, $P=0.03$) were significantly associated with a ≥50% eGFR decline or ESRD.

Comparison between the Clinical Findings in Groups According to Serum Uric Acid Levels in the Total Cohort

We compared the clinical characteristics of two groups according to the UA value at the time of the kidney biopsy (**Table 2**). The serum UA levels (7.8±1.3 vs. 6.5±1.1 mg/dL, $P=<0.0001$), blood urea nitrogen levels (22.5±7.4 vs. 17.2±5.8 mg/dL, $P=0.01$), and serum creatinine levels (1.35±0.40 vs. 1.10±0.37 mg/dL, $P=0.04$) were significantly higher in the HU group than in the non-HU group, and eGFR (46.4±17.9 vs. 60.0±21.5 mL/min/1.73 m^2,

Table 2. Patient characteristics divided by uric acid status at the kidney biopsy (Total cohort $n=45$)

Variables	Total cohort				
	Total $n=45$	HU (UA ≧8 mg/dL) $n=18$	Non HU (UA <8 mg/dL) $n=27$	*P*-value	Standardized Differences
Clinical Findings					
Age (years)	49.4±12.5	50.4±13.2	48.8±12.2	0.7	0.126
Gender (Male; %)	64.4	61.1	66.7	0.7	0.117
SBP (mmHg)	136.1±17.3	133.8±17.5	137.7±17.2	0.5	0.225
DBP (mmHg)	83.4±14.6	80.5±10.9	85.3±16.6	0.4	0.342
BMI (kg/m^2)	25.7±4.3	26.4±4.0	25.3±4.6	0.4	0.255
Laboratory Findings					
Serum Albumin (g/dL)	4.1±0.4	4.1±0.4	4.1±0.4	1.0	0.000
Blood Urea Nitrogen (mg/dL)	19.3±6.9	22.5±7.4	17.2±5.8	0.01	0.797
Serum Creatinine (mg/dL)	1.20±0.40	1.35±0.40	1.10±0.37	0.04	0.649
eGFR (mL/min/1.73 m^2)	54.6±21.0	46.4±17.9	60.0±21.5	0.03	0.687
Uric Acid (mg/dL)	6.8±1.4	7.8±1.3	6.1±1.1	<0.0001	1.412
Total Cholesterol (mg/dL)	218.4±42.4	223.2±36.1	215.1±46.5	0.5	0.195
LDL Cholesterol (mg/dL)	124.5±31.2	126.7±25.8	123.0±34.7	0.2	0.121
HDL Cholesterol (mg/dL)	51.1±18.9	54.1±24.6	49.1±14.1	0.4	0.249
Triglyceride (mg/dL)	199.0±116.7	218.5±94.1	186.0±129.7	0.4	0.287
Proteinuria (g/day)	0.84±0.80	0.94±0.69	0.77±0.88	0.5	0.215
Concomitant drugs					
Antihypertensive agent (%)	84.4	94.4	77.8	0.1	0.494
Antihyperuricemic agents (%)	31.1	77.8	0.0	<0.0001	2.647
Antidyslipidemic agents (%)	35.6	50.0	25.9	0.1	0.513
Antiplatelet agent (%)	48.9	61.1	40.7	0.2	0.417
Antidiabetic agents (%)	4.4	5.6	3.7	0.8	0.090
Diuretics (%)	6.7	16.7	0.0	0.03	0.633
Comorbidities					
Hypertension (%)	91.1	94.4	88.9	0.5	0.200
HU (UA ≧8 mg/dL) (%)	40.0	100.0	0.0	<0.0001	–
Hypercholesterolemia (%)	55.6	66.7	48.1	0.2	0.383
Hypertriglyceridemia (%)	53.3	66.7	44.4	0.1	0.461
Diabetes mellitus (%)	22.2	22.2	22.2	1.0	0.000
Clinical Findings (Follow-up Data)					
f/u SBP (mmHg)	127.3±13.0	127.8±10.9	126.9±14.4	0.8	0.070
f/u DBP (mmHg)	77.5±8.3	77.7±6.5	77.3±9.4	0.9	0.049
f/u BMI (kg/m^2)	25.6±3.9	25.9±4.3	25.5±3.6	0.4	0.101
Laborator Findings (Follow-up Data)					
f/u Serum Albumin (g/dL)	4.2±0.3	4.2±0.4	4.2±0.3	0.8	0.000
f/u Uric Acid (mg/dL)	6.3±1.0	6.6±1.1	6.2±0.9	0.1	0.398
f/u Total Cholesterol (mg/dL)	198.6±31.4	205.0±35.9	194.1±27.8	0.3	0.339
f/u LDL Cholesterol (mg/dL)	108.9±25.1	111.0±23.7	107.5±26.5	0.7	0.139
f/u HDL Cholesterol (mg/dL)	59.2±20.5	59.8±20.5	58.7±21.1	0.9	0.053
f/u Triglyceride (mg/dL)	170.0±68.2	180.5±72.2	162.4±65.6	0.4	0.262

$P=0.03$) was significantly lower in the HU group than in the non-HU group. The percentages of patients being treated with an antihyperuricemic agent (77.8% vs. 0.0%, $P<0.0001$) and a diuretic (16.7% vs. 0.0%, $P=0.03$) were significantly higher in the HU group than non-HU group.

(Cont Table 2)

(Propensity score matched cohort $n=30$)					
Variables	Propensity score matched cohort				
	Total $n=30$	HU (UA ≧8 mg/dL) $n=15$	Non HU (UA <8 mg/dL) $n=15$	*P*-value	Standardized Differences
Clinical Findings					
Age (years)	49.9±12.1	48.3±13.3	51.5±11.0	0.5	0.262
Gender (Male; %)	66.7	66.7	66.7	1.0	0.000
SBP (mmHg)	135.7±18.4	135.2±18.0	136.3±19.5	0.9	0.059
DBP (mmHg)	82.5±14.9	81.1±11.1	83.9±18.3	0.6	0.185
BMI (kg/m^2)	26.4±4.8	26.6±4.3	26.2±5.5	0.8	0.081
Laboratory Findings					
Serum Albumin (g/dL)	4.1±0.4	4.1±0.4	4.1±0.4	0.8	0.000
Blood Urea Nitrogen (mg/dL)	19.9±7.0	21.1±7.1	18.7±6.9	0.3	0.343
Serum Creatinine (mg/dL)	1.27±0.38	1.27±0.39	1.27±0.38	1.0	0.000
eGFR (mL/min/1.73 m^2)	49.9±18.1	50.0±17.1	49.9±19.7	1.0	0.005
Uric Acid (mg/dL)	7.1±1.3	7.8±1.2	6.5±1.1	0.004	1.129
Total Cholesterol (mg/dL)	219.0±42.3	222.7±31.8	215.2±51.6	0.6	0.175
LDL Cholesterol (mg/dL)	123.7±29.3	125.0±25.9	122.3±33.3	0.8	0.091
HDL Cholesterol (mg/dL)	50.7±20.0	56.0±25.8	45.3±10.1	0.1	0.546
Triglyceride (mg/dL)	213.4±129.9	216.3±93.0	210.5±162.1	0.9	0.044
Proteinuria (g/day)	0.88±0.86	0.88±0.69	0.89±1.02	1.0	0.011
Concomitant drugs					
Antihypertensive agent (%)	86.7	100.0	73.3	0.03	0.854
Antihyperuricemic agents (%)	36.7	73.3	0.0	<0.0001	2.343
Antidyslipidemic agents (%)	36.7	46.7	26.7	0.3	0.424
Antiplatelet agent (%)	46.7	53.3	40.0	0.5	0.269
Antidiabetic agents (%)	6.7	6.7	6.7	1.0	0.000
Diuretics (%)	3.3	6.7	0.0	0.3	0.379
Comorbidities					
Hypertension (%)	93.3	100.0	86.7	0.1	0.554
HU (UA ≧8 mg/dL) (%)	50.0	100.0	0.0	<0.0001	−
Hypercholesterolemia (%)	53.3	66.7	40.0	0.1	0.555
Hypertriglyceridemia (%)	58.6	73.3	42.9	0.1	0.648
Diabetes mellitus (%)	26.7	20.0	33.3	0.4	0.304
Clinical Findings (Follow-up Data)					
f/u SBP (mmHg)	128.5±13.3	127.1±11.4	130.2±15.5	0.6	0.228
f/u DBP (mmHg)	78.1±7.8	77.9±6.6	78.3±9.2	0.9	0.050
f/u BMI (kg/m^2)	26.0±4.4	26.1±4.7	26.0±4.3	0.9	0.022
Laborator Findings (Follow-up Data)					
f/u Serum Albumin (g/dL)	4.3±0.3	4.2±0.4	4.3±0.2	0.6	0.316
f/u Uric Acid (mg/dL)	6.5±0.8	6.7±0.8	6.3±0.8	0.1	0.500
f/u Total Cholesterol (mg/dL)	197.1±34.3	202.0±36.6	191.3±32.1	0.5	0.311
f/u LDL Cholesterol (mg/dL)	108.2±24.9	108.3±22.2	108.2±28.6	1.0	0.004
f/u HDL Cholesterol (mg/dL)	58.2±17.7	60.6±21.7	55.3±11.9	0.5	0.303
f/u Triglyceride (mg/dL)	177.9±73.8	177.5±73.8	178.3±76.8	1.0	0.011

Continuous values are expressed as means±standard deviation. Count data are expressed as percentages. Abbreviation: HU (UA ≧8 mg/dL), Hyperuricemia (Uric Acid ≧8 mg/dL or with treatments); Non HU (UA <8 mg/dL), Non Hyperuricemia (Uric Acid <8 mg/dL or without treatments); n, number; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; eGFR, estimated glomerular filtration rate; f/u, follow-up

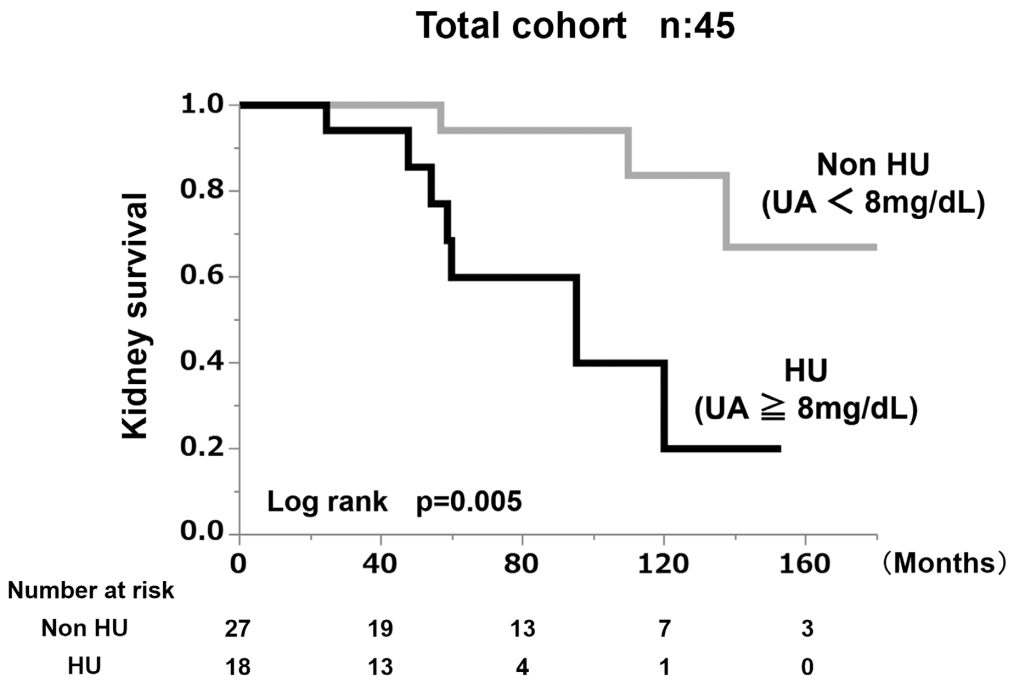

Fig. 4A. Kidney survival rate of the group with serum uric acid levels >8 mg/dL and the group with serum uric acid levels <8 mg/dL in the total cohort.

We performed a Kaplan–Meier analysis to assess kidney survival with a ≥50% eGFR decline or ESRD as the end-point. According to the kidney survival curves, the kidney survival rate of the nephrosclerosis patients in the HU group was significantly lower than in the non-HU group (**Fig. 4A**). At the 10-year follow-up examination, at least a 50% decrease in eGFR value was observed in 80% of the HU group (log rank, $P=0.005$).

Comparison between the Clinical and Laboratory Findings in Groups According to Serum Uric Acid Levels in the Propensity Score-Matched Cohort

Since the serum UA levels may have been affected by age, sex, BMI, SBP, and kidney function, we created a propensity score-matched cohort of HU patients and non-HU patients. Comparisons between the clinical and laboratory findings at the time of kidney biopsy in the two groups are summarized in **Table 2**. There were no significant differences between the propensity score-matched groups in any of the parameters except the parameters associated with UA level and BMI value. The serum UA level in the HU group (7.8±1.2 mg/dL) was significantly higher than in the non-HU group (6.5±1.1 mg/dL, $P=0.004$). The percentage of patients being treated with an antihyperuricemic agent (73.3% vs. 0.0%, $P<0.0001$) was higher in the HU group than in the non-HU group. In this propensity score-matched cohort, we also performed univariate and multivariate regression analyses based on the Cox hazard model for associations between the clinical findings and a ≥50% eGFR decline or ESRD during the follow-up (**Table 3**). As is the case with the total cohort, HU (HR=17.7, $P=0.02$) was significantly associated with a ≥50% eGFR decline or ESRD.

Lastly, we performed a Kaplan–Meier analysis to assess kidney survival with a ≥50% eGFR decline or ESRD as the end-point. According to the kidney survival curves, the kidney survival rate of the HU group of nephrosclerosis patients was significantly lower than in the non-HU group (**Fig. 4B**). At the 10-year follow-up examination, there was at least a 50% decrease in eGFR value or ESRD in 81.4% of the HU patients (log rank, $P=0.03$).

Discussion

Several problems need to be solved in the research on nephrosclerosis. The first problem is that the diagnosis of nephrosclerosis is generally made on the basis of the characteristic clinical features, and confirmation by renal biopsy is rarely indicated. As a result, the pathophysiology of nephrosclerosis has not been fully elucidated.

The second problem is that there are several different opinions regarding the pathological diagnosis of nephrosclerosis[20, 24-27]. Because arterial and arteriolar

Table 3. Univariate and multivariate analysis of risk factors associated with ≥50% eGFR decline or ESRD (Propensity score matched cohort $n=30$)

Variables	Univariate analysis		Multivariate analysis	
	Hazard Ratio (95% CI)	*P*-value	Hazard Ratio (95% CI)	*P*-value
Age (1 year increase)	1.03 (0.98−1.10)	0.2	−	−
Male (vs. female)	0.60 (0.17−2.26)	0.4	−	−
BMI (1 kg/m^2 increase)	1.19 (1.04−1.36)	0.01	1.25 (0.96−1.62)	0.1
eGFR (1 mL/min/1.73 m^2 increase)	0.99 (0.96−1.03)	0.7	−	−
U-Prot (1 g/day increase)	1.91 (1.00−3.52)	0.04	2.20 (0.85−6.70)	0.1
Hypertension (vs. no)	1.53 (0.25−30.4)	0.7	−	−
Hypercholesterolemia (vs. no)	6.49 (1.57−44.0)	0.02	3.08 (0.61−27.7)	0.2
Hypertriglyceridemia (vs. no)	3.39 (0.90−16.3)	0.09	0.22 (0.03−1.75)	0.1
Diabetes mellitus (vs. no)	1.05 (0.27−3.50)	0.9	−	−
Hyperuricemia (UA ≧8 mg/dL) (vs. no)	4.14 (1.10−19.9)	0.04	17.7 (2.26−307.4)	0.02

Abbreviation: CI=confidence interval; BMI, body mass index; eGFR, estimated glomerular filtration rate; U-Prot, urinary protein excretion; vs, versus

sclerosis is generally accompanied by global glomerulosclerosis and interstitial fibrosis, glomerular and interstitial lesions tend to be included among the diagnostic criteria for nephrosclerosis, but their inclusion may cause confusion influenced by aging, primary glomerular disease, or primary interstitial disease. We chose simple diagnostic criteria for nephrosclerosis focusing on initiators of kidney injury. In the present study, nephrosclerosis was defined as the renal pathology associated with sclerosis of renal arterioles and small arteries from the pathophysiological point[20].

The third problem, which is the main topic of this study, is that arterial/arteriolar nephrosclerosis can be influenced by various causes and multiple risk factors. Arterial/arteriolar nephrosclerosis is usually associated with hypertension[20, 28]. Hypertension is thought to be both a cause of arterial/arteriolar nephrosclerosis and a renal prognostic factor[29]. On the other hand, Hsu doubted the conventional theory that non-malignant hypertension is a common cause of CKD and ESRD, because there is little evidence[30], and Tracy *et al.* reported finding that arterial/arteriolar nephrosclerosis precedes the development of hypertension[31]. Furthermore, renal vascular lesions are sometimes observed in the absence of hypertension in animal models[32].

Based on the definition of nephrosclerosis as renal pathology associated with sclerosis of renal arterioles and small arteries[20], we postulate that the etiology of arterial/arteriolar nephrosclerosis is multifactorial. In addition to hypertension[33], other clinical factors, including aging[26, 34], systemic atherosclerosis[35], systemic vasculitis[36, 37], obesity[38], and diabetes mellitus[39], may contribute to development of the pathological features of arterial/arteriolar nephrosclerosis. In the same manner, we also consider that arterial/arteriolar nephrosclerosis can have multiple renal risk factors. Since there is little evidence regarding prognostic risk factors of biopsy-proven nephrosclerosis, we attempted to identify clinical prognostic risk factors for biopsy-proven arterial/arteriolar nephrosclerosis, focusing especially on the UA level.

The results of our multivariate analysis of the Cox proportional hazards model showed that HU ($P=0.01$) and BMI ($P=0.03$) were significantly associated with a ≥50% eGFR decline or ESRD in the patients with biopsy-proven arterial/arteriolar nephrosclerosis (**Table 1**). Since the blood pressure of our cohort was relatively well controlled (mean SBP/DBP=136/83 mmHg) with antihypertensive agents (84.4%), hypertension was not a significant prognostic risk factor. Rather, HU was proved to be the most significant prognostic risk factor of arterial/arteriolar nephrosclerosis in the blood pressure-controlled cohort. Furthermore, the Kaplan−Meier analysis showed that the kidney survival rate of the biopsy-proven arterial/arteriolar nephrosclerosis patients with HU was significantly lower than that of arterial/arteriolar nephrosclerosis patients without HU in a propensity-matched cohort (**Fig. 4B**; $P=0.03$).

HU has been found to be a risk factor for development of hypertension[40-43], and the results of several epidemiologic studies have indicated the existence of an association between the development of CKD and HU[44, 45]. HU has been found to independently predict the progression of kidney disease in diabetic

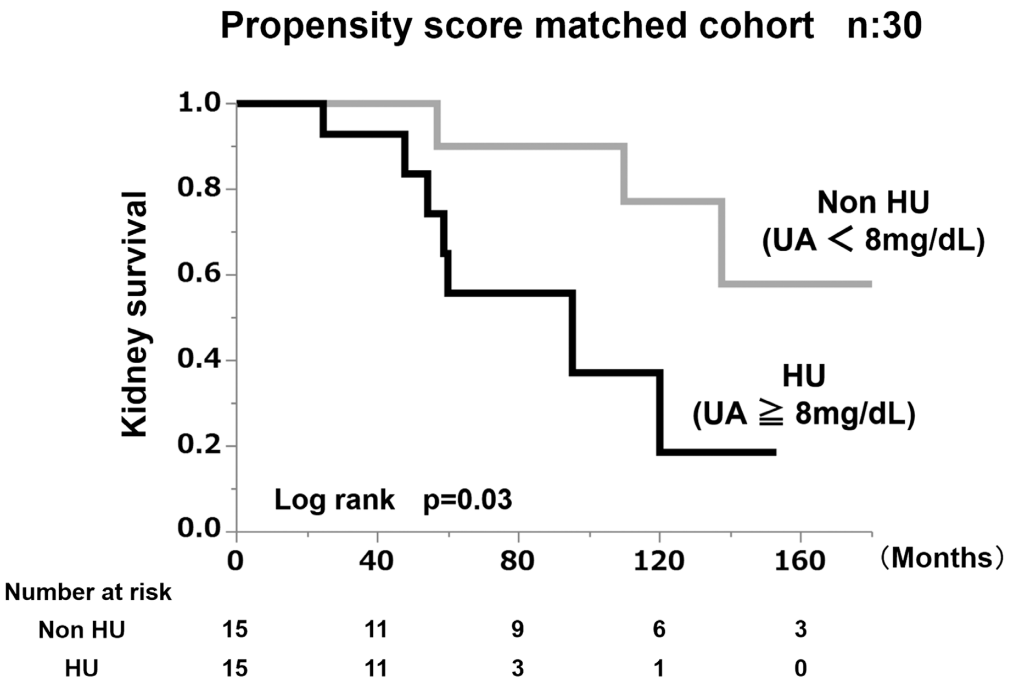

Fig. 4B. Kidney survival rate of the group with serum uric acid value >8 mg/dL and the group with serum uric acid <8 mg/dL in the propensity score-matched cohort.

nephropathy[46, 47], IgA nephropathy[48-51], chronic allograft nephropathy[52], and CKD[45, 53, 54]. However, although HU has been associated with the presence of kidney arteriolar sclerosis[33, 50, 55, 56] in CKD patients, there is little evidence of an association between UA and disease progression of biopsy-proven nephrosclerosis. In animal models, HU has been found to induce systemic hypertension and afferent arteriolar sclerosis[57, 58]. Although the precise mechanism of the nephrotoxicity of HU has not been fully elucidated, recent data showed a direct harmful effect of UA on endothelial cells[59] and smooth muscle cells[60]. In humans, it has been reported that serum uric acid level is independently associated with an elevated carotid intima-media thickness[61]. Therefore, UA injures renal vessels, which are the major lesion of arterial/arteriolar nephrosclerosis.

Conclusion

In conclusion, the results obtained by using a propensity score-matched cohort in the present study showed that HU is a clinical predictive marker for progression of biopsy-proven arterial/arteriolar nephrosclerosis. Since treatment of hypertension has recently become widespread, treatment for HU will become more important in patients with arterial/arteriolar nephrosclerosis.

Competing Interests

The authors have declared that no competing interests exist.

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Supplemental Table 1. Baseline and follow-up patient characteristics according to renal outcome

Variables	Total $n=45$	Poor outcome $n=11$	Benign outcome $n=34$	*P*-value
Clinical Findings				
Age (years)	− 49.4 ± 12.5	− 53.8 ± 9.0	− 48.0 ± 13.3	− 0.2
Gender (Male; %)	− 64.4	− 63.6	− 64.7	− 0.9
SBP (mmHg)	− 136.1 ± 17.3	− 137.1 ± 15.4	− 135.8 ± 18.0	− 0.8
DBP (mmHg)	− 83.4 ± 14.6	− 80.5 ± 12.2	− 84.3 ± 15.4	− 0.5
BMI (kg/m^2)	− 25.7 ± 4.3	− 28.8 ± 4.3	− 24.7 ± 3.9	− 0.005
Laboratory Findings				
Serum Albumin (g/dL)	− 4.1 ± 0.4	− 4.1 ± 0.4	− 4.1 ± 0.4	− 0.9
Blood Urea Nitrogen (mg/dL)	− 19.3 ± 6.9	− 21.5 ± 7.8	− 18.6 ± 6.6	− 0.2
Serum Creatinine (mg/dL)	− 1.20 ± 0.40	− 1.23 ± 0.33	− 1.19 ± 0.43	− 0.8
eGFR (mL/min/1.73 m^2)	− 54.6 ± 21.0	− 48.2 ± 15.0	− 56.6 ± 22.4	− 0.2
Uric Acid (mg/dL)	− 6.8 ± 1.4	− 7.7 ± 1.4	− 6.5 ± 1.3	− 0.02
Total Cholesterol (mg/dL)	− 218.4 ± 42.4	− 228.9 ± 50.9	− 214.9 ± 39.5	− 0.3
LDL Cholesterol (mg/dL)	− 124.5 ± 31.2	− 120.7 ± 29.6	− 125.8 ± 32.0	− 0.6
HDL Cholesterol (mg/dL)	− 51.1 ± 18.9	− 53.0 ± 27.7	− 50.5 ± 15.5	− 0.7
Triglyceride (mg/dL)	− 199.0 ± 116.7	− 249.7 ± 177.0	− 182.6 ± 116.7	− 0.1
Proteinuria (g/day)	− 0.84 ± 0.80	− 1.29 ± 0.97	− 0.69 ± 0.70	− 0.03
Concomitant drugs				
Antihypertensive agents (%)	− 84.4	− 90.9	− 82.4	− 0.5
Antihyperuricemic agents (%)	− 31.1	− 36.4	− 29.4	− 0.7
Antidyslipidemic agents (%)	− 35.6	− 54.5	− 29.4	− 0.1
Antiplatelet agents (%)	− 48.9	− 72.7	− 41.2	− 0.1
Antidiabetic agents (%)	− 4.4	− 9.1	− 2.9	− 0.4
Diuretics (%)	− 6.7	− 9.1	− 5.9	− 0.7
Comorbidities				
Hypertension (%)	− 91.1	− 90.9	− 91.2	− 1.0
Hyperuricemia (UA ≧ 8 mg/dL) (%)	− 40.0	− 63.6	− 32.4	− 0.1
Hypercholesterolemia (%)	55.6	72.7	50.0	0.2
Hypertriglyceridemia (%)	53.3	63.6	50.0	0.4
Diabetes mellitus (%)	22.2	36.4	17.6	0.2
Clinical Findings (Follow-up Data)				
f/u SBP (mmHg)	127.3 ± 13.0	133.0 ± 9.5	125.5 ± 13.5	0.1
f/u DBP (mmHg)	77.5 ± 8.3	80.4 ± 6.8	76.5 ± 8.6	0.2
f/u BMI (kg/m^2)	25.6 ± 3.9	27.6 ± 3.6	25.0 ± 3.8	0.048
Laboratory Findings (Follow-up Data)				
f/u Serum Albumin (g/dL)	4.2 ± 0.3	4.1 ± 0.3	4.2 ± 0.3	0.5
f/u Uric Acid (mg/dL)	6.3 ± 1.0	6.7 ± 0.8	6.2 ± 1.0	0.2
f/u Total Cholesterol (mg/dL)	198.6 ± 31.4	207.0 ± 28.8	195.6 ± 32.2	0.3
f/u LDL Cholesterol (mg/dL)	108.9 ± 25.1	112.5 ± 20.2	108.0 ± 26.4	0.7
f/u HDL Cholesterol (mg/dL)	59.2 ± 20.5	60.2 ± 21.2	58.9 ± 20.7	0.9
f/u Triglyceride (mg/dL)	170.0 ± 68.2	197.6 ± 89.8	161.6 ± 59.4	0.1
eGFR slope (mL/min/1.73 m^2/year)	− 2.6 ± 3.1	− 5.4 ± 2.6	− 1.8 ± 2.8	0.0004

Continuous values are expressed as means ± standard deviation. Count data are expressed as percentages. Abbreviation: n, number; SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; eGFR, estimated glomerular filtration rate; HU (UA ≧ 8 mg/dL), Hyperuricemia (Uric Acid ≧ 8 mg/dL or with treatments); f/u, follow-up