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The effect of trajectory of serum uric acid on survival and renal outcomes in patients with stage 3 chronic kidney disease

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Abstract

Uric acid (UA) is associated with renal disease and patient survival, but the causal associations remain unclear. Also, the longitudinal UA control (trajectory) is not well understood.

We enrolled 808 subjects diagnosed with stage 3 chronic kidney disease from 2007 to 2017. We plotted the mean UA over a period of 6 months with a minimum requirement of 3 samples of UA. From the sampled points, we generated an interpolated line for each patient by joining mean values of UA levels over time. Using lines from all patients, we classified them into 3 groups of trajectories (low, medium, and high) through group-based trajectory modeling, and then we further separated them into either treatment or nontreatment subgroups. Due to multiple comparisons, we performed post hoc analysis by Bonferroni adjustment. Using univariate competing-risks regression, we calculated the competing risk analysis with subdistribution hazard ratio of possible confounders.

All of the 6 trajectories appeared showed a gradual decline in function over time without any of the curves crossing over one another. For all-cause mortality risk, none of the variables (including age, gender, coronary arterial disease, cerebrovascular disease, diabetes mellitus, renin–angiotensin–aldosterone system inhibitors, trajectories of UA, and treatment of UA) were statistically significant. All 6 trajectories appeared as steady curves without crossovers among them over the entire period of follow-up. Patients with diabetes mellitus were statistically more likely to undergo dialysis. The only trend was seen in the on-treatment trajectories, which showed lower risks for dialysis compared to their nontreatment trajectories. There was no effect of UA control on survival.

Initial treatment of UA is crucially important for UA control. However, the long-term effects on patients and renal survival appeared to be minor and without statistical significance.

Abbreviations: ALT = alanine transaminase, ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker, CV = cardiovascular mortality, CVA = cerebrovascular attack, CKD = chronic kidney disease, CAD = coronary arterial disease, CHF = congestive heart failure, DBP = diastolic blood pressure, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate, SCr = serum creatinine, SHR = subdistribution hazard ratio, SBP = systolic blood pressure, UA = uric acid.

Keyword: competing risk analysis, long-term effect, patient survival, renal survival, trajectory, uric acid

1. Introduction

Uric acid (UA) is known to be associated with gout, and hyperuricemia is the major risk factor for the development of gout.[1] Nutrition and health surveys in Taiwan 2005–2008[2] revealed that the prevalence of gout is around 7.20% in men and 1.02% in women. However, the prevalence of hyperuricemia is 6.73% in men and 4.65% in women.[2] Therefore, having the condition

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All data generated or analyzed during this study are included in this published article [and its supplementary information files]. The individual patient-level data were not made publically available due to containing potentially identifying patient data; however, the study data may be made available from the authors upon reasonable request.

This study was approved by the Ethics Committee of Taichung Veterans General Hospital (IRB number: CE16235A). All methods were carried out in accordance with relevant guidelines and regulations and all participants signed an informed consent form.

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of hyperuricemia does not necessarily mean that a gout attack will occur. That is why all guidelines worldwide (except Japan) do not recommend treatment for asymptomatic hyperuricemia. Recently, UA was shown to be an inflammatory factor leading to increased oxidative stress in the renin–angiotensin–aldosterone system.[3] However, the associations of hyperuricemia with all-cause mortality, cardiovascular mortality (CV), and renal survival, especially in patients with chronic kidney disease (CKD), remain unclear. In the general population, hyperuricemia usually implies high mortality,[4,5] while other investigators disagree on the existence of any causal associations. In this context, the association between hyperuricemia and mortality in patients with CKD has not yet been determined.[6] As for the association of UA with renal survival, no consensus has been reached.[7–10] Due to the absence of strong evidence on any causal relationship of hyperuricemia with renal survival and patient survival, all meta-analyses have failed to prove a causal effect[11] and there is no recommended treatment for asymptomatic hyperuricemia in guidelines. In addition, some factors compete in renal survival. For patients who die with functional kidneys, both patient death and dialysis are usually recorded. Thus, competing risk analyses with subdistribution hazard need to be performed accordingly.[12]

Another important issue in UA control is the variation or long-term control over time. The role of the trajectory (trend) of UA on patient outcome, CV outcome, and renal outcome remains unexplored. Nonetheless, Ceriello et al[13] reported that a high variability in UA (hazard ratio = 1.54) conferred the highest risk of decline in estimated glomerular filtration rate (eGFR). In that study, they evaluated the role of interaction between the variability of UA and the increased risk of CKD. They separated the variability of UA into 4 groups according to quartiles. However, there was no long-term evaluation of trends in UA control in relation to patient survival outcomes and renal survival. In the present study, we aimed to investigate the long-term trend (trajectory) of UA, and the effects on patient survival and renal survivals (competing risk analysis for renal survival). The study enrolled outpatients with stage 3 CKD who were separated into subgroups based on their trajectories of UA recorded over 7 years.

2. Methods

2.1. Study population

We conducted this retrospective study in a medical center in central Taiwan. A flowchart of patients' inclusion and exclusion is summarized in Figure S1 (Supplemental Digital Content, http://links.lww.com/MD/G967). Patients with acute kidney were not excluded in this study because acute kidney injury is one of the effects of hyperuricemia, which caused more gout and more nonsteroidal anti-inflammatory drug usage. This nonsteroidal anti-inflammatory drug usage in patients CKD further made renal function deterioration. From 2007 to 2017, outpatients with stage 3 CKD aged >20 years old were enrolled. Patients who had died within 2 years after enrollment were excluded. We calculated every mean UA level from UA samples measured within 6 months. We required at least 3 samples to generate the mean UA used for our analysis. Finally, 808 subjects were successfully enrolled in this study. This study was approved by the Ethics Committee of Taichung Veterans General Hospital (institutional review board number CE16235A). All methods were carried out in accordance with relevant guidelines and regulations, and all participants signed an informed consent form.

2.2. Data collection and outcome assessment

All data were retrospectively collected from the medical records of patients. Tests of renal function were serum creatinine (SCr) level (mg/dL) and eGFR (mL/min/1.732 m^2; eGFR was calculated by the equation of modification of diet of renal disease).[14] Other demographic and laboratory data were also collected from medical records, including systolic blood pressure (SBP), diastolic blood pressure, glycated hemoglobin, total cholesterol, triglyceride, UA, hematocrit, and alanine transaminase (ALT).

The primary outcome was all-cause mortality. CVD, coronary arterial disease (CAD), and congestive heart failure were defined according to the definitions used in a previous CV outcome trial in type 2 diabetes mellitus (DM).[15] Dialysis was defined as the requirement to undergo a regular course of dialysis for 30 or more days.[16] Use of medications such as angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs), and medications used for gout were collected if the duration of prescriptions was >3 months.

2.3. Statistical methods

Continuous variables were reported as means ± standard deviations and categorical data were reported as numbers (percentages). Statistical significance across trajectories were determined using the chi-square test for categorical variables or 1-way analysis of variance for continuous variables. To evaluate the UA trajectory, we used group-based trajectory modeling analysis, a statistical methodology, which can be applied in the analysis of developmental trajectories, that is, the evolution of an outcome over time.[17] This analysis is typically used to describe data with a time-based dimension to provide an empirical foundation for analyzing developmental trajectories. It can be used to identify unique subgroups within a cohort of participants following the same temporal trajectory.[18] It can also be used to analyze developmental trajectories of distinct but related behaviors (group-based method).[18] It is an alternative method for analyzing the longitudinal data to evaluate outcomes.[19] We used this method to identify optimal groups of UA trajectory over time (Figure S2, Supplemental Digital Content, http://links.lww.com/MD/G967). Detailed methods of model building process).

The Cox proportional hazards model was used to compare the differences in all-cause mortality, dialysis, and either one of them among the different UA trajectories. As for dialysis, due to competing risk of death and dialysis, we used competing risk analysis as a sensitivity test for dialysis.[20] Competing risk analysis with subdistribution hazard ratio and 95% confidence interval (95% CI) of the subdistribution hazard ratio of possible confounders were calculated using competing-risks regression.[12] This model was used to determine factors confounding patient death to renal survival.

All statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC). Regarding statistical significance, a P value of <.05 was considered significant in the initial analysis for 3 trajectories of UA. Due to multiple comparisons, we performed post hoc analysis by Bonferroni adjustment (total 6 analyses). Therefore, after Bonferroni correction, the significance for this study was 0.008 (0.05/6) if 6 comparisons were done, and it was 0.017 (0.05/3) for 3 comparisons.

3. Results

3.1. Longitudinal data of long-term UA treatment

A total of 5742 patients with stage 3 CKD were enrolled, and among them, 808 patients were analyzed in this study (Supplemental Digital Content (Figure S1, http://links.lww.com/MD/G967)). Each subject was then grouped into 1 of the 3 trajectories based on the mean UA curve calculated over 6 months. Initially, 3 distinct trajectories (low [UA = 6.21 ± 1.76 mg/dL], medium [UA = 7.78 ± 1.85 mg/dL], and high UA [UA = 8.83 ± 1.44 mg/dL]) were identified (Table 1). We further separated each trajectory into 2 subgroups according to whether or

Table 1

Baseline characteristics of study subjects by trajectory of serum UA.

Variable	overall	Low UA	Medium UA	High UA	*P* value
Patients, n	808	124	555	129	
Age, yr	71.08 ± 14.53	73.07 ± 14.65	71.25 ± 14	68.44 ± 16.27	.0356
Female, n (%)	230 (28.47)	43 (34.68)	162 (29.19)	25 (19.38)†	.021
Serum creatinine, mg/dL	1.72 ± 0.3	1.66 ± 0.3	1.72 ± 0.3	1.8 ± 0.29	.0015
eGFR, mL/min/1.732 m2	40.31 ± 6.72	41.26 ± 7.26	40.22 ± 6.55	39.75 ± 6.83	.2021
Systolic BP, mm Hg	133.16 ± 17.24	129.66 ± 16.07	133.05 ± 16.49	137.03 ± 20.2	.0283
Diastolic BP, mm Hg	74.53 ± 10.3	72.56 ± 10.47	74.89 ± 10.09	75.17 ± 10.79	.1782
HbA1C, %	7.18 ± 1.45	7.18 ± 1.24	7.25 ± 1.54	6.88 ± 1.23	.3796
Total cholesterol, mg/dL	189.2 ± 42.34	187.5 ± 42.75	190.22 ± 42.63	186.53 ± 40.92	.6666
Triglyceride, mg/dL	154.54 ± 92.68	160.05 ± 102.97	154.69 ± 92.13	148.42 ± 84.35	.6713
UA, mg/dL	7.7 ± 1.92	6.21 ± 1.76	7.78 ± 1.85†	8.83 ± 1.44†	<.0001
Hematocrit	37.07 ± 5.17	37.5 ± 4.91	37.06 ± 5.19	36.62 ± 5.37	.478
ALT, U/L	22.5 ± 15.58	19.57 ± 11.41	21.54 ± 13.21	31.44 ± 26.31	.0399
Diabetes mellitus, n (%)	255 (31.56)	42 (33.87)	168 (30.27)	45 (34.88)	.4981
CAD, n (%)	29 (3.59)	6 (4.84)	17 (3.06)	6 (4.65)	.4907
CVA, n (%)	32 (3.96)	5 (4.03)	20 (3.6)	7 (5.43)	.6325
CHF, n (%)	11 (1.36)	2 (1.61)	6 (1.08)	3 (2.33)	.5283
Malignancy, n (%)	57 (7.05)	8 (6.45)	37 (6.67)	12 (9.3)	.5515
Liver disease, n (%)	42 (5.2)	5 (4.03)	26 (4.68)	11 (8.53)	.1703
Smoking	321 (39.73)	46 (37.1)	215 (38.74)	60 (46.51)	.216
ACEIs or ARBs, n (%)	444 (54.95)	67 (54.03)	301 (54.23)	76 58.91)	.6138
Treatment for gout	260 (32.18)	25 (20.16)	198 (35.68)†	37 (28.68)	.0024
Death	18 (2.23)	1 (0.81)	13 (2.34)	4 (3.1)	.0324
Dialysis	17 (2.1)	1 (0.81)	11 (1.98)	5 (3.88)	.0188

Values are means ± SD or n (%).

ACEI = angiotensin-converting enzyme inhibitor, ALT = alanine transaminase, ARB = angiotensin II receptor blocker, BP = blood pressure, CAD = coronary arterial disease, CHF = congestive heart failure, CVD = cerebral vascular disease, eGFR = estimated glomerular filtration rate, HbA1c = glycated hemoglobin, SD = standard deviation, UA = uric acid.

*Fisher exact test, $P < .05$

†Bonferroni adjustment, $P < .05/3$.

not patients received treatment. Finally, we obtained 6 trajectories as presented in Table 2 and Figure 1. All 6 trajectories appeared as steady curves without crossovers among them over the entire period of follow-up (Fig. 1). As shown in Table 1, patients with a low level of UA were older ($P = .036$), had a greater prevalence of female gender ($P = .021$), had better renal function (lower SCr; $P = .001$), lower SBP ($P = .028$), lower UA ($P < .0001$), lower ALT ($P = .040$), lower mortality ($P = .032$), and received fewer dialyses ($P = .019$). On the other hand, no significant differences were found in the rates of DM, CAD, cerebrovascular attack (CVA), congestive heart failure, malignancy, liver disease, smoking, or receiving ACEIs or ARBs. As shown in Table 2, male patients received more UA-lowering treatments in all 3 UA trajectories ($P = .0281$, 0.0126, and 0.040 for low, medium, and high UA trajectory, respectively). Among the patients in the low UA trajectory, those treated for UA showed significantly higher SCr levels as compared to those not treated for UA.

3.2. Longitudinal data of the 3 UA trajectories on mortality and dialysis

Regarding all-cause mortality risk (Fig. 2A), no variables (age, gender, CAD, CVA, DM, ACEI, ARB, trajectories of UA, and treatment of UA) were found to be significant. However, compared with the "low UA no-treatment" trajectory, we observed no events on the "low UA on-treatment" trajectory. As for the renal outcome, patients with DM had a significantly greater likelihood of receiving dialysis (Log HR = 0.771 [95% CI = 0.0278–1.265], as shown in Fig. 2B and Log HR = 0.72 [95% CI = 0.149–1.292] in Fig. 2D). As for all-cause mortality or dialysis (Fig. 2C), only DM (Log HR = 0.334 [95% CI = 0.031–0.638]) and use of ACEi or ARB (Log HR = 0.365 [95% CI = 0.027–0.704]) were associated with different outcomes. Despite the lack of statistical significance, there was a trend for "on-treatment" trajectory across all 3 UA trajectories showing lower risks for dialysis, when compared to all 3 "nontreatment" trajectory counterparts (Fig. 2D). Patient mortality and renal outcome between all 6 trajectories are shown in Table S3 (Supplemental Digital Content, http://links.lww.com/MD/G967).

4. Discussion

In the general population, serum UA level is associated with CVD,[4,5] and UA is considered an independent risk factor of CV mortality.[21] UA may be involved in the pathogenesis of CVD, but the causal relationship between UA and CVD remains unclear.[22] This relationship is similar to the correlation that exists between UA and renal injury.[11,23] Moreover, the association between CVD and renal injury in patients with CKD has rarely been investigated,[6] and there is no consensus on the exact nature of this. In addition to UA level, the association between UA variability and patient survival or renal survival has not been well studied.[13] That is to say, the long-term effect and longitudinal tendency of UA is not known. The strength of our present study is that we have clarified the relationship between the long-term effect of UA and patient or renal survival in the CKD groups. Currently, our study is the first to investigate research the trajectory of UA to determine patient survival and renal survival.

As shown in Figure 1, the 6 trajectories of UA did not cross one another during the entire period of follow-up, which indicated that the treatment response rapidly achieved a stable level. As a result, the curves did not cross over. This finding is compatible with studies on the pharmacodynamics of allopurinol, febuxosate, and uricosuric agents.[24] According to the prescription guideline of allopurinol, the drop in serum UA level begins on day 2 before reaching the peak on day 7. Normal serum UA levels can be achieved typically within 1 to 3 weeks. Similarly, the peak UA-lowering effect of febuxostat also appears during

Table 2

Baseline characteristics of study subjects by trajectory of serum UA with or without treatments.

Variable	Low UA no treatment	Low UA on treatment	*P* value (between no/on treatment)	Medium UA no treatment	Medium UA on treatment	*P* value (between no/on treatment	High UA no treatment	High UA on treatment	*P* value (between no/on treatment	*P* value (all 6 variables)
Patients, n	99	25		357	198		92	37		
Age, yr	72.34 ± 15.13	75.96 ± 12.43	.2719	71.18 ± 13.86	71.37 ± 14.29	.8756	67.76 ± 15.78	70.14 ± 17.56	.4558	.1246
Female, n (%)	39 (39.39)	4 (16)	.0281	117 (32.77)	45 (22.73)†	.0126	22 (23.91)	3 (8.11)†	.0400	.0004
Serum creatinine, mg/dL	1.63 ± 0.29	1.78 ± 0.34	.0294	1.7 ± 0.31	1.75 ± 0.27	.0843	1.8 ± 0.29	1.8 ± 0.3	.9626	.0008
eGFR, mL/min/1.732 m2	41.64 ± 7.09	39.72 ± 7.44	.2431	40.43 ± 6.72	40.32 ± 6.66	.8561	39.29 ± 7.02	41.1 ± 6.91	.1928	.3051
Systolic BP, mm Hg	129.89 ± 15.28	128.73 ± 19.59	.8049	131.96 ± 16.19	135.15 ± 16.95	.1250	138.69 ± 21.2	133.89 ± 18.1	.3214	.0571
Diastolic BP, mm Hg	72.47 ± 10.7	72.93 ± 9.79	0.8784	74.33 ± 9.9	75.96 ± 10.42	0.2002	74.41 ± 10.57	76.59 ± 11.25	.3991	.3223
HbA1c, %	7.28 ± 1.35	6.88 ± 0.83	0.4052	7.34 ± 1.61	7.06 ± 1.39	0.2933	7.05 ± 1.27	6.48 ± 1.08	.1988	.4286
Total cholesterol, mg/dL	189.18 ± 44.99	181.14 ± 33.03	0.4463	191.2 ± 44.34	188.58 ± 39.66	0.5377	191.32 ± 43.43	176.22 ± 33.22	.0844	.4707
Triglyceride, mg/dL	156.62 ± 108.54	172.36 ± 80.84	.5286	152.15 ± 86.09	158.99 ± 101.66	.4773	153.68 ± 87.79	137.06 ± 76.48	.3595	.7713
UA, mg/dL	5.98 ± 1.54	7.03 ± 2.25	.0561	7.56 ± 1.64	8.14 ± 2.1†	.0027	8.67 ± 1.35†	9.2 ± 1.58	.0837	<.0001
Hematocrit	37.15 ± 5.02	38.91 ± 4.27	.1412	36.52 ± 5.08	38.08 ± 5.26	.0027	35.95 ± 5.12	38.06 ± 5.7	.0662	.0063
ALT, U/L	18.79 ± 11.92	23.25 ± 8.92	.4901	20.44 ± 12.45	23.26 ± 14.36	.3576	33.6 7 ± 33.05	28.57 ± 16.05	.7147	.1731
Diabetes mellitus, n (%)	35 (35.35)	7 (28)	.4876	117 (32.77)	51 (25.76)	.0848	33 (35.87)	12 (32.43)	.7110	.4233
CAD, n (%)	4 (4.04)	2 (8)	.2529*	11 (3.08)	6 (3.03)	.9734	2 (2.17)	4 (10.81)	.0486*	<.0001*
CVA, n (%)	5 (5.05)	0 (0)	.3177*	1 2(3.36)	8 (4.04)	.6809	4 (4.35)	3 (8.11)	2172*	.0003*
CHF, n (%)	2 (2.02)	0 (0)	.6361*	4 (1.12)	2 (1.01)	.3285*	1 (1.09)	2 (5.41)	.1753*	.0017*
Malignancy, n (%)	8 (8.08)	0 (0)	.1555*	27 (7.56)	10 (5.05)	.2557	7 (7.61)	5 (13.51)	.1460*	.3254
Liver disease, n (%)	4 (4.04)	1 (4)	.4180*	16 (4.48)	10 (5.05)	.7613	11 (11.96)	0 (0)	.0202*	<.0001*
Smoking	32 (32.32)	14 (56)	.0285	132 (36.97)	83 (41.92)	.2520	39 (42.39)	21 (56.76)	.1390	.0455
ACEIs or ARBs, n (%)	55 (55.56)	12 (48)	.4982	185 (51.82)	116 (58.59)	.1254	54 (58.7)	22 (59.46)	.9364	.5789
Treatment for gout	0 (0)	25 (100)†	<.0001	0 (0)	198 (100)†	<.0001	0 (0)	37 (100)†	<.0001	<.0001
Death	1 (1.01)	0 (0)	.7984*	8 (2.24)	5 (2.53)	.2206*	2 (2.17)	2 (5.41)	.2532*	.0014*
Dialysis	1 (1.01)	0 (0)	.7984*	9 (2.52)	2 (1.01)	.1311*	5 (5.43)	0 (0)	.1787*	.0004*

Values are means ± SD or n (%).

ACEI = angiotensin-converting enzyme inhibitor, ALT = alanine transaminase, ARB = angiotensin II receptor blocker, BP = blood pressure, CAD = coronary arterial disease, CHF = congestive heart failure, CVD = cerebral vascular disease, eGFR = estimated glomerular filtration rate, HbA1c = glycated hemoglobin, SD = standard deviation, UA = uric acid.

*Fisher exact test, $P < .05$

†Bonferroni adjustment, $P < .05/3$.

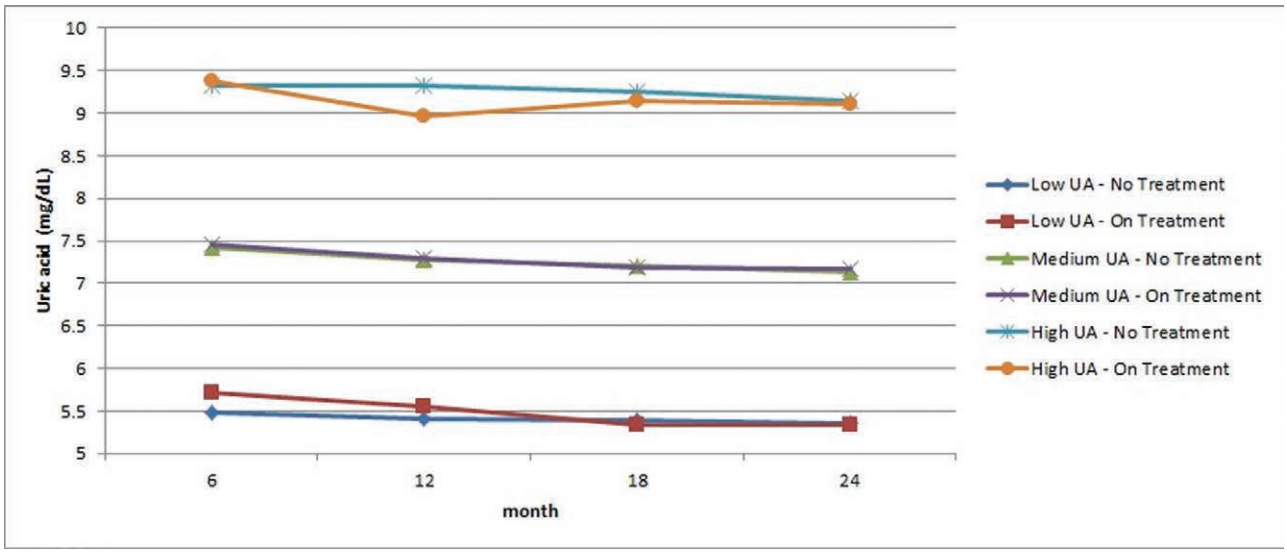

Figure 1. Trajectories of mean serum UA with or without treatments. UA = uric acid.

the first 5 to 7 days of treatment. Therefore, the long-term effect of UA control is based on the treatment decision (treat or not treat) during the first few weeks.

In the group of low UA trajectory, participants had better renal function, lower SCr ($P = .001$), lower SBP ($P = .028$), lower UA ($P < .0001$), lower ALT ($P = .040$), fewer deaths ($P = .032$), and lower prevalence of dialysis ($P = .019$). These findings suggest that patients in this group had the lowest risk for metabolic syndrome and oxidative stress.[3,25,26] Moreover, we chose the low UA no-treatment trajectory as the reference group for analysis rather than the low UA on-treatment trajectory. This is because patients in the trajectory of the low UA on-treatment must have been diagnosed with hyperuricemia before receiving UA-lowering agents. Those patients had already experienced a higher risk of metabolic syndrome and oxidative stress before the treatment. Thus, it is reasonable to expect that the risk of metabolic disease for the "on-treatment" trajectory would be higher than for the "no-treatment" trajectory. In summary, choosing the low UA no-treatment trajectory as the reference group is reasonable.

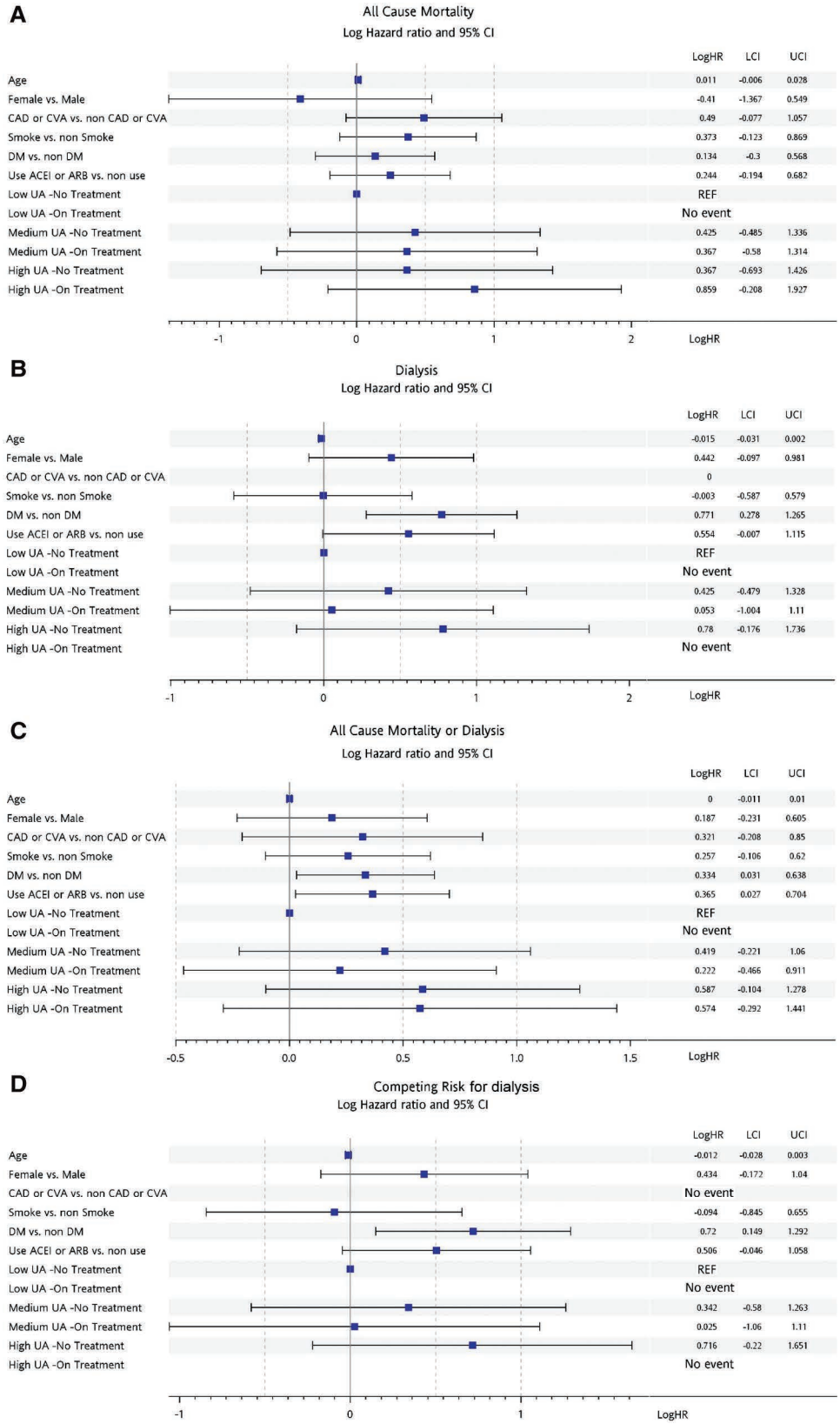

Figure 2. Adjusted HRs for all-cause mortality (A), dialysis (B), dialysis or patient death (C), and competing risk for dialysis (D). ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker, CI = confidence interval, CVA = cerebrovascular attack, CAD = coronary arterial disease, DM = diabetes mellitus, HR = hazard ratio, LCI = lower 95% confidence interval, REF = reference, UA = uric acid, UCI = upper 95% confidence interval.

The pleotropic effect of UA-lowering agents is still a matter of debate. In animal models, xanthine oxidase may cause kidney fibrosis through inflammation, endothelial dysfunction, oxidative stress,[3,25,26] and activation of the renin–angiotensin system.[27] In some studies, both allopurinol[28–31] and febuxosate[32–36] show renal protection independent of their

UA-lowering effect. Our present results did not support that UA-lowering agents provide any significant renal protective effect. The only trend was for "on-treatment" trajectory across all 3 UA trajectories, which showed lower risks for dialysis, when compared to all 3 "no-treatment" trajectory counterparts (Fig. 2D). However, the same trend was not observed for all-cause mortality. Our study is the first to report the long-term effect of UA control on patient survival and renal survival. The long-term benefit of UA control may be relatively minor compared to the benefits by control of BP, hyperlipidemia, and DM.

There were some limitations in this study. First, detailed medication data were not available. However, regarding the therapy for our patients with stage 3 CKD, xanthine oxidase inhibitor therapy is the consensus first-line treatment according to previous studies[37] and guidelines in Taiwan.[38] The effect of this limitation may be not large. Second, only patients surviving ≥ 2 years from the time of enrollment were included in this study. This could imply a minor bias toward good adherence to medical follow-ups. Third, this was a retrospective cohort study conducted on a heterogeneous population. Further prospective studies are needed to confirm the long-term effect of UA variability on patients and renal outcome.

5. Conclusion

Earlier treatment for hyperuricemia is important for UA control due to the rapid response of medications. However, the beneficial effects of UA control on patient survival and renal outcomes may be minor in long-term follow-up, after accounting for the competing risk of death.

Author contributions

SFT, CHC, MJW, and CLL for the design of the work; SFT and CLL for the acquisition and analysis. SFT and CLL for the interpretation of data; SFT drafted the work; SFT and CLL substantively revised this article; SFT, CHC, MJW, and CLL approved the submitted version; SFT, CHC, MJW, and CLL read and approved the final manuscript.

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