Trajectory of serum uric acid as a predictor for renal outcome and mortality in stage -3 chronic kidney disease patients

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Abstract

Introduction

Uric acid (UA) is associated with renal and patient survival but the association is causal in nature remains unclear. Also, no finding is yet available regarding longitudinal UA control (trajectory).

Methods

We enrolled 808 subjects diagnosed with stage 3 CKD from 2007 to 2017. We plotted based on follow-ups the mean UA over a period of 6 months with a minimum of three samples of UA was required. From the sampled points, we generated for each patient an interpolated line by joining mean values of the UA levels over time. And from the lines from all patients, we classified them into three groups of trajectories (low, medium and high UA) through group-based trajectory modeling, and then further separated into either a treatment or no-treatment subgroups. Using the univariate competing-risks regression, we calculated the competing risk analysis with subdistribution hazard ratio of possible confounders.

Results

All of the 6 trajectories appeared as gradually falling functions with time without any of the curves crossed over one another. For all-cause mortality risk, none of the variables was statistically significant. Patients with DM were statistically more likely to undergo dialysis. There was also a trend that the on-treatment trajectories, compared to their no-treatment trajectories, had lower risks for dialysis.

Conclusions

Initial treatment of UA is utterly important. Xanthine oxidase inhibitors may lead to renal protection without effects on patient death, independent from the UA-lowering effects. This is the first study on the long-term effects of UA trajectory on patient survivals and renal outcomes.

Introduction

Uric acid (UA) is no doubt associated with gout, and hyperuricemia is the major risk factor for the development of gout[1]. The prevalence of gout is around 1% in the general population but the prevalence of hyperuricemia is way higher, up to 70.2% (i.e., serum uric acid >6.0 mg/dl) (NAHSIT_Taiwanese). Therefore, having the condition of hyperuricemia does not mean gout attack. That is why all guidelines worldwide (except Japan) do not recommend treatment for asymptomatic hyperuricemia. Recently, UA is shown to be an inflammatory factor to increase oxidative stress in the renin angiotensin aldosterone system[2]. However, it remains unclear regarding the associations between hyperuricemia and all-cause mortality, cardiovascular mortality (CV) or renal survivals, especially in patients with chronic kidney disease (CKD). In the general population, hyperuricemia usually implies high mortality[3,4], while other investigators disagree on any causal association between the two. In this context, the association between hyperuricemia and mortality in CKD patients is not yet determined[5]. As for the association with renal survival, no consensus is found[6–9]. Due to the absence of strong evidence on any causal relationship between hyperuricemia and renal and patient survivals, all meta-analyses failed to prove the causal effect[10] and with guideline recommending treatment for asymptomatic hyperuricemia. In addition, some factors compete in renal survival, and also in patient death. Patients who died with functional kidneys were usually recorded as both patient death and renal death. Thus competing risk analyses with subdistribution hazard need to be conducted accordingly[11].

Another important issue in UA control is its variations or long term control over time. The role of the trajectory (trend) of UA on patient outcome, CV outcome and renal outcome remains unexplored. Currently, only Ceriello et al have reported a study[12] that high variability in UA (HR = 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 in increasing the risk of CKD. They separated serum UA variability into 4 groups according to its quartiles. However, there is no long term evaluation of tendency for UA control and its outcome to patients and renal survivals. In the present study, we aimed to investigate the long term tendency (trajectory) of UA, and its effect on patients and renal survivals (competing risk analysis for renal survival) on the risk of mortality. The study enrolled stage 3 CKD outpatients who were separated into subgroups based on their trajectories of UA recorded over 7 years.

Materials And Methods

Study population

We conducted this retrospective study in a medical center in central Taiwan. A flow chart of patients’ inclusion and exclusion is summarized in Figure S1 (supplementary data). From 2007 to 2017, outpatients with stage 3 CKD aged ≥20 years were enrolled. Patients who had died within two years after enrollment were excluded. We calculated every mean UA level from UA samples measured within 6 months. We required at least three samples to generate the mean UA used for our analysis. Finally, 808 subjects were successfully enrolled for study. This study was approved by 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 informed consents.

Data Collection and outcome assessment

All data were retrospectively collected from medical records of patients. The tests of renal function were on serum creatinine level (mg/dl) and eGFR (ml/min.1.73m²) (The eGFR was calculated using the modification of diet in renal disease equation)[13]. Other demographic and laboratory data were also
collected from medical records, including systolic blood pressure (SBP), DBP, glycated hemoglobin (HbA1c), total cholesterol, triglyceride, UA, hematocrit, and alanine transaminase (ALT).

The primary outcome is all-cause mortality. The CVD, coronary arterial disease, and congestive heart failure were defined as previous CV outcome trial in type 2 diabetes mellitus (DM)[14]. The renal death was defined if patients should undergo regular course of dialysis for 30 or more days[15]. Medication use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs), and medications used for gout were collected if the duration of prescriptions was longer than three months.

### Statistical methods

Continuous variables were reported as means ± SDs and categorical data as numbers (percentages). Statistical significances across trajectories were determined using the Chi-square test for categorical variables, or one-way analysis of variance for continuous variables. To evaluate the uric acid trajectory, we used Group-based trajectory modeling analysis as a statistical methodology to analyze developmental trajectories - the evolution of an outcome over time[16]. This analysis is typically used to describe the data with a time-based dimension - providing the empirical foundation for analyzing developmental trajectories. It can be used to identify unique subgroups within a cohort with participants following the same temporal trajectory[17]. Analyzing developmental trajectories of distinct but related behaviors: a group-based method[17]. It is the alternative method for analyzing the longitudinal data to evaluate outcomes[18]. We used this method to identify optimal groups of uric acid trajectory over time (Supplementary data, S2. detailed methods of model building process).

Cox's proportional hazards model was used to compare the differences of all-cause mortality, dialysis, and either one of them among different uric acid trajectories. As for dialysis, due to competing risk of death and dialysis, we used competing risk analysis as a sensitivity test for dialysis[19]. Competing risk analysis with subdistribution hazard ratio (SHR) and 95% confidence interval (95% CI) of the SHR of possible confounders were calculated using competing-risks regression[11]. This model was used to determine factors confounding patient death to renal death.

All statistical analyses were performed using the SAS software, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

### Results

#### Longitudinal data of long-term UA treatment

A total of 5742 patients of stage 3 CKD were enrolled, and among them, 808 patients were analyzed in this study (Figure S1). Each subject was then grouped into one of the three trajectories based on the mean UA curve calculated over 6 months. Initially, three 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 two subgroups according to whether or not treatment was received. Finally, we obtained in total 6 trajectories as presented in Table 2 and Figure 1. All 6 trajectories appeared as steady curve with no crossovers among them over the entire period of follow-up (Figure 1). As shown in Table 1, patients with low levels of UA were older (p = 0.036), more females (p = 0.021), better renal function (lower serum creatinine levels) (p = 0.001), lower levels of SBP (p = 0.028), UA (p<0.0001), and ALT (p = 0.040), less likely died (p = 0.032) and received fewer dialyses (p = 0.019). On the other hand, no significant differences were found in the rates of DM, CAD, CVA, CHF, malignancy, liver disease, smoking or receiving ACEIs or ARBs. As shown in Table 2, male patients received more UA-lowering treatments in all three UA trajectories (p = 0.0281, 0.0126, 0.040, respectively). In the low UA trajectory, patients had higher serum creatinine levels (p = 0.0294). More smoking habits (p = 0.0285) tended to receive treatments for hyperuricemia. In the medium UA trajectory, patients with higher levels of UA (p = 0.003) and hematocrit (p = 0.003) received more UA-lowering treatments.

#### Longitudinal data of the three UA trajectories on mortality and dialysis

Regarding all-cause mortality risk (Figure 2A), no variables we studied were found to be significant. However, compared with the low UA-no treatment trajectory, we observed no events on low UA-on treatment trajectory. As for the renal outcome, patients with DM had significantly more chances in receiving dialysis treatment (Log HR = 0.771 (95% CI = 0.227–1.265) as shown in Figure 2B, and 0.72 (95% CI = 0.149–1.292)) as shown in figure 2D. While statistically insignificant, we found a trend that on-treatment trajectory across all UA trajectories had lower risks for dialysis, when compared to the no-treatment trajectory counterpart (no event vs. reference, Log HR = 0.025 vs. 0.342, no event vs. Log HR = 0.716 for low UA, medium UA and high UA trajectories, respectively) (Figure 2D).

#### Discussion

In the general population, serum UA level is associated with CVD [3,4], and UA is considered an independent risk factor of CV mortality[20]. UA may be pathogenic in origin and is involved in the pathogenesis of CVD, but the causal relationship between UA and CVD remains unclear[21]. The situation is similar to the relationship between UA and renal injury[10,22]. Besides, the association between CVD and renal injury in patients with CKD is rare[5] and the exact relationship has no consensus. In addition to UA level, the association between UA variability and patient survival or renal survival is not well-studied[12]. The long-term effect and longitudinal tendency of UA level is not known. The strength of our present study is that we have clarified the relationship between long-term effect of UA and patient or renal survival in the CKD groups. Currently, our study is the first one to see the trajectory of UA to patients and renal survival.

The treatment response rates of allopurinol is ~ 40% and of febuxostat ~70%[23]. In our study, the controlled levels of all three on-treatment trajectories were as follows: 9.6% in the low UA group (level = 7.03±2.25 mg/dl), 76.2% in the medium UA group (level = 8.14±2.1 mg/dl), and 14.2% in the high UA group (level
Most on-treatment patients (85.8%) were maintained at UA levels ≤8.14 mg/dl.

As shown in Figure 1, 6 trajectories of UA did not cross one another during the entire follow-up period. The treatment response was very rapid to achieve the stable l level, resulting in no crossing over the curves. This finding is compatible with the studies on the pharmacodynamics of allopurinol, febuxostat 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. The normal serum UA levels can be achieved typically within one to three weeks. The peak UA-lowering effect of febuxostat on UA also appears during the first 5 to 7 days of treatment. Therefore, the long-term effect of UA control (on-treatment of no-treatment) 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 serum creatinine level) (p = 0.001), lower SBP (p = 0.028), less UA (p<0.0001), less ALT (p = 0.040), fewer deaths (p = 0.032) and fewer receiving dialysis (p = 0.019). These findings suggested patients of this group had the lowest risk for metabolic syndrome and oxidative stress. Therefore, we chose low UA-no treatment trajectory as the reference group for analysis. Reasonably, in the low UA-no treatment group, participants had low levels of baseline UA had needed no treatments. These patients likely belong to the group of the lowest risk for mortality.

The pleotropic effect of UA –lowering agents is still under debate. In animal models, xanthine oxidase may cause kidney fibrosis through inflammation, endothelial dysfunction, oxidative stress, and activation of the renin-angiotensin system[25]. In some studies, both allopurinol [26–29] and febuxosate[30–34] show renal protections independent from their UA lowering effect. Our present results also supported renal protection of the UA-lowering agents. In the medium UA group (Figure 2D), we found a trend that the on-treatment group (UA = 8.14±2.1 mg/dl) had less risk for dialysis than no-treatment group (UA = 7.56±1.64 mg/dl) despite of its higher UA levels (p = 0.0027). The condition is similar to low UA trajectory (no event vs. 1%) (similar UA level: 7.03±2.25 vs. 5.98±1.52mg/dl, p = 0.0561) and high UA trajectory (no event vs. 5.43%) (similar UA level:9.2±1.58 vs. 8.67±1.35, p = 0.0837). Across the three trajectories, even similar (low or high UA) or higher UA levels (medium UA), the on-treatment groups had fewer tendencies to receiving dialysis. However, The same trend was not observed regarding the all-cause mortality.

There are some limitations of this study. Firstly, detailed medication data were not available. Regarding the therapy for our stage 3-CKD patients, xanthine oxidase inhibitor therapy is the consensus first-line treatment in line with previous [35] and guidelines in Taiwan[36]. Such limitation may not have affected much of the results we obtained. Secondly, only patients surviving ≥ 2 years from the time of enrolment were included in this study. This could imply minor bias toward good adherence to medical follow-ups. Thirdly, this is a retrospective cohort study on a heterogeneous population. It still needs more prospective studies to confirm the long-term effect of UA variability on CV and renal outcome.

**Conclusion**

Firstly, we reported here the first study, based on long-term follow-ups of the effects of UA trajectories on patients and renal outcomes. In clinical practice, initial treatment of UA is the most important decision to make. Xanthine oxidase inhibitors may have renal protection effects independent from lowering UA without confounded by patient death. Thus, earlier and timely treatment for hyperuricemia is suggested for better renal outcomes.

**Declarations**

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**DISCLOSURES:** No competing interest was declared

**Author Contribution statement**

Shang-Feng Tsai, Chia-Lin Lee, Ming-Ju Wu, and Cheng-Hsu Chen conceived of the presented idea. Shang-Feng Tsai, and Cheng-Hsu Chen developed the theory and performed the computations. Ming-Ju Wu, and Cheng-Hsu Chen verified the analytical methods. All authors discussed the results and contributed to the final manuscript. Shang-Feng Tsai, and Chia-Lin Lee wrote the manuscript with input from all authors. Ming-Ju Wu, Chia-Lin Lee and Cheng-Hsu Chen conceived the study and were in charge of overall direction and planning.

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Table 1 Baseline characteristics of study subjects by trajectory of serum uric acid (UA)

| Variable                  | overall          | Low UA          | Medium UA       | High UA         | P value |
|---------------------------|------------------|-----------------|-----------------|-----------------|---------|
| Patients, n               | 808              | 124             | 555             | 129             |         |
| Age, years                | 71.08±14.53      | 73.07±14.65     | 71.25±14        | 68.44±16.27     | 0.0356  |
| Female, n (%)             | 230 (28.47)      | 43 (34.68)      | 162 (29.19)     | 25 (19.38)      | 0.021   |
| Serum creatinine, mg/dl   | 1.72±0.3         | 1.66±0.3        | 1.72±0.3        | 1.8±0.29        | 0.0015  |
| eGFR, ml/min.1.732m²      | 40.31±6.72       | 41.26±7.26      | 40.22±5.65      | 39.75±6.83      | 0.2021  |
| Systolic BP, mmHg         | 133.16±11.24     | 129.66±16.07    | 133.05±16.49    | 137.03±20.2     | 0.0283  |
| Diastolic BP, mmHg        | 74.53±10.3       | 72.56±10.47     | 74.89±10.09     | 75.17±10.79     | 0.1782  |
| HbA1C, %                  | 7.18±1.45        | 7.18±1.24       | 7.25±1.54       | 6.88±1.23       | 0.3796  |
| Total cholesterol, mg/dl  | 189.2±42.34      | 187.5±42.75     | 190.22±42.63    | 186.53±40.92    | 0.6666  |
| Triglyceride, mg/dl       | 154.54±92.68     | 160.05±102.97   | 154.69±92.13    | 148.42±84.35    | 0.6713  |
| Uric acid, mg/dl          | 7.7±1.92         | 6.21±1.76       | 7.78±1.85       | 8.83±1.44       | <0.0001 |
| Hematocrit                | 37.07±5.17       | 37.5±4.91       | 37.06±5.19      | 36.5±5.37       | 0.478   |
| ALT, U/L                  | 22.5±15.58       | 19.57±11.41     | 21.54±13.21     | 21.44±26.31     | 0.0399  |
| Diabetes mellitus, n (%)  | 255 (31.56)      | 42 (33.87)      | 168 (30.27)     | 45 (34.88)      | 0.4981  |
| CAD, n (%)                | 29 (3.59)        | 6 (4.84)        | 17 (3.06)       | 6 (4.65)        | 0.4807  |
| CVA, n (%)                | 32 (3.96)        | 5 (4.03)        | 20 (3.6)        | 7 (5.43)        | 0.6225  |
| CHF, n (%)                | 11 (1.36)        | 2 (1.61)        | 6 (1.08)        | 3 (2.33)        | 0.5283  |
| Malignancy, n (%)         | 57 (7.05)        | 8 (6.45)        | 37 (6.67)       | 12 (9.3)        | 0.5515  |
| Liver disease, n (%)      | 42 (5.2)         | 5 (4.03)        | 26 (4.68)       | 11 (8.53)       | 0.1703  |
| Smoking                   | 32 (3.97)        | 46 (37.1)       | 215 (38.74)     | 60 (46.51)      | 0.216   |
| ACEIs or ARBs, n (%)      | 44 (54.95)       | 67 (54.03)      | 301 (54.23)     | 76 (58.91)      | 0.6138  |
| Treatment for gout        | 260 (32.18)      | 25 (20.16)      | 198 (35.68)     | 37 (28.68)      | 0.0024  |
| Death                     | 18 (2.23)        | 1 (0.81)        | 13 (2.34)       | 4 (3.1)         | 0.0324  |
| Dialysis                  | 17 (2.1)         | 1 (0.81)        | 11 (1.98)       | 5 (3.88)        | 0.0188  |

*Fisher's exact test

Values are means ± SD or n (%); BP: blood pressure; HbA1c: glycated hemoglobin; eGFR: estimated glomerular filtration rate; ALT: alanine transaminase; CAD: coronary arterial disease; CVD: cerebral vascular disease; CHF: congestive heart failure; ACEIs: angiotensin-converting enzyme inhibitors; ARBs: angiotensin II receptor blockers

Table 2 Baseline characteristics of study subjects by trajectory of serum uric acid (UA) with or without treatments

| Variable                  | overall          | Low UA          | Medium UA       | High UA         | P value |
|---------------------------|------------------|-----------------|-----------------|-----------------|---------|
| Patients, n               | 2018             | 21               | 772             | 787             |         |
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| Variable                      | Low UA No Treatment | Low UA On Treatment | P value | Medium UA No Treatment | Medium UA On Treatment | P value | High UA No Treatment | High UA On Treatment | P value |
|-------------------------------|---------------------|---------------------|---------|------------------------|------------------------|---------|----------------------|----------------------|---------|
| Patients, n                  | 99                  | 25                  |         | 357                    | 198                    |         | 92                   | 37                   |         |
| Age, years                   | 72.34±15.13         | 75.96±12.43         | 0.2719  | 71.18±13.86            | 71.37±14.29            | 0.8756  | 67.76±15.78          | 70.14±17.56          | 0.4558  |
| Female, n (%)                | 39(39.39)           | 4(16)               | 0.0281  | 117(32.77)             | 45(22.73)              | 0.0126  | 22(23.91)            | 3(8.11)              | 0.0400  |
| Serum creatinine, mg/dl      | 1.63±0.29           | 1.78±0.34           | 0.0294  | 1.7±0.31               | 1.75±0.27              | 0.0843  | 1.8±0.29             | 1.8±0.3              | 0.9626  |
| eGFR, ml/min.1.73m²          | 41.64±7.09          | 39.72±7.44          | 0.2431  | 40.43±6.72             | 40.32±6.66             | 0.8561  | 39.29±7.02           | 41.1±6.91            | 0.1928  |
| Systolic BP, mmHg            | 129.89±15.28        | 128.73±19.59        | 0.8049  | 131.96±16.19           | 135.15±16.95           | 0.1250  | 138.69±21.22         | 133.89±18.1          | 0.3214  |
| Diastolic BP, mmHg           | 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          | 0.3991  |
| 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            | 0.1988  |
| Total cholesterol, mg/dl     | 189.18±44.99        | 181.14±33.03        | 0.4463  | 191.2±44.34            | 188.5±39.66            | 0.5377  | 191.3±43.43          | 176.2±33.22          | 0.0844  |
| Triglyceride, mg/dl          | 156.62±108.54       | 172.36±80.84        | 0.5286  | 152.15±86.09           | 158.99±101.66          | 0.4773  | 153.68±87.79         | 137.06±76.48         | 0.3595  |
| Uric acid, mg/dl             | 5.98±1.54           | 7.03±2.25           | 0.0561  | 7.56±1.64              | 8.14±2.1               | 0.0027  | 8.67±1.35            | 9.2±1.58             | 0.0837  |
| Creatinine, mg/dl            | 37.15±5.02          | 38.91±4.27          | 0.1412  | 36.52±5.08             | 38.08±5.26             | 0.0027  | 35.95±5.12           | 38.06±5.7            | 0.0662  |
| ALT, U/L                     | 18.79±11.92         | 23.25±8.92          | 0.4901  | 20.44±12.45            | 23.26±14.36            | 0.3576  | 33.67±33.05          | 28.57±16.05          | 0.7147  |
| Diabetes mellitus, n (%)     | 4(4.04)             | 2(8)                | 0.2529* | 11(3.08)               | 6(3.03)                | 0.9734  | 2(2.17)              | 4(10.81)             | 0.0486* |
| CAD, n (%)                   | 5(5.05)             | 0(0)                | 0.3177* | 12(3.36)               | 8(4.04)                | 0.6809  | 4(4.35)              | 3(8.11)              | 0.0631  |
| CVA, n (%)                   | 2(2.02)             | 0(0)                | 0.6361* | 4(1.12)                | 2(1.01)                | 0.3285* | 1(1.09)              | 2(5.41)              | 0.1753* |
| CHF, n (%)                   | 8(8.08)             | 0(0)                | 0.1555* | 27(7.56)               | 10(5.05)               | 0.2557  | 7(7.61)              | 5(13.51)             | 0.1460* |
| Malignancy, n (%)            | 4(4.04)             | 1(4)                | 0.4180* | 16(4.48)               | 10(5.05)               | 0.7613  | 11(11.96)            | 0(0)                 | 0.0205* |
| Liver disease, n (%)         | 32(32.32)           | 14(56)              | 0.0285  | 132(36.97)             | 83(41.92)              | 0.2520  | 39(42.39)            | 21(56.76)            | 0.1390  |
| Smoking                      | 55(55.56)           | 12(48)              | 0.4982  | 185(51.82)             | 116(58.59)             | 0.1254  | 54(58.7)             | 22(59.46)            | 0.9364  |
| ACEIs or ARBs, n (%)         | 0(0)                | 25(100)             | <.0001  | 198(100)               | <.0001                 | 0(0)    | 37(100)              | <.0001               | <.0001  |
| Treatment for gout Death     | 1(1.01)             | 0(0)                | 0.7984* | 8(2.24)                | 5(2.53)                | 0.2206* | 2(2.17)              | 2(5.41)              | 0.2532* |
| Dialysis                     | 1(1.01)             | 0(0)                | 0.7984* | 9(2.52)                | 2(1.01)                | 0.1311* | 5(1.43)              | 0(0)                 | 0.1787* |

### Figures

**Figure 1**

Trajectories of mean serum uric acid (UA) with or without treatments
Figure 2

Adjusted hazard ratios (HRs) for all-cause mortality (A), renal death (B), renal death or patient death (C), and competing risk for dialysis (D).

Supplementary Files

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