Hyperuricemia is associated with progression of CKD: uric acid aggravates renal function

Shulei Fan (✉ fsl0311@163.com)

Sichuan Academy of Medical Sciences and Sichuan People's Hospital

Yang Zou

Sichuan Academy of Medical Sciences and Sichuan People's Hospital

Amanda Y Wang

George Institute for Global Health

Mingjie Xu

Sichuan Academy of Medical Sciences and Sichuan People's Hospital

Guisen Li

Sichuan Academy of Medical Sciences and Sichuan People's Hospital

Daqing Hong

Sichuan Academy of Medical Sciences and Sichuan People's Hospital

---

Research article

Keywords: hyperuricemia, chronic kidney disease, renal function, progression

Posted Date: August 3rd, 2019

DOI: <https://doi.org/10.21203/rs.2.12363/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background: With the change of living standard and dietary structure, the incidence of hyperuricemia is on the rise. Hyperuricemia has become one of the metabolic diseases threatening human health. There is paucity of literature on the association between serum uric acid levels and the progression of CKD. This study aimed at assessing the effect of serum baseline uric acid level on the progression of CKD.

Methods: This retrospective study included 800 CKD patients in our center. The information on baseline and follow-up characteristics were collected from our Renal Treatment System (RTS) database. Cox regression analysis was used to evaluate the risk factors for CKD progression. The Kaplan–Meier analysis was used to test associations between serum uric acid levels and renal survival rates. **Results:** A total of 800 patients were included in the study, and the mean age at entry was 36.6 ± 14.4 years. There was no significant difference in gender distribution. The mean eGFR, Cr, serum uric acid at baseline were 99.23 ± 31.54 ml/min/1.73 m^2 , 82.08 ± 41.40 $\mu\text{mol/L}$, 371.60 ± 103.18 $\mu\text{mol/L}$, respectively. 306 (38.3%) patients had HUA and 494 (61.7%) had non-HUA. We established different adjusted models and found that HUA was a risk factor for CKD patients to reach the composite endpoint after adjustment in six models. All models show that HUA was a risk factor for the progression of CKD. Among them, model 4 (adjusted for Cr + Alb + age + BP + gender) was the best model with the largest HR value (HR:2.010, 95%CI:1.310-3.084, $P < 0.05$). The cumulative survival rate of non-hyperuricemia group was higher than that of hyperuricemia group ($P < 0.001$). **Conclusions:** Hyperuricemia was not only widespread in patients with CKD, but also a risk factor for the progression of CKD. Anti-hyperuricemia therapy may need to be considered in CKD patients to slow the disease progression, which needs to be tested further in clinical studies. **Key words:** hyperuricemia, chronic kidney disease, renal function, progression

Background

The incidence of chronic kidney disease (CKD) is increasing. Prevention and slowing progression of CKD has been a focus of public health[1, 2]. At present, no definitive pharmacological agents to completely reverse the development of CKD. However, early intervention of risk factors for CKD progression can prolong the time to develop **end-stage renal disease** (ESRD) and improve the prognosis of kidney disease[3].

Uric acid is the product of purine metabolism in human body. Hyperuricemia (HUA) can not only lead to gout clinically, but is also associated with an increased risk of development of hypertension, diabetes, coronary heart disease, stroke and other diseases[4-9]. Furthermore, HUA is a common phenomenon seen in patients with CKD[2, 10]. Previous studies have shown that hyperuricemia was a risk factor for CKD[5-7]. However, due to the complex and bidirectional interactions between HUA and renal function, the exact

association between HUA and the progression of CKD remains uncertain. We have therefore conducted a retrospective cohort study assessing the effect of baseline serum uric acid levels on the progress of CKD.

Methods

Study Participants and Data Collection

Patients with CKD in our renal center (Renal Department and Nephrology Institute, Sichuan Provincial People's Hospital) were screened from our Renal Treatment System (RTS) database and the selection period was from 2010 to 2016 January 2010 to December 2016. Those with adequate information on baseline and follow-up (more than 3 months) characteristics were included in this study. Exclusion criteria was defined as familial hyperuricemia, transient hyperuricemia, primary gout, transient tubular injury, malignant hypertension, pregnancy, renal cancer, cirrhosis, recent chemotherapy or immunosuppressive therapy, solid organ transplantation, or patients receiving dialysis therapy[11]. Patients who were unable to provide consent or enrolling in competing studies were excluded as well. Finally, 800 individuals (383 males and 417 females) were included in the present study. The baseline and follow up clinical and demographic characteristics were collected from our RTS database, including age, gender, serum uric acid level, estimated glomerular filtration rate (eGFR), serum creatinine, urea, albumin level, 24 hours urinary protein quantitation (24h-u-pro) and blood pressure measurements (BP). The eGFR was calculated by the CKD-EPI (CKD Epidemiology Collaboration) equation[12].

The study was approved by the Ethics Committee of the Sichuan Provincial People's Hospital (Chengdu, China, No.2017-124) and all patients signed informed consents to join in this study.

Definitions

ESRD was defined as eGFR <15 mL/min/1.73 m², initiation of dialysis for more than 3 months or receiving transplantation[13]. The **primary endpoint** was defined as a composite of a decline in eGFR by > 30% from baseline, doubling creatinine and development of ESRD. Hyperuricemia was defined as a fasting serum uric acid more than 420μmol/L (7mg/dl) for male and more than 357μmol/L (6mg/dl) for female [14].

Statistical analysis

Proportions was used to describe categorical variables. Mean $\pm$ standard deviation (SD) (normally distributed) or median (range) with interquartile ranges (IQR) (non-normally distributed) were used to displayed continuous variables. When comparing the differences between groups, continuous data were compared using the student t-test and comparisons of categorical variables were performed by the Chi-square test. Cox regression model analysis was used to evaluate the risk factors for CKD progression. The Kaplan–Meier analysis was used to test associations between serum uric acid levels and renal survival rates.

Results

Baseline and follow-up clinical characteristics

Among all the 800 individuals, the median follow up was 10.3 months, and the mean baseline serum uric acid level was 371.60 $\mu\text{mol/L}$ (21.73mg/dl). Hyperuricemia was seen in 306 (157 males and 149 females) of 800 (38.3%) (383 males and 417 females) patients. Patients with hyperuricemia had worse renal function, as compared to those without hyperuricemia (Table 1).

With a median follow-up period of 10.3 months, a total of 107 (13.4%) patients reached the primary endpoint. The number of patients who had reductions in eGFR by $> 30\%$, doubling Cr and development of ESRD were 105, 19, 8 (13.1%, 2.4%, 1.0%), respectively. The average annual declining rate of eGFR in all patients, HUA group and non-HUA group were 1.5%, 1.1%, 1.6%, respectively (Table 2).

Uric acid levels contributed to the complex endpoint

The univariate Cox regression analysis showed that age, gender, serum uric acid levels, Cr, eGFR were associated with the primary outcome (Table 3). The previous literature showed that urinary protein and serum albumin level were also closely related to the progression of renal function in CKD patients. Therefore, we added these two variables to perform the multivariate Cox regression analysis. Six different models (Model 1: Cr + age + BP + gender; Model 2: eGFR + age + BP + gender; Model 3: Cr + 24h-u-pro + age + BP + gender; Model 4: Cr + Alb + age + BP + gender; Model 5: eGFR + 24h-u-pro + age + BP + gender; Model 6: eGFR +Alb + age + BP + gender) were constructed. All the models suggested that HUA

was a risk factor for the progression of CKD. Furthermore, model 4 (adjusted for Cr + Alb + age + BP + gender) showed the highest risk with the largest HR value (HR:2.010, 95%CI:1.310-3.084, $P<0.05$) (Table 4).

Endpoints and survivals from combined renal endpoint in patients with different baseline **uric acid levels**

The cumulative survival rate of non-hyperuricemia group was higher than that of hyperuricemia group ($P<0.001$) (Figure 1).

Discussion

In this retrospective cohort study, we included 800 CKD patients and found that baseline hyperuricemia was associated with worse renal function. Patients with baseline hyperuricemia were more likely develop the composite renal outcomes. Our study also identified that age, gender, baseline renal function were predictors for CKD progression. A number of models used in our study confirmed that HUA was a risk factor for CKD progression. Furthermore, HUA in the model with adjustment for serum creatinine, albumin, age, gender and blood pressure demonstrated the highest risk of CKD progression by 2.1 folds.

With the change of life style and dietary structure, the incidence of hyperuricemia is on the rise due to the excessive production of uric acid or the decrease of uric acid excretion[15]. As the kidney is the main organ to excrete uric acid, renal impairment can cause hyperuricemia[16-19]. Hyperuricemia, in turn may also be associated with worsening renal function and has some effects on the development of CKD and the progression of CKD to ESRD[20, 21]. Most scholars believe that uric acid itself may harm patients with CKD by contributing to increased inflammation and CKD progression[7, 21, 22]. However, some studies did not show an effect of hyperuricemia on worsening renal function. For example, a study involving 5808 patients with 5 years of follow-up showed no significant association between increased serum uric acid levels and CKD progression[4]. Our finding was in line with most studies, and showed that hyperuricemia was a strong risk factor for CKD progression. In addition, our previous study showed that serum uric acid not only correlated with renal function, but also with renal pathology. Hyperuricemia was an independent risk factor for segmental glomerulosclerosis and tubular atrophy/interstitial fibrosis[11]. Uric acid may be considered as a marker for tubulointerstitial lesions in early stage of IgAN[23]. In this

study, further subgroup analysis in patients with IgA nephropathy also showed that hyperuricemia was associated with worse renal function and lower survivals (Table 5).

Our study has the following strength. Firstly, in this retrospective study, we included 800 CKD patients and found that the baseline and follow-up data were recorded. Baseline uric acid levels were found to be associated with end-point renal events. Secondly, uric acid predicts adverse outcomes in renal function. What is more, the association of HUA and the progression of CKD, suggests that early treatment of hyperuricemia is necessary in order to slow CKD progression.

Our study has several limitations. Firstly, short duration of follow up of the study did not allow us to assess the long-term prognosis of patients. Secondly, we were unable to justify if patients received uric acid-lowering drugs or not due to lack of information on pharmaceutical therapies in this dataset. Thirdly, as a retrospective study, potential confounders may not be collected and included in our analyses, which may have an impact on the results.

Conclusion

Hyperuricemia was not only widespread in patients with CKD, but also a risk factor for the progression of CKD. Anti-hyperuricemia therapy may need to be considered in CKD patients to slow the disease progression, which needs to be tested further in clinical studies.

Abbreviations

CKD: chronic kidney disease

HUA: hyperuricemia

RTS: Renal Treatment System

UA: uric acid

eGFR: glomerular filtration rate

Cr: creatinine

Alb: albumin

24h-u-pro: 24 hours protein quantitation

BP: blood pressure

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Sichuan Provincial People's Hospital (Chengdu, China, No.2017-124). The de-identified data was obtained from RTS database. All patients gave fully informed written consent.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interest

All authors declare that they have no competing interests.

Funding

This study was supported by Health and Family Planning Commission of Sichuan Province Research Project (17PJ062), Youth Science and Technology Creative Research Groups of Sichuan Province (2015TD0013), Sichuan Science and Technology Department project (2015SZ0245, 19PTDJ0018). Dr Amanda Y Wang was supported by National Heart Foundation Postdoctoral fellowship.

Authors' contribution

FSL collected and processed the data, helped with the study design and drafted the manuscript. ZY collected the data and helped to draft the manuscript. XMJ processed the data and performed the statistical analysis. HDQ, WAY, and LGS conceived the study, participated in its design and coordination. All authors read and approved the final manuscript.

Acknowledgement

This study was supported by Health and Family Planning Commission of Sichuan Province Research Project (17PJ062), Youth Science and Technology Creative Research Groups of Sichuan Province (2015TD0013), Sichuan Science and Technology Department project (2015SZ0245, 19PTDJ0018). Dr Amanda Y Wang was supported by National Heart Foundation Postdoctoral fellowship.

We are grateful to all the subjects who participated in this study.

References

1. Mortality GBD, Causes of Death C: **Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013.** *Lancet* 2015, **385**(9963):117-171.
2. Zhang L, Wang F, Wang L, Wang W, Liu B, Liu J, Chen M, He Q, Liao Y, Yu X *et al*: **Prevalence of chronic kidney disease in China: a cross-sectional survey.** *Lancet* 2012, **379**(9818):815-822.
3. Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, Fok M, McAlister F, Garg AX: **Chronic kidney disease and mortality risk: a systematic review.** *Journal of the American Society of Nephrology : JASN* 2006, **17**(7):2034-2047.
4. Chonchol M, Shlipak MG, Katz R, Sarnak MJ, Newman AB, Siscovick DS, Kestenbaum B, Carney JK, Fried LF: **Relationship of uric acid with progression of kidney disease.** *American journal of kidney diseases : the official journal of the National Kidney Foundation* 2007, **50**(2):239-247.
5. Li L, Yang C, Zhao Y, Zeng X, Liu F, Fu P: **Is hyperuricemia an independent risk factor for new-onset chronic kidney disease?: A systematic review and meta-analysis based on observational cohort studies.** *BMC nephrology* 2014, **15**:122.
6. Mohandas R, Johnson RJ: **Uric acid levels increase risk for new-onset kidney disease.** *Journal of the American Society of Nephrology : JASN* 2008, **19**(12):2251-2253.
7. Obermayr RP, Temml C, Gutjahr G, Knechtelsdorfer M, Oberbauer R, Klauser-Braun R: **Elevated uric acid increases the risk for kidney disease.** *Journal of the American Society of Nephrology : JASN* 2008, **19**(12):2407-2413.

8. Keenan T, Zhao W, Rasheed A, Ho WK, Malik R, Felix JF, Young R, Shah N, Samuel M, Sheikh N *et al*: **Causal Assessment of Serum Urate Levels in Cardiometabolic Diseases Through a Mendelian Randomization Study**. *Journal of the American College of Cardiology* 2016, **67**(4):407-416.
9. Perez-Ruiz F, Martinez-Indart L, Carmona L, Herrero-Beites AM, Pijoan JI, Krishnan E: **Tophaceous gout and high level of hyperuricaemia are both associated with increased risk of mortality in patients with gout**. *Annals of the rheumatic diseases* 2014, **73**(1):177-182.
10. Liu R, Han C, Wu D, Xia X, Gu J, Guan H, Shan Z, Teng W: **Prevalence of Hyperuricemia and Gout in Mainland China from 2000 to 2014: A Systematic Review and Meta-Analysis**. *BioMed research international* 2015, **2015**:762820.
11. Fan S, Zhang P, Wang AY, Wang X, Wang L, Li G, Hong D: **Hyperuricemia and its related histopathological features on renal biopsy**. *BMC nephrology* 2019, **20**(1):95.
12. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T *et al*: **A new equation to estimate glomerular filtration rate**. *Annals of internal medicine* 2009, **150**(9):604-612.
13. Inker LA, Lambers Heerspink HJ, Mondal H, Schmid CH, Tighiouart H, Noubary F, Coresh J, Greene T, Levey AS: **GFR decline as an alternative end point to kidney failure in clinical trials: a meta-analysis of treatment effects from 37 randomized trials**. *American journal of kidney diseases : the official journal of the National Kidney Foundation* 2014, **64**(6):848-859.
14. Weisman MH, Gano AD, Jr., Gabriel SE, Hochberg MC, Kavanaugh A, Ofman JJ, Prashker M, Suarez-Almazor ME, Yelin E, Nakelsky SD *et al*: **Reading and interpreting economic evaluations in rheumatoid arthritis: an assessment of selected instruments for critical appraisal**. *The Journal of rheumatology* 2003, **30**(8):1739-1747.
15. Diamond HS, Paolino JS: **Evidence for a postsecretory reabsorptive site for uric acid in man**. *The Journal of clinical investigation* 1973, **52**(6):1491-1499.
16. Ryu ES, Kim MJ, Shin HS, Jang YH, Choi HS, Jo I, Johnson RJ, Kang DH: **Uric acid-induced phenotypic transition of renal tubular cells as a novel mechanism of chronic kidney disease**. *American journal of physiology Renal physiology* 2013, **304**(5):F471-480.
17. Aroor AR, Jia G, Habibi J, Sun Z, Ramirez-Perez FI, Brady B, Chen D, Martinez-Lemus LA, Manrique C, Nistala R *et al*: **Uric acid promotes vascular stiffness, maladaptive inflammatory responses and proteinuria in western diet fed mice**. *Metabolism: clinical and experimental* 2017, **74**:32-40.
18. Cai W, Duan XM, Liu Y, Yu J, Tang YL, Liu ZL, Jiang S, Zhang CP, Liu JY, Xu JX: **Uric Acid Induces Endothelial Dysfunction by Activating the HMGB1/RAGE Signaling Pathway**. *BioMed research international* 2017, **2017**:4391920.
19. Jalal DI, Decker E, Perrenoud L, Nowak KL, Bispham N, Mehta T, Smits G, You Z, Seals D, Chonchol M *et al*: **Vascular Function and Uric Acid-Lowering in Stage 3 CKD**. *Journal of the American Society of Nephrology : JASN* 2017, **28**(3):943-952.
20. Johnson RJ, Nakagawa T, Jalal D, Sanchez-Lozada LG, Kang DH, Ritz E: **Uric acid and chronic kidney disease: which is chasing which?** *Nephrology, dialysis, transplantation : official publication of the*

European Dialysis and Transplant Association - European Renal Association 2013, **28**(9):2221-2228.

21. Tsai CW, Chiu HT, Huang HC, Ting IW, Yeh HC, Kuo CC: **Uric acid predicts adverse outcomes in chronic kidney disease: a novel insight from trajectory analyses.** *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association* 2018, **33**(2):231-241.
22. Weiner DE, Tighiouart H, Elsayed EF, Griffith JL, Salem DN, Levey AS: **Uric acid and incident kidney disease in the community.** *Journal of the American Society of Nephrology : JASN* 2008, **19**(6):1204-1211.
23. Zhou J, Chen Y, Liu Y, Shi S, Li X, Wang S, Zhang H: **Plasma uric acid level indicates tubular interstitial lesions at early stage of IgA nephropathy.** *BMC nephrology* 2014, **15**:11.

Tables

Table 1 Baseline and follow-up clinical characteristics of HUA and non-HUA groups

	Total n=800	HUA n=306	non-HUA n=494	<i>P</i>
Age at entry(years)	36.6±14.4	27.1±14.1	36.3±14.6	0.487
Male (n, %)	383(47.8)	157(51.3)	226(45.7)	0.126
Cr (μmol/L)	82.08±41.40	98.55±51.28	71.87±29.63	<0.001
eGFR (ml/min/1.73m ²)	99.23±31.54	87.11±34.90	106.73±26.68	<0.001
Urea (mmol/L)	6.41±3.28	7.60±4.11	5.67±2.36	<0.001
Alb (g/L)	33.24±9.29	33.72±9.16	32.94±9.37	0.257
UA (μmol/L)	371.60±103.18	472.0±76.41	309.39±59.20	<0.001
24h-u-pro (g/d)	1.64(0.52,3.99)	1.71(0.76,3.86)	1.54(.031,4.05)	0.725
IgAN (n, %)	331(41.4)	143(46.7)	188(38.1)	0.015

Table 2 Follow-up clinical characteristics of HUA and non-HUA groups

	Total n=800	HUA n=306	non-HUA n=494	P
Cr (μmol/L)	90.58±80.45	103.17±63.90	82.79±88.34	<0.001
eGFR (ml/min/1.73m ²)	96.58±33.44	85.80±36.51	103.26±29.52	<0.001
Urea (mmol/L)	6.45±3.40	7.44±4.12	5.85±2.71	<0.001
Alb (g/L)	40.01±7.66	39.58±8.00	40.27±7.44	0.242
UA (μmol/L)	386.70±109.46	442.86±101.14	352.01±99.64	<0.001
24h-u-pro (g/d)	0.39(0.09,1.61)	0.49(0.15,1.72)	0.35(0.07,1.58)	0.456
Follow-up time (month)	10.3(4.4,22.5)	11.4(4.3,23.6)	10.0(4.6,21.6)	0.271
Change rate of eGRF	-1.5%(-14.9%,5.9%)	-1.1%(-19.5%,9.7%)	-1.6%(-13.6%,5.0%)	0.420
Endpoint (n, %)	107(13.4)	58(19.0)	49(9.9)	<0.001
eGFR drops by 30%	105(13.1)	57(18.6)	48(9.7)	
Cr doubling	19(2.4)	4(1.3)	15(3.0)	
ESRD	8(1.0)	3(1.0)	5(1.0)	

Change rate of eGRF: Average annual change rate of eGRF. When the rate is greater than 0 indicates an increase in eGFR and renal function improves. When the rate is less than 0 indicates a decline in eGFR and renal function deteriorates.

Table 3 Univariate Cox regression analysis for outcome in the whole cohort

Index	HR	95%CI	P
age	1.021	1.008-1.034	0.002
gender	0.666	0.450-0.985	0.042
BP	1.152	0.735-1.803	0.538
UA	1.002	1.001-1.004	0.006
HUA	2.032	1.389-2.972	<0.001
Cr	1.003	1.000-1.007	0.078
eGFR	0.988	0.983-0.994	<0.001
Urea	1.072	1.025-1.121	0.002
24h-u-pro	1.021	0.989-1.053	0.201
Alb	0.984	0.964-1.004	0.116
IgAN	1.282	0.877-1.873	0.200

Table 4 Multivariate Cox regression analysis for composite endpoint in the whole cohort

	HR ¹	HR ²	HR ³	HR ⁴	HR ⁵	HR ⁶
	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)
HUA	1.909 △	1.699 △	1.872 △	2.010 △	1.658 △	1.774 △
	(1.250-2.916)	(1.101-2.623)	(1.198-2.923)	(1.310-3.084)	(1.050-2.620)	(1.154-2.749)

△: P<0.05

HR1: adjusted for Cr + age + BP + gender

HR2: adjusted for eGFR + age + BP + gender

HR3: adjusted for Cr + 24h-u-pro + age + BP + gender

HR4: adjusted for Cr + Alb + age + BP + gender

HR5: adjusted for eGFR + 24h-u-pro + age + BP + gender

HR6: adjusted for eGFR +Alb + age + BP + gender

HUA: hyperuricemia

Table 5 Multivariate Cox regression analysis for composite endpoint in IgAN

	HR ¹	HR ²	HR ³	HR ⁴	HR ⁵	HR ⁶
	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)	(95%CI)
HUA	2.608 △	2.058 △	2.637 △	2.921 △	2.010	2.280 △
	1.358-5.009	1.047-4.045	1.295-5.369	1.491-5.723	0.958-4.214	1.141-4.555

△: P<0.05

HR1: adjusted for Cr + age + BP + gender

HR2: adjusted for eGFR + age + BP + gender

HR3: adjusted for Cr + 24h-u-pro + age + BP + gender

HR4: adjusted for Cr + Alb + age + BP + gender

HR5: adjusted for eGFR + 24h-u-pro + age + BP + gender

HR6: adjusted for eGFR +Alb + age + BP + gender

HUA: hyperuricemia

Figures

Figure 1

The cumulative survival rate of non-hyperuricemia group (blue) was higher than that of hyperuricemia group (green). P-value was less than 0.001 according to Log-rank test.