GAVIN PUBLISHERS

OPEN ACCESS

Journal of Urology and Renal Diseases

Research Article

Zhang Y, et al. J Urol Ren Dis 05: 1198.

DOI: 10.29011/2575-7903.001198

Hyperuricemia is the Independent Risk Factor of All-Cause Mortality in Aged Patients with Chronic Kidney Disease

Yun-qiang Zhang[1], Min-jia Li[1], Hong-yong Liu[1], Shu-xia Fu[1], Rong Li[1] and Xun-Liu[2*]

[1]Department of nephrology, The Third Affiliated Hospital, Sun Yat-Sen University, Yuedong Hospital, Meizhou city, Guangdong province, China

[2]Department of Nephrology, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

[*]**Corresponding author:** Xun Liu, Department of Nephrology, The Third Affiliated Hospital of Sun Yat-sen University, Guangzhou 510630, China

Citation: Zhang Y, Li M, Liu H, Fu S, Li R (2020) Hyperuricemia is the Independent Risk Factor of All-Cause Mortality in Aged Patients with Chronic Kidney Disease. J Urol Ren Dis 05: 1198. DOI: 10.29011/2575-7903.001198

Received Date: 01 September, 2020; **Accepted Date:** 21 September, 2020; **Published Date:** 25 September, 2020

Abstract

Objectives: To investigate the relationship between hyperuricemia and all-cause mortality in aged chronic kidney disease (CKD) patients.

Methods: A retrospective case-controlled study was carried out on 536 Chinese patients (age; 64-74 years) with CKD. The link between hyperuricemia and all-cause mortality in these patients was analyzed using Cox proportional hazards model. In this study, baseline data included: demographic data (age and gender), eGFR (CKD-Epi equation), urate-lowering drug application, nutritional index (BMI, albumin, total cholesterol, triglyceride, fasting blood glucose, low density lipoprotein, high density lipoprotein, pre-albumin), kidney function indices (potassium, carbon dioxide combining power, calcium, phosphorus, urea nitrogen) and proteinuria.

Results: Out of the 536 patients (age range; 64–74 years; median age; 69 years), 274 (51.1%) had hyperuricemia and 82 deaths (15.3%) were recorded. After the data was corrected for confounding factors, the results showed hyperuricemia（HUA ≥360 μmol/L in females and ≥420 μmol/L in males）as the independent risk factor of all-cause mortality in aged patients with CKD (β=1.81, P=.0032).This was corroborated by a positive correlation between the levels of uric acid in the serum and all-cause mortality (β=1.002, P=.0036), whereby, the lowest group（serum uric acid：90.8-310.14μmol/L）was protected from all-cause mortality (β=0.445, P=0.004) unlike the next highest group（serum uric acid：310.15-401.54μmol/L).

Conclusion: Herein, we found that hyperuricemia could be a distinctive risk factor of all-cause mortality in aged CKD patients. Also, uric acid levels in the serum were positively related to all-cause mortality. The 4th serum uric acid quartile was protective for all-cause mortality, compared with the 2nd serum uric acid quartile.

Keywords: Aged; All-cause mortality; Chronic kidney disease; Hyperuricemia

List of Abbreviations: ANOVA: Analysis Of Variance; BMI: Body Mass Index; CKD: Chronic Kidney Disease; eGFR: Estimated Glomerular Filtration Rate; ESRD: End-Stage Renal Disease; GFR: Glomerular Filtration Rate; HUA: Hyperuricemia; WHO: World Health Organization

Introduction

The current global prevalence of Chronic Kidney Disease (CKD) is 13.4% [1]. However, the awareness rate is 9.5% and its mortality is 1.5% [2]. The condition is one of the top 20 causes of death globally. Deaths due to CKD increased by 34% worldwide between 1990 and 2013 [3], making CKD a "silent killer" [4]. Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation using creatinine measurement is used globally to estimate glomerular filtration rate (eGFR) [5]. An aging population is a global issue [6] with the number of individuals older than 60 years increasing at an annual rate of 2.6% [7]. Although there is no exact definition of "elderly" most developed countries define it as an age ≥ 65 years [8] , while the standard is ≥ 60 years in most developing countries [9]. The structure and functionality of kidneys gradually decline at a rate of 6.3mL/min per 1.73m^2 every 10 years, with increase in age [10]. Renal efficiency has been shown to diminish with age [11] with an incidence rate of between 23.4% and 58.5% in the

elderly [12-15]. As people age, renal uric acid excretion is reduced, hence becoming more susceptible to Hyperuricemia (HUA) [16]. The prevalence of HUA in American adults was 21.4% [17]. CKD has a higher prevalence in those suffering from hyperuricemia relative to the rest of the population [18]. Evidence indicates that the possibility of kidney function deterioration increases by 14% for each 1 mg/dl rise in uric acid level in the serum [19]. One study showed that for every 60umol/L rice in the levels of uric acid in the serum, there is a 17% increase in all-cause mortality [20] but other studies have concluded otherwise [21]. So far, only a few papers have examined the link between uric acid levels in the serum and death in aged CKD patients. Considering that CKD occurs more frequently, understanding the potential connection between these two will improve the clinical management of CKD patients. Herein, we enrolled aged CKD patients to delineate the impact of uric acid levels in the serum on mortality rates.

Methodology

Patient recruitment and methods

From January 1, 2009 to July 31, 2016 536 inpatients were enrolled from the Third Affiliated Hospital of Sun Yat-sen University and were followed up until December 31, 2016. The inclusion criteria included: age ≥18 years, CKD and complete (99m) Tc-DTPA renal dynamic imaging. Patients with incomplete clinical data and initiation of renal replacement therapy were excluded from the study.

Baseline data collection and Biochemical Evaluation

Baseline data included demographic characteristics (age and gender) and measurement index (BMI and eGFR). The data also included blood Analysis Of Albumin (ALB), Fasting Blood Glucose (FBS), Total Cholesterol (CHOL), triglyceride, High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), Hemoglobin (HGB), pre-albumin, Potassium (K), carbon dioxide combining power (CO_2CP), Calcium (Ca), Phosphorus (P) and Blood Urea Nitrogen (BUN). We applied the CKD-EPI equation to compute the urine routine including, medication status of urate-lowering drug use and eGFR [22].

CKD-EPI equation for eGFR

$GFR=141\times\min(Scr/0.9,1)^{-0.4111}\times\max(Scr/0.9,1)^{-1.209}\times0.993^{Age}\times1.159$ (if black), if male

$GFR=141\times1.018\times\min(Scr/0.7,1)^{-0.329}\times\max(Scr/0.7,1)^{-1.209}\times0.993^{Age}\times1.159$ (if black), if female

Definition

Hyperuricemia referred to serum UA ≥360 μmol/L in females and ≥420 μmol/L in males [23].

Statistical analyses

Data analysis was completed with SPSS statistical software version 22.0. Normality of the data was determined with Kolmogorov-Smirnov test (P>0.05) Table 1). Continuous variables that met the normal distribution parameters were reported as the mean ± SD. Other variables were presented as median (interquartile range). Chi-square and Wilcoxon rank sum tests were employed to analyze continuous variables and compare the categorical variables, respectively. Analysis of Variance (ANOVA) was used to compare different treatments. Cox proportional hazards model was utilized for multivariate analysis. Confounding factors were adjusted by 7 models as described below. Variables with P<0.1 in univariate evaluations were subjected to multivariate assessments.

Model I: non-adjusted.

Model II: adjusted demographic data (gender & age).

Model III: adjusted demographic data (gender & age), eGFR and urate-lowering drug application.

Model IV: adjusted model 3 plus nutritional index (BMI, albumin, fasting blood glucose, triglyceride, CHOL, HDL, LDL, prealbumin, HGB).

Model V: adjusted model 3 plus kidney function indices (potassium, carbon dioxide combining power, calcium, phosphorus, urea nitrogen).

Model VI: adjusted model 3 plus proteinuria.

Model VII: adjusted all factors.

Variables	Normal Parameters[a,b]		Most Extreme Differences			Test Statistic	Asymp. Sig. (2-tailed)
	Mean	Std. Deviation	Absolute	Positive	Negative		
Age	69.752	6.625	0.083	0.083	-0.071	0.083	.000[c]
BMI	24.444	3.497	0.047	0.047	-0.025	0.047	.007[c]
ALB	38.189	4.632	0.056	0.032	-0.056	0.056	.000[c]
K	4.111	0.521	0.066	0.066	-0.042	0.066	.000[c]
CO_2CP	22.741	3.331	0.036	0.018	-0.036	0.036	.086[c]
CA	2.273	0.162	0.043	0.043	-0.043	0.043	.018[c]
P	1.190	0.263	0.095	0.095	-0.068	0.095	.000[c]
FBS	7.273	3.796	0.176	0.176	-0.152	0.176	.000[c]

BUN	9.766	6.786	0.189	0.189	-0.148	0.189	.000[c]
UA	410.498	142.881	0.047	0.047	-0.023	0.047	.007[c]
CHOL	4.724	1.293	0.055	0.055	-0.034	0.055	.001[c]
TRI	1.955	1.634	0.182	0.182	-0.181	0.182	.000[c]
HDL-C	1.203	0.675	0.228	0.228	-0.168	0.228	.000[c]
LDL-C	2.780	1.091	0.043	0.043	-0.033	0.043	.018[c]
HGB	115.935	22.216	0.079	0.041	-0.079	0.079	.000[c]
Prealbumin	228.441	69.432	0.036	0.036	-0.034	0.036	.095[c]
e-GFR	54.805	30.668	0.089	0.069	-0.089	0.089	.000[c]

a. Test distribution is Normal.
b. Calculated from data.
c. Lilliefors Significance Correction.

Table 1: One-Sample Kolmogorov-Smirnov Test.

Results

Baseline characteristics of all the patients

Baseline features were presented based on quartiles of uric acid levels in the serum with the participants being classified into 4 groups according to SUA quartiles. The 1st, 2nd, 3rd and 4th quartiles were: 808-504.15μmol/L, 401.55-504.14μmol/L, 310.15-401.54μmol/L and 90.8-310.14μmol/L, respectively. The patient's age was between 64-74 years, with the median age being 69 years. Out of the 536 patients, 285 (53.2%) were males and 251 (46.8%) females. The estimated GFR（CKD-Epi equation）was24.093 (22.195.26.573)/ min/1.73m^2. Deaths recorded were 82(15.3%) and 274 patients (51.1%) had hyperuricemia (Table 2).

Item	All participants	Q1：808-504.15μmol/L	Q2：401.55-504.14μmol/L	Q3：310.15-401.54μmol/L	Q4：90.8-310.14μmol/L	P
	n=536	n=134	n=134	n=134	n=134	
Age(Years）	69(64,74)	70(64,75.25)	68(64,74)	70(65,75)	68(63,73)	0.159
Gender, (% male)	285(53.2)	88(16.4)	84(15.7)	66(12.3)	47(8.8)	0.000
BMI(kg/m^2)	24.093(22.195,26.573)	24.529(22.642,26.819)	24.719(22.86,26.977)	23.788(22.006,25.904)	23.379(20.944,25.921)	0.000
ALB(g/L)	38.6(35.4,41.2)	38.6(35.2,41.)	38.55(34.975,41.15)	38.05(35.175,40.825)	39.3(36.075,41.125)	0.578
K(mmol/L)	4.07(3.77,4.37)	4.24(3.938,4.593)	4.04(3.76,4.333)	4.075(3.808,4.36)	3.925(3.63,4.283)	0.000
CO_2CP（mmol/l）	22.741±3.331	21.855±3.747	22.634±2.949	22.643±3.206	23.831±3.101	0.022
CA(mmol/L)	2.28(2.18,2.37)	2.295(2.180,2.393)	2.305(2.19,2.39)	2.28(2.18,2.383)	2.25(2.16,2.33)	0.149
P(mmol/L)	1.16(1.04,1.308)	1.24(1.1,1.383)	1.18(1.06,1.34)	1.13(1.03,1.25)	1.12(0.99,1.243)	0.000
FBS(mmol/L)	6.02(4.83,8.11)	5.515(4.708,7.053)	5.64(4.78,7.07)	6.485(5.11,8.77)	6.805(4.948,10.843)	0.000
BUN(mmol/L)	7.39(5.583,11.248)	10.55(7.818,19.08)	7.93(5.94,12.055)	6.775(5.16,9.485)	5.725(4.525,7.443)	0.000

UA(μmol/L)	401.55(310.15,504.15)	587.25(540.725,656.5)	448.75(423.775,474.95)	347.5(330.925,374.775)	242.5(206.375,279.025)	0.000
Diabetes[n, (%)]	389(72.6)	87(16.2)	95(17.7)	102(19)	105(19.6)	0.065
Proteinuria[n, (%)]						0.004
(-)	323(60.3)	70(13.1)	71(13.2)	85(15.9)	97(18.1)	
(±)~(+)	97(18.1)	25(4.7)	26(4.9)	27(5)	19(3.5)	
(++) or more	116(21.6)	39(7.3)	37(6.9)	22(4.1)	18(3.4)	
CHOL (mmol/L)	4.605(3.805,5.54)	4.41(3.748,5.54)	4.615(3.798,5.4)	4.68(3.8,5.648)	4.675(3.878,5.345)	0.738
TRI(mmol/L)	1.555(1.07,2.276)	1.75(1.208,2.7)	1.5(1.008,2.29)	1.575(1.163,2.213)	1.4(0.94,1.925)	0.002
HDLC(mmol/L)	1.035(0.853,1.26)	0.95(0.78,1.18)	0.98(0.85,1.235)	1.07(0.88,1.303)	1.135(0.975,1.435)	0.000
LDLC(mmol/L)	2.695(1.93,3.48)	2.63(1.905,3.618)	2.695(1.905,3.338)	2.66(1.985,3.583)	2.79(1.955,3.483)	0.908
HGB(g/L)	120(102,132)	11(92,128)	120.5(103,135.25)	121(107,133)	124(103.75,132.25)	0.002
Prealbumin(mg/L)	228.44±69.432	252.16±71.335	238.48±66.910	220.81±62.805	202.32±66.837	0.023
eGFR (CKD-EPI equation) (min/1.73m^2)	53.997(27.551,83.957)	31.663(15.107,51.758)	48.746(23.987,71.49)	60.289(36.645,87.11)	85.739(58.829,94.751)	0.000
CKD stage 1:(eGFR ≥ 90 mL/min/1.73m^2)[n,（%）]	92(17.2)	2(0.4)	11(2.1)	27(5)	52(9.7)	0.000
Hyperuricemia(%)	274(51.1)	134(25)	118(22)	22(4.1)	0(0)	0.000
Urate-lowering drug application [n, (%)]	28(5.2)	28(5.2)	8(1.5)	8(1.5)	5(0.9)	0.000
Death [n, (%)]	82 (15.3)	33(6.2)	24(4.5)	13(2.4)	12(2.2)	0.001

Table 2: Characteristics of the study participants.

Hyperuricemia versus all-cause mortality

In model I, hyperuricemia was positively correlated with all-cause mortality (β=2.319, P＜0.001). After correcting for confounding factors as per model II (β=2.37, P＜.001), model IV (β=1.793, P=.0027) and model VII (β=1.81, P=.0032), (the same correlation as in model I was observed. However, in model III (β=1.531, P=0.085), model V (β=1.59, P=.0069) and model VI (β=1.547, P=0.078) there was no correlation with regards to hyperuricemia versus all-cause mortality (Table 3A).

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
model 1								
hyperuricemia	0.841	0.236	12.75	1	0	2.319	1.462	3.68
model 2								

hyperuricemia	0.797	0.236	11.396	1	0.001	2.22	1.397	3.527
Age	0.063	0.016	15.254	1	0	1.065	1.032	1.099
Gender	0.433	0.23	3.55	1	0.06	1.542	0.983	2.421
model 3								
hyperuricemia	0.426	0.247	2.967	1	0.085	1.531	0.943	2.487
Age	0.058	0.016	12.59	1	0	1.06	1.026	1.094
Gender	0.365	0.23	2.516	1	0.113	1.44	0.918	2.26
eGFR (CKD-EPI)	-0.019	0.004	18.445	1	0	0.981	0.972	0.99
Urate-lowering drug application	-0.017	0.361	0.002	1	0.961	0.983	0.485	1.993
model 4								
hyperuricemia	0.584	0.264	4.874	1	0.027	1.793	1.068	3.01
Age	0.056	0.017	11.376	1	0.001	1.058	1.024	1.093
Gender	0.84	0.267	9.886	1	0.002	2.315	1.372	3.908
eGFR (CKDEPI)	-0.011	0.006	3.401	1	0.065	0.989	0.977	1.001
Urate-lowering drug application	0.348	0.375	0.858	1	0.354	1.416	0.679	2.953
BMI	-0.01	0.034	0.084	1	0.772	0.99	0.927	1.058
ALB	0.007	0.029	0.053	1	0.818	1.007	0.951	1.066
FBS	0.027	0.036	0.568	1	0.451	1.028	0.957	1.104
CHOL	-0.016	0.201	0.006	1	0.936	0.984	0.664	1.459
TRI	0.192	0.09	4.537	1	0.033	1.212	1.015	1.446
HDLC	0.202	0.186	1.177	1	0.278	1.224	0.85	1.762
LDLC	0.225	0.18	1.558	1	0.212	1.252	0.88	1.781
HGB	-0.024	0.007	12.703	1	0	0.977	0.964	0.989
Prealbumin	-0.006	0.002	8.339	1	0.004	0.994	0.99	0.998
model 5								
hyperuricemia	0.464	0.255	3.312	1	0.069	1.59	0.965	2.62
Age	0.059	0.017	12.232	1	0	1.06	1.026	1.096
Gender	0.333	0.232	2.053	1	0.152	1.395	0.885	2.2
eGFR (CKDEPI)	-0.016	0.006	6.754	1	0.009	0.984	0.973	0.996
Urate-lowering drug application	0.038	0.366	0.011	1	0.917	1.039	0.507	2.131
K	0.012	0.219	0.003	1	0.957	1.012	0.659	1.554
CO_2CP	0.014	0.036	0.149	1	0.7	1.014	0.945	1.088
CA	-0.917	0.722	1.614	1	0.204	0.4	0.097	1.645
P	-0.001	0.478	0	1	0.999	0.999	0.392	2.55
BUN	0.01	0.022	0.197	1	0.658	1.01	0.967	1.055
model 6								
hyperuricemia	0.436	0.247	3.112	1	0.078	1.547	0.953	2.511

Age	0.069	0.017	15.929	1	0	1.071	1.036	1.108
Gender	0.346	0.23	2.254	1	0.133	1.413	0.9	2.219
eGFR (CKDEPI)	-0.013	0.005	6.557	1	0.01	0.987	0.978	0.997
Urate-lowering drug application	-0.073	0.362	0.04	1	0.841	0.93	0.457	1.891
proteinuria	0.399	0.146	7.427	1	0.006	1.491	1.119	1.986
model 7								
hyperuricemia	0.594	0.277	4.599	1	0.032	1.81	1.052	3.114
Age	0.063	0.017	13.144	1	0	1.065	1.03	1.103
Gender	0.802	0.275	8.479	1	0.004	2.231	1.3	3.827
eGFR (CKDEPI)	-0.007	0.007	1.078	1	0.299	0.993	0.979	1.007
Urate-lowering drug application	0.318	0.383	0.686	1	0.407	1.374	0.648	2.912
BMI	-0.019	0.035	0.298	1	0.585	0.981	0.916	1.051
ALB	0.014	0.033	0.181	1	0.671	1.014	0.951	1.081
FBS	0.031	0.037	0.684	1	0.408	1.031	0.959	1.109
CHOL	-0.022	0.201	0.012	1	0.913	0.978	0.66	1.451
TRI	0.183	0.094	3.802	1	0.051	1.201	0.999	1.443
HDLC	0.129	0.19	0.464	1	0.496	1.138	0.784	1.651
LDLC	0.196	0.181	1.169	1	0.28	1.217	0.853	1.736
HGB	-0.023	0.007	10.115	1	0.001	0.978	0.964	0.991
Prealbumin	-0.007	0.002	9.489	1	0.002	0.993	0.989	0.998
K	-0.023	0.219	0.011	1	0.916	0.977	0.636	1.501
CO_2CP	0.007	0.037	0.038	1	0.846	1.007	0.937	1.082
CA	0.594	0.819	0.525	1	0.469	1.811	0.363	9.024
P	-0.077	0.494	0.025	1	0.876	0.926	0.351	2.438
BUN	0.009	0.023	0.148	1	0.7	1.009	0.964	1.056
proteinuria	0.299	0.16	3.494	1	0.062	1.349	0.986	1.846

Model 1: non-adjusted.
Model 2: adjusted demographic data (age and gender).
Model 3: adjusted demographic data (age and gender),eGFR and urate-lowering drug application.
Model 4: adjusted model 3 plus nutritional index(BMI,ALB, FBS，CHOL, TRI, HDLC, LDLC,HGB, prealbumin).
Model 5: adjusted model 3 plus kidney function indices (eGFR,K, CO2CP, calcium, phosphorus, urea nitrogen).
Model 6: adjusted model 3 plus proteinuria.
Model 7: adjusted all factors.

Table 3A: Cox proportional hazard regression analysis for association between hyperuricemia and all-cause mortality.

Serum uric acid levels versus all-cause mortality

The levels of uric acid in the serum was positively linked to all-cause mortality in; model I (β=1.003, P＜0.001), model II (β=1.003, P＜0.001), model V (β=1.002, P=.0047), model VI (β=1.002, P=0.022) and model 7 (β=1.002, P=.0036). No correlation was observed with regards to serum uric acid levels versus all-cause mortality in; model 3(β=1.002, P=0.053) and model 4(β=1.002, P=0.061) (Table 3B).

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
model 1								
UA	0.003	0.001	19.13	1	0	1.003	1.002	1.005
model 2								
UA	0.003	0.001	15.425	1	0	1.003	1.001	1.004
Age	0.061	0.016	14.544	1	0	1.063	1.03	1.097
Gender	0.333	0.232	2.053	1	0.152	1.395	0.885	2.199
model 3								
UA	0.002	0.001	3.74	1	0.053	1.002	1	1.003
Age	0.057	0.016	12.196	1	0	1.059	1.025	1.093
Gender	0.313	0.231	1.839	1	0.175	1.368	0.87	2.151
eGFR (CKD-EPI)	-0.019	0.005	17.155	1	0	0.981	0.973	0.99
Urate-lowering drug application	-0.073	0.362	0.041	1	0.839	0.929	0.457	1.889
model 4								
UA	0.002	0.001	3.505	1	0.061	1.002	1	1.003
Age	0.057	0.017	11.37	1	0.001	1.058	1.024	1.094
Gender	0.769	0.272	7.973	1	0.005	2.157	1.265	3.678
eGFR (CKDEPI)	-0.011	0.006	3.318	1	0.069	0.989	0.977	1.001
Urate-lowering drug application	0.269	0.377	0.511	1	0.475	1.309	0.626	2.739
BMI	-0.01	0.034	0.086	1	0.769	0.99	0.926	1.058
ALB	0.003	0.028	0.01	1	0.92	1.003	0.949	1.06
FBS	0.021	0.037	0.309	1	0.579	1.021	0.949	1.097
CHOL	0.008	0.199	0.002	1	0.969	1.008	0.682	1.489
TRI	0.179	0.09	3.926	1	0.048	1.196	1.002	1.428
HDLC	0.176	0.183	0.926	1	0.336	1.192	0.833	1.705
LDLC	0.194	0.178	1.186	1	0.276	1.214	0.856	1.721
HGB	-0.023	0.007	12.129	1	0	0.977	0.965	0.99
Prealbumin	-0.006	0.002	7.191	1	0.007	0.994	0.99	0.998
model 5								
UA	0.002	0.001	3.931	1	0.047	1.002	1	1.003
Age	0.057	0.017	11.616	1	0.001	1.059	1.025	1.094
Gender	0.276	0.234	1.386	1	0.239	1.318	0.832	2.086
eGFR (CKDEPI)	-0.016	0.006	6.641	1	0.01	0.985	0.973	0.996
Urate-lowering drug application	-0.027	0.368	0.005	1	0.942	0.974	0.473	2.003
K	0.038	0.222	0.029	1	0.865	1.039	0.672	1.605
CO_2CP	0.008	0.036	0.05	1	0.822	1.008	0.94	1.082

CA	-0.904	0.723	1.564	1	0.211	0.405	0.098	1.67
P	-0.046	0.487	0.009	1	0.925	0.955	0.368	2.481
BUN	0.007	0.022	0.096	1	0.757	1.007	0.964	1.052
model 6								
UA	0.002	0.001	5.277	1	0.022	1.002	1	1.004
Age	0.069	0.017	15.938	1	0	1.071	1.036	1.108
Gender	0.287	0.232	1.538	1	0.215	1.333	0.847	2.098
eGFR (CKDEPI)	-0.011	0.005	4.772	1	0.029	0.989	0.979	0.999
Urate-lowering drug application	-0.15	0.363	0.171	1	0.679	0.861	0.422	1.753
proteinuria	0.439	0.147	8.868	1	0.003	1.551	1.162	2.07
model 7								
UA	0.002	0.001	4.377	1	0.036	1.002	1	1.004
Age	0.065	0.018	13.602	1	0	1.067	1.031	1.105
Gender	0.724	0.279	6.714	1	0.01	2.062	1.193	3.564
eGFR (CKDEPI)	-0.006	0.007	0.709	1	0.4	0.994	0.98	1.008
Urate-lowering drug application	0.203	0.388	0.274	1	0.601	1.225	0.573	2.618
BMI	-0.021	0.035	0.351	1	0.554	0.979	0.914	1.049
ALB	0.011	0.032	0.116	1	0.733	1.011	0.95	1.076
FBS	0.023	0.038	0.372	1	0.542	1.023	0.95	1.101
CHOL	0.001	0.199	0	1	0.998	1.001	0.678	1.478
TRI	0.167	0.094	3.123	1	0.077	1.182	0.982	1.422
HDLC	0.098	0.185	0.282	1	0.595	1.103	0.767	1.587
LDLC	0.165	0.18	0.842	1	0.359	1.179	0.829	1.677
HGB	-0.022	0.007	9.884	1	0.002	0.978	0.965	0.992
Prealbumin	-0.006	0.002	8.242	1	0.004	0.994	0.99	0.998
K	0.009	0.221	0.002	1	0.967	1.009	0.654	1.558
CO_2CP	-0.003	0.037	0.006	1	0.938	0.997	0.928	1.072
CA	0.72	0.818	0.775	1	0.379	2.055	0.414	10.207
P	-0.165	0.507	0.105	1	0.745	0.848	0.314	2.291
BUN	0.006	0.023	0.071	1	0.79	1.006	0.962	1.053
proteinuria	0.359	0.165	4.762	1	0.029	1.432	1.037	1.977

Model 1: non-adjusted.
Model 2: adjusted demographic data (age and gender).
Model 3: adjusted demographic data (age and gender),eGFR and urate-lowering drug application.
Model 4: adjusted model 3 plus nutritional index(BMI,ALB, FBS，CHOL, TRI, HDLC, LDLC, prealbumin).
Model 5: adjusted model 3 plus kidney function indices (eGFR,K, CO2CP, calcium, phosphorus, urea nitrogen).
Model 6: adjusted model 3 plus proteinuria.
Model 7: adjusted all factors.

Table 3B: Cox proportional hazard regression analysis for association between serum uric acid levels and all-cause mortality.

Serum uric acid quartiles versus all-cause mortality

Serum uric acid quartiles were grouped into 4. Uric acid levels in the serum from the highest to the lowest group were;808-504.15μmol/L，401.55-504.14μmol/L，310.15-401.54μmol/L and 90.8-310.14μmol/L respectively. The third group was considered as the reference group. The lowest serum uric acid was protective for all-cause mortality in model 1 (β=0.398, P=0.009). In addition, the same correlation was observed in; the third serum uric acid quartile in model II (β=0.502, 0.423，P=0.047, 0.017) and the lowest serum uric acid group in model IV (β=0.478, 0.45, P=0.041, 0.039) and model VII (β=0.445, P=0.004). No correlation was observed with regards to serum uric acid quartiles versus all-cause mortality in models III, V and VII (Table 3C).

	B	SE	Wald	df	Sig.	Exp(B)	95.0% CI for Exp(B)	
							Lower	Upper
model 1								
The next highest group			.	0[a]	.			
The highest group	0.329	0.269	1.5	1	0.221	1.39	0.821	2.352
The next lowest group	-0.669	0.345	3.774	1	0.052	0.512	0.261	1.006
The lowest group	-0.921	0.355	6.755	1	0.009	0.398	0.199	0.797
model 2								
The next highest group			.	0[a]	.			
The highest group	0.255	0.269	0.895	1	0.344	1.29	0.761	2.188
The next lowest group	-0.689	0.347	3.941	1	0.047	0.502	0.254	0.991
The lowest group	-0.859	0.359	5.737	1	0.017	0.423	0.21	0.855
Age	0.062	0.016	14.938	1	0	1.064	1.031	1.098
Gender	0.302	0.234	1.662	1	0.197	1.352	0.855	2.138
model 3								
The next highest group			.	0[a]	.			
The highest group	0.021	0.276	0.006	1	0.941	1.021	0.594	1.753
The next lowest group	-0.538	0.348	2.39	1	0.122	0.584	0.296	1.155
The lowest group	-0.501	0.366	1.866	1	0.172	0.606	0.296	1.243
Age	0.059	0.016	12.725	1	0	1.06	1.027	1.095
Gender	0.299	0.232	1.665	1	0.197	1.348	0.856	2.123
eGFR (CKD-EPI)	-0.019	0.005	16.647	1	0	0.981	0.973	0.99
Urate-lowering drug application	-0.021	0.364	0.003	1	0.954	0.979	0.48	1.999
model 4								
The next highest group			.	0[a]	.			
The highest group	-0.166	0.289	0.33	1	0.566	0.847	0.481	1.492
The next lowest group	-0.739	0.361	4.183	1	0.041	0.478	0.235	0.97
The lowest group	-0.799	0.388	4.248	1	0.039	0.45	0.21	0.962
Age	0.059	0.017	12.067	1	0.001	1.06	1.026	1.096
Gender	0.763	0.273	7.826	1	0.005	2.145	1.257	3.66
eGFR (CKDEPI)	-0.01	0.006	2.764	1	0.096	0.99	0.978	1.002
Urate-lowering drug application	0.375	0.379	0.979	1	0.322	1.454	0.693	3.054

BMI	-0.015	0.034	0.183	1	0.669	0.985	0.921	1.054
ALB	0.01	0.029	0.127	1	0.722	1.011	0.954	1.071
FBS	0.028	0.037	0.578	1	0.447	1.028	0.957	1.104
CHOL	0.055	0.201	0.075	1	0.785	1.056	0.713	1.565
TRI	0.161	0.09	3.228	1	0.072	1.175	0.985	1.4
HDLC	0.117	0.179	0.425	1	0.515	1.124	0.791	1.596
LDLC	0.154	0.177	0.754	1	0.385	1.166	0.824	1.651
HGB	-0.025	0.007	13.747	1	0	0.975	0.962	0.988
Prealbumin	-0.006	0.002	8.325	1	0.004	0.994	0.99	0.998
model 5								
The next highest group			.	0[a]	.			
The highest group	-0.014	0.287	0.002	1	0.961	0.986	0.561	1.731
The next lowest group	-0.585	0.351	2.78	1	0.095	0.557	0.28	1.108
The lowest group	-0.585	0.376	2.42	1	0.12	0.557	0.267	1.164
Age	0.06	0.017	12.423	1	0	1.062	1.027	1.097
Gender	0.258	0.234	1.217	1	0.27	1.295	0.818	2.048
eGFR (CKDEPI)	-0.015	0.006	5.712	1	0.017	0.985	0.974	0.997
Urate-lowering drug application	0.048	0.371	0.017	1	0.898	1.049	0.507	2.17
K	0.007	0.22	0.001	1	0.973	1.007	0.654	1.552
CO_2CP	0.011	0.036	0.087	1	0.768	1.011	0.941	1.085
CA	-0.938	0.722	1.689	1	0.194	0.392	0.095	1.611
P	-0.052	0.485	0.012	1	0.914	0.949	0.367	2.456
BUN	0.012	0.023	0.298	1	0.585	1.012	0.968	1.058
model 6								
The next highest group			.	0[a]	.			
The highest group	0.124	0.279	0.196	1	0.658	1.132	0.654	1.957
The next lowest group	-0.485	0.35	1.915	1	0.166	0.616	0.31	1.224
The lowest group	-0.468	0.367	1.624	1	0.203	0.626	0.305	1.286
Age	0.069	0.017	16.026	1	0	1.072	1.036	1.109
Gender	0.275	0.233	1.399	1	0.237	1.317	0.835	2.078
eGFR (CKDEPI)	-0.012	0.005	5.255	1	0.022	0.988	0.979	0.998
Urate-lowering drug application	-0.088	0.365	0.059	1	0.809	0.915	0.448	1.872
proteinuria	0.408	0.148	7.595	1	0.006	1.503	1.125	2.008
model 7								
The next highest group			.	0[a]	.			
The highest group	-0.114	0.305	0.14	1	0.709	0.892	0.491	1.623
The next lowest group	-0.699	0.366	3.635	1	0.057	0.497	0.242	1.02
The lowest group	-0.81	0.395	4.199	1	0.04	0.445	0.205	0.965

Age	0.066	0.018	13.999	1	0	1.068	1.032	1.106
Gender	0.713	0.278	6.592	1	0.01	2.04	1.184	3.517
eGFR (CKDEPI)	-0.006	0.007	0.602	1	0.438	0.994	0.98	1.009
Urate-lowering drug application	0.341	0.388	0.771	1	0.38	1.406	0.657	3.006
BMI	-0.023	0.035	0.425	1	0.515	0.977	0.912	1.047
ALB	0.018	0.033	0.285	1	0.593	1.018	0.954	1.086
FBS	0.03	0.037	0.668	1	0.414	1.031	0.958	1.109
CHOL	0.044	0.2	0.049	1	0.824	1.045	0.706	1.548
TRI	0.152	0.093	2.666	1	0.103	1.164	0.97	1.398
HDLC	0.05	0.183	0.074	1	0.786	1.051	0.735	1.503
LDLC	0.133	0.179	0.553	1	0.457	1.142	0.805	1.621
HGB	-0.024	0.007	11.033	1	0.001	0.976	0.963	0.99
Prealbumin	-0.007	0.002	9.538	1	0.002	0.993	0.989	0.998
K	-0.028	0.221	0.016	1	0.898	0.972	0.63	1.499
CO_2CP	0.002	0.037	0.002	1	0.964	1.002	0.932	1.077
CA	0.606	0.815	0.553	1	0.457	1.833	0.371	9.063
P	-0.114	0.501	0.052	1	0.82	0.892	0.334	2.383
BUN	0.012	0.023	0.262	1	0.609	1.012	0.967	1.059
proteinuria	0.306	0.164	3.469	1	0.063	1.358	0.984	1.874

Model 1: non-adjusted.
Model 2: adjusted demographic data (age and gender).
Model 3: adjusted demographic data (age and gender),eGFR and urate-lowering drug application.
Model 4: adjusted model 3 plus nutritional index(BMI,ALB, FBS，CHOL, TRI, HDLC, LDLC,HGB, prealbumin).
Model 5: adjusted model 3 plus kidney function indices (eGFR,K, CO2CP, calcium, phosphorus, urea nitrogen).
Model 6: adjusted model 3 plus proteinuria.
Model 7: adjusted all factors.

Table 3C: Cox proportional hazard regression analysis for association between Serum uric acid quartiles and all-cause mortality.

Discussion

After correcting for confounding factors, cox proportional hazards analysis revealed that hyperuricemia is the distinct risk factors of all-cause mortality in aged CKD patients, with 81% increment risk. The uric acid levels in the serum were positively correlated with all-cause mortality, with lower levels exhibiting significant protective effect for all-cause mortality. The results presented herein are similar to findings from other studies [24-27]. Nevertheless, hyperuricemia was also a protective factor of all-cause death but such results were only observed in hemodialysis patients [28,29]. Hyperuricemia may thus considered a marker in hemodialysis patients. Some studies have shown a J-shaped link in serum uric acid levels versus mortality [30,31]. Moreover,a clinical and cohort studies showed that hyperuricaemia was an independent risk factor for CKD progression in children and adolescents [32]. These studies however, did not target the aged population whereas this study majorly focused on an aged CKD population, a large sample size, complete follow-up and exclusion of confounding factors. Since the number of people suffering from hyperuricemia or CKD is constantly increasing with the aging of the population, aged CKD patients were the preferred study population. Furthermore, there was exclusion of most factors such as; demographic data, eGFR, urate-lowering drug application, nutritional index, kidney function indices and proteinuria.The results showed that hyperuricemia had a detrimental effect onall-cause mortality. Excellent medical care should therefore be accorded t to hyperuricemia in aged non-dialysis CKD patients, as it may offer a survival benefit when the serum uric acid is maintained at a low level. If not well- treated, hyperuricemia can negatively influence multiple mechanisms in the body such as; platelet function and subsequently the blood rheology [33], proliferation of vascular smooth muscle cells , reduce nitric oxide production , vascular endothelial cell dysfunction , activating the renin angiotensin system and many others [34-37].

Limitations of The Study

This research had a few limitations of limited sample size, being retrospective. Additionally, the serum uric acid was only assessed at baseline, without follow-up data.

Conclusion

This study showed that hyperuricemia is the independent risk factor of all-cause mortality in aged CKD patients with 81% increment risk. Nevertheless, a low level of uric acid in the serum has a significant protective effect for all-cause mortality. This insight will help improve diagnostic and treatment measures for hyperuricemia in aged patients with CKD, remarkably reducing the all- cause mortality in aged populations.

References

1. Hill NR, Fatoba ST, Oke JL, et al. (2016) Global prevalence of chronic kidney disease–a systematic review and meta-analysis. PloS one 2016.
2. Zhang L, Wang F, Wang L, et al. (2012) Prevalence of chronic kidney disease in China: a cross-sectional survey. The Lancet 379: 815-822.
3. Abubakar I I, Tillmann T, Banerjee A (2015) 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 385: 117-171.
4. Coresh J, Astor BC, Greene T, et al. (2003) Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. American journal of kidney diseases 41: 1-12.
5. Chen M, Xia J, Pei G, et al. (2016) A more accurate method acquirement by a comparison of the prediction equations for estimating glomerular filtration rate in Chinese patients with obstructive nephropathy. BMC nephrology 17: 150.
6. Yusuf S, Reddy S, Ôunpuu S, et al. (2001) Global burden of cardiovascular diseases: part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. Circulation 104: 2746-2753.
7. Jakovljevic MM, Netz Y, Buttigieg SC, et al. (2018) Population aging and migration–history and UN forecasts in the EU-28 and its east and south near neighborhood–one century perspective 1950–2050. Globalization and health 14: 30.
8. Seo JH, Kim DH, Cho E, et al. (2019) Characteristics and outcomes of extreme elderly patients with hepatocellular carcinoma in South Korea. *in vivo* 33: 145-154.
9. Swaminathan V, Audisio RA (2012) Cancer in older patients: an analysis of elderly oncology. Ecancermedicalscience 6.
10. Denic A, Glassock RJ, Rule AD (2016) Structural and functional changes with the aging kidney. Advances in chronic kidney disease 23: 19-28.
11. Magnason RL, Indridason OS, Sigvaldason H, et al. (2002) Prevalence and progression of CRF in Iceland: a population-based study. American journal of kidney diseases 40: 955-963.
12. Zhang QL, Rothenbacher D (2008) Prevalence of chronic kidney disease in population-based studies: systematic review. BMC public health 8: 117.
13. Wasen E, Isoaho R, Mattila K, et al. (2004) Estimation of glomerular filtration rate in the elderly: a comparison of creatinine□based formulae with serum cystatin C. Journal of internal medicine 256: 70-78.
14. Hemmelgarn BR, Zhang J, Manns B J, et al. (2006) Progression of kidney dysfunction in the community-dwelling elderly. Kidney international 69: 2155-2161.
15. Garg AX, Papaioannou A, Ferko N, et al. (2004) Estimating the prevalence of renal insufficiency in seniors requiring long-term care. Kidney international 65: 649-653.
16. Veronese N, Stubbs B, Trevisan C, et al. (2016) Hyperuricemia is a significant predictor of poor physical performance in the elderly: THE Pro. VA Study. Arthritis Care Res (Hoboken) 10: 3-33.
17. Zhu Y, Pandya BJ, Choi HK (2011) Prevalence of gout and hyperuricemia in the US general population: the National Health and Nutrition Examination Survey 2007–2008. Arthritis & Rheumatism 63: 3136-3141.
18. Hsu C, Iribarren C, McCulloch CE, et al. (2009) Risk factors for end-stage renal disease: 25-year follow-up. Archives of internal medicine 169: 342-350.
19. Chonchol M, Shlipak MG, Katz R, et al. (2007) Relationship of uric acid with progression of kidney disease. American Journal of Kidney Diseases 50: 239-247.
20. Madero M, Sarnak MJ, Wang X, et al. (2009) Uric acid and long-term outcomes in CKD. American Journal of Kidney Diseases 53: 796-803.
21. Beberashvili I, Erlich A, Azar A, et al. (2016) Longitudinal study of serum uric acid, nutritional status, and mortality in maintenance hemodialysis patients. Clinical Journal of the American Society of Nephrology 11: 1015-1023.
22. Earley A, Miskulin D, Lamb EJ, et al. (2012) Estimating equations for glomerular filtration rate in the era of creatinine standardization: a systematic review. Annals of internal medicine 156: 785-795.
23. Qiu L, Cheng X, Wu J, et al. (2013) Prevalence of hyperuricemia and its related risk factors in healthy adults from Northern and Northeastern Chinese provinces. BMC public health 13: 664.
24. Amaro S, Urra X, Gómez-Choco M, et al. (2011) Uric acid levels are relevant in patients with stroke treated with thrombolysis. Stroke 42: S28-S32.
25. Madero M, Sarnak MJ, Wang X, et al. (2009) Uric acid and long-term outcomes in CKD. American Journal of Kidney Diseases 53: 796-803.
26. Kowalczyk J, Francuz P, Swoboda R, et al. (2010) Prognostic significance of hyperuricemia in patients with different types of renal dysfunction and acute myocardial infarction treated with percutaneous coronary intervention. Nephron Clinical Practice 116: c114-c122.
27. Miyaoka T, Mochizuki T, Takei T, et al. (2014) Serum uric acid levels and long-term outcomes in chronic kidney disease. Heart and vessels 29: 504-512.
28. Bae E, Cho HJ, Shin N, et al. (2016) Lower serum uric acid level predicts mortality in dialysis patients. Medicine 95.

29. Park C, Obi Y, Streja E, et al. (2017) Serum uric acid, protein intake and mortality in hemodialysis patients. Nephrology Dialysis Transplantation 32: 1750-1757.

30. Hsu SP, et al. (2004) Serum uric acid levels show a 'J-shaped' association with all-cause mortality in haemodialysis patients. Nephrol Dial Transplant 19: 457-462.

31. Suliman ME, Johnson RJ, Garcíalópez E, et al. (2006) J-shaped mortality relationship for uric acid in CKD.. American Journal of Kidney Diseases 48: 761-771.

32. Rodenbach, Kyle E, et al. (2015) Hyperuricemia and progression of CKD in children and adolescents: the chronic kidney disease in children (CKiD) cohort study. American Journal of Kidney Diseases 66.6: 984-992.

33. Vannorsdall TD, Jinnah HA, Gordon B, et al. (2008) Cerebral ischemia mediates the effect of serum uric acid on cognitive function. Stroke; a journal of cerebral circulation 39: 3418.

34. Kang DH, Park SK, Lee IK, et al. (2005) Uric acid–induced C-reactive protein expression: implication on cell proliferation and nitric oxide production of human vascular cells. Journal of the American Society of Nephrology 16: 3553-3562.

35. Wang KJ, Hong WC (2011) Competitive advantage analysis and strategy formulation of airport city development—The case of Taiwan. Transport Policy 18: 276-288.

36. Tang Z, Cheng LT, Li HY, et al. (2009) Serum uric acid and endothelial dysfunction in continuous ambulatory peritoneal dialysis patients. American journal of nephrology 29: 368-373.

37. Yu MA, Sanchez-Lozada LG, Johnson RJ, et al. (2010) Oxidative stress with an activation of the renin–angiotensin system in human vascular endothelial cells as a novel mechanism of uric acid-induced endothelial dysfunction. Journal of hypertension 28: 1234-1242.