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NEPHROLOGY - ORIGINAL PAPER

Correlation analysis of low-level serum uric acid and cardiovascular events in patients on peritoneal dialysis

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Abstract

Background The impact of serum uric acid (SUA) on development of cardiovascular disease (CVD) in patients undergoing peritoneal dialysis (PD) remains controversial, especially the impact of hypouricemia (HUA) on CVD. The aim of our study was to investigate the influence of low-level SUA on cardiovascular (CV) events in PD patients.

Methods A retrospective cohort study was conducted.728 PD patients from February 1, 2010 to May 31, 2019 were enrolled. All demographic and laboratory data were collected at baseline and 6 months after PD treatment. The study cohort was divided into four groups according to SUA level (μmol/L) after 6 months of PD: Group1 (< 360), Group2 (360–420), Group3 (420–480), Group4 (≥ 480). The clinical characteristics of each group were analyzed. With Group2 as reference, logistic regression analysis was performed to investigate the correlation between SUA levels and risk of CV events in patients undergoing PD. Use Kaplan–Meier method to generate CV events risk graph.

Results 728 patients were enrolled in this study, including 403 (55.4%) males and 325 (44.6%) females, with an average age of 48.66 ± 13.98 years; of which 158 (21.7%) patients developed CV events. Multivariate COX regression showed that after adjusting for multiple clinical factors, Group1 (HR = 1.92, 95% CI 1.17–3.15, $P = 0.01$), Group3 (HR = 1.89, 95% CI 1.13–3.15, $P = 0.015$), and Group4 (HR = 2.38, 95% CI 1.35–4.19, $P = 0.003$) are all independent risk factors for developing CV events. The Kaplan–Meier risk curve of CV events showed that the risk of CV events in the Group1, Group3 and Group4 were significantly higher (Log-Rank = 12.67; $P = 0.005$). Restricted cubic spline (RCS) showed that SUA level is non-linearly associated with the risk of CV events, showing an *U*-shaped curve (χ^2_4=13.3 $P = 0.01$).

Conclusions Our study suggested that patients with SUA level less than 360 μmol/L also exhibited the higher risk for developing CV events, an U-shaped association between SUA level and risk of CV events in patients undergoing PD. Both SUA levels below 360 μmol/L and above 420 μmol/L were found to be significant risk factors for developing CV events in patients undergoing long-term PD.

Keywords Peritoneal dialysis · Cardiovascular events · Hypouricemia

Abbreviations

BMI	Body mass index
CVD	Cardiovascular disease
CKD	Chronic kidney disease
PD	Peritoneal dialysis
SUA	Serum uric acid
BUN	Blood urea nitrogen
HDL	High density lipoprotein
LDL	Low density lipoprotein
ALP	Alkaline phosphatase
CRP	C-reactive protein
eGFR	Estimated glomerular filtration rate
OR	Odds ratio

Background

It is estimated that approximately 260,000 new end-stage renal disease (ESRD) cases emerges in China yearly, rendering it a heavy economic and social burden on the health care system [1]. Peritoneal dialysis (PD) is a dialysis method that uses the body's own peritoneum as the dialysis membrane.

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In many countries, patient outcomes with peritoneal dialysis are comparable to or better than those with haemodialysis (HD). Use of this therapy is increasing in countries including China, the USA and Thailand. While the incidence of CVD in healthy population is about 5.8%, it is dramatically increased in CKD patients, in some studies reaching as high as 63% [2]. This suggests that CKD may play an important role in the development and progression of CVD. As well, CVDs are the most common complications and causes of death in ESRD patients. One study found that the cardiovascular-related mortality rate of ESRD patients was more than four times higher than that of the general population, while the non-cardiovascular related mortality was only three times higher [3].

With improvement of living standards and changes in diet structure, the prevalence of hyperuricemia (HUA) is on the rise worldwide [4]. UA is the end product of purine metabolism, and is mainly excreted by the kidneys. HUA has been regarded as the fourth leading risk factor for CVD after hypertension, hyperlipidemia, and hyperglycaemia. Epidemiological studies have confirmed the correlation between HUA and CVD-related mortality in the general population as well as in CKD patients. Most studies have shown that HUA is associated with CV events in dialysis patients, the initial HUA [5] and the HUA at 6 months of dialysis [6] are both risk factors for CVD-related death in PD patients. The relationship between serum uric acid (SUA) and cardiovascular (CV) mortality in patients with chronic kidney disease (CKD) has been described as either a J- or U-shaped function. Some study concluded that higher SUA was associated with lower risk of all-cause and cardiovascular mortality among haemodialysis (HD) patients [7], lower SUA levels increase the risk of CV events [5] and closely relate to all-cause mortality in HD patients [8]. The main reason was SUA has strong antioxidant properties, as 60% of the free radical scavenging ability of human plasma is derived from the role of uric acid [9]. When the SUA level is too low, its antioxidant capacity is weakened and oxidative stress is increased. In moderate non-Diabetes Mellitus (DM) CKD, a level of SUA $\geq$540 μmol/L is associated with higher all-cause mortality. However, once progressing to severe non-DM CKD, a level of SUA $<$300 μmol/L is associated with higher all-cause mortality [10]. Some studies have shown that elevated SUA level is an independent risk factor for all-cause and CV mortality in men treated with PD [11], and also significantly associated with risk of mortality in patients with CKD [12]. The studies of lower SUA levels in CV events in CKD patients undergoing PD are limited. The 2019 Chinese Guidelines for Diagnosis and Treatment of hyperuricemia and gout [13] have suggested that the SUA should be maintained below 360 μmol/L in CKD, diabetes, hypertension, abnormal lipid metabolism, obesity, stoke, coronary heart disease, cardiac, and insufficiency patients, even controlled below 300 μmol/L if combined with gout. The aim of our study was to investigate the influence of low-level SUA on CV events in PD patients, focus on the association between low-level SUA and CV event risks, to explore the optimum control range of SUA in PD patients.

Methods

Participants

This study was a retrospective cohort study. A total of 728 patients were recruited in the PD center within the first affiliated hospital of nanchang university between February 1, 2010 to May 31, 2019. All patients were followed-up until November 30, 2019. Inclusion criteria were age $\geq$18 years at the start of PD and survival for at least 6 months from the first PD therapy. The exclusion criteria were: (1) The patients who were catheterized in other hospitals, transferred from permanent HD, or failed renal transplantation; (2) SUA data at 6 months of dialysis was absent; (3) unsuccessful follow-ups; (4) the use of xanthenes oxidise inhibitors within 3 months; (5)history of myocardial infarction, stroke, heart failure, unstable angina, peripheral vascular disease.

All participants provided written informed consent and this study was approved by the Ethics Committee of First Affiliated Hospital of Nanchang University in accordance with the 1964 Helsinki declaration and amendments.

Data collection

The medical records of patients registered in the PD center were collected, including age, sex, start time of dialysis, dialysis duration, blood pressure, body mass index (BMI), medical history of diabetes mellitus, hypertension, and the etiology of diseases which caused ESRD. Laboratory examination from routine serum test was also collected, including parameters of liver function, kidney function, blood glucose, blood lipids, electrolytes, estimated glomerular filtration rate (eGFR), C-reactive protein (C-reactive protein, CRP), SUA, KT/V(K represents the urea clearance rate by dialyzer, T stands for dialysis time and V stands for volume of urea distribution) and other relevant clinical, demographic and laboratory data after 6 months of dialysis.

Research methods

Using a retrospective cohort study method, all patients were followed up until they either withdraw from PD treatment, death, transferred to another dialysis center, or until study deadline of November 30, 2019. The main clinical outcomes of this study are CV events, which includes: the first occurrence of myocardial infarction, stroke, heart failure, unstable

angina, peripheral vascular events, sudden death, death related to cardiovascular surgery, death caused by aneurysm dissection or rupture, fatal pulmonary embolism or death from other unknown cardiovascular causes [14].

Grouping criteria

The 2019 Chinese Gout Diagnosis and Treatment Guidelines [13] have suggested that the SUA of CKD patients with gout should be maintained below 360 μmol/L, or even below 300 μmol/L, so all enrolled patients were divided into four groups according to their respective SUA level at 6 months of PD: Group1, SUA < 360 μmol/L; Group2, 360 μmol/L ≤ SUA < 420 μmol/L; Group3, 420 μmol/L ≤ SUA < 480 μmol/L; Group4, SUA ≥ 480 μmol/L.

Statistics

All data are analyzed using IBM SPSS version 26.0 (SSPS Inc, Chicago, IL) and R version 4.0.4 (Free Software Foundation Inc, http://www.R-project.org). Comprehensively evaluate whether the data meets the normal distribution through the Kolmogorov–Smirnov test, Quantile–Quantile Plot, and Histogram. Normally distributed continuous data are mainly represented as mean ± standard deviation, data that are not normally distributed are expressed as the median and interquartile range (IQR), count data are expressed by frequency (%). One-way analysis of variance or Kruskal–Wallis test was used for comparison between groups. Comparison between groups of continuous variables that conform to the normal distribution is performed using single-factor analysis of variance, Evaluate the homogeneity of variance through the Levene's test, and comparison of groups of non-normally distributed continuous variables are performed using the nonparametric test, count data were analyzed using the chi-square test, Kaplan–Meier method is used to generate a cardiovascular event risk curve to compare the cardiovascular event risk between different SUA groups, and the Log-Rank method was used for significance test. Univariate Cox proportional hazards model was used to analyze risk factors for CV events, Variables with $P < 0.1$ in univariate Cox regression or clinically valuable indicators are included in multivariate cox model. Results were described by hazard ratio (HR) and 95% confidence interval (95% CI). Restricted cubic spline(RCS) evaluates non-linear relationships between SUA and CV events. $P < 0.05$ was considered statistically significant.

Results

Baseline patient characteristics at 6 months after PD

A total of 1031 incident PD patients were recruited and monitored in our hospital. 303 patients were excluded by our experimental criteria and listed as below: 5 subjects were under 18 years of age, 10 subjects were transferred from HD, 56 subjects lacked SUA data at 6 months,77 subjects used xanthenes oxidise inhibitors within 3 months, 155 subjects had history of myocardial infarction, stroke, heart failure, unstable angina, peripheral vascular disease. During the PD procedure, the conventional PD dialysis fluids include 1.5% or 2.5% dextrose and the twin-bag system was applied for all PD patients. As shown in Fig. 1, Finally, 728 patients were found to be eligible for analysis, including 403 (55.4%) males and 325 (44.6%) females, with an average age of 48.66 ± 13.98 years and a total of 158 (21.7%) which had CV events, the average follow-up time was 27 months, the average dialysis duration for patients with CV event was 31.42 ± 20.75 months, The etiology of PD patients were mostly chronic glomerulonephritis(CGN) which was 505 cases (69.4%), followed by 88 cases (12.1%) of diabetic kidney disease(DKD), and 80 cases (11.0%) of hypertensive renal injury(HRI). Other detailed demographic, clinical and biological characteristics were presented in Table 1.

Comparison of clinical and laboratory indexes of SUA group

In total there are 198 patients (27.2%) in Group1, 259 patients (35.6%) in Group2, 157 patients (21.6%) in Group3 and 114 patients (15.7%) in Group4 group; the percentage of patients which developed CV events are respectively 47 cases (23.7%), 36 cases(13.9%), 44 cases (28.0%), and 31 cases (27.2%); the mean SUA levels at 6 months of PD for Group1-Group4 were: 315.11 ± 42.26 μmol/L, 390.94 ± 16.41 μmol/L, 443.43 ± 16.59 μmol/L, 537.92 ± 67.69 μmol/L.

With Group2 as reference, the incidence of CV events, DKD patients, high-density lipoprotein (HDL), initial total Kt/V, and total Kt/V at 6 months PD in Group1 were significantly higher; while males, BMI, albumin, creatinine, blood urea nitrogen(BUN), baseline SUA, and serum phosphorus levels were lower ($P < 0.05$); the incidence of CV events, hemoglobin, baseline SUA level, baseline residual renal function(RRF), and RRF at 6 months PD in Group3 were higher than in Group2 ($P < 0.05$), while creatinine and phosphorus levels were lower ($P < 0.05$); the proportion of CV events, BMI, baseline SUA level and

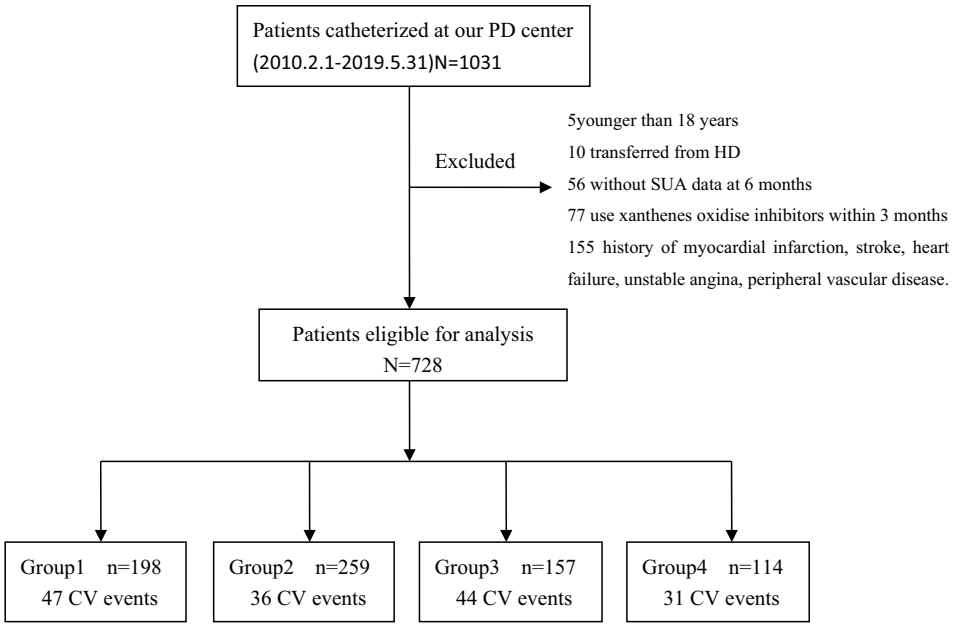

Fig. 1 Enrollment flow chart for analysis

initial RRF in Group4 were higher than those in Group2 ($P < 0.05$), the levels of serum creatinine and HDL were lower than in Group2 ($P < 0.05$).

DKD patients, baseline total Kt/V, and total Kt/V at 6 months in Group1were higher than in Group3 ($P < 0.05$), while males, BMI, albumin and baseline SUA value were lower than in Group3 ($P < 0.05$); DKD patients, HDL, baseline total Kt/V, total Kt/V at 6 months PD in Group-1were higher than in Group4 ($P < 0.05$), while males, BMI, albumin, baseline SUA, baseline RRF and RRF at 6 months PD were lower than in Group4 ($P < 0.05$); The dialysis duration of patients which developed CV events and HDL levels was higher in Group3 than in Group4 ($P < 0.05$), while BMI and triglyceride(TG) level was lower than in Group4 ($P < 0.05$); see Table 1 for details.

Comparison of clinical and laboratory indicators with or without cardiovascular events

There were in total 158 patients (21.7%) which developed CV events and 570 patients (78.3%) that did not. Within the CV events group, the proportion of male, DKD, and systolic blood pressure(SBP) were significantly higher than those which did not develop CV events ($P < 0.05$); whereas the proportion of patients with CGN was lower than that without CV events ($P < 0.05$). There were significant differences between the four groups separated by SUA levels in view of CV events ($P < 0.05$); which was not found in other variables including age, dialysis duration, BMI, RRF and Kt/V. See Table 2 for details.

Univariant COX regression of cardiovascular events in PD patients

Univariate COX regression analysis showed that males (HR = 1.48, 95% CI 1.075–2.049, $P = 0.016$), Group1 (HR = 1.67, 95% CI 1.081–2.577, $P = 0.021$), Group3 (HR = 1.87, 95% CI 1.205–2.909, $P = 0.005$), Group4 (HR = 2.2, 95% CI 1.361–3.559, $P = 0.002$), DKD (HR = 1.83, 95% CI 1.115–2.527, $P = 0.013$) are all significant risk factors for CV events. On the contrary, patients with CGN (HR = 0.64, 95% CI 0.464–0.878, $P = 0.006$) showed lower risk. See Table 3 for details.

Multivariate COX regression of cardiovascular events in PD patients

The clinical indicators of $P < 0.1$ and some clinically significant indicators in the results of univariate COX regression were subjected to multivariate COX stepwise regression analysis. Model 1 adjusted age, sex and BMI, and model 2 adjusted causes of kidney disease on the basis of model 1, model 3 adjusted significant clinical biochemical indicators on the basis of model 2. The results showed that after adjusting for multiple clinical factors, Group1 (HR = 1.92, 95% CI 1.17–3.15, $P = 0.01$), Group3 (HR = 1.89, 95% CI 1.13–3.15, $P = 0.015$), and Group4 (HR = 2.38, 95% CI 1.35–4.19, $P = 0.003$) are all independent risk factors for developing CV events. See Table 4 for details.

Table 1 The demographic and clinical characteristics of enrolled patients in the study

Variables	Total	Group1 (< 360 μmol/L)	Group2 (360–420 μmol/L)	Group3 (420–480 μmol/L)	Group4 (≥ 480 μmol/L)	*P* value
Number of patients [*n* (%)]	728	198 (27.2)	259 (35.6)	157 (21.6)	114 (15.7)	
CE [*n* (%)]	158 (21.7)	47 (23.7)^{aa}	36 (13.9)^{ddd}	44 (28)	31 (27.2)^{ee}	0.001
Dialysis duration for patients with CV events	27.23 (14.53, 43.52)	25.67 (14.38, 45.11)	27.23 (15.00, 43.27)	30.33 (16.07, 45.47)	25.50 (12.38, 38.04)	0.26
(months) Male [*n* (%)]	403 (55.4)	88 (44.4)^{a}	142 (54.8)	101 (64.3)^{bbb}	72 (63.2)^{cc}	0.001
Age (year)	48 (38,58)	50 (39,61)	48 (36,57)	47 (39,58)	48 (38,58)	0.31
BMI (kg/m^2)	21.97 ± 3.35	21.17 ± 3.15^{aa}	22.02 ± 3.31	21.91 ± 3.38^{bff}	23.29 ± 3.31^{ccceee}	< 0.001
Systolic blood pressure (mmHg)	145.07 ± 24.41	147.64 ± 25.58	143.73 ± 23.05	145.46 ± 25.83	143.13 ± 23.24	0.29
Diastolic blood pressure (mmHg)	87.43 ± 14.77	88.42 ± 14.94	87.20 ± 14.26	87.28 ± 15.95	86.43 ± 13.99	0.68
Etiology of CKD [*n* (%)]						
Chronic glomerulonephritis	505 (69.4)	132 (66.7)	181 (69.9)	111 (70.7)	81 (71.1)	0.80
Diabetic kidney disease	88 (12.1)	37 (18.7)^{a}	28 (10.8)	15 (9.6)^{b}	8 (7.0)^{cc}	0.01
Hypertensive renal disease	80 (11.0)	18 (9.1)	28 (10.8)	17 (10.8)	17 (14.9)	0.47
Baseline eGFR (ml/min)	3.57 (1.84,5.80)	3.33 (1.68,5.88)	3.27 (1.76,5.01)^{d}	3.77 (1.98,6.19)	4.81 (2.38,6.71)^{cceee}	0.002
eGFR after 6 months PD (ml/min)	3.03 (1.50,5.13)	2.73 (1.55,4.93)	2.81 (1.30,4.67)^{d}	3.36 (1.59,5.43)	3.99 (1.98,6.37)^{cee}	0.01
Baseline Kt/V urea	2.20 (1.73,2.75)	2.45 (1.81,3.08)^{aa}	2.16 (1.74,2.73)	2.15 (1.68,2.68)^{bb}	2.05 (1.65,2.64)^{cc}	0.01
Kt/V urea after 6 months PD	2.12 (1.69,2.66)	2.41 (1.82,2.94)^{a}	2.07 (1.68,2.65)	2.07 (1.64,2.57)^{bb}	1.93 (1.61,2.42)^{cc}	0.03
Hemoglobin (g/L)	78.00 (68.00, 90.00)	76.00 (67.25, 88.00)	76.00 (67.00, 89.00)	80.00 (69.00, 93.00)	80.50 (73.00, 90.00)	0.05
Total serum protein (g/L)	60.56 ± 7.25	59.63 ± 7.82	60.57 ± 6.98	60.75 ± 6.97	61.86 ± 7.05^{c}	0.07
Albumin (g/L)	35.71 ± 4.98	34.71 ± 5.22^{aa}	35.94 ± 4.55	36.00 ± 4.94^{b}	36.51 ± 5.34^{cc}	0.01
Creatinine (μmol/L)	700.3 (558.3, 872.9)	666.9 (528.3, 855.3)	737.60 (596.9, 919.9)	702.0 (560.5, 824.0)	675.3 (509.9, 836.0)	0.01
BUN (mmol/L)	23.68 ± 8.93	22.57 ± 9.06^{a}	24.69 ± 9.61	23.52 ± 7.90	23.56 ± 8.30	0.09
Baseline SUA (μmol/L)	441.51 ± 129.49	397.68 ± 116.35^{aaa}	437.24 ± 125.27^{d}	466.80 ± 127.41^{bbb}	492.44 ± 138.24^{ccceee}	< 0.001
SUA after 6 months PD (μmol/L)	404.65 ± 81.92	315.11 ± 42.26^{aaa}	390.94 ± 16.41^{ddd}	443.43 ± 16.59^{bbbfff}	537.92 ± 67.69^{ccceee}	< 0.001
Total cholesterol (mmol/L)	4.06 (3.40,4.85)	4.21 (3.36,4.96)	4.03 (3.40,4.79)	4.03 (3.41,4.75)	4.03 (3.45,4.75)	0.78
Triglyceride (mmol/L)	1.32 (0.93,1.80)	1.28 (0.93,1.74)	1.35 (0.93,1.83)	1.20 (0.93,1.71)^{f}	1.39 (0.96,2.20)	0.17
HDL (mmol/L)	1.16 ± 0.39	1.23 ± 0.39^{a}	1.15 ± 0.38	1.18 ± 0.42^{ff}	1.03 ± 0.32^{cccee}	< 0.001
LDL (mmol/L)	2.48 ± 0.91	2.54 ± 0.95	2.44 ± 0.86	2.47 ± 0.96	2.48 ± 0.91	0.71
ALP (U/L)	74.00 (58.75,99.00)	75.50 (56.75,104.25)	73.00 (60.00,96.25)	73.50 (59.00,98.75)	76.00 (62.00,97.25)	0.89
Blood glucose (mmol/L)	4.90 ± 1.50	5.12 ± 1.73	4.80 ± 1.13	4.77 ± 1.63	4.93 ± 1.59	0.09
Corrected calcium (mmol/L)	2.11 ± 0.25	2.13 ± 0.23	2.09 ± 0.25	2.10 ± 0.25	2.10 ± 0.25	0.47
Phosphorus (mmol/L)	1.79 (1.50,2.10)	1.74 (1.49,1.99)^{aa}	1.86 (1.54,2.20)^{d}	1.75 (1.47,2.04)	1.79 (1.47,2.16)	0.02
Potassium (mmol/L)	4.38 ± 0.75	4.50 ± 0.83	4.38 ± 0.74	4.32 ± 0.69	4.35 ± 0.73	0.70

Table 1 (continued)

Variables	Total	Group1 (< 360 μmol/L)	Group2 (360–420 μmol/L)	Group3 (420–480 μmol/L)	Group4 (≥ 480 μmol/L)	*P* value
CRP (mg/L)	4.20 (2.19,10.33)	4.27 (2.13,9.35)	3.71 (2.08,10.50)	4.45 (1.93,10.50)	4.92 (2.56,16.28)	0.43

Group1 vs. Group2: $^{a}P<0.05$, $^{aa}P<0.01$, $^{aaa}P<0.001$

Group1vs. Group3: $^{b}P<0.05$, $^{bb}P<0.01$, $^{bbb}P<0.001$

Group1 vs. Group4: $^{c}P<0.05$, $^{cc}P<0.01$, $^{ccc}P<0.001$

Group2 vs. Group3: $^{d}P<0.05$, $^{dd}P<0.01$, $^{ddd}P<0.001$

Group2vs. Group4: $^{e}P<0.05$, $^{ee}P<0.01$, $^{eee}P<0.001$

Group3 vs. Group4: $^{f}P<0.05$, $^{ff}P<0.01$, $^{fff}P<0.001$

Values are presented as mean value ± SD or medians (interquartile range) for continuous variables and count (percentage) for categorical variables

The K-M risk curve of cardiovascular events in SUA groups

Compared with patients in Group2, the risk of CV events in the Group1, Group3 and Group4, were significantly higher (Log-Rank = 12.67; $P=0.005$), as shown in Fig. 2.

RCS evaluates non-linear relationships between SUA and CV events

RCS showed that SUA level is non-linearly associated with the risk of CV events, showing a *U*-shaped curve (χ^2_4=13.3 $P=0.01$), as shown in Fig. 3.

Discussion

Our study suggested that patients with SUA level less than 360 μmol/L also exhibited the higher risk for developing CV events, possible explanation may be that patients with low SUA have lower serum albumin levels and suboptimal nutritional status, as well as lower BMI and blood phosphorus, and higher chance of having DM as comorbidities. SUA levels have been shown to reflect nutritional status [15]. Low SUA may indicate malnutrition, which can easily lead to micro inflammation, infection and CVD. Over time, an increase in SUA levels may improve the nutritional status of patients [16]. Second, SUA has strong antioxidant properties, as 60% of the free radical scavenging ability of human plasma is derived from the role of SUA [9]. Domínguez [17] confirmed that patients on hemodialysis with hyperuricemia had higher antioxidant capacity and less oxidative damage, and they also had better nutritional status in general, mainly according to impedance vectors. When the SUA level is too low, its antioxidant capacity is weakened and oxidative stress is increased. Likewise, SUA is capable of forming stable complexes with iron ions, which can significantly inhibit Fe3 + catalyzed ascorbic acid oxidation. Therefore, multiple clinical guidelines including Europe, Taiwan, and China do not recommend long-term control of SUA to less than 180 μmol/L [18, 19].

The biological role of SUA in the human body is mainly reflected in two aspects. Firstly, the combination of SUA with ammonia and urea plays an important role in the removal of nitrogen-containing compounds. Secondly, UA is also an antioxidant. It can interact with hydrogen peroxide and hydroxyl radicals to effectively scavenge free radicals in the body, thus protecting vascular endothelial cells [20]. A large multicenter study involving more than 4000 dialysis patients found that low SUA is an independent risk factor for cardiovascular and all-cause death in haemodialysis (HD) patients[5], low SUA level may increase the risk of all-cause death or cardiovascular event death in HD dialysis patients, and the risk ratio is even higher than that of patients with high SUA, a lower SUA level < 330 μmol/L predicted all-cause mortality in patients with chronic dialysis[21].The mechanism was unclear. It could essentially be the result of the comprehensive influence of many factors. Studies have shown that UA levels were positively correlated with albumin and negatively correlated with the Charlson comorbidity index [16, 22]. Thus, the risk of high mortality due to low UA levels might be because of bad nutritional status associated with hypoalbuminemia, and heavier comorbidities led to higher risk of death; Secondly, it could also be that excessive oxidative stress caused by low UA levels, and by inducing endothelial dysfunction, indirectly led to a higher risk of death [9, 23, 24] and its antioxidant property could ameliorate the indoxyl sulfate-related vascular toxicity [7]; Third, the so-called "reverse epidemiology", also known as "risk factor reversal", cannot be completely excluded, such as obesity paradox in ESRD; Fourth, inflammatory cytokines appear to cause low UA as a result of impaired net renal tubular reabsorption of urate [25]. A Taiwanese study of patients with severe acute respiratory syndrome showed that marked renal hypouricemia due to a defect in renal UA handling was associated with a higher serum IL-8 level [26].

At present, there are few studies on the impact of lower SUA on the prognosis of patients undergoing PD. Some

Table 2 Demographic and clinical characteristics of patients with or without CV events

Variables	With CV events	Without CV events	*P* value
Number of patients [*n* (%)]	158 (21.7)	570 (78.3)	
Dialysis duration (months)	34.42 ± 20.52	33.17 ± 21.22	0.51
Male [*n* (%)]	99 (62.7)	304 (53.3)	0.04
Age (year)	49.97 ± 14.17	48.30 ± 13.93	0.19
BMI (kg/m^2)	21.87 ± 3.39	22.00 ± 3.34	0.67
Systolic blood pressure (mmHg)	150.56 ± 25.98	143.56 ± 23.77	0.001
Diastolic blood pressure (mmHg)	88.79 ± 15.50	87.06 ± 14.55	0.19
Etiology of CKD [*n* (%)]			
Chronic glomerulonephritis	95 (60.1)	410 (71.9)	0.004
Diabetic kidney disease	28 (17.7)	60 (10.5)	0.01
Hypertensive renal disease	21 (13.3)	59 (10.4)	0.30
Hemoglobin (g/L)	79.28 ± 16.52	79.43 ± 16.52	0.92
Total serum protein (g/L)	60.40 ± 7.58	60.60 ± 7.16	0.77
Albumin (g/L)	35.44 ± 5.14	35.78 ± 4.94	0.44
Creatinine (μmol/L)	745.12 ± 342.31	744.20 ± 267.26	0.97
BUN (mmol/L)	23.25 ± 9.35	23.80 ± 8.82	0.50
Baseline SUA (μmol/L)	446.43 ± 134.42	440.14 ± 128.23	0.59
SUA after 6 months PD (μmol/L)	410.97 ± 95.77	402.90 ± 77.65	0.27
SUA groups [*n* (%)]			0.001
Group1	47 (29.7)	151 (26.5)	
Group2	36 (22.8)	223 (39.1)	
Group3	44 (27.8)	113 (19.8)	
Group4	31(19.6)	83 (14.6)	
Baseline eGFR(ml/min)	3.68 (1.67,5.90)	3.55 (1.89,5.78)	0.95
eGFR at 6 months PD (ml/min)	3.23 (1.40,5.65)	3.01 (1.51,5.03)	0.84
Baseline KT/V	2.15 (1.58,2.69)	2.21 (1.75,2.76)	0.10
KT/V at 6 months PD	2.12 (1.75,2.69)	2.12 (1.68,2.64)	0.52
Total cholesterol (mmol/L)	4.12 (3.39,5.00)	4.06 (3.40,4.81)	0.71
Triglyceride (mmol/L)	1.30 (0.90,1.86)	1.32 (0.95,1.80)	0.81
HDL (mmol/L)	1.12 ± 0.34	1.17 ± 0.40	0.19
LDL (mmol/L)	2.53 ± 0.95	2.46 ± 0.90	0.40
ALP (U/L)	72.00 (58.00,94.50)	75.00 (59.00,101.50)	0.24
Blood glucose (mmol/L)	5.01 ± 1.82	4.87 ± 1.40	0.31
Corrected calcium (mmol/L)	2.10 ± 0.25	2.11 ± 0.25	0.83
Phosphorus (mmol/L)	1.76 (1.44,2.06)	1.80 (1.52,2.11)	0.15
Potassium (mmol/L)	4.47 ± 0.79	4.36 ± 0.74	0.11
CRP(mg/L)	4.58 (2.44,10.90)	4.09 (2.07,10.06)	0.29

Values are presented as mean value ± SD or medians (interquartile range) for continuous variables and count (percentage) for categorical variables

research found an inverse relationship between UA level and all-cause, CV, and infection-associated mortality in female patients on CAPD [27]. Previous most of the studies use 420 μmol/L as a cut-off point for SUA in a binary analysis, sometimes grouped according to the quartile of mean SUA levels, which may not fully recapitulate the relationship between SUA and risk of CV events in dialysis patients. As well, previous studies mostly used baseline SUA level at the initiation of PD treatment, which is often affected by many variables, including the timing in which patients enters their PD treatment, diet, medication, and nutritional status. However, patients with regular PD for more than 6 months would have received health education, dietary guidance, and consistent peritoneal dialysis treatment, which make their SUA level more stable and hence more informative. The management of SBP in PD patients is also critical. Although the blood pressure of different SUA groups analyzed in our study was not significantly different, but the blood pressure of the CV events group was significantly higher than that of the non-CV events group. Our study also found that the

Table 3 Univariant COX regression analysis of CV events

Characteristics	Hazard ratio	95% CI	*P* value
Male	1.48	1.075–2.049	0.016
Age	1.01	0.994–1.017	0.351
BMI	0.98	0.937–1.033	0.507
Systolic blood pressure	1.01	0.999–1.011	0.083
Diastolic blood pressure	1	0.989–1.009	0.814
Etiology of CKD			
Chronic glomerulonephritis	0.64	0.464–0.878	0.006
Diabetic kidney disease	1.68	1.115–2.527	0.013
Hypertensive renal disease	1.18	0.743–1.861	0.49
White blood cell	1.03	0.963–1.11	0.357
Hemoglobin	1	0.992–1.011	0.782
Platelet	1	0.998–1.002	0.954
Alanine aminotransferase	1	0.986–1.008	0.613
Aspartate transaminase	0.99	0.982–1.008	0.44
Albumin	0.98	0.95–1.013	0.251
Creatinine	1	0.999–1.001	0.9
BUN	0.99	0.975–1.011	0.457
Baseline SUA	1	0.999–1.001	0.642
SUA at 6 months PD	1	0.999–1.003	0.155
SUA groups			
Group1	1.67	1.081–2.577	0.021
Group2	Ref		
Group3	1.87	1.205–2.909	0.005
Group4	2.2	1.361–3.559	0.001
eGFR at admission	1.02	0.973–1.068	0.415
eGFR after 6 months PD	0.99	0.94–1.046	0.752
Alkaline phosphatase	1	0.993–1.002	0.279
Blood glucose	1.04	0.945–1.142	0.427
Total cholesterol	1.05	0.913–1.205	0.501
Triglycerides	1.06	0.92–1.217	0.428
HDL	0.68	0.442–1.037	0.073
LDL	1.11	0.941–1.299	0.223
Corrected calcium	1.1	0.59–2.051	0.765
Phosphorous	0.9	0.656–1.245	0.535
Potassium	1.172	0.958–1.433	0.123
Magnesium	1.72	0.868–3.402	0.12
CRP	1	0.999–1.01	0.087

HR hazard ratio, *95% CI* 95% confidence interval

proportion of DKD in the lower SUA group was significantly higher than that in the higher SUA groups. We believe that this observation may be reflective of the osmotic diuresis caused by higher blood sugar level, which may lead to increased excretion of SUA. As well, diabetic patients often need to manage their diet carefully, resulting in reduced food intake and decreased SUA levels. Although SUA of patients with CGN was associated with a lower risk of CV events in univariate Cox analysis, but was not a risk factor for CV events in multivariate Cox stepwise regression analysis. The reason may be that the base number of CGN patients in our study was very large with 505 cases, and in the past 10 years we may not be very rigorous in the diagnosis of CGN, the etiology of patients with renal failure is usually diagnosed by exclusion method.

Febuxostat is currently the most commonly used UA lowering drug, and haves shown adverse cardiac effects, including angina, atrial fibrillation/atrial flutter, abnormal ECG, palpitations, sinus bradycardia, and increased heartbeat. In consideration of these incidences, FDA have also issued a warning that febuxostat increases the risk of heart-related death and all-cause death [28], however, there was insufficient evidence for an increased risk of sudden cardiac death in the Asian population, the expert group recommends febuxostat as the first-line reduction in patients with gout [29]. A multi-center prospective randomized controlled study (FREED) conducted by Kojima [30] in 2019 showed that febuxostat intervention in asymptomatic HUA patients can significantly reduce the incidence of cardiovascular and cerebrovascular adverse events and delay the progression of renal insufficiency, but Benjamin [31] did not support the use of SUA lowering medication in HD patients with asymptomatic HUA. Our study did not include patients who used xanthine oxidase inhibitors.

Recent research suggests [32] SUA and microvascular remodeling was mediated by endothelial function and nitric oxide (NO) availability. A *U*-shaped association was observed between SUA and both media-to-lumen (M/L) ratio and media cross-sectional area (MCSA). When SUA is greater than 480 μmol/L, the risk of CV events is the greatest. After correcting for multiple cardiovascular risk factors, this relationship remains significant. The effect of SUA on patients is multifactorial as discussed previously. However, SUA level is also closely related to the nutritional status and antioxidative properties in patients. It would be unethical to use malnutrition or excessive weight loss to reduce SUA in patients as these can also lead to poor prognosis in ESRD patients with PD. The BMI and serum albumin of patients in the hypouricemia group in this study were significantly lower than those in other SUA groups, which also supports this view. The findings of this study offer guiding significance for clinical practice in managing PD patients. It supports that patients with significantly low SUA level may have comparative risk of developing CV events as patients presented with high SUA. Careful clinical management of patient SUA level may improve patient prognosis and inhibit progression to ESRD. It may be more appropriate to manage the SUA level in PD patients at a higher value within the normal accepted range. Because UA is the most abundant antioxidant in plasma, further research is needed to assess the safety of lowering serum UA to specific thresholds to produce safe guidelines [33], for men and women, and in patients with and without CVD or CKD [34].

Table 4 Multivariant COX regression analysis of CV events

	Model1			Model2			Model3		
	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Group1	1.73	1.11–2.70	0.015	1.65	1.06–2.58	0.027	1.92	1.17–3.15	0.01
Group2	Ref			Ref			Ref		
Group3	1.57	1.00–2.47	0.051	1.63	1.04–2.58	0.034	1.89	1.13–3.15	0.015
Group4	2.05	1.26–3.36	0.004	2.19	1.34–3.60	0.002	2.38	1.35–4.19	0.003

HR hazard ratio, *95% CI* 95% confidence interval

Model 1: adjusted for age, sex and BMI

Model 2: adjusted for Model 1, chronic glomerulonephritis, diabetic kidney disease, hypertensive renal disease

Model 3: adjusted for Model 2, systolic blood pressure, hemoglobin, albumin, creatinine, blood glucose, HDL, Phosphorous, CRP

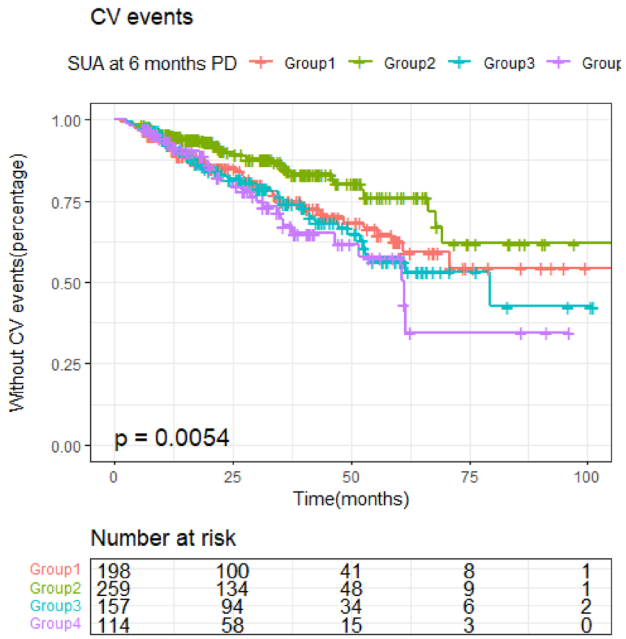

Fig. 2 K-M risk curve for CV events separated by SUA levels

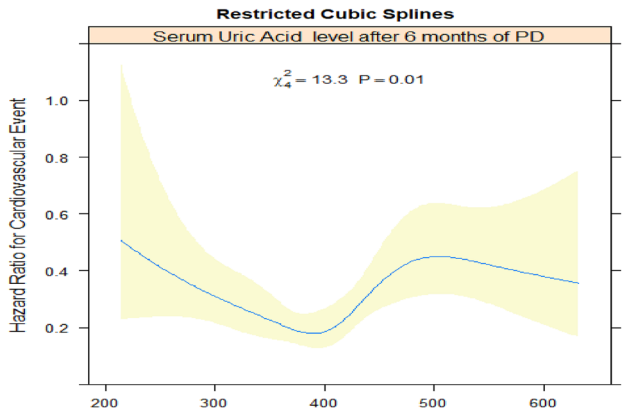

Fig. 3 RCS of risk of occurrence of CV events and SUA

Our study also had defects and deficiencies, we did not further classify lower SUA, less than 300 μmol/L or even less than 180 μmol/L, because the number of patients with hypouricemia was not enough. Our results showed that both very higher and lower SUA levels are all risk factors for development of CV events in patients undergoing PD, that is a U-shaped relationship between SUA level and the occurrence of CV events, optimal SUA control range should be defined in patients undergoing dialysis.

Conclusion

In summary, both very higher and lower SUA are all risk factors for development of CV events in patients undergoing long-term PD treatment. It should be beneficial to manage SUA levels within the suitable accepted range, which could prevent CV events and help improve PD patient prognosis.

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Author contributions QYL and CW designed the research, XJZ and QYL conducted the research, CW and WLK collected and analyzed the data, JZ and XJZ interpreted the findings, QYL and CW wrote the paper, JZ had the primary responsibility for the whole content and final approval of the version to be published. And all authors read and approved the final manuscript.

Declarations

Ethics approval and consent to participate All participants provided written informed consent and this study was approved by the Ethics Committee of First Affiliated Hospital of Nanchang University in accordance with the 1964 Helsinki declaration and amendments.

Conflict of interest The authors declare that they have no competing interests.

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