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Factors influencing the occurrence of hyperuricemia and poor cardiac and renal outcomes in chronic kidney disease

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Abstract. – OBJECTIVE: The aim of our study was to analyze the factors influencing the occurrence of hyperuricemia and poor cardiac and renal outcomes in chronic kidney disease (CKD).

PATIENTS AND METHODS: One hundred and sixteen patients with CKD admitted to our hospital from January 2022 to September 2022 were picked as the subjects. Fasting venous blood of these subjects was collected to value the serum uric acid (SUA) levels on an automatic biochemical analyzer. Patients were then grouped as the CKD-only group (n=80) and hyperuricemia group (n=36), according to the SUA results, or the good prognosis group (n=88) and poor prognosis group (n=28), according to the presence of cardiovascular diseases. The changes in laboratory indexes and clinical data were analyzed and compared. Multivariate logistic regression analysis was used to analyze the risk factors for combined hyperuricemia and the risk factors for poor cardiac and renal outcomes in patients with CKD. The correlation between SUA level and cardiac and renal indexes was analyzed by Pearson analysis.

RESULTS: Patients in the CKD hyperuricemia group had markedly higher content of systolic blood pressure (SBP), diastolic blood pressure (DBP), B-type natriuretic peptide (BNP), urinary retinol-binding protein (RBP), urinary N-acetyl-β-D glucosidase (NAG), much higher proportion of heart failure episodes history, and much lower content of total cholesterol (TC), albumin (Alb), hemoglobin (Hb), urinary α1-microglobulin (α1-MG), and glomerular filtration rate (eGFR) than the CKD-only group ($p < 0.05$). SUA, BNP, SBP, and history of heart failure episodes were independent risk factors for combined hyperuricemia in CKD patients ($p < 0.05$). Besides, eGFR, albumin, and hemoglobin were independent protective factors for combined hyperuricemia in CKD patients ($p < 0.05$). Compared with the good prognosis group, the content of BNP, SBP, DBP, urinary RBP, urinary NAG, and SUA was much higher, the proportion of heart failure episodes history was obviously higher, and the levels of Alb, Hb, TC, eGFR, and urinary α1-MG were sharply lower in the poor prognosis group ($p < 0.05$). SUA, BNP, SBP, and history of heart failure episodes were independent risk factors for poor cardiac and renal outcomes ($p < 0.05$), and eGFR was an independent protective factor for poor cardiac and renal outcomes in patients with CKD ($p < 0.05$). The SUA level in CKD patients was positively correlated with BNP and SBP (r=0.463, 0.215, $p < 0.05$), but negatively correlated with eGFR (r=0.463, 0.215, $p < 0.05$).

CONCLUSIONS: The serum SUA level was elevated with the aggravation of the CKD stage. High serum SUA level is a risk factor for the development of hyperuricemia and poor cardio-renal outcomes in CKD patients, suggesting that early monitoring of changes in SUA levels may help assess the risk of cardio-renal outcomes in CKD patients.

Key Words:
Hyperuricemia, Chronic kidney disease, Cardio-renal outcome, Impact.

Introduction

Chronic kidney disease (CKD) is a disease of chronic kidney structure and dysfunction (the history of kidney damage is more than 3 months) caused by various reasons. It is generally considered that the estimated glomerular filtration rate (eGFR), normal and abnormal pathological damage, abnormal blood or urine composition, abnormal imaging examination, or unexplained GFR (< 60 ml/min 1.73 m^2) that has lasted for more than 3 months is CKD[1,2]. With the change in diet structure and the aggravation of population aging in recent years, the number of CKD patients has increased year by year, with a

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younger trend. At the same time, cardiovascular events are important complications of patients with end-stage CKD, which seriously threaten the lives and health of patients. Therefore, the cardiac and renal outcomes of CKD patients have attracted the attention of medical scholars[3]. Recent studies in the literature have found that long-term renal dysfunction can damage the excretion function of serum uric acid (SUA). The high content of SUA in serum can further induce the occurrence of hyperuricemia. Hyperuricemia is a common complication of CKD, which is not only the result of decreased renal function but also a risk factor for deterioration of renal function.

Serum SUA level increases with the development of CKD. However, whether serum SUA plays an independent role in the pathogenesis of CKD remains controversial. At present, some scholars have carried out a retrospective study on patients with hyperuricemia and found that the increase in blood SUA level is closely related to the rapid decline of glomerular filtration rate and the risk of renal failure, especially for patients without proteinuria. This phenomenon may be related to the underlying pathogenesis of chronic nephritis itself and the existence of proteinuria. The effect of proteinuria on the progress of renal function masks the adverse effect of high blood SUA, and serum SUA may also affect the progress and prognosis of CKD patients[4,5].

Patients and Methods

Participant Information

A total of 156 patients with CKD admitted to our hospital from January 2022 to September 2022 were selected, and 116 patients were finally included after screening according to the inclusion and exclusion criteria. Inclusion criteria: (1) all patients met the diagnostic criteria of CKD in NKF-KDIGO guidelines; (2) the informed consent form was signed by the patients and their families. Exclusion criteria: (1) patients with important organ dysfunction; (2) patients treated with drugs affecting serum SUA within 1 month; (3) patients with malignant tumors; (4) patients who had been treated with hypoSUA. According to the level of eGFR, there were 39 cases in stage 1, 32 cases in stage 2, 23 cases in stage 3, 15 cases in stage 4, and 7 cases in stage 5. Fasting venous blood of these subjects was collected to value the SUA levels on an automatic biochemical analyzer. Patients were then grouped as the CKD-only group (SUA ≤ 420 μmol/l, n = 80) and hyperuricemia group (SUA > 420 μmol/l, n = 36), according to the SUA results, or the good prognosis group (n = 88) and poor prognosis group (n = 28), according to the presence of cardiovascular and renal diseases. This experimental operation was approved by the Ethics Committee of the Seventh People's Hospital of Shanghai University of Traditional Chinese Medicine (approval number: 2022-7th-HIRB-012), and the informed consent form was obtained from all the patients. The process of general data selection is shown in Figure 1.

Outcome Measures

Blood index detection

The fasting venous blood of patients in each group was collected and centrifuged at 3,000 r/min for 5 min. The supernatant was collected and stored in a refrigerator at –80°C. The levels of serum SUA, total cholesterol (TC), triglyceride (TG), albumin (Alb), and hemoglobin (Hb) were measured by an automatic biochemical analyzer (Shanghai Yuyan Scientific Instrument Co., Ltd., Minhang District, Shanghai, China). The serum level of B-type natriuretic peptide (BNP) was measured by electrochemiluminescence with the commercial kits purchased from Shanghai Yuduo Biotechnology Co., Ltd. (Lugang Town, Jinshan District, Shanghai, China).

Urine index detection

5 ml of the midstream urine of patients in each group was collected in the morning. The content of urinary retinol-binding protein (RBP), urine β2 Microglobulin (β 2-microglobulin, β2-MG), urine α1 Microglobulin (α 1-microglobulin, α1-MG), urinary N-acetyl- β-D-glucosidase (N-acetyl-β-D-Glucosaminidase, NAG) was detected using enzyme-linked immunosorbent assay with the commercial kits purchased from Shanghai Aiyan Biotechnology Co., Ltd. (Fengxian District, Shanghai, China). The value of eGFR was calculated according to the formula. The specific steps are as follows: the sample was diluted. Human serum and all other reagents were diluted to room temperature and shaken gently to avoid foam. A total of 100 μl diluted human serum (1 IU/ml), diluted human plasma (10 IU/ml), diluted human serum (30 IU/ml), diluted serum (100 IU/ml), diluted human serum (300 IU/ml) and diluted samples were added into corresponding wells. Each hole was covered and incubated at room temperature for 60 min. Then, 300 μl diluted detergent was added into each hole for washing, repeated for three times. After discarding the de-

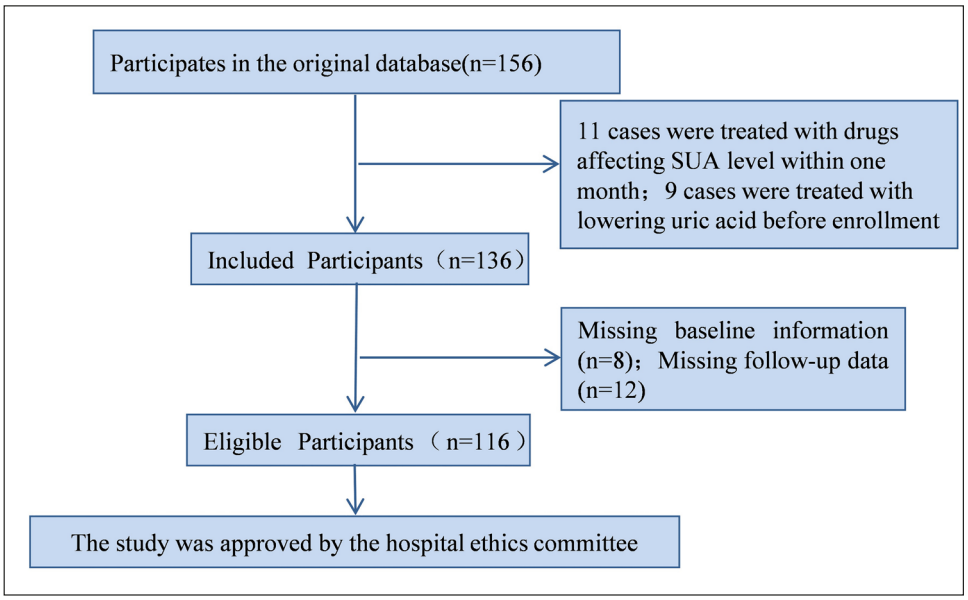

Figure 1. The process of general data selection.

tergent, 100 µl of sheep anti-human IgG labeled with peroxidase was added into each hole, and the mixture was incubated at room temperature for 30 min. Then, 300 µl diluted detergent was added into each hole for washing, repeated for three times. After discarding the detergent, 100 µl of 3,35,5-tetramethylbenzidine (TMB) was added into each hole, and the mixture was incubated for 15 min to avoid the light. 100 µl stop solution containing sulfuric acid was added to each hole and fully mixed. Within 30 minutes after the termination of the reaction, the absorbance was read at the wavelength of 450 nm on a microplate reader. The standard curve was drawn on the coordinate paper with the concentration of the standard as the abscissa and the absorbance value as the ordinate. The concentration of relevant indicators in the tested sample was calculated according to the standard curve.

Clinical Materials

The clinical data of age, gender, BMI, systolic blood pressure (SBP), diastolic blood pressure (DBP), smoking history, drinking history, hypertension history, and heart failure episode history of each patient were collected and compared.

Statistical Analysis

SPSS 20.0 software was used to analyze the experimental data (IBM Corp., Armonk, NY, USA). Age, SUA, and other measurement data were expressed in the form of ($\bar{x}\pm s$) and were compared using a *t*-test. Gender and other ($\bar{x}\pm s$) were expressed in (%) and compared using χ^2 test. Multivariate logistic regression was adopted to analyze the risk factors of hyperuricemia in CKD patients and the risk factors of poor cardiac and renal outcomes in CKD patients. The correlation between SUA level and cardiac and renal indexes was analyzed using Pearson analysis. $p < 0.05$ indicated that the statistical results were statistically significant.

Results

Comparison of Serum SUA Levels in Patients with CKD at Different Stages

Compared with CKD1 patients, the SUA level of CKD2 patients had no difference ($p > 0.05$), and the SUA level of CKD patients in stages 3, 4, and 5 was much higher. Compared with CKD2 patients, the SUA level of CKD patients in stages 3, 4, and 5 was strongly higher ($p < 0.001$, Table I and Figure 2).

Comparison of Clinical Indicators of Patients with Different Levels of SUA in CKD

Patients in the CKD hyperuricemia group had markedly higher content of systolic blood pressure (SBP), diastolic blood pressure (DBP), BNP, urinary retinol-binding protein (RBP), urinary N-acetyl-β-D glucosidase (NAG), much higher proportion of heart failure episodes history, and much lower content of TC, Alb, Hb, urinary α1-MG, and eGFR than the CKD-only group ($p < 0.05$, Table II).

Multivariate Logistic Regression Analysis of the Influencing Factors of Hyperuricemia in CKD Patients

Take the statistically significant indicators in Table II as the independent variable and take whether CKD patients have hyperuricemia as the dependent variable to carry out multivariate logistic regression analysis. The results showed that SUA, BNP, SBP, and history of heart failure episodes were independent risk factors for combined hyperuricemia in CKD patients ($p < 0.05$), and eGFR, albumin, and hemoglobin were independent protective factors for combined hyperuricemia in CKD patients ($p < 0.05$, Table III).

Comparison of Clinical Indicators in Patients with Different Kidney Outcomes of CKD

Compared with the good prognosis group, the content of BNP, SBP, DBP, urinary RBP, urinary NAG, and SUA was much higher, the proportion of heart failure episodes history was obviously higher, and the levels of Alb, Hb, TC, eGFR, and urinary α1-MG were sharply lower in the poor prognosis group ($p < 0.05$, Table IV).

Multivariate Logistic Regression Analysis of Risk Factors Affecting Adverse Cardiac and Renal Outcomes in CKD Patients

The statistically significant indicators in Table IV were taken as the independent variables, and the adverse prognosis of heart and kidney in CKD patients was taken as the dependent variable to carry out multivariate Logistic regression analysis. SUA, BNP, SBP, and history of heart failure episodes were independent risk factors for poor cardiac and renal outcomes ($p < 0.05$), and eGFR was an independent

Table I. Comparison of serum SUA levels in patients with CKD at different stages ($\bar{x}\pm s$).

CKD stage	Cases	SUA (μmol/l)
Stage 1	39	328.45±85.46
Stage 2	32	342.85±56.12
Stage 3	23	452.15±56.96[ab]
Stage 4	15	465.12±56.48[ab]
Stage 5	7	472.15±85.41[ab]
F		22.530
p		< 0.001

[a]$p < 0.05$ compared with CKD patients in stage 1; [b]$p < 0.05$ compared with CKD patients in stage 2.

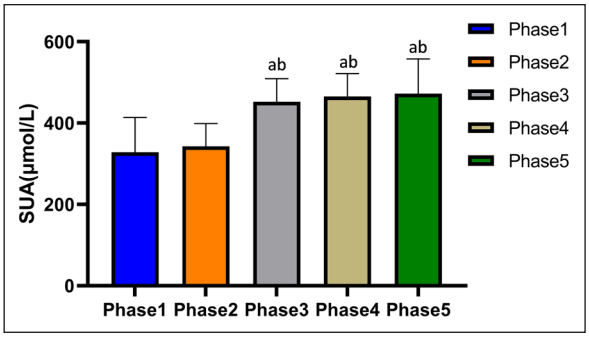

Figure 2. Comparison of serum SUA levels in patients with CKD at different stages.

Table II. Comparison of clinical indicators of patients with different levels of SUA in CKD ($\bar{x}\pm s$).

Indicators		CKD-only group (n=80)	CKD combined with hyperuricemia group (n=36)	χ^2/t	*p*
Gender	Male	55 (68.75%)	28 (77.78%)	0.994	0.319
	Female	25 (31.25%)	8 (22.22%)		
Age (year)		55.36±6.63	55.86±9.45	0.328	0.744
BMI (kg/m^2)		27.32±2.89	27.46±3.19	0.234	0.816
BNP (pg/ml)		135.89±30.15	498.63±25.46	62.777	< 0.001
Alb (g/l)		39.45±6.15	26.85±5.46	10.558	< 0.001
Hb (g/l)		134.96±25.74	106.45±23.16	5.688	< 0.001
Smoking history		10 (12.50%)	2 (5.56%)	1.291	0.256
Drinking history		6 (7.50%)	6 (16.67%)	2.249	0.134
Heart failure episodes history		19 (23.75%)	16 (44.44%)	5.047	0.025
SBP (mmHg)		129.56±20.16	142.89±25.46	3.030	0.003
DBP (mmHg)		72.63±5.96	88.79±6.48	13.148	< 0.001
TG (mmol/l)		140.85±20.63	134.85±21.45	1.432	0.155
TC (mmol/l)		5.69±2.01	4.41±2.36	3.003	0.003
eGFR [ml/min/(1.73 m^2)]		86.49±7.48	24.68±4.96	45.250	< 0.001
Urinary RBP (mg/l)		1.39±0.56	2.15±0.63	6.502	< 0.001
Urinary NAG (U/l)		9.78±1.36	15.46±1.56	19.869	< 0.001
Urinary α1-MG (mg/l)		32.46±7.95	27.45±8.45	3.079	0.003
Urinary β2-MG (mg/l)		1.26±0.36	1.12±0.35	1.954	0.053

Table III. Multivariate logistic regression analysis of the influencing factors of hyperuricemia in CKD patients.

Indicators	β	SE	Wald	p	OR	95%CI
BNP	0.140	0.058	11.823	< 0.001	4.150	1.062-9.236
SUA	0.062	0.036	10.351	< 0.001	4.021	1.236-8.452
Alb (g/l)	-0.615	0.266	5.367	0.021	0.540	0.321-0.910
Hb (g/l)	-0.589	0.312	4.216	0.033	0.687	0.223-0.974
Heart failure episodes history	1.419	0.913	6.341	0.012	4.726	1.673-8.396
SBP	1.456	0.781	8.429	0.015	4.326	2.918-7.465
DBP	0.465	0.689	0.356	0.564	1.542	0.385-5.461
TC	-0.482	0.726	0.459	0.498	0.611	0.021-1.535
eGFR	-0.827	0.226	13.381	< 0.001	0.287	1.452-3.552
Urinary RBP	0.136	0.016	1.026	0.401	1.632	0.361-2.025
Urinary NAG	0.942	0.882	1.925	0.165	1.002	0.925-1.045
Urinary α1-MG	-0.904	0.872	1.075	0.300	0.401	0.069-2.255

Table IV. Comparison of clinical indicators in patients with different kidney outcomes of CKD ($\bar{x}$±s).

Indicators		Good prognosis group (n=88)	Poor prognosis group (n=28)	χ^2/t	p
Gender	Male	65 (73.86%)	18 (64.29%)	0.957	0.328
	Female	23 (26.14%)	10 (35.71%)		
Age (year)		54.12±15.63	56.13±17.49	0.576	0.566
BMI (kg/m^2)		27.45±3.16	27.35±3.45	0.143	0.887
BNP (pg/ml)		146.31±26.45	506.23±21.63	65.330	< 0.001
Alb (g/l)		38.45±6.31	27.46±5.12	8.373	< 0.001
Hb (g/l)		136.53±26.13	108.46±20.13	5.208	< 0.001
Smoking history		9 (10.23%)	3 (10.71%)	0.005	0.941
Drinking history		8 (9.09%)	4 (14.29%)	0.618	0.432
Heart failure episodes history		21 (23.86%)	14 (50.00%)	6.887	0.009
SBP (mmHg)		130.48±21.48	141.26±23.16	2.270	0.025
DBP (mmHg)		75.14±16.38	86.56±5.12	3.624	< 0.001
TG (mmol/l)		142.16±30.16	132.63±25.78	1.505	0.135
TC (mmol/l)		5.79±2.34	4.46±2.12	2.677	0.009
eGFR [ml/min/(1.73 m^2)]		88.45±6.38	25.63±5.63	46.619	< 0.001
Urinary RBP (mg/l)		1.45±1.26	2.06±0.56	2.480	0.015
Urinary NAG (U/l)		9.56±1.45	15.96±1.32	20.768	< 0.001
Urinary α1-MG (mg/l)		32.56±8.36	28.46±6.51	2.374	0.019
Urinary β2-MG (mg/l)		1.25±0.25	1.16±0.16	1.789	0.076
SUA (μmol/l)		316.85±115.63	461.38±89.56	6.055	< 0.001

protective factor for poor cardiac and renal outcomes in patients with CKD ($p < 0.05$, Table V).

Correlation Between SUA Level and Cardiac and Renal Indexes in Patients with CKD

Pearson correlation analysis showed that SUA level in CKD patients was positively correlated with BNP and SBP (r=0.463, 0.215, $p < 0.05$), but negatively correlated with eGFR (r=0.463, 0.215, $p < 0.05$, Table VI and Figure 3).

Discussion

CKD is a clinical syndrome of renal endothelial injury and dysfunction caused by various risk factors, accompanied by the progressive and irreversible decline of renal function until a series of symptoms and metabolic disorders occur. CKD is a common clinical kidney and renal disease, which can be manifested as a glomerular filtration rate and/or renal tubular secretion dysfunction. CKD causes chronic kidney disease, including various primary and secondary glomerulonephritis, renal tubular injury, and renal vascular disease, which has a great impact on the life and work of patients[6,7]. According to the survey in 2010[8], the prevalence of CKD in men was 10.40%, while in women, it was about 11.80% worldwide, which seriously threatens the life and health of people around the world. CKD is characterized by high mortality, and the study believes that the

Table V. Multivariate logistic regression analysis of risk factors affecting adverse cardiac and renal outcomes in CKD patients.

Indicators	β	SE	Wald	*p*	OR	95% CI
BNP	1.145	0.845	1.956	0.012	3.465	1.485-15.234
SUA	1.356	0.798	2.563	0.008	3.958	1.459-16.568
Alb	-0.052	0.008	1.152	0.085	0.985	0.936-0.989
Hb	-0.041	0.009	1.895	0.074	0.956	0.945-0.996
Heart failure episodes history	1.645	0.798	4.658	0.026	5.269	1.457-24.635
SBP	2.564	0.892	6.398	0.015	21.563	3.485-141.65
DBP	0.465	0.689	0.356	0.564	1.542	0.385-5.461
TC	-0.046	0.086	28.451	0.501	0.985	0.912-0.996
eGFR	-0.045	0.012	25.614	0.006	0.954	0.941-0.987
Urinary RBP	3.798	0.958	1.451	0.112	1.263	0.451-2.322
Urinary NAG	3.145	0.816	1.569	0.101	1.165	0.568-2.422
Urinary α1-MG	-0.765	0.654	1.235	0.096	0.895	0.845-0.956

combination of cardiovascular diseases is the main cause of death in CKD patients. Early prediction of the risk of cardiovascular disease in CKD and early preventive intervention may help to improve the prognosis of CKD patients.

Asymptomatic uric acid refers to the symptoms or signs caused by the increase of serum SUA concentration but no SUA crystal deposition. Gout, uric acid nephropathy, and kidney stones are three main crystal deposition-related diseases associated with hyperuricemia. Persistent asymptomatic hyperuricemia will increase the risk of clinical events related to uric acid or uric acid crystals and is related to the degree and duration of hyperuricemia[9]. It is believed that a certain correlation existed between the serum SUA level and the occurrence of cardiovascular diseases[10]. Long-term hyperuricemia can damage the intima of arteries by reducing the content of nitric oxide and increasing the activity of alkaline phosphatase, resulting in vascular calcification and vascular endothelial dysfunction, causing atherosclerosis and leading to the occurrence of coronary heart disease[11,12]. At the same time, hyperuricemia can induce the formation of coronary artery thrombosis by activating platelet activity and increasing blood viscosity[13]. In addition, hyperuricemia can also promote the formation of thrombus by inducing oxidative stress and inflammatory reactions, leading to cardiovascular disease in the body[14]. The kidney is an important organ for SUA metabolism, and long-term CKD can lead to hyperuricemia. Therefore, hyperuricemia is more common in end-stage CKD patients, and may be an important factor leading to

Table VI. Correlation between SUA level and cardiac and renal indexes in patients with CKD.

	SUA	
Indicators	***r***	***p***
BNP	0.463	< 0.001
SBP	0.215	0.020
eGFR	-0.492	< 0.001

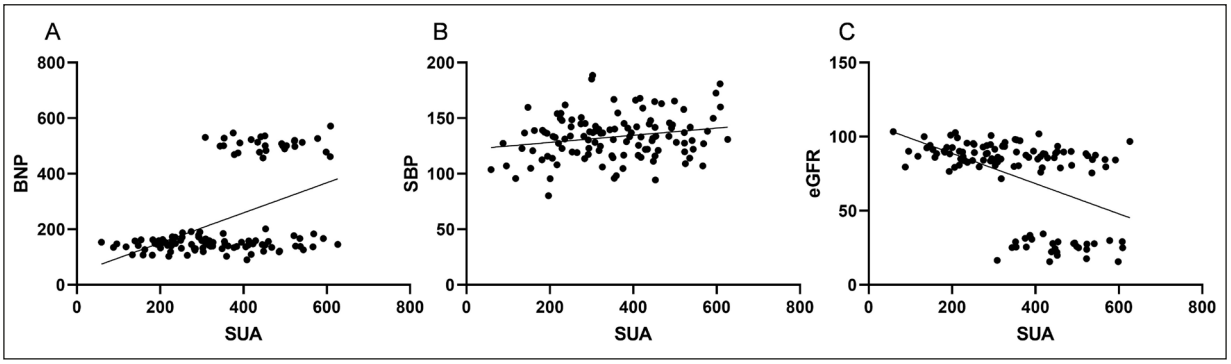

Figure 3. Correlation between SUA level and cardiac and renal indexes in patients with CKD. **A**, Correlation between SUA level and BNP. **B**, Correlation between SUA level and SBP. **C**, Correlation between SUA level and eGFR.

cardiovascular events. In this experiment, the serum SUA level of patients with CKD stages 3, 4, and 5 was much higher than that of patients with CKD stages 1 and 2. SUA, BNP, SBP, and history of heart failure were independent risk factors for hyperuricemia in CKD patients ($p < 0.05$), and eGFR, Alb, and Hb were independent protective factors for hyperuricemia in CKD patients. It is suggested that the level of SUA is related to the renal function and cardiac function of CKD patients. CKD hyperuricemia may be more prone to the progression of kidney disease and higher risk of cardiovascular disease and can be used as one of the important indicators to evaluate the cardiac and renal outcomes of CKD patients.

Previous studies[15,16] have shown that CKD patients are often accompanied by cardiovascular events such as cardiac failure, ischemic heart disease, and peripheral artery disease, which not only aggravate the patient's condition but also greatly increase the difficulty of treatment and affect the prognosis of patients. There were also relevant data showing that, among CKD patients over 45 years old, about 87% had cardiovascular diseases at the end stage, and about 50% of them died of cardiovascular diseases. About half of end-stage CKD patients died of cardiovascular diseases[17,18]. Therefore, early analysis of the risk of cardiovascular events in patients with CKD is crucial to evaluate the prognosis of patients. Multivariate logistic regression analysis in this experiment also considered that SUA, BNP, SBP, and history of heart failure attack were independent risk factors, and eGFR was an independent protective factor for adverse cardiac and renal outcomes in CKD patients. SUA level was positively correlated with BNP and SBP, and negatively correlated with eGFR. Therefore, early monitoring of the change of SUA level, reducing the content of SUA in the serum of CKD patients, and reducing the occurrence of hyperuricemia may delay the occurrence of cardiovascular events in CKD patients, and help to improve the prognosis of patients and prolong their lives.

Conclusions

In general, the serum SUA level was elevated with the aggravation of the CKD stage. High serum SUA level is a risk factor for the development of hyperuricemia and poor cardio-renal outcomes in CKD patients, suggesting that early monitoring of changes in SUA levels may help assess the risk of cardio-renal outcomes in CKD patients. However, due to the short duration of this experimental study and the fact that the subjects are all patients in our hospital, the experimental results may have some deviation. In the future, the sample size and the research time should be expanded for further research.

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Ethics Approval
The operation in the present experiment was approved by the Seventh People's Hospital of Shanghai University of Traditional Chinese Medicine (approval number: 2022-7th-HIRB-012).

Informed Consent
The written informed consents were obtained from patients.

Authors' Contributions
W.-W. Liu and G.-B. Yang edited the manuscript and performed the experiment. Z.-Y. Liu and Y. Guo collected data. J.-H. Yuan and L.-X. Duan processed the data and the statistics. L. Liao and C.-F. Zhang gave us the support we needed. J.-R. Lu, J. Hu and J. Chen designed the research, provided critical comments, and revised the manuscript. All authors contributed to the article and approved the submitted version.

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Data Availability Statement
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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

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