The Association Between the Serum Uric Acid to Creatinine Ratio and All-Cause Mortality in Elderly Hemodialysis Patients

Zhihui Ding

Tai zhou NO.2 people's Hospital

Yao Fan

Affiliated Geriatric Hospital of Nanjing Medical University

Chunlei Yao

Tai zhou NO.2 people's Hospital

Liubao Gu (✉ abobgu@126.com)

Affiliated Geriatric Hospital of Nanjing Medical University

Research Article

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Abstract

Purpose: The present study investigated the association between the serum uric acid to creatinine ratio (SUA/Scr) and all-cause mortality among elderly hemodialysis patients.

Methods: A total of 222 patients (≥ 60 years) who received hemodialysis more than 8 hours per week at Tai Zhou No. 2 People's Hospital for at least 3 months were enrolled in the present study from January 2015 to December 2019. Clinical characteristics were obtained from the hemodialysis database, and survival information was recorded during the follow-up period. Multiple Cox regression was carried out to analyze the association between SUA/Scr and all-cause mortality. The survival rate of each group was calculated by the Kaplan-Meier method, and the ratio of survival curves was analyzed by the log-rank test.

Results: During the 19-month observation period, 78 patients died. Individuals in the nonsurviving group had significantly older ages ($P < 0.001$), body mass index (BMI) ($P = 0.004$), serum creatinine ($P = 0.005$) and prealbumin ($P = 0.006$) than surviving patients. After adjusting for age, sex, BMI, prealbumin and serum creatinine, a higher ratio of SUA/Scr was independently associated with a higher risk of all-cause mortality (HR: 1.375; 95% CI: 1.023-1.848; $P = 0.035$).

Conclusion: The serum uric acid to creatinine ratio is strongly associated with all-cause mortality in elderly hemodialysis patients.

1. Introduction

According to the 2019 United States Renal Data System (USRDS) annual data report[1], the crude incidence rate of end-stage renal disease (ESRD) was 370.2 per million per year in the United States, with 86.9% of ESRD patients receiving hemodialysis treatment. Currently, hemodialysis is the main renal replacement therapy among elderly ESRD patients. However, elderly hemodialysis patients still had a three- to six-fold higher mortality risk than nonelderly hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study (DOPPS) study[2]. There are many identified factors contributing to the increased mortality risk in these patients, such as blood pressure, urine albumin, anemia, and serum creatinine[3–8].

Among these multiple risk factors increasing the mortality risk of hemodialysis patients, serum uric acid (SUA) has recently captured much interest and has been considered a new member. It has been extensively shown that the SUA level is positively correlated with all-cause mortality[9–11]. However, the actual association between SUA and all-cause mortality remains unclear and controversial. For example, Zawada AM *et al.* revealed that SUA level and all-cause mortality showed a U-shaped pattern among hemodialysis patients[12]. Thus, more data are needed to clarify this issue.

Given that SUA is mainly eliminated in the urine, a decrease in glomerular filtration rate (GFR) may cause an increased level of SUA[13], which means that renal function might be the major confounder in studies on the association between SUA levels and other diseases. Thus, the renal function-normalized SUA (SUA to creatinine ratio, abbreviated SUA/Scr) might be more predictive than SUA alone in such studies. As

expected, SUA/Scr is truly more sensitive than SUA in relation to Parkinson's disease, metabolic syndrome (MetS), liver function, nonalcoholic fatty liver disease (NAFLD) and chronic obstructive pulmonary disease (COPD) [14–21]. Our previous study also found that SUA/Scr could predict renal disease progression (incident CKD and ESRD) and correlate with β -cell function among type 2 diabetes patients[22–24]. Interestingly, a recent study from a US national survey also showed that a higher ratio of SUA/Scr was associated with increased all-cause mortality among adults[25].

To date, the relationship between SUA/Scr and mortality risk among hemodialysis patients has rarely been reported. Therefore, we explored the relationship between SUA/Scr and all-cause mortality among elderly hemodialysis patients in the present study.

2. Material And Methods

2.1 Ethics

The present study was approved by the Ethics Committee of Tai Zhou No. 2 People's Hospital. Written informed consent was obtained from each participant.

2.2 Participants

The present retrospective, observational and single-center study observed 481 patients who received hemodialysis more than 8 hours per week at Tai Zhou No. 2 People's Hospital for at least 3 months from January 2015 to December 2019. Patients who had a history of malignancy, were less than 60 years old, and patients who combined or switched to other renal replacement therapies were excluded. Finally, 222 patients were included for the analysis.

2.3 Clinical and laboratory data

Clinical baseline characteristics, such as age, sex, height and body weight, were obtained from our hospital hemodialysis database. Blood pressure was measured by trained hemodialysis nurses. BMI was calculated by dividing weight (kilograms) by the square of the height (meters). The laboratory data were collected before hemodialysis, including hemoglobin (Hb), albumin (ALB), total cholesterol (TC), serum uric acid (SUA), serum creatinine (Scr), calcium (Ca) and other laboratory indexes [Siemens Pipeline Biochemical Analyzer (Siemens, Inc, Munich, Germany)]. The serum uric acid to creatinine ratio was calculated by dividing serum uric acid by serum creatinine. We examined all-cause mortality from our medical record system, including cardio-cerebrovascular death and cancer during the follow-up period.

2.4 Statistical analysis

Continuous variables conforming to a normal distribution are described by means $\pm$ standard deviations, while nonnormally distributed data are represented by medians (interquartile ranges [IQRs]). The difference between groups of normally distributed continuous variables was tested by Student's t test. For nonnormally distributed data, the nonparametric Mann-Whitney U test was used. Chi-square (χ^2) tests were used for the comparison of categorized variables. The Spearman correlation coefficient was used to

calculate the selected variables related to SUA/Scr. Multiple Cox regression was used to analyze the association of SUA/Scr and all-cause mortality. The survival rate of each group was calculated by the Kaplan-Meier method, and the ratio of survival curves was analyzed by the log-rank test. $P \leq 0.05$ was considered statistically significant. IBM SPSS Statistics 23.0 (SPSS, Inc., Chicago, USA) was used for data analysis.

3. Results

3.1 Demographic and baseline characteristics of elderly hemodialysis patients

A total of 222 patients were enrolled in the analysis, including 133 males and 89 females. The median age of all patients was 71.0 (65.0, 77.0) years old. During the 19-month observation period, 78 patients died.

The demographic and baseline characteristics of surviving and nonsurviving patients are shown in Table 1. Individuals in the nonsurviving group had significantly older ages than surviving patients ($P < 0.001$). Furthermore, the patients who died had lower BMI ($P = 0.004$), serum creatinine ($P = 0.005$) and prealbumin ($P = 0.006$). Other baseline characteristics did not show significant differences between groups. Apparently, patients in the nonsurviving group had a higher SUA/Scr than surviving patients ($P = 0.001$).

3.2 The correlation between SUA/Scr and selected variables

Table 2 shows that SUA/Scr was significantly positively correlated with age ($P = 0.002$) and uric acid ($P = 0.001$). The SUA/Scr was significantly negatively correlated with diastolic blood pressure ($P = 0.012$), serum creatinine ($P = 0.001$), albumin ($P = 0.001$), prealbumin ($P = 0.001$), serum calcium ($P = 0.002$) and serum phosphorus ($P = 0.037$).

3.3 A higher ratio of SUA/Scr increases the risk of all-cause mortality among elderly hemodialysis patients.

Patients were divided into four groups according to SUA/Scr quartile. The Kaplan-Meier curve was used to compare the accumulated mortality among the four groups. As shown in Figure 1, the higher SUA/Scr group had significantly higher all-cause mortality than the lower SUA/Scr group ($P = 0.011$).

3.4 SUA/Scr was an independent risk factor for all-cause mortality among elderly hemodialysis patients.

Consistently, as shown in Table 3, SUA/Scr was positively associated with all-cause mortality (HR=1.522 [95% CI 1.233-1.879], $P = 0.001$) in the crude model. Furthermore, SUA/Scr was an independent risk factor for all-cause mortality (HR=1.375 [95% CI 1.023-1.848], $P = 0.035$) after adjusting for age, sex, BMI, prealbumin and serum creatinine.

4. Discussion

The present study demonstrated that a higher serum uric acid to creatinine ratio increased all-cause mortality among elderly hemodialysis patients. To our knowledge, this is the first study to explore the relationship between SUA/Scr and all-cause mortality in elderly hemodialysis patients.

The influence of serum uric acid on the survival of hemodialysis patients is complex and paradoxical. The Framingham study was the first to indicate that serum uric acid was linked to cardiovascular outcomes among the general male population[26]. Interestingly, the same association was not shown among the female population. Previous studies also demonstrated that high serum uric acid levels predicted a high risk of death in hemodialysis patients[10, 27]. In contrast, other studies showed that high uric acid levels were associated with a low risk of all-cause and cardiovascular mortality [28–30]. A large cohort study in Japan showed that uric acid levels may have a U-shaped association with all-cause mortality among the general population, which means that both low and high uric acid levels may increase mortality[31]. Consistently, a multicenter prospective cohort study in Chinese hemodialysis patients also certified a U-shaped pattern between serum uric acid level and all-cause mortality, cardiovascular disease (CVD) mortality and non-CVD mortality[32].

Serum uric acid and creatinine may be associated with the status of nutrition among hemodialysis patients. Considering the paradoxical effect of uric acid on hemodialysis patients, we sought to assess the relationship between serum uric acid and survival status in elderly hemodialysis patients using renal function-normalized SUA (SUA/Scr). Additionally, SUA/Scr can reduce the interference of sex and renal function abnormalities[33]. Our previous studies have already revealed the relationship between SUA/Scr and renal progression[22–24]. The present study showed that a higher ratio of SUA/Scr predicted a higher risk of all-cause mortality among elderly hemodialysis patients. The link remained significant but attenuated after adjusting for other factors, such as age, sex, BMI, prealbumin and serum creatinine.

The present study has several limitations. First, the present study is a single-center study, which might cause selection bias. Further multicenter studies are needed to clarify the relationship between SUA/Scr and all-cause mortality. Second, the study did not distinguish the effects of dialysis frequency, such as the effect of dialysis twice a week versus three times a week. Third, this study only verified the predictive value of the serum uric acid to creatinine ratio in all-cause mortality, and its predictive value for cardiovascular mortality was insufficient.

In summary, the present study demonstrated that the serum uric acid to creatinine ratio is strongly associated with all-cause mortality in elderly hemodialysis patients. Further verification is needed in multicenter and multipopulations.

Abbreviations

SUA/Scr, serum uric acid to creatinine ratio

BMI, body mass index

USRDS, United States Renal Data System

ESRD, end-stage renal disease

DOPPS, Dialysis Outcomes and Practice Patterns Study

SUA, serum uric acid

GFR,glomerular filtration rate

MetS, metabolic syndrome,

NAFLD, nonalcoholic fatty liver disease

COPD, chronic obstructive pulmonary disease

CKD, chronic kidney disease

Hb, hemoglobin

ALB, albumin

TC, total cholesterol

Scr, serum creatinine

Ca, calcium

CVD, cardiovascular disease

Declarations

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Tai Zhou No. 2 People's Hospital. Written informed consent was obtained from each participant. The research was done according to the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

The data that support the findings of this study are available from Ethics Committee of Tai Zhou No. 2 People's Hospital but restrictions apply to the availability of these data, which were used under license for

the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Ethics Committee of Tai Zhou No. 2 People's Hospital.

Competing interests

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Author Contributions

All authors made substantial contributions to the conception, design, and acquisition of data. Zhihui Ding, Yao Fan, Chunlei Yao and Liubao Gu made substantial contributions to the analysis and interpretation of the data. Zhihui Ding drafted the manuscript. All authors were involved in revising the manuscript. All authors gave approval of the final manuscript to be published.

Authors' information

^a Department of Nephrology, Tai Zhou No. 2 People's Hospital, Tai Zhou, China.

^b Division of Clinical Epidemiology, Affiliated Geriatric Hospital of Nanjing Medical University, Nanjing, China.

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Tables

Table 1. The baseline data of elderly hemodialysis patients grouped by whether death

	Survival Group	Death Group	<i>p</i> -value
Age(years)	68.00(64.25, 74.00)	74.50(68.00, 80.00)	0.001***
Gender(male/female)	87/57	46/32	0.834
BMI(Kg/m ²)	21.87(20.26, 24.42)	20.96(18.81, 23.33)	0.004**
SBP (mmHg)	146.62±24.18	147.04±28.48	0.908
DBP (mmHg)	80.00(70.00, 88.00)	79.00(65.00, 87.25)	0.448
Hb(g/L)	90.00(72.00, 110.00)	91.00(71.75, 112.50)	0.754
BUN (mmol/L)	22.85(16.02, 31.03)	21.98(15.82, 30.74)	0.652
Scr (umol/L)	664.52±267.49	561.03±238.80	0.005**
SUA (umol/L)	417.00(322.50, 507.75)	433.50(350.25, 545.50)	0.243
ALB(g/L)	35.65(32.70, 39.38)	35.00(30.83, 38.00)	0.12
PA (mg/L)	253.95±86.94	215.54±91.50	0.006**
TC (mmol/L)	3.66(3.05, 4.12)	3.61(2.98, 4.00)	0.419
TG (mmol/L)	1.09(0.69, 1.64)	0.98(0.70, 1.49)	0.482
Ca(mmol/L)	2.12(1.95, 2.26)	2.12(2.01, 2.21)	0.936
P(mmol/L)	1.76(1.41, 2.06)	1.63(1.31, 2.09)	0.422
SUA/Scr	0.60(0.47, 0.88)	0.80(0.54, 1.14)	0.001**

Note: *, $P \leq 0.05$; **, $P \leq 0.01$; ***, $P \leq 0.001$

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; Hb, hemoglobin; BUN, blood urea nitrogen; SUA, serum uric acid; Scr, serum creatinine; ALB, albumin; PA, prealbumin; TC, total cholesterol; TG, triglyceride; Ca, calcium; P, phosphorus; SUA/Scr, serum uric acid to serum creatinine ratio.

Table 2. Spearman correlation between SUA/Scr and variables

variables	Correlation coefficient	<i>p</i> -value
Age	0.202	0.002**
BMI	0.025	0.708
SBP	-0.120	0.073
DBP	-0.168	0.012*
Hb	-0.119	0.077
BUN	-0.025	0.714
Scr	-0.682	0.001***
UA	0.520	0.001***
ALB	-0.265	0.001***
PA	-0.243	0.001**
TC	0.074	0.274
TG	0.108	0.107
Ca	-0.208	0.002**
P	-0.140	0.037*

Note: *, $P \leq 0.05$ **, $P \leq 0.01$ ***, $P \leq 0.001$

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; Hb, hemoglobin; BUN, blood urea nitrogen; SUA, serum uric acid; Scr, serum creatinine; ALB, albumin; PA, prealbumin; TC, total cholesterol; TG, triglyceride; Ca, calcium; P, phosphorus.

Table 3. Multiple Cox hazards regression analysis of SUA/Scr on elderly patients' survival on hemodialysis

	Wald	SEM	<i>HR</i>	(95% <i>CI</i>)	<i>P</i> -value
Crude Model	15.271	0.107	1.522	1.233-1.879	0.001***
Model 1	12.738	0.106	1.459	1.186-1.795	0.001***
Model 2	4.444	0.151	1.375	1.023-1.848	0.035*

Model 1: adjusted for age, gender and BMI;

Model 2: adjusted for age, gender, BMI, PA and Scr.

Note: *, $P \leq 0.05$ **, $P \leq 0.01$ ***, $P \leq 0.001$

Abbreviations: BMI, body mass index; Scr, serum creatinine; PA, prealbumin.

Figures

Figure 1

Kaplan-Meier curves for all-cause mortality among elderly hemodialysis patients grouped by SUA/Scr level