

# Risk factors for acute kidney injury among patients with rhabdomyolysis

**Jia Yang**

Division of Nephrology, West China Hospital of Sichuan University, Chengdu, 610041, China

**Jiaojiao Zhou**

Division of Ultrasound, West China Hospital of Sichuan University, Chengdu, 610041, China

**Xin Wang**

Division of Nephrology, West China Hospital of Sichuan University, Chengdu, 610041, China

**Siwen Wang**

Division of Nephrology, West China Hospital of Sichuan University, Chengdu, 610041, China

**Yi Tang**

Division of Ultrasound, West China Hospital of Sichuan University, Chengdu, 610041, China

**Lichuan Yang** (✉ [glcgh@163.com](mailto:glcgh@163.com))

Sichuan University West China Hospital

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## Research

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# Abstract

**Background:** Acute kidney injury (AKI) is a life-threatening complication of rhabdomyolysis (RM). The aim of the present study was to assess patients at high risk for the occurrence of AKI defined by the Kidney Disease Improving Global Outcomes criteria and in-hospital mortality. **Methods:** We performed a retrospective study of patients with creatine kinase levels >1000 U/L, who were admitted to the West China Hospital of Sichuan University between January 2011 and March 2019. The sociodemographic, clinical and laboratory data of these patients were obtained from an electronic medical records database, and univariate and multivariate regression analyses were subsequently conducted. **Results:** For the 329 patients included in our study, the incidence of AKI was 61.4%, and the overall mortality rate was 19.8%; furthermore, patients with AKI tended to have higher mortality rates than those without AKI (24.8% vs. 11.8%;  $P < 0.01$ ). The clinical conditions most frequently associated with RM were trauma (28.3%), sepsis (14.6%), bee sting (12.8%), thoracic and abdominal surgery (11.2%) and exercise (7.0%). Furthermore, patients with RM resulting from sepsis, bee sting and acute alcoholism were more susceptible to AKI. The risk factors for the occurrence of AKI among RM patients included age  $\geq 60$  years (OR=3.070), chronic alcoholism (OR=3.256), hypertension (OR=4.252), multiple organ dysfunction syndrome (MODS; OR=7.244), high levels of white blood cell count (OR=1.047) and elevated serum phosphorus (OR=5.526). Age  $\geq 60$  years (OR=3.188), MODS (OR=2.262), diabetes (OR=2.746) and elevated prothrombin time (OR=1.079) were independent risk factors for in-hospital mortality in RM patients with AKI. **Conclusions:** AKI is independently associated with mortality in patients with RM, and several risk factors were found to be associated with the occurrence of AKI and in-hospital mortality. These findings suggest that, to improve the quality of medical care, the early prevention of AKI should focus on high-risk patients and more effective management.

## Background

Rhabdomyolysis (RM) is a syndrome characterized by the disruption of skeletal muscle cell integrity, with subsequent release of intracellular components into the extracellular environment. There are numerous reported causes of RM, and the most frequently associated etiologies are trauma, immobilization, sepsis and surgery [1–3]. The clinical manifestations of RM (and their subsequent severity) vary based on the specific cause. These range from isolated elevation of laboratory indices, such as myoglobin and creatine kinase (CK), to life-threatening electrolyte disturbances and organ dysfunction [4, 5]. AKI is a common complication of RM, and the pathogenesis of RM-associated AKI includes tubular obstruction caused by myoglobin, myoglobin cytotoxicity by lipid peroxidation, and the production of reactive oxygen species. Intracellular components released into the circulation cause capillary damage, which leads to leakage and edema, secondary hypovolemia and decreased renal blood flow, and ultimately reduce renal function [2, 6]. The incidence of AKI is reported to be between 37.8 and 79.5% in patients with RM [7–10], and is independently associated with a 19.2–59% increase in mortality [9, 11, 12]. The occurrence of AKI is associated with a worse outcome in patients with RM, which increases medical burden; thus, the

prevention and early diagnosis of AKI are critical to improving patient prognosis. Therefore, we conducted a retrospective analysis of patients with RM to identify those at high risk of AKI.

## Methods

### Study population

The present study was a retrospective analysis of data collected from the West China Hospital of Sichuan University, from patients admitted between January 2011 and March 2019. All patients over 18 years old with CK levels > 1000U/L were eligible. The exclusion criteria were as follows: (i) Patients with pre-existing end-stage renal disease; (ii) patients who had received a kidney transplant; (iii) patients with abnormal CK elevation from acute myocardial infarction; and (iv) patients with incomplete data. To avoid bias among patients who were repeatedly admitted to hospital during the study period, only the first admission was included.

### Data Collection

Patient sociodemographic, clinical and laboratory data were obtained from an electronic medical records database. Sociodemographic data included age, sex and date of admission. Clinical data included etiology, smoking history, alcoholism and chronic disease history (hypertension, diabetes and hyperlipidemia), the presence of comorbidities, including sepsis and multiple organ dysfunction syndrome (MODS), and the outcomes (length of stay in hospital and mortality). Laboratory data comprised blood levels of CK, baseline biomarkers of renal function (serum creatinine (SCr), blood urea nitrogen (BUN), cystatin C and uric acid), levels of phosphate, calcium, potassium, aminotransferase, albumin, bilirubin, hemoglobin, lipoprotein and prothrombin time, as well as white blood cell (WBC) and platelet counts.

### Definition

In the present study, AKI was defined per the Kidney Disease Improving Global Outcomes criteria [13]: An absolute increase in serum creatinine of  $\geq 26.4 \mu\text{mol/L}$  within 48 h, or  $\geq 50\%$  baseline serum creatinine within 7 days. Due to incomplete urine output data, only the serum creatinine readings were available. For the baseline creatinine levels, we used the lowest value of serum creatinine recorded in the 2 days prior to admission, and if not available, the first serum creatinine reading within 2 days after admission [14]. In this study, the AKI was categorized as AKI I, II, III, respectively, according to increase in serum creatinine  $\geq 26.4 \mu\text{mol/L}$  or increase to  $\geq 1.5$ -fold to twofold from baseline, > twofold to threefold from baseline and > threefold from baseline or serum creatinine  $\geq 354 \mu\text{mol/L}$  with an acute increase of at least  $44 \mu\text{mol/L}$ . Individuals who receive renal replacement therapy were considered to have met the criteria of AKI III regardless of their serum creatinine value. The AKI stage was evaluated weekly, and the maximum degree

was regarded as the final AKI stage. By reviewing the medical records of all patients, the etiologies of rhabdomyolysis and outcomes of patients during hospitalization were confirmed.

## Statistical analysis

Categorical covariates were recorded as frequency distributions and proportions. According to the distribution pattern, continuous variables were recorded as the mean  $\pm$  standard deviation (SD). Univariate analysis was employed to predict disease etiology, using a binomial distribution; the Students t-test and Pearson  $\chi^2$  test were used to estimate baseline characteristics. Independent predictors of AKI incidence and in-hospital mortality were evaluated by univariate and multivariate logistic regression, which were utilized to calculate odds ratios (ORs) and 95% confidence intervals. Only the significant risk factors identified by univariate analysis were considered for multiple regression analysis. The data were analyzed using SPSS 22.0 (IBM Corp., Armonk, NY, USA) and  $P < 0.05$  (two-sided) was considered to indicate a statistically significant difference.

## Results

In the present study, we identified 383 hospitalizations of adults with a CK level  $> 1000$  U/L between January 2011 and March 2019. After excluding 6 patients with pre-existing end-stage renal disease or who had received a kidney transplant, 1 case of acute myocardial infarction, 7 patients aged  $< 18$  years and 40 with incomplete data, the final study population included 329 patients. There were 202 (61.4%) RM-induced AKI patients, among which 18.8% were classified as AKI stage I, 14.9% as AKI stage II and 66.3% as AKI stage III according to the KDIGO criteria. The patient age (mean  $\pm$  SD) was  $45.7 \pm 15.9$  years, and 74.8% of the patients were male. The overall in-hospital mortality rate was 19.8%, and patients with secondary AKI tended to exhibit higher mortality rates than those without AKI (24.8% vs. 11.8%,  $P < 0.01$ ). The clinical conditions most frequently associated with RM were trauma (28.3%), sepsis (14.6%), bee sting (12.8%), thoracic and abdominal surgery (11.2%) and exercise (7.0%). Other causes are shown in Table 1. Patients with RM resulting from sepsis, bee sting and acute alcoholism were more susceptible to AKI.

Table 1  
The cause of Rhabdomyolysis according to Non-AKI and AKI group

Variables	Non-AKI(n = 127)	AKI(n = 202)	P
Trauma, n (%)	54(58.1)	39(41.9)	0.146
Sepsis, n (%)	12(25.0)	36(75.0)	0.001
Bee sting, n (%)	2(4.8)	40(95.2)	0.000
Thoracic and abdominal operations, n (%)	16(43.2)	21(56.8)	0.511
Exercise, n (%)	11(47.8)	12(52.2)	1.000
Vascular surgery, n (%)	9(42.9)	12(57.1)	0.664
Acute alcoholism, n (%)	1(9.1)	10(90.9)	0.012
Drug, n (%)	3(50.0)	3(50.0)	1.000
Osteofascial compartment syndrome, n (%)	0(0.0)	5(100.0)	0.063
Myopathy, n (%)	3(75.0)	1(25.0)	0.625
Hyperthermia, n (%)	1(33.3)	2(66.7)	1.000
Orthopedic surgery, n (%)	2(66.7)	1(33.3)	1.000
Cardiac arrest, n (%)	1(50.0)	1(50.0)	1.000
Langoustine, n (%)	2(100.0)	0(0.0)	0.500
Seizure, n (%)	0(0.0)	1(100.0)	1.000
Diabetic ketoacidosis, n (%)	0(0.0)	1(100.0)	1.000
Unknown, n (%)	10(37.0)	17(63.0)	0.248
AKI acute kidney injury.			

The baseline characteristics and their comparison between RM patients with and without AKI are displayed in Table 2. Compared with the non-AKI group, the proportions of patients aged  $\geq 60$  years, chronic alcoholism, hypertension, diabetes, sepsis, MODS, CK  $\geq 40000$  and those that succumbed to the disease were significantly higher in the AKI group. Higher WBC counts, serum bilirubin, alanine aminotransferase (ALT), aspartate aminotransferase (AST), biomarkers of baseline renal function (SCr, BUN and cystatin C), potassium and phosphorus levels were detected in patients with AKI. The level of high density lipoprotein cholesterol (HDL) in patients with AKI was lower than that in those without AKI. However, in terms of smoking history, hyperlipidemia, hemoglobin, blood platelet count, serum albumin, uric acid, triglyceride, cholesterol, low-density lipoprotein cholesterol (LDL), calcium and prothrombin time, there were no significant differences between the two groups.

Table 2  
Comparison of baseline characteristics between Non-AKI and AKI group

Variables	Non-AKI(n = 127)	AKI(n = 202)	P
Age, mean ± SD, days	40.9 ± 15.2	48.7 ± 15.7	0.000
Age group, n (%)			0.000
Age ≤ 40	58(45.7)	59(29.2)	
40 < Age < 60	57(44.9)	94(46.5)	
Age ≥ 60	12(9.4)	49(24.2)	
Gender, n (%)			0.189
Male	100(78.7)	146(72.3)	
Female	27(21.3)	292	
Smoking, n (%)	44(34.6)	75(37.1)	0.648
Chronic alcoholism, n (%)	16(12.6)	65(32.2)	0.000
Disease history, n (%)			
Hypertension	7(5.5)	44(21.8)	0.000
Diabetes	4(3.1)	23(11.4)	0.008
Hyperlipidemia	11(8.7)	18(8.9)	0.938
Comorbidity, n (%)			
Sepsis	63(49.6)	132(65.3)	0.005
MODS	9(7.1)	71(35.1)	0.000
Laboratory data, mean ± SD			
Hemoglobin(g/L)	105.3 ± 35.1	102.3 ± 38.3	0.471
Platelets(109/L)	153.1 ± 92.1	136.4 ± 81.3	0.086
WBC(109/L)	13.1 ± 7.2	16.8 ± 10.6	0.000
Total bilirubin(μmol/L)	24.1 ± 23.3	49.7 ± 87.7	0.000
Direct bilirubin(μmol/L)	11.5 ± 12.7	27.2 ± 52.9	0.000
ALT(IU/L)	200.3 ± 318.9	418.1 ± 876.7	0.001

AKI acute kidney injury, MODS multiple organ dysfunction syndrome, WBC white blood cell, ALT alanine aminotransferase, AST aspartate transaminase, BUN blood urea nitrogen, Scr serum creatinine, HDLC high density lipoprotein, LDLC low density lipoprotein, PT prothrombin time.

Variables	Non-AKI(n = 127)	AKI(n = 202)	P
AST(IU/L)	388.7 ± 553.6	1022.4 ± 2040.4	0.000
Albumin(g/L)	28.9 ± 9.7	29.2 ± 7.5	0.756
Baseline BUN(mmol/L)	6.3 ± 2.4	11.6 ± 7.2	0.000
Scr(μmol/L)	74.4 ± 20.6	168.0 ± 130.4	0.000
Cystatin C (μmol/L)	1.5 ± 0.2	2.0 ± 1.2	0.000
Uric acid(umol/L)	265.4 ± 152.4	280.5 ± 143.6	0.364
Triglycerides(mmol/L)	1.6 ± 2.6	2.1 ± 2.4	0.094
Cholesterol (mmol/L)	3.2 ± 1.8	2.9 ± 1.7	0.197
HDLC(mmol/L)	1.0 ± 0.4	0.7 ± 0.4	0.000
LDLC(mmol/L)	1.6 ± 1.1	1.4 ± 1.2	0.308
Potassium(mmol/L)	3.8 ± 0.6	4.2 ± 0.8	0.000
Calcium (mmol/L)	2.0 ± 0.3	1.9 ± 0.3	0.053
Phosphate(mmol/L)	0.9 ± 0.4	1.4 ± 0.8	0.000
PT(s)	14.9 ± 4.2	16.1 ± 8.9	0.174
creatine kinase >= 40000(IU/L), n (%)	45(35.4)	135(66.8)	0.000
Outcome			
Length of stay, mean ± SD, days	27.9 ± 23.8	28.0 ± 25.7	0.953
Mortality, n (%)	15(11.8)	50(24.8)	0.004
AKI acute kidney injury, MODS multiple organ dysfunction syndrome, WBC white blood cell, ALT alanine aminotransferase, AST aspartate transaminase, BUN blood urea nitrogen, Scr serum creatinine, HDLC high density lipoprotein, LDLC low density lipoprotein, PT prothrombin time.			

We then evaluated the effects of the independent risk factors on the occurrence of AKI, using univariate and multivariate logistic regression. Univariate analysis revealed that an age  $\geq 60$  years, chronic alcoholism, hypertension, diabetes, sepsis, MODS, decreased HDLC and increased laboratory markers (including WBC count, serum bilirubin, ALT, AST, serum potassium, phosphorus, baseline BUN, Scr and cystatin C) were significant risk factors for AKI (Table 3). Multivariate logistic regression highlighted several distinguishing variables between the two groups, including age  $\geq 60$  years (OR = 3.070; 95% CI 1.231–7.658), chronic alcoholism (OR = 3.256; 95% CI 1.603–6.612), hypertension (OR = 4.252; 95% CI 1.584–11.411), MODS (OR = 7.244; 95% CI 3.126–16.786), elevated WBC count (OR = 1.047; 95% CI 1.011–1.084) and serum phosphorus (OR = 5.526; 95% CI 3.045–10.027) (Table 4). Similarly, risk factors for in-hospital mortality in patients with RM-induced AKI were analyzed. Age  $\geq 60$  years (OR = 3.188; 95%

CI 1.186–8.570), MODS (OR = 2.262; 95% CI 1.053–4.858), diabetes (OR = 2.746; 95% CI 1.023–7.369) and elevated prothrombin time (OR = 1.079; 95% CI 1.004–1.160) were identified as independent risk factors, which may be associated with increased mortality rates among these patients (Table 5).

Table 3  
Univariate analysis of risk associated with AKI for patients with rhabdomyolysis

Variables	B	SE	Wald	p	OR
Age	0.033	0.008	17.957	0.000	1.033(1.018–1.049)
Age ≤ 40			14.361	0.001	1
40 < Age < 60	0.483	0.250	3.743	0.053	1.621(0.994–2.645)
Age ≥ 60	1.390	0.371	14.004	0.000	4.014(1.938–8.312)
Chronic alcoholism	1.191	0.307	15.068	0.000	3.292(1.804–6.007)
Hypertension	1.563	0.425	13.557	0.000	4.774(2.077–10.971)
Diabetes	1.374	0.554	6.146	0.013	3.951(1.333–11.708)
Sepsis	0.650	0.231	7.919	0.005	1.916(1.218–3.013)
MODS	1.961	0.376	27.213	0.000	7.106(3.401–14.846)
WBC	0.048	0.014	11.174	0.001	1.049(1.020–1.079)
Total bilirubin	0.012	0.004	8.502	0.004	1.012(1.004–1.020)
Direct bilirubin	0.023	0.008	8.924	0.003	1.023(1.008–1.039)
ALT	0.001	0.000	6.753	0.009	1.001(1.000-1.002)
AST	0.001	0.000	13.958	0.000	1.001(1.000-1.001)
Baseline BUN	0.297	0.043	48.391	0.000	1.346(1.238–1.463)
Scr	0.036	0.006	40.987	0.000	1.036(1.025–1.047)
Cystatin C	0.765	0.134	46.493	0.000	2.274(1.553–3.232)
HDLC	-1.434	0.275	27.176	0.000	0.238(0.139–0.409)
Potassium	0.852	0.189	20.344	0.000	2.344(1.619–3.395)
Phosphate	1.560	0.252	38.269	0.000	4.761(2.904–7.805)
creatine kinase ≥ 40000	1.077	0.359	9.025	0.003	2.937(1.454–5.931)
AKI acute kidney injury, MODS multiple organ dysfunction syndrome, WBC white blood cell, ALT alanine aminotransferase, AST aspartate transaminase, BUN blood urea nitrogen, Scr serum creatinine, HDLC high density lipoprotein.					

Table 4  
Multivariate logistic regression analysis of risk factors for AKI

Variables	B	SE	Wald	p	OR
Age ≥ 60	1.122	0.466	5.784	0.016	3.070(1.231–7.658)
Chronic alcoholism	1.180	0.361	10.668	0.001	3.256(1.603–6.612)
Hypertension	1.447	0.504	8.258	0.004	4.252(1.584–11.411)
MODS	1.980	0.429	21.330	0.000	7.244(3.126–16.786)
WBC	0.046	0.018	6.646	0.010	1.047(1.011–1.084)
Phosphorus	1.709	0.304	31.612	0.000	5.526(3.045–10.027)

AKI acute kidney injury, MODS multiple organ dysfunction syndrome, WBC white blood cell.

Table 5  
Risk factors for in-hospital mortality in patients with RM-induced AKI according to multivariate logistic regression analysis

Variables	B	SE	Wald	p	OR
Age ≥ 60	1.159	0.505	5.279	0.022	3.188(1.186–8.570)
MODS	0.816	0.390	4.382	0.036	2.262(1.053–4.858)
Diabetes	1.010	0.504	4.024	0.045	2.746(1.023–7.369)
PT	0.076	0.037	4.289	0.038	1.079(1.004–1.160)

RM rhabdomyolysis, AKI acute kidney injury, MODS multiple organ dysfunction syndrome, PT prothrombin time.

## Discussion

The causes of RM can be classified in a number of ways. According to the mechanisms of skeletal muscle damage, the causes have been categorized into four mechanisms: Hypoxic, physical, chemical and biological [4]. Other classification categories include surgical/medical, acquired/inherited and physical/non-physical [1, 15, 16]. In the present study, the most common cause of RM was trauma (a condition largely associated with RM [1, 2]), followed by sepsis and bee sting. Compared with other causes, patients with RM resulting from sepsis, bee sting and acute alcoholism were observed more frequently in the AKI group. In our study, the morbidity rate of AKI was 61.4%, which is almost in accord with previous reports [7–10], although this number varies between different studies.

Patients with RM-related AKI are associated with an increased risk of death and total health-related costs than those who do not develop AKI. Our analysis showed that the total mortality rate of these patients

was 19.8%, whereas AKI patients experienced a significantly higher mortality rate than those without it (24.8% vs 11.8%,  $P < 0.01$ ), which was within the wide range of reported mortality rates for his condition [9, 11, 12].

Different study populations (such as those with RM associated with drug use, trauma, wasp stings, infection and hospitalization) play an important role in the variations in AKI-associated morbidity, and the subsequent mortality rates of RM patients. In addition, different inclusion criteria (such as elevated CK, race and the definition of AKI itself) may also affect these results. A previous study reported that the incidence of AKI was highest according to the KDIGO definition, followed by the AKIN and RIFLE criteria [17].

Our results have identified several independent risk factors for secondary AKI, including age  $\geq 60$  years, chronic alcoholism, hypertension, MODS, elevated WBC count and increased serum phosphorus levels. The incidence of AKI was increased in patients aged  $> 60$  years, according to the epidemiology of AKI in hospitalized Chinese adults [18]. Organ function decreases with age, and is accompanied by the onset of arteriosclerosis, diabetes and hypertension, which may increase susceptibility to AKI. We revealed that hypertension was one of the independent risk factors for AKI in RM patients; likewise, a previous study reported that diagnosed hypertension was an independent risk factor for AKI in patients with chronic kidney disease or intracerebral hemorrhage [19, 20]. In addition, a retrospective study of 43,611 patients demonstrated that the occurrence of AKI in hospitalized, previously normotensive adults was independently associated with increased blood pressure during the first 2 years after discharge [21]. However, there are also reports that patients with hypotension are at an increased risk of developing renal failure, decreased renal perfusion aggravate renal function [22, 23].

Consistent with a previous study of severe renal failure in patients with RM resulting from illicit drug use [24], the present study identified chronic alcoholism and leukocytosis as significant risk factors for the development of AKI. Moreover, animal research has confirmed that alcohol intoxication exacerbates RM-induced AKI through its oxidant and inflammatory effects [25].

Hyperphosphatemia is a common complication of RM with several proposed pathogenic factors, including the release of inorganic phosphorus into the plasma and reduced urinary phosphate excretion [26, 27]. In the present study, increased serum phosphate was determined to be an independent predictor for AKI-associated RM, which is in accordance with previously reported findings [28, 29]. Furthermore, phosphate has also been verified as a potential biomarker of disease severity and prognosis in AKI patients undergoing continuous renal replacement therapy [30]; this phenomenon was not observed in our study, which included patients with AKI of all stages.

Several studies have illustrated that MODS is one of the main drivers of mortality in a number of clinical conditions associated with secondary AKI, including severe acute pancreatitis and patients admitted to the intensive care unit [31, 32]. Our study was the first to identify a similar association in patients with RM, and that MODS is not only associated with the occurrence of secondary AKI, but also a worse patient prognosis.

The significant correlation between serum CK level and the risk of AKI has also been demonstrated in previous studies [33–36]. In our study, according to univariate logistic regression analysis, a CK level  $\geq$  40000U/L was found to be a risk factor for the occurrence of RM-induced AKI, but this was not supported by the results of multivariate logistic regression. Differences in race, study population and inclusion criteria may also have influenced these results.

## Conclusion

AKI is independently associated with the mortality rates of patients with RM. The early evaluation and diagnosis are crucial for the prevention of AKI and improved patient prognosis. Our study demonstrated that age  $\geq$  60 years, chronic alcoholism, hypertension, MODS, elevated WBC count and serum phosphorus were significant risk factors for RM-induced AKI. Age  $\geq$  60 years, MODS, diabetes and elevated prothrombin time were independent risk factors for in-hospital mortality in RM patients with AKI. Moreover, patients with RM resulting from sepsis, bee sting and acute alcoholism were at a higher risk of developing AKI. These findings may facilitate the effective prevention and management of RM patients with AKI.

## Study Limitations

The present study includes the following limitations. Firstly, most of the recruited patients were identified by discharge diagnoses in an electronic medical record database; hence, a proportion of the patients with elevated serum CK were missed due to a lack of RM diagnosis. Secondly, where existing urine volume data were not available, AKI diagnosis was based on SCr alone; thus, the incidence of AKI may have been underestimated. Thirdly, some of the possible risk factors for AKI, such as the level of myoglobin and lactic acid, as well as the severity-of-illness scores, were not included due to incomplete data. Finally, no follow-up study was conducted; thus, long-term patient prognoses (including recovery of renal function, risk of recurrent AKI and late mortality) were not determined.

## Declarations

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### Authors' contributions

Conception and design: LCY, JJZ, JY. Administrative support: LCY, JJZ. Collection and assembly of data: JY, XW, YT, SWW. Data analysis and interpretation: JY, JJZ. Manuscript writing: All authors. All authors read and approved the final manuscript.

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### **Availability of data and materials**

The datasets generated and/or analyzed during this study are not publicly available on account of privacy policy but are available from the corresponding author on reasonable request.

### **Ethics approval and consent to participate**

This study was approved by the Ethics Committees of the West China Hospital of Sichuan University. Our retrospective research was in compliance with ethical standards.

### **Consent for publication**

All authors have approved the publication of this manuscript.

### **Competing interests**

we do not have any conflicts of interest to declare.

### **Author details**

<sup>1</sup> Division of Nephrology, Department of Medicine, West China Hospital of Sichuan University, Chengdu, Sichuan, China. <sup>2</sup> Division of Ultrasound, West China Hospital of Sichuan University, Chengdu, Sichuan, China.

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