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# The Related Risk Factors Analysis of Snake-Bite Induced Acute Kidney Injury

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**Background:** The pathogenic mechanism of snake-bite induced acute kidney injury (AKI) remains unclear. Analyzing the risk factors for snake-bite induced AKI may provide the guidance needed for AKI prevention and early treatment.





**Material/Methods:** This retrospective study included 119 snake-bite patients who were hospitalized at the emergency department of Sichuan Provincial People's Hospital from January 2011 to September 2013. The patients were divided into AKI and non-AKI groups according to the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guideline. Gender, age, and clinical examination data of the patients were recorded. The Mann-Whitney U test and Fisher exact test were performed to analyze the collected data; preliminary analysis of independent risk factors was performed with multivariate logistic regression.

**Results:** Among the snake-bite patients, 98.3% were farmers. The mean age of patients was 46±12 years. Of the 119 patients (13.4%), 16 suffered from AKI. There were statistically significant differences between the AKI and non-AKI groups with respect to age, time interval from snake bite to antivenin therapy, creatine kinase, blood myoglobin, advanced age, regional lymphadenopathy, incision drainage, and hemoglobin. Preliminary analysis with multivariate logistic regression showed that advanced age and increased time interval from snake bite to antivenin therapy might be independent risk factors for snake-bite induced AKI.

**Conclusions:** Age, time interval from snake bite to antivenin therapy, creatine kinase, blood myoglobin, advanced age, regional lymphadenopathy, incision drainage, and hemoglobin were risk factors for snake-bite induced AKI. Advanced age and delayed antivenin therapy might be independent risk factors for snake-bite induced AKI.

**MeSH Keywords:** **Acute Kidney Injury • Risk Factors • Snake Bites**

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## Background

Snake-bite events are mainly distributed in the subtropical and tropical regions, and have been reported in Sri Lanka, India, Sahara, Latin America, Australia, and around the world [1–6]. According to the World Health Organization (WHO) statistics [7], more than 250,000 victims suffer poisonous snake bites worldwide each year, resulting in almost 125,000 deaths [8,9].

Snake-bite events happen frequently in the summer season around the world. Snake venom is distributed to various organs and tissues after it is injected into injured patients. Snake venom frequently causes kidney damage because the snake venom is excreted through the kidneys.

The clinical manifestations of kidney damage caused by snake bite consist of acute kidney injury (AKI), hematuria, and proteinuria [10]. The pathogenic mechanisms of snake-bite induced AKI have not been elucidated. It is reported that snake-bite induced AKI was associated with disseminated intravascular coagulation (DIC), intravascular hemolysis, and rhabdomyolysis. DIC could cause hemoglobin deposition in kidney tubules and lead to degenerative necrosis [9].

There are about 200 snake species, including more than 50 species of venomous snakes, in China. *Agkistrodon*, including *A. blomhoffi* and *A. halys*, and *Trimeresurus*, including *T. stejnegeri*, *T. mucroquamatus*, and *T. jerdonii*, are the most common venomous snakes in Sichuan province of north China. Antivenins (*Agkistrodon*) can neutralize *Agkistrodon* and *T. mucroquamatus* venom [11].

In China, snake-bite events happen frequently in the summer and autumn in the south region, and there are almost 100,000 snake-bite patients each year; moreover, snake-bite events result in a mortality rate of 5% and a disability rate of 25–30% [12]. In the case of China, which is a large agriculture country, snake bite causes severe harm to massive numbers of peasants. The pathophysiological mechanism of snake-bite induced AKI has not been elucidated. In China, the main treatments depend on antivenin injection, Chinese traditional snake medicine, and surgical intervention to prevent the complications.

Among snake-bite patients, AKI is a common serious complication that affects the prognosis. In our study, we collected the patients' information and analyzed the risk factors for AKI. Our research was adjuvant to clinical early treatment of snake-bite induced AKI and achieved the aim of improving snake-bite patients' prognosis.

## Material and Methods

### Patients

A total of 119 snake-bite patients were included in this retrospective study from January 2011 to September 2013 according to inclusion and exclusion criteria. The patient's information, including gender, age, time interval from snake bite to antivenin therapy, regional lymphadenopathy, incision drainage surgery, urine output, blood myoglobin, serum creatinine, and creatine kinase, were recorded. Antivenin therapy (5000 units) and supportive management were given when the patients were hospitalized; incision drainage surgery was used to treat patients with severe limb swelling and gangrene. Patients were operated on using a skin, deep fascia incision at the site of the swollen tissue; necrotic tissue was removed after anesthesia was given; and then a vacuum suction device was placed at the incision for suction for 5–7 days [13].

### Inclusion and exclusion criteria

Inclusion criteria were the following: (1) a definitive history of snake bite and (2) clinical features consistent with the presence of fang marks.

Exclusion criteria were the following: (1) patients with a pre-existent renal disease (serum creatinine >1.5 mg/dL prior to the snake bite or ultrasonography suggestive of bilateral small kidneys/obstructive nephropathy), (2) patients with an explicit diagnosis of hypertension or diabetes mellitus, and (3) exposure to nephrotoxic drugs or toxins.

### AKI diagnostic criteria

AKI patients were diagnosed according to the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) guideline [14]. The criteria covered the following: (1) increase in the serum creatinine concentration of  $\geq 0.3$  mg/dL from the baseline that was measured at admission, (2) serum creatinine concentration after snake bite was 1.5-fold compared with that at baseline, or (3) urine output was less than 0.5 mL/kg/h for more than six hours.

### Ethics

The project was approved by the Clinical Trials and Biomedical Ethics Committee, Sichuan Academy of Medical Science & Sichuan Provincial People's Hospital. The ethics committee approved the relating screening, inspection, and data collection of the patients.

### Statistical analysis

Patients were classified into two groups according to absence or presence of AKI. Statistical analysis was performed using

**Table 1.** 119 Patients' demographics.

Parameter	Number	Percentage (%)
Gender		
Male	71	59.7
Female	48	40.3
Occupation		
Farmer	117	98.3
Others	2	1.7
Resident area		
Rural	116	97.5
Urban	3	2.5

SPSS version 17.0, and measurement data were described as means  $\pm$  standard deviation. The differences between the two groups were compared by using the Mann-Whitney U test and the Fisher exact test; multivariate logistic regression was performed to do independent risk factors analysis.  $P < 0.05$  was considered as a significant difference.

#### Bias control

To avoid man-made interference, the total of patients' clinical information collection, processing, and analysis were completed by different persons.

## Results

### Basic information for 119 patients

A total of 119 cases, including 71 male and 48 female snake-bite patients, were included in our study. The demographic profiles of the cases have been provided in Table 1. The mean age of patients was  $46 \pm 12$  years. More than 98% of the snake-bite patients were farmers; 97.5% of the patients were from rural areas. The patients were mainly from Sichuan province.

### Significant difference analysis between the AKI group and the non-AKI group

The clinical profiles of the 119 snake-bite patients are shown in Table 2. In our study, 16 cases and 103 cases had AKI and non-AKI, respectively. The mean age of the 16 AKI patients was  $66 \pm 7$  years as compared with a mean age of  $43 \pm 9$  years for the 103 non-AKI patients; this difference was statistically significant. The time interval between snake bite and antivenin in the AKI group was  $31.69 \pm 21.48$  hours, which was significantly longer than the time interval of  $9.90 \pm 7.27$  hours in the non-AKI group. The variables of creatine kinase and blood myoglobin in the AKI group were significantly higher than those in the non-AKI group. The numbers of patients with advanced age, regional lymphadenopathy, and incision drainage surgery in the AKI group were significantly higher than those in the non-AKI group. Hemoglobin concentration

**Table 2.** Significant difference analysis between AKI group and non-AKI group.

Parameter	AKI group (n=16)	Non-AKI group (n=103)	P-value
Age (years)	$66 \pm 7$	$43 \pm 9$	$< 0.001$
Time interval (hours)	$31.69 \pm 21.45$	$9.90 \pm 7.27$	$< 0.001$
Creatine kinase (U/L)	$8384.43 \pm 4302.09$	$272.96 \pm 379.21$	$< 0.001$
Blood myoglobin (ng/mL)	$7060.09 \pm 3179.68$	$210.39 \pm 287.32$	$< 0.001$
Advanced age ( $\geq 60$ years)	14 (87.5%)	5 (4.9%)	$< 0.001$
Regional lymphadenopathy	13 (81.3%)	9 (8.7%)	$< 0.001$
Incision drainage	12 (75.0%)	10 (9.7%)	$< 0.001$
HGB (g/L)	$133 \pm 12$	$143 \pm 16$	0.016
Male	8 (50.0%)	63 (61.2%)	NS
ALT(U/L)	$32.19 \pm 29.8$	$29.74 \pm 20.55$	NS
AST(U/L)	$55.50 \pm 37.49$	$53.75 \pm 28.93$	NS
WBC ( $10^9/L$ )	$11.52 \pm 3.83$	$11.65 \pm 4.29$	NS
Hypotension ( $< 90/60$ mmHg)	1 (6.3%)	0	NS

Time interval – time interval from snake-bite to antivenin therapy; HGB – hemoglobin; ALT – alanine aminotransferase; AST – aspartate aminotransferase; WBC – white blood cell; NS – no significance.

**Table 3.** Independent risk factor analysis of snake-bite induced AKI.

Parameter	B	S.E.	Wald	P-value	OR-value	95%CI
Advanced age	0.424	0.143	8.804	0.003	1.528	(1.155, 2.022)
Time interval	0.198	0.086	5.310	0.021	1.219	(1.030, 1.444)
Incision drainage	1.261	2.128	0.351	0.553	3.529	(0.055, 228.407)
Regional lymphadenopathy	3.012	1.629	3.417	0.065	20.32	(0.834, 495.081)
Creatine kinase	4.487	4.69	0.916	0.339	13.028	(0.027, 60.524)

Time interval – time interval from snake-bite to antivenin therapy; OR – odds ratio; S.E. – standard error; CI – confidence interval.

in the AKI group was significantly lower than that in the non-AKI group.

There was 1 death in the AKI group, and no patient died in the non-AKI group. None of patients required amputation in the AKI and non-AKI groups. Except for 1 patient who suffered permanent injury from a high level of serum creatinine, the other patients in the AKI group recovered. The duration of hospitalization of the AKI and non-AKI groups was  $11.62 \pm 2.66$  days and  $5.33 \pm 1.96$  days, respectively.

### Multivariate logistic regression analysis

The small sample size might result in low reliability of the results of logistic regression analysis. To explore the potentially independent risk factors for snake-bite induced AKI, the preliminary analysis was performed by multivariate logistic regression. The risk factors described above, including age, time interval between snake bite and antivenin therapy, creatine kinase, blood myoglobin, advanced age, regional lymphadenopathy, incision drainage surgery, and hemoglobin, were analyzed by multivariate logistic regression. As Table 3 shows, advanced age and increased time interval from snake bite to antivenin therapy might be independent risk factors for snake-bite induced AKI. It is indispensable that the initial results should be validated in a large sample of patients in the future.

### Discussion

The pathogenic mechanism of snake-bite induced AKI is unclear. Our study indicated that advanced age and increased time interval from snake bite to antivenin administration were independent risk factors for snake-bite induced AKI. Advanced age patients were characterized as having angiosclerosis, poor renal reserve and compensatory ability, and microcirculation dysfunction, which resulted in AKI. Increased time interval from snake bite to antivenin therapy makes the snake venom circulate in bodies longer, which is associated with AKI. Snake venom spreads along lymph circulation, leading to regional lymphadenopathy. Tissue swelling and necrosis lead to

rhabdomyolysis and increases in blood myoglobin and creatine kinase concentration. Higher concentrations of blood myoglobin cause tubule obstruction, including tubule degeneration and necrosis, which results in AKI. Reports confirm that high levels of blood myoglobin and creatine kinase increase the risk of AKI [15].

The AKI group had a higher incidence of regional lymphadenopathy and incision drainage surgery than the non-AKI group. The concentrations of blood myoglobin and creatine kinase in the AKI group were significantly higher than those in the non-AKI group. Snake-bite induced AKI is the main lethal factor [2]. In our study the incidence of snake-bite induced AKI was 13.4%, lower than the rate in other reports; this may be related to different snake venom toxicity [2,15,16].

In addition, our results coincided with studies from other countries [17–19]. In our study, the mean age of snake-bite patients was  $46 \pm 12$  years, with more male than female patients; and 98% of the snake-bite patients were farmers (farming is a major source of employment). This may be related to snakes biting frequently in rural areas; the males were vulnerable to be attacked by poisonous snakes because they were the primary outworkers for their families.

In our study, increased time interval from snake bite to antivenin administration might be an independent risk factor for snake-bite induced AKI. A total of 16 patients suffered from snake-bite induced AKI. Some of the snake-bite patients initially received traditional treatment instead of going to the nearest hospital, which could potentially have delayed time to admission.

Researchers have reported that the risk factors of hypotension and neurological symptoms may affect AKI [19], but our study indicated that there were no significant differences between the AKI group and the non-AKI group. This may be related to the different snake species in Sichuan province and to some patients with critical conditions being diverted to other departments and hospitals.

Our results showed that advanced age and increased time interval from snake bite to antivenin therapy were the risk factors for snake-bite induced AKI. These risk factors can be potential indicators to evaluate the clinical risk for AKI, to guide the patients to receive early prevention and early treatment, and to effectively improve the prognosis of patients.

There are limitations to our retrospective study. First is the lack of knowledge of the snake species in our study. Snake bite marks, clinical manifestation, and history were the main indicators of snake-bite diagnosis in our study. The natural latex agglutination inhibition test (NLAIT) is an accurate method for rapid diagnosis of snake species [20]. Second, the quantity of snake venom was not detected. Radio immunoassay and enzyme-linked immunosorbent assay can be used to detect the quantity of snake venom [21]. Third was lack of knowledge regarding local therapies applied before visiting our hospital. We did not stratify the patients to analyze this. Chinese herbs such as Hong Bei Si Chou [*Cissus assamica* (Laws.) Craib] and Ban Bian Lian (*Lobelia chinensis*) are traditional treatments to relieve snake-bite inflammatory effects [22–25]. Fourth, we excluded patients with diabetes or hypertension although they did not have a history of prior renal dysfunction. Fifth, the sample size was relatively small. We will expand the sample

size, confirm the snake species and quantity of venom, and stratify patients who received traditional treatment in our follow-up study.

## Conclusions

Age, delayed antivenin therapy, creatine kinase, blood myoglobin, advanced age, regional lymphadenopathy, incision drainage, and hemoglobin were risk factors for snake-bite induced AKI. Our research will be of benefit to the early treatment of snake-bite induced AKI and will improve the prognosis of snake-bite patients.

## Compliance with ethical requirements

Our study had been carried out in accordance with the ethical standard of the Declaration of Helsinki.

## Declaration of interest

Wei Li, Fang Chen, and Shukun Wu declare that they have no conflict of interest.

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