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A Study of Acute Kidney Injury in Patients with Snakebite Envenomation

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Abstract
Background and Objectives: *Since long Snakebite-related acute kidney injury (AKI) is a common community-acquired AKI in tropical countries leading to death and disability. The aims of this study were to (1) determine the occurrence of snakebite-related AKI, (2) assess factors at presentation that are associated with snakebite-related AKI, and (3) determine the outcomes of patients with snakebite-related AKI.*
Methods: *We conducted a prospective observational study of patients with snake envenomation at our tertiary hospital during the calender year of 2016. Patient data including baseline characteristics, clinical and laboratory findings, hospital management, and outcomes were recorded in a case report form. A stepwise multivariate logistic regression analysis using a backward selection method determined independent factors significantly associated with AKI.*
Results: *AKI was observed in 140 patients (54.3%), the majority of whom were AKI stage III (110 patients, 78.6%). AKI occurred at presentation and developed during hospitalization in 88 (62.9%) and 52 patients (37.1%), respectively. Twenty-seven patients died (19.3%), and 69 patients (49.3%) required dialysis. On multivariate logistic regression analysis, (1) snakebites from the Viperidae family (odds ratio [OR]: 9.65, 95% confidence interval [CI]: 2.42–38.44; p = 0.001), (2) WBC >10 × 10^3 cells/μL (OR: 3.55, 95% CI: 1.35–9.34; p = 0.010), (3) overt disseminated intravascular coagulation (OR: 2.23, 95% CI: 1.02–4.89; p = 0.045), (4) serum creatine kinase >500 IU/L (OR: 4.06, 95% CI: 1.71–9.63; p = 0.001), (5) serum sodium <135 mmol/L (OR: 4.37, 95% CI: 2.04–9.38; p < 0.001), (6) presence of microscopic hematuria (OR: 3.60, 95% CI: 1.45–8.91; p = 0.006)*
Conclusions: *If we dentify factors associated with snakebite-related AKI might help clinicians to be aware of snakebite patients who are at risk of AKI, particularly patients who demonstrate renal tubular dysfunction after Viperidae bites.*
Keywords: *Snakebite-related acute kidney injury, Prospective study.*

Introduction

Since long, Community-acquired acute kidney injury (cAKI) is a major public health problem in tropical countries, particularly in Asia [1,2]. cAKI in tropical countries commonly affects young adults (age range 37–47 years) without pre-existing comorbidities [2]. These patients are at risk of developing chronic kidney disease [3]. cAKI in tropical countries is usually caused by a single etiology including tropical infections, environmental exposure to a toxin, or occupant-ional risk of snakebite envenomation [1,2]. South Asia, Southeast Asia, and sub-Saharan Africa have the highest burden of snakebite envenom-ation [4]. In Southeast Asia, envenomation by two families of venomous snakes, Elapidae and Viperidae, are associated with significant morbidity and mortality, with fatality rates of 0.4–20.0% [5,6]. Following snakebite envenomation by snakes of the family *Viperidae* and *Colubridae*, patients may develop renal manifestations including proteinuria, hematuria, pigmenturia, and AKI [7,8].

Snakebite-related AKI (sAKI) is a type of cAKI reported to affect from 8.0–43.0% of patients with snakebite envenomation [9–15], among whom approximately 15.0–55.0% required renal replacement therapy (RRT) [9–11, 13] and the fatality rate was 8.0–39.0% [9–11, 13, 14]. Previous reports from Brazil have shown greater susceptibility to sAKI with increasing age [16, 17]. Reported factors associated with sAKI included age <12 years, time from hospitalization to antivenom treatment >2 h, time from snakebite to receiving antivenom >2 h, longer duration from snakebite to hospital arrival, cellulitis, regional lymphadenopathy, hypotension, higher total bilirubin level, lower hemoglobin level, intravascular hemolysis, incoagulable blood on 20-min whole blood clotting test (20WBCT), prolonged bleeding time, prolonged prothrombin time (PT), hemorrhagic manifestations, serum creatine kinase >2000 IU/L, dark or brown urine color, albuminuria, and longer length of hospitalization [9,10,12,13,15].

Overall, the factors associated with sAKI varied across studies due to differences in the study population, potency and composition of snake venom, which differs across geographic regions of the study sites; accessibility of management facilities; and study design [9,10,12,13,15–17].

Therefore, we conducted this study in our tertiary care hospital among patients during the calender year 2016 with snakebite envenomation with the aims to assess (1) the occurrence of sAKI from presentation until discharge, (2) clinical and laboratory factors at presentation that independently associated with the development of sAKI, and (3) outcomes of patients with sAKI. This information might help clinicians to identify patients who are at risk for sAKI in order to provide optimal management for decreasing the incidence of cAKI in tropical countries.

Materials and Methods

Study design and population

This prospective observational study was conducted at our tertiary care hospital in central India. The procedure indicated by the Standards for the Reporting of Observation Studies in Epidemiology (STROBE) was followed [20]. The study's inclusion criteria were patients at least 12 years old and presenting with clinical parameters of snake envenomation. Patients with (1) a history of underlying medical illness including diabetes mellitus, hypertension, neurological diseases, cardiovascular diseases, renal diseases, pulmonary diseases, liver diseases, and hematologic diseases; (2) receiving any antiplatelet or anticoagulant drugs; or (3) currently pregnant were excluded from this study. All snakebite patients in this study were admitted to the hospitals for observation and management. Neurological symptoms and signs were observed every 30 min for 12 h, and then hourly for 12 h in cases of unknown snakebite.

Laboratory parameters including complete blood counts, incoagulable blood on 20WBCT, PT, international normalized ratio (INR), activated partial thromboplastin time (aPTT), fibrinogen

level, D-dimer, blood glucose, electrolytes, serum urea, serum creatinine, liver function test, and electrocardiography (ECG) were evaluated at presentation and then as appropriate. Chest X-ray was performed when abnormal lung sounds were detected or upon clinical suspicion of respiratory complications. Urinalysis and spot urine analysis for sodium, potassium, protein, and creatinine were also performed at presentation. Spot urine tests for calcium and phosphate were performed when patients demonstrated hypocalcemia and hypophosphatemia, respectively. Spot urine test for magnesium was performed in patients with hypokalemia.

Treatment outcomes including duration of hospitalization, requirement of RRT, and survival status were summarized on discharge. Patient data including baseline characteristics, location where the snakebite occurred, anatomical site of the bite, type of snake, pre-hospital management, clinical parameters, laboratory findings, hospital management, and outcomes were recorded in a pre-defined case report form.

Clinical parameters of envenoming from snakes

The clinical parameters of both local and systemic envenoming were defined according to the WHO 2010 guidelines for the management of snakebites [6]. Local bleeding was defined as prolonged bleeding from fang marks, prolonged bleeding from venipuncture site, and/or bleeding from a recent wound. Spontaneous systemic bleeding manifested as skin bleeding (defined as petechiae, purpura, and/or ecchymosis), mucosal bleeding (defined as gum bleeding, hematemesis, melena, hematochezia, gross hematuria, and/or vaginal bleeding), and/or conjunctival bleeding. Hypotension was defined as systolic blood pressure of <90 mmHg without evidence of tissue hypoperfusion. Capillary leakage was defined as a rise in hematocrit >2.0% above the reference range of adults adjusted for sex and serum albumin <3.0 g/dL. Disseminated intravascular coagulation (DIC) was diagnosed according to the International Society for Thrombosis and Haemostasis (ISTH) scoring system for DIC, with a score ≥5 considered indicative of overt DIC. The score was calculated based on platelet (PLT) count ($\geq 100 \times 10^3/\mu L = 0$, $< 100 \times 10^3/\mu L = 1$, $< 50 \times 10^3/\mu L = 2$); D-dimer (<0.5 μg/L = 0, 0.5 to <1.0 μg/L = 1, ≥1.0 to <2.0 μg/L = 2, ≥2 μg/L = 3); PT (<15 s = 0, ≥15 s = 1, >20 s = 2); and fibrinogen level (≥100 mg/dL = 0, <100 mg/dL = 1) [21].

Management of patients with snake envenoming

Antivenom treatment was indicated when patients developed local envenoming with the clinical signs of (1) local swelling in more than half of the bitten limb (in the absence of a tourniquet) within 48 h of the bite, (2) rapid extension of swelling over 1 joint within 2 h of a bite on the hands or feet, and/or (3) development of tender lymphadenitis. Antivenom was also indicated for all cases of systemic envenoming, as indicated by the following: (1) hemostatic abnormalities including spontaneous systemic bleeding, incoagulable blood on 20WBCT, and/or thrombocytopenia defined as PLT count $< 100 \times 10^3/\mu L$; (2) neurotoxic signs including ptosis, external opthalmoplegia, and/or muscle paralysis; (3) cardiovascular abnormalities including hypotension, shock, and/or abnormal ECG; and/or (4) renal abnormalities including reduced urine volume and/or AKI.

Reduced urine volume was classified as oliguria, defined as <400 mL of urine volume in 24 h, or anuria, defined as no urine volume in 24 h. AKI was defined as the increase of serum creatinine ≥0.3 mg/dL within 48 h or increase in serum creatinine ≥1.5 times baseline. AKI staging was performed according to the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines. AKI stage I was defined as serum creatinine increased to 1.5 to 1.9 times baseline. AKI stage II was defined as serum creatinine increased to 2.0 to 2.9 times baseline. AKI stage III was defined as serum creatinine increased to 3.0 times baseline or higher, serum creatinine ≥4.0 mg/dL, or receipt of RRT [22]. The

dosage of acute peritoneal dialysis was assessed using a weekly Kt/V measurement of urea according to the International Society of Peritoneal Dialysis (ISPD) guideline [23]. 'K' was defined as the volume of dialysate drained multiplied by dialysate/plasma urea concentration, and 't' was defined as the duration of dialysis over 1 week. 'V' was defined as the volume of distribution of urea (total body water = 0.5 [female] or 0.6 [male] multiplied by body weight). Snake identification was performed if the snake that definitely bit the patient was brought to the hospital either dead or alive for identification or based on the patients' description of the snake to the investigators. If the snake could not be identified, the clinical syndrome of envenoming was considered according to the WHO 2010 guidelines for specific antivenom treatment [6]. The clinical syndrome of *Viperidae* envenoming consisted of presentation with (1) local envenoming and (2) clinical bleeding and/or incoagulable blood on 20WBCT. The clinical syndrome of Russell's viper envenoming consisted of presentation with (1) local envenoming, (2) clinical bleeding and/or incoagulable blood on 20WBCT, and (3) shock defined by a systolic blood pressure of <90 mmHg with evidence of tissue hypoperfusion, i.e., <0.5 mL/kg/h decrease in urine output, cold skin, and/or receipt of inotropic drugs. The clinical syndrome of cobra envenoming consisted of presentation with (1) local envenoming and (2) muscle paralysis.

Sample size calculation

We estimated the required sample size based on a 2013 study from India, which reported a 15% rate of AKI occurrence among patients with snake envenoming [14]. Based on this data, a minimum of 196 venomous snakebite patients were needed to achieve this rate with 5% margin of error. We predicted a dropout rate of 20% during this study; therefore, the required sample size was at least 235 patients.

Statistical Analyses

All data were analyzed using SPSS software (version 18.0; SPSS Inc., Chicago, IL). Numerical variables were tested for normality using the Kolmogorov-Smirnov test. Variables with non-normal distribution were summarized as medians and interquartile ranges (IQRs) and compared using Mann-Whitney *U* tests for two-group comparisons and Kruskal-Wallis tests for greater than two-group comparisons. A significant result on Kruskal-Wallis tests was subjected to further post-hoc pair-wise comparison by using the Mann-Whitney *U* test with Bonferroni correction to adjust significance values. Categorical variables were expressed as frequencies and percentages and analyzed using chi-squared or Fisher's exact tests, as appropriate. A univariate logistic regression analysis was used to determine which of the collected baseline characteristics, pre-hospital management, clinical parameters, laboratory findings, and management, were associated with AKI among patients with venomous snakebites. All clinical factors potentially associated with AKI were included in the univariate logistic regression analysis as independent variables, with the occurrence of AKI as the dependent variable. Any variable with a p value ≤ 0.2 was included in a stepwise multivariate logistic regression analysis using a backward selection method for determining significant independent factors. Linear regression analysis was used to predict urine sodium-to-creatinine ratio from serum sodium and urine potassium-to-creatinine ratio from serum potassium. All tests of significance were two-sided, with a p value ≤ 0.05 indicating statistical significance.

Results

Snake identification was possible in 174 patients (67.4%). Identified snakes included Russell's viper (147 patients, 84.5%), cobra (20 patients, 11.5%), green pit viper (6 patients, 3.4%), and sea snake (1 patient, 0.6%). The median (IQR) age of patients with venomous snakebites was 31.0

(23.0–42.0) years, and the majority of patients were male (203 patients, 78.7%). Renal manifestations among patients with venomous snakebites at presentation are shown in Table 1.

Potential factors related to the development of AKI including clinical and laboratory parameters are summarized in Table 2. For any potential factors that had multi-collinearity with each other, only one appropriate factor was chosen.

Comparison of management and outcomes among patients with and without AKI

The potential management characteristics related to the development of AKI are shown in Table 2. Regarding patient outcomes, patients with AKI had a significantly longer duration of hospitalization, greater requirement for RRT, and higher mortality rate (all $p < 0.001$).

Of 140 patients with AKI, 27 (19.3%) died, and 113 (80.7%) survived. Clinical parameters and management of deceased and surviving patients with AKI are shown in Table 3. Patients who died were more likely to develop shock, receive inotropic drugs, and demonstrate acute respiratory distress syndrome (ARDS) or respiratory failure (all $p < 0.001$). Of 140 patients with AKI, 69 (49.3%) required RRT. The indications for dialysis included uremia in 39 patients (56.5%), severe metabolic acidosis in 15 (21.7%), fluid overload in 9 (13.0%), and severe hyperkalemia in 6 (8.7%). The proportions of patients who required RRT were similar between those who died and those who survived. Acute peritoneal dialysis was performed in 62 patients who required RRT (89.8%), and the remaining 7 patients (10.2%) received hemodialysis. The methods of dialysis used in both groups were similar ($p = 0.118$). Weekly Kt/V was evaluated in only 52 patients who received acute peritoneal dialysis, including 8 patients (15.4%) who died and 44 (84.6%) who survived. The median (IQR) weekly Kt/V was similar in both groups (1.9 [1.1–3.0] vs. 2.7 [2.2–3.9], $p = 0.116$).

Using a univariate logistic regression model, the following clinical parameters were associated with AKI: snakebites of the family *Viperidae* or presenting the clinical syndrome of *Viperidae* envenoming, local swelling of grades II to IV, presence of hypotension, WBC count $>10 \times 10^3$ cells/μL, overt DIC, presence of capillary leakage, serum creatine kinase >500 IU/L, blood sugar ≥150 mg/dL, serum sodium <135 mmol/L, presence of microscopic hematuria, management on a ward, and duration from bite to receipt of antivenom ≥2 h (Table 4).

In a multivariate logistic regression model, the following clinical and laboratory parameters were independently associated with AKI: snakebites of the family *Viperidae* or presenting the clinical syndrome of *Viperidae* envenoming (odds ratio [OR]: 9.65; 95% CI: 2.42–38.44; $p = 0.001$), WBC count $>10 \times 10^3$ cells/μL (OR: 3.55, 95% CI: 1.35–9.34; $p = 0.010$), overt DIC (OR: 2.23, 95% CI: 1.02–4.89; $p = 0.045$), serum creatine kinase >500 IU/L (OR: 4.06, 95% CI: 1.71–9.63; $p = 0.001$), serum sodium <135 mmol/L (OR: 4.37, 95% CI: 2.04–9.38; $p < 0.001$), presence of microscopic hematuria (OR: 3.60, 95% CI: 1.45–8.91; $p = 0.006$), and duration from snakebite to receipt of antivenom ≥2 h (OR: 3.73, 95% CI: 1.48–9.37; $p = 0.005$) (Table 4).

AKI is a common complication after snakebite envenomation from members of the *Viperidae* family [5–8]. Thus, factors associated with AKI at presentation and during hospitalization among patients bitten by *Viperidae* or presenting the clinical syndrome of *Viperidae* envenoming were identified in this study. Of 214 patients bitten by *Viperidae* or presenting the clinical syndrome of *Viperidae* envenoming, 136 (63.6%) developed AKI, including 86 patients (63.2%) with AKI at presentation and 50 (36.8%) who developed AKI during hospitalization. The remaining 78 patients (36.4%) did not develop AKI. Of the 50 patients who developed AKI during hospitalization, 47 (94.0%) developed AKI within 48 h of hospitalization and the remaining 3 patients (6.0%) developed AKI after 48 h of hospitalization.

Clinical parameters, laboratory findings, and management characteristics possibly affecting renal function are shown in Table 5. Patients with the parameters of presence of hypotension ($p < 0.001$), WBC count $>10 \times 10^3$ cells/μL ($p < 0.001$), overt DIC ($p < 0.001$), presence of capillary leakage ($p = 0.001$), serum creatine kinase >500 IU/L ($p < 0.001$), blood sugar ≥150 mg/dL ($p = 0.015$), serum sodium <135 mmol/L ($p < 0.001$), presence of microscopic hematuria ($p < 0.001$), and duration from snakebite to receipt of antivenom ≥2 h ($p = 0.021$) were more likely to develop AKI at presentation (Table 5).

These parameters were also associated with AKI at presentation using a univariate logistic regression model (Table 6). In a multivariate logistic regression model, the following clinical and laboratory parameters were independently associated with AKI at presentation: presence of hypotension (odds ratio [OR]: 3.56; 95% CI: 1.05–12.09; $p = 0.042$), serum creatine kinase >500 IU/L (OR: 6.24, 95% CI: 2.10–18.49; $p = 0.001$), serum sodium <135 mmol/L (OR: 7.81, 95% CI: 2.87–21.24; $p < 0.001$), presence of microscopic hematuria (OR: 11.45, 95% CI: 3.76–34.82; $p < 0.001$), and duration from snakebite to receipt of antivenom ≥2 h (OR: 7.98, 95% CI: 2.06–30.92; $p = 0.003$) (Table 6).

Clinical parameters, laboratory findings, and management characteristics possibly affecting renal function are shown in Table 7. Patients with the parameters of overt DIC ($p = 0.007$), presence of capillary leakage ($p < 0.001$), serum creatine kinase >500 IU/L ($p < 0.001$), serum sodium <135 mmol/L ($p < 0.001$), and who received a total dose of antivenom >160 mL ($p = 0.016$) were more likely to develop AKI during hospitalization (Table 7).

These parameters were also found to be associated with AKI during hospitalization using a univariate logistic regression model (Table 8). In a multivariate logistic regression model, the following parameters were independently associated with AKI during hospitalization: presence of capillary leakage (odds ratio [OR]: 6.30; 95% CI: 1.13–35.22; $p = 0.036$), serum creatine kinase >500 IU/L (OR: 4.80, 95% CI: 1.86–12.37; $p = 0.001$), and serum sodium <135 mmol/L (OR: 4.27, 95% CI: 1.74–10.45; $p = 0.001$) (Table 8).

Table 1: Renal manifestations among 258 adults with snakebite envenomation, Yangon, Myanmar, 2015–2016

Characteristic	All	*n* (%)
Clinical manifestations		
Reduced urine volume	258	128 (49.6)
Renal tenderness	258	114 (44.2)
Gross hematuria	258	46 (17.8)
Dark- colored urine	258	25 (9.7)
Urinalysis and urine chemistries		
Urine protein-to-creatinine ratio ≥1	186	112 (60.2)
Microscopic hematuria	255	81 (31.4)
Pigmenturia	255	38 (14.7)
Leukocyturia	255	22 (8.5)
Blood chemistry		
Acute kidney injury	258	140 (54.3)
At presentation	140	88 (62.9)
During hospitalization	140	52 (37.1)
Serum sodium		
Hyponatremia	258	115 (44.6)
Hypernatremia	258	5 (1.9)
Serum potassium		
Hypokalemia	258	52 (20.2)
Hyperkalemia	258	19 (7.4)
Serum calcium		
Hypocalcemia	256	88 (34.4)
Hypercalcemia	256	6 (2.3)
Serum phosphate		
Hypophosphatemia	256	20 (7.8)
Hyperphosphatemia	256	68 (26.6)
Serum bicarbonate		
Metabolic acidosis	258	22 (8.5)
Metabolic alkalosis	258	1 (0.4)

Table 2: Clinical parameters, laboratory findings, and management characteristics among 258 adults with snakebite envenomation, Yangon, Myanmar, 2015–2016

Characteristics	All	With acute kidney injury, *n* (%)	Without acute kidney injury, *n* (%)	*p* value
Clinical parameters				
Bites from *Viperidae* or presenting the clinical syndrome of *Viperidae*				
Yes	214	136 (63.6)	78 (36.4)	<0.001
No	44	4 (9.1)	40 (90.9)	
Local swelling				
Grades II–IV	167	111 (66.5)	56 (33.5)	<0.001
Grades 0-I	91	29 (31.9)	62 (68.1)	
Hypotension				
Yes	69	60 (87.0)	9 (13.0)	<0.001
No	189	80 (42.3)	109 (57.7)	
Laboratory parameters				
WBC (cells/μL)				
$>10\times10^3$	194	126 (64.9)	68 (35.1)	<0.001
$\leq10\times10^3$	64	14 (21.9)	50 (78.1)	
Overt DIC				
Yes	147	103 (70.1)	44 (29.9)	<0.001
No	111	37 (33.3)	74 (66.7)	
Capillary leakage				
Yes	35	30 (85.7)	5 (14.3)	<0.001
No	223	110 (49.3)	113 (50.7)	
Creatine kinase (IU/L)				
>500	104	87 (83.7)	17 (16.3)	<0.001
≤500	152	51 (33.6)	101 (66.4)	
Blood sugar (mg/dL)				
≥150	53	37 (69.8)	16 (30.2)	0.017
<150	205	103 (50.2)	102 (49.8)	
Serum sodium (mmol/L)				
<135 mmol/L	115	91 (79.1)	24 (20.9)	<0.001
≥135 mmol/L	143	49 (34.3)	94 (65.7)	
Microscopic hematuria				
Yes	81	70 (86.4)	11 (13.6)	<0.001
No	174	67 (38.5)	107 (61.5)	
Management				
Site of management				
Ward	211	129 (61.1)	82 (38.9)	<0.001
ICU	47	11 (23.4)	36 (76.6)	
Time from bite to receiving antivenom (hours)				
≥2	174	107 (61.5)	67 (38.5)	0.007
<2	76	32 (42.1)	44 (57.9)	

Table 3: Clinical parameters and management among 140 adults with acute kidney injury (deceased and survivors)

Characteristics	Deceased		Survivors		*p* value
	All	*n* (%)	All	*n* (%)	
Time from bite to hospital ≥1 h	27	24 (88.9)	113	91 (80.5)	0.408
Time from bite to receiving antivenom ≥2 h	27	21 (77.8)	112	86 (76.8)	1.000
Management in ICU	27	7 (25.9)	113	4 (3.5)	0.001
Shock	27	20 (74.1)	113	34 (30.1)	<0.001
Received inotropic drugs	27	20 (74.1)	113	23 (20.4)	<0.001
ARDS or respiratory failure	27	13 (48.1)	113	9 (8.0)	<0.001
Required renal replacement therapy	27	13 (48.1)	113	56 (49.6)	1.000
Received peritoneal dialysis	13	10 (76.9)	56	52 (92.9)	0.118
Weekly Kt/v, median (IQR)	8	1.9 (1.1–3.0)	44	2.7 (2.2–3.9)	0.116

Table 4: Logistic regression analysis of parameters associated with acute kidney injury, Yangon, Myanmar, 2015–2016

Characteristic	Univariate analysis			Multivariate analysis		
	n	OR (95% CI)	*p* value	*n*	OR (95% CI)	*p* value
Clinical parameters						
Bites from *Viperidae* or presenting clinical syndrome of *Viperidae*	258			244		
Yes		17.44 (6.01–50.57)	<0.001		9.65 (2.42–38.44)	0.001
No		1.00 (Reference)			1.00 (Reference)	
Local swelling	258					
Grades II–IV		4.24 (2.45–7.31)	<0.001			
Grades 0-I		1.00 (Reference)				
Hypotension	258					
Yes		9.08 (4.26–19.38)	<0.001			
No		1.00 (Reference)				
Laboratory parameters						
WBC (cells/μL)	258			244		
$> 10 \times 10^3$		6.62 (3.41–12.83)	<0.001		3.55 (1.35–9.34)	0.010
$\leq 10 \times 10^3$		1.00 (Reference)			1.00 (Reference)	
Overt DIC	258			244		
Yes		4.68 (2.76–7.95)	<0.001		2.23 (1.02–4.89)	0.045
No		1.00 (Reference)			1.00 (Reference)	
Capillary leakage	258					
Yes		6.16 (2.31–16.46)	<0.001			
No		1.00 (Reference)				
Creatine kinase (IU/L)	256			244		
> 500		10.14 (5.46–18.83)	<0.001		4.06 (1.71–9.63)	0.001
≤ 500		1.00 (Reference)			1.00 (Reference)	

Blood sugar (mg/dL)	258					
≥ 150		2.29 (2.00–4.37)	0.012			
< 150		1.00 (Reference)				
Serum sodium (mmol/L)	258			244		
< 135 mmol/L		7.27 (4.13–12.82)	<0.001		4.37 (2.04–9.38)	<0.001
≥ 135 mmol/L		1.00 (Reference)			1.00 (Reference)	
Microscopic hematuria	255			244		
Yes		10.16 (5.02–20.57)	<0.001		3.60 (1.45–8.91)	0.006
No		1.00 (Reference)			1.00 (Reference)	
Management						
Site of management	258					
Ward		5.15 (2.48–10.68)	<0.001			
ICU		1.00 (Reference)				
Time from bite to receiving antivenom (hours)	250			244		
≥ 2		2.20 (1.27–3.80)	0.005		3.73 (1.48–9.37)	0.005
< 2		1.00 (Reference)			1.00 (Reference)	

Table 5: Clinical parameters, laboratory findings, and management characteristics of 164 adults bitten by *Viperidae* or presenting the clinical syndrome of *Viperidae* (86 patients with acute kidney injury at presentation and 78 patients without acute kidney injury)

Characteristics	All	With acute kidney injury, *n* (%)	Without acute kidney injury, *n* (%)	*p* value
Hypotension				
Yes	46	39 (84.8)	7 (15.2)	<0.001
No	118	47 (39.8)	71 (60.2)	
WBC (cells/μL)				
$> 10 \times 10^3$	122	75 (61.5)	47 (38.5)	<0.001
$\leq 10 \times 10^3$	41	10 (24.4)	31 (75.6)	
Overt DIC				
Yes	100	64 (64.0)	36 (36.0)	<0.001
No	64	22 (34.4)	42 (65.6)	
Capillary leakage				
Yes	19	17 (89.5)	2 (10.5)	0.001
No	145	69 (47.6)	76 (52.4)	
Creatine kinase (IU/L)				
> 500	69	57 (82.6)	12 (17.4)	<0.001
≤ 500	95	29 (30.5)	66 (69.5)	
Blood sugar (mg/dL)				
≥ 150	38	27 (71.1)	11 (28.9)	0.015
< 150	126	59 (46.8)	67 (53.2)	
Serum sodium (mmol/L)				
< 135	77	61 (79.2)	16 (20.8)	<0.001
≥ 135	87	25 (28.7)	62 (71.3)	
Microscopic hematuria				
Yes	61	51 (83.6)	10 (16.4)	<0.001
No	101	33 (32.7)	68 (67.3)	
Time from bite to receiving antivenom (hours)				
≥ 2	112	68 (60.7)	44 (39.3)	0.021
< 2	44	17 (38.6)	27 (61.4)	

Table 6: Univariate and multivariate analysis of clinical and laboratory parameters of adults bitten by *Viperidae* or presenting the clinical syndrome of *Viperidae* for identifying acute kidney injury at presentation

Characteristics	All	With acute kidney injury, *n* (%)	Without acute kidney injury, *n* (%)	*p* value
Hypotension				
Yes	46	39 (84.8)	7 (15.2)	<0.001
No	118	47 (39.8)	71 (60.2)	
WBC (cells/μL)				
$> 10 \times 10^3$	122	75 (61.5)	47 (38.5)	<0.001
$\leq 10 \times 10^3$	41	10 (24.4)	31 (75.6)	
Overt DIC				
Yes	100	64 (64.0)	36 (36.0)	<0.001
No	64	22 (34.4)	42 (65.6)	
Capillary leakage				
Yes	19	17 (89.5)	2 (10.5)	0.001
No	145	69 (47.6)	76 (52.4)	
Creatine kinase (IU/L)				
> 500	69	57 (82.6)	12 (17.4)	<0.001
≤ 500	95	29 (30.5)	66 (69.5)	
Blood sugar (mg/dL)				
≥ 150	38	27 (71.1)	11 (28.9)	0.015
< 150	126	59 (46.8)	67 (53.2)	
Serum sodium (mmol/L)				
< 135	77	61 (79.2)	16 (20.8)	<0.001
≥ 135	87	25 (28.7)	62 (71.3)	
Microscopic hematuria				
Yes	61	51 (83.6)	10 (16.4)	<0.001
No	101	33 (32.7)	68 (67.3)	
Time from bite to receiving antivenom (hours)				
≥ 2	112	68 (60.7)	44 (39.3)	0.021
< 2	44	17 (38.6)	27 (61.4)	

TABLE 7: Clinical parameters, laboratory findings, and management characteristics of 128 adults bitten by *Viperidae* or presenting the clinical syndrome of *Viperidae* (50 patients who developed acute kidney injury during hospitalization and 78 patients without acute kidney injury)

Characteristics	All	With acute kidney injury, *n* (%)	Without acute kidney injury, *n* (%)	*p* value
Hypotension				
Yes	46	39 (84.8)	7 (15.2)	<0.001
No	118	47 (39.8)	71 (60.2)	
WBC (cells/μL)				
$> 10 \times 10^3$	122	75 (61.5)	47 (38.5)	<0.001
$\leq 10 \times 10^3$	41	10 (24.4)	31 (75.6)	
Overt DIC				
Yes	100	64 (64.0)	36 (36.0)	<0.001
No	64	22 (34.4)	42 (65.6)	
Capillary leakage				
Yes	19	17 (89.5)	2 (10.5)	0.001
No	145	69 (47.6)	76 (52.4)	
Creatine kinase (IU/L)				
> 500	69	57 (82.6)	12 (17.4)	<0.001
≤ 500	95	29 (30.5)	66 (69.5)	
Blood sugar (mg/dL)				
≥ 150	38	27 (71.1)	11 (28.9)	0.015
< 150	126	59 (46.8)	67 (53.2)	
Serum sodium (mmol/L)				
< 135	77	61 (79.2)	16 (20.8)	<0.001
≥ 135	87	25 (28.7)	62 (71.3)	
Microscopic hematuria				
Yes	61	51 (83.6)	10 (16.4)	<0.001
No	101	33 (32.7)	68 (67.3)	
Time from bite to receiving antivenom (hours)				
≥ 2	112	68 (60.7)	44 (39.3)	0.021
< 2	44	17 (38.6)	27 (61.4)	

Table 8: Univariate and multivariate analysis of clinical and laboratory parameters of adults bitten by *Viperidae* or presenting the clinical syndrome of *Viperidae* for identifying acute kidney injury during hospitalization

Characteristic	Univariate analysis			Multivariate analysis		
	n	OR (95% CI)	*p* value	*n*	OR (95% CI)	*p* value
Overt DIC	128					
Yes		3.00 (1.40–6.42)	0.005			
No		1.00 (Reference)				
Capillary leakage	128			119		
Yes		12.00 (2.56–56.36)	0.002		6.30 (1.13–35.22)	0.036
No		1.00 (Reference)			1.00 (Reference)	
Creatine kinase (IU/L)	126			119		
> 500		7.70 (3.32–17.86)	<0.001		4.80 (1.86–12.37)	0.001
≤ 500		1.00 (Reference)			1.00 (Reference)	
Serum sodium (mmol/L)	128			119		
< 135 mmol/L		5.35 (2.44–11.74)	<0.001		4.27 (1.74–10.45)	0.001
≥ 135 mmol/L		1.00 (Reference)			1.00 (Reference)	
Total dose of antivenom (mL)	121					
> 160		3.01 (1.30–7.00)	0.010			
≤ 160		1.00 (Reference)				

DISCUSSION

Snakebite envenomation is one of the common causes of cAKI in tropical countries, particularly in Southeast Asia [1, 2, 4]. The reported incidence of renal involvement with snakebite envenomation ranges from 1.4–28.0% [25, 26]. Renal involvement including proteinuria, hematuria, pigmenturia, and AKI is commonly observed among patients with snakebites from snakes of the family *Viperidae* [5–8]. Hemotoxic and myotoxic venom, particularly from Russell's viper and sea snake, are common causes of renal involvement [7, 8]. Similarly, in our study, the majority of patients were bitten by Russell's viper (84.5%) and clinical renal manifestations were frequent among patients with snakebite envenomation, particularly reduced urine volume (49.6%), renal tenderness (44.2%), and urine protein-to-creatinine ratio ≥1 (60.2%). In Myanmar, proteinuria >1 g/24 h was previously reported in 50.0% of patients with Russell's viper bites [27] and hematuria in 35.0% of patients with hemotoxic snakebites or the occurrence of glomerulonephritis after snakebite envenomation [7,8]. Previous reports showed that Russell's viper can cause both intravascular hemolysis and rhabdomyolysis, which is induced by phospholipase A_2 in snake venom [7,8].

In our cohort, 140 patients (54.3%) had sAKI according to the criteria of the KDIGO clinical practice guidelines [22]. In previous reports, sAKI was observed in 8.0–43.0% of patients with snakebite envenomation. The higher observed rate

in the present study might be due to differences in criteria for AKI diagnosis, snake species, snake venom potency, and genetic variation of the victims [9–15, 19]. In our study, 62.9% of AKI patients had sAKI at presentation, and the rest (37.1%) developed sAKI during hospitalization. Multivariate logistic regression analysis revealed the following parameters to be independently associated with sAKI: bites from snakes of the *Viperidae* family or presenting the clinical syndrome of *Viperidae* envenoming, leukocytosis, overt DIC, rhabdomyolysis, hyponatremia, glomerulonephritis, and duration from snakebite to receipt of antivenom ≥2 h. Among patients bitten by *Viperidae*, the presence of hypotension, rhabdomyolysis, hyponatremia, glomerulonephritis, and duration from snakebite to receipt of antivenom ≥2 h were independently associated with sAKI at presentation. In addition, patients bitten by *Viperidae* who presented with capillary leakage, rhabdomyolysis, and hyponatremia were at increased risk for the development of sAKI during hospitalization. Previous studies reported similar factors associated with the sAKI, including receipt of antivenom >2 h after snakebite, cellulitis, hypotension, and rhabdomyolysis [9, 10, 13]. A previous case series from Taiwan showed that early specific antivenom treatment within 3 to 6 h after snake envenoming could restore coagulation abnormalities in 1 to 2 days and was effective in reducing the severity of renal damage [28].

Our finding that leukocytosis was associated with sAKI is consistent with a previous experimental study in which leukocytosis was observed after injection of phospholipase A_2 and metalloprotease from Russell's viper venom, which resulted in the elevation of interleukin-6, tumor necrosis factor-α, and prostaglandin E_2 leading to increased renal vascular resistance and decreased blood pressure [29].

A previous report from India also showed that the renal pathology of AKI patients with *Viperidae* bites involved acute tubular necrosis, which might be due to the direct toxicity of the snake venom [30]. However, our patients with sAKI had significantly lower fractional excretion of urea (28.5%) than those without sAKI (42.3%), as well as serum urea-to-creatinine ratio >20 and urine specific gravity of 1.020, indicating renal ischemia that might contribute to the development of sAKI. A previous experimental study revealed massive fibrin deposition in glomerular capillaries, proximal and distal tubular necrosis, and hemolyzed red blood cell casts in the renal tubules of rats subjected to intravascular injection of snake venom, indicating that DIC contributed to renal ischemia in sAKI [31].

Furthermore, snake venom, particularly *Viperidae* snake venom containing proteolytic enzymes, can destruct the endothelium and basal membrane of capillaries. Thus, capillary permeability increases, albumins escape to the perivascular space, tissue oncotic pressure increases, and plasma oncotic pressure decreases, resulting in a shift of fluid balance from the intravascular to interstitial space, or capillary leakage. The decrease in intravascular volume may be sufficiently severe to compromise circulation, resulting in shock [32]. In cases of severe envenomation, snake venom can induce the release of auto pharmacological vasoactive substances, particularly bradykinin, resulting in vasodilatation and myocardial depression, and consequently reduce myocardial contractility [32]. Therefore, our findings support the pathophysiology of sAKI as multifactorial, including hemodynamic changes, direct toxicity of snake venom, immunologic reaction and pigmenturia [33]. This pathophysiology would explain pathological observation of tubular necrosis, mesangiolysis, cortical necrosis, vasculitis, glomerulonephritis, interstitial nephritis, and renal infarction after snakebite envenomation [33].

In our study, 49.3% of patients with sAKI required RRT, which is within the range of previous reports (15.0–55.0%) [9–11, 13]. The fatality rate was 19.3%, which is also in the reported range (8.0–39.0%) among patients with snakebite envenomation [9–11, 13, 14]. When clinical parameters and management of patients with

sAKI were compared between patients who died and those who survived, patients who died were more likely to develop shock, have pulmonary complications, and receive management in the intensive care unit. However, the proportions of patients who received RRT and peritoneal dialysis as a dialysis method were similar between those who died and survived. The adequacy of dialysis determined by weekly Kt/V was less than 2.1 among AKI patients who died (median: 1.9, IQR: 1.1–3.0), but not among those who survived (median: 2.7, IQR: 2.2–3.9). However, there was no statistically significant difference between the groups, and it is probable that a small number of patients who died ($n = 8$) were evaluated for weekly Kt/V. According to the ISPD guideline for peritoneal dialysis in AKI, the target weekly Kt/V of 3.5 provides outcomes comparable to that of daily hemodialysis. However, a target weekly Kt/V of 2.1 may be acceptable [23].

In our study, electrolyte abnormalities were common among patients with snakebite envenomation. Patients with snakebite envenomation by a member of the *Viperidae* family who had hyponatremia at presentation and developed AKI during hospitalization had a significantly higher urine sodium-to-creatinine ratio. Our findings also indicated a significant negative correlation between urine sodium-to-creatinine ratio and serum sodium ($r = –0.478$), suggesting that hyponatremia among patients with *Viperidae* snakebites resulted from the renal tubular loss of sodium. Similarly, patients with hypokalemia who developed AKI during hospitalization had a significantly higher urine potassium-to-creatinine ratio. The significant negative correlation of urine potassium-to-creatinine ratio and serum potassium ($r = –0.468$) suggests that hypokalemia among patients with *Viperidae* bites resulted from the renal tubular loss of potassium. Moreover, hypomagnesemia was observed in 21.4% of patients with hypokalemia, all of whom had urinary loss of magnesium. Our findings suggested that the renal tubular loss of electrolytes including sodium, potassium and magnesium might be caused by the direct toxicity of snake venom from the *Viperidae* family. A previous experimental study of Russell's viper venom demonstrated decreased renal tubular absorption of sodium in proximal and distal renal tubules resulting in increased fractional excretion of sodium due to $Na + -K + -ATPase$ activity inhibition of renal tubules in both the renal cortex and medulla [34].

None of the patients with hypocalcemia had fractional excretion of calcium >20.0% and none of the patients with hypophosphatemia had fractional excretion of phosphate >15.0%, indicating extrarenal causes of hypocalcemia and hypophosphatemia. By contrast, hyperphosphatemia was more commonly observed compared to hypophosphatemia among patients with snakebite envenomation in our study. Thus, hypocalcemia might be caused by the process of intravascular thrombosis following the occurrence of DIC and rhabdomyolysis, and the occurrence of rhabdomyolysis would result in hyperphosphatemia among patients with snakebite envenomation [35, 36]. However, the possibility that hyperphosphatemia might occur secondary to AKI snake envenoming cannot be excluded [37].

Strengths and limitations

Our study has some limitations. First, all the data came from anacademic tertiary care hospital, which limits the generalizability of the study findings. Second, the snake could be identified in only 67.4% of cases. In case of unidentified snake bites, patient management relied on the clinical syndromes of snakebites defined in the WHO 2010 guidelines. However, our study was conducted as a prospective observational study in order to reduce bias, and the number of study patients achieved the required sample size for adequate statistical power. In addition, this study was the first to demonstrate the occurrence of impaired renal tubular function among patients with normal renal function who received bites from snake of the family *Viperidae* or having clinical syndrome of *Viperidae* envenoming.

Conclusion

Renal manifestations among patients with snake envenomation included reduce urine volume, renal tenderness, proteinuria, hematuria, electrolytes abnormalities, and AKI, and sAKI was a common and significant complication. The factors associated with sAKI included bites from snakes of the family *Viperidae* or presenting the clinical syndrome of *Viperidae* envenoming, duration from bite to receipt of antivenom ≥2 h, leukocytosis, overt DIC, rhabdomyolysis, hyponatremia and presence of microscopic hematuria. Our findings support the hypothesis of multifactorial involvement in the pathogenesis of sAKI. After sustaining *Viperidae* bites, a significant number of patients with normal renal function developed proximal and distal renal tubular dysfunction. These findings might help clinicians to provide optimal management of patients who are at risk for the development of sAKI in order to reduce the incidence of cAKI in tropical countries in the future.

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