Prognosis and long-term outcomes of acute kidney injury due to snake envenomation

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ABSTRACT

Background. Snakebite is a common occupational hazard in tropical countries. To date, the literature on snakebite-related acute kidney injury (AKI) has been limited by retrospective study designs, lack of uniformity in case definitions of AKI and limited follow-up. This study aims to identify the in-hospital outcomes and long-term changes in kidney function that follow haemotoxic envenomation.

Methods. All adult patients admitted with AKI following haemotoxic envenomation from January 2016 to June 2017 were recruited and followed up until July 2018. Predictors of in-hospital mortality was assessed. Long-term follow-up data on kidney function were collected from survivors.

Results. In total, 184 patients with haemotoxic envenomation and AKI were recruited. The mean age of the subjects was 42.2 years [95% confidence interval (CI) 40.3–44.7]. The majority were male (71.2%). The mortality of patients with haemotoxic envenomation was 21.5%. The mortality was considerably higher in patients with Kidney Disease: Improving Global Outcomes (KDIGO) Stage 3 AKI [relative risk (RR) 4.45 (95% CI 1.14–17.42)] and those who met KDIGO urine output criteria [RR 20.45 (95% CI 2.84–147.23)]. A Cox regression model identified mechanical ventilation [odds ratio (OR) 5.59 (95% CI 2.90–10.81)], hypotension [OR 2.48 (95% CI 1.31–4.72)] and capillary leak syndrome [OR 2.02 (95% CI 1.05–3.88)] as independent predictors of mortality. Long-term follow-up data were available for 73 patients. A total of 21 patients (28.7%) developed adverse renal outcomes (glomerular filtration rate < 60 mL/min/1.73 m², urine albumin excretion > 30 mg/g and new-onset hypertension or prehypertension).

Conclusions. AKI resulting from snake envenomation is associated with considerable risk of mortality. The greater the AKI stage the greater the likelihood of mortality. One-third of patients with AKI developed long-term complications like chronic kidney disease, prehypertension and hypertension over the follow-up period.

Keywords: acute kidney injury, capillary leak syndrome, long-term renal outcomes, prognosis, snake envenomation
**INTRODUCTION**

Snakebite is a common occupational hazard in southeast Asia. The World Health Organization estimates that snakebites account for ~138,000 deaths per annum, while direct estimates have shown that envenomation accounts for 0.5% of all deaths in India each year [1]. Daboia russelli (Russell’s viper) and Echis carinatus (saw-scaled viper) are the predominant species responsible for haemotoxic envenomation in India. Envenomation is a common cause of community-acquired acute kidney injury (AKI) in tropical and subtropical areas, contributing to significant morbidity and mortality [2, 3]. Even though AKI is a recognized complication of snakebite, the existing data concerning outcomes of AKI resulting from haemotoxic envenomation have been limited by retrospective study designs, a lack of uniformity in case definitions of AKI and limited follow-up [4–8]. The recent Kidney Disease: Improving Global Outcomes (KDIGO) definition and staging criteria have facilitated the early diagnosis of AKI, but the prognostic utility of these classification schemas in snakebite-related AKI is not known. The majority of outcome data are limited to in-hospital outcomes. Capillary leak syndrome (CLS), characterized by generalized vascular leak and significant fluid accumulation in the third space, is a unique complication following D. russelli envenomation that contributes to mortality [9–11]. However, very few reports on the impact of CLS on outcomes have been published to date and there is limited literature regarding the predictors of progression to chronic kidney disease (CKD) following envenomation-related AKI [12, 13]. This study aims to identify the in-hospital outcomes and long-term changes in kidney function that follow haemotoxic envenomation.

**MATERIALS AND METHODS**

All adult patients admitted with AKI following haemotoxic envenomation from January 2016 to June 2017 were recruited. A diagnosis of snakebite was made from a clinical history of systemic haemotoxicity with any one of the following symptoms: new-onset bleeding tendencies following snakebite, a whole-blood clotting time >20 min or a platelet count <100,000 cells/mm³. AKI was defined according to the KDIGO criteria [14]. Disseminated intravascular coagulation was defined as a prolonged prothrombin time/international normalized ratio (>1.3) and platelet counts <100,000 cell/mm³ with the presence of bleeding. CLS was defined as the presence of chomosis, periorbital oedema and bilateral parotid swelling with any two of the following: systolic blood pressure <90 mmHg, increase in haematocrit by >20% from baseline, serum albumin <3.0 g/dL and evidence of fluid in the third space on imaging. Bite-to-needle time was defined as the time interval between snakebite and the administration of the first dose of ASV. Adverse renal outcomes were defined as the presence of any one of the following: eGFR <60 mL/min/1.73 m², urine albumin/creatinine ratio >30 mg/g, and new onset hypertension or prehypertension. Systemic hypertension was defined as systolic blood pressure >140/90 mmHg and prehypertension was defined as systolic blood pressure 120–139 mmHg and diastolic blood pressure 80–89 mmHg on two or more office visits.

**Case definitions**

Systemic haemotoxicity was defined as a history of snakebite with any one of the following symptoms: new-onset bleeding tendencies following snakebite, a whole-blood clotting time >20 min or a platelet count <100,000 cells/mm³. AKI was defined according to the KDIGO criteria [14]. Disseminated intravascular coagulation was defined as a prolonged prothrombin time/international normalized ratio (>1.3) and platelet counts <100,000 cell/mm³ with the presence of bleeding. CLS was defined as the presence of chomosis, periorbital oedema and bilateral parotid swelling with any two of the following: systolic blood pressure <90 mmHg, increase in haematocrit by >20% from baseline, serum albumin <3.0 g/dL and evidence of fluid in the third space on imaging. Bite-to-needle time was defined as the time interval between snakebite and the administration of the first dose of ASV. Adverse renal outcomes were defined as the presence of any one of the following: eGFR <60 mL/min/1.73 m², urine albumin/creatinine ratio >30 mg/g, and new onset hypertension or prehypertension. Systemic hypertension was defined as systolic blood pressure >140/90 mmHg and prehypertension was defined as systolic blood pressure 120–139 mmHg and diastolic blood pressure 80–89 mmHg on two or more office visits.

**Statistical analysis**

All categorical variables were expressed as frequencies and percentages, and continuous variables were expressed as mean with 95% confidence intervals or median with interquartile range (IQR) based on the normality of the data. All categorical variables were compared by chi-square test. All continuous variables were compared by Student’s t-test or Mann–Whitney U test according to the distribution. Mortality between groups was expressed as relative risk (RR) with confidence intervals (CIs). A Cox regression analysis was done to assess the independent predictors of in-hospital mortality. The changes in eGFR between groups over the follow-up period were compared by linear mixed models. A P-value <0.05 was taken as significant. The data was analysed using the statistical software SPSS version 19.0 (IBM, Armonk, NY, USA).

**RESULTS**

In total, 420 patients with haemotoxic snakebites were assessed over the study period. Of these, 214 (50.9%) had systemic haemotoxicity and 184 patients (43.8%) satisfied the KDIGO criteria for AKI (Figure 1). A total of 164 patients had AKI on admission (AKI 1–14 (7.6%), AKI 2–35 (19%) and AKI 3–115 (62.5%)) and 20 (10.8%) patients developed AKI within 48 h of admission. KDIGO urine output and creatinine criteria were met in 106 (57.6%) patients, while 45 (24.5%) patients met only creatinine criteria and 33 (17.9%) met only urine output criteria. Daboia russelli accounted for 22.2% (n = 41) of bites and E. carinata was responsible for 14.1% (n = 26). The species of snake was not identified in 117 patients (63.6%). Bite-to-needle time was ≤2 h in 113 (61.4%) patients, but was >4 h in 34 patients (18.5%). Comorbidities present in the population were systemic hypertension (n = 7) and diabetes mellitus (n = 2). Four patients had neurological manifestations in addition to haemotoxic manifestations. Eighteen patients (9.8%) had sought traditional remedies before seeking medical attention. CLS was present in 26 (14.1%) patients, among which 11 patients had hypotension requiring inotropic support, 12 needed mechanical ventilation and 21 needed dialysis.
All patients requiring renal replacement therapy were given haemodialysis or sustained low-efficiency dialysis. The mortality for patients with haemotoxic envenomation was 21.5% ($n=46/214$; AKI = 44, no AKI = 2). Among the 44 AKI deaths, 19 (10.3%) occurred in the first 48 h, 12 (06.5%) occurred between 48 h and 7 days, 7 (3.8%) occurred in the second week and 6 (3.2%) occurred $>2$ weeks after snakebite. The characteristics of survivors and non-survivors with AKI are given in Table 1. Mortality was considerably higher in patients with Stage 3 AKI and those who only met the KDIGO urine output criteria (Table 2). A Cox regression analysis identified the need for mechanical ventilation, hypotension and CLS as independent predictors of mortality (Table 3).

Recovery and follow-up

Among survivors ($n=140$), at the time of discharge 44 patients (31.4%) had an eGFR level $>$60 mL/min/1.73 m². Among the 69 patients who attended their first follow-up appointments scheduled $\sim$2 weeks post-discharge, 23 patients had eGFR values $<$60 mL/min/1.73 m² (33.3%). Follow-up data beyond 3 months were available for 73 patients. Median follow-up duration was 15.5 months (IQR 6–21). Two patients had hypertension and one had diabetes mellitus. Mean eGFR at the end of follow-up was 80.9 mL/min/1.73 m² (95% CI 74.8–87). A total of 21 patients (28.7%) developed adverse renal outcomes (Table 4). Among the 14 patients with an eGFR $<$60 mL/min/1.73 m², 2 were CKD Stage 4, 5 were CKD Stage 3b and 6 patients were CKD Stage 3a. One patient did not recover from the AKI and remained dialysis-dependent; renal biopsy showed thrombotic microangiopathy. Kidney biopsy was performed in two more patients with CKD, which showed chronic thrombotic microangiopathy in one and persistent acute tubular necrosis in the other. The characteristics of patients who developed adverse renal outcomes are shown in Table 5. Patients with adverse renal outcomes had lower GFRs from the point of hospitalization ($P \leq 0.001$, Figure 2).

DISCUSSION

Snake envenomation is a common cause of AKI in tropical countries and predominantly affects young individuals engaged

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**FIGURE 1:** Flow chart showing patients admitted with snake envenomation during the study period.
In agriculture-related activities. In this study, we observed that 44% of patients with poisonous snakebites developed AKI. The reported prevalence rates of AKI following haemotoxic envenomation vary from 14 to 44% [4–8, 15]. Relatively higher AKI prevalence rates have been reported in studies that have employed both urine output and creatinine-based criteria for the diagnosis of AKI, compared with studies that have employed creatinine-based criteria alone [5, 8, 16].

The bite-to-needle time is considered to be the most important determinant of AKI following envenomation. The venom should be neutralized as early as possible to prevent complications and mortality; however, the optimum bite-to-needle time to prevent complications has not yet been defined. Dharod et al. observed a mean bite-to-needle time of 7.6 h in patients with AKI as opposed to 20 h in those who did not develop AKI [15], while Athappan et al. reported that a bite-to-needle time >2 h is associated with a higher chance of kidney failure [17]. On the other hand, Paul and Dasgupta reported much shorter bite-to-needle times (66 min) in patients who developed AKI [18]. These reported variations might be secondary to the varied definitions

| Table 1. Demographic and clinical characteristics of survival and non-survival groups (n = 184) |
|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| Parameter | Total (n = 184) | Survivors (n = 140) | Non-survivors (n = 44) | P  |
| Age (years)* | 42.2 (40.3–44.1) | 42.3 (40.1–44.4) | 41.9 (37.5–46.3) | 0.888 |
| Male gender, n (%) | 131 (71.2) | 99 (70.7) | 32 (72.7) | 0.797 |
| Requirement of inotropes, n (%) | 32 (17.4) | 12 (8.6) | 20 (45.5) | 0.000 |
| Mechanical ventilation, n (%) | 33 (17.9) | 6 (4.3) | 27 (61.4) | 0.000 |
| Renal replacement therapy, n (%) | 114 (61.9) | 79 (56.4) | 35 (79.5) | 0.007 |
| CLS, n (%) | 26 (14.1) | 9 (6.4) | 17 (38.6) | 0.000 |
| Time from snakebite to ASV administration (h)* | 2.00 (1.5–4) | 2.00 (1.62–4.00) | 2.00 (1.00–4.00) | 0.461 |
| Total dose of ASV received (vials)* | 18.33 (16.8–19.9) | 17.6 (15.9–19.3) | 20.8 (17.2–24.3) | 0.081 |
| Duration of hospitalization (days)* | 12.3 (10.9–13.7) | 14.3 (12.6–15.6) | 6.8 (4.1–9.6) | 0.000 |
| Requirement of inotropes, n (%) | 32 (17.4) | 12 (8.6) | 20 (45.5) | 0.000 |
| Mechanical ventilation, n (%) | 33 (17.9) | 6 (4.3) | 27 (61.4) | 0.000 |
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| CLS, n (%) | 26 (14.1) | 9 (6.4) | 17 (38.6) | 0.000 |

*Mean with CIs.  
**Median with IQR.  
P < 0.05 taken as significant.

| Table 2. RR of mortality according KDIGO AKI stage and diagnostic criteria |
|-------------------------------------------|-------------------------------------------|
| Haemotoxic envenomation (n = 214) | Death (n = 46) | Survival (n = 168) | RR (95% CI) |
| Haemotoxic snakebite without AKI (n = 30) | 2 | 28 | Reference |
| AKI Stage 1 (n = 22) | 0 | 22 | 0.27 (0.01–5.35) |
| AKI Stage 2 (n = 24) | 0 | 2 | 1.87 (0.34–10.34) |
| AKI Stage 3 (n = 138) | 41 | 97 | 4.45 (1.14–17.42) |
| Haemotoxic envenomation with AKI (n = 184) | Death (n = 44) | Survival (n = 168) | RR (95% CI) |
| Creatinine criteria (n = 45) | 1 | 44 | Reference |
| Urine output criteria (n = 33) | 15 | 18 | 20.45 (2.84–147.23) |
| Both (n = 106) | 28 | 78 | 11.89 (1.67–84.72) |

| Table 3. Cox regression analysis for independent predictors of mortality (N = 184) |
|-------------------------------------------|-------------------------------------------|
| Parameter | OR (95% CI) | P  |
| Mechanical ventilation | 5.59 (2.90–10.81) | 0.000 |
| Hypotension | 2.48 (1.31–4.72) | 0.005 |
| CLS | 2.02 (1.05–3.88) | 0.036 |
| AKI Stage 3 | 1.83 (0.50–6.64) | 0.370 |
| Renal replacement therapy | 1.45 (0.64–3.25) | 0.362 |

| Table 4. Adverse renal outcomes on follow-up (n = 73) |
|-------------------------------------------|-------------------------------------------|
| Patients with adverse renal outcomes* | 21 (28.7) |
| GFR <60 mL/min/1.73 m² | 14 (19.2%) |
| Urine albumin/creatinine ratio >30 mg/g | 5 (66.8%) |
| Systemic hypertension | 4 (56.5%) |
| Prehypertension | 1 (01.4%) |

*Some patients have more than one adverse renal outcomes. Total numbers might exceed 21.
of AKI as well the effect of ease of access to health care. In this study, 42/44 patients who succumbed received ASV within 2 h of sustaining the bite. We did not find any evidence that early administration of ASV protected patients from AKI or mortality.

One-half of the deaths in this study happened in the initial 48 h after snakebite, and resulted from cardiorespiratory failure and CLS. The contribution of CLS towards mortality in snakebite is often overlooked. CLS commonly occurs following D. russelii envenomation and results from widespread endothelial injury. The pathogenesis of CLS is poorly understood. One mechanism that has been proposed is endothelial apoptosis secondary to vascular apoptosis-inducing proteins (VAP 1 and VAP 2) and L-amino oxidase present in the snake venom [11]. Other suggested mechanisms include phospholipase A2-mediated activation of cytokines and direct vascular toxicity by zinc metalloproteinases present in the venom [11]. CLS is associated with increased risk of hypotension, respiratory failure and death [9–11]. It is believed that ASV available in India is ineffective in preventing CLS [11]. The features of CLS start to appear 12–24 h after envenomation, with the development of the full-blown syndrome by 48–72 h. There is high variability in the reported prevalence and outcomes of CLS. It is believed that CLS resulting from envenomation is subject to significant regional variations. The majority of CLS cases following envenomation are reported in the state of Kerala in Southern India [11] and the reported mortality rates range from 43 to 67%. A lack of uniformity in case definitions and non-recognition of milder variants of CLS might be responsible for these differences. Moreover, the presence of elevated haematocrit, a cardinal feature of CLS, might be masked due to the presence of venom-induced haemolysis.

The current polyvalent ASV available in India neutralizes the venom of N. naja, D. russelii, E. carinatus and B. caeruleus. There is increasing evidence that other viper species, like hump-nosed pit vipers (Hypnale hypnale), might be responsible for lethal envenomations in southeast Asia [11, 19]. Pit vipers can be easily mistaken for saw-scaled vipers and were reported to account for one-third of envenomations in a case series from Sri Lanka [20]. Minimal data on the prevalence of AKI and mortality following envenomation by pit vipers are available from India. A study from Kerala, India reported a high incidence of kidney failure among patients who sustained pit viper bites [21]. On the other hand, a study from Brazil reported a lower prevalence of AKI (15%) and no mortality following envenomation predominantly by Bothrops species, which represent a type of pit viper [22]. It should be recalled that, in this study, species identification was not possible in more than two-thirds of all cases. To date, no published data are available regarding the diversity of the reptile population in the geographical area where the study was conducted. Another potential contributory factor might be regional variations in snake venom observed across different parts of India, which might influence the toxicity profile as well as the neutralizing capacity of ASV [23].

### Table 5. Characteristics at the time of admission for patients with and without adverse renal outcomes

| Parameter                                      | Adverse renal outcomes (n = 21) | Normal kidney function (n = 52) | P    |
|------------------------------------------------|---------------------------------|---------------------------------|------|
| Age (years)                                    | 48.5 (44.8–53.1)                | 39.3 (36.08–42.42)              | 0.002|
| Haemoglobin at admission (g/dL)*               | 10.5 (8.7–12.1)                 | 12.3 (11.4–13.2)                | 0.034|
| Stage 3 AKI, n (%)                             | 17 (81.0)                       | 44 (84.6)                       | 0.734|
| Need for dialysis, n (%)                       | 16 (76.2)                       | 37 (71.2)                       | 0.777|
| Bite-to-needle time (h)*                       | 02 (01–3)                       | 02 (01–04)                      | 0.621|
| Total ASV received (vials)*                    | 14 (10–23)                      | 16 (10–23)                      | 0.807|
| Serum creatinine (at admission) (mg/dL)*       | 3.7 (2.0–4.5)                   | 2.9 (1.1–4.4)                   | 0.158|
| Serum albumin (at admission) (g/dL)*           | 3.2 (2.9–3.4)                   | 3.0 (2.9–3.3)                   | 0.397|
| Duration of hospitalization (days)*            | 19 (9.5–28)                     | 12.5 (9–18)                     | 0.040|
| eGFR 2 weeks post-discharge*                   | 49.6 (35.6–63.6)                | 78 (70.1–85.6)                  | 0.001|

*aMean with CIs.

*bMedian with IQR.

*cThe median duration was 30 days (IQR 24–35) since the envenomation.
AKI is an established risk factor for the development of CKD in the long-term and limited data exist regarding the long-term outcomes of patients who develop AKI following envenomation. We observed that one-third of our patients developed adverse renal outcomes on long-term follow-up. Herath et al. [13] reported that 37% of patients who sustain AKI following envenomation develop CKD by the end of 1 year. However, the patients were a decade older than the participants in our study, and the majority had comorbidities like hypertension and diabetes, which are independent risk factors for CKD. Waikhom et al. [12] reported that 41% of patients who sustain envenomation develop persistent renal abnormalities in the long-term. The patients who developed adverse renal outcomes in this study were older and had a lower GFR at the time of hospital discharge. Advanced age and severe renal failure are established risk factors for CKD progression [24]. However, in our study, we did not observe any differences in the dialysis requirements or severity of AKI among patients who developed adverse renal outcomes. This might be due to the considerable attrition on follow-up. Most of the Stage 1 and 2 AKI cases were lost to follow-up, resulting in selective inclusion of patients with more severe renal failure.

In this study, the severity of the envenomation did not appear to be a major determinant of future adverse renal events. There was no relationship between ASV dosage, bite-to-needle time, or serum albumin levels and long-term renal damage. Similar findings were reported by Waikhom et al. [12]. On the other hand, it appeared that a longer duration of renal failure was associated with a higher risk of CKD. Patients who developed adverse renal outcomes had lower nadir eGFRs as well as longer recovery times. The tendency to have a lower GFR was evident at the time of discharge as well as at the first follow-up appointment. In addition to the severity of AKI, the duration of AKI is also an important prognostic determinant of long-term outcome [25, 26]. Early recovery from AKI, especially with in first 7 days, is reported to be an associated with better long-term prognosis [27]. Lower haemoglobin levels in patients who develop adverse renal outcomes might be secondary to the venom-induced haemolysis.

To the best of our knowledge, this study is the largest series on AKI following envenomation to date. The data were collected prospectively from the time of hospitalization. The limitations of the study include considerable loss of follow-up, especially for patients with milder degrees of AKI. Follow-up data were available for only half of the patients who survived envenomation. As most of the patients were manual labourers, logistical issues stood in the way of periodic follow-up. Even though the study protocol included a follow-up visit at 3 and 6 months, the majority of the patients could not attend their scheduled appointments. Baseline eGFRs taken prior to the illness were not available for any of the recruited patients. In a developing country like India, apparently healthy individuals, especially belonging to low-income groups, seldom undergo any periodic health check-ups. Abdomen ultrasound was performed for all patients to rule out any abnormalities in kidney size. However, it is still possible that some of the patients had milder renal dysfunction with normal kidney size.

CONCLUSIONS
AKI resulting from snake envenomation is accompanied by considerable risk of mortality. The greater the stage number of AKI, the poorer the outcome. The presence of CLS, hypotension and respiratory failure are independent predictors of a mortality. One-third of patients with AKI develop long-term complications like CKD, prehypertension and hypertension on follow-up. Early recovery from AKI is associated with better preservation of GFR in the long-term.

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CONFLICT OF INTEREST STATEMENT
None declared.

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