



# Prevalence of Capillary Leak Syndrome in Hemotoxic Envenoming: A Prospective Observational Study from Himachal Pradesh, India

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## ABSTRACT

**Background:** Himachal Pradesh, India, has a distinct *Viperidae* snake fauna and includes northern white-lipped pit viper (*Trimeresurus septentrionalis*), Himalayan pit viper (*Gloydius himalayanus*), Chamba pit viper (*Gloydius chambensis*), in addition to Russell's viper (*Daboia russelii*) and saw-scaled viper (*Echis carinatus*). The study was conducted to assess the prevalence of capillary leak syndrome (CLS) in patients with hemotoxic venomous snakebites.

**Materials and methods:** This open-cohort descriptive study was conducted among patients admitted with hemotoxic envenoming. The patients were enrolled through nonprobability sampling, and the study period was 1 year. Hemotoxic envenoming was defined as a positive bedside 20-min whole-blood clotting time (20-min WBCT) following a snakebite. CLS was defined by the clinical criteria of periorbital edema, conjunctival chemosis, parotid swelling, and systolic BP less than 90 mm Hg. Laboratory criteria for diagnosis included hemoglobin greater than 17 gm/dL in males and greater than 15 gm/dL in females, hematocrit greater than 50% in males and greater than 45% in females, and serum albumin less than 3.5 gm/dL. CLS was defined as the presence of one clinical feature and one laboratory criterion.

**Results:** 62 patients were enrolled in this study. The prevalence of CLS was 19.3% (12/62). Of the 12 patients with CLS, 6 (50%) improved, 5 (42.9%) received referral on request, and 1 (8.3%) patient expired.

**Conclusion:** CLS is not an uncommon entity following *Viperidae* envenoming in the Himachal Pradesh region of India.

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## INTRODUCTION

Himachal Pradesh, India, falls in the lower burden snakebite envenomation region. The probability of death from snakebite is less than 0.25% before age 70 in the state.<sup>1</sup> The snakes of medical importance in the state are the "big four," i.e., Indian or spectacled cobra (*Naja naja*), common krait (*Bungarus caeruleus*), Russell's viper (*Daboia russelii*), and saw-scaled viper (*Echis carinatus*). In addition, the presence of "six more" species of medical importance has been identified and added to the list of the "big four." The three neurotoxic species are the king cobra (*Ophiophagus hannah*), central Asian cobra (*Naja oxiana*), and Maclelland's coral snake (*Sinomicrurus maclellandi*), and the three hemotoxic species are Northern white-lipped pit viper (*Trimeresurus septentrionalis*), Himalayan pit viper (*Gloydius himalayanus*), and Chamba pit viper (*Gloydius chambensis*). The geographical distribution of these species varies from the hills to the plains of the state. The state has an ideal environment for the human animal conflict, which coincides with increases in agricultural activity during the rainy season of monsoons and the postmonsoon period, the location of human dwellings in and around

fields, sleeping on the floor, and abundant vegetation. The local distinct reptilian fauna makes it imperative to study the spectrum of envenomation from this geographic region. The classic toxidrome triggered by the venoms of the family *Viperidae* snakes includes local tissue damage and hemotoxic envenoming. Venom-induced consumption coagulopathy (VICC) is the most common hemotoxicity related to snake envenoming. Capillary leak syndrome (CLS) is recognized in a subgroup of patients with VICC and is characterized by facial and conjunctival edema, bilateral parotid enlargement, serous cavity effusion, hypotension, pulmonary edema, and laboratory evidence of hemoconcentration and hypoalbuminemia.<sup>2</sup> CLS has been reported in toxidrome with eastern (*D. russelii* in India) and western (*D. siamensis* in Myanmar) Russell's viper in Asia.<sup>3</sup> In India, the patients have been diagnosed in the medical institutions from the southern states of Kerala, Tamil Nadu, and Puducherry.<sup>2</sup> Clinical manifestations such as CLS have not been reported in the hospital-based studies from the hills of Himachal Pradesh, India. The objective of the study was to estimate the prevalence of capillary leak syndrome among patients with hemotoxic envenoming admitted

to a tertiary care hospital located in the Kangra valley of Himachal Pradesh, India.

## MATERIALS AND METHODS

The design of this hospital-based study was an open-cohort prospective descriptive model. Participants were recruited between June 2023 and May 2024 using a nonprobability sampling method. The included patients were above the age of 18 years and admitted with hemotoxic envenomation after a snakebite. The exclusion criteria were patients with known preexisting kidney disease, chronic liver disease, hypothyroidism, and heart failure. Patients discharged within 48 hours of admission were not included in the study.

## Definitions

### Hemotoxic Envenomation

It was defined as a positive 20-min whole-blood clotting test (20 WBCT) subsequent to a snakebite.<sup>4</sup>

### Capillary Leak Syndrome

It was defined by the clinical criteria of periorbital edema, conjunctival chemosis, parotid swelling, and systolic blood pressure of less than 90 mm Hg. Laboratory criteria for diagnosis included hemoglobin greater than 17 gm/dL in males and greater than 15 gm/dL in females, hematocrit greater than 50% in males and greater than 45% in females, and serum albumin less than 3.5 mg/dL. CLS was defined with the documentation of one clinical feature and one laboratory criterion.<sup>5</sup>

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### Thrombotic Microangiopathy

Thrombotic microangiopathy was defined as the presence of thrombocytopenia, acute kidney injury (AKI), and microangiopathic hemolytic anemia (MAHA).<sup>6</sup>

### Procedure

The information about the demographic profile, clinical features, treatment received, and investigations performed was recorded for each patient on a clinical research form. The laboratory investigations included complete blood counts, peripheral blood films, liver and renal profiles, and examination of urine. The time ranges for understanding the serial changes were defined as less than 48 hours, 48–96 hours, and at discharge. The maximum or the minimum value observed was used for analysis. Ultrasonographic evidence for the presence of pleural effusion and ascites was gathered. Species identification of the likely envenoming snake was done using the video and/or photographs provided by the patients or their attendants. To corroborate, the patient or his accompanied were shown images of various snake species prevalent in Himachal Pradesh, which were available on the public platform and provided by the authors AG and SR. Attempts were made to identify the snakes in the local dialect and to verify them against zoological names. Consultation with an expert was conducted to confirm the identity of the species. The data were entered in the Microsoft Excel spreadsheet and analyzed through Epi-Info 7. Quantitative data were stated as means with standard deviation, and qualitative data as frequencies and percentages. Median  $\pm$  IQR was calculated for variable and wide distribution data. The Student's *t*-test and the Chi-square test were used to analyze continuous variables and proportions, respectively. Mann-Whitney *U* test was used for non-normal distribution. The study has been conducted after approval by the institutional ethics committee.

## RESULTS

In the present study, 62 patients were recruited over a period of 1 year. Information about the demography profile, presentation features, admission duration, and outcome is shown in Table 1. All the subjects were residents of rural localities. All the subjects were presented in the warm season from March to November. In the monsoon months of August and September, 54.8% patients were admitted. The biting snake could be identified in 48.4% (30/62) cases by the victim or their attendants. 12 cases

identified the snake as Ghug (vernacular name for Russell's viper), 2 as Kodi wala saanp (vernacular name for Russell's viper), 6 as Sotad (vernacular name for both Himalayan pit viper and Russell's viper), 4 as "Saledu" (green colored *Trimeresurus septentrionalis*), and 1 each as Dhartranga (Russell's viper) and Surail (unidentified). Four were identified as Russell's viper, but patients and their attendants were unaware of their local names. Four were identified as green colored snakes. We could not come across any patient who could identify the Himalayan pit viper (*G. himalayanus*), Chamba pit viper (*G. chambensis*), or saw-scaled viper (*Echis carinatus*), or spell their local names. The frequency distribution of clinical manifestations is shown in Figure 1. The results of laboratory investigations are shown in Table 2. The prevalence of CLS was 19.3% (12/62) in this study. Of the 12 patients with CLS, 6 (50%) improved, and 5 (42.9%) were referred on request and were therefore lost to follow-up. One (8.3%) patient expired. Eight patients with CLS required hemodialysis. Ultrasonography for evidence

of pleural effusion and ascites was carried out in 58 patients. 12 patients had evidence of pleural effusion, and 4 patients had ascites. Pleural effusion was bilateral in eight, on the right side in one, and on the left side in three (Fig. 2A). Isolated ascites was observed in two, and bilateral pleural effusion with ascites was observed in two patients.

Among the 12 patients with CLS, 11 had ultrasonographic evidence of pleural effusion and ascites. In one patient with CLS, ultrasonography could not be done. One patient with bilateral pleural effusion, one patient with left-sided pleural effusion, and one patient with ascites did not fulfill the defined diagnostic criteria of CLS. All these three patients had periorbital puffiness (Fig. 2B). A comparison of demography, clinical features, and investigations of patients with and without CLS are illustrated in Table 3. Bilateral parotid enlargement was observed in one patient with CLS. The patient had a favorable outcome and recovered.

Proteinuria was observed in 67.7% (42/62) of patients. 20 (32.3%) patients had 2+, 16

**Table 1:** Demography, presentation profile, duration of admission, and outcome among study subjects

Parameter	Frequency distribution (%) (n = 62)
Sex	
Males	35 (56.5)
Females	27 (43.5)
Mean age (years $\pm$ SD)	43.2 $\pm$ 16.2
Median (IQR) time duration of snakebite to admission (hours)	4 (2–12)
Number of patients reporting within 1 hour	12 (19.3)
Site of distribution	
Lower limb	42 (67.7)
Upper limb	19 (30.6)
Head	1 (1.6)
First aid	
Allopathy centers	44 (70.9)
Alternative medicine	18 (29.0)
Tourniquet	45 (72.6)
Single	38 (61.3)
Multiple	7 (11.3)
Median (IQR) time duration of tourniquet application (minutes)	25 (0–60)
Median (IQR) duration of admission (days)	4 (3–5)
Median (IQR) duration for which 20-min WBCT remained positive (hours)	16 (12–24)
20-min WBCT normalized with ASV dose (mL)	
100	11 (17.7)
200	18 (29.0)
300	31 (50.0)
Outcome	
Expired	2 (3.2)
Recovered	53 (85.4)
Referred	7 (11.2)

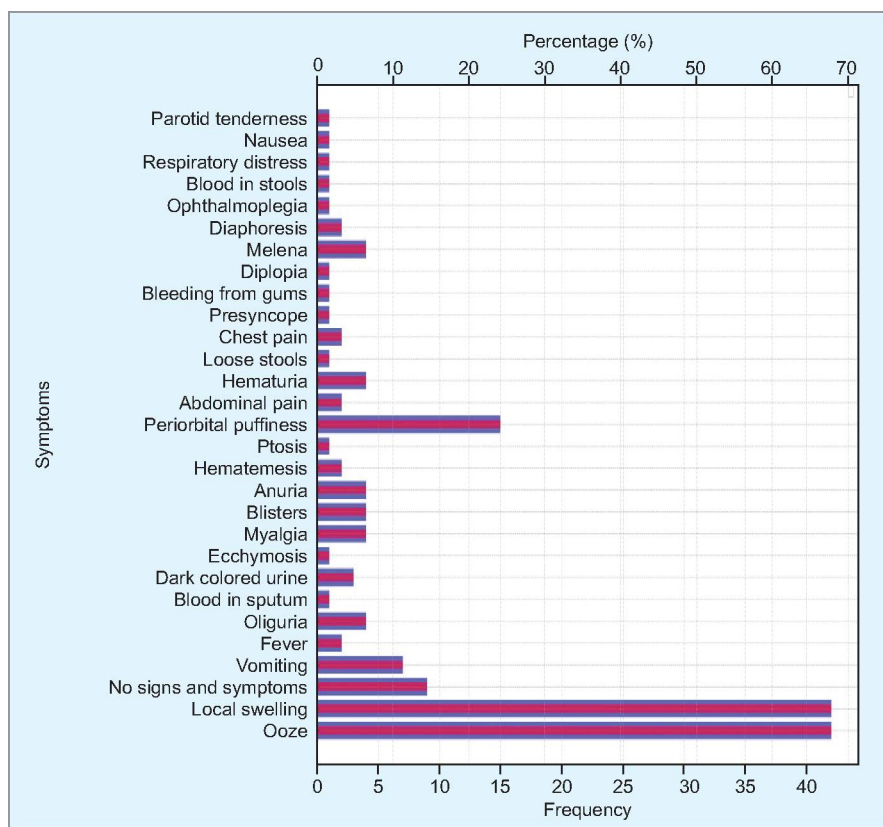


Fig. 1: Distribution of symptoms and signs among patients

(25.8%) patients had 1+, 5 (8.1%) patients had 3+ and 1 (1.6%) patient had 4+ proteinuria.

The prevalence of TMA was 6.4% (4/62). Among the four patients having TMA, concomitant CLS features were observed in three. All four patients with TMA were treated with hemodialysis. Two patients with TMA improved, and two were referred.

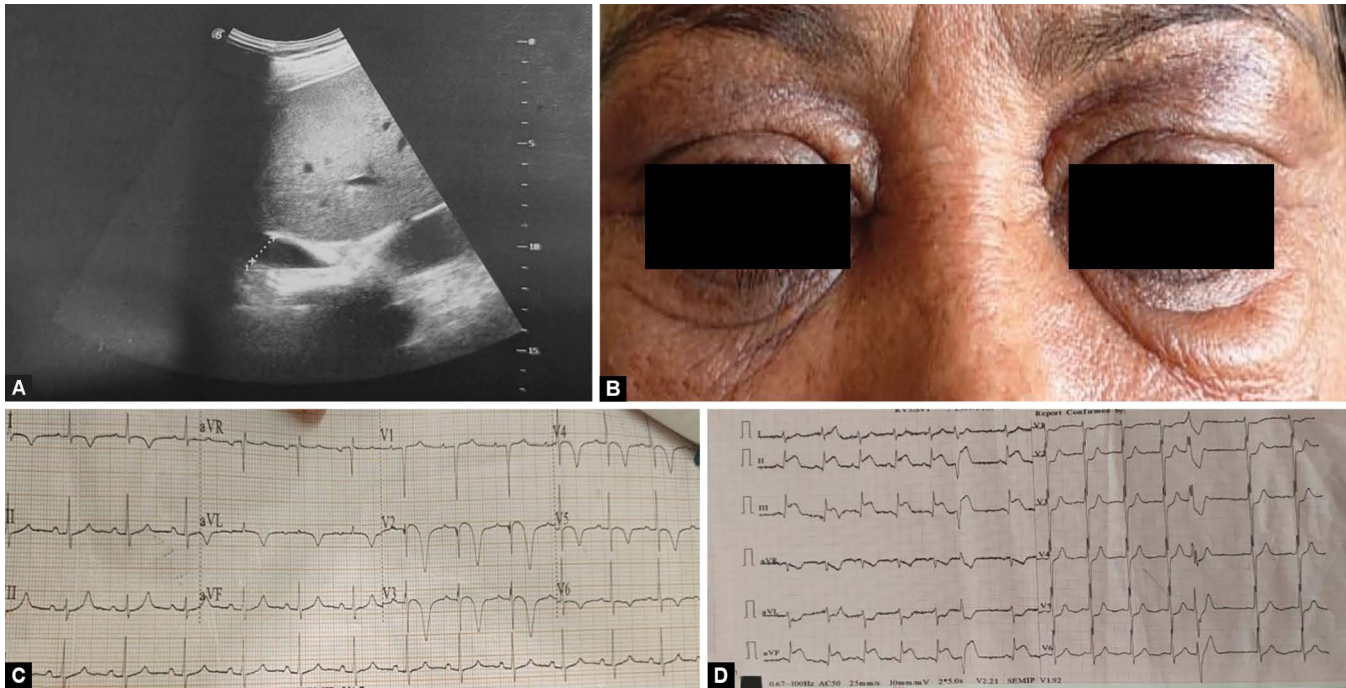
The 20 WBCT remained positive in two patients in spite of receiving the ASV dose of 300 mL. The 20-min WBCT became negative with 100 mL of ASV in 17.7% (11/62), with 200 mL of ASV in 29% (18/62), and with 300 mL of ASV in 50% (31/62). Adverse reactions in the form of anaphylaxis (1.6%), rash and urticaria (4.8%) were observed.

All patients received prophylactic antibiotics as oral amoxicillin-clavulanate. Secondary wound infection developed in two patients and was treated with oral linezolid. Three patients developed acute coronary syndrome, which included two patients with anterior wall non-ST-segment-elevated myocardial infarction (NSTEMI) and one patient with inferior wall ST-segment-elevated myocardial infarction (STEMI) (Figs 2C and D). One patient had features of myocarditis. One patient received FFP because of the hematemesis and mucosal bleeding.

Table 2: Distribution of laboratory, hematology parameters, prevalence of CLS, and TMA among study subjects

Parameter	Total (%) (n = 62)	Male (%) (n = 35)	Female (%) (n = 27)
Anemia	51 (82.2)	25 (40.3)	26 (41.9)
Leukocytosis	44 (70.9)	23 (37.0)	21 (33.8)
AKI	25 (40.3)	10 (16.1)	15 (24.1)
Transaminasemia (AST > ALT)	37 (59.6)	22 (35.4)	15 (24.1)
Thrombocytopenia	53 (85.4)	29 (46.7)	24 (38.7)
Schistocytes	6 (9.6)	3 (4.8)	3 (4.8)
Hypoalbuminemia	34 (54.8)	15 (24.1)	19 (30.6)
Raised LDH	57 (91.9)	25 (40.3)	32 (51.6)
Urine			
RBC	46 (74.1)	24 (38.7)	22 (35.4)
Proteinuria	42 (67.7)	23 (37.0)	19 (30.6)
Myoglobinuria	3 (4.8)	1 (1.6)	2 (3.2)
Raised CPK	45 (72.5)	25 (40.3)	20 (32.2)
Bilateral pleural effusion	7 (11.2)	4 (6.4)	3 (4.8)
Ascites	3 (4.8)	2 (3.2)	1 (1.6)
Bilateral effusion and ascites	2 (3.2)	1 (1.6)	1 (1.6)
Thrombocytopenia and AKI	25 (40.3)	10 (16.1)	15 (24.1)
RBC morphology			
Normocytic	46 (74.1)	29 (46.7)	17 (27.4)
Microcytic	2 (3.2)	-	2 (3.2)
Macrocytic	2 (3.2)	2 (3.2)	-
Dimorphic	10 (16.1)	3 (4.8)	7 (11.2)
TMA	4 (6.4)	1 (1.6)	3 (4.8)
Capillary leak syndrome	12 (19.3)	4 (6.4)	8 (12.8)

n, number; AKI, acute kidney injury; AST, aspartate transaminases; ALT, alanine transaminases; LDH, lactate dehydrogenase; RBC, red blood cells; CPK, creatine phosphokinase; TMA, thrombotic microangiopathy



**Figs 2A to D:** (A) Sagittal grayscale ultrasound of chest showing pleural effusion (dotted arrow) in subhepatic space; (B) Periorbital swelling; (C) ECG showing deep T-wave inversion in I, aVL, V2–V6; (D) ECG showing ST-segment elevation in II, III, aVF

## DISCUSSION

Capillary leak syndrome is a recognized complication of *Daboia russelii* envenoming, described from Southern India, Sri Lanka, and Myanmar. In southern India, CLS following snakebite has been reported from Kerala, Tamil Nadu, and Puducherry.<sup>5,7–14</sup>

Patients recruited in the present study had hemotoxic envenoming diagnosed on the basis of a positive 20 WBCT. The prevalence of capillary leak syndrome was 19.3% among patients in this study. The prevalence of CLS was 23% in a prospective hospital-based observational study on viper envenomation from Pondicherry, India.<sup>14</sup> In a study from the Malabar region, India, the prevalence of CLS among Russell's viper, hump-nosed pit viper (HNPV), and saw-scaled viper was 17%, 1.3%, and 0.09%, respectively. None of the patients with Malabar pit viper and bamboo pit viper envenomation developed CLS.<sup>9</sup> The striking feature of the study is that CLS is a manifestation of HNPV and saw-scaled viper, in addition to the already recognized complication of Russell's viper envenomation. These results are relevant from our study point of view due to the presence of Northern white-lipped pit viper (*Trimeresurus septentrionalis*), Himalayan pit viper (*G. himalayanus*) and Chamba pit viper (*G. chambensis*) in our region. Species identification was performed in the current study. Out of the 12 cases with CLS, nine patients had envenoming because of Russell's viper, and one due to Northern white-lipped pit viper. In the other two cases,

with CLS species identification by the patients or their attendants was not possible. In a prospective study carried out in a cohort of children below 12 years and snakebite in a Kerala hospital, the prevalence of CLS was 6.9%.<sup>11</sup>

Capillary leak syndrome is due to additional permeability of proteins from capillaries and the spectrum of manifestations includes hypotension, pitting edema, noncardiogenic pulmonary edema, exudative serous cavity effusions, and hypovolemic shock with multiple-organ dysfunction. Diseases associated with CLS are sepsis, idiopathic systemic capillary leak syndrome or Clarkson's disease, cardiac surgery using cardiopulmonary bypass, anaphylaxis, major burns, engraftment syndrome, viral hemorrhagic fevers, hemophagocytic lymphohistiocytosis, snakebite envenomation, differentiation (retinoic acid) syndrome, the ovarian hyperstimulation syndrome, autoimmune diseases, and drugs.<sup>15,16</sup> Snake venom is a composite mixture of toxins, and the compound varies significantly from one species to another. The three dominant protein families in the venoms of Viperidae include snake venom metalloprotease (SVMP), phospholipase A<sub>2</sub> (PLA<sub>2</sub>), and snake venom serine protease (SVSP). The secondary protein families include disintegrins (DIS), cysteine-rich secretory protein (CRISP), C-type lectins (CTL), L-amino acid oxidase (LAAO), kunitz peptides (KUN), and natriuretic peptides (NP).<sup>17</sup> Two snake venom vascular apoptosis-

inducing proteins (VAPs), VAP1 and VAP2, belonging to the SVMP family, have been postulated to be responsible for CLS.<sup>2</sup> Vascular endothelial growth factor, which injures endothelium, augments permeability, causes edema, and hypotension, has been indicated in the pathogenesis of CLS.<sup>18</sup>

Capillary leak syndrome can occur in spite of receiving adequate doses of ASV.<sup>2</sup> Antisnake venom and its neutralizing effect on CLS manifestations have been studied in a mouse model. It was observed that ASV has limited efficacy in neutralizing the CLS effect.<sup>19</sup> CLS has been identified as associated with increased mortality in adults and children with snakebite envenoming. The presence of CLS signs has been described as one of the seven admission clinical parameters that predict mortality in patients with viper envenoming in India.<sup>20</sup>

In India, CLS as a toxidrome due to snakebite envenoming has not been described from areas other than southern India. The likely reason could be that it is less recognized, overlooked, and underreported. The documentation of CLS among patients with hemotoxic snake envenoming in our study demonstrates that Russell's viper venom composition variability does not exist between the northern Himalayan state of Himachal Pradesh and the southern Indian state species. The current study further emphasizes that the venom components of the Russell's viper responsible for CLS are not unique to southern India. These

**Table 3:** Comparison of demographic, clinical features, and investigations in patients with and without CLS

Parameter	CLS absent (n = 50)	CLS present (n = 12)	p-value
Sex distribution			
Male	31	4	0.07
Female	19	8	
Age (years)	41.60 ± 16.1	50.08 ± 13.3	0.49
Median (IQR) time duration of snakebite to admission (hours)	4 (2–6)	13 (5–36)	0.01
Tourniquet applied			
Yes	35	10	0.35
No	15	2	
Median (IQR) time duration of tourniquet application (minutes)	25 (0–60)	42 (12–72)	0.31
Periorbital puffiness	3	12	0.02
Hypoalbuminemia	22	12	0.00
Pleural effusion	3	11	0.04
Median (IQR) duration for which 20-min WBCT remained positive (hours)	12 (6–24)	24 (15–27)	0.01
Total ASV dose received (mL)			
100	11	0	0.07
200	17	3	0.54
250	1	1	0.26
300	21	8	0.12
Median (IQR) duration of admission (days)	4 (3–4)	8 (4–12)	0.00
Hemoglobin (gm/dL)	11 ± 1	8.5 ± 3	0.00
TLC (per µL)	13682 ± 4110	15935 ± 8012	0.17
Platelet (per µL)	92960 ± 39301	61833 ± 27859	0.01
Urea (IQR), mg/dL	36 (26–48)	103 (83–141)	0.00
Creatinine (IQR), mg/dL	1 (0.7–1.4)	6.1 (3.4–7.2)	0.00
AST (IQR), U/L	52 (36–90)	111 (47–320)	0.05
ALT (IQR), U/L	30 (21.5–62.5)	51 (33.5–200)	0.01
ALP (IQR), U/L	103 (83.5–117)	101 (84–107)	0.83
S. albumin (gm/dL)	3.5 ± 0.5	3 ± 0.2	0.00
LDH (IQR), U/L	431 (329–639)	1995 (907–1995)	0.00
Total CPK (µg/L)	234 (129–547)	434 (312–576)	0.27
Uric acid (mg/dL)	5.8 ± 1.4	6.8 ± 2.8	0.09
TMA	1	3	0.01
Outcome			
Improved	47	6	0.00
Referred out	2	5	0.00
Expired	1	1	0.35

n, number; IQR, interquartile range; TLC, total leukocyte count; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; CPK, creatine phosphokinase

observations may help formulate the state action plan envisaged under the National Action Plan for Prevention and Control of Snakebite Envenoming (NAPSE) in India, which aims to reduce disability and mortality due to snakebite by 50% before 2030.

## LIMITATIONS

The number of cases included in this study was limited to a single center to derive a reliable conclusion on the epidemiology of Viperidae envenomation in this region. Further, given the low burden, either a single-center, longer study or a diverse-

center study will be more informative. Follow-up of all the patients with CLS could not be established, as five patients were referred for treatment at other centers. Hemotoxic envenoming diagnosis was based on a positive 20-minute WBCT, and the prevalence of VICC or anticoagulant coagulopathy was not estimated in the present study. For snake species identification, immunodiagnostic methods were not used.

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of the snake species and Mr Sushant Sharma for statistical analysis.

## ETHICAL APPROVAL

The Institutional Ethics Committee approved the study vide no. HFW-H DRPGMC/Ethics/2023/016 dated: April 6, 2023.

## CONFLICT OF INTERESTS

None.

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