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Research article

# Viperidae snake envenomation from a highly complex hospital in southwestern Colombia

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ABSTRACT

*Background:* Snake envenomation is a medical condition with high morbidity and mortality in southwestern Colombia.
*Objectives:* To describe the characteristics of the envenomation caused by Viperidae snakes view in a highly complex hospital in Southwestern Colombia.
*Methods:* A cross-sectional study was carried out. Patients treated for Viperidae snake envenomation from 2001 to 2020 in a Hospital Fundación Valle del Lili, Cali, Colombia, were studied.
*Results:* Twenty-eight patients were included. Envenomation was caused by the genera *Bothrops*, *Bothriechis*, *Porthidium,* and *Bothrocophias*. The median age was 37.7 (±20.6), and they were predominantly male (19, 68%). Bites occurred on the upper extremities in 16 (57%) patients. Pain (23, 81%) and edema (22, 78%) were the most common clinical symptoms. Thirteen (46%) patients presented coagulopathy. Prolonged prothrombin and activated partial thromboplastin times were common: (22, 78% and 15, 53%, respectively). Twenty (71%) patients were treated with polyvalent antivenom (median dose of 6 (2–15) vials). The median time between the accident and antivenom administration was 9 h (5.5–17). Door-to-needle time was 37.5 (0–62) min. Eighteen (64%) patients were admitted to the intensive care unit. Three (11%) patients had serum sickness. Seven (25%) developed infectious complications, four (14%) had surgery, one (3%) had compartment syndrome, one (3%) underwent amputation of the affected limb, and one (3%) patient died.
*Conclusions:* Local manifestations and coagulopathy were common clinical features. Polyvalent antivenom was an effective treatment for disease control. Significant complications were associated with delays in seeking medical care.

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## 1. Introduction

Snake envenomation is a significant public health problem worldwide due to its high morbidity and lethality [1]. According to the World Health Organization (WHO), snakebites affect more than 5.4 million people yearly, and snake envenomation occurs in 2.7 million [2]. The overall disease burden of this recently categorized Neglected Tropical Disease (NTD) [3] is high, with mortality rates ranging from 81,000 to 138,000 deaths per-y, and approximately 400,000 people experience permanent disabilities such as amputations and long-term psychological impacts [4,5]. However, these rates may underestimate the disease burden because most snakebites occur in rural areas with underdeveloped healthcare and notification systems [6–8]. Snakebites have been called a disease of poverty, as most cases occur among the world's most impoverished communities with lower socioeconomic status and limited access to education, housing, and high-quality health care [9].

In Latin America, the estimated annual incidence of snakebites is 57,500 per-y, with total mortality of 370 patients (<0.6%) [10]. It is estimated that 5434 snakebite cases occur in Colombia annually, with a national incidence of 10.9 cases per 100,000 citizens. Its highest incidence is in departments such as the Amazon, Orinoquía, Chocó, and Pacific regions. The lethality in Colombia for 2018 was 0.6%, affecting primarily young men and rural area workers [11].

Despite its mandatory notification in Colombia, snakebites are still underreported, as most cases occur in rural areas with limited access to quality health services. In Colombia, there are some case report series regarding the clinical characteristics and complications in patients who suffer from snakebites from different Colombian departments, such as the Amazon, Antioquia, Caldas, Cauca, Chocó, La Guajira, Nariño, Casanare, and Santander. However, there is no information on the behavior of snake envenomation in the Valle del Cauca Department.

This study aims to describe the clinical, demographic, and laboratory features and the treatment and outcomes of patients with Viperidae snake envenomation view in a highly complex hospital in Cali, Valle del Cauca, department in southwestern Colombia.

## 2. Patients and methods

### 2.1. Geographic localization

The Valle del Cauca department is in the torrid equatorial zone of Southwestern Colombia, part of the Andean and Pacific natural regions.

### 2.2. Study design and patients

A cross-sectional study was carried out. We included patients who suffered Viperidae snake envenomation and attended Fundación Valle del Lili Hospital, Cali, Colombia, between 2001 and 2020. Electronic clinical records were reviewed to obtain the data. Demographic, clinical, laboratory, treatment, and patient outcomes were analyzed. In these records clinical and the snake photography were collected. The corpses of the snakes were deposited in a file that is kept in our laboratory with data on species classification and identification of the victims. Some patients did not bring the specimen or photograph of the snake and the envenomation is classified based on the evaluation of the geographical origin of the patient, the description of the snake by the patient and the clinical characteristics of the envenomation.

The diagnosis of coagulopathy was assigned when testing of conventional blood tests such as prothrombin time (PT) and activated partial thromboplastin time (aPTT) were prolonged, and fibrinogen was consumed (below 65.5 mg/dL).

The severity of snake envenomation classification, which helps decide the dose of antivenom to use, was done as follows: Grade 0, patient with no local or systemic signs or symptoms, no antivenom is needed; Grade I, local edema of no more than 20 cm, local moderate pain, no signs or symptoms of systemic compromise, the use of 1–2 vials of antivenom is needed; Grade II, local edema larger than 20 cm, local pain and bleeding, mild systemic symptoms, mild alteration in coagulation test results, the use of 3–5 vials of antivenom is needed; Grade III, severe local and systemic symptoms, vomiting, diarrhea, systemic bleeding, abnormal renal function, and coagulation test results are present, the use of 6–9 vials of antivenom is needed; Grade IV, edema with rapid proximal extension to the trunk, oliguria, anuria, and shock are present, and the use of 10–15 vials of antivenom is needed [12].

### 2.3. Snake species identification

Snake identification was performed by expert herpetologists (authors of this paper: FCH, SCV).

### 2.4. Antivenom treatment

Treatment is based on polyvalent antivenom (Laboratorios Probiol, Bogotá, Colombia) that contained 10 mL of equine polyvalent antivenom, which neutralized at least 25, 10, and 5 mg of the venom of *B atrox/asper*, *Crotalus durissus*, and *Lachesis muta*, respectively. The number of vials is calculated according to the severity classification. Additional doses of antivenom (between 2 and 4 vials) are indicated every 6 h until the PT, aPTT, and fibrinogen tests normalize.

### 2.5. Statistical analysis

Data were analyzed using Stata® version 14 (StataCorp, College Station, TX, USA). Categorical variables are expressed as absolute and relative frequencies. The Shapiro-Wilk test was used to verify whether the variables presented a normal distribution. According to these results, data are presented as the mean ± standard deviation or medians with interquartile ranges.

## 3. Results

### 3.1. Patients' general and clinical characteristics

Between 2001 and 2020, 36 patients were admitted with snake envenomation; 28 (78%) were caused by Viperidae snakes; 8 cases were caused by Elapidae snakes. The patients' median age at inclusion was 37.7 (±20.6), primarily male (N = 19, 68%). Sixteen (57%) patients were bitten on the upper extremities, 11 (39%) on the lower extremities, and one (3%) on the head. Snakebites occurred in rural areas, and the main activities that were being performed by the patients when bitten were farming (6, 21%), trekking (4, 14%), and working in a rural field as a professional soldier (2, 7%).

The most common clinical symptoms were local tissue symptoms, manifested by pain at the wound site in 23 (81%) patients, and local signs, such as redness, edema, necrosis, and blistering (Fig. 1a), in more than two-thirds (22, 78%) of the cohort.

These patients' most common systemic findings were coagulopathy (13, 46%) (Fig. 1b) and myotoxicity. A patient (3%), after the development and resolution of coagulopathy, presented with atypical hemolytic uremic syndrome (aHUS). Acute kidney injury (AKI) was present in five (17%) patients.

Regarding laboratory evaluations, most patients had leukocytosis with a mean white blood cell count of 11917/mm$^3$ (±4132). Most patients presented neutrophilia with a mean absolute neutrophil count of 9190/mm$^3$ (±4075). Clotting parameter abnormalities were common in this study, as 22 (78%) patients had a prolonged PT, 15 (53%) had an aPTT prolonged, and five (18%) patients had a positive D-dimer. Fibrinogen consumption was also seen, as the median fibrinogen level was 167 mg/dL (65.5–268.7). The median creatinine level was 0.86 mg/dL (0.7–1); however, patients with AKI had higher values, with a mean creatinine level of 2.3 mg/dL (±1.8).

Regarding the severity classification of envenomation, most patients were classified as having a grade I (8, 28%) or II (10, 36%) type of envenomation. Two (10%) patients were classified as type III, and eight (28%) had type IV envenomation.

### 3.2. Snake species identification

Snake species identification that caused the envenomation was performed in 20/28 (71%) cases by photographs or by directly evaluating the living or dead specimen. A broader characterization of the snake taxonomy is shown in Table 1.


**Fig. 1.** **(a)** Case of a patient bitten by *B. rhombeatus* on the right hand is presented; there was edema and blisters, **(b)** case of a patient bitten by *B. punctatus* and the development of severe coagulopathy; bleeding is observed in the oral mucosa, **(c)** patient who required fasciotomy in the right thigh, **(d)** patient who required amputation of his left lower limb.

**Table 1**
Species of snake identified in the present case series.

| Snakes' type | | N = 28, 100% | |
|---|---|---|---|
| Genus | | **Species** | |
| *Bothrops* | 13 | *B. asper* | 5 (17.8) |
| | | *B. rhombeatus* | 5 (17.8) |
| | | *B. punctatus* | 3 (10.7) |
| *Bothriechis* | 3 | *B. schlegelii* | 3 (10.7) |
| *Porthidium* | 2 | *P. lansbergii* | 1 (3.6) |
| | | *P. nassutum* | 1 (3.6) |
| *Bothrocophias* | 2 | *B. colombianus* | 1 (3.6) |
| | | *B. myersi* | 1 (3.6) |
| *Unidentified species* | 8 | | 8 (28.6) |

### 3.3. Treatment

Concerning treatment, 10 (36%) patients received nonhospital care from local healers, mainly empirical and traditional measures such as herbal plasters (2, 7%), tourniquets (2, 7%), and oral suction of the venom (1, 3%). The lead measures provided by the initial primary health care facility before admission to our hospital were antivenom administration (11, 39%), use of intravenous antibiotics (6, 21%), tetanus prophylaxis (3, 11%), and pain management (2, 7%). Once the patient is hospitalized in our institution, the degree of envenomation is classified to define whether the antivenom is administered and in what dose. Some patients had already received antivenom in other hospitals; the number of vials was noted. If patients still have active envenomating, the additional vials that were needed were applied. 18 patients (64%) received polyvalent antivenom. The median number of vials administered was 6 (2–15). The median time between the accident and antivenom administration was 9 h (5.5–17); data that is independent of whether the antivenom was administered before or after being admitted. Our institution's door-to-needle time for antivenom administration was 37.5 min (0-62). The mean length of hospital stay was 3.5 days (±18.5). Eighteen (64%) patients required admission to the intensive care unit (ICU), and the median length of ICU stay was 2.5 days (1–7). Vasopressor support was needed in four (14%) of them; two (7%) patients required mechanical ventilation, and renal replacement therapy was given to 2 patients (7%).

### 3.4. Outcomes

Three (11%) patients presented adverse effects to antivenom administration (serum sickness) and were successfully treated with glucocorticoids. Seven (25%) patients developed local infectious complications: Four had cellulitis, and three multiple abscesses. The bacteria isolated from abscesses were *Morganella morganii* (2, 7%) and *Klebsiella* spp. (1, 3%). Compartment syndrome developed in one (3%) patient. Four (14%) patients underwent a surgical procedure due to envenomation complications, two (7%) required surgical washout and debridement of the wound, one (3%) patient required a fasciotomy (Fig. 1c), and one needed amputation of the affected limb (3%) (Fig. 1d). These last two patients received the antivenom 18 h after the bite.

Mortality occurred in a 36 years-old woman bitten on her left foot by a *Bothrops asper* snake, who developed a severe coagulopathy manifested by hypofibrinogenemia, prolonged PT and aPTT, local hemorrhagic blisters, bleeding in the oral mucosa. The time between envenoming and initiation of antivenin was approximately 22 h. Four days after bite and established treatment suffered a devastating brainstem ischemic stroke. She dies on the third day of admission.

### 3.5. Comparison with other Colombian case series

This work is the first report of a case series of Viperidae snake envenomation within the department of Valle del Cauca in Southwestern Colombia. Several Colombian series have been reported from other departments, such as Amazonas [13], Antioquia and Chocó [14], Caldas [12], Cauca [15], La Guajira [16], Nariño [17], Orinoquia [18], and Santander [19]. A comparison between the demographic characteristics and clinical features of patients with envenomation caused by Viperidae snakes between our series and different Colombian cohorts from other regions is shown in Table 2. The geographic location of the available case series is shown in Fig. 2.

## 4. Discussion

This study describes the epidemiological, clinical, and laboratory characteristics of 28 patients admitted to a high-complexity referral health center in the department of Valle del Cauca in Cali, Southwest Colombia, with Viperidae snake envenomation.

Patients in this study were primarily young (median age of 37 years old) and male, which is supported by global literature where snakebites mainly occur in males of economically productive age [20]. The primary location of the bite site was in the upper extremities while conducting activities related to agriculture; this differs from other Colombian series, where it was more frequent in the lower limbs. *Bothriechis schlegelii* is arboreal and othe especies as *B. asper and B. punctatus* are semi-arboreal which may explain the cases of bites in the upper limbs, in addition to workers rural people put their hands to the ground in certain activities.

The most common clinical characteristics found in this cohort were pain and edema. Coagulopathy was present in many patients,

**Table 2**
Demographic and clinical features of patients with Viperidae snakebites in different Colombian cohorts.

| References | Present study | Silva JJ 1989 Ref. 13 | Otero R. 1992 Ref. 14 | Cañas CA et al. 1991 Ref. 12 | Sevilla-Sánchez MJ et al. 2021 Ref. 15 | Múnera G. et al. La 2010 Ref. 15 | Sevilla et al. 2019 Ref. 17 | Pineda D et al. 2002 Ref. 18 | Badillo et al. 1989 Ref. 19 |
|---|---|---|---|---|---|---|---|---|---|
| Department | **Valle del Cauca** | **Amazonas** | **Antioquia y Chocó** | **Caldas** | **Cauca** | **Guajira** | **Nariño** | **Casanare** | **Santander** |
| Patients included | 28 | 279 | 524 | 88 | 1653 | 21 | 1110 | 56 | 55 |
| Crotalinae Envenomation (%) | 100 | 94 | 89 | 100 | 79 | 62 | 48 | 100 | 92 |
| Male (%) | 68 | 57 | 76 | 82 | 68 | 95 | 70 | 54 | 69 |
| Age | 38 (20.6) * | 15-44 (63) + | 15-44 (54) + | 28 (3–69) ** | 15-44 (48) + | 19 (1–52) ** | 33.1 (18) * | 15-44 (41%) + | 19.8 (3–58) ** |
| Bite in upper extremities (%) | 57 | 12 | 27 | | 51 | 9 | 47 | 82 | ND |
| Bite in lower extremities (%) | 39 | 82 | 71 | 79 | 43 | 90 | 46 | 16 | 80 |
| Grade of envenomation rowhead | | | | | | | | | |
| Mild N (%) | 18 (64) | ND | 216 (41) | 32(36) | 841 (51) | 8 (38) | 647 (58) | 17 (31) | 7 (14) |
| Moderate N (%) | 2 (10) | ND | 245 (47) | 40 (45) | 480 (29) | 6 (29) | 352 (32) | 19 (35) | 38 (76) |
| Severe N (%) | 8 (28) | ND | 22 (9) | 16 (18) | 175 (10) | 6 (29) | 96 (9) | 14 (25) | 5 (10) |
| Mortality N (%) | 1 (3) | 1(0.5) | 3 (0.5) | 8 (9) | ND | 2 (8) | 28 (0.6) | 1 (2) | 1 (2) |
| Symptoms and signs | **Manifestation N (%)** | | | | | | | | |
| Local Tissue | Pain | 23 (82%) | 211 (97) | 88 (100) | ND | 18 (88) | 421 (79) | 56 (100) | 50 (100) |
| | Edema (without reference to severity | 22 (78) | 211 (97) | 88 (100) | ND | 18 (88) | 389 (75) | ND | 50 (100) |
| | Ecchymoses | 6 (21) | ND | 28 (32) | ND | ND | 53 (10) | ND | 22 (45) |
| | Blistering | 3 (11) | 27 (12) | 28 (32) | ND | 6 (29) | 36 (7) | ND | 11 (22) |
| | Tissue bleeding | 3 (11) | 211 (97) | 28 (32) | ND | ND | ND | 33 (60) | 28 (56) |
| | Hematoma | 2 (7) | ND | ND | ND | ND | 34 (6) | ND | ND |
| | Tissue necrosis | 1 (3) | 20 (9) | 22 (25) | ND | 3 (14) | 20 (4) | ND | 7 (14) |
| Unspecific symptoms | Fever | 3 (11) | 44 (20) | 20 (25) | ND | 1 (5) | 0 | ND | 9 (18) |
| | Vomiting | 2 (7) | 61 (28) | 20 (25) | ND | 1 (5) | 89 (17) | ND | 20 (40) |
| | Headache | 1 (3) | 61 (28) | 20 (25) | ND | ND | ND | ND | 10 (21) |
| | Malaise | 1 (3) | ND | 20 (25) | ND | ND | ND | ND | ND |
| | Abdominal Pain | ND | ND | ND | ND | ND | 38 (7) | ND | ND |
| | Diarrhea | ND | ND | ND | ND | ND | 9 (2) | ND | ND |
| | Myalgias | ND | ND | ND | ND | ND | ND | ND | ND |
| Coagulopathy | Hemorrhagic coagulopathy | 13 (46) | ND | ND | ND | 7 (33) | ND | ND | ND |
| | Hematemesis | 3 (11) | ND | ND | ND | ND | 27 (5) | ND | ND |
| | Hematuria | 2 (7) | 28 (13) | 14 (16) | ND | ND | 24 (4) | ND | 3 (6) |
| | Gingival bleeding | 2 (7) | 50 (23) | 16 (18) | ND | 3 (12) | 46 (9) | 15 (28) | ND |
| | Upper gastrointestinal bleeding | 2 (7) | 26 (12) | ND | ND | ND | 4 (0.7) | ND | 5 (10) |
| | Intracranial hemorrhage | ND | ND | 1 (2.2) | ND | ND | 3 (0.5) | ND | 3 (6) |
| Acute Kidney Injury | | 5 (18) | 23 (11) | 6 (13) | ND | ND | 0 | ND | ND |

*Mean (SD). **Median (IQR). + Interval (%).
ND, no data.

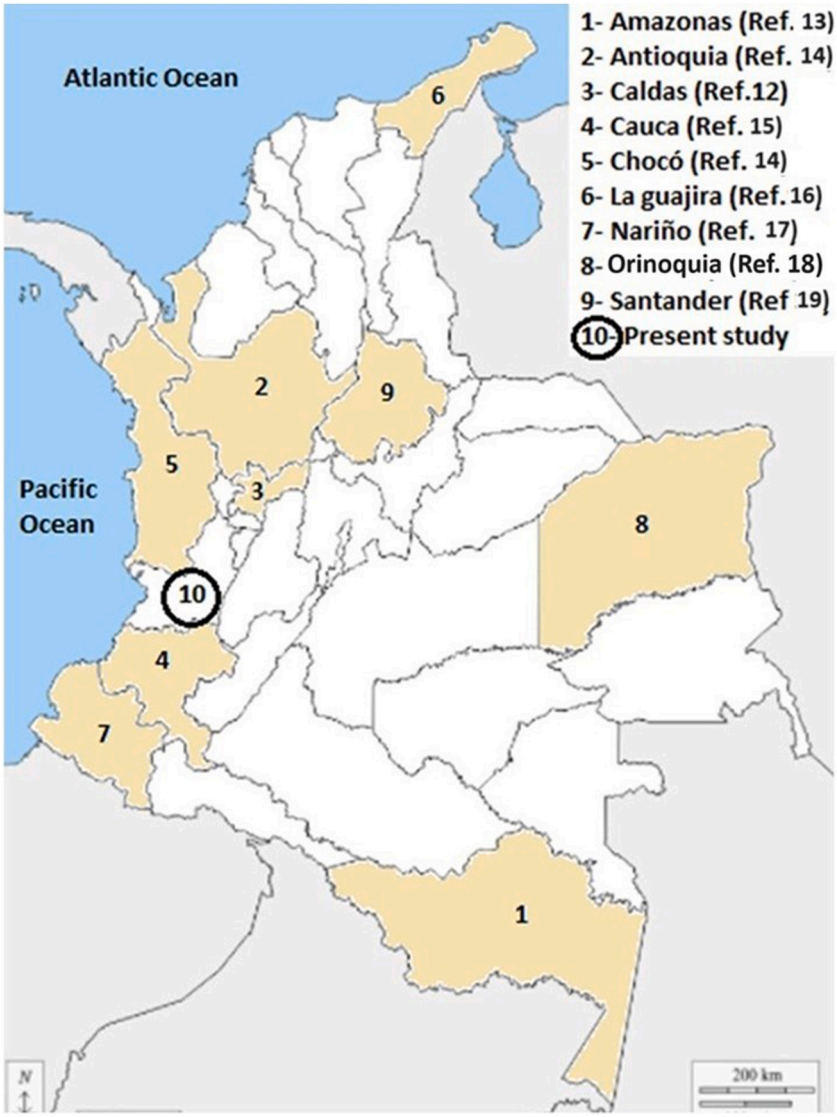


**Fig. 2.** Map of Colombia showing the division by region. The regions where there are reported case series of patients with envenomation caused by Crotalinae snakes are indicated. The case series are numbered in alphabetical order, and the number indicates their geographic location. The present case series is number 10, highlighted with a circle; the area of Valle del Cauca can be seen.

supporting the statement in some studies that hematologic abnormalities are one of the most common effects of snake envenomation worldwide [21].

Colombia is a Latin American country characterized by its richness in flora and fauna with a broad spectrum of biodiversity within its 32 regions or departments. Three hundred and seventeen species of snakes are found in Colombia, and at least 51 (17%) of them are venomous. Three mountain ranges cross the Colombian territory; the largest population of snakes is found in the areas with the lowest altitude gradient. The Amazonas and Chocó regions have the highest snake density; however, the occurrence of envenomation is relatively low due to their low population index [12].

Three snake families are medically relevant in our country: the Viperidae, Elapidae, and Colubridae. The Viperidae family includes snakes from the genus *Bothrops, Bothriopsis, Bothrocophias, Bothriechis, Crotalus, Lachesis*, and *Porthidium* [22]. In Colombia, they account for approximately 83% of all reported snakebite envenomation [23]. These data are consistent with our findings, as 78% of the snakebites in our cohort were secondary to snakes from the Viperidae Family.

Viperidae snake envenomation is known to produce both local and systemic effects. Our findings agree with those described in the global medical literature, and other Colombian case series in which immediate radiating wound pain is the main clinical symptom most patients report, followed by rapidly progressing proximal edema and erythema [24]. Local bleeding, blistering, and ecchymosis are common, as well as tissue necrosis and secondary infection [25]. Crotalinae snake envenomation may produce severe coagulopathic disorders, leading to early thrombosis in some cases [26] and a bleeding tendency minutes after the bite in most cases because

clotting factors are rapidly consumed. Clotting times are prolonged, hypofibrinogenemia develops, and D-dimer increases [27]. In the specific case of snakes of the genus *Bothrops*, prothrombin activators [28,29], Factor X activators [30], and thrombin-like enzymes [31] have been identified. Like thrombin, thrombin-like enzymes share the property of the transition of fibrinogen to fibrin. Nevertheless, they do not activate factor XIII, which is responsible for stabilizing fibrin clotting and thus leads to hemorrhagic coagulopathy. One patient, after the development and resolution of coagulopathy, presented with atypical hemolytic uremic syndrome (aHUS) (this case was previously reported) [32]. AKI can be present in approximately 15% of the cases of Crotalinae envenomation [33]; we found that 17% of our cohort presented with this complication.

Antivenom remains the cornerstone of treatment. Education campaigns at the local level have reduced the door-to-needle time of its application with respect to the last decade of the twentieth century. Previously, this time was approximately 4 h [12]; now, we are approaching a half-hour interval. Only 10% of our cohort showed adverse effects to antivenom administration, which is an expected rate, as antivenom administration causes adverse effects from 10% up to 50% of the time [14]. Other common complications were infectious-related complications and compartment syndrome, like other series [12]. The patient who required amputation as well as the patient who died, the cause of thier unfortunate outcome was associated with the delay in the application of the antivenom, which began almost a day after the bite.

In Colombia, two commercial antivenoms are available; one produced by INS (Instituto Nacional de Salud), another by Laboratorios Probiol generated from plasma of hyperimmunized horses with mixtures of venoms from *B. asper, B. atrox and Crotalus dusrissus cumanensis;* Laboratorios Probiol additionally includes venom of *Lachesis muta* in the immunization mixture. Mora-Obando D et al. conducted a study based in third-generation antivenomics, to demonstrate the neutralizing effectiveness of several antivenoms available in Latin America including INS and Laboratorios Probiol polyvalent antivenoms. The authors showed that the cross-immunorecognizing capacity and In vivo neutralization assays of the lethal, hemorrhagic, coagulant, defibrinogenating, myotoxic, edematogenic, indirect hemolytic, and proteolytic activities against the individual components of venoms of three *B. asper* lineages, *B. ayerbei* and *B. rhombeatus*, were equally effective [34]. In our institution, the antivenom of Laboratorios Probiol is used purely as a condition of commercial facilities. Historically it has been effective in the treatment of our patients. Both antivenoms are used in our geographic region included Hospital Universitario del Valle.

In the Valle del Cauca department, more information on the characterization of the clinical behavior of snakebite envenomation is essential. Some clinical syndromes have been preliminarily characterized based on the species that caused the envenomation [35].

The limitations of the study are that it was carried out in a single institution and that it had a low number of cases. In eight of the patients (28.6% of the series) included, the snake was not identified and its inclusion in the study was based on geographical aspects of origin, clinical characteristics of the envenomation and information given by the patients regarding the characteristics of the animal (including local names).

In conclusion, this study describes the clinical behavior of envenomation by Viperidae snakes in the Valle del Cauca department, Southwest Colombia. Most envenomation causes were secondary to *Bothrops asper* and *Bothrops rhombeatus* species bites. Most snakebites occurred in males, and their anatomic location was in the upper extremities. Severe complications were due to a delay in seeking medical attention and application of antivenoms. However, educational campaigns at the local level have reduced the door-to-needle time of its application in comparison to the last decade of the twentieth century.

## Ethical approval

This study was approved by the Fundación Valle del Lili's Ethics Committee, with study protocol number #1694.

## Data availability statement

The data that support the findings of this study are available from the corresponding author CAC, upon reasonable request.

## CRediT authorship contribution statement

**Valeria Erazo-Martínez:** Writing – original draft, Validation, Supervision, Methodology, Formal analysis, Conceptualization. **Iván Posso-Osorio:** Writing – original draft, Supervision, Methodology, Investigation, Conceptualization. **Ingrid Ruiz-Ordoñez:** Writing – original draft, Methodology, Formal analysis. **Fernando Castro-Herrera:** Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Santiago Castaño-Valencia:** Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Tatiana Delgado-Mora:** Methodology, Investigation, Data curation, Conceptualization. **Carlos A. Cañas:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Investigation, Formal analysis, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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