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## EVALUATION OF THE SNAKEBITE SEVERITY IN THE BRAZILIAN MIDWEST

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### ABSTRACT

Snakebites are of important public health concern as they can progress in severity and they may cause death, especially in populations with low socioeconomic status or in rural areas of tropical countries. In this retrospective cross-sectional study, we evaluated the clinical-epidemiological profiles of patients admitted for snakebites envenoming at a Reference Hospital in Goiás State, Brazil, from January 2018 to November 2019 with criteria and definitions for venomous accidents notified by the Epidemiological Surveillance Center. Of 326 reported cases, 268 (82.2%) involved *Bothrops*, 56 (17.9%) involved *Crotalus*, and 1 (0.3%) involved an elapid. The remaining case (0.3%) was caused by an unidentified snake, as the clinical signs were suggestive of both *Bothrops* and *Crotalus* envenomation and the patient received bivalent antivenom serum. Most snakebites occurred in men (n= 252, 77%) and in individuals from rural areas (n= 215, 65.9%). Pain occurred in 315 (96.9%) patients and edema in 274 (84.3%), being more common in the bothropic accidents. In the crotalic accidents, pain occurred in 50 (89.3%) patients and edema in 24 (44.9%). The snakebite severity was considered mild in 107 (32.8%), moderate in 129 (39.8%), and severe in 90 (27.6%) patients. Acute renal injury was the most common systemic complication, occurring in 64 patients (19.9%), while secondary infection was the most important local complication, occurring in 155 (47.5%) patients. Most cases were classified as moderate or severe, probably because our tertiary level hospital service handles with more complex cases. Additionally, a significant number of crotalic accidents had a local presentation, indicating that the venom of snakes in the region has a particular composition.

KEY WORDS: Ophidian envenomation; *Crotalus*; *Bothrops*; secondary infection.

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## INTRODUCTION

Snakebites are a serious public health problem, especially in tropical countries, with approximately 2.7 million annual accidents worldwide (Willians et al., 2019; Ferreira et al., 2020). Although intertropical America contributes significantly to this incidence, the related clinical and epidemiological data are fragmented, and the Notifiable Diseases Information System (SINAN) since reporting these cases to the Brazilian Ministry of Health was only implemented in 2001 (Chippaux, 2017). The main venomous species that cause snakebites in Brazil are those of the genera *Bothrops* (jararaca, 87% of the cases), *Crotalus* (rattlesnake, 9%), *Lachesis* (bushmaster, 3%), and *Micrurus* (coral snake, 1%), with crotalic accidents tending to be more predominant in regions of the Cerrado biome (Ferreira et al., 2020; Matos & Ignoti, 2020).

Snakebite complications are diverse and they include extensive necrosis by direct action of the venom, secondary infections, sepsis, shock, renal, cardiac, and muscle damage, which increase the morbidity rate (Ferreira et al., 2020; FUNASA, 2001). The severity of the case will depend on the type of snake, the amount of venom inoculated, access to the health care system, and the administration of the correct treatment (Ferreira et al., 2020).

In addition, epidemiological evaluation studies are essential, providing descriptive information about the characteristics and prognosis of snakebites in Brazil. The goal of this study was to determine both, the regional epidemiology of snakebites, and their severity in order to guide the conception of strategies to prevent envenomation and its complications.

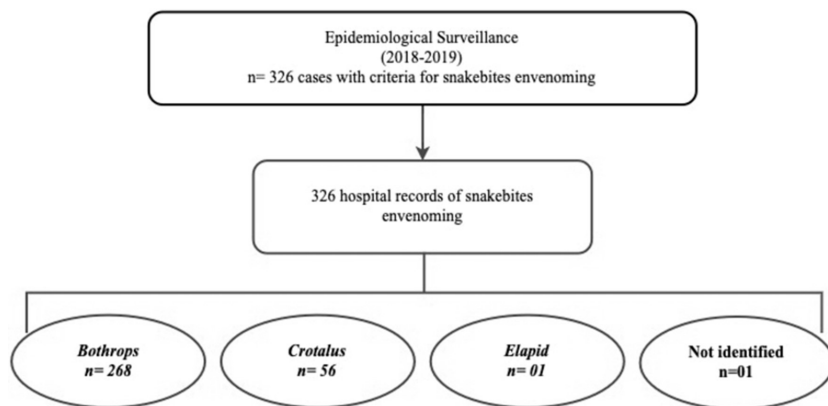
## METHODS

### *Study design*

This was a retrospective and descriptive study of patients treated for snakebites at the Hospital for Tropical Diseases (HDT), in Goiânia, Goiás, Brazil.

We selected the cases from the notification records of the Hospital Center Epidemiological Surveillance, which actively searches for all accidents with venomous animals. In our routine, the diagnosis and classification of snakebites are frequently performed considering the clinical and epidemiological manifestations reported by the victims. Identifying venomous snake species is not a standard procedure due to the risks of trying to capture, transport, or manipulate these animals. Besides, wildlife conservation laws for animals in Brazil discourage people from killing or capturing them. According to the severity of the clinical manifestations presented by the victims, the accidents were classified and treated as mild, moderate, and severe, following

the Brazilian Health Ministry recommendations (FUNASA, 2001). We excluded accidents involving non-venomous snakes, since we aimed to evaluate the clinical and epidemiological characteristics of casualties of the venomous snake group (Figure 1).



*Figure 1.* Flowchart with the criteria of the selected snakebites cases selected in the Hospital for Tropical Diseases, Goiás, Brazil from January 2018 to November 2019.

The following variables were evaluated: the patient's age, sex, city of origin, work status, geographical area where the bite occurred, type of snake involved, anatomical region affected, time elapsed between the bite and medical care, clinical presentation, classification of severity, number of antivenom ampoules administered, need for extra ampoules, local and systemic complications (kidney injury, secondary infection, and compartment syndrome) defined from medical records and imaging tests, need for intensive care unit (ICU) admission, need for hemodialysis, and outcome.

#### *Ethical considerations*

This study was approved by the HDT Ethics Committee (CAE 26164619.4.0000.0034). It was not necessary to obtain formal consent of patients, as it is a retrospective study without any direct contact with the patients. All researchers that had access to the data vowed to keep the patient's identities anonymous.

## Statistical analysis

The data were recorded on an Excel® spreadsheet and analyzed using STATA statistical software (StataCorp, College Station, TX, USA). Data distribution was verified using histograms. Categories were described as absolute and relative frequencies, and numerical variables are presented as the mean and standard deviation or the median and interquartile range (IQR) where applicable. The map was made on R Studio software, the registries about accident location, date of occurrence, type of serpent and State of residence were obtained on medical records. The geobr package provides access to official spatial data sets from Brazil and, the ggplot2 package to construct the map.

## RESULTS

In total, 326 cases of venomous snakebites were evaluated. Figure 2 shows the number of cases per month from the years of 2018 and 2019. In general, the highest number of snakebite occurred in the first half of both years, with a peak of 45 cases in February and a decline in the period from March to July, followed by 18 and 21 cases over the next three months until a further increase to 25 events in November.

Regarding the distribution of the various snake types by geographic region, there was a higher occurrence of bothropic and crotalic accidents in southern Goiás, overlapping of bothropic and crotalic accidents in the Central region, and a dispersion of snake types in the North, with only one case involving an elapid in the Central region in the city of Anicuns (Figure 3). The age of the patients ranged from 1 to 93 years, with a median of 38 years (IQR, 23–54 years). Most of the study sample comprised of young male adults (n= 252, 77%). The accidents occurred predominantly in rural areas (n= 215, 65.9%), being associated with work activities in 45 (13%) cases (Table 1).

Most accidents were attributed to the genus *Bothrops* (268, 82.2%), whereas the genus *Crotalus* contributed to 56 cases (17.2%), and there was only one case (0.3%) involving an elapid. The lower limbs were the most affected (totaling 76.4%), with 149 (45.7%) cases occurring on the feet and 100 (30.7%) cases on the legs. Most of the patients (249, 76.4%) received specialized medical care within 12 hours after the accident, with the majority of bites being classified as moderate in severity (n= 129, 39.6%) (Table 1).

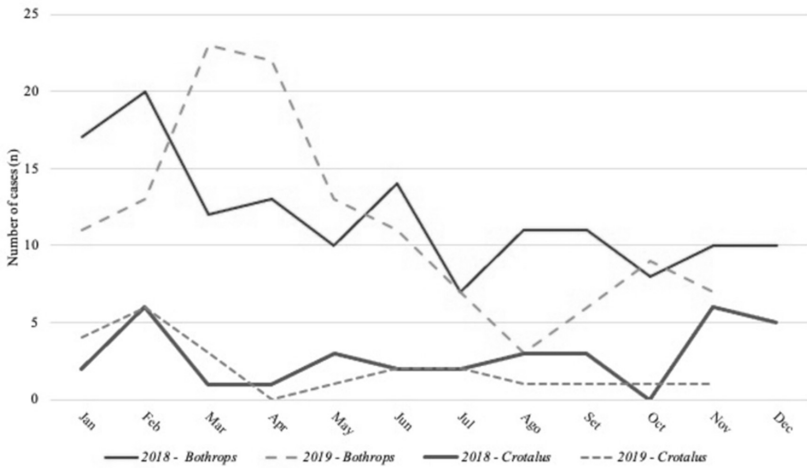


Figure 2. Monthly numbers of snakebite cases treated at the Hospital for Tropical Diseases, Goiás, Brazil from January 2018 to November 2019.

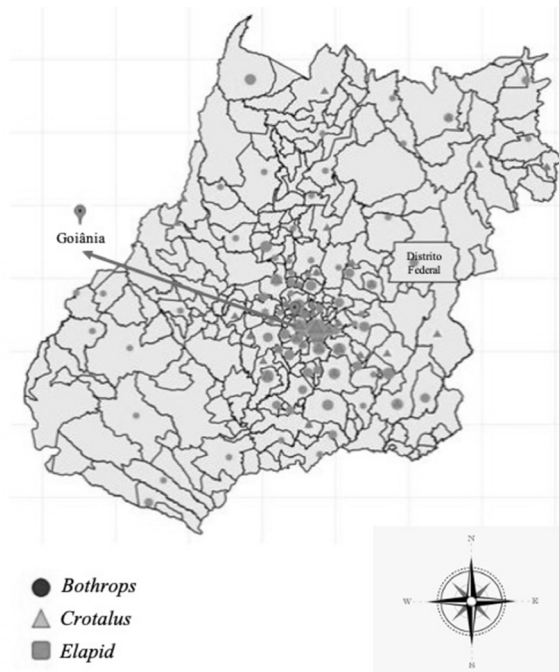


Figure 3. Map of the State of Goiás (Brazil) showing the distribution of snakebite cases by snake type. Hospital for Tropical Diseases, Goiás, Brazil from January 2018 to November 2019.

*Table 1.* Sociodemographic characteristics of 326 patients treated for snakebites at the Hospital for Tropical Diseases, Goiás, Brazil, from 2018 to 2019.

	n	%
Median age, years (interquartile range)	38 (23–54)	
<18 years	56	17.1
18–60 years	218	66.8
≥60 years	52	15.9
Sex		
Men	252	77.3
Women	74	22.7
Race		
Brown	282	86.5
White	23	7.1
Black	10	3.1
Asian	8	2.4
Ignored	3	0.9
Education		
Illiterate	10	3.1
1st–4th grade of Elementary School	56	17.2
5th–8th grade of Elementary School	64	19.6
High school	61	18.7
College education	11	3.4
Ignored	110	33.7
Not applicable	14	4.3
Zone of occurrence		
Rural	215	65.9
Urban	77	23.6
Peri-urban	6	1.8
Ignored	28	8.6
Work related	45	13.8
Snakebite type		
Bothropic	268	82.2
Crotalic	56	17.2
Elapid	1	0.3
Indeterminate	1	0.3
Bite site		
Head	1	0.31
Arm	8	2.46

Hand	66	20.2
Leg	100	30.6
Foot	149	45.7
Ignored	2	0.6
Time between snakebite and medical care		
0–1 h	30	9.2
1–3 h	78	23.9
3–6 h	83	25.5
6–12 h	58	17.8
12–24 h	25	7.7
>24 h	51	15.6
Ignored	1	0.3
Severity classification		
Mild	107	32.8
Moderate	129	39.8
Severe	90	27.6

Of the 326 patients, 14 (4.3%) required ICU support, with a median stay of 4 days (IQR, 1–10 days). Pain and edema were present in more than 90% of the bothropic accidents. By contrast, approximately 40% of patients with crotalic bites developed paresthesia and edema and 90% of those individuals also experienced pain. Blisters, necrosis, heat, pruritus, and cyanosis occurred only in the patients bitten by a *Bothrops* species. Neuroparalytic and myelitic presentations occurred predominantly in the patients bitten by a member of the *Crotalus*, whereas bleeding and fever occurred more frequently in the bothropic accidents (Table 2).

Of the 325 patients for which the snake was identified, 64 (19.6%) developed acute kidney injury (documented in the medical records), which was the most common systemic complication. Of those 64 patients, 44 (68.7%) were bitten by a *Bothrops* species and 20 (31.2%) by a *Crotalus* species. Moreover, 9 (14%) of those 64 patients required hemodialysis during hospitalization, with four of them being from the 44 patients who had bothropic accidents (9%) and five being from the 20 individuals who experienced crotalic accidents (25%).

Of the four *Bothrops*-bitten patients who required hemodialysis, three (75%) received electrolyte and volume control and one (25%) received electrolyte control only. Moreover, two (50%) of those patients recovered renal function during hospitalization whereas the other two (50%) did not. As for the five *Crotalus*-bitten patients who required hemodialysis, four (80%) received electrolyte and volume control and one (20%) needed volume control only. Of these five patients, two (40%) recovered their renal function during hospitalization whereas the other three (60%) did not.

*Table 2.* Characteristics of the clinical presentations on admission and its associated complications according to the snakebite type. Hospital for Tropical Diseases, Goiás, Brazil, from 2018 to 2019.

	Bothropic (n= 268)		Crotalic (n= 56)		Elapid (n= 1)		Total (n= 325*)	
	n	%	n	%	n	%	n	%
<b>Local presentations</b>								
Pain	264	98.5	50	89.3	1	100	315	96.9
Edema	249	92.9	24	42.9	1	100	274	84.3
Ecchymosis	53	19.8	6	10.7	0	0	59	18.2
Erythema	51	19	4	7.1	0	0	55	16.9
Paresthesia	26	9.7	20	35.7	0	0	46	14.2
Blister	29	10.8	0	0	0	0	29	8.9
Bleeding	24	9	2	3.6	0	0	26	8
Necrosis	14	5.2	0	0	0	0	14	4.3
Heat	11	4.1	0	0	0	0	11	3.4
Pruritus	3	1.1	0	0	0	0	3	0.9
Cyanosis	3	1.1	0	0	0	0	3	0.9
<b>Systemic signs and symptoms</b>								
Vagal	72	26.9	17	30.4	1	100	90	27.7
Neuroparalytic	36	13.4	45	80.4	1	100	82	25.2
Myolytic	25	9.3	33	58.9	1	100	59	18.2
Bleeding	16	6	2	3.6	0	0	18	5.5
Fever	13	4.9	1	1.8	0	0	14	4.3
Headache	10	3.7	3	5.4	0	0	13	4
Vertigo	3	1.1	5	8.9	0	0	8	2.5
Dyspnea	2	0.7	4	7.1	1	100	7	2.2
<b>Systemic complications</b>								
Acute kidney injury	44	16.4	20	35.7	0	0	64	19.7
Sepsis	5	1.9	1	1.8	0	0	6	1.8
ARF/APE	3	1.1	2	3.6	0	0	5	1.5
Mechanical ventilation	2	0.7	2	3.6	0	0	4	1.2
Shock	3	1.1	1	1.8	0	0	4	1.2
Myocarditis	0	0.0	2	3.6	0	0	2	0.6
DIC	1	0.4	1	1.8	0	0	2	0.6
PTE	2	0.7	0	0.0	0	0	2	0.6
CHF	0	0.0	1	1.8	0	0	1	0.3
Pericardial effusion	1	0.4	0	0.0	0	0	1	0.3



Inflammatory acute abdomen	1	0.4	0	0.0	0	0	1	0.3
Local complications								
Secondary infection	148	55.2	6	10.7	1	100	155	47.6
Compartment syndrome	57	21.3	2	3.6	0	0	59	18.2
Extensive necrosis	8	3.0	0	0.0	0	0	8	2.5
Monoplegia in the affected limb	0	0.0	1	1.8	1	100	2	0.6
Osteomyelitis	2	0.7	0	0.0	0	0	2	0.6
Amputation of the affected limb	1	0.4	0	0.0	0	0	1	0.3

\*One patient with the snake type classified as indeterminate was excluded from these characterizations

ARF/APE: acute respiratory failure; APE: acute pulmonary edema; CHF: congestive heart failure; DIC: disseminated intravascular coagulation; PTE: pulmonary thromboembolism  
Vasovagal signs: vomit, diarrhea. Neuroparalytic signs: eyelid ptosis, blurred vision. Myolitic signs: myalgia, anemia, dark urine

Myocarditis was a complication found only in the crotalic accidents. By contrast, events such as pulmonary thromboembolism, pericardial effusion, and acute inflammatory abdomen were observed only in cases of bothropic snakebites.

Secondary infection was the most common local complication among all snakebites; however, it occurred predominantly in the bothropic accidents, with two patients progressing to osteomyelitis. Compartment syndrome also occurred more frequently among bothropic accidents (57/268, 21.3%).

All 326 patients received antivenom serotherapy (Table 3). Of these patients, 80 (24.6%) required additional serotherapy, the main reason being reclassification of the case severity or changed clinical presentation with consideration of envenomation by snakes of another genus (Table 3).

Concerning the clinical outcomes, 305 (93%) patients were discharged from the hospital, and 18 (6%) evaded or were transferred. The remaining three (1%) patients died as a result of associated complications, with the *Bothrops*-related lethality rate being 0.7% (2 deaths in 268 cases) and the *Crotalus*-related lethality rate being 1.7% (1 death in 56 cases). The patient who died from the crotalic snakebite had presented to our service 3 hours after the accident, having only local pain and edema, and it was initially treated as a mild bothropic accident. Only 6 hours after the accident, the patient started presenting crotalic characteristic envenomation symptoms and it was considered a severe case, giving several systemic complications. The other two deaths were due to severe bothropic accidents involving compartment syndrome, extensive necrosis of the affected limb, secondary infection, and kidney injury.

Table 3. Antivenom serotherapy. Hospital for Tropical Diseases, Goiás, Brazil, from 2018 to 2019.

	Bothropic (n= 268)		Crotalic (n= 56)		Elapid (n= 1)		Total (n= 325*)	
	n	%	n	%	n	%	n	%
Serotherapy								
Bothropic	253	94.4	4	7.1	0	0	257	79.1
Crotalic	9	3.4	46	82.1	0	0	55	16.9
Bothropic and crotalic	3	1.1	6	10.7	0	0	9	2.8
Elapid	0	0.0	0	0.0	1	0	1	0.3
Ignored	3	1.1	0	0.0	0	0	3	0.9
Number of antivenom ampoules								
Bothropic								
Mild (2 - 4)	119	44.4	-	-	-	-	-	-
Moderate (4 – 8)	108	40.3	-	-	-	-	-	-
Severe (12)	22	8.2	-	-	-	-	-	-
Crotalic								
Mild (5)	-	-	11	19.6	0	0	-	-
Moderate (10)	-	-	21	37.5	0	0	-	-
Severe (20)	-	-	17	30.4	1	100	-	-
Needed extra ampoules	65	24.3	15	26.8	0	0	80	24.6
Additional serotherapy								
Bothropic	59	22.0	2	3.6	0	0	61	18.8
Crotalic	5	1.9	13	23.2	0	0	18	5.5
Bothropic and crotalic	1	0.4	0	0.0	0	0	1	0.3
Number of extra ampoules								
<5	34	12.7	0	0.0	0	0	34	10.5
5–9	24	9.0	6	10.7	0	0	30	9.2
≥10	7	2.6	9	16.1	0	0	16	4.9

\*One patient with the snake type classified as indeterminate was excluded from this profile analysis.

## DISCUSSION

The relatively high incidence of snakebites, which continues to worry health authorities worldwide, is due to several factors, such as the climate and increased anthropogenic activity in rural environments (Ferreira et al., 2020; Pinho et al., 2004). In relation to the climate, there are more snakebite accidents in warmer and rainy areas, which is well described in several Brazilian regions and other tropical countries such as India (Ferreira et al., 2020; Vaivapuri et al., 2013). In the driest periods of the year, the reproductive activity of snakes increases, as does the mammals they feed on (Ferreira et al., 2020; Sazima, 1988; Oliveira et al., 2013). In rural environments, such increased snake activity coincides with increased human activities, favoring snakebites (Ferreira et al., 2020; Oliveira et al., 2013).

Our study was conducted on a reference hospital in Goiânia, Goiás (Brazil). We observed that 25.5% of the casualties were in the metropolitan area of Goiânia (the capital of the Goiás State) and 66% of the events were in rural areas of the State (Figure 3). In Goiás, the period from October to April is usually hot and rainy, with greater agricultural activity, which explains the high number of cases within this period in our study (Figure 2) and it corroborates the findings by Pinho and colleagues (Pinho et al., 2004). Because the Cerrado biome favors the reproduction and survival of species of the genus *Crotalus*, a greater number of crotalic accidents occur in that area rather than in other Brazilian regions (Matos & Ignoti, 2020; Moraes et al., 2021).

The higher frequency of accidents involving young adult men from rural areas corroborates the findings in the literature (FUNASA, 2001; Pinho et al., 2004; Lemos et al., 2009). Men are more likely to be bitten by snakes because of their field of work in the agricultural and the mining sectors (Ferreira et al., 2020; Pinho et al., 2004; Borges et al., 1999; Lemos et al., 2009; Albuquerque et al., 2013).

Crotalic venom is neurotoxic, myotoxic, and a coagulant, with local symptoms of pain and swelling being rare or even nonexistent (FUNASA, 2001). However, this study shows a large number of crotalic accidents that has presented these characteristics. In this regard, another study conducted in the state of Roraima (Brazil), demonstrates the toxic pathophysiology observed in accidents with *Crotalus durissus ruruima* species includes more frequent pain, edema, noncoagulable blood, kidney functional impairment, and dyspnea (Pucca et al., 2021). In addition, some studies conducted on several species of *Crotalus* from different regions of Mexico have shown differences in the venom composition, with greater edema and pain occurring in snakebites in which the venom had a more significant amount of phospholipase A2 and vasoactive peptides, which may be the case in the species from the Cerrado biome (Pozas-Ocamp et al., 2020; Sanchez et al., 2020).

With regard to the systemic complications, although kidney injury is common both in bothropic and crotalic accidents, the mechanism that leads to this complication is different among snake genera. The most common anatomopathological kidney changes in bothropic accidents are tubular necrosis, interstitial nephritis, cortical necrosis, and glomerular alterations (FUNASA, 2001; Pinho et al., 2008; Sgrinoli et al., 2011; Alves et al., 2018). By contrast, the nephropathy related to crotalic bites is more associated with rhabdomyolysis, circulatory shock, disseminated intravascular coagulation, and direct venom toxicity (Daher et al., 2008).

Complications associated with acute kidney injury (e.g., acute pulmonary edema and electrolyte and acid-base disorders refractory to medical treatment; hyperkalemia  $> 6.5$  mEq/L; oliguria (diuresis  $< 0.5$  mL·kg<sup>-1</sup>·h<sup>-1</sup> in 12 hours); anuria; and hypervolemia) should be treated with renal replacement therapy as soon as possible (Bosh & Poch, 2009). Secondary infection is the most common local complication, occurring predominantly in bothropic accidents as a result of intense local inflammation, with a higher risk being associated with the delayed administration of specific antivenom serotherapy (FUNASA, 2001; Silva et al., 2016; Seifert et al., 2022).

With regard to the time elapsed between the accident and serotherapy, the first 6 hours are the most important to avoid complications and mortality (Seifert et al., 2022). Specific antivenom serotherapy is the definitive treatment. As demonstrated in prospective clinical studies, serotherapy is largely responsible for reducing snakebite morbidity and mortality, changing the natural history of the disease (Seifert et al., 2022; Dart & McNally, 2001; Bush et al., 2015). It should be administered after the identification of the accident-causing snake, which is not always easy owing to overlapping clinical presentations in some cases of envenomation and the impossibility of capturing the causative animal. Bivalent serum is available for these situations, and it is also possible to obtain confirmatory laboratory tests of the species in some countries and research centers (Seifert et al., 2022).

In our study, 249 (76.4%) of the patients sought treatment at the hospital service within 12 hours of the accident. Despite this, 219 (67.4%-219) of those cases were classified as moderate and severe, which may be due to the care profile of the hospital, which not only operates as an open-door treatment center for envenomation accidents but also receives an important demand of referral patients from the countryside from Goiás State with serious snakebite complications.

In one case, the patient showed signs of a venomous snakebite but exhibited clinical overlapping of bothropic and crotalic envenomation and neuropathological presentation, with local pain and edema described in the medical record. These led the attending physician to treat the case as an indeterminate snake envenomation and the patient was administered a combined bothropic and crotalic antivenom serum.

The limiting factors of this study include it being a retrospective analysis with secondary data (e.g., the presence of secondary infection) that depended on the subjective analysis of the observer. Thus, prospective and pragmatic studies are necessary for a better evaluation of snakebite complications in the region.

Understanding the epidemiology, clinical presentations, and particularities of the snakebite envenomation in a region is extremely useful for disease prevention and management. The data still indicate a considerable number of unfavorable outcomes for complications such as secondary infection, compartment syndrome, and acute kidney injury. Thus, it is of vital importance to facilitate access to antivenom serotherapy, reinforce preventive measures through public campaigns, and ensure that supplies for hemodialysis and antibiotic therapy are available. Additionally, further studies are needed to elucidate the components of *Crotalus* venom in the region so that patient complaints of pain and edema can be better attended.

#### CONFLICT OF INTEREST

The authors declare that there is no conflict of interest to disclose.

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