Journal of Acute Disease

Original Article

doi: 10.4103/2221-6189.312155 jadweb.org

Early severity predictors of snakebite envenomation in the southern region of Tunisia: a multivariate analysis

Olfa Chakroun-Walha✉, Fadhila Issaoui, Abdennour Nasri, Haifa Bradai, Ayman Farroukh, Rim Karray, Mouna Jerbi, Noureddine Rekik

Emergency Department, University Hospital Habib Bourguiba Sfax, Tunisia

ABSTRACT

Objective: To identify the early predictors of severe envenomation in the southern region of Tunisia.

Methods: It was a retrospective monocentric study including consecutive patients admitted to the emergency department for snakebite envenomation. Snakebite envenomation was defined by a history of snakebite. Predictors of severe envenomation were determined by univariate and multivariate analyses.

Results: Our sample consisted of 109 patients aged 30 (20-44) years with a 1.1:1 sex-ratio (56 males and 53 females). During the 24-hour surveillance period, 25 patients developed severe envenomation (22.9%). The in-hospital mortality rate was 4.6% (n=5). The independent predictors of severe snakebite envenomation were leucocyte count over 11550/mm^3 (*OR*: 18.7, 95% *CI*: 3.3-107.8), creatine kinase over 155 IU/L (*OR*: 6.16, 95% *CI*: 1.1-35.6), and/or tourniquet before arrival to the ED (*OR*: 32.14, 95% *CI*: 3.5-295.9).

Conclusions: This study emphasizes the importance of early evaluation of snakebite envenomation. Further studies are required to approve a severity scale proper to snakebite envenomation in Tunisia.

KEYWORDS: Snakebite envenomation; Outcomes; Emergency Department; Severity predictors; Tunisia

1. Introduction

Snakebite is a serious threat to human health globally[1]. The mortality caused by snake envenomation is high with more than 100 000 deaths annually[2-5]. The most common mode of snake envenomation is biting[6]. Snakebites vary for an asymptomatic dry bite to the severe form. Life-threatening presentations are characterized by shock, and/or hemorrhage, limb necrosis, organ failure, and death[1,3]. In Tunisia, a few experimental studies were conducted, however, epidemiological researches are still rare[5-7]. The historical features, clinical findings, and laboratory test results have different abilities to early predict the outcomes, in part because of the wide number of snake species. Besides, there is still no validated severity scale of snakebite envenomation in Tunisia. Therefore, we aim to identify the predicting factors of the severe form of snakebite envenomation in our region.

2. Materials and methods

2.1. Clinical setting

This is a retrospective study conducted over five years (from January 1st, 2014 to December 31st, 2019). The records of 2016 were not analyzed (missing data). The study population consisted of consecutive patients admitted to the emergency department (ED) for snakebite.

2.2. Inclusion criteria and exclusion criteria

We reviewed all medical records and included consecutive patients who presented with snakebite at the ED. Patients with a history of coagulopathy or antiplatelet administration were excluded. Each time the snakebite envenomation was not clear, the case was excluded. Medical files with missing data were also excluded.

✉To whom correspondence may be addressed. E-mail: chakroun_olfa@medecinesfax.org

How to cite this article: Chakroun-Walha O, Issaoui F, Nasri A, Bradai H, Farroukh A, Karray R, et al. Early severity predictors of snakebite envenomation in the southern region of Tunisia: a multivariate analysis. J Acute Dis 2021; 10(2): 71-77.

Article history: Received 8 December 2020; Revision 19 March 2021; Accepted 23 March 2021; Available online 29 March 2021

2.3. Management protocol in the ED

Following a snakebite, the patient is hospitalized in the emergency room, regardless of the clinical presentation on arrival to the ED. Patients presenting to a regional ED are also transferred to our institution.

On admission to the emergency room, blood tests are performed (prothrombin, platelets, serum creatine kinase level, serum creatine kinase level). These blood tests are repeated 12 and 24 h after admission.

The severe form was defined as a snake envenomation with at least one of the following complications: hematologic abnormalities, hemorrhage, organ failure (respiratory failure, shock, neurological abnormalities), limb necrosis, compartment syndrome or impending compartment syndrome requiring emergency fasciotomy, and death[3,8-12].

We compared the group of patients who developed a severe form of snake envenomation, and those who had a moderate form within the 24-hour of follow-up.

2.4. Ethical approval

Given the nature of the study, the Habib Bourguiba Hospital Institutional Review Board considered this analysis to be exempt from ethical review. Patients' data were anonymous in this study.

2.5. Used definitions

(1) Hematologic abnormalities (thrombocytopenia, low prothrombin rate, or disseminated intravascular coagulation). Thrombocytopenia was defined as a platelet count below the lower limit (150 000/mm^3)[14]; Prothrombin rate was considered low when lower than 60%; Leukocytosis was defined as a leukocyte count over 10 000/mm^3; Disseminated intravascular coagulation was defined by the presence of thrombocytopenia and low prothrombin rate. D-Dimer and fibrinogen measurements were not available during the study period in our laboratory.

(2) Organ failure (respiratory failure, shock, cardiac arrest, or neurological abnormalities).

Respiratory failure: pulse oximetry<90%, or needing for mechanical ventilation; Shock: systolic blood pressure<90 mmHg in adults, use of catecholamine (dobutamine, adrenaline or noradrenaline); Neurological abnormalities included in the severity signs were: seizures, confusion, paralysis, agitation, Glasgow coma scale<13; Rhabdomyolysis was defined as a serum creatine kinase level greater than 1 000 IU/L[13].

2.6. Statistical analysis

Statistical analysis was done using SPSS vision 20. Numeric variables were expressed as mean±standard deviation (SD), and dichotomous variables were expressed as percentages or ranges. To

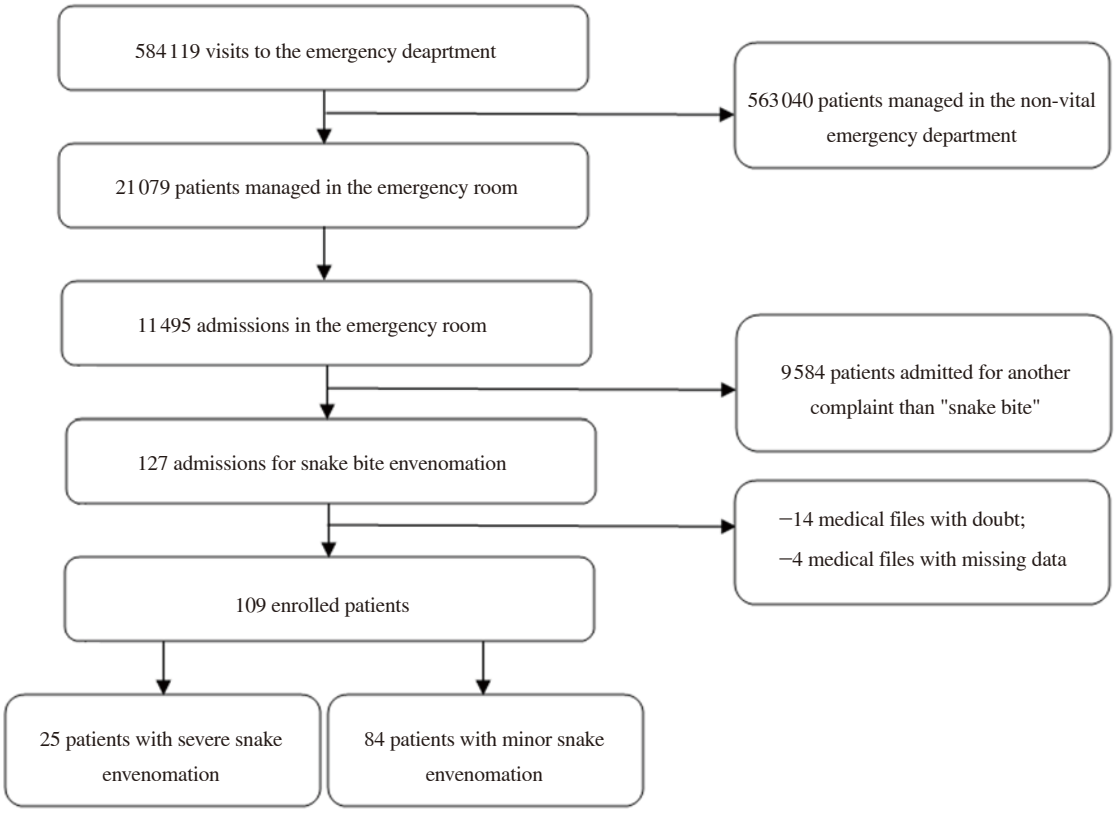

Figure 1. The study flowchart.

compare qualitative variables, we used the Pearson *Chi*-square test and the Fisher exact test. The Student's *t*-test or Fisher exact test and the nonparametric Mann Whitney, test were used for between-group comparisons of discrete and continuous variables, respectively. Receiver-operating characteristic (ROC) curve was used to analyze the correlation between the levels of leucocytes, creatine kinase, prothrombin rate, and platelets and the risk of severe snake bite presentation. The area under the ROC curve was estimated by the method of Hanley and McNeill[15]. Snakebite circumstances (delay of arrival to the hospital, age, tourniquet carried at home), clinical findings on admission (dizziness, vomiting, diarrhea), and blood tests results (leucocytes, platelets, prothrombin rate, creatine kinase level) were evaluated by a multiple logistic stepwise regression procedure. Odds ratios were estimated from the b coefficients obtained, with respective 95% confidence intervals (95% *CI*). The significance level of the study was set at α=0.05.

3. Results

We enrolled 109 out of 127 cases of suspected snakebite envenomation admitted in the ED (Figure 1). The incidence was decreasing each year, and the monthly distribution of the cases showed a peak in the hottest and less rainy months in Tunisia (July, August, and September) (Figure 2). Limbs were the most common injured parts (94.5% of the cases, *n*=103) (Table 1). The snake species were identified in 84 patients (77.1%), encompassing *Macrovipera lebetina* (*n*=78; 71.6%), and *Naja haje Vipera latastei* (*n*=6; 5.5%). The species was not identified in 25 cases (22.9%).

The age of all patients was 30 (20-44) years. Thirteen patients were under 15 years old (11.9%) and 8 patients were above 65 years (7.0%) (range: 4 to 82 years). The sex-ratio was 1.1:1 (56 males and 53 females). Most patients (*n*=77; 70.6%) were from rural areas. Only 32 patients were from Sfax city (29.4%). In 26% of cases, patients were transferred from other regional hospitals. The arrival to the ED was within the first hour after the snakebite in 26% of cases (*n*=28) (Table 1).

On admission, blood tests showed leukocytosis in 29 patients (26.6%), thrombocytopenia in 10 patients (9.2%), low prothrombin rate in 11 patients (10.1%).

Table 1. Demographic and baseline features on admission.

Variables	*N*	%
Past medical condition		
None [*n* (%)]	97	89.0
Hypertension [*n* (%)]	8	7.3
Diabetes [*n* (%)]	10	9.2
Bite site [*n* (%)]		
Lower limb	64	58.7
Upper limb	39	35.8
Thorax	3	2.8
Head	3	2.8
Number of bites [*n* (%)]		
One	94	86.2
Two	9	8.2
More than two	6	5.5
First-aid methods [*n* (%)]		
Local incisions or pricks/punctures	33	30.2
Tourniquets	15	13.8
Local incisions or pricks/punctures and tourniquets	6	5.5
Time from bite to hospital [*n* (%)]		
< 1 h	28	26.0
1-2 h	46	42.2
>2 h	35	32.1
Clinical findings on admission [*n* (%)]		
Local pain	89	81.7
Local paresthesia	31	28.4
Vomiting	21	19.3
Diarrhea	4	3.7
Abdominal pain	4	3.7
Dizziness	13	11.9
Agitation	7	6.4
Ptosis	6	5.5
Ocular muscle paralysis	3	2.8
Bite site examination [*n* (%)]		
Bleeding	4	3.7
Necrosis	20	18.3

During the 24-hour follow-up, the observed complications were as follows: respiratory distress (*n*=16; 14.7%), cardiac arrest (*n*=5; 4.6%); shock (*n*=4; 3.7%); neurological trouble (*n*=6; 5.5%), deep vein thrombosis (*n*=2; 1.8%), disseminated intravascular coagulation (*n*=1; 0.9%), compartment syndrome (*n*=12; 11.0%) and necrosis (*n*=10; 9.2%).

Administered treatments were analgesics (*n*=84; 77.1%), oxygen (*n*=16; 14.7%), endotracheal intubation (*n*=7; 6.4%), catecholamine (*n*=5; 4.6%), transfusion (*n*=9; 8.3%), heparin (*n*=15; 13.8%),

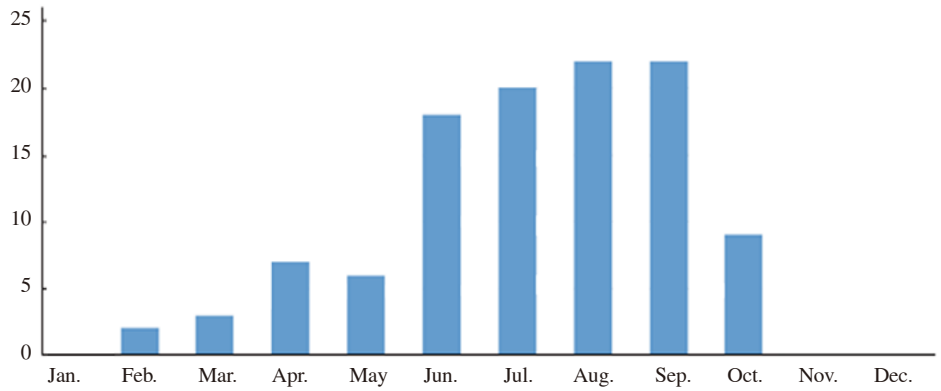

Figure 2. Monthly distribution of snakebite cases (*n*).

antivenom therapy (*n*=18; 16.5%), fasciotomy (*n*=9; 8.3%), tetanus prophylaxis (*n*=31; 28.4%), and/or antibiotics (*n*=37; 33.9%).

Forty patients were not discharged within 24 h; the mean in-hospital length of stay was (2.9±0.5) d. Eleven patients were transferred to the intensive care unit. The in-hospital mortality rate was 4.6% (*n*=5).

The severe form was observed in 25 patients (22.9%). Table 2 shows the predictors of developing severe snakebite envenomation. The sex proportions were comparable in the two groups of patients (*P*=0.5). On admission, leucocytes count higher than 11 550/mm^3, creatine kinase level higher than 155 IU/L, prothrombin rate lower than 76.5%, and/or platelets count lower than 190 000 /mm^3 were statistically associated with the severe form (Figure 3).

Multivariate analysis showed that leukocyte count over 11 550/mm^3, creatine kinase over 155 IU/L, and/or carried tourniquet before arrival to the ED were early independent predictors of severe snake bite presentation (Table 3).

Table 2. Univariate analysis of predictors of severe snake envenomation.

Variables	Moderate envenomation (*n*=84)	Severe envenomation (*n*=25)	$t/U/\chi^2$	*P*-value
Age (years) [median (IQR)]	29 (19-49)	33 (21-63)	844.50	0.100
Age between 15 and 65 years [*n* (%)]	73 (86.9)	15 (60.0)	8.80	0.030
Medical condition [*n* (%)]				
Hypertension	5 (6.0)	3 (12.0)	1.02	0.300
Diabetes	8 (9.5)	2 (8.0)	0.05	0.800
Time between snake bite and admission in the ED over 2 h [*n* (%)]	21 (25.0)	14 (56.0)	724.50	0.040
Number of snakebites [*n* (%)]				
One	72 (85.7)	24 (96.0)	942.00	0.200
Two	8 (9.5)	1 (4.0)	992.00	0.700
More than two	4 (4.8)	0 (0.0)	999.00	0.600
First-aids at home [*n* (%)]				
Tourniquet	7 (8.3)	8 (32.0)	801.50	0.003
Local incisions or pricks/punctures	24 (28.6)	9 (36.0)	972.00	0.500
Clinical features [*n* (%)]				
Agitation	4 (4.8)	3 (12.0)	974.00	0.200
Dizziness	7 (8.3)	6 (24.0)	876.00	0.040
Vomiting	8 (9.5)	13 (52.0)	560.00	0.001
Diarrhea	2 (2.4)	2 (8.0)	650.00	0.010
Blood tests on admission in the ED				
Creatine kinase (IU/L) [median (IQR)]	100 (74-146)	160 (97.5-465.0)	664.00	0.010
Urea (mmol/L) (mean±SD)	4.5±1.2	5.2±2.5	46.10	0.140
Creatinin (micomol/L) (mean±SD)	63.1±10.6	73.1±26.4	49.40	0.070
Leucocytes (/mm^3) [median (IQR)]	8 450 (7 100-10 000)	10 000 (8 400-18 700)	574.50	0.005
Hemoglobin (g/dL) (mean±SD)	13.8±1.2	12.7±1.6	0.47	0.420
Platelets (/mm^3) [median (IQR)]	238 500 (195 750-264 250)	178 000 (146 000-250 500)	600.50	0.005
Prothrombin rate (%) (mean±SD)	82±15	67±20	3.90	0.002

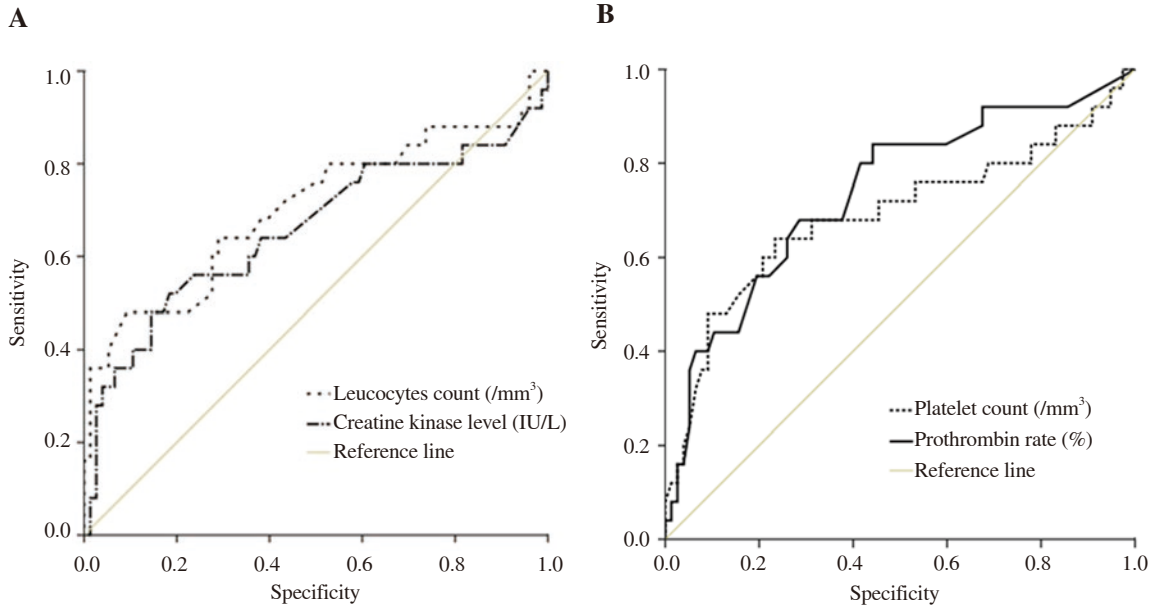

Figure 3. Receiver-operating characteristic curve. A: The relationship between severe snake envenomation, and the leucocytes count, creatin kinase level. B: The relationship between severe snake envenomation, and platelets count, the prothrombin rate. Areas under the curves: 0.7, 0.7, 0.7 and 0.6 respectively. Sensitivity: 0.6, 0.6, 0.5 and 0.5 respectively. Specificity: 0.8, 0.7, 0.9 and 0.8 respectively.

Table 3. The independent predictors of severe snakebite envenomation.

Variables	Odds ratio	95% *CI*	*P*-value
Leucocytes >11 550 /mm^3	18.70	3.3-107.8	0.001
Creatine kinase >155 IU/L	6.16	1.1-35.6	0.042
Tourniquet prior to admission	32.14	3.5-295.9	0.002

4. Discussion

Snakebites account for one of the serious injuries worldwide[16]. Accurate statistics on snake envenomation are still lacking, and the number of injured patients is expected to be much higher than reported[2,16]. In Tunisia, during the '90s, the annual incidence of snake envenomation is about 250, with two deaths per year[17]. Nevertheless, snakes are still among the least known reptile species in Tunisia. Compared to scorpions, snakes' diversity and distribution are rarely studied as well[18,19]. The most-reported species in Tunisia are *Daboia deserti*, *Daboia mauritanica*, *Echis leucogaster*, *Macrovipera lebetina*, *Cerastes cerastes*, and *Naja haje Vipera latastei*[20]. The three latter ones are the most species found in our region. In our study, the snake species were not systematically recorded in the medical file. However, our data are coinciding with the reported species in our region[20].

Snakebites vary from a dry, also called asymptomatic, bite to severe envenomation[8,9]. Clinical presentations of snake envenomation may include these three events: tissue injury, hematologic abnormalities, and/or systemic dysfunctions[8-10,21]. These different clinical presentations are explained by the complex effects of the venoms. In Tunisia, the venoms of *Macrovipera lebetina*, *Cerastes cerastes*, and *Naja haje Vipera latastei* have hemostatic, hemodynamic, and/or myotoxic effects[5].

The prevalence of severe envenomation is estimated between 14% and 27% globally[1,21]. In our study, we found severe snake envenomation in 22.9% of the cases. As reported in previous studies, historical factors (age, sex, site of snakebite, medical condition) did not discriminate severe snakebite envenomation[1]. Oppositely, the time between the snakebite and the first medical contact was associated with the severity of the envenomation as was reported in several studies[1]. One of the most concerning historical characteristics of snakebites is the size of the snake. Several studies have shown that patients bitten by large snakes have a threshold risk to develop systemic envenomation[1,22-24].

In-vitro researches have demonstrated that the pharmacological effects of snakes' poison are dose-dependent. The studied species were namely *Macrovipera lebetina* and *Cerastes cerastes*, which are major species in our region[7,25,26]. The poison dose is frequently correlated with snake size and/or bites number. Snake size description is commonly based on patients' or relatives' descriptions. In our study, this information had been missing in almost one-quarter of cases. The number of snakebites had no association with the envenomation severity. Among the historical features, faulty tourniquet application was the unique early independent predictor of severe snakebite envenomation. This finding is coinciding with previous studies[24].

Due to the enormous number of snake species, the physical examination findings are varying in the literature[1]. Their association with the outcomes is varying with the species and the regions[1,23,24,27]. In our sample, we found no clinical early predictors of severity in multivariate analysis.

Concerning the accuracy of laboratory tests in predicting the severity of snakebite envenomation, the data are rare[1,11,23,28]. In a recent literature review, laboratory values were not discriminatory in determining severe envenomation, and only one study found a correlation between thrombocytopenia four days after the snakebite and the severe form[1,23]. None of these studies has been conducted in the North African region. In our study, we aim to determine early biological predictors of severity. In multivariate analysis, leukocyte count over 11 550/mm^3 and/or creatine kinase over 155 IU/L were associated with a severe snakebite form (*OR*: 18.7 and 6.16; 95% *CI*: 3.3-107.8 and 1.1-35.6, respectively). This finding can be explained by the pharmacological mechanisms of snake venoms. Recently, Baîram *et al.* characterized the biochemical effects of snake venom phospholipases A2 isolated from *Cerastes cerastes* and *Macrovipera lebetina transmediterranea*[7]. This *in-vitro* research has demonstrated a higher activity of these phospholipases compared to a thermoactive enzyme activity in these species[7]. Phospholipases A2 plays an important role in diet lipid catabolism and the metabolism of lipid membranes. Furthermore, their hydrolysis products, namely the arachidonic acid, are the precursor of inflammatory activities, *via* prostaglandins, prostacyclins, thromboxanes, and leukotrienes[29-31]. Thanks to their antitumoral effect, snake venom inoculated in animals or humans induces an increase of polymorphonuclear leukocytes in the early stages of tumor growth[29,32]. Due to the enormous number of snake species, the physical examination findings are varying in the literature[1].

The management of snake envenomation is based on early symptomatic treatment of organ failures and specific antivenom. In Tunisia, the antivenom is provided by the Pasteur Institute of Tunis (Gamma-VIP). It was generated by hyper immunization of horses with a mixture of *Cerastes cerastes* and *Macrovipera lebetina* venoms. It consists of purified F(ab')2 fragments generated by digestion with pepsin of ammonium sulfate-precipitated IgG molecules[33]. The antivenom is indicated in patients of at least a Grade Ⅱ of severity. In our study, it was used in only 16.5% of cases. The in-hospital mortality rate in our study was 4.6%; which is quite higher than other studies[34]. The rate of compartment syndromes is also higher than in some studies[35-38]. These differences may be explained by the delays between the bite and the arrival to the ED. Besides, these rates are overestimated; several patients did probably not present to the hospital. Most snakebites are in rural areas where no health facility is available. At-home carried first-aids may also explain these outcomes; one-third of the patients with severe snakebite envenomation have had a tourniquet. Awareness about the risk of tourniquet has to be improved.

The limitations of this study are as follows. First, this study included the results of only one emergency department, and it

was based on a retrospective medical record review. The sample size was small, and there were insufficient factors to identify confounding variables to determine the historical or clinical features and outcomes of patients. Second, these results are among the species reported in Tunisia. Larger and multi-institutional studies are necessary to generalize these findings to other snake types.

Despite these limitations, we think that our work will be interesting to ED physicians. To the best of our knowledge, this is the one of the first studies evaluating early predictors of snakebite severity in Tunisia. It can be a new base for future studies to approve a severity scale.

In summary, this study shows that the snakebite envenomation is still a serious accidental pathology in Tunisia. Leukocytosis and rhabdomyolysis are predictors of severity. Further studies are required to confirm these findings.

Conflict of interest statement

The authors report no conflict of interest.

Authors' contributions

Study concept and design (O.C.W., F.I.); acquisition of the data (F.I., H.B., A.F.); analysis of the data (I.F., O.C.W.), drafting of the manuscript (A.N., R.K., M.J.); critical revision of the manuscript (O.C.W., N.R.); approval of final manuscript (O.C.W., N.R.).

References

[1] Gerardo CJ, Vissoci JRN, Evan S, Simel DL, Lavonas EJ. Does this patient have a severe snake envenomation? The rational clinical examination systematic review. *JAMA Surg* 2019; **154**(4): 346-354.

[2] World Health Organization. Guidelines for the management of snakebites, 2nd edition. [Online] Available from: http: //www.who.int/iris/handle/10665/249547. [Accessed on 16th March 2020].

[3] Kyung Hoon Park, Hyungoo Shin, Hyunggoo Kang, Changsun Kim, Hyuk Joong Choi, Kyunghun Yoo, et al. Effectiveness of repeated antivenom therapy for snakebite-related systemic complications. *J Int Med Res* 2019; **47**: 4808-4814.

[4]Warrell DA. *Envenoming and their treatments*. In: Bon C, Goyffon M, (Eds.). Lyon: Foundation Marcel Merieux; 1996, p. 63-76.

[5] Bazaa A, Marrakchi N, El Ayeb M, Sanz L, Calvete JJ. Snake venomics: Comparative analysis of the venom proteomes of the *Tunisian snakes Cerastes cerastes*, *Cerastes vipera* and *Macrovipera lebetina*. *Proteomics* 2005; **5**(16): 4223-4235.

[6] Chaari AN, Bahloul M, Tlijani M, Dammak H, Bouaziz M. An unusual mode of snake poisoning in Tunisia. *Med Trop* 2010; **70**(2): 201-202.

[7] Baîram D, Aissa I, Louati H, Othman H, Abdelkafi-Koubaa Z, Krayem N, et al. Biochemical and monolayer characterization of Tunisian snake venom phospholipases. *Int J Biol Macromol* 2016; **89**: 640-646.

[8] Dart RC, Hurlbut KM, Garcia R, Boren J. Validation of a severity score for the assessment of crotalid snakebite. *Ann Emerg Med* 1996; **27**(3): 321-326.

[9] Gold BS, Dart RC, Barish RA. Bites of venomous snakes. *N Engl J Med* 2002; **347**(5): 347-356.

[10]Seifert SA, Kirschner RI, Martin N. Recurrent, persistent, or late, new-onset hematologic abnormalities in crotaline snakebite. *Clin Toxicol* 2011; **49**(4): 324-329.

[11]Bucaretchi F, Herrera SR, Hyslop S, Baracat EC, Vieira RJ. Snakebites by Crotalus durissus ssp in children in Campinas, São Paulo, Brazil. *Rev Inst Med Trop São Paulo* 2002; **44**(3): 133-138.

[12]Hifumi T, Sakai A, Kondo Y, Hifumi T, Sakai A, Kondo Y, et al. Venomous snake bites: clinical diagnosis and treatment. *J Intensive Care* 2015; **3**(1): 16.

[13]Chavez LO, Leon M, Einav S, Varon J. Beyond muscle destruction: a systematic review of rhabdomyolysis for clinical practice. *Critical Care* 2016; **20**(1): 135.

[14]Isbister GK. Snakebite doesn't cause disseminated intravascular coagulation: coagulopathy and thrombotic microangiopathy in snake envenoming. *Semin Thromb Hemost* 2010; **36**(4): 444-451.

[15]Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982; **143**(1): 29-36.

[16]Park KH, Shin H, Kang H, Kim Ch, Choi HJ, Yoo K, et al. Effectiveness of repeated antivenom therapy for snakebite-related systemic complications. *J Int Med Res* 2019; **47**(10): 4808-4814.

[17]Hamouda C. Envenimations par les serpents en Tunisie. *Tawarek* 2009; **4**: 33-40.

[18]Kalboussi M, Achour H. Modelling the spatial distribution of snake species in northwestern Tunisia using maximum entropy (Maxent) and Geographic Information System (GIS). *J For Res* 2018; **29**: 233-245.

[19]Nouira S, Blanc CH, Ktari H. Biodiversité de l'Herpétofaune tunisienne. I. Les Ophidiens. *Bull Soc Sci Nat* 1995; **24**: 76-94.

[20]World Health Organization. Venomous snakes distribution and species risk categories. 2017. [Online] Available from: https://apps.who.int/bloodproducts/snakeantivenoms/database/default.html. [Accessed on 16th March 2020].

[21]Long B, April M. What history, examination, and laboratory findings suggest severe snake envenomation? *Ann Emerg Med* 2019; **74**(3): 450-452.

[22]Janes DN Jr, Bush SP, Kolluru GR. Large snake size suggests increased snakebite severity in patients bitten by rattlesnakes in Southern California. *Wilderness Environ Med* 2010; **21**(2): 120-126.

[23]Ribeiro LA, Jorge MT, Lebrão ML. Prognostic factors for local necrosis in *Bothrops jararaca* (Brazilian pit viper) bites. *Trans R Soc Trop Med Hyg* 2001; **95**(6): 630-634.

[24]Bandyopadhyay SK, Ghosh S, Bandyopadhyay R, Dutta A. Prognostic factors in haemotoxic viper bite: analysis of data from a referral hospital. *J Indian Med Assoc* 2009; **107**(1): 12-13.

[25]Zouari-Kessentini R, Luis J, Karray A, Kallech-Ziri O, Srairi-Abid N, Bazaa A, et al. Two purified and characterized phospholipases A2 from *Cerastes cerastes* venom, that inhibit cancerous cell adhesion and migration. *Toxicon* 2009; **53**(4): 444-453.

[26]Bazaa A, Pasquier E, Defilles C, Limam I, Kessentini-Zouari R, Kallech-Ziri O, et al. MVL-PLA2, a snake venom phospholipase A2, inhibits angiogenesis through an increase in microtubule dynamics and disorganization of focal adhesions. *PLoS One* 2010; **5**(4): e10124.

[27]Jorge MT, Ribeiro LA, O'Connell JL. Prognostic factors for amputation in the case of envenoming by snakes of the *Bothrops genus* (Viperidae). *Ann Trop Med Parasitol* 1999; **93**(4): 401-408.

[28]Barraviera B, Bonjorno Júnior JC, Arkaki D, Domingues MA, Pereira PC, Mendes RP, et al. A retrospective study of 40 victims of Crotalus snake bites: analysis of the hepatic necrosis observed in one patient. *Rev Soc Bras Med Trop* 1989; **22**(1): 5-12.

[29]Calderon LA, Sobrinho JC, Zaqueo KD, de Moura AA, Grabner AN, Mazzi MV, et al. Antitumoral activity of snake venom proteins: new trends in cancer therapy. *Biomed Res Int* 2014; **2014**: 203639.

[30]Gutierrez J, Lomonte B. Phospholipase A2 myotoxins from Bothrops snake venoms. *Toxicon* 1995; **33**(11): 1405-1424.

[31]Teixeira CFP, Landucci ECT, Antunes E, Chacur M, Cury Y. Inflammatory effects of snake venom myotoxic phospholipases A2. *Toxicon* 2003; **42**(8): 947-962.

[32]da Silva RJ, da Silva MG, Vilela LC, Fecchio D. Cytokine profile of Ehrlich ascites tumor treated with *Bothrops jararaca* venom. *Mediators Inflamm* 2002; **11**(4): 197-201,

[33]Fahmi L, Makran B, Pla D, Sanz L, Oukkache N, Lkhider M, et al. Venomics and antivenomics profiles of north African *Cerastes cerastes* and *C. vipera* populations reveals a potentially important therapeutic weakness. *J Proteomics* 2012; **75**(8): 2442-2453.

[34]Senek MZF, Kong SY, Shin SD, Sun KM, Kim J, Ro YS. Epidemiological profile and outcomes of snakebite injuries treated in emergency departments in South Korea, 2011-2016: a descriptive study. *Trans R Soc Trop Med Hyg* 2019; **113**(10): 590-598.

[35]Hsu CP, Chuang JF, Hsu YP, Wang SY, Fu CY, Yuan KC, et al. Predictors of the development of post-snakebite compartment syndrome. *Scand J Trauma Resusc Emerg Med* 2015; **23**: 97.

[36]Juckett G, Hancox JG. Venomous snakebites in the United States: management review and update. *Am Fam Physician* 2002; **65**(7): 1367-1374.

[37]Frangides CY, Koulouras V, Kouni SN, Tzortzatos GV, Nikolaou A, Pneumaticos J, et al. Snake venom poisoning in Greece. Experiences with 147 cases. *Eur J Intern Med* 2006; **17**(1): 24-27.

[38]Hall EL. Role of surgical intervention in the management of crotaline snake envenomation. *Ann Emerg Med* 2001; **37**(2): 175-180.