ORIGINAL ARTICLE

Factors associated with severe envenomation of snakebite cases at emergency department, Hospital Sultan Abdul Halim, Kedah, Malaysia

Mhd Nazrul Fitri Mhd Nizar, MB Bch BAO[1,3], Andey Rahman, MMed (EM)[1,2], Kamarul Aryffin Baharuddin, MMed(EM)[1,2], Mohammad Zikri Ahmad, MMed(EM)[1,2], Mashitah Mohamed Ismail, MMed (EM)[3]

[1]Department of Emergency Medicine, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia
[2]Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia, [3]Department of Emergency and Trauma, Hospital Sultan Abdul Halim (HSAH), Sungai Petani, Kedah, Malaysia

ABSTRACT

Introduction: Snakebite envenomation is a medical emergency and cases continue to be encountered in Malaysian hospitals. This study aims to determine the prevalence of snakebite presentations and the associated factors with severe envenomation of snakebite in Sungai Petani, Kedah, Malaysia.

Materials and Methods: This was a retrospective, cross-sectional study involving snakebite patients presented at the Emergency Department (ED), Hospital Sultan Abdul Halim (HSAH), Kedah from 1 July 2015 to 30 June 2019. The cases were extracted from the computerized system and the case records of patients were retrieved from the Medical Record Unit. Patients that met the study criteria were included and their sociodemographic features, clinical presentations including use of anti-venom were collected. Logistic regression analysis was performed to determine the factors associated with severe envenomation.

Results: A total of 220 snakebite cases with the mean age of patients was 39.66 (SD±21.79) years old. Majority of them were Malay and males. 41.4% of snakebite cases occurred in late evenings and the mean time-lapsed to arrive at HSAH was 108.6 minutes. 81.4% of snakebite cases occurred while engaging in outdoor activities and 43.6% of the snakebite cases involved work-related incidents. 58.2% of the patients were bitten in the lower limb. 78.6% of patients were bitten by the identified snake species, predominantly from Viperidae family. The prevalence of severe envenomation was 50.9%. Malay ethnicity (adj. OR =2.549, 95% CI =1.277,5.089), bite to the upper limb (adj. OR =2.125, 95% CI =1.192, 3.790), and bite by snakes from Viperidae family (adj. OR =3.017, 95% CI =1.613, 5.642) were found to have significant associations with severe envenomation of snakebite.

Conclusion: The prevalence of severe envenomation was more than 50% of snakebite cases. Malay ethnicity, upper limb snake bites, and snakebite from a Viperidae family had a higher chance of severe envenomation

INTRODUCTION

Snakebite envenomation is a medical emergency and cases continue to be encountered in Malaysian hospitals. However, clinical management of snakebite cases may still be suboptimal due to negligence, failure to identify the species and anticipate the severity of envenomation in snakebite patients.[1,2] Furthermore, older age of victims, delayed presentation to the hospital and treatment by non-medical personnel also add to the risk of morbidity and mortality.[3-5] In addition, due to a lack of documentation, the true extent of snakebite mortality and morbidity in Malaysia is uncertain.[6]

The clinical severity of a snakebite is determined by its location on the body, depth, amount of venom injected, the species of the snakes and its size, the age and size of the victim, and susceptibility to the venom.[7] Although most snakes in Malaysia are non-venomous and regarded relatively harmless to humans, certain snakes can cause mild to severe envenomation and eventually mortality. According to the database, around 17 of Malaysia's 105 strictly land snakes are venomous.[8] The vast majority of the venomous terrestrial snakes in Malaysia are classified as Elapidae or Viperidae.[9] Nevertheless, most venomous snakebites reported are defensive in nature and snakes may not deliver sufficient amounts of venom.[10]

Currently, snakebite in Malaysia is not classified as a notifiable disease. Hence, it is one of many reasons causing the lack of reliable information as many cases were not adequately documented or reported. The demographic characteristics and clinical presentations also differ globally, even between states in Malaysia. This study aims to determine the prevalence of snakebite presentations and the associated factors with severe envenomation of snakebite in Sungai Petani, Kedah.

MATERIALS AND METHODS
Patients, setting, inclusion and exclusion criteria
This was a retrospective, cross-sectional study involving snakebite patients who presented at the Emergency Department (ED), Hospital Sultan Abdul Halim (HSAH), Sungai Petani, Kedah, Malaysia from July 1, 2015, to June 30, 2019. HSAH covers the emergency services for approximately 1/3 third of population in Kedah. Inclusion criteria were all

snakebite patients from all age groups, all identified snakebite (venomous and non-venomous) with or without envenomation, and all unidentified snakebite with evidence of local and/or systemic envenomation. Exclusion criteria were incomplete medical records and referral cases from other hospitals that arrived through ED HSAH, as there was a potential discrepancy in snakebite envenomation assessment and documentation. Geographical location of the cases came from Kuala Muda district or historically known as Central Kedah.

Sample size and sampling
The sample size was calculated using PS Power and Sample Size Calculations Version 3.0. The total number of samples required was 182 cases. Patient's registration numbers with the diagnosis of snakebite were extracted from the computerized system and the case records of patients were retrieved from the Medical Record Unit, HSAH. Case records that met the inclusion criteria were selected. All data were recorded in a data collection form. Logistic regression analyses were performed to determine the factors associated with severe envenomation.

Operational definition
Based on the Clinical Practice Guideline (CPG) for the Management of Snakebite, Ministry of Health Malaysia (MOH), severe envenomation of a snakebite is defined as clinical evidence of systemic manifestations that are potentially fatal and/or clinical evidence of progressive swelling of bitten limb to indicate local envenomation. Progressive swelling of the bitten limb should be measured using the rate of proximal progression rather than the circumference of the limb. These conditions warrant the administration of anti-venom.

On the other hand, non-severe envenomation is defined by the absence of significant swelling or redness, including dry bite, as well as the absence of clinical evidence of local gangrene or systemic symptoms.[6]

The decision for anti-venom administration was made by the emergency physician on duty. Some of the complicated cases were discussed with the Remote Envenomation Consultancy Services (RECS) team for snake species identification and anti-venom administration. The RECS team is a group of emergency physicians from the Malaysian Society on Toxinology who has strong enthusiasts in snakebite management in Malaysia. It is also recommended in the CPG to consult the RECS team, particularly on the identification of snake species and appropriate management.[6]

Statistical analysis
Data obtained were entered into and analyzed using IBM Social Package Social Sciences (SPSS) version 26.0 statistical software. For the descriptive analysis, numerical data were presented as mean (SD) and categorical data were presented as frequency (percentage). To determine which factors were associated with severe envenomation, single and multiple logistic regression were applied. A *p*-value < 0.25 which was significant in univariable analysis were selected for multivariable analysis. The adjusted odds ratio (Adj. OR) and 95% confidence interval (CI) were calculated. In

multivariable analysis, statistical significance was defined as a 2 tailed p-value of < 0.05.

Ethical considerations
This study received ethical boards approvals from Human Research Ethics Committee of USM (USM/JEPeM/19050330) and Medical Research and Ethics Committee of MOH (NMRR-19-2179-48616 (IIR). Permission from the Director of HSAH was also obtained to review the medical records.

RESULTS
A total of 246 snakebite cases were presented at the ED, HSAH, from July 2015 till June 2019. However, 26 cases were excluded from the study due to incomplete data and referral cases as defined in the exclusion criteria. Two hundred twenty snakebite cases were included in this study. The socio-demographic and clinical presentation of snakebite cases were presented in Table I.

The mean age of all the cases was 39.66 (SD±21.79) years old, and the mean age based on the envenomation are presented in Table I. The most affected age group was between 16 and 45 years old (45.9%). The youngest victim was one year old and the oldest was 90 years old. In all, 146 cases (66.4%) were males. Malay patients accounted for 76.8% (176 patients) of all snakebite cases.

The mean time-lapsed to arrive at the hospital was 1.81 hours or 108.6 minutes (SD±3.78). The mean of time-lapsed to hospital based on the envenomation are presented in Table I. The earliest time-lapsed from the data was 0.2 hour and the latest was 46 hours. Many cases were presented to the hospital within 0-6 hours (214 cases or 97.3%). Most of the cases occurred between 1800 to 2359 hours, which was late evening and night. A total of 179 (81.4%) snakebite cases occurred while engaging in outdoor activities. Most of the patients had tried non-medical intervention (185 cases; 84.1%) prior to arriving at the hospital.

In terms of anatomical bite location, most of the patients were bitten at the lower limb (128 cases; 58.2%) as compared to the upper limb (92 cases; 41.8%). A total of 173 cases (78.6%) were bitten by the identified snake species. 151 (68.6%), 17 (7.7%), 3 (1.4%), 2 (0.9%) and 47 (21.4%) patients were bitten by the snakes from the Viperidae family, Elapidae family, reticulated pythons, non-venomous water snakes and unidentified snakebites, respectively. Fang marks were noted in 212 snakebite cases (96.4%).

From these 220 cases, the prevalence of severe envenomation of snakebite cases was 112 (50.9%). A total of 78 and 15 of them had progressive local envenomation and systemic manifestations, respectively. There were 19 (8.6%) cases with mixed of local and systemic envenomation. There was one case of severe envenomation resulting in mortality due to a snakebite from Elapidae family. The prevalence of envenomation among the variables also presented in Table I. Table II showed a single logistic regression analysis where factors such as age group 46-64 and > 65, female gender, Malay ethnicity, time of injury between 1800-2359 hours and 0000-0559 hours, outdoor location, work-related incident,

Table I: Socio-demographic and clinical presentation of snakebite cases and prevalence of severity of envenomation among the variables

Variables	Mean SD	Frequency	Envenomation	
			Non-severe n (%)	Severe* n (%)
Total (N)			108 (49.1)	112 (50.9)
Socio-demographic				
Age, mean (SD)	39.66 ± 21.79		36.94 ± 21.12	42.29 ± 22.20
Age group (years)				
0-15		30 (13.6)	18 (60.0)	12 (40.0)
16-45		101 (45.9)	54 (53.5)	47 (46.5)
46-65		55 (25.0)	23 (41.8)	32 (58.2)
> 65		34 (15.5)	13 (12.0)	21 (61.8)
Gender				
Male		146 (66.4)	77 (52.7)	69 (47.3)
Female		74 (33.6)	31 (41.9)	43 (58.1)
Ethnicity				
Malay		169 (76.8)	74 (43.8)	95 (56.2)
Others				
Chinese		12 (5.5)	8 (66.7)	4 (33.3)
Indian		12 (5.5)	10 (83.3)	2 (16.7
Foreigners		27 (12.3)	16 (59.3)	11 (40.7)
Clinical presentation				
Time-lapsed to hospital, mean hours (SD)			1.61 ± 2.45	1.99 ± 4.71
Time-interval to hospital				
0-6 hours		214 (97.3)	106 (49.5)	108 (50.5)
> 6 hours		6 (2.7)	2 (33.3)	4 (66.7)
Time of injury (H)				
0600-1159		51 (23.2)	17 (33.3)	34 (66.7)
1200-1759		51 (23.2)	22 (43.1)	29 (56.9)
1800-2359		91 (41.4)	55 (60.4)	36 (39.6)
0000-0559		27 (12.3)	14 (51.9)	13 (48.1)
Location during bite				
Indoor		41 (18.6)	26 (63.4)	15 (36.6)
Outdoor		179 (81.4)	82 (45.8)	97 (54.2)
Work-related incident				
No		124 (56.4)	68 (54.8)	56 (45.2)
Yes		96 (43.6)	40 (41.7)	56 (58.3)
Pre-hospital intervention				
Medical		35 (15.9)	18 (51.4)	17 (48.6)
Non-medical		185 (84.1)	90 (48.6)	95 (51.4)
Anatomical location of bite				
Lower limb		128 (58.2)	75 (58.6)	53 (41.4)
Upper limb		92 (41.8)	33 (35.9)	59 (64.1)

*Requiring anti-venom.

bites to the upper limb, identified the type of snake, and bites by the snake from Viperidae family were statistically associated with severe envenomation outcome. However, multivariable logistic regression analysis found that Malay ethnicity, upper limb bites, and snakebites from the Viperidae family were significantly associated with severe envenomation (Table III).

Malays were 2.55 times more likely than other ethnic groups to experience severe envenomation (Adjusted OR =2.549, 95% CI =1.277,5.089). Patients who were bitten on the upper limb had a 2.13-fold higher risk of experiencing a severe outcome compared to those cases involving the lower limb (Adjusted OR =2.125; 95% CI =1.192, 3.790). This study also found that snakebites from the Viperidae family had a 3.02-fold higher risk of severe envenomation when compared to other snake groups (Adjusted OR =3.017; 95% CI =1.613, 5.642).

DISCUSSION

The high number of snakebite cases in our study indicates that the cases are not uncommon and continue to be seen today, particularly in the semi-rural district of Sungai Petani. This district is surrounded by agricultural sites such as rubber and palm oil estates, paddy fields and forests. A Kuala Muda River runs through the district, with mangrove forest growing along its banks. This forest has become a natural habitat for snakes from the Viperidae family, namely Malayan pit viper *(Calloselasma rhodostoma)* and Mangrove pit viper *(Cryptelytrops purpureomaculatus)*. In addition, both fishing and farming activities have become occupational hazards and presumably increase the risks of getting snakebite.[8]

Most of the patients were between the age of 16 and 45 years old. Our finding is consistent with the profiles of other tropical countries in South Asia (Bangladesh, Bhutan, India, Nepal, Pakistan, and Sri Lanka).[12–15] In contrast, a few of local studies in Perlis and Kelantan reported in a younger age range, between the age of 10-19 years old.[8,11] Our findings

Table II: Factors associated with severe envenomation by univariable logistic regression analysis

Variables	B	Crude OR (95% CI)	p-value*
Age group			
0-15		1	
16-45	0.267	1.306 (0.570,2.990)	0.528
46-65	0.736	2.087 (0.844,5.163)	0.111
> 65	0.885	2.423 (0.886,6.626)	0.085
Gender			
Male		1	
Female	0.437	1.548 (0.880,2.722)	0.129
Ethnicity			
Other ethnicities		1	
Malay	0.943	2.568 (1.331,4.952)	0.005
Time-interval to hospital			
0-6 hours		1	
> 6 hours	0.674	1.963 (0.352,10.945)	0.442
Time of injury (H)			
0600-1159		1	
1200-1759	-0.417	0.659 (0.295,1.472)	0.309
1800-2359	-1.117	0.327 (0.160,0.671)	0.002
0000-0559	-0.767	0.464 (0.179,1.205)	0.115
Location during bite			
Indoor		1	
Outdoor	0.718	2.050 (1.018,4.130)	0.044
Work-related incident			
No		1	
Yes	0.531	1.700 (0.992,2.912)	0.053
Pre-hospital intervention			
Medical		1	
Non-medical	0.111	1.118 (0.542,2.303)	0.763
Anatomical location of bite			
Lower limb		1	
Upper limb	0.928	2.530 (1.456,4.396)	<0.001
Snake identification			
Unidentified		1	
Identified	1.002	2.723 (1.375,5.390)	0.004
Snake group			
Non Viperidae		1	
Viperidae	1.148	3.152 (1.727,5.753)	<0.001

B= Regression Coefficient; CI = Confidence Interval; OR = Odds Ratio
*p-value < 0.25 which is significant on univariable analysis is selected for multivariable analysis.

Table III: Factors associated with severe envenomation by multivariable logistic regression analysis

Variables	B	Adjusted OR (95% CI)	p-value*
Ethnicity			
Other ethnicities		1	
Malay	0.936	2.549 (1.277,5.089)	0.008
Anatomical location of bite			
Lower limb		1	
Upper limb	0.754	2.125 (1.192,3.790)	0.011
Snake group			
Non Viperidae		1	
Viperidae	1.104	3.017 (1.613,5.642)	<0.001

*Multiple logistic regression with Forward LR method were applied; The model fits reasonably well; Constant = -1.765; Hosmer and Lemeshow test, p-value = 0.081; There are interaction between anatomical location of bite and species group; However, no multicollinearity problem was found; Classification table 64.1% correctly classified; Area under Receiver Operating Characteristic (ROC) curve was 70.3% (95% CI :63.5,77.2).

could be explained by the involvement of active groups of adults, especially those who live and work in rural areas, rural estates and agricultural areas. This condition could be considered as an occupational health-related injury that affects the farmers, plantation workers, herders and fishermen.

From our study, males were more exposed to snakebite with a ratio of 2:1. A similar ratio was reported from the earlier studies done in the northern states in Malaysia[8,10,16] and South Asia country.[15] However, this ratio varies across the states in Malaysia. Chew et al. reported a 1.5: 1 ratio in Kelantan and Jamaiah I et al reported a 3: 1 ratio in Kuala Lumpur.[11,17] In comparison, a Brazilian study had a higher male to female ratio of 4:1.[3]

The prevalence of severe envenomation cases was 50.9%, higher than the previous studies done in the state of Kelantan (37.7%)[11] and Brazil (8.1%).[3] The commonest snake species that lead to envenomation was from the Viperidae family. This finding is comparable with the old studies in Penang (1960s) and Central Kedah (1980s) that showed the majority of venomous bites were due to pit vipers.[10,16] Viperidae family are mostly lowland snakes that live in areas near plantation farms or estates and are widely distributed along the mangrove forest. Therefore, areas with those characteristics should expect similar dominant species and envenomation.

To date, factors associated with risks of getting severe envenomation, particularly in Malaysia, have not been fully studied. This study found three factors that were significantly associated with the severity of the snakebite cases. Firstly, Malay ethnicity was significantly associated with severe snakebite envenomation (adjusted OR =2.549, 95% CI =1.277,5.089). The up-to-date literature for ethnic differences in snakebite cases is scarcely reported. Previous epidemiology studies in Malaysia reported that the highest snakebite cases happened among Malays.[8,10,16] However, no evidence of significant association with the severity of envenomation was stated. Possible explanation in this study is the Malay ethnic group is a predominance in Sungai Petani district and living in outskirt areas.

Secondly, envenomation from the Viperidae family is a risk factor for severe envenomation (adjusted OR =3.017; 95% CI =1.613, 5.642). This finding is contrary to the studies in Kelantan, Perlis and Kuala Lumpur, where severe envenomation cases were caused by cobra bites (Elapidae family).[8,11,17] This finding should alert the high-risk group of people in Sungai Petani as Malayan pit viper is the predominant species in Penang and central Kedah.[10,16] In fact, it is always thought that pit vipers' envenomation are less lethal compared to cobra.

Thirdly, patients bitten on the upper limb were more likely to develop severe envenomation (adjusted OR =2.125; 95% CI =1.192, 3.790). This unexpected finding is in contrast with the Malaysian and global studies.[3,8,10,11] One of the studies found that most snakebites occurred due to stepping on the snake by accident.[10] Based on Table I, there were considerable number of cases occurred during work-related activities. Since fishing and agriculture are the main economic activities in the area, this might expose them to the natural habitat of the snakes. Therefore, being bitten on the upper limbs could be related to their works that require using one's hands, such as clearing bushes, gardening, farming, and fishing.

In this study, most snakebites occurred in the evening, from 1800-2359 hours. A similar pattern was observed in Kelantan by Chew et al., and most of them presented within 6 hours (97.3%).[11] Our study also found that 84.1% of patients had non-medical pre-intervention prior to their arrival at the hospital, but it was not a factor for the delay or severe envenomation. The finding can be explained in two ways: either the snakebite was non-venomous, or the patients arrived at the hospital in a short period despite non-medical interventions such as self-tourniquet, cloth tying, or herb application. The mean time-lapsed arrival to the hospital was 108.6 minutes, which is better than other Malaysian study.[11]

Identification of snake species had significant value in managing these cases. Some of the patients were able to recognize the snakes through the snake pictures catalog. Consultation with the RECS team also had contributed to a significant success in identifying the snakes. As a result, about 78.6% of snakes were identified, and the management plans were successfully implemented during the admission.

There were some limitations to this study. It was conducted in a single center in central Kedah, Malaysia, which might have limited heterogenicity of the data. The confidence interval can be wide and may be associated with a small number of certain variables, particularly ethnicity. Secondly, this is a retrospective study where researchers relied on accurate recordkeeping about the clinical features, management, and outcome findings.

CONCLUSION
The prevalence of severe envenomation among snakebite cases at HSAH is more than 50% of snakebite cases. Malay ethnicity, upper limb snake bites, and snakebite from the Viperidae family had a higher chance of severe envenomation. It is likely that work-related activities might expose the patients to snakebite envenomation. There was only one mortality case due to Elapidae envenomation.

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