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ORIGINAL RESEARCH

Predictive Factors for Death After Snake Envenomation in Myanmar

Kyi-Phyu Aye, MD; Vipa Thanachartwet, MD; Chit Soe, MD; Varunee Desakorn, MPH, MSc; Supat Chamnanchanunt, MD; Duangjai Sahassananda, MSc; Thanom Supaporn, MD; Visith Sitprija, MD, PhD

From the Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand (Drs Aye, Thanachartwet, Desakorn, and Chamnanchanunt); the Medical Ward, Medical Department, Naypyitaw, Myanmar (Dr Aye); the Department of Rheumatology, University of Medicine 1, Yangon, Myanmar (Dr Soe); the Information Technology Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok, Thailand (Dr Sahassananda); the Division of Nephrology, Phramongkutklao Hospital, Bangkok, Thailand (Dr Supaporn); the Division of Nephrology, Department of Medicine, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand (Dr Sitprija); and the Queen Saovabha Memorial Institute, Thai Red Cross, Bangkok, Thailand (Dr Sitprija).

Introduction—Factors predictive for death from snake envenomation vary between studies, possibly due to variation in host genetic factors and venom composition. This study aimed to evaluate predictive factors for death from snake envenomation in Myanmar.

Methods—A prospective study was performed among adult patients with snakebite admitted to tertiary hospitals in Yangon, Myanmar, from May 2015 to August 2016. Data including clinical variables and laboratory parameters, management, and outcomes were evaluated. Multivariate regression analysis was performed to evaluate factors predictive for death at the time of presentation to the hospital.

Results—Of the 246 patients with snake envenomation recruited into the study, 225 (92%) survived and 21 (8%) died during hospitalization. The snake species responsible for a bite was identified in 74 (30%) of the patients; the majority of bites were from Russell's vipers (63 patients, 85%). The independent factors predictive for death included 1) duration from bite to arrival at the hospital >1 h (odds ratio [OR]: 9.0, 95% confidence interval [CI]: 1.1–75.2; P=0.04); 2) white blood cell counts $>20 \times 10^3$ cells·μL^{-1} (OR: 8.9, 95% CI: 2.3–33.7; P=0.001); and 3) the presence of capillary leakage (OR: 3.7, 95% CI: 1.2–11.2; P=0.02). A delay in antivenom administration >4 h increases risk of death (11/21 deaths).

Conclusions—Patients who present with these independent predictive factors should be recognized and provided with early appropriate intervention to reduce the mortality rate among adults with snake envenomation in Myanmar.

Keywords: snakebites, prospective study

Introduction

Snake envenomation is an important yet neglected public health problem in rural tropical and subtropical areas.[1,2] The incidence of snake envenomation is reported to be >1.2 million bites per year with over 60,000 deaths each year in South and Southeast Asia and Africa.[3]

Corresponding author: Vipa Thanachartwet, MD, Department of Clinical Tropical Medicine, Faculty of Tropical Medicine, Mahidol University, 420/6 Rajvithi Road, Bangkok 10400, Thailand; e-mail: vipa.tha@mahidol.edu.

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In Southeast Asia, 3 families of venomous snakes, including the Elapidae, Viperidae, and Colubridae, are of medical importance; envenomation by these snakes can result in significant disability and death.[4] In a limited resource setting, the clinical manifestations of snake envenomation combined with reliable identification of snakebites are important for snake identification, which assists in appropriate selection of a specific antivenom treatment.[4,5] When snake identification is impossible, a syndromic approach for inferring the snake species, for members of the family Viperidae, Russell's viper, cobra or king cobra, krait, and sea snake, is recommended by the World Health Organization (WHO) guidelines,

published in 2010.[4] This syndromic approach can guide the selection of monospecific antivenom treatment.[4]

However, bites by the same species of venomous snake from different geographical locations may produce different symptoms and signs as a result of the venom composition.[4,6] For example, in response to bites from Russell's vipers, ptosis was observed only in Indian and Sri Lankan patients,[4,7] whereas pituitary gland infarction and capillary leakage were reported in patients from Myanmar,[8] India,[8] and Sri Lanka.[8,9] In addition, the clinical manifestations of snake envenomation may overlap among different snake species.[4]

In Myanmar, a 3-year study of patients with snakebite from 87 hospitals, conducted between 1998 and 2000, reported that the prevalence of snakebites decreased from 24.6 to 17.4 per 100,000.[10] However, more than 1000 individuals with snake envenomation died annually, particularly young adults, which exerted an economic impact on the country.[4,10] According to the WHO Guidelines, death from snake envenomation occurred in 8% of cases, and the case mortality rate was much higher in some townships, ranging from 10 to 40%.[4]

Predictive factors related to death from snake envenomation have been reported, but results vary among studies. The predictive factors previously identified include neurotoxicity, respiratory failure, acute kidney injury (AKI), capillary leakage, shock, intracerebral hemorrhage, coagulopathy, and dosage of antivenom. However, there may be regional differences in these predictive factors.[11–14]

Therefore, to further elucidate the factors predictive for death from snake envenomation in Myanmar, we performed a prospective observational study at 3 tertiary hospitals in Yangon, Myanmar, from May 2015 to August 2016. This information may assist clinicians in identifying patients who need urgent intervention after snake envenomation and, in turn, help decrease the mortality and disability rates in these patients.

Methods

The Ethics Committees of the Mahidol University in Bangkok, Thailand, and of the University of Medicine 2 in Yangon, Myanmar, approved the study protocol. The standards for the reporting of observation studies in epidemiology (STROBE) statement were followed, and the study adhered to the tenants of the Declaration of Helsinki.[15]

During May 2015 to August 2016, patients presenting with snake envenomation to the Thingangyun Sanpya General Hospital, Insein General Hospital, and North Okkalapa General Hospital (tertiary hospitals in Yangon, Myanmar) and fulfilling the study criteria were eligible for enrollment. Written informed consent was obtained before enrollment from each patient and from the parents or guardians of those below the age of 18 years.

STUDY DESIGN AND PATIENTS

Patients aged 12 years or older who presented with clinical criteria that suggested snake envenomation were enrolled in the study. Patients excluded from the study were 1) those with a history of underlying medical diseases; 2) those taking an anticoagulant or antiplatelet medications; 3) those who were currently pregnant; or 4) those who had received antivenom treatment sourced from a pharmaceutical company whose base country was unknown. After hospital arrival, patients were assessed by emergency medical officers and then transferred to a medical ward or to the intensive care unit, followed by prompt treatment.

On admission, all study patients with snake envenomation were closely observed for management purposes. Snakes were identified by well-trained investigators only if the actual snakes were brought in (dead or alive) with the patients they had bitten. All patients received standard care according to Myanmar national guidelines, following the WHO guidelines,[4] with slight modifications. This included the addition of a 20-min whole blood clotting test (20WBCT) at 2-h intervals for 12 h and then 4-h intervals for an additional 12 h for monitoring snakebite patients. In addition, neurologic symptoms and signs were monitored at 30-min intervals for 12 h and then 1-h intervals for an additional 12 h if the type of snakebite was unknown. Laboratory findings at presentation and thereafter included complete blood counts, 20WBCT, blood sugar (BS), electrolytes (serum sodium, serum potassium, and serum bicarbonate), renal function test (blood urea nitrogen and serum creatinine [SCr]), liver function test, coagulation tests (prothrombin time and activated partial thromboplastin time), fibrinogen level, d-Dimer, and electrocardiography. Chest radiography was performed when abnormal lung sounds were observed. The antivenom treatments used were manufactured by the Myanmar pharmaceutical factory and pharmaceutical companies in India, produced in both liquid form and freeze-dried form and stored at 2 to 8°C until use.

A predefined case report form was constructed for recording patients' data, which included duration from the time of the snakebite to arrival at hospital, place of snakebite, type of snake, anatomic site of bite, clinical variables, laboratory test results, prehospital and hospital management, duration from the time of the snakebite to receiving antivenom treatment, and treatment outcomes.

The data were checked for reliability and accuracy before data analysis.

CLINICAL VARIABLES OF PATIENTS WITH SNAKE ENVENOMATION

Clinical variables of snake envenomation included local and systemic envenomation according to the WHO guidelines.[4] Cardiovascular abnormalities included dizziness, physical collapse, conjunctival edema, hypotension (defined as a systolic blood pressure of less than 90 mm Hg), and cardiac arrhythmia (assessed by electrocardiography). Hemostatic abnormalities included local bleeding, spontaneous systemic bleeding, uncoagulable blood (assessed by 20WBCT), and disseminated intravascular coagulation (DIC) using the international society for thrombosis and hemostasis scoring system.[16] Neurologic abnormalities included blurred vision, muscle paralysis, bulbar palsy, ptosis, external ophthalmoplegia, and paresthesia. Renal abnormalities included dark-colored urine, costovertebral angle tenderness (assessed by physical examination), reduced urine volume including oliguria (urine of less than 400 mL per day) and anuria (no urine), and/or AKI. AKI was diagnosed by an increase in SCr of 0.3 $mg{\cdot}dL^{-1}$ or more within 48 h or an increase in SCr 1.5-fold from baseline. The "Kidney Disease: Improving Global Outcomes" clinical practice guidelines were used for staging of AKI.[17] Capillary leakage was determined by a rise in hematocrit of more than 40% for women and more than 45% for men, with conjunctival edema, pulmonary edema, and/or pleural effusion.[18] Treatment outcomes were summarized at discharge, which included death and occurrence of panhypopituitarism.

SAMPLE SIZE CALCULATION

The sample size was estimated based on data from Myanmar, where a case mortality rate of 10% for adults with snake envenomation was found.[4] It was estimated that a minimum of 216 patients with venomous snakebite would be required to estimate the case mortality rate within 4 percentage points of the true value within a 95% confidence interval (CI).

STATISTICAL ANALYSES

Data were analyzed by SPSS (version 18.0; SPSS Inc, Chicago, IL). Numerical data are presented as medians and interquartile ranges (IQRs), and 2-group comparisons were performed by Mann-Whitney *U* tests in cases of nonnormally distributed data. Categorical data are summarized by numbers (percentages) and were tested by χ^2 test or by Fisher's exact test in cases of expected counts of <5. The association between the occurrence of death and the duration from the time of snakebite to arrival at hospital was analyzed by the χ^2 test for trend. A univariate logistic regression analysis was performed, which included any potential factor as an independent variable and either survival or death as the dependent variable; subjective factors were not chosen. In addition, only 1 appropriated potential factor was chosen when multicollinearity between factors was observed. Any potential factor with a P value of ≤ 0.2 was considered significant. Using a stepwise multivariate logistic regression model, any significant factors from the univariate logistic regression analysis were incorporated into the model, and the stepwise regression selection by backward elimination analysis was introduced to identify significant independent parameters with a $P<0.05$.

Results

PATIENTS AND SNAKEBITE CHARACTERISTICS

A total of 261 adults with snake envenomation were enrolled at tertiary hospitals, including Thingangyun Sanpya General Hospital (231 patients, 88%), Insein General Hospital (24 patients, 9%), and North Okkalapa General Hospital (6 patients, 2%). Of these patients, 15 were excluded because they were treated with antivenom from a pharmaceutical company in an unidentified base country (12 patients), their blood samples were unavailable (2 patients), or they had a history of chronic kidney disease (1 patient). Finally, 246 adults with snake envenomation were recruited into the study. Snake identification was attempted for 74 (30%) patients; the snake species identified were the Russell's viper (63 patients, 85%), cobra (7 patients, 10%), and green pit viper (4 patients, 5%).

BASELINE CHARACTERISTICS, CLINICAL MANIFESTATIONS, MANAGEMENT, AND OUTCOMES OF ADULTS WITH SNAKE ENVENOMATION (EITHER DEATH OR SURVIVAL)

Among the 246 patients, 225 (92%) survived and 21 (8%) died. The median (IQR) duration of hospitalization was 5 (3–13) days for patients who survived and 3 (1–10) days for those who died. Of the 21 patients who died, 6 (29%) died within 1 day after hospitalization, 5 (23%) died on day 2 to 3 of hospitalization, 4 (19%) died between days 4 and 7 of hospitalization, and 6 (29%) died after 1 week of hospitalization. The causes of death were AKI complications (20 patients, 95%), including fluid overload, severe metabolic acidosis, and/or severe

Table 1. Baseline parameters and prehospital management among adults with snake envenomation

Characteristics	*Total (n=246)*	*Death (n=21)*	*Survival (n=225)*	P *value*
Baseline parameters				
Age (y), median (IQR)	32 (23–42)	32 (18–42)	31 (24–42)	0.41
Male sex	196 (80)	15 (71)	181 (80)	0.39
Study site				
TGH	219 (89)	20 (95)	199 (88)	0.48
IGH or NOGH	27 (11)	1 (5)	26 (12)	
Ethnicity				
Burmese	211 (86)	19 (90)	192 (85)	0.75
Other ethnic groups[a]	35 (14)	2 (10)	33 (15)	
Residence				
Yangon city	170 (69)	13 (62)	157 (70)	0.62
Outside Yangon city[b]	76 (31)	8 (38)	68 (30)	
Bitten in a field	178 (72)	18 (86)	160 (71)	0.24
Bitten in lower extremities	194 (79)	19 (90)	175 (78)	0.26
Known snake type	74 (30)	2 (10)	72 (32)	0.06
Prehospital management				
Tight tourniquets	201 (82)	19 (90)	182 (81)	0.38
Immobilization of affected limb	71 (29)	8 (38)	63 (28)	0.47
Wound cleaning	36 (15)	3 (14)	33 (15)	1.00
Wound incision or suction	26 (11)	3 (14)	23 (10)	0.47
Traditional healer	24 (10)	2 (10)	22 (10)	1.00

IQR, interquartile ratio; TGH, Thingangyun Sanpya General Hospital; IGH, Insein General Hospital; NOGH, North Okkalapa General Hospital. Values for total, death, and survival are n (%) unless otherwise noted.

[a] Other ethnic groups included 15 patients from Kayin, 9 patients from India, 7 patients from Mon, 2 patients from Rakhine, and 2 patients from Chin.

[b] Outside Yangon city included Lower Myanmar (36 patients from Bago division and 11 patients from Ayeyarwady division), South Eastern Myanmar (16 patients from Mon state and 4 patients from Kayin state), and Central Myanmar (9 patients from Magway division).

hyperkalemia; refractory shock (8 patients, 38%); and DIC (5 patients, 24%). Cardiovascular complications (4 patients, 19%), including congestive heart failure and cardiac arrhythmia, and neurologic complications (4 patients, 19%), including intracerebral hemorrhage and cerebral edema, were also causes of death.

Baseline characteristics were similar in both the surviving and nonsurviving patients (Table 1). First aid was started in the field by patients themselves or by attendants, traditional healers, or primary healthcare workers. The patients were transported from the field by available transportation, such as bullock cart, boat, motorcycle, or car, with the help of attendants. Prehospital management, including the application of tight tourniquets, immobilization of the affected limb, wound cleaning, wound incision or suction, and management by a traditional healer, were also similar in both groups (Table 1).

Regarding the clinical manifestations (Table 2), patients who died had a significantly higher proportion of local symptoms and signs, including tender lymphadenitis (P=0.03) and bruising (P=0.01). In relation to the systemic symptoms and signs (Table 2), patients who died had a significantly higher proportion of nonspecific systemic symptoms and signs, including 1) vomiting (P=0.03), 2) drowsiness (P=0.01), 3) nausea (P=0.001), 4) prostration (P=0.03), and 5) malaise (P=0.002). Cardiovascular manifestations, including 1) cardiac arrhythmia ($P<0.001$), 2) conjunctival edema ($P<0.001$), 3) pulmonary edema ($P<0.001$), 4) collapse (P=0.04), and 5) hypotension ($P<0.001$), were also significantly more common among the patients who died. Regarding hemostatic manifestations, incoagulable blood on 20WBCT (P=0.01) and spontaneous systemic bleeding ($P<0.001$) were commonly observed among patients who died. Renal manifestations, including oliguria (P=0.002), anuria (P=0.03), and CVA tenderness (P=0.01), were also commonly observed among patients who died. However, neurologic manifestations were similar between patients who died and those who survived.

Regarding hospital management (Table 2), patients who arrived at the hospital more than 1 h after snake envenomation were more likely to die (P=0.01). Of the 21 patients who died, the time between a bite and arrival at the hospital was ≤1 h (1 patient, 5%), >1–4 h (11

Table 2. Clinical manifestations and hospital management among adults with snake envenomation

Characteristics	*Total (n=246)*	*Death (n=21)*	*Survival (n=225)*	P *value*
Local manifestations				
Fang marks	237 (96)	19 (90)	218 (97)	0.17
Pain	230 (94)	20 (95)	210 (93)	1.00
Swelling	217 (88)	19 (90)	198 (88)	1.00
Tender lymphadenitis	165 (67)	19 (90)	146 (65)	0.03
Cellulitis or abscess	72 (29)	4 (19)	68 (30)	0.41
Skin necrosis or gangrene	46 (19)	2 (10)	44 (20)	0.38
Bleeding per fang mark	41 (17)	5 (26)	36 (16)	0.34
Bruising	30 (12)	7 (33)	23 (10)	0.01
Blistering	22 (9)	3 (14)	19 (8)	0.41
Nonspecific manifestations				
Vomiting	138 (56)	17 (81)	121 (54)	0.03
Muscle pain	66 (27)	7 (33)	59 (26)	0.66
Drowsiness	65 (26)	11 (52)	54 (24)	0.01
Abdominal pain	59 (24)	9 (43)	50 (22)	0.06
Nausea	58 (24)	12 (57)	46 (20)	0.001
Prostration	23 (9)	5 (24)	18 (8)	0.03
Malaise	4 (2)	3 (14)	1 (0.4)	0.002
Cardiovascular manifestations				
Dizziness	88 (36)	9 (43)	79 (35)	0.64
Arrhythmia	35 (14)	14 (67)	21 (9)	<0.001
Conjunctival edema	34 (14)	11 (52)	23 (10)	<0.001
Pulmonary edema	18 (7)	9 (43)	9 (4)	<0.001
Collapse	16 (6)	4 (19)	12 (5)	0.04
Hypotension	62 (25)	17 (81)	45 (20)	<0.001
Hemostatic manifestations				
20WBCT incoagulable blood	151 (61)	19 (90)	132 (59)	0.01
Systemic bleeding	82 (33)	16 (76)	66 (29)	<0.001
Local bleeding	48 (20)	6 (29)	42 (19)	0.26
Neurologic manifestations				
Blurred vision	92 (37)	10 (48)	82 (36)	0.44
Ptosis	43 (18)	4 (19)	39 (17)	0.77
Bulbar palsy	23 (9)	3 (14)	20 (9)	0.43
Ophthalmoplegia	22 (9)	2 (10)	20 (9)	1.00
Muscular paralysis	16 (6)	2 (10)	14 (6)	0.63
Paresthesia	12 (5)	2 (10)	10 (4)	0.27
Renal manifestations				
Reduced urine volume				
Oliguria	102 (41)	16 (76)	86 (38)	0.002
Anuria	15 (6)	4 (19)	11 (5)	0.03
CVA tenderness	104 (42)	15 (71)	89 (40)	0.01
Dark-colored urine	23 (9)	3 (14)	20 (9)	0.43
Hospital management				
Bite to hospital >1 h	169 (69)	20 (95)	149 (66)	0.01
Bite to needle >4 h[a]	66 (28)	11 (52)	55 (25)	0.02
Pharmaceutical company[a]				
MPF	156 (66)	17 (81)	139 (64)	0.19[b]
India	38 (16)	1 (5)	37 (17)	
Combined	44 (18)	3 (14)	41 (19)	
Monovalent antivenom[a]	156 (66)	17 (81)	139 (64)	0.19
Total antivenom[a] (mL)	115 (80–180)	140 (100–190)	100 (80–175)	0.08
Antibiotics	229 (93)	21 (100)	208 (92)	0.38

20WBCT, 20-min whole blood clotting test; CVA, costovertebral angle; MPF, Myanmar pharmaceutical factory.

Values for total, death and survival are n (%) unless otherwise noted.

[a] There were 238 patients who had indications for antivenom treatment, including 21 patients who died and 217 who survived.

[b] Patients receiving antivenom produced from a MPF (monovalent antivenom) versus those receiving pooled antivenom produced from other pharmaceutical companies in India (polyvalent antivenom) and those receiving antivenom produced from MPF, combined with antivenom produced in India (monovalent and polyvalent antivenom).

patients, 52%), >4–12 h (6 patients, 29%), and >12 h (3 patients, 14%). Of the 225 patients who survived, the time between a bite and arrival at the hospital was ≤1 h (76 patients, 34%), >1–4 h (118 patients, 52%), >4–12 h (23 patients, 10%), and >12 h (8 patients, 4%). The association between the occurrence of death and time between a bite and arrival at the hospital was observed using the χ^2 test for trend (χ^2=14.0 with 1 degree of freedom, $P<0.001$), indicating strong evidence of a trend for an increasing proportion of patients who died with increasing time between a bite and arrival at the hospital. Increasing time between a bite and arrival at the hospital (≤1 h, >1–4 h, >4–12 h, and >12 h, respectively) showed an increasing odds ratio (OR) for death (1.0, 7.1, 20.0, and 28.5, respectively).

Of the 246 patients, 238 exhibited indications for antivenom treatment, including local envenomation (215 patients, 90%), hemostatic abnormalities (151 patients, 63%), renal abnormalities (128 patients, 54%), cardiovascular abnormalities (69 patients, 29%), and neurotoxic signs (46 patients, 19%). Eight patients did not receive antivenom treatment, including 4 patients who had no indications for antivenom treatment and 4 patients bitten by green pit vipers, for which there was no available monovalent antivenom in Myanmar. A significantly higher proportion of the patients who died (11/21 patients, 52%), compared with those who survived (55/217 patients, 25%), had received antivenom treatment >4 h after the time of the bite (P=0.02) (Table 2). The median time from arrival at the hospital to receipt of antivenom treatment among patients who died was not different from those who survived (0.7 [IQR 0.2–3.1] h vs 0.5 [IQR 0.2–1.1] h, P=0.19). There was no association between the administration of antivenom manufactured by different pharmaceutical companies or the use of a monovalent antivenom and the occurrence of death. The median total dose of antivenom administered was also not different among the patients who died and those who survived (140 [IQR 100–190] mL vs 100 [IQR 80–175] mL, P=0.08) (Table 2). In addition, panhypopituitarism was observed in 14 (6%) of the patients, including 2 of 21 (10%) patients who died and 13 of 225 (5%) patients who survived; these results were similar between the 2 groups (P=0.34).

Of the 246 patients, 47 (19%) patients received management in the intensive care unit. The proportion of patients who received management in the intensive care unit was not different among patients who died and those who survived (7/21 [33%] patients vs 40/225 [18%] patients, P=0.14). Of the 246 patients, 21 (8%) received endotracheal intubation. The proportion of patients who were intubated was significantly higher among patients who died than among those who survived (10/21 [48%] patients vs 11/225 [5%] patients, $P<0.001$). Of the 246 patients, 22 (9%) received wound debridement. The proportion of patients who received wound debridement was not different among patients who died and those who survived (2/21 [10%] patients vs 20/225 [9%] patients, P=1.00). The amputation of a gangrenous toe was performed in 1 patient who survived.

LABORATORY FINDINGS AT PRESENTATION AMONG ADULTS WITH SNAKE ENVENOMATION WHO DIED COMPARED WITH THOSE WHO SURVIVED

The laboratory test results are summarized in Table 3. Patients who died had significantly higher 1) hemoglobin levels (P=0.03); 2) hematocrit levels (P=0.03); 3) white blood cell (WBC) counts ($P<0.001$); 4) absolute neutrophils counts ($P<0.001$); 5) absolute lymphocyte counts ($P<0.001$); 6) prothrombin time levels ($P<0.001$); 7) activated partial thromboplastin time levels (P=0.001); 8) d-Dimer ($P<0.001$); 9) BS (P=0.01); 10) SCr (P=0.002); 11) serum potassium ($P<0.001$); 12) serum aspartate aminotransferase ($P<0.001$); and 13) serum alanine aminotransferase ($P<0.001$) than those who survived (Table 3). In contrast, platelet counts (P=0.002), serum bicarbonate (P=0.01), and serum albumin (P=0.01) were significantly lower among patients who died than among survivors. When these laboratory parameters were categorized based on reference ranges (Table 3), patients with 1) WBC counts >20 $\times 10^3$ cells·μL^{-1} ($P<0.001$); 2) DIC (P=0.003); 3) capillary leakage ($P<0.001$); 4) BS ≥130 mg·dL^{-1} (P=0.03); and 5) AKI stages II to III (P=0.02) were commonly observed among patients who died.

IDENTIFYING PREDICTIVE FACTORS FOR DEATH AMONG ADULTS WITH SNAKE ENVENOMATION

In the univariate analysis, the following variables were identified as clinical parameters associated with death: 1) duration from bite to arrival at the hospital >1 h, 2) WBC counts >20 × 10^3 cells·μL^{-1}, 3) the presence of DIC, 4) the presence of capillary leakage, 5) BS ≥130 mg·dL^{-1}, and 6) AKI stages II to III (Table 4). The multivariate analysis revealed that the independent clinical parameters that were predictive of death

Table 3. Laboratory parameters at presentation among adults with snake envenomation

Characteristics	*Total (n=246)*	*Death (n=21)*	*Survival (n=225)*	P *value*
Hemoglobin ($g \cdot dL^{-1}$)	13.2 (11.6–15.2)	15.2 (12.8–17.4)	13.0 (11.6–15.0)	0.03
Hematocrit (%)	40.0 (34.5–44.8)	44.0 (38.4–52.4)	39.0 (34.4–44.5)	0.03
WBC ($\times 10^3$ cells$\cdot \mu L^{-1}$)	14.8 (10.1–23.5)	40.5 (25.6–57.3)	13.8 (9.8–21.4)	<0.001
ANC ($\times 10^3$ cells$\cdot \mu L^{-1}$)	11.8 (7.1–19.7)	29.8 (21.2–46.3)	10.6 (6.6–16.6)	<0.001
ALC ($\times 10^3$ cells$\cdot \mu L^{-1}$)	2.0 (1.3–2.8)	4.7 (2.7–5.2)	1.9 (1.2–2.6)	<0.001
PLT ($\times 10^3$ cells$\cdot \mu L^{-1}$)	171 (60–234)	65 (44–112)	178 (70–239)	0.002
PT (s)	16.7 (15.4–20.2)	22.1 (17.6–32.7)	16.5 (15.3–19.3)	<0.001
APTT (s)	36.6 (28.5–49.5)	60.2 (34.2–103.8)	36.1 (28.3–48.9)	0.001
Fibrinogen ($g \cdot L^{-1}$)	374 (226–859)	367 (200–980)	383 (227–854)	0.79
d-Dimer ($\mu g \cdot L^{-1}$)	1.8 (0.7–5.1)	7.8 (2.0–25.6)	1.7 (0.6–4.6)	<0.001
BS ($mg \cdot dL^{-1}$)	122 (105–145)	143 (114–170)	121 (104–143)	0.01
BUN ($mg \cdot dL^{-1}$)	32 (20–62)	49 (22–85)	31 (20–62)	0.35
SCr ($mg \cdot dL^{-1}$)	1.1 (0.8–2.4)	2.3 (1.3–3.3)	1.0 (0.8–2.0)	0.002
Na ($mmol \cdot L^{-1}$)	136 (131–139)	134 (133–138)	136 (131–139)	0.75
K ($mmol \cdot L^{-1}$)	4.0 (3.6–4.6)	4.9 (4.2–5.6)	4.0 (3.5–4.4)	<0.001
HCO_3 ($mmol \cdot L^{-1}$)	21 (18–24)	18 (16–21)	21 (18–24)	0.01
ALB ($g \cdot dL^{-1}$)	3.5 (2.8–4.0)	2.7 (2.5–3.4)	3.6 (2.9–4.0)	0.01
AST ($IU \cdot L^{-1}$)	29 (19–63)	104 (40–459)	27 (18–51)	<0.001
ALT ($IU \cdot L^{-1}$)	9 (6–18)	19 (10–128)	9 (6–16)	<0.001
Categorical data				
WBC $>20 \times 10^3$ cells$\cdot \mu L^{-1}$	76 (31)	18 (86)	58 (26)	<0.001
DIC	140 (57)	19 (90)	121 (54)	0.003
Capillary leakage	33 (13)	10 (48)	23 (10)	<0.001
BS $\geq$130 $mg \cdot dL^{-1}$	102 (42)	14 (67)	88 (39)	0.03
AKI stages II–III	68 (28)	11 (52)	57 (25)	0.02

WBC, white blood cells; ANC, absolute neutrophils counts; ALC, absolute lymphocyte counts; PLT, platelets; PT, prothrombin time; APTT, activated partial thromboplastin time; BS, blood sugar; BUN, blood urea nitrogen; SCr, serum creatinine; Na, serum sodium; K, serum potassium; HCO3, serum bicarbonate; ALB, serum albumin; AST, serum aspartate aminotransferase; ALT, serum alanine aminotransferase; DIC, disseminated intravascular coagulation; AKI, acute kidney injury.

Values for total, death and survival are median (IQR), with the exception of categorical data, which are n (%).

included 1) duration from bite to arrival at the hospital >1 h (OR: 9.0, 95% CI: 1.1–75.2; *P*=0.04), 2) WBC counts $>20 \times 10^3$ cells$\cdot \mu L^{-1}$ (OR: 8.9, 95% CI: 2.3–33.7; *P*=0.001), and 3) capillary leakage (OR: 3.7, 95% CI: 1.2–11.2; *P*=0.02) (Table 4).

Discussion

Snake envenomation is a neglected tropical disease, particularly in Southeast Asia.[1,19] In Myanmar, snakebites occur in all geographical regions and affect the young population.[10] The majority of snakebites occur during the ploughing (May through June) and harvesting (October through December) seasons.[10] In the current study, the Russell's viper was the major cause of snake envenomation, accounting for 85% of cases in which the snake species was identified, followed by cobras in 10% and green pit vipers in 5%. Similar to the WHO report in 2010, the most common cause of snake envenomation in Myanmar was the Russell's vipers (90%), with the remainder of cases (10%) caused by cobras, kraits, and green pit vipers.[4] However, in the current study, the type of snake was identified in 30% of patients. This is similar to a report from India in which the type of snake was identified in 23 to 34% of cases[12,14,20]; however, these results are lower than those reported in Brazil (91%)[21] and Nigeria (95%).[22] The higher proportion of snake identification observed in Brazil and Nigeria might because of the terrain in these 2 regions, forest in Brazil[21] and farm land in Nigeria,[22] which differed from the terrain in Myanmar.

In Myanmar, rice fields in various divisions, including Mandalay, Sagaing, Yangon, Bago, Magwe, and Ayeyarwady, are endemic areas for Russell's viper bites. Cobra bites occurred in the divisions of Shan State, Mandalay, Bago, Magwe, Yangon, and Rakhine. Green pit viper bites were reported in Yangon, Bogalay, Moegoke, and Kukkhine.[10] Therefore, patients with

Table 4. Clinical parameters predictive of death among adults with snake envenomation using univariate and multivariate regression analysis

	Univariate analysis			*Multivariate analysis*		
Characteristics	*n*	*OR (95% CI)*	P *value*	*n*	*OR (95% CI)*	P *value*
Bite to hospital >1 h	246	10.2 (1.3–77.5)	0.02	246	9.0 (1.1–75.2)	0.04
WBC $>20 \times 10^3$ cells·μL^{-1}	246	17.3 (4.9–60.8)	<0.001	246	8.9 (2.3–33.7)	0.001
DIC	246	8.2 (1.8–35.9)	0.005			
Capillary leakage	246	8.0 (3.1–20.8)	<0.001	246	3.7 (1.2–11.2)	0.02
BS $\geq$130 mg·dL^{-1}	246	3.1 (1.2–8.0)	0.02			
AKI stages II–III	246	3.2 (1.3–8.0)	0.01			

WBC, white blood cells; DIC, disseminated intravascular coagulation; BS, blood sugar; AKI, acute kidney injury.

snakebite in the current study were recruited from endemic areas of snake envenomation in Myanmar, including 4 divisions (Yangon, Bago, Ayeyarwady, and Magway) and 2 states (Mon and Kayin).

In the current study, the mortality rate was 8%, which is similar to the previous report from Myanmar.[10] Previous reports from India have shown a mortality rate ranging from 3 to 22%, where Viperidae was the most common cause of snake envenomation.[11–14] The causes of death reported in the current study included complications of AKI, refractory shock, DIC, cardiovascular complications, and neurologic complications. Similarly, a previous study reported that causes of death from snake envenomation included cardiovascular complications and respiratory failure.[14] In the current study, of the 63 patients bitten by Russell's vipers, only 4 (6%) had neurologic abnormalities; this figure is less than a previous study from Sri Lanka that reported neurologic abnormalities in 53% of Russell's viper bite patients.[7] In the current study, the neurologic abnormalities observed were ptosis (3 patients, 75%), blurred vision (3 patients, 75%), paresthesia (2 patients, 50%), ophthalmoplegia (1 patient, 25%), and bulbar palsy (1 patient, 25%); these findings are also lower than those from the Sri Lankan study, which reported neurologic abnormalities including ptosis (100%), blurred vision (93%), and ophthalmoplegia (90%).[7]

The current study identified 3 predictive factors for death from snake envenomation. First, duration from bite to arrival at the hospital >1 h (OR 9.0); second, WBC counts $>20 \times 10^3$ cells·μL^{-1} (OR 8.9); and third, the presence of capillary leakage (OR 3.7).

Regarding the duration between snakebite and the time a patient presents to clinical staff, a previous report by Habib and Abubakar showed that each hour of delay from bite to hospitalization increases the odds of death by 1%.[22] These findings support those of the current study, which found that delays >1 h led to an increased likelihood of death, with the highest OR (28.5) associated with delays of >12 h.

The current study reports that WBC count $>20 \times 10^3$ cells·μL^{-1}, which may be a result of inflammation, was one of the major predictive factors for death after snakebite.[23,24] Moreover, we report that patients who died had significantly higher absolute neutrophils counts and absolute lymphocyte counts than those who survived ($P<0.001$). A study by Elbey et al found that neutrophil counts begin to elevate within the first hour after a venomous snakebite as a result of inflammation.[23] Moreover, a previous study by Açikalin and Gökel showed that increased interleukin-6 and tumor necrosis factor-alpha levels, indicators of inflammation, occur with snakebites.[25] However, there were limited data regarding inflammation in patients with snakebites, and further studies are needed.

A prospective study from India reported that the presence of capillary leakage was one of the predictive factors for death and resulted in 100% mortality.[14] Moreover, capillary leakage is commonly observed among patients envenomed by the Russell's viper in Myanmar,[7] and these results are similar to those of the current study. Snake venom, particularly viper venom, contains hemorrhagins and hyaluronidase, which can degrade the compact proteins of the basement membrane underlying endothelial cells and can induce apoptosis.[26] These can lead to increased capillary permeability, which results in a fluid shift from the intravascular to the interstitial space. When this process continues, intravascular volume is severely decreased, leading to shock.[26]

The current results differ from those of studies conducted in different geographic regions.[4,11–14] These could be explained by 1) the different types of snakes in those regions; 2) the geographic variation of venom composition within the same snake species, which is potentially associated with difference in diets among

populations of snakes[27]; 3) the genetic variation of the study population, which may result in different outcomes after envenomation by the same type of snake[7]; and 4) the retrospective nature of the prior studies.[4,11–14]

LIMITATIONS

There were limitations to the current study: 1) most patients with snake envenomation were enrolled from a single hospital, Thingangyun Sanpya General Hospital, which might cause bias; 2) the types of antivenom treatment were prescribed to the patients based on their availability in the hospital; and 3) the snake species was identified in only 30% of cases.

The strengths of the current study included 1) the prospective design of the study to minimize the bias; 2) the availability of data in this study, including clinical variables, laboratory findings, and prehospital and hospital management; and 3) the ability to assess the outcomes.

Conclusions

Adults with snake envenomation who had a duration between bite and arrival at the hospital >1 h, WBC counts $>20 \times 10^3$ cells·μL^{-1}, and capillary leakage at presentation require urgent management, including antivenom treatment and organ support. Such attention may help to reduce both the case mortality and disability rates of patients with snake envenomation in Myanmar. These predictive factors should be explored to provide better outcomes in future research.

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