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Does This Patient Have a Severe Snake Envenomation? The Rational Clinical Examination Systematic Review

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IMPORTANCE Venomous snakebite severity ranges from an asymptomatic dry bite to severe envenomation and death. The clinical evaluation aids in prognosis and is essential to determine the risks and potential benefits of antivenom treatment.

OBJECTIVES To identify historical features, clinical examination findings, basic laboratory testing, and clinical grading scales that will risk-stratify patients with pit viper snake envenomation for severe systemic envenomation, severe tissue injury, and/or severe hematologic venom effects.

DATA SOURCES We conducted a structured search of PubMed (1966-October 3, 2017) and Embase database (1980-October 3, 2017) to identify English-language studies that evaluated clinical features predictive of severe envenomation.

STUDY SELECTION We included studies that evaluated the test performance of at least 1 clinical finding with an acceptable reference standard of severe envenomation for venomous snakes of the Western Hemisphere. Only studies involving the most common subfamily, *Crotalinae* (pit vipers), were evaluated. Seventeen studies with data were available for abstraction.

DATA EXTRACTION AND SYNTHESIS The clinical features assessed and severity outcome measures were extracted from each original study. We assessed severity in 3 categories: systemic toxicity, tissue injury, and hematologic effects. Differences were resolved by author consensus.

RESULTS The pooled prevalence of severe systemic envenomation was 14% (95% CI, 9%-21%). The pooled prevalence of severe tissue injury and severe hematologic venom effects were 14% (95% CI, 12%-16%) and 18% (95% CI, 8%-27%), respectively. Factors increasing the likelihood of severe systemic envenomation included the time from bite to care of 6 or more hours (likelihood ratio [LR], 3.4 [95% CI, 1.1-6.4]), a patient younger than 12 years (LRs, 3.2 [95% CI, 1.5-7.1] and 2.9 [95% CI, 1.3-6.2]), large snake size (LR, 3.1 [95% CI, 1.5-5.7]), and ptosis (LRs, 1.4 [95% CI, 1.0-2.1] and 3.8 [95% CI, 1.8-8.3]). Envenomation by the genus *Agkistrodon* (copperhead and cottonmouth), as opposed to rattlesnakes, decreased the likelihood of severe systemic envenomation (LR, 0.28 [95% CI, 0.10-0.78]). Initial hypofibrinogenemia (LR, 5.1 [95% CI, 1.7-15.0]) and thrombocytopenia (LR, 3.7 [95% CI, 1.9-7.3]) increased the likelihood of severe hematologic venom effects. Other clinical features from history, physical examination, or normal laboratory values were not discriminative.

CONCLUSIONS Clinical features can identify patients at increased risk of severe systemic envenomation and severe hematologic venom effects, but there are few features that are associated with severe tissue injury or can confidently exclude severe envenomation. Physicians should monitor patients closely and be wary of progression from nonsevere to a severe envenomation and have a low threshold to escalate therapy as needed.

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Supplemental content

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Clinical Scenarios

Case 1

A 10-year-old girl presents to the emergency department 6 hours after sustaining a rattlesnake bite to the finger while camping. She has no chronic medical problems and is not taking any medications. She is hemodynamically stable but has swelling, ecchymosis, and tenderness up to the elbow. She has a platelet count of 80 000 cells/mm^3 (reference range, 150 000-400 000/mm^3) and serum fibrinogen level of 100 mg/dL (reference range, 150-400 mg/dL). Her hemoglobin concentration, prothrombin time, and partial thromboplastin times are normal. Is she at risk for severe systemic envenomation or severe hematologic venom effects?

Case 2

A 28-year-old man presents 2 hours after sustaining a bite from a juvenile copperhead snake at the ankle while clearing debris from his yard. He has pain and swelling at the site of the bite but no further progression. He has no other medical conditions, and he is hemodynamically stable. What laboratory studies could be obtained that would help a clinician assess the prospective severity of his clinical course?

Importance of This Question

More than 5 million people worldwide are bitten by venomous snakes annually, causing 125 000 deaths.[1,2] In the United States, there are nearly 9000 venomous snakebites per year, with 5 to 10 deaths.[3] Of these US bites, 98% are from pit vipers (of family Viperidae and subfamily Crotalinae), which includes rattlesnakes (genera *Crotalus*), pygmy rattlesnakes (*Sistrurus*), and cottonmouth or copperheads (*Agkistrodon*).

Snakebite syndromes may range from a dry or asymptomatic bite to severe envenomation. Severe envenomation may result in shock, internal hemorrhage, limb necrosis, compartment syndrome, renal failure, respiratory failure, or even death. The historical features, examination findings, and laboratory test results have varying ability to establish the clinical course and inform patient management. The high cost of currently available therapies and the potential morbidity associated with unnecessary interventions places a premium on accurate assessment of whether the patient has experienced severe envenomation.[4,5]

Pathophysiology of Snake Envenomation

Pit viper snakes inject their venom through replaceable, mobile, hollow, upper fangs. Their venom is a complex mixture of proteins, peptides, and small-molecule toxins. The individual effects and interactions of these toxins produce clinical venom effects in a variety of organ systems. For simplicity, these venom effects are often grouped into several domains, which include tissue injury, hematologic, and systemic venom effects (cardiovascular, neurologic, gastrointestinal, renal, and pulmonary effects).[6] The derangements in organ systems may be primarily from the venom or secondary to hypoperfusion, thrombosis, bleeding, endothelial leak, or the patient's inflammatory response.

Once the venom is injected into the subcutaneous tissue, enzymes such as hyaluronidase and collagenase cause connective tissue destruction and allow for the local spread of the venom.[7,8] Proteolytic enzymes including metalloproteinases, phospholipases, and analogs of tumor necrosis factor α directly injure skin, subcutaneous tissues, and muscle.[9] The patient mounts an acute inflammatory response with increased blood flow, increased vascular permeability, cytokine release, inflammatory cell infiltration, complement activation, and antibody production.[9,10] As a result, most patients present with pain, tenderness, and edema spreading from the site of venom injection. Ecchymosis, erythema, bullae, and tissue necrosis are common.[11]

Crotaline venom contains both procoagulant and anticoagulant toxins, including thrombin-like enzymes and thrombin inhibitors. Other toxins can either induce or inhibit platelet aggregation or cause platelet sequestration or destruction. The results may be localized bleeding at the site of tissue injury or systemic hemorrhage.[12]

Although uncommon, neurotoxicity may range from benign paresthesias to localized or generalized fasciculations or myokymia, generalized motor weakness, and respiratory compromise. Although the venom of snakes found outside the United States can cause direct cardiac depression, hypotension from pit viper snake venom is usually caused by increased vascular permeability and/or systemic bleeding leading to hypovolemia. Envenomation can cause other systemic effects, such as vomiting, acute kidney injury, or pulmonary compromise.[11]

Patients with snake envenomation may present in a variety of locations and come into contact with multiple specialists, although most physicians will encounter patients with snakebites only a few times in their careers. Thus, a clear understanding of the test characteristics of various findings for determining severity would be helpful. We conducted a systematic review to determine the accuracy of historical features, physical examination findings, laboratory testing, and combinations of findings that assess the severity of snake envenomation.

Key Points

Question What clinical features risk-stratify patients with snakebite as having severe envenomations?

Findings In this systematic review, the pooled prevalence of severe systemic envenomation, severe tissue injury, and severe hematologic venom effects was 14%, 14%, and 18%, respectively. Time from bite to care longer than 6 hours, patient age younger than 12 years, large snake size, and ptosis increased the likelihood of severe systemic envenomation, while envenomation by cottonmouth and copperhead (*Agkistrodon*) snakes (compared with rattlesnakes) decreases the likelihood of severe systemic envenomation and initial hypofibrinogenemia and thrombocytopenia increases the likelihood of severe hematologic venom effects.

Meaning Physicians should evaluate patients with snakebites for these features to determine which are at increased likelihood of severe envenomation and should also be wary of progression from nonsevere to a severe envenomation.

Methods

Search Strategy and Study Selection

We sought articles that evaluated the test characteristics of history, physical examination, widely used, immediately available labo-

ratory tests, and severity grading scales. A medical librarian performed a structured search of PubMed (1950-October 3, 2017) and Embase database (1980-October 3, 2017) to identify English-language studies examining the identification of severe snakebite. Keys words and phrases included *snake bite*, *snakebite*, *sensitivity*, *specificity*, *diagnosis*, *history*, *examination*, *physical examination*, *medical history taking*, *professional competence*, *reproducibility of results*, *observer variation*, *diagnostic tests*, *decision support techniques*, and *Bayes theorem*. Additional articles were identified from searching the bibliographies of relevant studies. All articles with data available to calculate sensitivity and/or specificity for each index test in pit viper snakes were candidates for inclusion.

This review evaluates only envenomation by *Crotalinae* (pit viper) species native to the Americas, because snake envenomation is an extremely heterogenous disease depending on which family or subfamily of snake is involved. The *Crotalinae* subfamily predominates in the United States, and our search did not reveal any articles about envenomation from coral snakes in the Americas (of the family Elapidae and genera *Micrurus* or *Micruroides*). Although health care outside the United States may lead to markedly different outcomes, we included studies from North America and South America because the index tests for severity across these locales are likely to be generalizable, given that the snakes are of the same *Crotalinae* subfamily.

Two authors (C.J.G. and C.S.E.) reviewed all studies to determine if they met inclusion criteria and assessed the methodologic quality of all selected articles using the Rational Clinical Examination grading scale.[13] We assessed for bias using Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS 2) standards and determined study quality level 1 through 4 based on this assessment. Studies graded level 1 were the highest quality, with an independent blinded comparison of the index test with a valid reference standard in more than 200 consecutively enrolled patients. Studies at level 4 were the lowest-quality studies included and used a non-independent comparison of index test with a valid reference standard (eTables 1 and 2 in the Supplement).[14] All data points were dually abstracted. For articles that evaluated more than 1 index test, the methodologic quality of the study was evaluated for each test. Disagreements were resolved by article review and discussion between the authors.

Because death owing to snake envenomation is rare in the United States, morbidity is the important reference standard evaluated in this systematic review. Because snake envenomation can affect several organ systems, we assessed severity by 3 categories: systemic toxicity, tissue injury, and hematologic effects. Severe systemic toxicity was determined using commonly used comprehensive grading scales.[6,11,15] Severe tissue injury is defined as tissue necrosis. Severe hematologic venom effect is reported as recurrent, persistent, or late coagulopathy.[16]

Statistical Analysis

We calculated sensitivity, specificity, likelihood ratios (LRs), and 95% CI from 2 × 2 tables for each historical feature, examination finding, or laboratory test result at predicting severe envenomation. We accepted the original investigators' classification of severe envenomation but grouped and reported these data by severe systemic envenomation, severe tissue injury, and severe hematologic effects.

For studies with a 0-cell value, 0.5 was added to each to calculate the LR.[17] The summary prevalence (pretest probability) was calculated with random-effects measures. For clinical features evaluated in a single study, we report the point estimate and 95% CIs. For clinical features that were only evaluated in 2 studies, we provide statistics from each study. For findings with 3 or more studies graded as at least level 3, we report a summarized point estimates using bivariate random effects model diagnostic meta-analysis. Heterogeneity for findings reported in at least 3 level 3 studies were assessed. Meta-analysis was modeled through the mada and meta packages of the R software, version 3.2.3 (R Foundation for Statistical Computing).

Data for findings from Rational Clinical Examination studies graded level 4 were not combined with studies graded level 3. Instead, studies graded level 4 are shown as single point-estimates in all cases.

Results

Search Results

The search strategy identified a total of 2203 studies. Of these, we excluded 109 as duplicates and 1894 after review of their abstracts and titles. We reviewed the full text of 200 studies, of which 17 met the inclusion criteria (eTable 3 and the eFigure in the Supplement). Twenty-two individual clinical features (eTable 4 in the Supplement) were identified in 17 studies.[15,16,18-32] There were 6 studies graded level 3 and 11 studies graded level 4. The major source of bias (eTable 5 in the Supplement) was from performance of the reference standard, which was often done without blinding to the index test and/or was limited by incorporation of the index test within the reference standard.

There were 5915 total patients in the 17 included studies.[15,16,18-32] Individual patient demographic data was not reported in all studies. Of the 5690 participants whose sex was reported, 4167 (73.2%) were male. Of the 1129 whose ages were reported, 836 (74.0%) were adults (typically, but not always, defined as 18 years and older). There were 4786 patients in studies with both children and adults. Based on reported median ages, it appears that most participants were adults; however, exact proportions were not reported.

Some patients had evaluation of more than 1 clinical feature compared with the defined reference standard. There were 3120 patients with evaluation of a historical feature, 4233 with evaluation of a physical examination finding, 356 with evaluation of a laboratory test, and 176 with evaluation of combined findings. Of these patients, 1547 were evaluated for severe systemic toxicity, 3989 were evaluated for severe tissue injury, and 379 were evaluated for severe hematologic venom effects.

Prevalence of Severe Snakebite in Patients With Possible Snakebite

The summary prevalence of severe systemic envenomation among the studies graded level 3[15,21,22,24,26,28,31] using comprehensive severity scales was 14% (95% CI, 9%-21%]; I^2 = 60%). The prevalence of severe tissue injury was 14% (95% CI, 12%-16%). The geographic locales for these studies were North America[6,16,21,29-31] and South America.[15,18-20,22,24-28,32] The prevalence of severe hematologic venom effects was 18% (95% CI, 8%-27%).

Accuracy of Findings From Clinical History and Physical Examination

Historical factors and symptoms (**Table 1**) including patient age, patient sex, large snake size, time from bite to medical care or treatment, snake species, and myalgias were evaluated in these studies. Most of these features could not adequately discriminate severe snakebite. The most significantly positive historical feature was the time from envenomation to initial treatment 6 or more hours (LR, 3.4 [95% CI, 1.1-6.4]) for severe systemic envenomation.[15,24,26,28] A patient 12 years or younger had similarly increased the likelihood of severe systemic envenomation (LRs, 3.2 [95% CI, 1.5-7.1][26] and 2.9 [95% CI, 1.3-6.2][30]). Patients bitten by a large snake were more likely to have a severe systemic envenomation (LR, 3.1 [95% CI, 1.5-5.7])[21,24,28] and severe tissue injury (LR, 2.3 [95% CI, 2.0-2.7]).[22,27] Generally, snake size was reported as an adult or juvenile based on patients' or clinicians' description. When the snake was brought in to the emergency department, live snake sizes were estimated by an expert, and snake carcasses were measured.

Snakebites from copperhead or cottonmouth snakes were less likely to cause severe systemic envenomation than rattlesnake envenomation (LR, 0.28 [95% CI, 0.10-0.78]).[30] Bites from smaller snakes decreased the likelihood of severe systemic envenomation (LR, 0.45 [95% CI, 0.23-0.74]).[21,24,28] Other clinical features from patient histories had poor performance, wide ranges, or LR confidence intervals that included 1.0.

Physical examination findings (Table 1) have been less well studied than demographic or historical factors. The presence of ptosis was associated with severe systemic envenomation and even death (LRs, 1.4 [95% CI, 1.0-2.1][18] and 3.8 [95% CI, 1.8-8.3][19]). Bite to the upper extremity, bite to a digit, local edema, bleeding distant to the bite site, and ptosis were assessed. Patients who had been bitten on a digit as opposed to elsewhere on the body (LRs, 3.1 [95% CI, 2.4-4.0][22] and 1.3 [95% CI, 1.0-1.6][27]) and those presenting with bleeding distant to the bite site (LR, 2.8 [95% CI, 1.8-4.4])[27] were more likely to have a severe tissue injury resulting in necrosis.

In cases of South American pit viper envenomation, the absence of ptosis was a good prognostic sign; such patients had a lower likelihood of a severe systemic envenomation or death (LRs, 0.21 [95% CI, 0.02-3.0][18] and 0.08 [95% CI, 0.01-0.14][19]). The absence of distant bleeding did not have a strong association with the development of necrosis (LR, 0.85 [95% CI, 0.77-0.94]).[27]

Accuracy of Laboratory Testing

Laboratory values were evaluated in 4 studies (**Table 2**), and all patients in these studies had laboratory samples obtained prior to receiving antivenom. All symptomatic patients in the studies received antivenom, with the exclusion of 20 of 110 patients (18.2%) with mild envenomation in a study evaluating whole-blood clotting time.[20] Laboratory values were not discriminatory in determining severe systemic envenomation or tissue injury (Table 2). The most useful findings came from a single study[16] that compared initial laboratory results against a clinical reference standard of severe hematologic venom effects, defined as coagulopathy or thrombocytopenia 4 or more days after a snakebite. Initial hypofibrinogenemia, defined as any measured fibrinogen lower than normal limits, significantly increased the likelihood of a severe hematologic venom effects by this definition (LR, 5.1 [95% CI, 1.7-15]).[16] Initial thrombocytopenia, defined as a platelet count less than 150 000/mm^3, was also associated with a severe hematologic venom effects (LR, 3.7 [95% CI, 1.9-7.3]).[16] Absence of thrombocytopenia (defined as a platelet count ≥150,000/mm^3) decreased the likelihood (LR, 0.36 [95% CI, 0.15-0.88]).[16] All other normal coagulation tests had confidence intervals that crossed 1.0 and did not allow conclusions about their usefulness.

Accuracy of Clinical Grading Scales

Several different scales have been developed to assess snakebite severity in the clinical and research settings.[6,11,15,29,33,34] The most commonly used clinical grading scale for pit viper envenomation evaluates the 3 domains of tissue, systemic, and coagulation venom effects to determine 1 of 3 levels of severity (minimal, moderate, and severe).[11,35,36] The overall clinical assessment is based on the most serious of the domains. Although this scale is easily applied clinically, it has limitations in parsing the degrees of severity for minimal and moderate envenomations. Additionally, it has never been evaluated using a reference standard for severe outcomes, and to our knowledge, no data are available to determine performance.

A snakebite severity scale (SSS) was developed to allow for serial assessments of severity during clinical trials[6,35,36] of currently available antivenom agents. The purpose of the scale was to quantify the findings used by experts in pit viper envenomation, so that the factors that informed their clinical impressions could be used as a measurable study outcome. The SSS uses venom effects in 6 venom effect domains (pulmonary, cardiovascular, local wound, gastrointestinal, hematologic, and central nervous system) and allows for a detailed description of the severity of the snake envenomation. The domains appear to be independently useful because of their pairwise correlations coefficients that range from 0.17 to 0.39.

In the original study, the scale was correlated with the expert physician consensus at presentation, with mean scores categorized as no effect (SSS ≤1), mild (SSS = 2), moderate (SSS = 3-7), and severe (SSS ≥8).[6] Among 108 patients hospitalized following snakebites, experts' clinical impression of no clinical worsening was present in 21 of 108 patients (19.4%; mean change in SSS, 0.2), slight worsening in 44 of 108 patients (40.7%; mean change, 1.9), moderate worsening in 30 of 108 patients (27.8%; mean change, 3.8), and marked worsening in 13 of 108 patients (12.0%; mean change, 6.6). When following the clinical course, a change in score of only 1 point had a sensitivity of 97% (95% CI, 90%-99%) and specificity of 81% (95% CI, 57%-94%) compared with the expert clinicians' clinical assessment of a worsening condition. Despite the accuracy of the SSS in establishing existing severity and detecting a change in severity, its ability to prognosticate the severity of the course of envenomation has never been assessed.

Only the Brazilian Ministry of Health Grading Scale for assessing the likelihood of a severe envenomation has been compared with an independent reference standard.[29] The reference standard for severe envenomation in 1 study[29] required thrombosis or death, and in a second study[15] the presence of infection, acute renal failure, or death. For these outcomes, a grade of severe effects had an LR range of 2.3 to 7.7, while a grade of mild or moderate effects had an LR of 0.36 to 0.41 for severe envenomation.

Discussion

The cornerstone of venous snakebite treatment is antivenom, which binds the active venom components with the hope of mitigating

Table 1. Diagnostic Accuracy of History and Examination Findings for Severe Snake Envenomation[a]

Source	Reference Standard[b]	Quality Level	Sensitivity, % (95% CI)[c]	Specificity, % (95% CI)[c]	Positive Likelihood Ratio (95% CI)[c]	I^2, %	Negative Likelihood Ratio (95% CI)[c]	I^2, %
Demographic and Historical Features								
Time from bite to treatment ≥6 h								
Level 3 studies (n = 4)[15,24,26,28]	A severe BMHSGS score,[15,24] a severe CGS score,[28] and acute renal failure[26]	3	38 (14-69)	88 (83-92)	3.4 (1.1-6.4)	12	0.69 (0.34-0.98)	33
Level 4 studies (n = 4)								
Bucharetchi et al,[19] 2002	A severe BMHSGS score	4	88 (40-99)	85 (65-94)	5.8 (2-16.2)	NA	0.15 (0.01-1.98)	NA
Otero et al,[25] 2002	A severe CGS score		85 (68-94)	68 (39-88)	2.7 (1.1-6.4)		0.22 (0.09-0.56)	
Ribeiro et al,[27] 2001	necrosis		5 (2-11)	93 (90-94)	0.7 (0.3-1.6)		1.03 (0.98-1.08)	
Thomas et al,[29] 1998	death or thrombosis		97 (97-100	78 (69-86)	4.5 (3.0-6.7)		0.04 (0.00-0.65)	
Patient age ≤12 y								
Pinho et al,[26] 2005	Acute renal failure	3	38 (23-56)	88 (79-94)	3.2 (1.5-7.1)	NA	0.70 (0.52-0.94)	NA
White and Weber,[30] 1991	Severe CGS score	4	48 (30-67)	83 (70-91)	2.9 (1.3-6.2)		0.63 (0.42-0.94)	
Large (adult) snake for given species								
Level 3 studies (n = 3)[21,24,28]	A severe BMHSGS score,[24] a severe CGS score,[28] and an SSS score ≥8[21]	3	66 (32-89)	88 (44-94)	3.1 (1.5-5.7)	31	0.45 (0.23-0.74)	0
Level 4 studies (n = 3)[22,27,32]								
Jorge et al,[22] 1999	Amputation	4	92 (52-99)	64 (61-67)	2.6 (2.0-3.3)	NA	0.13 (0.01-1.85)	NA
Ribeiro et al,[27] 2001	Death		70 (61-78)	70 (66-73)	2.3 (2.0-2.7)		0.43 (0.32-0.57)	
Milani et al,[32] 1997	Necrosis		19 (7-42)	100 (78-100)	5.1 (0.3-90)		0.84 (0.65-1.1)	
Snake genus rattlesnake								
White and Weber,[30] 1991	A severe CGS score	4	85 (67-95)	51 (36-66)	1.8 (1.2-2.5)	NA	0.28 (0.10-0.78)	NA
Myalgia								
Barravierra et al,[18] 1989	Death	4	50 (13-87)	0.94 (0.81-0.98)	7.8 (1.5-41)	NA	0.53 (0.17-1.70)	NA
Bucharetchi et al,[19] 2002	A severe BMHSGS score	4	87 (65-96)	0.46 (0.24-0.7)	1.6 (1.0-2.7)		0.28 (0.08-1.00)	
Time from bite to treatment ≥2 h								
Otero et al,[25] 2002	Death or thrombosis	4	92 (72-98)	20 (9-41)	1.2 (0.9-1.5)	NA	0.39 (0.07-2.2)	NA
Male patient								
Yin et al,[31] 2011	Difficulty achieving initial control[d]	3	88 (75-94)	18 (13-24)	1.1 (0.9-1.2)	NA	0.68 (0.30-1.6)	NA
Signs								
Bleeding distant to bite site								
Ribeiro et al,[27] 2001	Necrosis	4	22 (15-30)	92 (90-94)	2.8 (1.8-4.4)	NA	0.85 (0.77-0.94)	NA
Ptosis								
Barraviera et al,[18] 1989	Death	4	100 (22-100)	78 (63-88)	3.8 (1.8-8.3)	NA	0.21 (0.02-3.0)	NA
Bucharetchi et al,[19] 2002	A severe BMHSGS score	4	100 (85-100)	32 (14-58)	1.4 (1.0-2.1)		0.08 (0.01-0.14)	
Bite on digit								
Jorge et al,[22] 1999	Amputation	3	75 (54-88)	76 (74-77)	3.1 (2.4-4.0)	NA	0.33 (0.16-0.68)	NA
Ribeiro et al,[27] 2001	Necrosis	4	40 (31-49)	68 (65-71)	1.3 (1.0-1.6)		0.88 (0.75-1.00)	

(continued)

Table 1. Diagnostic Accuracy of History and Examination Findings for Severe Snake Envenomation[a] (continued)

Source	Reference Standard[b]	Quality Level	Sensitivity, % (95% CI)[c]	Specificity, % (95% CI)[c]	Positive Likelihood Ratio (95% CI)[c]	I^2, %	Negative Likelihood Ratio (95% CI)[c]	I^2, %
Upper extremity bite								
Yin et al,[31] 2011	Difficulty achieving initial control of envenomation syndrome[d]	3	77 (63-87)	38 (32-45)	1.2 (1.0-1.5)	NA	0.61 (0.35-1.1)	NA
Ribeiro et al,[15] 2001	Necrosis	4	41 (32-50)	67 (64-71)	1.2 (1.0-1.6)	NA	0.88 (0.75-1.00)	NA
Local edema								
Barraviera et al,[18] 1989	Death	4	50 (13-87)	83 (69-92)	3.0 (0.8-11.0)	NA	0.60 (0.19-1.90)	NA
Bucharetchi et al,[19] 2002	A severe BMHSGS score	4	61 (39-79)	32 (14-58)	0.9 (0.53-1.50)		1.23 (0.48-3.20)	

Abbreviations: BMHSGS, Brazilian Ministry of Health Severity Grading Scale; CGS, clinical grading scale; NA, not applicable; SSS, snakebite severity score.

[a] See eTable 2 in the Supplement for results from individual studies.

[b] Severity was based on a defined severe clinical outcome, a severe CGS score, SSS of 8 or more, or a severe BMHSGS score.

[c] Findings from 1 study reported as point estimate (95% CI), 2 studies as range, and 3 or more studies as random effects bivariate summary measure.

[d] Defined as the arrest of these venom effects after antivenom administration.

Table 2. Diagnostic Accuracy of Coagulation Tests for Severe Snake Envenomation

Clinical Factor[a]	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive Likelihood Ratio (95% CI)	Negative Likelihood Ratio (95% CI)
Seifert et al,[16] 2011				
Abnormal fibrinogen	46 (22-71)	91 (80-96)	5.1 (1.7-15)	0.60 (0.35-1.0)
Platelets <150 000/mm^3	71 (43-89)	81 (68-89)	3.7 (1.9-7.3)	0.36 (0.15-0.88)
Abnormal partial thromboplastin time	46 (22-71)	85 (73-92)	3.1 (1.2-7.5)	0.64 (0.37-1.1)
Abnormal prothrombin time	96 (70-100)	63 (49-75)	2.6 (1.8-3.1)	0.07 (0.00-1.0)
Abnormal D dimer	100 (47-100)	57 (43-70)	2.2 (1.6-3.1)	0.07 (0.00-1.1)
All coagulation parameters checked and normal[b]	100 (74-100)	100 (37-100)	1.7 (0.2-18)	0.71 (0.09-5.5)
Abnormal coagulation or platelet count[c]	71 (43-89)	81 (68-89)	3.7 (1.9-7.3)	0.36 (0.15-0.88)
Moss et al,[23] 1998				
Urine abnormal[d]	93 (73-98)	33 (17-53)	1.4 (1.0-1.9)	0.23 (0.04-1.2)
Bucharetchi et al,[15] 2001				
Abnormal coagulation or platelet count[c]	72 (47-88)	45 (33-58)	1.3 (0.9-1.9)	0.63 (0.27-1.4)
Gaus et al,[20] 2014				
Whole-blood clotting time	100 (74-100)	20 (14-29)	1.2 (1.0-1.4)	0.22 (0.02-3.4)

[a] The reference standard for Seifert et al[16] was coagulopathy, defined as recurrent, persistent, or late, new-onset coagulopathy at 4 or more days after a snakebite; for Moss et al,[23] a moderate snakebite severity score; for Bucaretchi et al,[15] a severe Brazilian Ministry of Health Severity Grading Scale score; and for Gaus et al,[20] a severe Clinical Grading Scale score. All studies were graded level 4, except Bucaretchi et al[15] (level 3).

[b] All coagulations parameters that were available were normal. Measurement of all coagulation parameters was not required.

[c] All coagulation parameters were measured and all normal, including normal fibrinogen, D dimer, platelets, prothrombin time, partial thromboplastin time, and less than a 20% rise in platelets after antivenom treatment.

[d] Defined as positive chemical analysis for blood in urine (without microscopic analysis).

venom effects. Thus, individuals with venomous snakebites who are unable to get care within 6 hours are more likely to experience severe systemic envenomation. We assessed 8 studies[15,19,24-29] showing consistency of this association, although only 4[15,24,26,28] were of high enough quality to include in the meta-analysis.

Patients younger than 12 years and those bitten by large snakes have an increased likelihood of severe systemic snake envenomation. Large snake size also increased the likelihood of severe tissue injury. It is intuitive that younger patients have less body mass and will have a higher concentration of venom for any given amount delivered. It has also been shown that larger snakes have more venom available and deliver more venom, thereby increasing the likelihood of a severe bite.[37,38] This does not eliminate the possibility that patients older than 12 years or those bitten by a juvenile snake can experience severe envenomation. For example, with a prevalence of severe systemic envenomation at 14%, patients older than 12 years still have more than a 9% chance of having a severe snakebite. As most patients with snakebites are adults, most cases of severe snake envenomation will occur in adult patients.

The *Agkistrodon* genus (which includes copperhead and cottonmouth snakes) is widely considered to deliver less severe envenomation than rattlesnakes do.[39-43] The only study available to assess this clinical feature showed a modest decrease in the likelihood of severe envenomation. Based on these results, snake genus alone should not be used to determine likelihood of severe envenomation.

No physical finding significantly increased the likelihood of severe systemic envenomation. However, in South American pit viper envenomation, the absence of ptosis did decrease the likelihood of severe systemic envenomation. This clinical feature was evaluated in 2 Brazilian studies involving *Crotalus durissus*.[18,19] Neurotoxins and clinical neurotoxic effects of envenomation from this species are well described. In North America, clinical neurotoxic venom effects are uncommon and primarily seen in *Crotalus scutulatus* (Mojave rattlesnake), *Crotalus helleri* (Southern Pacific rattlesnake), and *Crotalus horridus* (timber rattlesnake).[44-46] Consequently, the LR for ptosis after South American pit viper snakebites may not generalize to pit viper bites in the United States. In the United States, absence of ptosis should not be reassuring, because it is lacking in most severe envenomations from North American species.

Bleeding distant to the site of envenomation increased the likelihood of severe tissue injury in 1 South American study,[27] but its absence was not shown to be protective. This is an interesting finding, because other work has shown little correlation between severity of different venom effect domains.[6] It is likely that a severe venom effect in 1 domain increases the likelihood of severe venom effect in another, but the absence of a severe effect in a single venom effect domain does not exclude a severe effect in another.

Laboratory values are more useful in assessing severe hematologic venom effects. Patients with hypofibrinogenemia or thrombocytopenia have an increased likelihood of severe disease, specifically late venom-induced coagulopathy and thrombocytopenia. The caveat is that these test results are continuous variables that were treated dichotomously in the studies. In reality, the degree of thrombocytopenia, hypofibrinogenemia, prothrombin time, or partial thromboplastin time elevation likely play a more important role in determining the likelihood of severe hematologic venom effects. Likewise, a normal platelet count decreases the likelihood of severe hematologic effects. Other coagulation parameters should be used more cautiously because the confidence intervals around the negative LR point estimates are wide and cross 1.0.

Scenario Resolution

Case 1

This patient has multiple factors that increase her likelihood of having a severe systemic envenomation or hematologic venom effects. Her age increases her risk of severe systemic envenomation (LR range, 2.9-3.2). Additionally, her risk of bleeding is increased by presenting thrombocytopenia (LR, 3.7 [95% CI, 1.9-7.3]) and hypofibrinogenemia (LR, 5.1 [95% CI, 1.7-15]), despite the fact that they are not severe derangements. Although her other laboratory values are normal, they should not be used to exclude severe envenomation. Using a baseline prevalence of severe systemic envenomation of 14% and severe hematologic venom effects of 18%, these findings increase the probability of severe systemic envenomation to 32% (younger age) and severe hematologic venom effects to 53% (hypofibrinogenemia).

Case 2

This patient has no factors that increase the likelihood of a severe snakebite over the baseline prevalence. He was bitten by a juvenile (not large) snake (LR, 0.45 [95% CI, 0.23-0.74]), and it was a cottonmouth (LR, 0.28 [95% CI, 0.10-0.78]). Using the baseline probability of 14%, the absence of these 2 findings decreases the probability of severe systemic envenomation to 4.4 to 6.8%. The physician should obtain a platelet count and coagulation parameters to determine if the patient has other features that increase his risk of severe hematologic venom effects.

Limitations

This review has limitations inherent in the study question, design, and the available study data. The reference standard of severe snakebite is defined differently across studies and is based on which venom effect the study evaluated. National or international consensus on clinical scales with standardized outcome measures could facilitate clinical care and future research. We addressed this lack of clear consensus by grouping and reporting severity by primary venom effect domain: systemic envenomation, tissue injury, or hematologic venom effects. When evaluating severity, we used consistent definitions within these groups.

The reference standard in the studies evaluating severe systemic envenomation use a severity grading scale that incorporates the multiple organ systems venom effects. This has face validity, since there are no single laboratory or pathological tests that confirms a patient's position on the continuum from no envenomation to mild, moderate, or severe envenomation. However, the components of these scales often contain elements of the index test, thereby creating incorporation bias in the evaluation of test performance. The SSS has been correlated with expert opinion on severity; however, no prospective validation study has been performed in which the SSS is used to prognosticate outcomes of severe envenomation.

Another limitation of this review is the lack of generalizability to other snake types. As the available publications limited our review to snake envenomation from *Crotalinae* (pit viper) genera found in the Americas, these results are not generalizable to snake envenomation from other snake families or subfamilies nor European or Asian pit vipers. Different snake venoms cause different clinical presentations, and the factors associated with severity are likely to be quite different.

Lastly, the analysis does not assess the ability of any clinical or laboratory factor alone to determine when to initiate antivenom treatment. Rather these factors should be used in conjunction with the overall clinical picture when weighing the potential benefits and potential harms of administration of a specific antivenom in the individual patient.

Conclusions

Few clinical features can be easily used to exclude severe envenomation in a patient with a snakebite. The time from snakebite to care of more than 6 hours, a patient younger than 12 years, envenomation by a large snake, and ptosis increase the likelihood that a bite was severe. Coagulation parameters should be obtained as abnormalities of these test results increase the likelihood of a severe hematologic venom effects. Severe bites remain difficult to exclude even with normal laboratory testing. Antivenom is currently recommended in both severe and nonsevere envenomation, but timing and amount of antivenom varies with severity.[47] Consequently,

physicians should be monitor patients closely, be wary of progression of symptoms after an apparently nonsevere bite, and have a low threshold to escalate therapy as needed. Because the timeframe for observing patients and decisions about antivenom require expertise, emergency departments should identify experts that they can access for consultation.

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Supplementary Online Content

Gerardo CJ, Vissoci JRN, Evans CS, Simel DL, Lavonas EJ. Does this patient have a severe snake envenomation? the Rational Clinical Examination systematic review. *JAMA Surg*. Published online February 13, 2019. doi:10.1001/jamasurg.2018.5069

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. QUADAS 2 Criteria for Scoring Bias of Individual Items by Study[1]

Domain 1: Patient Selection	Question	Answers
Risk of Bias	1. Was consecutive or random sample of patients enrolled?	Yes/No/Unclear
	2. Was a case-control design avoided?	Yes/No/Unclear
	3. Did the study avoid inappropriate exclusions?	Yes/No/Unclear
	Overall risk of bias: could the selection of patients introduced bias?	Low/High
Application	4. Is there concern that the included patients do not match the review questions?	Low/High
Domain 2: Index Test		
Risk of Bias	5. Was the index test interpreted without knowledge of the reference standard?	Yes/No/Unclear
	6. If a threshold was used, was it specified beforehand?	Yes/No/Unclear
	Overall risk of bias: could the index test, its conduct or interpretation introduced bias?	Low/High
Application	7. Is there concern that the index test, its conduct or interpretation differ from the review question?	Low/High
Domain 3: Reference Standard		
Risk of Bias	8. Is the reference standard likely to classify the target condition?	Yes/No/Unclear
	9. Was the reference standard interpreted without knowledge of the index test?	Yes/No/Unclear
	10. Were uninterpretable/intermediate results reported?	Yes/No/Unclear
	Overall risk of bias: could the reference standard, its conduct or interpretation have introduced bias?	Low/High
Application	11. Is there concern that the target condition as defined by the reference standard does not meet the review question?	Low/High
Domain 4: Flow and Timing		
	12. Was there an appropriate interval between determination of the index test and reference standard?	Yes/No/Unclear
	13. Did all patients receive a reference standard?	Yes/No/Unclear
	14. Did patients receive the same reference standard?	Yes/No/Unclear
	Overall risk of bias: could the patient flow or timing have introduced bias?	Low/High

eTable 2. Determination of Study Quality Level

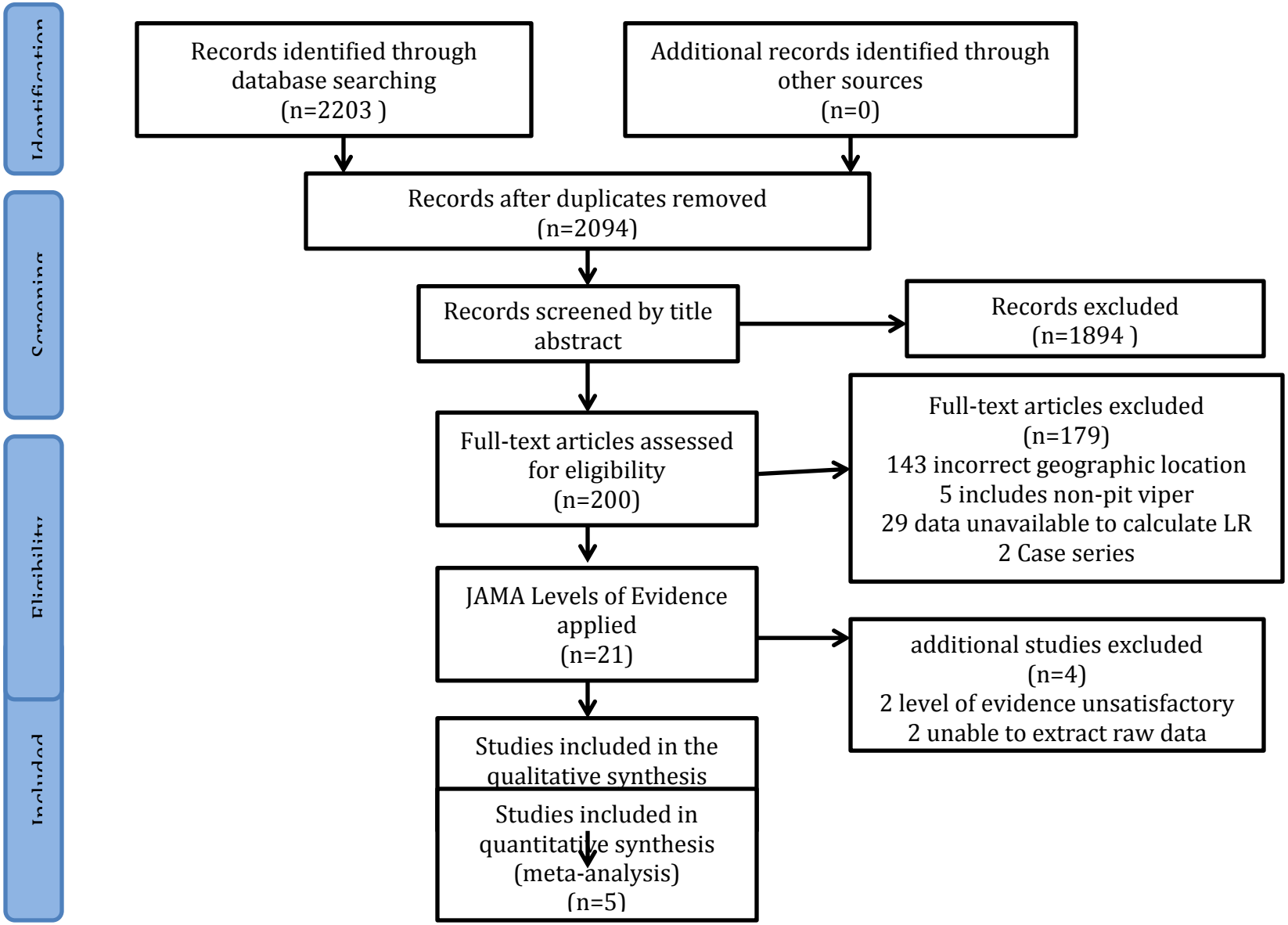
Level	Description
1	Highest quality study (independent blinded comparison of index test with a valid reference standard in large number [≥200] consecutive patients that match the review question. (eg. low risk of bias domains 1, 2, 3, 4)
2	Similar to level 1, but enrolled <200 patients. (eg. low risk of bias domains 1, 2, 3, 4)
3	Independent blinded comparison of index test with a valid reference standard in convenience sample. (eg. High risk of bias domain 1, low risk of bias domain 2 and 3.
4	Non-independent comparison of index test with a valid reference standard. (all others)

eTable 3. Create new eTABLE that shows inclusion/exclusion criteria of included studies

Author, year	Location(s)	Inclusion criteria	Exclusion criteria	Sample size, n	Comments
Barrarviera 1989	Brazil	Hospitalized patients with crotalid envenomation	Not defined	40	Retrospective cha review with minim methods describe
Bucharetchi 2001	Brazil	Admitted to hospital with *Bothrops* spp envenomation Age ≤ 15 yrs	Age > 15 yrs Unable to identify as Bothrops	73	Prospective Multisystem reference standard
Bucharetchi 2002	Brazil	Admitted to hospital with *Crotalus durissus* envenomation	Not identified	31	Retrospective Low numbers
Gaus 2013	Ecuador	All snakebite that presented to facility using electronic medical record search	WBCT laboratory not drawn	110	Retrospective
Janes 2010	United States	Rattlesnake bite with documented size of snake	Other venomous or non-venomous snakebite	142	Comprehensive multi-system reference standard
Jorge 1999	Brazil	*Bothrops* envenomation	None reported	801	Reference standard is uncommon outcome Single system venom effect
Milani Jr 1997	Brazil	*Botrhops jararacucu* envenomation	None reported	29	Low numbers
Moss 1998	United States	Minimal to moderate N. American crotalid envenomation	Age <10 yrs Pregnant No progression of envenomation syndrome Copperhead envenomation Severe on presentation Antivenom infusion prior to enrollment of initial trial	41	Post hoc analysis of 2 clinical trials
Nicoleti 2010	Brazil	*Bothrops jararacucu* envenomation	None reported	689	Retrospective
Otero 2002	Columbia	Envenomation by *Bothrops*	No sings or symptoms of envenomation	39	Spectrum bias due treatment

		porthidium* pr *Bothriechis			**by traditional healers**
Pinho 2005	**Brazil**	***Crotalus durissis* envenoamtion**	**Chronic kidney disease**	**100**	**Prospective with strict definitions of outcomes**
Ribiero 2001	**Brazil**	***Bothrops jararacucu* envenomation**	**None reported**	**779**	**Retrospective**
Santoro 2008	**Brazil**	***Bothrops* envenomation confirmed by either dead snake or ELISA immunodiagnostics**	**Severe on presentation Massive hemorrhage, hemodynamic disturbances and/or acute renal failure**	**100**	**Prospective**
Seifert 2011	**United States**	**US *Crotalus* or *Sistrurus* envenomation treated with Fab antivenom and labs available**	**No laboratory values available for analysis**	**60**	**Retrospective Multiple index tests evaluated**
Thomas 1998	**Martinique**	***Bothrops lancelatus* envenomation in their database**	**No signs or symptoms**	**103**	**Retrospective**
White 1990	**United States**	**Hospitalized with snake envenomation**	**None reported**	**67**	**Retrospective**
Yin 2011	**United States (17 centers)**	**All envenomations who received Fab antivenom. Clinical signs and symptoms**	**No signs or symptoms**	**247**	**Retrospective with reporting of high qualities methods for this study design**

eFigure. PRISMA Diagram



eTable 4. Results of Clinical Feature by Individual Studies

Study Name	Index Test (Clinical Feature)	Reference Standard	Quality Grade[2]	Number of patient (% severe outcome)	Sensitivity (95% CI)	Specificity (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)
Barraviera[3]	Myalgia	Death	4	40, (5)	0.5 (0.13 - 0.87)	0.94 (0.81 - 0.98)	7.8 (1.5 - 41)	0.53 (0.17 - 1.7)
Barraviera[3]	Local Edema	Death	4	40, (5)	0.5 (0.13 - 0.87)	0.83 (0.69 - 0.92)	3 (0.8 - 11)	0.6 (0.19 - 1.9)
Barraviera[3]	Ptosis	Death	4	40, (5)	1 (0.22 - 1)	0.78 (0.63 - 0.88)	3.8 (1.8 - 8.3)	0.21 (0.02 - 3.0)
Bucaretchi[4]	Time ≥6 hrs	BMHSGS Severe	3	56, (18)	1.0 (0.37 - 1)	0.82 (0.69 - 0.9)	2.8 (1.2 - 6.5)	0.61 (0.33 - 1.1)
Bucaretchi [4]	Coagulation Studies	BMHSGS Severe	3	73, (21)	0.72 (0.47 - 0.88)	0.45 (0.33 - 0.58)	1.3 (0.9 - 1.9)	0.63 (0.27 - 1.4)
Bucaretchi [4]	BMHSGS Severe	Complications [b]	4	73, (21)	0.66 (0.41 - 0.84)	0.91 (0.81 - 0.96)	7 (2.9 - 17)	0.38 (0.19 - 0.75)
Bucaretchi [5]	Myalgia	BMHSGS Severe	3	31, (58)	0.87 (0.65 - 0.96)	0.46 (0.24 - 0.7)	1.6 (1 - 2.7)	0.28 (0.08 - 1.0)
Bucaretchi [5]	Time ≥6 hrs	ARF	4	25, (12)	0.88 (0.4 - 0.99)	0.85 (0.65 - 0.94)	5.8 (2 - 16)	0.15 (0.01 - 2.0)
Bucaretchi [5]	Local Edema	BMHSGS Severe	4	31, (58)	0.61 (0.39 - 0.79)	0.32 (0.14 - 0.58)	0.9 (0.53 - 1.5)	1.23 (0.48 - 3.2)
Bucaretchi [5]	Ptosis	BMHSGS Severe	4	31, (58)	1 (0.85 - 1)	0.32 (0.14 - 0.58)	1.4 (1.0 - 2.1)	0.08 (0.01 - 0.14)
Gaus[6]	WBCT	Clinical Grade Severe (Fig 1)	4	110, (9.1)	1 (0.74 - 1)	0.2 (0.14 - 0.29)	1.2 (1 - 1.4)	0.22 (0.01 - 3.4)
Janes[7]	Large snake	SSS >8	3	142, (22)	0.36 (0.22 - 0.53)	0.93 (0.87 - 0.97)	5.4 (2.3 - 12)	0.69 (0.53 - 0.89)

Jorge[8]	Large snake	Amputation	4	801, (0.6)	1 (0.55 - 1)	0.64 (0.61 - 0.67)	2.6 (2 - 3.3)	0.13 (0.01 - 1.8)
Jorge[8]	Digit (finger/toe)	Amputation	4	3137, (0.7)	0.75 (0.54 - 0.88)	0.76 (0.74 - 0.77)	3.1 (2.4 - 4.0)	0.33 (0.16 - 0.68)
Milani Jr[9]	Large snake	Death	4	29, (59)	0.19 (0.07 - 0.42)	1 (0.78 - 1)	5.1 (0.3 - 90)	0.84 (0.65 - 1.1)
Moss[10]	Abnl Urinalysis	SSS ≥5	4	41, (46)	0.93 (0.73 - 0.98)	0.33 (0.17 - 0.53)	1.4 (1 - 1.9)	0.23 (0.04 - 1.2)
Nicoleti[11]	Large snake	BMHSGS Severe	3	689, (2.9)	0.74 (0.52 - 0.88)	0.71 (0.68 - 0.74)	2.6 (1.9 - 3.4)	0.37 (0.18 - 0.76)
Nicoleti[11]	Time ≥6 hrs	BMHSGS Severe	3	675, (3.0)	0.26 (0.12 - 0.48)	0.92 (0.89 - 0.94)	3.2 (1.5 - 6.8)	0.8 (0.62 - 1.0)
Otero[12]	Time ≥6 hrs	Clinical Grade Severe	4	39, (74)	0.85 (0.68 - 0.94)	0.68 (0.39 - 0.88)	2.7 (1.1 - 6.4)	0.22 (0.09 - 0.56)
Otero[12]	Time ≥2 hrs	Death or complication	4	39, (46)	0.92 (0.72 - 0.98)	0.2 (0.09 - 0.41)	1.2 (0.9 - 1.5)	0.39 (0.07 - 2.2)
Pinho[13]	Patient age ≤12 yrs	ARF	3	100, (29)	0.38 (0.23 - 0.56)	0.88 (0.79 - 0.94)	3.2 (1.5 - 7.1)	0.7 (0.52 - 0.94)
Pinho[13]	Time ≥6hrs	ARF	3	100, (29)	0.72 (0.54 - 0.85)	0.88 (0.79 - 0.94)	6.1 (3.1 - 12)	0.32 (0.18 - 0.57)
Ribeiro[14]	Large snake	Necrosis	4	779, (14)	0.7 (0.61 - 0.78)	0.7 (0.66 - 0.73)	2.3 (2 - 2.7)	0.43 (0.32 - 0.57)
Ribeiro[14]	Time ≥6 hrs	Necrosis	4	779, (14)	0.05 (0.02 - 0.11)	0.93 (0.9 - 0.94)	0.7 (0.3 - 1.6)	1.03 (0.98 - 1.1)
Ribeiro[14]	Digit bite	Necrosis	4	779, (14)	0.4 (0.31 - 0.49)	0.68 (0.65 - 0.72)	1.3 (1 - 1.6)	0.88 (0.75 - 1.0)
Ribeiro[14]	Upper extremity	Necrosis	4	779, (14)	0.41 (0.32 - 0.5)	0.67 (0.64 - 0.71)	1.2 (1 - 1.6)	0.88 (0.75 - 1.0)

Ribeiro[14]	Distant Bleed	Necrosis	4	779, (14)	0.22 (0.15 - 0.3)	0.92 (0.9 - 0.94)	2.8 (1.8 - 4.4)	0.85 (0.77 - 0.94)
Santoro[15]	Large snake	Clinical Grade Severe	3	38, (29)	0.79 (0.51 - 0.93)	0.52 (0.34 - 0.69)	1.6 (1 - 2.7)	0.4 (0.13 - 1.3)
Santoro[15]	Time ≥6 hrs	Clinical Grade Severe	3	100, (26)	0.13 (0.05 - 0.3)	0.85 (0.75 - 0.91)	0.8 (0.3 - 2.6)	1.0 (0.86 - 1.2)
Seifert[16]	All negative (all checked)	Coagulopathy[c]	4	13, (77)	1 (0.74 - 1)	1 (0.37 - 1)	1.7 (0.2 - 18)	0.71 (0.09 - 5.5)
Seifert[16]	Coagulation Studies (Any Abnl)	Coagulopathy[c]	4	132, (14)	0.71 (0.43 - 0.89)	0.81 (0.68 - 0.89)	3.7 (1.9 - 7.3)	0.36 (0.15 - 0.88)
Seifert[16]	Thrombocytopenia (Plt<150K)	Coagulopathy[c]	4	51, (16)	0.71 (0.43 - 0.89)	0.81 (0.68 - 0.89)	3.7 (1.9 - 7.3)	0.36 (0.15 - 0.88)
Seifert[16]	Fibrinogen (Abnl)	Coagulopathy[c]	4	42, (12)	0.46 (0.22 - 0.71)	0.91 (0.8 - 0.96)	5.1 (1.7 - 15)	0.6 (0.35 - 1.0)
Seifert[16]	D-dimer (Abnl)	Coagulopathy[c]	4	38, (11)	1 (0.47 - 1)	0.57 (0.43 - 0.7)	2.2 (1.6 - 3.1)	0.07 (0 - 1.1)
Seifert[16]	PT (Abnl)	Coagulopathy[c]	4	48, (10)	0.96 (0.7 - 1)	0.63 (0.49 - 0.75)	2.6 (1.8 - 3.8)	0.07 (0 - 1.0)
Seifert[16]	PTT (Abnl)	Coagulopathy[c]	4	28, (7.1)	0.46 (0.22 - 0.71)	0.85 (0.73 - 0.92)	3.1 (1.2 - 7.5)	0.64 (0.37 - 1.1)
Thomas[17]	Time >6 hrs	Death or thrombosis[d]	4	103, (14)	1 (0.81 - 1)	0.78 (0.69 - 0.86)	4.5 (3 - 6.7)	0.04 (0 - 0.65)
Thomas[17]	BMHSGS (Severe)	Death or thrombosis[d]	4	103, (14)	0.7 (0.45 - 0.87)	0.69 (0.59 - 0.78)	2.3 (1.5 - 3.6)	0.43 (0.2 - 0.95)
White[18]	Patient Age ≤12 yrs	Clinical Grade Severe	4	67, (34)	0.48 (0.3 - 0.67)	0.83 (0.7 - 0.91)	2.9 (1.3 - 6.2)	0.63 (0.42 - 0.94)
White[18]	Genus Rattlesnake	Clinical Grade Severe	4	62, (37)	0.85 (0.67 - 0.95)	0.51 (0.36 - 0.66)	1.8 (1.2 - 2.5)	0.28 (0.1 - 0.78)
Yin[19]	Patient Sex	Difficulty achieving control	3	247, (18)	0.88 (0.75 - 0.94)	0.18 (0.13 - 0.24)	1.1 (0.9 - 1.2)	0.68 (0.3 - 1.6)

Yin[19]	Upper extremity	Difficulty achieving control	3	246, (18)	0.77 (0.63 - 0.87)	0.38 (0.32 - 0.45)	1.2 (1.0 - 1.5)	0.61 (0.35 - 1.1)

Abbreviations: Abnl, Abnormal; BMHSGS: Brazilian Ministry of Health Grading Scale; WBCT: Whole Blood Clotting Time; PT: Prothrombin time; PTT: Partial thromboplastin time; ARF: Acute Renal Failure; SSS: Snakebite Severity Score

a Rational Clinical Examination Quality Grade

b Complications defined as local infection, cellulitis, gangrene, abscess, compartment syndrome, and/or acute renal failure.

[c] Recurrent, persistent, or late, new-onset coagulopathy at ≥4d after snakebite

[d] Cerebral infarction, myocardial infarction, or pulmonary infarction

eTable 5. QUADAS 2 Quality Ratings for Clinical Feature of Included Studies

Study	Clinical Feature	Patient Selection					Index Test				Reference Standard					Flow and Timing				Level
		Q1	Q2	Q3	Overall Risk of Bias	Q4	Q5	Q6	Overall Risk of Bias	Q7	Q8	Q9	Q10	Overall Risk of Bias	Q11	Q12	Q13	Q14	Overall Risk of Bias	
Barraviera 1989[3]	Myalgia	N	Y	U	High	Low	N	Y	High	Low	Y	N	NA	High	Low	Y	Y	Y	Low	4
Barraviera 1989[3]	Local Edema	N	Y	U	High	Low	N	Y	High	Low	Y	N	NA	High	Low	Y	Y	Y	Low	4
Barraviera[3]	Ptosis	N	Y	U	High	Low	N	Y	High	Low	Y	N	NA	High	Low	Y	Y	Y	Low	4
Bucaretchi 2001[4]	Time ≥6 hrs	Y	Y	Y	Low	High	Y	Y	Low	Low	Y	Y	Y	Low	Low	Y	Y	Y	Low	3
Bucaretchi 2001[4]	Coagulation Studies	Y	Y	Y	Low	High	Y	Y	Low	Low	Y	Y	Y	Low	Low	Y	Y	Y	Low	3
Bucaretchi 2001[4]	BMHSGS Severe	Y	Y	Y	Low	High	Y	Y	Low	Low	N	Y	Y	High	High	Y	Y	Y	Low	4
Bucaretchi 2002[5]	Myalgias	N	Y	Y	Low	High	Y	Y	Low	Low	Y	N	Y	High	Low	Y	Y	Y	Low	4
Bucaretchi 2002[5]	Time ≥6 hrs	N	Y	Y	High	High	Y	Y	Low	Low	Y	N	Y	High	Low	Y	Y	Y	Low	4
Bucaretchi 2002[5]	Local Edema	N	Y	Y	High	High	Y	Y	Low	Low	Y	N	Y	High	Low	Y	Y	Y	Low	4
Bucaretchi 2002[5]	Ptosis	N	Y	Y	High	High	Y	Y	Low	Low	Y	N	Y	High	Low	Y	Y	Y	Low	4
Gaus 2013[6]	Whole Blood Clotting Time	Y	Y	Y	Low	Low	N	Y	High	Low	Y	N	Y	High	Low	Y	Y	Y	Low	4
Janes 2010[7]	Large snake	N	Y	Y	High	Low	Y	Y	Low	Low	Y	Y	Y	Low	Low	Y	Y	Y	Low	3
Jorge 1999[8]	Large snake	N	Y	Y	High	Low	Y	Y	Low	Low	N	Y	NA	High	High	Y	Y	Y	Low	4

Jorge 1999[8]	Digit (finger/ toe)	N	Y	Y	High	Low	Y	Y	Low	Low	N	N	NA	High	High	Y	Y	Y	Low	4
Milani Jr 1997[9]	Large snake	N	Y	Y	High	Low	Y	Y	Low	Low	Y	N	Y	High	Low	Y	Y	Y	Low	4
Moss 1998[10]	Abnl Urinalysis	Y	Y	Y	Low	High	N	Y	High	Low	Y	N	Y	High	Low	N	Y	Y	High	4
Nicoleti 2010[11]	Large snake	N	Y	Y	High	Low	Y	Y	Low	Low	Y	Y	Y	Low	Low	Y	Y	Y	Low	3
Nicoleti 2010[11]	Time ≥6 hrs	N	Y	Y	High	Low	Y	Y	Low	Low	Y	Y	Y	Low	Low	Y	Y	Y	Low	3
Otero 2002[12]	Time ≥6 hrs	Y	Y	Y	Low	High	Y	Y	Low	Low	Y	N	Y	High	Low	Y	Y	Y	Low	4
Otero 2002[12]	Time ≥2 hrs	Y	Y	Y	Low	High	Y	Y	Low	Low	Y	N	Y	High	Low	Y	Y	Y	Low	4
Pinho 2005[13]	Patient age ≤12 years	U	Y	Y	High	Low	Y	Y	Low	Low	Y	Y	Y	Low	Low	Y	Y	Y	Low	3
Pinho 2005[13]	Time ≥6 hrs	U	Y	Y	High	Low	Y	Y	Low	Low	Y	Y	Y	Low	Low	Y	Y	Y	Low	3
Ribeiro 2001[14]	Large snake	N	Y	Y	High	Low	Y	Y	Low	Low	N	N	Y	High	Low	Y	Y	Y	Low	4
Ribeiro 2001[14]	Time ≥6 hrs	N	Y	Y	High	Low	Y	Y	Low	Low	N	N	Y	High	Low	Y	Y	Y	Low	4
Ribeiro 2001[14]	Digit bite	N	Y	Y	High	Low	Y	Y	Low	Low	N	N	Y	High	Low	Y	Y	Y	Low	4
Ribeiro 2001[14]	Upper extremity	N	Y	Y	High	Low	Y	Y	Low	Low	N	N	Y	High	Low	Y	Y	Y	Low	4
Ribeiro 2001[14]	Distant Bleed	N	Y	Y	High	Low	N	Y	High	Low	N	N	Y	High	Low	Y	Y	Y	Low	4
Santoro 2008[15]	Large snake	U	Y	Y	High	Low	Y	Y	Low	Low	Y	Y	Y	Low	Low	Y	Y	Y	Low	3
Santoro 2008[15]	Time ≥6 hrs	U	Y	Y	High	Low	Y	Y	Low	Low	Y	Y	Y	Low	Low	Y	Y	Y	Low	3
Seifert 2011[16]	All negative (all	N	Y	Y	High	Low	N	Y	High	Low	Y	N	Y	High	Low	Y	Y	Y	Low	4

	checked)																			
Seifert 2011[16]	Coagulation Studies (Any Abnl)	N	Y	Y	High	Low	N	Y	High	Low	Y	N	Y	High	Low	Y	Y	Y	Low	4
Seifert 2011[16]	Thrombocytopenia (Plt<150K)	N	Y	Y	High	Low	N	Y	High	Low	Y	N	Y	High	Low	Y	Y	Y	Low	4
Seifert 2011[16]	Fibrinogen (Abnl)	N	Y	Y	High	Low	N	Y	High	Low	Y	N	Y	High	Low	Y	Y	Y	Low	4
Seifert 2011[16]	D-dimer (Abnl)	N	Y	Y	High	Low	N	Y	High	Low	Y	N	Y	High	Low	Y	Y	Y	Low	4
Seifert 2011[16]	PT (Abnl)	N	Y	Y	High	Low	N	Y	High	Low	Y	N	Y	High	Low	Y	Y	Y	Low	4
Seifert 2011[16]	PTT (Abnl)	N	Y	Y	High	Low	N	Y	High	Low	Y	N	Y	High	Low	Y	Y	Y	Low	4
Thomas 1998[17]	Time >6 hrs	Y	Y	Y	Low	Low	Y	Y	Low	Low	Y	N	Y	High	Low	Y	Y	Y	Low	4
Thomas 1998[17]	BMHSGS (Severe)	Y	Y	Y	Low	Low	N	Y	High	Low	Y	N	Y	High	Low	Y	Y	Y	Low	4
White 1991[18]	Patient Age ≤12 yrs	N	Y	Y	High	Low	Y	Y	Low	Low	N	N	Y	High	High	Y	Y	Y	Low	4
White 1991[18]	Genus Rattlesnake	N	Y	Y	High	Low	Y	NA	Low	Low	N	N	Y	High	High	Y	Y	Y	Low	4
Yin 2011[19]	Patient Sex	Y	Y	Y	Low	Low	Y	Y	Low	Low	Y	N	Y	High	Low	Y	Y	Y	Low	3
Yin 2011[19]	Upper extremity	Y	Y	Y	Low	Low	Y	Y	Low	Low	Y	N	Y	High	Low	Y	Y	Y	Low	3

U = unclear, N = No, Y = Yes, NA = not applicable

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