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# Clinical Characteristics and Analysis of Risk Factors Associated with Rhabdomyolysis in Snakebite Victims

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**Objective:** To enhance the understanding of rhabdomyolysis (RM) caused by snakebites and to promptly identify and intervene in the risk factors associated with RM.

**Methods:** A retrospective analysis involving 209 snakebite victims who visited our hospital for snakebite cases was conducted. Among these, 43 were related to RM, while 166 did not exhibit RM (NRM). The clinical characteristics, treatment, and prognostic outcomes of both groups were statistically analyzed, with the aim of interpreting the risk factors associated with snakebites concurrent with RM through logistic regression analysis.

**Results:** Snakebite incidents commonly manifest during the summer and autumn seasons, predominantly affecting middle-aged and elderly populations, with injuries mostly occurring in the limbs. Creatine kinase (CK), CK isoenzyme MB, and lactate dehydrogenase indicators exhibited significantly elevated levels in the RM group compared to the NRM group ($P < 0.05$). Moreover, the RM Group displayed heightened susceptibility to complications such as osteofascial compartment syndrome, multiple organ dysfunction (MODS), acute kidney injury, etc. ($P < 0.05$). Debridement and blood purification procedures were more frequently administered to the RM group in comparison to the NRM group ($P < 0.05$). Notably, visitation beyond 6 hours post-bite and hemoglobin levels below 90 mg/dl emerged as independent risk factors for those with RM following snakebites, while female gender and albumin levels >40 g/L were identified as protective factors against such occurrences.

**Conclusion:** Snakebite victims with RM have more severe clinical conditions, necessitating prolonged treatment duration, and exhibit heightened mortality rates in comparison to those without RM.

**Keywords:** acute kidney injury, clinical features, rhabdomyolysis, risk factors, snakebite

## Introduction

Snakebites are indicative of not just a tropical disease but also of being a global public health concern.[1] Annually, an estimated 5.5 million individuals worldwide are bitten by snakes, with 1.8 million cases involving venomous snakes, resulting in approximately 100,000 fatalities.[2] Particularly in tropical and subtropical nations such as India and China, the incidence rate of snakebites is relatively high.[3] Differentiated from conventional traumatic injuries, snakebites pose distinctive challenges, especially in severe instances where there is a pronounced risk of cutaneous necrosis, necessitating amputation and leaving residual limb sequelae.[2] Such outcomes significantly impact the subsequent quality of life of snakebite victims.

According to snake venom classification, it can be typically divided into three primary categories: neurotoxic, hematotoxic, and cytotoxic.[4] However, there were snake venom that involves both hemotoxins and neurotoxins.[5] Cytotoxins

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delivered by snakebite predominantly enhance oxidative stress through the action of phospholipase A2 (PLA2) and L-amino acid oxidase (LAAO), thereby inhibiting cell proliferation and inducing cell apoptosis. Hematotoxins snake venom, either directly or indirectly, impacts the circulatory system by damaging the relevant structures of blood vessel walls, inhibiting platelet aggregation, prolonging coagulation times, and subsequently causing bleeding, hemolysis, or disseminated intravascular coagulation (DIC).[2] Neurotoxins primarily target the neuromuscular junction, causing symptoms similar to those observed in myasthenia gravis. At a later stage, muscle relaxation may culminate in paralysis, leading to respiratory obstruction or failure.[6] After snakebites, various complications, such as rhabdomyolysis (RM), acute kidney injury (AKI), shock, and multiple organ dysfunction syndrome (MODS), may occur, significantly influencing patient prognosis and even endangering their lives.

RM represents a clinical syndrome characterized by various causes of muscle fiber cell damage, followed by the release of intracellular contents that lead to pathological and physiological changes within the body, often accompanied by manifestations of muscle pain and weakness.[7] Venom introduced into the body through snakebites can induce oxidative stress, thereby causing muscle damage and concurrent RM, facilitated by toxins such as phospholipase A2 (PLA2) and metalloproteinases (SVMP).[8] Clinical manifestations of RM are diverse, with muscle pain, fatigue, and brown urine being typical triads, but they are rare in clinical practice, and typical triads can be observed in less than 10% of cases.[9] Therefore, the clinical symptoms are diverse, especially in snakebite victims, masking the traditional triad of RM. Clinical diagnosis is often based on testing blood creatine kinase (CK) levels exceeding 1000 U/L.[10] Notably, AKI emerges as the most prevalent RM complication, with reported incidence rates ranging from 10% to 55%.[11] This indicates that snakebite victims presenting with concurrent RM often exhibit complex clinical profiles, with significantly elevated AKI incidence rates correlating with unfavorable prognostic outcomes and heightened mortality.[12] Furthermore, snake venom can cause AKI, worsen renal injury and concurrent RM, and even be irreversible in some patients.

While considerable research has explored risk factors associated with RM and concurrent AKI,[13,14] investigations specifically targeting risk factors in snakebite victims presenting with concurrent RM remain notably scarce.

# Study Participants and Methods

## Study Participants

During the period spanning January 2018 to September 2023, a total of 209 individuals who presented with snakebites and sought medical attention at the Longyan First Affiliated Hospital of Fujian Medical University, were retrospectively included in the study. The case system of the hospital was collected and medical data of the patients who were bitten by snakes in the time period were collected. The course and examination results of each patient were analyzed, followed by inclusion and exclusion based on the criteria. Among them, 43 cases with concurrent rhabdomyolysis were included in the RM Group, whereas 166 cases without rhabdomyolysis constituted the NRM Group. The inclusion criteria were as follows: 1. age ≥ 18 years old; 2. documentation of a clear history of snakebites; 3. seeking treatment within 24 hours of snakebite occurrence; 4. availability of comprehensive clinical data. The exclusion criteria comprised: 1. individuals who could not follow medical advice and only receive wound dressing or pain relief for various factors; 3. individuals who had previously received treatment at or were referred by another medical institution; 4. individuals with concurrent liver and kidney dysfunction; and 5. the presence of other etiological factors or diseases that can cause rhabdomyolysis, such as trauma, drug poisoning, seizures, and alcoholism, among others.

## Methods

Patient demographics, including name, gender, age, occupation, address, medical history, smoking and alcohol consumption history, and vital signs upon admission, were collected. Snakebite-related variables included the timing and season of snakebites, snake species involved, site of snakebites, treatment of wounds after snake bites, time elapsed from bite to hospital visit (hours), as well as clinical symptoms and objective manifestations. Biochemical tests including renal function and hepatic function (Olympus/Beckmann AU5800; Beckman Coulter Inc., Brea, CA), blood routine examination (Sysmex XN-9000; XN, Sysmex, Kobe, Japan), coagulation function test (ACL TOP750-CTS; Instrumentation Laboratory, Bedford, USA), urine analysis (Sysmex UF-5000; Sysmex Co., Kobe, Japan), troponin I levels (PATHFAST;

Mitsubishi Chemical Medience Corporation, Japan) were conducted with matching reagents within 48 hours of admission.

Assessment of treatment modalities and prognosis entailed documentation of receipt of anti-venom serum treatment after admission, performance of wound debridement, incision, or decompression surgeries, administration of steroidal anti-inflammatory medications including specific agents such as methylprednisolone, dexamethasone, or betamethasone, implementation of blood purification replacement therapy during hospitalization, admission to the intensive care unit (ICU), total duration of hospital stay (days), and the occurrence of complications such as RM, shock, AKI, coagulation abnormalities, liver dysfunction, MODS, and disseminated intravascular coagulation (DIC) throughout the treatment period.

## Diagnostic Criteria

Currently, there is no universally definitive diagnostic standard for RM on an international scale. Nevertheless, clinical consensus suggests that patients exhibit symptoms such as muscle weakness, pain, and excretion of brown urine; CK ≥ 1000 U/L; heightened blood and urine myoglobin concentrations exceeding normal thresholds; and urine occult blood is positive.[10]

AKI: According to the 2012 kidney disease: Improving Global Outcomes (KDIGO) guidelines, they offer a standard for enhancing prognostic accuracy. Diagnosis entails either a 26.5% increase in blood creatinine levels within 48 hours or a surge in blood creatinine exceeding 1.5 times the baseline value within 7 days. Additionally, if the incident has transpired more than 6 hours ago, a urine output of less than 0.5 mL/kg/h serves as an additional diagnostic criterion.[15] Any one of these parameters should be met for an AKI diagnosis.

Osteofascial compartment syndrome: Patients are highly suspected of having the complication when they have any of the following symptoms: There is severe pain in the affected limb that is not consistent with the original clinical injury or passive traction pain of the affected limb (finger or toe). The skin temperature of the affected limb decreases, or there is severe swelling or presence of tension blisters. The affected limb has abnormal skin sensation. In addition, when patients have typical 5p symptoms (pain, pallor, pulselessness, paralysis, and paresthesia), the patients can be diagnosed with the syndrome.

Respiratory failure: There are clinical manifestations of hypoxia and carbon dioxide retention. Blood gas analysis: $PaO_2$ < 8.0 kPa, PaCO2 can be normal or decreased (type I respiratory failure), $PaO_2$ < 8.0 kPa and PaCO2 > 6.67 kPa (type II respiratory failure); Chest X-ray examination: there may be manifestations of corresponding pulmonary diseases.

Shock: The diagnostic criteria for shock are as follows: 1) hypotension: systolic blood pressure <90 mmHg, 2) respiratory system: shallow and rapid breathing, 3) nervous system: apathy and slow response, 4) skin: pallor, 5) kidney: oliguria or anuria.

DIC: There is bleeding, microcirculation failure, and microvascular embolism. The corresponding laboratory tests are as follows: (1) PLT decreases progressively to less than $100\times10^9$/L (less than $50\times10^9$/L in patients with liver disease and leukemia), or plasma levels of two or more platelet activation molecular markers increase: β-TG; PF4; thromboxane B2, and P-selectin. (2) The plasma Fb level is less than 1.5g/L (less than 1.0g/L in patients with liver disease, leukemia less than 1.8g/L in patients with leukemia) or more than 4.0g/L, or decreases progressively. (3) Positive 3P test, plasma FDP is >20mg/L (>60mg/L in patients with liver disease) or plasma D-dimer is more than 4 times higher than normal (positive). (4) PT prolongation or shortening is more than 3 seconds (more than 5 seconds in patients with liver disease); The APTT is prolonged or shortened by more than 10 seconds. (5) Antithrombin activity (AT:A) is less than 60% (not applicable for patients with liver disease) or protein C activity (PC:A) is decreased. (6) Plasma plasminogen antigen (PLG:Ag) is less than 200mg/L. (7) Factor VIII: C activity is less than 50% (essential for patients with liver disease). (8) Plasma endothelin-1 (CE-1) level is higher than 80pg/mL or thrombomodulin (TM) is more than 2 times higher than normal. The diagnosis can be made if more than three laboratory tests are met at the same time.

MODS refers to the reversible dysfunction of two or more organs at the same time or in sequence on the basis of the primary disease caused by a variety of acute pathogenic factors.

Hepatic dysfunction: ALT>3ULN may be accompanied by increased AST and bilirubin, with or without hypoproteinemia and coagulopathy.

Abnormal coagulation: There is any of the following conditions: Platelet count <100*$10^9$/L; PT prolongation >3s; APTT prolonged >10s or TT prolonged >3s; Plasma fibrinogen <1.5g/L, D-dimer >1ug/mL, or FDPs>10 ug/mL.

Intravascular hemolysis: The disease has an acute onset and the patients may have low back pain, headache, nausea, vomiting, fever, jaundice, or dark urine. Laboratory tests: blood routine examination: red blood cells and hemoglobin decrease, urine routine: urine occult blood positive, urine protein positive, red blood cells negative.

## Statistical Methods

Data analysis was conducted utilizing SPSS 25.0 statistical software. The Kolmogorov Smirnov method was employed to assess the normality of the quantitative data. Normally distributed quantitative data were represented by the mean ± SD (x ± s). Inter-group comparisons were performed using independent sample *t*-tests under conditions of homogenous variances, while Welch's t-tests were utilized in instances of non-homogenous variances. Measurement data that do not follow a normal distribution were represented by M (P25, P75), with intergroup comparisons conducted using the Mann–Whitney *U*-test. Qualitative data were represented by the number of cases (rate), and inter-group comparisons were conducted using the $X^2$ test or Fisher's exact probability method. The stepwise regression method was employed for both single-factor and multivariate logistic regression analyses to explore potential risk factors.

# Results

## General Information

Snakebite incidents predominantly occurred during the summer and autumn seasons, with 94 individuals (45.0%) affected in the summer; 79 individuals (37.8%) in autumn. Middle-aged and elderly individuals were more commonly affected. Upon admission, the clinical manifestations of snakebites vary depending on the species of snake or the type and content of the toxin. General manifestations were local manifestations such as tooth marks, varying degrees of pain, bleeding, lymph node enlargement, lymphangitis, local swelling, erythema, elevated skin temperature, blisters (hemorrhagic and non-hemorrhagic), and ecchymosis. Some patients had non-specific systemic manifestations, such as nausea, vomiting, fatigue, abdominal pain, dizziness, headache, fever, sweating or diarrhea. Neurotoxic triad (bilateral ptosis, descending paralysis, dyspnea/acute respiratory failure), hemotoxic triad (venom-induced consumption coagulopathy, local and systemic bleeding), and cytotoxic triad (severe pain, progressive swelling, and tissue damage) might also occurred in some patients. There was no significant difference between both groups in gender, occupational composition (farmers vs non-farmers), age distribution, smoking, alcohol consumption history, hypertension, or diabetes ($P > 0.05$). The duration between the time of snakebite and hospital visit was significantly longer in the RM Group, with a median of 4.00 (interquartile range: 2.50, 7.50) hours compared to 3.00 (interquartile range: 2.00, 4.00) hours in the NRM Group ($P < 0.05$).

Upon admission, individuals in the RM group exhibited a higher heart rate compared to those in the NRM group ($P < 0.05$); however, there was no statistically significant difference in body temperature or blood pressure between both groups ($P > 0.05$). The limbs were the predominant sites of snakebites, while trunk bites were comparatively rare. There was no statistically significant difference in the season and location of snake bites between both groups ($P > 0.05$). The most frequently encountered snake species in the RM Group were Protobothrops mangshanensis (*Viperidae, Ovophis, Ovophis monticola*; 39.53%), whereas Trimeresurus stejnegeri (37.95%) were predominant in the NRM Group. The difference in snake species distribution between the two groups was statistically significant ($P < 0.05$). Some patients treated their wounds before seeking medical treatment, with a statistically significant difference noted in wound treatment practices between the two groups ($P < 0.05$). For further details, refer to Table 1.

## Clinical Manifestations

The WBC in the RM group is higher, while the RBC, Hb, and PLT are lower compared to the NRM group ($P < 0.05$).

Biochemical Assessments: Significantly elevated levels of creatine kinase (CK), albumin (ALB), creatine kinase-MB (CKMB), lactate dehydrogenase (LDH), uric acid (UA), creatinine (CRE), blood urea nitrogen (BUN), indirect bilirubin (IBIL), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and blood potassium (K) were observed in the RM Group compared to the NRM Group ($P < 0.05$). Refer to Table 2 for detailed findings.

**Table 1** Baseline Characteristics of Patients

| Items | RM Group (n = 43) | NRM Group (n = 166) | Total (n = 209) | Z/$\chi^2$ | P |
|---|---|---|---|---|---|
| 1. Age | 60.00 (49.50, 67.50) | 58.00 (49.00, 66.00) | | 0.75 | 0.453 |
| 2. Gender | | | | 0.640 | 0.424 |
| • Male | 27 (62.79) | 93 (56.02) | 120(57.42) | | |
| • Female | 16 (37.21) | 73 (43.98) | 89 (42.58) | | |
| 3. Occupation | | | | 1.452 | 0.228 |
| • Farmer | 37 (86.05) | 129 (77.71) | 166(79.43) | | |
| • Non-agricultural | 6 (13.95) | 37 (22.29) | 43 (20.57) | | |
| 4. Smoking history | 11 (25.58) | 51 (30.72) | 62 (29.67) | 0.433 | 0.511 |
| 5. Drinking history | 10 (23.26) | 23 (13.86) | 33 (15.79) | 2.270 | 0.132 |
| 6. Hypertension | 13 (30.23) | 32 (19.28) | 45 (21.53) | 2.426 | 0.119 |
| 7. Diabetes | 3 (6.98) | 5 (3.01) | 8 (3.83) | 0.580 | 0.446 |
| 8. Heart rate (Beats/minute) | 88.00 (73.50, 99.00) | 80.00 (71.00, 88.75) | | 2.282 | <0.05 |
| 9. Blood pressure Upon admission | | | | 0.452 | 0.798 |
| 10. Normal blood Pressure | 15(34.88) | 66(39.76) | | | |
| 11. Elevated blood Pressure | 27(62.79) | 95(57.23) | | | |
| 12. Reduced blood Pressure | 1(2.33) | 5(3.01) | | | |
| 13. Systolic blood Pressure (mmHg) | 143.00 (128.50, 163.50) | 140.00 (125.00, 154.75) | | 0.828 | 0.408 |
| 14. Diastolic blood Pressure (mmHg) | 87.00 (79.00, 97.00) | 84.00 (76.00, 92.00) | | 1.933 | 0.053 |
| 15. Season, n (%) | | | | 4.254 | 0.264 |
| • Spring | 6 (13.95) | 25 (15.06) | 31 (14.83) | | |
| • Summer | 19 (44.19) | 75 (45.18) | 94 (44.98) | | |
| • Autumn | 15 (34.88) | 64 (38.55) | 79 (37.8) | | |
| • Winter | 3 (6.98) | 2 (1.20) | 5 (2.39) | | |
| 16. Bite site, n (%) | | | | 1.705 | 0.453 |
| • Upper limbs | 18 (41.86) | 85 (51.20) | 103(49.28) | | |
| • Lower limbs | 25 (58.14) | 80 (48.19) | 105(50.24) | | |
| • Other | 0 (0.00) | 1 (0.60) | 1 (0.48) | | |
| 17. Snake species, n (%) | | | | 14.65 | <0.01 |
| • Trimeresurus stejnegeri | 8 (18.60) | 63 (37.95) | 71 (33.49) | | |
| • Protobothrops mangshanensis | 17 (39.53) | 25 (15.06) | 42 (20.10) | | |
| • Naja naja | 3 (6.98) | 16 (9.64) | 19 (9.09) | | |
| • Deinagkistrodon acutus | 1 (2.33) | 2 (1.20) | 3 (1.44) | | |
| • Bungarus multicinctus | 1 (2.33) | 2 (1.20) | 3 (1.44) | | |
| • Unknown | 13 (30.23) | 58 (34.94) | 71(33.49) | | |
| 18. Wound treatment, n (%) | | | | 10.17 | <0.05 |
| • Binding | 14(32.56) | 20 (12.05) | 34 (16.27) | | |
| • Incision | 7 (16.28) | 41 (24.70) | 48 (22.97) | | |
| • Applying herbs | 3 (6.98) | 22 (10.84) | 25 (10.05) | | |
| • Two or more types | 4 (9.30) | 15 (9.04) | 19 (9.09) | | |
| • No processing | 15 (34.88) | 68 (40.96) | 83 (39.71) | | |

Complications: The most prevalent complication following snakebites was abnormal coagulation (45.45%), followed by abnormal liver function (35.41%). The RM Group was more prone to osteofascial compartment syndrome, wound infection, shock, DIC, MODS, AKI, abnormal liver function, and intravascular hemolytic complications compared to the NRM Group ($P < 0.05$). Conversely, there were no statistically significant differences in the manifestations of respiratory failure and coagulation complications between the two groups ($P > 0.05$). The detailed results are presented in Table 3.

**Table 2** Comparison of Inspection Results

| Items | RM Group (n = 43) | NRM Group (n = 166) | t/ Z | P |
|---|---|---|---|---|
| WBC(×10$^9$/L) | 15.27 (11.81, 18.27) | 11.63 (8.14, 15.84) | 3.537 | <0.01 |
| RBC(×10$^9$/L) | 3.92 ± 1.15 | 4.62 ± 0.81 | 3.759 | <0.01 |
| Hb(mg/dl) | 116.74 ± 32.86 | 130.59 ± 22.18 | 2.613 | <0.05 |
| PLT(×10$^9$/L) | 151.42 ± 78.91 | 191.11 ± 90.28 | 2.633 | <0.05 |
| ALB(IU/L) | 33.26 ± 5.18 | 40.42 ± 3.83 | 8.487 | <0.01 |
| CK(IU/L) | 3047.00 (1588.00, 5394.50) | 165.50 (96.00, 300.75) | 10.097 | <0.01 |
| CKMB(IU/L) | 108.00 (76.50, 203.00) | 20.00 (14.00, 27.00) | 9.778 | <0.01 |
| LDH(IU/L) | 354.00 (294.00, 518.00) | 210.50 (176.25, 243.75) | 8.182 | <0.01 |
| UA(umol/L) | 486.95 ± 100.17 | 338.49 ± 94.62 | 9.059 | <0.01 |
| CRE(umol/L) | 86.00 (64.00, 123.50) | 67.00 (53.00, 86.75) | 3.174 | <0.05 |
| BUN(mmol/L) | 9.51 (7.30, 11.80) | 6.11 (4.82, 7.20) | 6.513 | <0.01 |
| TB-DB(umol/L) | 21.10 (14.65, 30.85) | 8.10 (6.50, 12.07) | 7.545 | <0.01 |
| ALT(IU/L) | 54.00 (29.25, 89.70) | 19.15 (14.00, 31.08) | 6.114 | <0.01 |
| AST(IU/L) | 104.00 (63.50, 232.00) | 27.00 (22.00, 38.00) | 8.435 | <0.01 |
| CTNI(ng/mL) | 0.01 (0.00, 0.03) | 0.00 (0.00, 0.01) | 5.539 | <0.01 |
| K(mmol/L) | 4.37 (4.04, 5.02) | 3.83 (3.61, 4.03) | 6.538 | <0.01 |
| Ca(mmol/L) | 2.25 ± 0.22 | 2.24 ± 0.14 | −0.252 | 0.802 |
| PT | 12.10 (11.60, 14.70) | 11.80 (11.00, 13.57) | 1.629 | 0.103 |
| APTT | 29.50 (27.20, 33.45) | 28.65 (27.00, 31.80) | 1.200 | 0.230 |
| Fib | 2.84 (2.14, 3.17) | 2.56 (1.69, 2.93) | 1.934 | 0.053 |
| FDP | 2.41 (1.05, 5.22) | 1.71 (0.70, 11.73) | 0.491 | 0.623 |
| D-2 polymer | 0.45 (0.24, 1.81) | 0.36 (0.18, 1.06) | 1.080 | 0.280 |
| Urinary red blood cells | 7.30 (3.80, 15.70) | 3.60 (1.33, 8.60) | 2.848 | <0.05 |

**Table 3** Comparison of Complications in Snake Bite Victims

| Items | RM Group (n = 43) | NRM Group (n = 166) | Total (n = 209) | $\chi^2$ | P |
|---|---|---|---|---|---|
| 1. Osteofascial compartment syndrome | 7 (16.28) | 1 (0.60) | 8 (3.83) | 18.741 | <0.001 |
| 2. Respiratory failure | 5 (11.63) | 6 (3.61) | 11 (5.26) | 2.938 | 0.087 |
| 3. Wound infection | 14 (32.56) | 21 (12.65) | 35 (16.75) | 9.708 | <0.05 |
| 4. Shock | 6 (13.95) | 5(3.03) | 11 (5.29) | 6.091 | <0.05 |
| 5. Disseminated intravascular coagulation | 5 (11.90) | 3 (1.81) | 8 (3.85) | 6.713 | <0.05 |
| 6. Multiple organ dysfunction | 3 (6.98) | 1 (0.60) | 4 (1.91) | – | <0.05 |
| 7. Acute renal injury | 15 (34.88) | 28 (16.87) | 43 (20.57) | 6.784 | <0.05 |
| 8. Abnormal liver function | 36 (83.72) | 38 (22.89) | 74 (35.41) | 55.257 | <0.001 |
| 9. Coagulation abnormalities | 20 (46.51) | 75 (45.18) | 95 (45.45) | 0.024 | 0.876 |
| 10. Intravascular hemolysis | 21 (48.84) | 12 (7.23) | 33 (15.79) | 44.469 | <0.001 |

## Comparison of Treatment and Prognosis

There was no statistically significant difference in the use of antivenom serum, steroidal anti-inflammatory medications, or ICU admission rate between the RM and NRM groups ($P > 0.05$). However, a notably higher proportion of patients in the RM Group underwent debridement and blood purification treatment compared to the NRM Group ($P < 0.05$). Moreover, the hospitalization time and mortality rate were significantly higher in the RM group relative to the NRM group ($P < 0.05$). Detailed findings are presented in Table 4.

**Table 4** Treatment and Prognosis of Snake Bite Victims

| Items | RM Group (n = 43) | NRM Group (n = 166) | Total (n = 209) | $\chi^2$ | P |
|---|---|---|---|---|---|
| 1. Debridement and decompression Surgery, n (%) | 10 (23.26) | 7 (4.22) | 17 (8.13) | 14.118 | <0.001 |
| 2. ICU, n (%) | 16 (37.21) | 50 (30.12) | 66 (31.58) | 0.794 | 0.373 |
| 3. Antivenom serum, n (%) | 43(1.00) | 165(99.4) | 208(99.5) | | 1.00 |
| 4. Steroidal anti-inflammatory medications, n (%) | | | | – | 0.093 |
| Methylprednisolone Sodium Succinate for Injection | 6 (13.95) | 44 (26.51) | 50 (23.92) | | |
| Dexamethasone | 1 (2.33) | 5 (3.01) | 6 (2.87) | | |
| Betamethasone | 2 (4.65) | 13 (7.83) | 15 (7.18) | | |
| Methylprednisolone+ dexamethasone | 20 (46.51) | 46 (27.71) | 66 (31.58) | | |
| Methylprednisolone+ Betamethasone | 14 (32.56) | 48 (28.92) | 62 (29.67) | | |
| Not used | 0 (0.00) | 10 (6.02) | 10 (4.78) | | |
| 5. Blood purification therapy, n (%) | 6 (13.95) | 4 (2.41) | 10 (4.78) | 7.617 | <0.05 |
| 6. Hospitalization days | 6.0(3.0, 14.0) | 3.00(2.00, 5.00) | | 5.095 | <0.001 |
| 7. Death, n (%) | 3 (6.98) | 1 (0.60) | 4 (1.91) | | <0.05 |

# Risk Factor Analysis of RM After Snakebites

## Single-Factor Logistic Analysis of Snakebite with Concurrent RM

A univariate logistic regression analysis was conducted, with the presence or absence of RM serving as the dependent variable. Factors potentially influencing the occurrence of RM post-snakebite were included in the analysis. The results are detailed in Table 5 and illustrated in Figure 1. Identified factors affecting the development of RM subsequent to snakebites include visiting the hospital more than 6 hours after the snakebite incident, albumin >40 g/L, hemoglobin <90mg/dl, and wound treatment method.

**Table 5** Single Factor Logistic Analysis of Snake Bite Complicated with RM

| Items | B | S.E | Wald | P | OR (95% CI) |
|---|---|---|---|---|---|
| 1. Age (>50 years old) | 0.11 | 0.39 | 0.28 | 0.780 | 1.12 (0.52–2.40) |
| 2. Gender: Female | −0.28 | 0.35 | −0.76 | 0.425 | 0.75 (0.38–1.51) |
| 3. Smoking | −0.25 | 0.39 | −0.66 | 0.511 | 0.78 (0.36–1.66) |
| 4.Drinking | 0.63 | 0.43 | 1.49 | 0.136 | 1.88 (0.82–4.34) |
| 5. Hypertension | 0.60 | 0.39 | 1.54 | 0.123 | 1.81 (0.85–3.87) |
| 6. Diabetes | 0.88 | 0.75 | 1.17 | 0.241 | 2.41 (0.55–10.53) |
| 7. Delay time post envenomation (>6 hours) | 1.36 | 0.37 | 3.67 | <0.001 | 3.90 (1.89–8.07) |
| 8. Albumin (>40g/L) | −2.45 | 0.55 | −4.47 | <0.001 | 0.09 (0.03–0.25) |
| 9. Hgb (<90mg/dL) | 1.92 | 0.45 | 4.25 | <0.001 | 6.80 (2.81–16.46) |
| 10. Snake species | | | | | |
| • Trimeresurus stejnegeri | −1.37 | 1.28 | 1.15 | 0.29 | 0.25 (0.02–3.13) |
| • Protobothrops mangshanensis | 0.31 | 1.26 | 0.60 | 0.81 | 1.36 (0.11–16.21) |
| • Naja naja | −0.98 | 1.38 | 0.51 | 0.48 | 0.38 (0.03–5.57) |
| • Deinagkistrodon acutus | 0.00 | 1.73 | 0.00 | 1.00 | 1.00 (0.34 −29.81) |
| • Bungarus multicinctus | −0.80 | 1.26 | 0.40 | 0.53 | 0.45 (0.04–5.32) |
| 11.Wound treatment method | | | | | |
| • Binding | 1.16 | 0.45 | 6.58 | 0.01 | 3.17 (1.31–7.67) |
| • Incision | −0.26 | 0.50 | 0.26 | 0.61 | 0.77 (0.29–2.06) |
| • Applying herbs | −0.48 | 0.68 | 0.50 | 0.48 | 0.62 (0.16–2.34) |
| • Two or more types | 0.19 | 0.63 | 0.9 | 0.76 | 1.21 (0.35–4.16) |

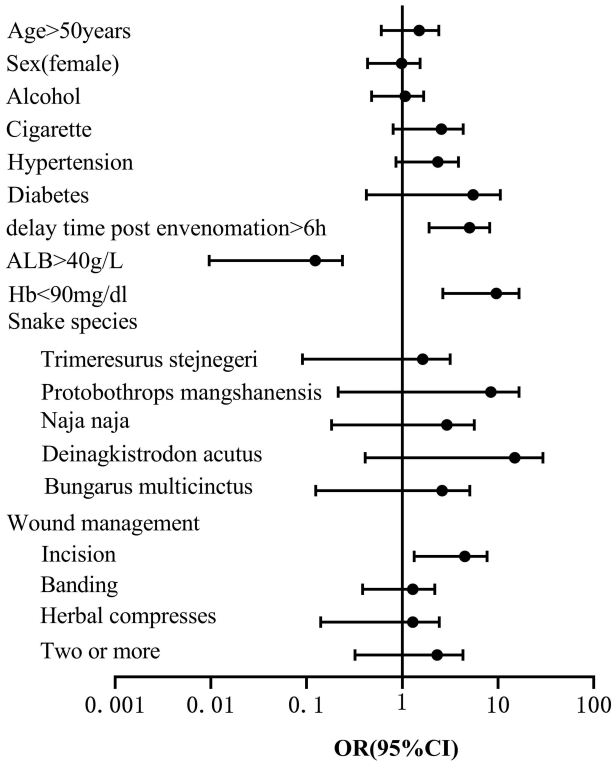


**Figure 1** Single Factor Forest Diagram of Snake Bite Complicated by RM.

### Multivariate Logistic Analysis of Snakebite with Concurrent RM

The significant variables ($P < 0.05$) in the univariate logistic regression analysis were included in the multivariate logistic regression model. Following adjustment for confounding factors such as smoking, alcohol consumption, hypertension, and diabetes, the results are presented in Table 6. Specifically, prolonged duration from snakebite to medical intervention (>6 hours) and hemoglobin levels below 90 mg/dl emerged as independent risk factors for the development of rhabdomyolysis subsequent to snake bites. Conversely, female gender and serum albumin levels >40 g/L were delineated as independent protective factors for rhabdomyolysis against the onset of rhabdomyolysis following snakebites. For detailed insights, refer to Figure 2.

## Discussion

Poisonous snake bite is a common acute toxic disease in clinical practice. It has a high incidence, disability, and mortality rate, thereby constituting a substantial global public health concern.[1] Annually, an estimated 5.5 million individuals worldwide are bitten by snakes, with 1.8 million of these incidents involving venomous snakes, culminating in approximately 100,000 fatalities.[2] Currently, there is a dearth of retrospective studies focusing on snakebites as a precipitating factor for RM. Notably, a study conducted in Australia revealed an incidence of RM of 16%, with a concurrent mortality rate of 2%.[12] Similarly, a study

**Table 6** Multivariate Logistic Regression Analysis of RM Caused by Snake Bites

| Items | *B* | *S.E* | *Wald* | *P* | OR (95% CI) |
|---|---|---|---|---|---|
| Gender: Female | 0.94 | 0.42 | 4.88 | 0.027 | 0.39 (0.17–0.90) |
| Visit time (> 6 h) | 1.41 | 0.42 | 7.25 | 0.007 | 3.12 (1.36–7.14) |
| Albumin (> 40 g/L) | 2.33 | 0.58 | 16.33 | 0.00 | 0.10(0.03–0.30) |
| Hgb(<90mg/dL) | 1.37 | 0.50 | 7.58 | 0.006 | 3.95(1.49–10.50) |

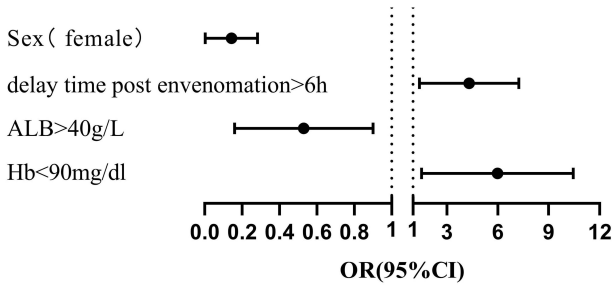


**Figure 2** Multivariate Forest Map of RM Risk After Snake Bite.

conducted in South Korea reported RM incidence of 38.9%.[16] The probability of RM occurring from snake bites in this study stands at 20.57%, which is between the rates documented in Australia and South Korea. Moreover, the mortality rate among patients with concurrent RM status is as high as 6.98%, indicating that RM increases the risk of mortality in snakebite victims.

Snakebite is an acute toxic disease caused by snake venom, causing systemic inflammation and multiple organ damage.[17,18] The precise mechanism underlying RM subsequent to snakebites remains unclear; however, a current study suggests that it is related to phospholipase $A_2$ (PLA2) and metalloproteinases (SVMP) present in snake venom.[8] PLA2 in snake venom can directly attack the phospholipid ester bond of the cell membrane, destroy the integrity of the muscle cell membrane, cause calcium influx, and lead to pressure-related effects or inflammatory responses in the muscle compartment. It can also directly affect the myocardium, leading to RM.[19,20] Intracellular calcium overload will destroy the oxidative phosphorylation coupling and lead to energy generation disorders, increase arachidonic acid metabolites in mitochondria,[21] activate calcium-dependent proteases to destroy protein structure and lead to cell necrosis.[22] SVMP is a broad group of multi-domain proteins, which can cause the release of inflammatory mediators with a variety of biological activities in the human body, directly causing microvascular damage, and thus leading to further tissue destruction.[8] Snake bites cause RM, in a narrow sense, only snake venom causes RM; Broadly speaking, heavy bleeding after the bite, increased osteofascial pressure, and ligating the wound can lead to muscle hypoperfusion and myocyte necrosis. Therefore, the occurrence of RM caused by snake bite is a complex pathophysiological process with multiple factors.

Typical RM manifestations include weakness, muscle pain, and brown urine.[9] After snakebites, various symptoms may mask the manifestations of RM, thereby leading it to be overlooked in some cases. Notably, the RM group exhibited a higher prevalence of encounters with *Protobothrops mangshanensis* (*Viperidae, Ovophis, Ovophis monticola*), a venomous snake species known for its hemotoxic effects on tissue cells, which directly compromise cell membranes and induce cell apoptosis, rendering individuals susceptible to RM.[23] Additionally, the RM group showed an increase in troponinI, accompanied by myocardial cell damage.

While direct myocardial damage induced by snake venom has been documented, mimicking manifestations akin to myocardial infarction, preliminary identification can be achieved through indicators such as cardiac ultrasound and electrocardiogram.[24,25] Furthermore, patients in the RM Group displayed a heightened susceptibility to complications such as liver dysfunction, AKI, intravascular hemolysis, and shock. At present, it is reported that snakebites can cause liver cell damage.[26] Silva et al injected snake venom into mice and confirmed through pathological biopsy of the mouse liver that snake venom can cause liver damage, but the specific mechanism is as yet unclear.[27]

The overall muscle damage for patients in the RM Group was relatively severe, especially tissue necrosis and swelling, which cause increased pressure within the osteofascial compartment, thereby increasing the risk of osteofascial compartment syndrome and prolonged wound infection.[28] Early and timely treatment can improve the prognosis of patients. Mohsin et al and Spyres et al studied the diagnosis, optimal timing for decompression surgery, and prognostic factors of RM in snakebite victims.[28–30] Some studies have reported that the incidence rate of AKI caused by snake bites is 1.4% to 38.5%,[31] which is consistent with our study results.[31] Myoglobin has been implicated as a pathogenic factor in AKI, eliciting endothelial oxidative damage, augmenting vasoconstrictor release, exacerbating renal vasoconstriction, and diminishing glomerular filtration rate.[14,32] Notably, during glomerular filtration, overloaded myoglobin in the circulation binds to T-H protein in the renal tubules to form tubular structures, causing acute kidney injury.[33,34]

Therefore, early blood purification can quickly eliminate toxins and inflammatory mediators, and improve kidney function.

Furthermore, during RM, extensive muscle cell necrosis leads to augmented endogenous nucleic acid metabolism and the subsequent release of intracellular potassium into circulation. Consequently, blood uric acid and potassium levels were found to be elevated in the RM group. Patients in the RM group have more severe conditions, longer treatment times, and poorer prognostic outcomes. Therefore, early clinical identification and intervention of RM can reduce various complications and mortality rates.

It is necessary to explore the important risk factors for the onset of rhabdomyolysis to enhance the management and prevention of acute kidney injury in snakebite victims. Univariate analysis conducted herein revealed noteworthy associations, indicating that delayed diagnosis exceeding 6 hours, hemoglobin levels <90mg/dl, female gender, and serum albumin levels >40 g/L were statistically significant. Subsequent multivariate logistic regression analysis identified prolonged visitation exceeding 6 hours and hemoglobin levels <90 mg/dl as independent risk factors for RM among snakebite victims, while female gender and serum albumin levels >40 g/L emerged as independent protective factors for RM in snakebite victims.

A group study was conducted in France on the risk factors for developing RM with statins, while Mokhtari et al conducted a prospective study observing RM incidence in 235 patients with COVID-19, both confirming male gender as a risk factor for RM development.[13,35] This is consistent with our study's findings. Moreover, existing literature underscores that independent risk factors for postoperative patients with concurrent RM include excessive intraoperative bleeding, young age, and a history of diabetes.[36]

Although our study did not ascertain specific bleeding thresholds or postoperative hemoglobin levels, the observed association between increased postoperative bleeding and heightened RM risk when hemoglobin levels fall below 90 mg/dl partially corroborates our findings. RM is common in snakebite victims and is crucial for the progression and prognosis of renal function. Therefore, clinical practitioners should diligently attend to RM risk factors, enabling early intervention to ameliorate prognostic outcomes.

According to the results of the study, the following two recommendations are made: 1. Do not bind as much as possible after a snake bite, or release the bandage for 1–2 minutes every 15–20 minutes. Try to seek medical attention within 6 hours after snakebite to reduce the probability of RM. 2. During hospitalization, patients should receive antivenom, fluid replacement and steroid hormone therapy as soon as possible. According to the condition, Hb >90g/L and albumin >40g/L should be kept as far as possible, which can effectively reduce the incidence of RM and progress to AKI.

## Limitations of This Study

This retrospective study is inherently susceptible to biases stemming from incomplete descriptions of snakes by the snakebite victims or limited understanding of snakes by novice physicians, potentially skewing study outcomes. Moreover, the patients in our study did not complete the detection of hematuria and myoglobin. Additionally, being a single-center retrospective inquiry, this study is constrained by its relatively modest sample size.

## Conclusion

1. Snakebite incidences in the Longyan District predominantly occur during the summer and autumn seasons, primarily involving encounters with green bamboo leaves and Protobothrops mangshanensis (*Viperidae, Ovophis, Ovophis monticola*) and are more common among middle-aged and elderly people. The clinical manifestations of RM in snakebite victims are diverse and lack specificity, making them more prone to various complications.
2. Visiting the hospital more than 6 hours after the snakebite incident and hemoglobin levels below 90mg/dl independently emerge as risk factors for rhabdomyolysis, while gender and serum albumin levels exceeding 40 g/L are protective factors for RM in snakebite victims. Vigilant consideration of these risk factors in clinical settings is imperative, facilitating early intervention strategies to enhance prognostic outcomes.
3. Snakebite victims with concurrent RM have a severe condition, long treatment durations, and heightened mortality rates compared to those without rhabdomyolysis. RM represents a prevalent yet often disregarded complication in snakebite victims, underscoring the importance of early diagnosis and intervention in clinical practice.

## Abbreviations

RM, Rhabdomyolysis; AKI, Acute Kidney Injury; MODS, Multiple Organ Dysfunction syndrome; DIC, Disseminated Intravascular Coagulation; CK, Creatine Kinase; CK-MB, Creatine Kinase Isoenzyme; ALB, Albumin; ALT, Alanine Aminotransferase; AST, Aspartate Transaminase; Hb, Haemoglobin; ICU, Intensive Care Unit; RBC, Red Blood Cells; WBC, White Blood Cells; PLT, Blood Platelet; PT, Prothrombin Time; APTT, Activated Partial Thromboplastin Time; Cre, Serum Creatinine; FIB, Fibrinogen; BUN, Blood Urea Nitrogen; LDH, Lactate Dehydrogenase; IBIL, Indirect Bilirubin; DD, D-dimer; UA, Uric Acid; BUN, Blood Urea Nitrogen; cTnI, Troponin I; PLA2, phospholipase A2; LAAO, L-amino acid oxidase.

## Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

## Ethics Approval and Consent to Participate

The retrospective study was approved by ethics committee of the Longyan First Affiliated Hospital of Fujian Medical University (No.LYREC2024-k084-01). This study was conducted in accordance with the declaration of Helsinki. Due to the retrospective nature of the study, the requirement of patient consent for inclusion was waived. Patient personal privacy and data confidentiality has been upheld.

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## Disclosure

The authors declare that they have no competing interests.

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