Original Article

Hematologic and Coagulation Trends Following Antivenom Administration in Snakebite Envenomation: A Retrospective Hospital-Based Study

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Abstract

Background: Snakebite envenomation is a significant global health concern associated with substantial morbidity and mortality, particularly due to hematologic and coagulation disturbances. Venom-induced coagulopathy and other systemic effects may persist despite antivenom therapy, and the temporal pattern of laboratory recovery remains incompletely understood. This study aimed to evaluate clinical features and longitudinal hematologic and coagulation changes following antivenom administration in patients with snakebite envenomation.

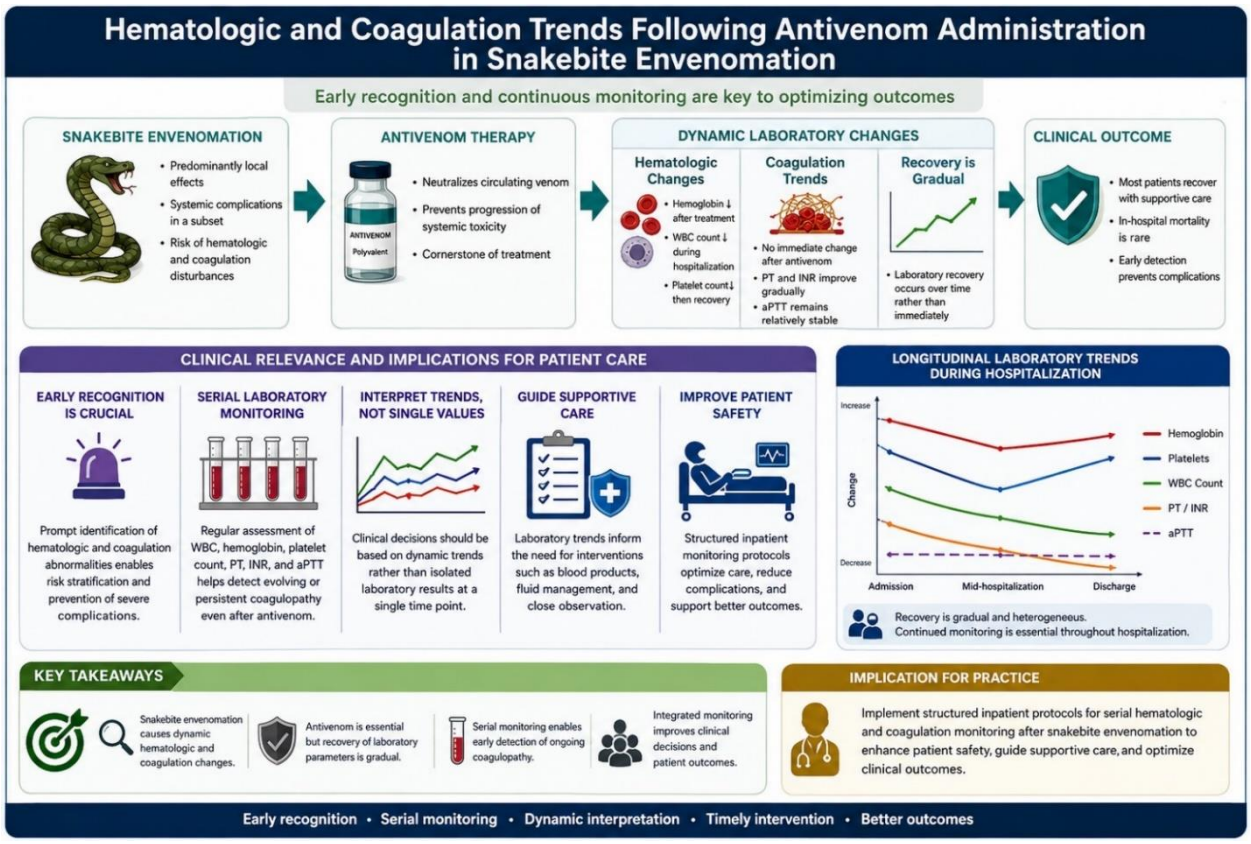
Methods: This retrospective observational study included 154 patients with confirmed snakebite envenomation admitted to a tertiary care center between 2016 and 2022. Demographic data, clinical manifestations, treatment characteristics, and laboratory parameters were extracted from medical records. Hematologic and coagulation indices included white blood cell count, hemoglobin, platelet count, prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (aPTT). Patients were analyzed in full, paired (pre- and post-antivenom), and longitudinal groups. Statistical analyses included paired t tests, Wilcoxon signed-rank tests, and repeated-measures ANOVA.

Results: The mean age was 37.5 ± 17.2 years, and 77.3% were male. Most bites involved the lower extremities (64.9%). Grade 1 envenomation accounted for 55.2% of cases, while 44.8% had Grade ≥2. Local manifestations were predominant. Hemoglobin levels significantly decreased after antivenom administration ($P < 0.001$), while no immediate changes were observed in coagulation parameters. Longitudinal analysis showed a significant decline in white blood cell count and gradual improvement in PT and INR during hospitalization ($P < 0.05$).

Conclusion: Snakebite envenomation is characterized by predominant local effects with dynamic hematologic alterations during hospitalization. Coagulation recovery appears gradual rather than immediately following antivenom therapy, emphasizing the importance of serial laboratory monitoring.

Implications for Patient Care: Continuous monitoring of hematologic and coagulation parameters is recommended even after antivenom administration. Serial assessment may improve early detection of ongoing or delayed coagulopathy and support informed clinical decision-making in inpatient management of snakebite envenomation.

Keywords: Snakebite envenomation; Antivenom therapy; Venom-induced coagulopathy; Hematologic changes; Coagulation parameters; Serial laboratory monitoring



Graphical Abstract. Hematologic and Coagulation Dynamics Following Antivenom Administration in Snakebite Envenomation. This graphical abstract summarizes hematologic and coagulation dynamics in patients with snakebite envenomation following antivenom administration. It highlights the importance of serial laboratory monitoring and dynamic interpretation of hematologic parameters during hospitalization. The integrated clinical approach supports early detection of coagulopathy, improved inpatient management, and enhanced patient safety outcomes.

Introduction

Snakebite envenomation remains a major global health problem, causing an estimated 1.8–2.7 million envenomations and up to 137,880 deaths annually worldwide (1). It remains a major public health challenge, particularly in rural and agricultural regions of low- and middle-income countries, where delayed access to healthcare and antivenom contributes significantly to morbidity and mortality (2, 3). Despite this substantial clinical and public health burden, snakebite envenoming remains classified by the World Health Organization as a neglected tropical disease (NTD) (4). In Iran, snakebite envenomation is an important public health problem, and the country is home to 25 venomous snake species, several of which are responsible for most snakebite incidents nationwide (5). Among these, Viperidae species are responsible for the majority of clinically significant envenomations (6). Viper bites are frequently associated with systemic complications, particularly hematologic and coagulation disturbances (6).

Coagulopathy is the most common systemic syndrome following snake envenomation, and VICC is a major cause of severe bleeding (7). It results from activation of the coagulation cascade by venom enzymes, leading to consumption of clotting factors (8). Laboratory abnormalities may include prolonged prothrombin time (PT), activated partial thromboplastin time (aPTT),

increased international normalized ratio (INR), and reduced fibrinogen levels (9). These laboratory abnormalities are characteristic of venom-induced consumption coagulopathy (VICC) and may help identify patients at risk of bleeding complications (9).

Antivenom therapy is the main specific treatment for systemic snake envenomation (10). Early administration can neutralize circulating venom and may prevent progression of systemic toxicity (10). However, the kinetics of hematologic and coagulation recovery following antivenom administration are not fully characterized, and clinical response may vary among patients (11). The temporal evolution and the precise relationship between hematologic abnormalities remains to be fully elucidated (12). Previous studies have primarily emphasized clinical manifestations, treatment efficacy, and acute management, while serial laboratory monitoring in routine or resource-limited clinical settings has been less well studied (12). Assessment of hematologic and coagulation parameters after snakebite envenomation may enhance clinical monitoring, facilitate early identification of patients at risk of ongoing coagulopathy, and optimize resource utilization in emergency care (13). Therefore, this study aimed to characterize early and in-hospital changes in hematologic and coagulation parameters among antivenom-treated patients with snakebite envenomation admitted to the Poison Center of Shahid Rahimi Hospital, Khorramabad, Iran, between 2016 and 2022.

Methods

Study design

This retrospective observational study was conducted to describe the clinical characteristics of snakebite envenomation and to evaluate hematologic and coagulation changes following antivenom administration and during hospitalization. The study was based on retrospective review of medical records and involved no research-related interventions. All clinical decisions were made according to routine hospital practice. The study protocol was approved by the institutional ethics committee. Patient identifiers were removed before data analysis, and all information was treated confidentially. As this was a retrospective record-based study, no additional intervention, risk, or cost was imposed on patients. The study protocol was approved by the Ethics Committee of Lorestan University of Medical Sciences (IR.LUMS.REC.1401.292).

Study population

Medical records of all patients admitted with suspected snakebite envenomation during the study period were reviewed. Confirmed snakebite envenomation was defined as a documented history of snakebite with compatible clinical manifestations and a physician diagnosis of clinically significant envenomation. Patients were included if they received polyvalent antivenom during hospitalization. Patients with known hematologic disorders, including leukemia, lymphoma, aplastic anemia, or other chronic blood diseases, as well as those who had received anticoagulant medications such as warfarin, heparin, or enoxaparin prior to admission, were excluded. All eligible patients during the study period were included in the analysis.

Data collection

Data were extracted from patients' medical records using a standardized data collection form. Demographic variables included age and sex. Clinical variables included bite site, severity of envenomation, time from bite to hospital admission, time to antivenom administration, number of antivenom vials, length of hospital stay, and documented clinical manifestations. Clinical manifestations recorded included local pain and swelling at the bite site, nausea, vomiting, tachycardia, headache, blister formation, altered mental status, respiratory

failure, necrosis, lymphadenopathy, rhabdomyolysis, hemorrhage, disseminated intravascular coagulation, and hematuria. Laboratory parameters collected included white blood cell count, hemoglobin level, platelet count, prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (aPTT). When available, additional laboratory tests including aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), creatine phosphokinase (CPK), blood urea nitrogen (BUN), creatinine, and urinalysis findings were also recorded. Hematuria was defined as the presence of ≥5 red blood cells per high-power field on microscopic examination of urine.

Severity classification

The severity of envenomation was classified based on a four-grade clinical system adapted from established clinical toxicology criteria. Grade 0 was defined as dry bite with no clinical or laboratory evidence of envenomation. Grade 1 included mild envenomation characterized by local pain, tenderness, and limited swelling without systemic involvement. Grade 2 was defined as moderate envenomation with local manifestations accompanied by systemic symptoms and/or laboratory evidence of coagulopathy without major bleeding. Grade 3 represented severe envenomation with systemic complications such as shock, respiratory failure, altered consciousness, seizures, significant hemorrhage, severe thrombocytopenia, or marked hemoglobin reduction. Grade 4 was defined as very severe envenomation with rapidly progressive local swelling potentially involving the ipsilateral trunk and high risk of compartment syndrome. For analytical purposes, patients were further grouped into mild (Grade 1) and moderate-to-severe envenomation (Grades 2–4) (14).

Analytical groups

Because laboratory investigations were not uniformly performed and repeated measurements were available only in a subset of patients, three analytical groups were defined. The full group consisted of all 154 patients and was used for descriptive analyses of demographic characteristics, clinical manifestations, laboratory abnormalities, and treatment patterns. A paired laboratory group consisting of patients with available laboratory measurements both before and after antivenom administration was used to evaluate immediate hematologic and coagulation changes associated with treatment. A longitudinal group consisting of patients with at least two serial laboratory measurements during hospitalization was used to assess temporal trends in hematologic and coagulation parameters from admission to discharge.

Treatment variables

Treatment-related variables included timing and dosage of antivenom administration, antibiotic therapy, corticosteroid use, antihistamine administration, diuretic therapy, blood product transfusion, and other supportive interventions documented in the medical records.

Statistical analysis

Statistical analyses were performed using SPSS version 24 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD). Categorical variables were presented as frequencies and percentages. Descriptive analyses were conducted on the full study population (n = 154). For patients with available paired laboratory measurements before and after antivenom administration, changes in hematologic and coagulation parameters were evaluated using paired-sample t tests for normally distributed variables and Wilcoxon signed-rank tests for non-normally distributed variables. For patients with serial laboratory measurements

during hospitalization, longitudinal changes were assessed using repeated-measures analysis of variance (ANOVA). When assumptions for parametric analysis were not met, equivalent non-parametric methods were applied. Because laboratory assessments were performed according to clinical indication rather than a standardized study protocol, the timing and number of measurements varied among patients. Consequently, analyses of serial laboratory changes were interpreted with caution due to variability in measurement timing. Missing laboratory data were not imputed, and analyses were conducted using available-case methodology. The number of observations included in each analysis was reported separately. A two-sided P value of less than 0.05 was considered statistically significant.

Results

Patient characteristics and clinical profile

A total of 154 patients with confirmed snakebite envenomation were included in the study. The mean age was 37.5 ± 17.2 years, and most patients were male (77.3%). The most common bite site was the lower extremity (64.9%), followed by the upper extremity (30.5%). Clinical characteristics are summarized in Table 1. Regarding severity, 55.2% of patients presented with Grade 1 envenomation, while 44.8% had Grade ≥2. Prehospital administration of antivenom was reported in 40.3% of cases. The mean time from bite to antivenom administration was 4.2 ± 4.6 hours. The mean total number of antivenom vials administered was 10.0 ± 6.3. The mean hospital stay was 5.7 ± 3.0 days (Table 1).

Variable	Value
Demographic characteristics	
Age (years), mean ± SD	**37.5 ± 17.2**
Male sex, n (%)	**119 (77.3)**
Female sex, n (%)	**35 (22.7)**
Bite location	
Lower extremity, n (%)	**100 (64.9)**
Upper extremity, n (%)	**47 (30.5)**
Other locations, n (%)	**7 (4.6)**
Clinical severity	
Grade 1 (mild), n (%)	**85 (55.2)**
Grade ≥2 (moderate–severe), n (%)	**69 (44.8)**
Prehospital management	
Prehospital antivenom administration, n (%)	**62 (40.3)**
Limb immobilization, n (%)	**26 (16.9)**
Tourniquet application, n (%)	**15 (9.7)**
Treatment characteristics	
Time from bite to antivenom (hours), mean ± SD	**4.2 ± 4.6**
Total antivenom vials administered, mean ± SD	**10.0 ± 6.3**
Length of hospital stay (days), mean ± SD	**5.7 ± 3.0**

Table 1. Demographic characteristics, clinical features, and management profile of patients (n = 154). Data are presented as mean ± standard deviation (SD) or number (percentage). Grade ≥2 includes patients with moderate to severe envenomation according to the study severity classification.

Clinical manifestations of envenomation

Local manifestations were the most common clinical findings. Pain at the bite site was reported in 90.9% of patients, and swelling in 87.0%. Systemic manifestations were less frequent. Nausea occurred in 27.9% of patients, vomiting in 16.9%, and hematuria in 12.3%. Most patients (62.3%) presented with local symptoms only, while 37.7% had both local and systemic manifestations. In-hospital mortality was 0.6% (Table 2).

Laboratory findings of tissue and organ involvement

Biochemical abnormalities were common among tested patients (Table 3). Elevated alkaline phosphatase was observed in 79.1% of tested patients. Elevated AST and ALT were less frequent (9.7% and 8.3%, respectively). Markers of tissue and muscle injury were highly prevalent. LDH was elevated in 85.2% and CPK in 77.8% of tested patients. Renal involvement was less common. Elevated BUN was observed in 24.0%, while elevated creatinine was found in 4.7%. Hematuria was present in 12.3% of patients.

Variable	n (%)
Local manifestations	
Pain at bite site	**140 (90.9)**
Swelling at bite site	**134 (87.0)**
Systemic manifestations	
Nausea	**43 (27.9)**
Vomiting	**26 (16.9)**
Hematuria*	**19 (12.3)**
Clinical presentation pattern	
Local manifestations only	**96 (62.3)**
Local + systemic manifestations	**58 (37.7)**
Clinical outcome	
In-hospital mortality	**1 (0.6)**

Table 2. Clinical manifestations of envenomation. Table 2 presents the distribution of local and systemic clinical manifestations in patients with snakebite envenomation. Data are expressed as number (percentage). *Hematuria was defined as ≥5 red blood cells per high-power field on urine microscopy.

Pharmacologic and supportive management

All patients received antivenom therapy as part of routine management. Antibiotics were administered to 89.0% of patients, corticosteroids to 87.7%, and antihistamines to 81.8%. Supportive therapies were less frequently used. Furosemide was given to 7.1%, mannitol to 4.5%, packed red blood cell transfusion to 3.9%, and fresh frozen plasma to 1.9% of patients (Table 4).

Parameter	Patients tested n (%)	Abnormal n (% among tested)
Liver function tests		
AST	**72 (46.8)**	**7 (9.7)**
ALT	**72 (46.8)**	**6 (8.3)**
ALP	**67 (43.5)**	**53 (79.1)**
Muscle injury markers		
LDH	**54 (35.1)**	**46 (85.2)**
CPK	**45 (29.2)**	**35 (77.8)**
Renal function tests		
BUN	**150 (97.4)**	**36 (24.0)**
Creatinine	**150 (97.4)**	**7 (4.7)**
Urinalysis		
Hematuria*	**154 (100)**	**19 (12.3)**

Table 3. Biochemical, renal, and urinary laboratory findings among tested patients. Table 3 summarizes biochemical and renal laboratory abnormalities among patients with snakebite envenomation who underwent laboratory testing. Data are presented as number (percentage) among tested patients. Hematuria was defined as ≥5 red blood cells per high-power field on urine microscopy.

Treatment	n (%)
Antivenom therapy	154 (100) *
Pharmacologic treatments	
Antibiotics	137 (89.0)
Corticosteroids	135 (87.7)
Antihistamines	126 (81.8)
Supportive treatments	
Furosemide	11 (7.1)
Mannitol	7 (4.5)
Packed red blood cells	6 (3.9)
Fresh frozen plasma	3 (1.9)

Table 4. Pharmacologic and supportive treatments in snakebite envenomation. Table 4 summarizes pharmacologic and supportive treatments administered to patients with snakebite envenomation. Data are presented as number (percentage). *All patients received antivenom therapy as part of standard clinical management.

Hematologic and coagulation changes after antivenom administration

Paired laboratory data were available for 47 patients.

White blood cell count showed a non-significant decrease after antivenom administration (9.15 ± 3.43 vs. 8.52 ± 3.08; P = 0.132). Platelet count also showed a non-significant reduction (209.51 ± 65.42 vs. 203.04 ± 61.59; P = 0.232). Hemoglobin levels decreased significantly after antivenom administration (14.62 ± 1.45 vs. 13.59 ± 1.68; P < 0.001). No significant changes were observed in coagulation parameters, including PT, INR, and aPTT (Table 5).

Variable	Before antivenom (Mean ± SD)	After antivenom (Mean ± SD)	P value
WBC (×10³/µL)	9.15 ± 3.43	8.52 ± 3.08	0.132
Hemoglobin (g/dL)	14.62 ± 1.45	13.59 ± 1.68	<0.001
Platelets (×10³/µL)	209.51 ± 65.42	203.04 ± 61.59	0.232
PT (s)	13.10 ± 2.86	12.73 ± 1.25	0.370
INR	1.08 ± 0.44	1.02 ± 0.16	0.354
aPTT (s)	30.60 ± 5.44	30.15 ± 4.81	0.606

Table 5. Comparison of hematologic and coagulation parameters before and after antivenom administration. Values represent paired laboratory measurements in patients with available pre- and post-antivenom data. Timing of post-antivenom sampling was not standardized and varied according to clinical practice. P values were calculated using paired t-test or Wilcoxon signed-rank test as appropriate.

Longitudinal trends during hospitalization

A total of 107 patients had serial laboratory measurements during hospitalization. White blood cell count showed a significant progressive decline from admission to discharge (11.21 ± 4.28 to 8.87 ± 3.20; P < 0.001). Hemoglobin levels decreased during hospitalization and partially stabilized at discharge (14.90 ± 2.30 to 12.76 ± 1.85; P < 0.001). Platelet counts showed a biphasic pattern, with an initial decrease at mid-hospitalization followed by recovery at discharge (P = 0.001). Coagulation parameters showed modest but significant changes over time. PT and INR decreased during hospitalization (P = 0.005 and P = 0.004, respectively), while aPTT remained stable (P = 0.410) (Table 6).

Variable	Admission (Mean ± SD)	Mid-hospitalization (Mean ± SD)	Discharge (Mean ± SD)	P value
WBC (×10³/µL)	11.21 ± 4.28	9.54 ± 2.92	8.87 ± 3.20	<0.001
Hemoglobin (g/dL)	14.90 ± 2.30	12.74 ± 2.02	12.76 ± 1.85	<0.001
Platelets (×10³/µL)	200.51 ± 59.67	180.09 ± 49.49	201.42 ± 65.87	0.001
PT (s)	14.82 ± 7.54	13.05 ± 1.36	12.69 ± 1.55	0.005
INR	1.16 ± 0.49	1.06 ± 0.16	1.02 ± 0.17	0.004
aPTT (s)	29.67 ± 13.56	28.29 ± 4.90	28.64 ± 5.05	0.410

Table 6. Longitudinal changes in hematologic and coagulation parameters during hospitalization. Table 6 summarizes longitudinal changes in hematologic and coagulation parameters during hospitalization in patients with snakebite envenomation. Data are presented as mean ± standard deviation. P values were calculated using repeated-measures analysis of variance (ANOVA) or equivalent non-parametric tests, as appropriate.

Discussion

In this retrospective observational study of 154 patients with snakebite envenomation, most cases occurred in young to middle-aged males and predominantly involved the lower extremities. Local manifestations, particularly pain and swelling at the bite site, were the most common clinical findings, whereas severe systemic complications were relatively uncommon. Hematologic evaluation demonstrated a significant decline in hemoglobin levels following antivenom administration and

throughout hospitalization, while coagulation parameters remained largely unchanged after antivenom treatment. Longitudinal analyses further showed progressive decreases in white blood cell count and modest improvements in coagulation indices during hospitalization. These findings provide insight into the clinical and laboratory course of snakebite envenomation in patients treated with polyvalent antivenom (15). Local manifestations, particularly pain and swelling at the bite site, were the most frequent clinical findings in our study. Systemic complications such as nausea, vomiting, and hemorrhagic manifestations were less common, and in-hospital mortality was rare. These findings are consistent with previous studies showing that local manifestations such as pain, swelling, cellulitis, and bleeding are frequent after snakebite envenomation, while systemic complications, including acute kidney injury, occur in a subset of envenomed patients (16). A key finding of the present study was the significant reduction in hemoglobin levels following antivenom administration and during hospitalization. Similar reductions have been reported in other studies of hemotoxic snake envenomation, although the magnitude and clinical significance vary across reports (17, 18). The decline is likely multifactorial, potentially related to hemodilution following fluid resuscitation, venom-induced endothelial injury with increased vascular permeability, and possible mild hemolysis or occult microhemorrhage. However, in the absence of standardized fluid balance data and specific hemolysis markers, these mechanisms remain speculative (19, 20). Previous studies have demonstrated improvements in PT, INR, and aPTT following antivenom administration, reinforcing its central role in the management of venom-induced coagulopathy and suggesting that it may help limit progression of VICC (21). In the present study, no immediate changes in coagulation parameters were observed following antivenom administration in paired analyses. However, longitudinal data demonstrated a gradual improvement in PT and INR during hospitalization, indicating that recovery of coagulation function may be delayed and occur over the course of inpatient care. These findings are consistent with previous reports describing partial reversal of venom-induced coagulopathy after timely antivenom therapy (22-24).

White blood cell count showed a significant decline during hospitalization, which may reflect resolution of acute inflammatory response triggered by envenomation. A decrease in the neutrophil-to-lymphocyte ratio may also reflect attenuation of the acute inflammatory response (25). Initial leukocytosis is a well-documented response to tissue injury and systemic inflammation in snakebite patients (26). The observed trend suggests gradual clinical stabilization following treatment and supportive care. Platelet counts were decreased in a subset of patients at admission and subsequently recovered to normal levels during hospitalization (27). This pattern is consistent with a transient consumptive process secondary to venom-induced coagulopathy, with subsequent improvement following antivenom administration and clinical recovery. The biphasic platelet pattern, characterized by an initial decline followed by recovery during hospitalization, is suggestive of a VICC-like mechanism rather than classical disseminated intravascular coagulation (19, 22).

Overall, the findings of this study highlight that while local manifestations dominate the clinical presentation of snakebite envenomation, significant hematologic alterations occur during the clinical course, particularly affecting hemoglobin and inflammatory markers. Early administration of antivenom may play a role in limiting progression of hematologic and coagulation disturbances.

Conclusion

In this retrospective study of patients with snakebite envenomation treated with polyvalent antivenom, local manifestations were predominant, whereas hematologic and coagulation changes evolved over the course of hospitalization. Hemoglobin declined significantly after treatment and remained lower during admission, while PT and INR showed gradual improvement over time. These findings suggest that laboratory recovery after envenomation may be delayed and heterogeneous, supporting continued inpatient monitoring of hematologic and coagulation parameters even after antivenom administration. Prospective studies with standardized serial testing are needed to better define the kinetics of recovery and predictors of persistent coagulopathy.

Limitations

This study has several limitations. First, its retrospective design limits causal inference. Second, it was conducted in a single center, which may limit generalizability. Third, laboratory measurements were not standardized in timing and were not available for all patients, leading to potential selection bias in subgroup analyses. Fourth, the identification of snake species was not consistently available, which may influence clinical heterogeneity. Finally, potential confounding factors such as fluid therapy and transfusion practices could not be fully controlled.

Clinical Relevance and Implications for Patient Care

Early recognition and continuous monitoring of hematologic and coagulation abnormalities are essential in the management of snakebite envenomation. Serial laboratory assessment may support timely identification of patients at risk for evolving or persistent coagulopathy, even after antivenom administration. Antivenom therapy remains the cornerstone of treatment, but clinical response should be interpreted alongside dynamic laboratory trends rather than single time-point measurements. These findings support the integration of structured inpatient monitoring protocols to optimize patient safety and guide supportive care decisions in clinical practice.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Author Contributions

All authors contributed to the conception and design of the study, literature search, data interpretation, drafting of the manuscript, and critical revision of the article. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Ethics Statement

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Data Availability Statement

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

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Publisher's Note

The graphical abstract was prepared by the journal's editorial team using artificial intelligence-assisted design tools and was reviewed and approved by the authors prior to publication.

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