

# Cardiac Profile in Patients with Snake Envenomation and Its Complications: A Retrospective Study from a Tertiary Care Center in South India

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## Abstract

**Background:** Snakebites continue to be a major public health concern throughout the world, and more in tropical countries. Cardiac implications are poorly understood due to the low frequency of cardiotoxicity combined with a lack of robust information. **Aims:** We aim to study the cardiac profile, complications in snake bite patients requiring admission in a medical unit. **Materials and Methods:** This retrospective study was conducted carried out from 01/05/2016 to 01/05/2021. The data was extracted from the inpatient medical records and it was analyzed. All adult patients requiring admission in a Medicine unit with a diagnosis of snake envenomation were included. Descriptive statistics were obtained for all variables in the study and appropriate statistical tests were employed to ascertain the significance. **Result:** The cohort consists of 80 patients with 45(56.3%) males and aged  $40.06 \pm 15.24$  years (mean, SD). The majority of the Snake species identification was not available 38(47.5%). Viper bite was the commonest bite 32 (40%). The commonest clinical presentation was hemotoxic 33 (31.3%) followed by neurotoxic 16(20%). Electrocardiogram abnormalities were seen in 23 (28.7%) patients and commonest abnormality noted was sinus tachycardia 34(42.5%) of cases. 69 (86%) patients had cellulitis and 16(20%) had acute kidney injury (AKI). Twenty-four (30%) required intensive care monitoring, 22 (27.5%) required mechanical ventilation and 7 (8.8%) patients required hemodialysis. The mean  $\pm$  SD duration of hospital stay was of  $5.56 \pm 3.76$  days. The median direct cost was Rs 19714.5 and cost on medicine was Rs 10798. The mortality in this cohort was 4(5%). **Conclusion:** Snake bite causes significant morbidity. Viper bite was the commonest bite in our study. The mortality in this cohort was 4(5%). Cardiac toxicity is a clearly defined toxicity following snake bite envenomation however it has no effect on mortality.

**Keywords:** Electrocardiogram abnormality, Regional wall motion abnormality, Renal failure, Sinus tachycardia, Snakebite

## INTRODUCTION

Snakebites continue to be a major public health concern throughout the world and more in tropical countries. Even though snakebite is an imminently treatable condition, it is a common life-threatening emergency.

Globally, there are nearly 2500 species of snakes, although not all species are venomous. Some venomous species include families: Elapidae, Hydrophidae, Crotalidae, Colubridae, and Viperidae.<sup>[1]</sup> Nevertheless, of the 236 species found in India, only 52 are poisonous.<sup>[2]</sup> According to reports, an estimated 200,000 persons per year fall prey to snakebite in India, with an estimated fatality rate of 35,000–50,000 per year.<sup>[3]</sup>

Cardiac complications are not considered prominent features of snakebites, and the clinical picture is usually dominated

by neurological, hematological, and vascular damage by the snakebite toxins.<sup>[4]</sup> Nevertheless, myocardial involvement is seen on some occasions which may contribute to morbidity and mortality.

Mechanism of cardiotoxicity includes direct toxic effect on the myocardium, coagulation abnormalities, and vasospasm induced by hemorrhagins or endothelins contained in the venom of some snakes.<sup>[5]</sup>

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Cardiac toxicity can result in hypotension and arrhythmias and changes in electrocardiogram (ECG), especially ST segment and T-wave changes and myocardial infarction.<sup>[6]</sup>

Till date, minimal work has been done in India on cardiotoxicity in snake envenomation.

Therefore, the present study was undertaken to find out the clinical and laboratory features of cardiac involvement in snakebite patients requiring admission in a tertiary care hospital in South India.

## MATERIALS AND METHODS

This was a single-center retrospective study conducted in the Department of Internal Medicine, Christian Medical College, Vellore, India. Cases were patients who were admitted in a medical unit between May 01, 2015, and May 01, 2020, with a diagnosis of snake envenomation.

After the ethics and research committee approval from the institute, data were extracted from the inpatient medical records.

The primary outcome assessed was clinical and laboratory features of cardiac involvement in the form of ECG characteristics, elevation of cardiac enzymes, and echocardiographic abnormalities.

Descriptive statistics were obtained for all variables in the study and appropriate statistical tests. The following statistical methods were applied in the present study-contingency table analysis and independent samples *t*-test.

## RESULTS

The cohort consists of 80 patients. The detailed demographic profiles of the snakebite victims are presented in Table 1. In this study sample, the mean age of victims was  $40.06 \pm 15.24$  years (mean and standard deviation [SD]), and 45 (56.3%) were males, and 35 (43.7%) were females. Viper bite was the most common bite 32 (40%), and in 47.5% of cases, the species of the snake was not known.

ECG abnormalities were seen in 23 (28.7%) patients, and the most common abnormality noted was sinus tachycardia 34 (42.5%) cases. A detailed pattern of ECG findings is presented in Table 2. Inpatient echocardiogram was done for 42 (52%) patients. Majority of them showed global normal left ventricular systolic function. Echocardiography of one patient showed akinesia of the apical and mid-ventricular segment with hypercontractile basal segments suggesting stress-induced takotsubo cardiomyopathy, and another patient showed reduced tricuspid annular plane systolic excursion suggestive of right ventricular systolic dysfunction. A detailed pattern of echocardiography findings is presented in Table 3. Sixteen (20%) had acute kidney injury. Twenty-four (30%) required intensive care monitoring, 22 (27.5%) required mechanical ventilation, and 7 (8.8%) patients required renal replacement therapy. The mean  $\pm$  SD duration of hospital stay

**Table 1: Demographic profiles of the snakebite victims**

Variable	Number of patients (n=80) (%)
Age (years), mean $\pm$ SD	40.06 $\pm$ 15.24
Male:female	49:31 (61.25:38.75)
Type of snake	
Viper	32 (40)
Krait	6 (7.5)
Cobra	4 (5)
Unknown	38 (47.5)
Clinical presentation	
Hemotoxic	33 (41.25)
Neurotoxic	16 (20)
Both hemotoxic and neurotoxic	21 (26.25)
No signs of envenomation	10 (12.5)
Location at time of bite	
Outdoor	66 (82.5)
Indoor	14 (17.5)
Site of bite	
Lower extremity	53 (66.25)
Upper extremity	21 (26.25)
Trunk	5 (6.25)
Face and head	1 (1.25)
Treated elsewhere before coming to this hospital	68 (85)
ASV received outside, median (IQR)	8 (0–10)
ASV given in this hospital, median (IQR)	10 (6–10)
ASV hypersensitivity reaction	12 (15)

IQR: Interquartile range, ASV: Anti-snake venom

**Table 2: Pattern of ECG findings**

Pattern of ECG findings	Number of patients (n=80) (%)
Normal ECG	47 (58.7)
Sinus tachycardia	23 (28.7)
Sinus bradycardia	5 (6.2)
First-degree AV block	2 (2.5)
Early repolarization	3 (3.75)
ST elevation	1 (1.25)
ST depression	7 (8.75)
Tall T-wave	11 (13.75)
T-wave inversion	6 (7.5)
Premature atrial complexes	2 (2.5)
Atrial fibrillation	2 (2.5)
Sinus arrhythmia	1 (1.25)
Long QTc	17 (21.2)

ECG: Electrocardiogram, AV: Atrioventricular

was  $5.56 \pm 3.76$  days. The median direct cost was Rs. 19,714.5, and the cost on medicine was Rs. 10,798. No fatal outcome was reported in the victims who were admitted within 24 h of the snakebite, thus highlighting the importance of an early initiation of specific treatment. The mortality in this cohort was 4 (5%). Complications observed following hospitalization are presented in Table 4. Patients who had an increased length of stay in the hospital had more abnormal findings in ECG. Overall mortality was more in cases where there was abnormal

ECG. However, overall outcome analysis with ECG was shown to have no significant impact on the prediction of mortality.

**Table 3: Pattern of ECHO findings**

Pattern of echo findings	Number of patients (n=42) (%)
Normal left ventricular systolic function	37 (88.1)
Left ventricular global hypokinesia	2 (4.76)
Takotsubo cardiomyopathy	1 (2.38)
Left ventricular regional wall motion abnormalities	1 (2.38)
Diastolic dysfunction	5 (11.9)
Right ventricular dysfunction	1 (2.38)
Pericardial effusion	2 (4.76)

**Table 4: Complications observed following hospitalization**

Variable	Value, n (%)
Complications	
Cellulitis	69 (86.25)
Renal failure	16 (20)
Bleeding manifestation	12 (15)
ARDS	8 (10)
Hospital-acquired infection	8 (10)
Encephalopathy	6 (7.5)
Thrombotic microangiopathy	4 (5)
Elevated CK-MB level	6 (7.5)
Elevated troponin level	21 (26.3)
Cost of care (INR), median (IQR)	19,714.5, (10,320.5–53,154.75)
Cost of medicine (INR), median (IQR)	10,798.5, (4714.75–22,665.25)
Duration of hospital stay (days), mean±SD	5.56±3.76
Mortality	4 (5)

CK-MB: Creatine kinase-myoglobin binding, IQR: Interquartile range, SD: Standard deviation, ARDS: Acute respiratory distress syndrome

## DISCUSSION

Snakebite envenomation is a neglected tropical disease which results in morbidity and mortality. Envenomation caused by snake venom is usually characterized by local manifestations, hemorrhagic alterations, nephrotoxicity, and neurotoxicity. Cardiac involvement is generally rare. Cardiac implications are poorly understood due to the low frequency of cardiotoxicity combined with a lack of robust information. This study explored the profile of 80 snakebite victims and analyzed their sociodemographic and epidemiological details. Out of 80 cases of snakebite reported in the hospital, two-thirds of the victims were males and one-third was females. Similar findings were reported by Lal *et al.*,<sup>[7]</sup> Inamdar *et al.*,<sup>[8]</sup> and Julian *et al.*<sup>[9]</sup> The mean age of victims in our study was 40.06 years, similar to the mean age of 41.9 years, identified in a similar cross-sectional study conducted from Manipal,<sup>[10]</sup> suggesting that working young men are more prone to become snakebite victims.

Cardiac complications are not considered prominent manifestations of venomous snakebites and are primarily linked to the genus Viperidae.<sup>[11]</sup> As per previous studies, the most specific sign indicating the involvement of the myocardium is the T-wave abnormalities on the ECG. Other rare complications of snakebite include arrhythmias. Arrhythmias reported following viper snakebite in literature include ventricular tachycardia, torsades de pointes, and sinus arrest.<sup>[4]</sup> ECG alterations are typically transient if they last for a long time; they point toward the toxin causing direct myocardial damage.

In our study, ECG abnormalities were noted in 41.25%, and common ECG findings were sinus tachycardia (28.7%), sinus arrhythmia (1.25%), sinus bradycardia (6.2%), tall T-wave (13.75%), T-wave inversion (7.5%), and ST depression (8.75%). In our study, prolonged QTc was seen in 21.2% of patients. There have been similar findings in previous studies.<sup>[12-14]</sup> ST-segment elevation was noticed in one of our

**Table 5: Snake venom toxins and their potential mechanism affecting the Cardiovascular system (CVS)**

Toxin	Biological target	Effect on CVS
Bradykinin-potentiating peptides	Angiotensin-converting enzyme	Lowering of blood pressure through a decrease in the concentration of angiotensin II and an increase in the concentration of bradykinin <sup>[25]</sup>
Natriuretic peptides	Natriuretic peptide receptors A, B, and C	Reduction of blood pressure by lowering vascular resistance (due to a decrease in the influx of calcium ions into muscle cells) and a decrease in the volume of circulating blood (due to an increase in the volume of excreted urine) <sup>[22]</sup>
Sarafotoxins	ETA and ETB receptors	Increased vasoconstriction followed by narrowing of the bronchi and increase in hydrostatic pressure of microvessels in the lungs causing pulmonary edema leading to left ventricular failure <sup>[22]</sup>
Three-finger toxins	Adrenergic receptors, cholinergic receptors, cell membrane	Suppression of contractility, blocking $\beta_1$ and $\beta_2$ adrenergic receptors <sup>[26]</sup> causing reduction in heart rate
CRISPs	Voltage-gated ion channels	Block smooth muscle contraction <sup>[27]</sup>
Alternagin-C	Integrin $\alpha\beta_1$ and VEGFR-2	expression of the vascular endothelial growth factor, proliferation and migration of endothelial cells, enhancement of angiogenesis, enhancement of cardiac activity; protection against hypoxia <sup>[28]</sup>
Endothelial vascular growth factors	Receptor tyrosine kinases VEGFR-1, VEGFR-2, and VEGFR-3	Cardioprotective effect; reduction in reperfusion injury to the heart <sup>[29]</sup>
PLA2	Cell membrane, secretory PLA2 receptors	Cardiotoxicity; myocardial contracture <sup>[30]</sup>

CRISPs: Cysteine-rich secretory proteins, ETA: Endothelin type A, ETB: Endothelin type B, VEGFR: Vascular endothelial growth factor receptor, PLA2: Phospholipase A2, cvs: cardiovascular system

patients. There are case reports of acute ST-segment elevation myocardial infarction.<sup>[12,15-17]</sup>

Hypercoagulability with consumption coagulopathy, direct cardiotoxic effect of snake venom causing myocarditis and extensive myocardial necrosis, coronary spasms due to endothelins or sarafotoxins, and hyperviscosity secondary to hypovolemia-induced hemoconcentration have been proposed as underlying mechanism.<sup>[18]</sup>

Mortality was reported as 5%, with all patients exhibiting abnormal ECGs.

Another study conducted by Nayak *et al.* (Rajasthan, India) on 30 patients revealed cardiotoxicity in 25% with viperine bites. Hypotension was seen in 16.7%. Common ECG changes were sinus tachycardia, sinus arrhythmia (6.6%), sinus bradycardia (10%), tall T-wave in V2 (3.3%), patterns suggestive of acute anterior wall infarction with reciprocal changes (3.3%), myocardial ischemia (10%), nonspecific ST-T changes (16.7%), and atrioventricular block (3.3%). Mortality was reported as 10%, with all patients exhibiting clotting disorders and abnormal ECGs.<sup>[19]</sup>

Data from a previous study conducted by Singh *et al.* (Jabalpur, Madhya Pradesh) revealed ECG changes in 39.2% of cases. Common electrocardiographic changes were sinus tachycardia (17.8%), sinus arrhythmia (2.3%), sinus bradycardia (9.5%), nonspecific ST-T changes (5.9%),

and atrioventricular block (3.5%). The mortality rate was 19%.<sup>[20]</sup>

Another study conducted by Kim *et al.* (Wonju, Korea) showed that 9 (13.8%) of the 65 patients had adverse cardiovascular events. Two (3.1%) patients had ischemic changes on ECGs, whereas T-wave inversion was observed in 4 (6.2%) patients and QT prolongation in 25 (38.5%) patients.<sup>[21]</sup>

Undoubtedly, ECG can be looked as a valuable source of information in snakebite patients to enhance and direct their care. However, more research is required to understand the detailed mechanism of their electrocardiographic changes.

In our study, most of the echocardiographic findings are normal. Only 4.7% of patients have global hypokinesia, 2.3% showed regional wall motion abnormality, and takotsubo cardiomyopathy in 2.3% in accordance with previous studies.<sup>[15]</sup> There were no serial echocardiograms to confirm the reversibility of cardiac toxicity.

The mechanism of myocardial damage from snakebite is proposed to be multifactorial:

- (a) hypovolemic shock due to increased vascular permeability;
- (b) coronary thrombosis resulting from hypercoagulability;
- (c) direct cardiotoxicity; and
- (d) vasospasm caused by snake venom.

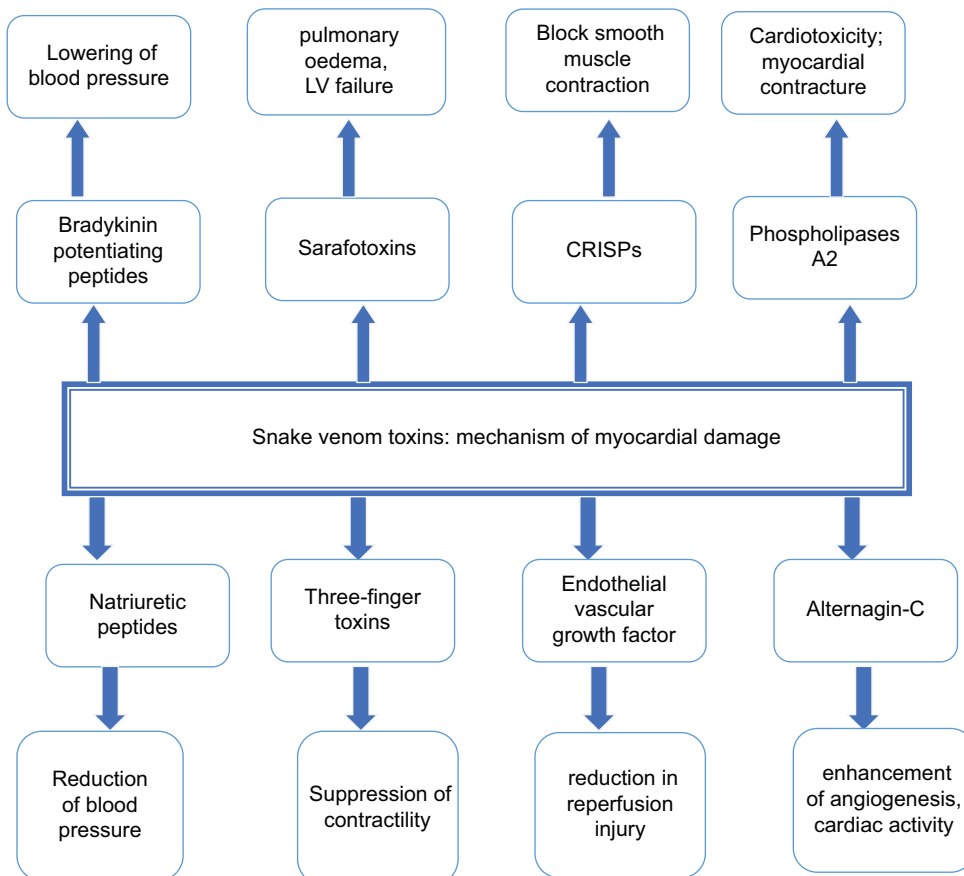


Figure 1: Snake venom toxins and their mechanism of myocardial damage

Snake venoms are complex mixtures of peptides and proteins. Snake venoms are classified as neurotoxic and hemotoxic. Neurotoxic venoms are typically found in snakes from the Elapidae family (cobras, kraits, mambas, and coral) and contain mainly nonenzymatic toxins that block nerve impulse conduction. Hemotoxic venoms are typical of snakes from the Viperidae family (vipers, moccasins, rattlesnakes, and some other snakes).<sup>[22]</sup> Snake venom poisoning is associated with a number of cardiovascular effects, including hypotension, myocardial infarction, cardiac arrest, hypertension, bradycardia or tachycardia, and atrial fibrillation.

Snake venom toxins that affect the Cardiovascular system (CVS) and their potential mechanism [Figure 1 and Table 5]<sup>[22]</sup> are listed in Table 4.

Previous studies have shown that most severe complications and fatalities are unrelated to cardiac abnormalities.<sup>[23,24]</sup> Similar findings were observed in our study where overall outcome analysis with ECG was shown to have no significant impact on mortality.

The mortality rate in our study was 5%, and all of them succumbed to hospital-acquired infection.

### Limitations of the study

The study was conducted using a retrospective design at one tertiary care center, and thus, the study may not be a real reflection of the original magnitude of the problem in the community. Second, we could not conclude for cardiac function in all patients because we performed echocardiography on only 42 out of 80 patients. Third, there were no long-term follow-up of the patients who showed ECG abnormalities. Limited sample size, missing echocardiography data, and unavailable ECG at discharge were other limitations of this study.

Therefore, further prospective studies with serial ECG and echocardiography are needed to investigate the prognosis of cardiac injury in patients with snakebite.

### CONCLUSION

Snakebite causes significant morbidity. Viper bite was the most common bite in our study. Overall analysis of results suggests that cardiac toxicity is a clearly defined toxicity following snakebite envenomation. Mortality results suggest that cardiovascular involvement may not be responsible for mortality in snake envenomation; however, it is important to recognize cardiovascular complications as it will have an impact on management.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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