CLINICAL AND INVESTIGATIVE PROFILE OF PATIENTS HAVING SNAKEBITE WITH SPECIAL REFERENCE TO ACUTE KIDNEY INJURY

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ABSTRACT

BACKGROUND

On the Indian subcontinent, almost all snakebite deaths have traditionally been attributed to the big four consisting of the Russell's viper, Indian cobra, saw-scaled viper and the common krait. In India, the incidence of acute kidney injury following Russell's viper(E. carinatus) bite is 13 to 32%. As many of the cases are not reported and many cases are falsely believed due to some other underlying factors, the actual figure may actually be upto 40%.[1] Tubular necrosis and cortical necrosis are the main causes of AKI.

The aim of the study is to-

1. Evaluate all patients with snakebite both clinically and by investigations.
2. Assess the risk factors and the prognostic factors in snakebite-induced Acute Kidney Injury (AKI).
3. Determine the in-hospital outcome of snakebite patients with AKI.

MATERIALS AND METHODS

Observational Study (A Descriptive and Prospective Type of Study)-

Period of Data Collection- December 2013 to November 2014 (total duration of 1 year).

Inclusion Criteria- All patients coming to emergency department with a definitive history of snakebite. A clinical history taking and a complete physical examination was done in each case. It was followed by laboratory investigations.

RESULTS

Out of 113 patients, 35 patients developed acute kidney injury. Primarily, symptoms complained by the patients were pain at local bite site (74.3%), local bite site swelling (38.1%), vomiting (37.2%), decreased urine output (30.1%), bleeding from any site (24.8%), black or brown urine (20.4%), giddiness (16.8%), limb weakness (15.0%), ptosis (12.4%), altered sensorium (6.2%) and abdominal pain (6.2%). Neurotoxicity was present in 36 (31.9%) patients. Haemotoxicity was present in 36 (31.9%) patients. Local toxicity was present in 42 (37.2%) patients. Primary renal toxicity was present in only 1 (0.8%) patient. IV haemolysis was observed in 12 patients in AKI group, which was seen in only 11 out of 78 patients in non-AKI group, which was statistically significant (p=0.013). All 6 AKI patients who expired had snakebite over lower limb, while 13 of 29 patients who survived had lower limb bite. It was significant statistically (p=0.013). All 6 patients with AKI who expired were observed to have intravascular haemolysis, while only 6 out of 29 AKI patients who survived had intravascular haemolysis. Statistically significant (p=0.002). 5 out of 6 patients with AKI who expired had hypotension on admission, while only 8 out of 29 AKI patients who survived had hypotension on admission. It was statistically significant (p=0.01). All 6 expired AKI patients were observed to have uraemic encephalopathy during their hospital stay, while only 7 out of 29 AKI patients who survived had uraemic encephalopathy. It was statistically significant (p=0.005). All 6 patients with AKI who expired had local toxicity. It was significant statistically (p=0.038). 2 out of 6 patients with AKI who expired had haematotoxicity. Not statistically significant (p=0.83). 2 out of 6 expired AKI patients had undergone haemodialysis, while 7 out of 29 AKI patients who survived received haemodialysis. Not statistically significant (p=0.63). 3 out of 6 patients with AKI who expired had neurotoxicity. Not statistically significant (p=0.93).

CONCLUSION

Overall mortality due to snakebite was 9.7%. Incidence of AKI in snakebite was 30.9%. Lack of education, lapse of time in seeking proper healthcare, visit to any traditional healer/quack therapy prior to hospitalisation, local toxicity (cellulitis, local sepsis, etc.), intravascular haemolysis (in form of black/brown urination), hypotension at presentation, prolonged hospitalisation after neurotoxicity and requirement of ASV on admission were significantly associated with occurrence of AKI and so they were predictors of AKI. Mortality in snakebite-induced AKI patients was 17.1%.

KEYWORDS

AKI- Acute Kidney Injury.

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BACKGROUND

Snakebite-induced morbidity and mortality is a common healthcare problem all over the world especially in tropical and subtropical areas.

Snakebite is an important environmental and occupational hazard particularly in India where farming is a major source of employment.[2]

Although, nearly all snakes with medical relevance can induce Acute kidney injury (AKI), it is unusual except with bites by Russell's viper, E. carinatus and members of the genera Crotalus and Bothrops. The most prevalent areas for these snakes are Asia and South America.[3]

Up to 90% of the approximately 1000 deadly snakebites occurring per annum in Burma are attributed to Russell's viper, which is also the fifth most common cause of death and the most common cause of AKI in Burma. In Thailand, 70% of AKI cases have been ascribed to Russell's viper envenomation. In India, AKI is mostly associated with Russell's viper and E. carinatus bites. The snakes of the genus Bothrops are the leading cause of venomous snakebite in South America.

In India, the incidence of AKI following E. carinatus or Russell's viper bite is 13 to 32%. As many of the cases are not reported and many cases are falsely believed due to some other underlying factors, the actual figure may actually be up to 40%.

Acute kidney injury is an important complication of snakebite in which proper supportive management after the antivenom administration is of utmost importance for a good patient outcome.[4]

OBJECTIVES

- To evaluate all patients with snakebite both clinically and by investigations.
- To assess the risk factors and the prognostic factors in snakebite-induced Acute Kidney Injury (AKI).
- To determine the in-hospital outcome of snakebite patients with AKI.

MATERIALS AND METHODS

Study Design- Observational study (a descriptive and prospective type of study).

Sample size- By expecting acute kidney injury rate in hospitalised cases of snakebite 28% (according to similar study carried out at Postgraduate Medical Institute, Chandigarh, India- it was 28.6%), desired precision 7 and α risk 5%- minimum sample size comes 100.

Study Population- Patients coming to outdoor department and being admitted under Medicine Department of SSG Hospital, Vadodara, fulfilling inclusion criteria.

Study Subjects- All patients who fulfilled the inclusion criteria.

Data Collection Period- December 2013 to November 2014 (total duration of 1 year).

Inclusion Criteria

All patients coming to emergency department with a definitive history of snakebite.

Exclusion Criteria

1. The patients with a preexistent renal disease (serum creatinine of >1.5 mg/dL prior to the snakebite or ultrasonography of the abdomen, which was suggestive of bilateral small kidneys/loss of the corticomedullary differentiation/obstructive nephropathy/other renal pathologies).
2. Diagnosed cases of hypertension/diabetes mellitus.
3. Exposure to nephrotoxic drugs/toxins.

Criteria for Diagnosis of Hypertension and Diabetes Mellitus

Hypertension was diagnosed when a patient had received medicine for hypertension or had systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg after taking 5 minutes rest.

Diabetes mellitus was diagnosed according to "American Diabetes Association" when a previous or current 12 hrs. fasting glucose level is 7 mmol/L or greater (≥126 mg%) (done by a "glucose oxidase peroxidase" method).

Data Collection and Methodology

- A written and informed consent about enrolment in the observational study and maintaining adequate privacy and confidentiality was taken from all patients included in study.
- All patients were subjected to a standardised interview including details regarding the event, e.g. time gap between snakebite and arrival to hospital, visit to any traditional healers, feeding habits after snakebite, etc.
- A clinical history taking and a complete physical examination was done in each case.
- It was followed by laboratory investigations (listed below).
- Patients with snakebite were classified in two groups according to presence or absence of acute kidney injury.
- Cases of acute kidney injury were identified according to the definition below.

The presence of an acute kidney injury defined as-

1. An abrupt (within 48 hours), absolute increase in the serum creatinine concentration of ≥0.3 mg/dL from the baseline value, which was measured at admission either in our hospital or elsewhere after the snakebite before referral to our hospital.

2. A percentage increase in the serum creatinine concentration of ≥50% above the baseline.
3. Oliguria of less than 0.5 mL/kg per hour for more than six hours.
4. Serum creatinine of more than 1.5 mg/dL.
5. Oliguria (urine output of less than 400 mL/day).

- Only those patients who had acute kidney injury were followed up for further management (pharmacological and/or dialysis) till the final outcome of the disorder. (e.g. cured and discharged/death/discharged against medical advice, etc.)
- Different parameters and factors were statistically analysed in all cases of snakebite by proper statistical methods.
- Differences between both above groups were compared by statistical methods.
- Data related to follow up of patients with acute kidney injury were also analysed for statistical significance.

Laboratory Investigations
- Complete CBC (haemoglobin, total and differential leucocyte counts, platelet counts, red cell counts and indices).
- Serial Whole Blood Clotting Time (WBCT) (at least 3 times 6 hours apart).
- In cases with WBCT was significantly higher even on third time. The coagulation profile including the Prothrombin Time (PT) with the International Normalised Ratio (INR) and the Activated Partial Thromboplastin Time (APTT).
- Urine examination including microscopy.
- Liver function tests.
- Renal function test with serum electrolytes.
- The radiological investigations including x-ray of the chest and ultrasonography of the abdomen.
- Serological tests including HBsAg, HIV and HCV were carried out if patient was to be subjected to haemodialysis.
- Some of the tests were repeated (mostly renal function tests, CBC, coagulation profile, etc.) according to patient's clinical condition and further management plan.

Data Analysis and Statistical Methods
All data related to all cases of snakebite patients were analysed using appropriate statistical tests by using MedCalc version 12.5. A p value <0.05 will be considered statistically significant.

The patients were classified into two groups according to the presence or absence of AKI.

Continuous variables in the two groups were expressed as mean ± standard deviation.

For comparison of categorical variables, Pearson's Chi-square test was used.

Fischer exact test was used for small numbers.

For continuously distributed variables, Student's t-test for the significance of difference between the means of two independent samples was used. P value of 0.05 or less was considered to be significant.

To determine the factors associated with snakebite-induced AKI, univariate and multivariate analysis was performed using linear regression method.

Outcome
Clinical and investigative parameters were observed in patients of snakebite.

Different parameters and factors were correlated with the presence of acute kidney injury associated with snakebite and prognostic factors related to this AKI were determined.

Data related to follow up of patients with snakebite-induced AKI was analysed and correlated with their final outcome.

RESULTS
In the present study, total 113 patients were included according to the inclusion criteria from all the patients coming to outdoor department and being admitted under Medicine Department of SSG Hospital, Vadodara.

Out of them, 35 patients developed acute kidney injury. This group was compared with the group of patients who did not develop acute kidney injury. Former group was followed up till final outcome.
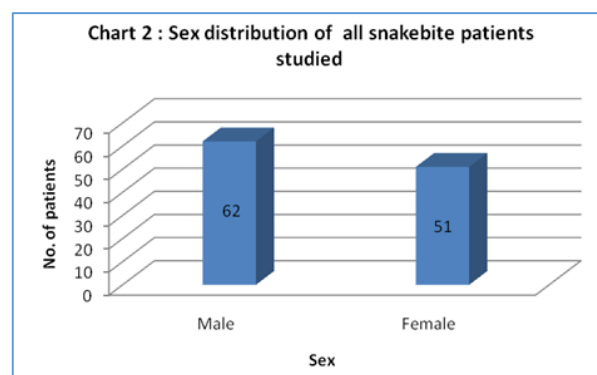
Study Period
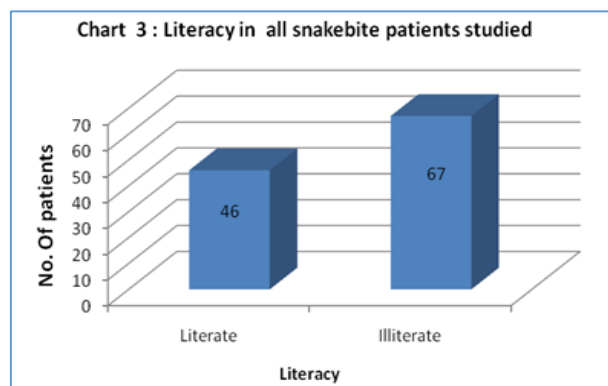December 2013 to November 2014 (total duration of 1 year).

Part 1- Study of all Patients with Snakebite

Chart 1 : Age distribution of all snakebite patients studied
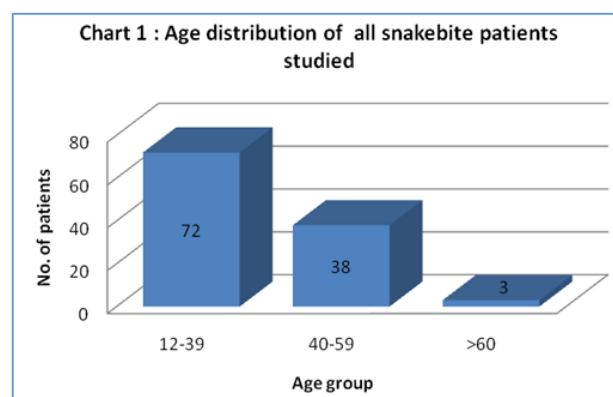
Mean age of study population was 34.6 ± 12.4.

Chart 2 : Sex distribution of all snakebite patients studied

In the present study, males account for 54.9% (62 out of 113) and females 45.1% (51 out of 113).

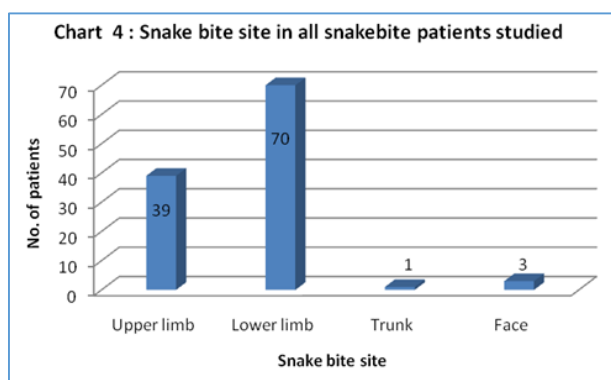Chart 3 : Literacy in all snakebite patients studied

In the present study, 40.7% (46 out of 113) patients were found to be literate and 59.3% (67 out of 113) illiterate.

| Time Zone (hrs.)	No. of Patients	%
00:00 to 05:59	19	16.8
06:00 to 11:59	33	29.2
12:00 to 17:59	26	23.0
18:00 to 23:59	35	31.0
Total	**113**	**100.0**
Table 1. Timing of Snakebite in all Snakebite Patients Studied		

In the present study, majority (60.2%) (68 out of 113) of the snakebites occurred during morning and evening hours.

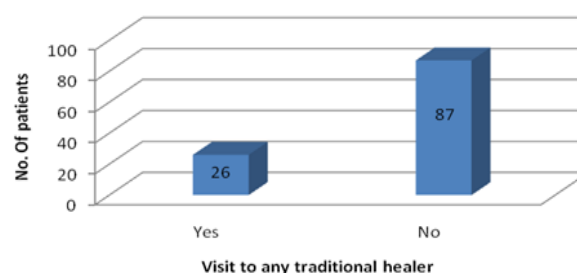Chart 4 : Snake bite site in all snakebite patients studied

In the present study, majority (61.9%) (70 out of 113) of the patients had bite over lower limb.

Chart 5 : Distribution of Lapse of time in hrs in all snakebite patients studied
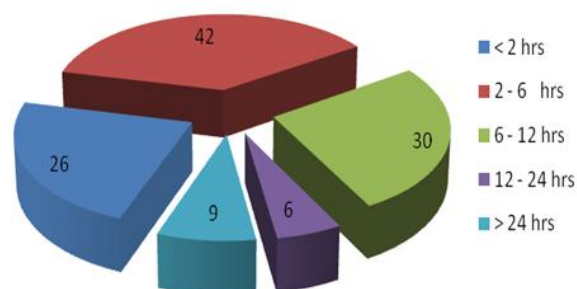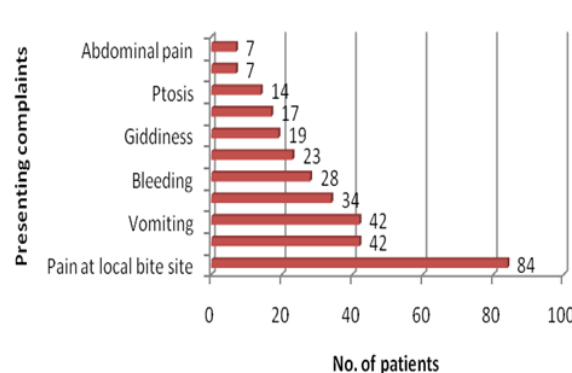
In the present study, 42 (37.2%) patients presented within 2-6 hours of snakebite and 30 (26.5%) patient within 6-12 hours. Only 9 (8%) patients presented after 24 hours.

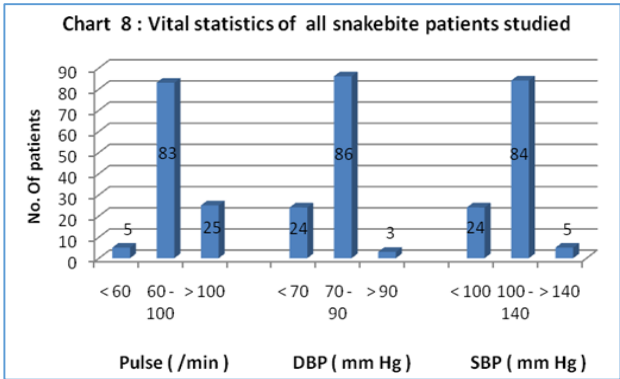Chart 6 : Prior visit to any traditional healer in all snakebite patients studied

In the present study, only 26 patients (23%) visited traditional healers, rest of them all directly visited medical facility.

Chart 7 : Presenting complaints of all snakebite patients studied

In this study, patients presented with multiple complaints.

Primarily, symptoms complained by the patients were pain at local bite site (74.3%), local bite site swelling (38.1%), vomiting (37.2%), decreased urine output (30.1%), bleeding from any site (24.8%), black or brown urine (20.4%), giddiness (16.8%), limb weakness (15.0%), ptosis (12.4%), altered sensorium (6.2%) and abdominal pain (6.2%).

Chart 8 : Vital statistics of all snakebite patients studied

In the present study, 24 patients (21.2%) were in hypotension at presentation. 25 patients (22.1%) were having tachycardia and 5 (4.4%) were having bradycardia.

Chart 9 : Whole Blood Cloting Time (WBCT) in all snakebite patients studied
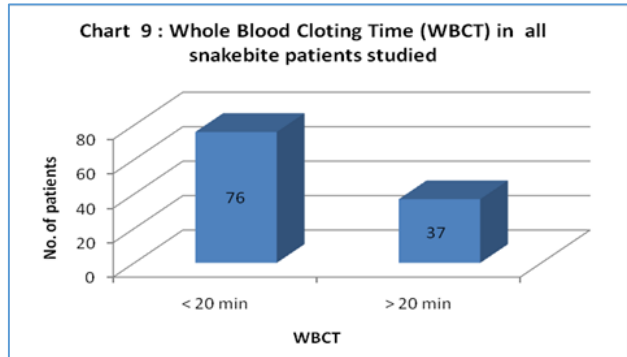
Out of 113 patients, 37 patients (32.7%) had more than 20 minutes of WBCT, i.e. 32.7% patients had haematotoxicity at presentation.
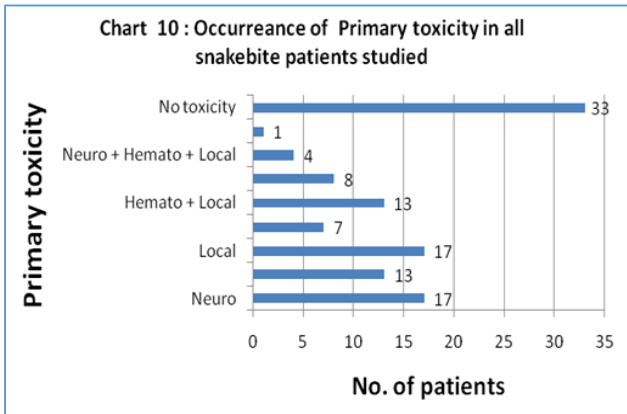
Chart 10 : Occurreance of Primary toxicity in all snakebite patients studied

Many patients (32 out of 113, 28.3%) had mixed toxicities at presentation. 33 patients (29.2%) did not develop any toxicity.

Chart 11 : Primary toxicity in all snakebite patients studied
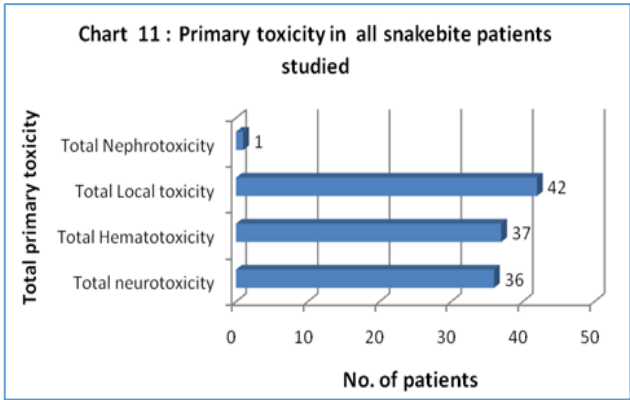
Neurotoxicity was present in 36 (31.9%) patients. Haematotoxicity was present in 36 (31.9%) patients. Local toxicity was present in 42 (37.2%) patients. Primary renal toxicity was present in only 1 (0.8%) patient.

Total ASV Vials Given	No. of Patients	%
0 vials	39	34.5
10 vials	38	33.6
20 vials	36	31.9
Total	**113**	**100.0**
Table 2. Requirement of ASV in all Snakebite Patients Studied		

Out of 113 patients, 39 patients (34.5%) did not require ASV. 38 patients (33.6%) were given 10 vials of ASV and 36 patients (31.9%) were given 20 vials of ASV as per their requirement.

Chart 12 : Final outcome of all snakebite patients studied
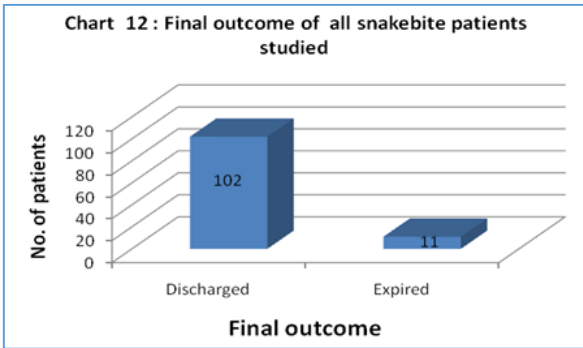
Out of 113 patients studied, 102 patients (90.3%) were cured and discharged. 11 patients (9.7%) expired of them.

Chart 13 : Total Hospital stay of all snakebite patients who survived

Out of 102 patients who survived, 72 patients (70.6%) were discharged within 3-7 days. Only 15 patients (14.7%) required hospital stay more than 7 days.

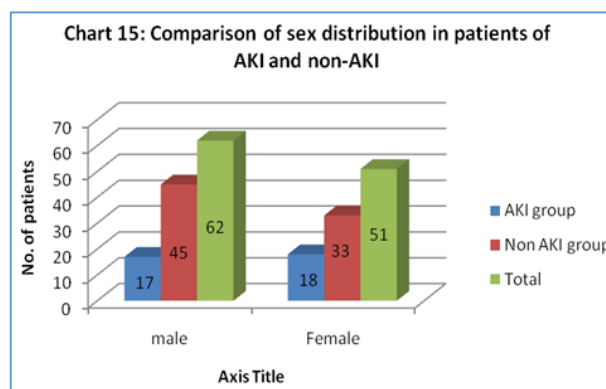**Mortality**- Overall mortality in cases of snakebite was 9.7%.

| Demographic Characters	Snakebite Patients
Number	113
Age (mean ± SD) (years)	34.6 ± 12.4
Male:female	62:51 (1.21:1)
Literacy	40.7%
Lower limb bite	61.9%
Time lapse of >12 hours	12.3%
Visit to traditional healers	23%
Hypotension at presentation	21.2%
Intravascular haemolysis	20.4%
>20 minutes WBCT	32.7%
Primary haematotoxicity	32.7%
Primary neurotoxicity	31.9%
Primary local toxicity	37.2%
Table 3. Demographic Data of all Patients with Snakebite Studied	

Part 2- Comparison of AKI Group and Non-AKI Group

Chart 14 : Comparison of Age distribution in patients of AKI and non-AKI
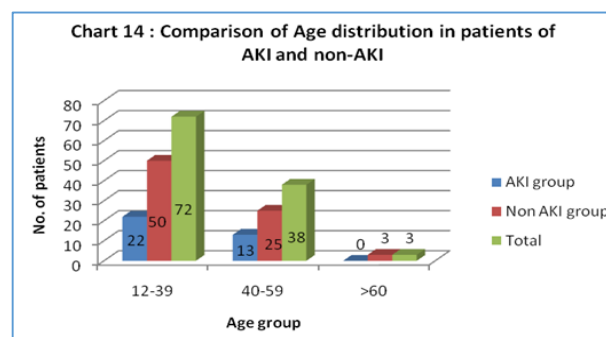
Difference between age groups was not statistically significant (p=0.404).

Chart 15: Comparison of sex distribution in patients of AKI and non-AKI

Male:female ratio in AKI group was 17:18 and in non-AKI group, it was 45:33. AKI was equally seen in both sexes, not different significantly (p=0.36).

Addiction	AKI				Total	
	+		-			
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Smoking	7	6.2	15	13.3	22	19.5
Alcohol	5	4.4	8	7.1	13	11.5
Other (incl. tobacco)	3	2.7	9	8.0	12	10.6
No addiction	23	20.4	49	43.4	72	63.7
Table 4. Comparison of AKI and Non-AKI Groups. Addiction History						

AKI was seen in both with and without addiction, not statistically significantly different (p value=0.76, CI 95%).

Chart 16: Comparison of Literacy in patients of AKI and non-AKI
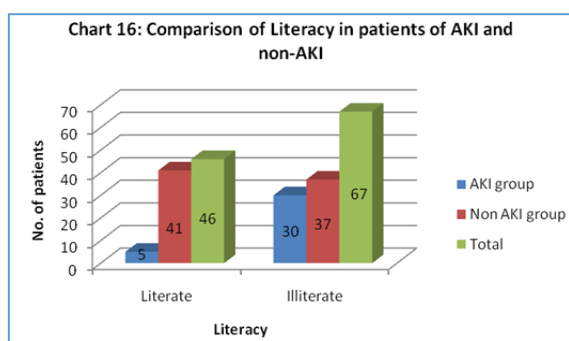
In this study, AKI was more commonly seen in illiterates, which was statistically significant (p=0.001).

Bite Site- In this study, snakebite to lower limb was present in 19 out of 35 patients in AKI group, while it was in 51 out of 8 patients in non-AKI group. It was not significant (p=0.26).

Chart 17 : Comparison of Time lapse between snakebite and hospitalization in patients of AKI and non-AKI
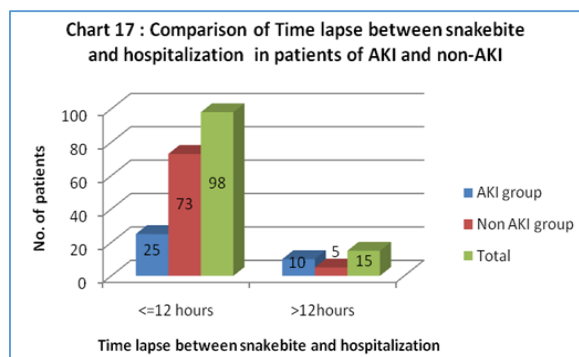
The time lapse between snakebite and hospitalisation was longer in AKI group than in non-AKI group, which was statistically significant (p value=0.01, CI; 95%).
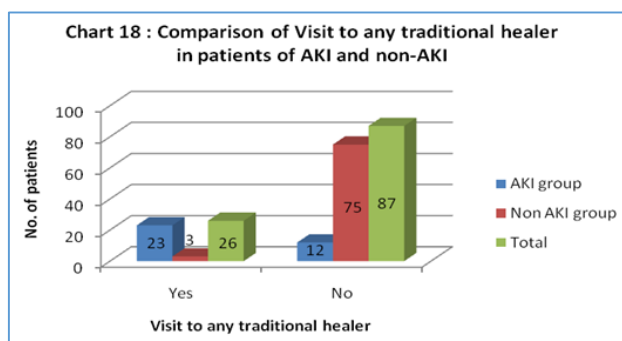
Chart 18 : Comparison of Visit to any traditional healer in patients of AKI and non-AKI

In this study, 23 out of 35 patients of AKI group visited some traditional healer and had some quack therapy before presentation to a proper healthcare facility, which was seen in only 3 out of 78 patients of non-AKI group. The difference was statistically significant (p value <0.0001).
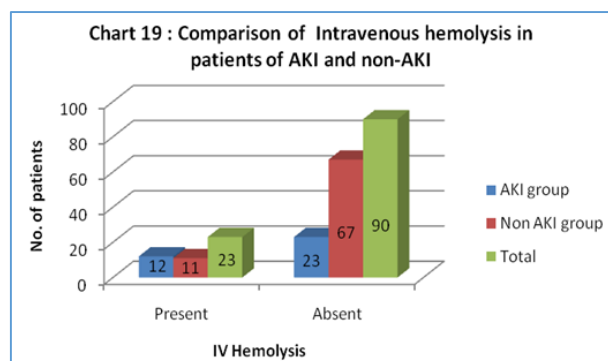
Chart 19 : Comparison of Intravenous hemolysis in patients of AKI and non-AKI

IV haemolysis was observed in 12 patients in AKI group, which was seen in only 11 out of 78 patients in non-AKI group, which was statistically significant (p=0.013).

Chart 20 : Comparison of hypotension in patients of AKI and non-AKI
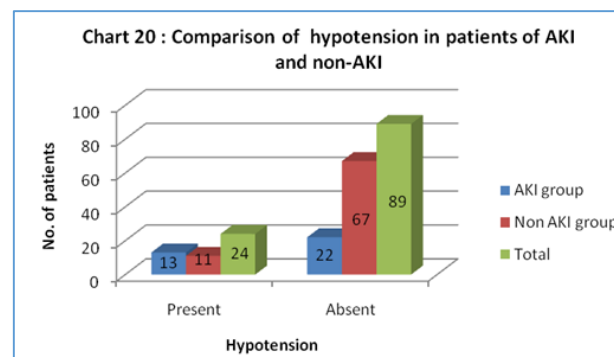
Hypotension was noted at presentation. 13 patients in AKI group, which was in only 11 patients in non-AKI group, which was statistically significant (p=0.005).

Chart 21 : Comparison of Local toxicity in patients of AKI and non-AKI
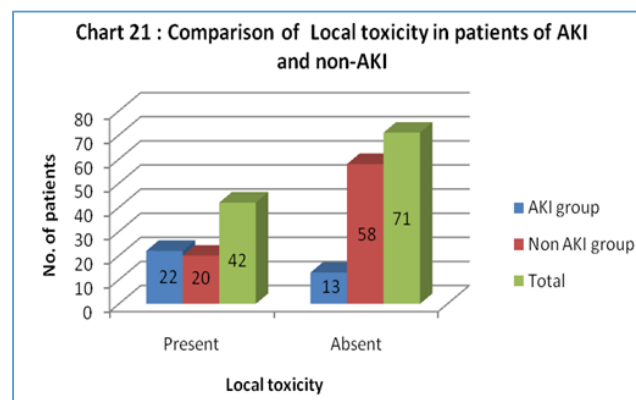
Local toxicity was found in 22 out of 35 patients in AKI group, while 20 out of 78 patients of non-AKI group had local toxicity. AKI was significantly more common in cases with local toxicity (p value=0.0002, CI; 95%).
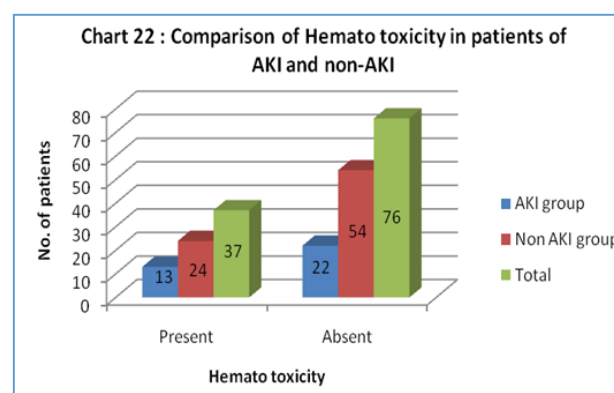
Chart 22 : Comparison of Hemato toxicity in patients of AKI and non-AKI

Haematotoxicity was found in 13 out of 35 patients in AKI group, while 24 out of 78 patients of non-AKI group had haematotoxicity.

P=0.41, AKI was more common in haematological manifestation, but not significant.

Chart 23 : Comparison of Neuro toxicity in patients of AKI and non-AKI

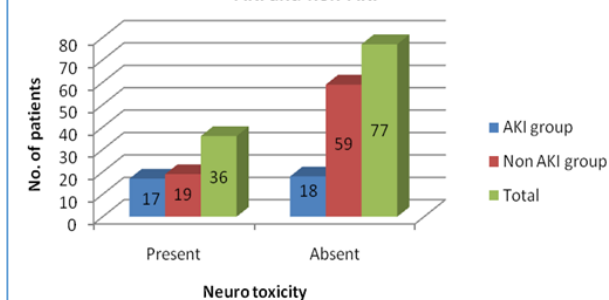Neurotoxicity was found in 17 out of 35 patients in AKI group, while 19 out of 78 patients of non-AKI group had neurotoxicity. AKI was more common in neuro complications, this was significant statistically (p value=0.01, CI; 95%).

Association with Requirement of ASV
34 out of 35 patients in AKI group had received ASV on admission, in contrast to that, only 40 out of 78 patients had received ASV on admission. AKI was seen more with the patients requiring ASV on admission, which was statistically significant (p<0.001).

Chart 24 : Comparison of final outcome in patients of AKI and non-AKI
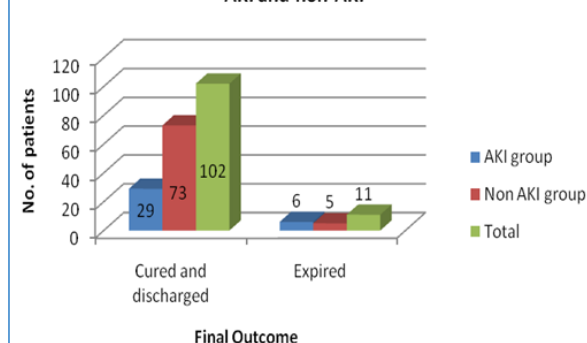
6 out of 35 patients of AKI group expired while 5 out of 78 patients of non-AKI group expired during their hospital stay. AKI was more commonly seen with poor outcome in the form of death, but it was not statistically significant (p =0.208).

Chart 25 : Comparison of Mean days of hospitalization in survived patients of AKI and non-AKI
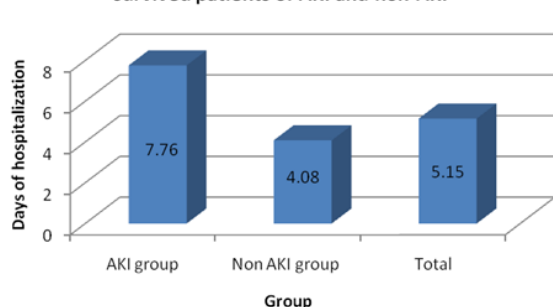
The average hospital stay for survived patients from AKI group was 7.76 ± 4.45, while it was 4.08 ± 2.78 for non-AKI group. The hospitalisation duration of AKI cases was longer than non-AKI significantly (p value=0.003, CI; 95%).

Part 3 - Comparison of Outcome in AKI Group

Chart 26 : Comparison of outcome in AKI group : Age distribution
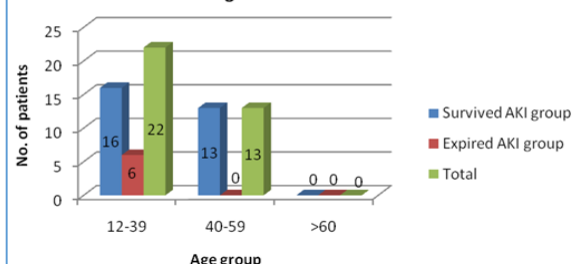
All the 6 expired AKI patients were of 12-39 years age group, which was significant (p=0.025).

Chart 27 : Comparison of outcome in AKI group : Sex distribution
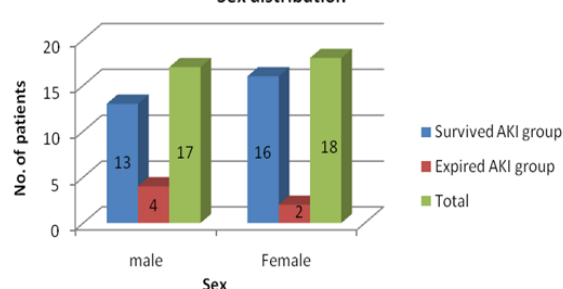
The male:female ratio in AKI group who survived was 13:16 while the ratio in expired patients was 4:2, which was not statistically significant (p=0.32).

Chart 28 : Comparison of outcome in AKI group : Literacy
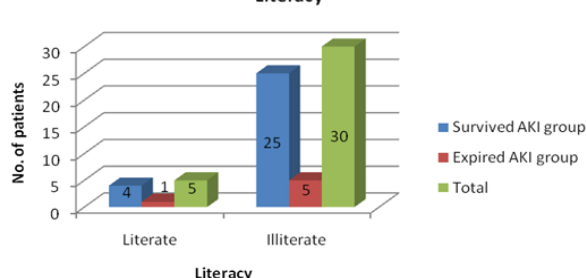
5 out of 6 expired AKI patients were illiterate, which was not statistically significant (p=0.85).

Chart 29 : Comparison of outcome in AKI group : Time lapse b/w snakebite and hospitalization
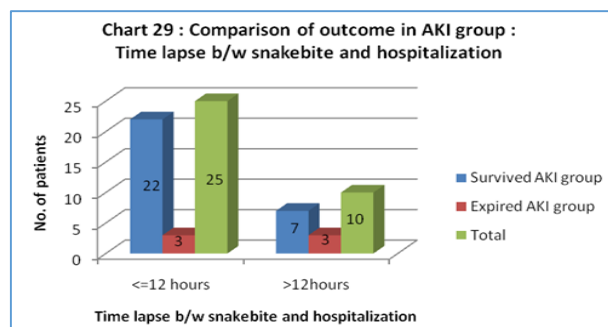
3 out of 6 AKI patients who expired presented to medical facility after a lapse of >12 hours. Not statistically significant (p=0.206).

Chart 30 : Comparison of outcome in AKI group : Visit to any traditional healer
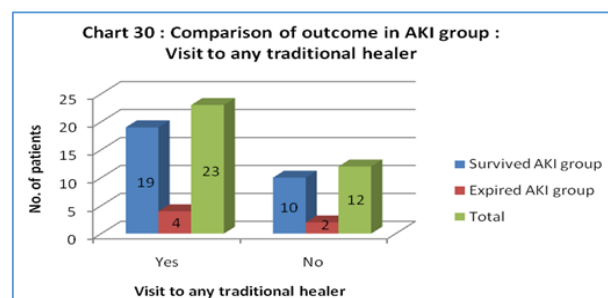
4 out of 6 AKI patients who expired had visited a traditional healer before coming to medical facility, which was 19 out of 29 AKI patients who survived. It was common, but not statistically significant (p=0.95).

Chart 31 : Comparison of outcome in AKI group : Bite Site

All 6 AKI patients who expired had snakebite over lower limb, while 13 of 29 patients who survived had lower limb bite. It was significant statistically (p=0.013).

Chart 32 : Comparison of outcome in AKI group : Intravenous hemolysis

All 6 patients with AKI who expired were observed to have intravascular haemolysis, while only 6 out of 29 AKI patients who survived had intravascular haemolysis. Statistically significant (p=0.002).

Chart 33 : Comparison of outcome in AKI group : Hypotension

5 out of 6 patients with AKI who expired had hypotension on admission, while only 8 out of 29 AKI patients who survived had hypotension on admission. It was statistically significant (p=0.01).

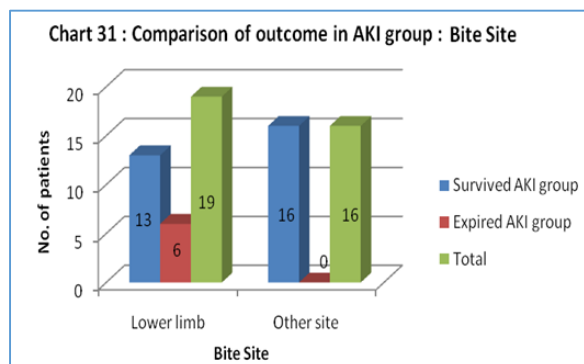Chart 34 : Comparison of outcome in AKI group : Uremic encephalopathy

All 6 expired AKI patients were observed to have uraemic encephalopathy during their hospital stay, while only 7 out of 29 AKI patients who survived had uraemic encephalopathy. It was statistically significant (p=0.005).

Chart 35 : Comparison of outcome in AKI group : Local toxicity

All 6 patients with AKI who expired had local toxicity. It was significant statistically (p=0.038).

| ASV Given | AKI (n=35) | | | | Total | |
| | Survived (n=29) | | Expired (n=6) | | | |
	No. of Patients	%	No. of Patients	%	No. of Patients	%
+	28	80.0	6	17.1	34	97.1
-	1	2.9	0	0.0	1	2.9
Total	29	82.9	6	17.1	35	100.0
Table 5. Comparison of Outcome in AKI Group- ASV Given						

All 6 patients with AKI who expired had received ASV on admission for some indication, 28 out of 29 AKI patients who survived also had received ASV. Not statistically significant (p=0.64).
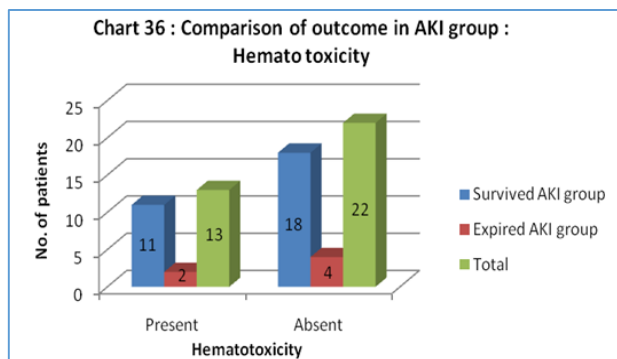
Chart 36 : Comparison of outcome in AKI group : Hemato toxicity

2 out of 6 patients with AKI who expired had haematotoxicity. Not statistically significant (p=0.83).

Association with Haemodialysis
2 out of 6 expired AKI patients had undergone haemodialysis, while 7 out of 29 AKI patients who survived received haemodialysis. Not statistically significant (p=0.63).

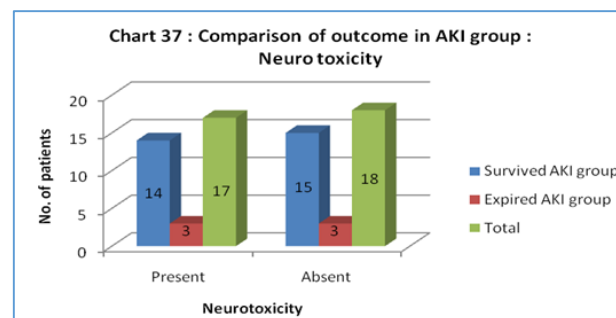Chart 37 : Comparison of outcome in AKI group : Neuro toxicity

3 out of 6 patients with AKI who expired had neurotoxicity. Not statistically significant (p=0.93).

Maximum Creatinine	AKI (n=35)		Total
	Survived (n=29)	Expired (n=6)	
Mean	3.31	2.95	3.76
SD	2.94	2.26	2.98
Table 6. Comparison of Outcome in AKI Group- Maximum Creatinine			

Maximum creatinine level in expired AKI patients was 2.95 ± 2.26, while it was 3.31 ± 2.94 in survived AKI patients. Not statistically significant (p=0.71).

Demographic Character		Patients of AKI Group (n=35)		Significance
		Favourable Outcome (Discharged) (n=29)	Poor Outcome (Expired) (n=6)	
Number		29	6	
Age (mean ± SD) (years)		37.17 ± 10.95	26.83 ± 8.11	Significant (p=0.025, CI; 95%)
Male:female		13:16 (1:1.23)	4:2 (2:1)	NS (p=0.32)
Literacy- Illiterate patients		25 (71.4%)	5 (14.3%)	NS (p=0.85)
Time lapse	>12 hours	7 (20%)	3 (8.6%)	NS (p=0.206)
	Mean ± SD	16.41 ± 27.08	22.25 ± 18.05	
Visit to any traditional healer		19 (54.3%)	4 (11.4%)	NS (p=0.95)
Lower limb bite		13 (37.1%)	6 (17.1%)	Significant (p=0.013, CI; 95%)
IV haemolysis		6 (17.1%)	6 (17.1%)	Significant (p= 0.002, CI; 95%)
Hypotension		8 (22.9%)	5 (14.3%)	Significant (p=0.01, CI; 95%)
Local toxicity		16 (45.7%)	6 (17.1%)	Significant (p=0.038, CI; 95%)
Haematotoxicity		11 (31.4%)	2 (5.7%)	NS (p=0.83)
Neurotoxicity		14 (14%)	3 (8.6%)	NS (p=0.93)
Uraemic encephalopathy		7 (20%)	6 (17.1%)	Significant (p=0.005, CI; 95%)
Maximum creatinine		3.31 ± 2.94	2.95 ± 2.26	NS (p=0.71)
Requirement of ASV		28 (80%)	6 (17.1%)	NS (p=0.64)
Requirement of HD		7 (20%)	2 (5.7%)	NS (p=0.63)
Table 7. Demographic Characters of Outcome in AKI Group				

DISCUSSION
Snakebites have the highest incidence in Asia and represent an important health problem. Snakebite is an important environmental and occupational hazard particularly in India, where farming is a major source of employment.

The involvement of predominantly young, healthy working population in poor rural areas compounded by lack of access to healthcare services in these areas signifies the social and economic impact of this problem. The poor healthcare infrastructure and lack of disease registries in areas where this problem is most frequently seen prevents an assessment of true burden.

In our study, predominantly, the younger population was involved. Out of total 113 patients of snakebite studied, 72 patients (63.7%) were found to be of 12-39 years age group, probably due to their more ambulant nature. A study which was done by Bhat et al had also noted that 80% of the cases occurred in this age group. Mean age group was 34.6 ± 12.4 years.

Out of 113 patients of snakebite, 62 patients were males and 51 patients were females. Males are affected more often than the females, which was similar to previous studies. As they constitute the working majority who are actively engaged in farming and other outdoor activities.

In this study, literacy rate was 40.7%, i.e. 46 out of 113 patients were literate. Illiterate rural population is more prone to attend to traditional healer or quack therapy, which delays proper pharmacological treatment of snakebite, which may lead to complications.

Majority of the snakebites occurred during morning and evening hours, especially in rural, i.e. during journey to the outdoors and working hours in the field. This may also be related to more active state of snakes during these hours.

In our study, 70 out of 113 patients (61.9%) of snakebite were bitten on the lower limbs. 39 patients had bite over upper limbs, 3 patients had bite over face and only 1 patient had bite over trunk. A similar observation was reported in a study, which was done by Viramani et al.[5] This is obvious as most snakebites occur while working day hours when people have upright posture. Therefore, this also shows that use of protective footwear can reduce the snakebites.

In the study, 26 out of 113 patients of snakebite presented to medical facility within 2 hours of snakebite. 42 snakebite patients presented within 2-6 hours. 15 patients of snakebite presented to medical facility after 12 hours of snakebite. The more lapse of time in presentation to hospital, more the chances of complications especially AKI, due to delay in treatment especially ASV. Finding was similar to study of Hayat AS et al.[6]

26 out of 113 snakebite patients (23%) had prior visit to traditional healer, whereas 87 patients directly went to a healthcare facility.

In this study, patients presented with multiple complaints. Majority patients had complaint of pain at local bite site (74.3%). Some other complaints by the snakebite patients in this study were- local bite site swelling (38.1%), vomiting (37.2%), decreased urine output (30.1%), bleeding from any site (24.8%), black or brown urine (20.4%), giddiness (16.8%), limb weakness (15.0%), ptosis (12.4%), altered sensorium (6.2%) and abdominal pain (6.2%).

In the present study, 24 patients (21.2%) were in hypotension at presentation. 25 patients (22.1%) were having tachycardia and 5 (4.4%) were having bradycardia. The patients presenting with hypotension and tachycardia needed the treatment, e.g. ASV, IV fluids. It was noted that early management of hypotension prevented occurrence of AKI. In this study, the toxicities observed were-

Primary Toxicity	No. of Patients	%
Neurotoxicity	36	31.9
Haematotoxicity	37	32.7
Local toxicity	42	37.2
Nephrotoxicity	1	0.9
Table 8. Primary Toxicities Observed in all Snakebite Patients		

Many patients (32 out of 113, 28.3%) had mixed toxicities at presentation. 33 patients (29.2%) did not develop any toxicity.

Of the 113 patients, 102 patients were discharged while 11 patients expired while their management during hospital stay. So, the mortality in cases of snakebite was 9.7%, which was higher than previous studies.[7]

Final Outcome	Number of Patients	Percentage
Discharged	102	90.3%
Expired	11	9.7%
Total	**113**	**100.0**
Table 9. Outcome of all Snakebite Patients		

Out of 102 patients who survived, 72 patients (70.6%) were discharged within 3-7 days. Only 15 patients (14.7%) required hospital stay more than 7 days.

The exact pathogenesis of AKI following snakebites is not well established. However, a number of factors contribute to it like bleeding, hypotension, circulatory collapse, intravascular haemolysis, disseminated intravascular coagulation, microangiopathic haemolytic anaemia and the direct nephrotoxicity of venom. Tubular necrosis (53.6%) and cortical necrosis (24.3%) are the main causes of acute renal failure. Acute interstitial nephritis has also been described.

In this study, incidence of Acute Kidney Injury (AKI) was found to be 30.9%. It was near to the incidence of 28.7% found in Chugh KS et al study[8] at Postgraduate Medical Institute, Chandigarh, India. Some studies showed that incidence of AKI due to snakebite is 15-29%. Slightly higher incidence found in this study incidence maybe due to (first) treatment delay of snakebite patients in our study area because they attended in-hospital after long delay; (second) the use of decreased urine output added earliest cases of AKI in the diagnosis; (third) due to lack of awareness regarding the early medical treatment of snakebite patients in people of our study area because patients attained some local nonmedical treatment before admission in hospital, which delay early medical treatment and (fourth) critically ill snakebite patients were referred to our tertiary healthcare hospital.

Incidence of AKI following snakebite is highly variable in different studies. It is described in wide range of 13-29%.

Study	Incidence of AKI in Snakebite
G Athappan et al[9]	13.5%
Harshavardhan L et al[10]	14.6%
Patil TB et al[11]	20.48%
Chugh KS et al[8]	28.66%
Paul J Dasgupta et al[12]	43.27%.
Table 10. Comparison of Incidence of AKI in Snakebite in Different Studies	

The mean age of patients with AKI was 35.4 ± 11.14 years, which was comparable to Patil BT et al and Paul J Dasgupta et al. So, AKI was more commonly seen in younger and early middle-aged group patients.

Study	Mean ± SD (Years)
Paul J Dasgupta et al[12]	37.45 ± 10.64
Patil TB et al[11]	35.77 ± 14.92
Present study	35.4 ± 11.14
Table 11. Comparison of Mean Age in AKI Patients in Different Studies	

In the present study, males account for 48.6%, which was comparably lower than other study groups. Difference

could be due to higher chances of initial neglect and traditional healer more in females.

Studies	Males	Females
Athappan G et al	62.6%	37.4%
Mittal BV et al[13]	58.53%	41.46%
Suma D RGUHS	62%	38%
Present study	48.6%	51.4%
Table 12. Comparison of Sex Distribution of AKI Patients in Different Studies		

We noticed that 85% of the snakebite victims who developed AKI were illiterate, which maybe because those who are illiterate tend to have more superstitious beliefs. This result was comparable to the findings of a study of Harshavardhan L et al, which showed 75% AKI patients were illiterate, it was also found in study done in Nepal.

In this study, it was found that occurrence of AKI was much more commonly seen with delay in presenting to medical facility. This may be associated with delayed administration of ASV to this patients. The finding is not unexpected because the venom continues to act until it is neutralised. In fact, early administration of antivenom has been demonstrated to completely reverse all clinical manifestations of snake envenomation. Hence, antivenom should be available in health centers and emergency services of small communities rather than being concentrated in reference hospitals. Delay in seeking medical aid or ignorance among the public and healthcare personnel can contribute to increased morbidity and mortality. Same findings were seen in studies of G Athappan et al, Harshavardhan L et al and Patil BT et al.

Studies	No. of Patients	%
Athappan G et al	78	55%
Patil TB et al	24	42%
Suma D, RGUHS	14	28%
Present study	10	28.6%
Table 13. Comparison of Lapse of Time in AKI Patients in Different Studies		

In this study, 23 out of 35 patients of AKI group visited some traditional healer and had some quack therapy before presentation to a proper healthcare facility, which was seen in only 3 out of 78 patients of non-AKI group.

Thus, the patients who had visited the traditional healers or had taken any form of quack therapy had a higher incidence of developing AKI, which maybe because of two reasons. Firstly, in this context, time had elapsed and the second being the tying of tourniquets or other treatments, which could have affected the patients. Similar finding was seen in study of Harshavardhan L et al.

Incidence of AKI in snakebite was not found to be associated with specific bite site or any prior addiction history.

In this study, 22 out of 35 AKI patients had significant local cellulitis and/or local sepsis, while only 20 out of 78 non-AKI patients of snakebite had such local toxicity. Thus, AKI development was significantly associated with local toxicity and features of local sepsis and cellulitis. The earliest

symptoms in patients bitten by vipers are pain and swelling of the bitten part appearing within a few minutes. In severe poisoning, the swelling can spread to involve the whole limb within 24 hours. Such severe cellulitis can also lead to compartment syndrome threatening the viability of the limb or its part. This can have important consequences if it leads to loss of digits due to ischaemia and gangrene. However, severe envenomation without much swelling can occur if the venom directly enters the blood stream. This finding was consistent with the studies of Chugh KS et al, G Athappan et al, Harshavardhan L et al and Patil BT et al.

Symptoms	Athappan G et al	Patil TB et al	Suma D, RGUHS	Present Study
Reduced urine output	100%	-	60%	97%
Bleeding from any site	30%	22.8%	50%	11.4%
Signs of local inflammation	98.7%	100%	98%	91%
Table 14. Comparison of Symptomatology in AKI Patients in Different Studies				

Haematotoxicity was found in 13 out of 35 patients (37.1%) in AKI group, while 24 out of 78 patients of non-AKI group had haematotoxicity. Haematotoxicity in the form of active bleeding or deranged WBCT was more commonly associated with AKI, but it was not statistically significant. In study of Harshavardhan L., 38.8% patients who suffered from AKI developed bleeding manifestations, which was less than the number in the study, which was conducted by Chugh K.S (60-65%).

Athappan et al showed in their study that presence of bleeding manifestations were identified as independent predictors of poor outcome in snakebite patients. Bleeding manifestations are the manifestations of coagulopathy, which was demonstrated in our study as 20 mins. WBCT >20 mins. In study of Patil BT et al, 29.8% patients had haematuria and other bleeding manifestations were present in 22.8% patients. Similar figures have been reported previously also.

By itself, coagulopathy is a marker of the vasculotoxicity and haemotoxicity of the poison, which means that these patients will have nephrotoxicity due to damage to renal microvasculature. Also, coagulopathy leads to bleeding and hypotension, which further leads to renal insufficiency as a result of prerenal insult. Haematemesis, melaena, haemoptysis, haematuria, epistaxis are well-known manifestations and may lead to severe hypovolaemic shock. Bleeding in snakebite victims is usually due to DIC. Low platelet count could also explain the bleeding due to DIC as noticed in the study.

In this study, AKI was significantly associated with neurotoxicity, which was different from other studies. Cause maybe associated with longer hospital stay, ventilator support and its related complications, prolonged parenteral medications with prolonged IV access all giving rise to raised chances of new infections.

Hypotension was also strongly associated with AKI. Findings were similar to studies of G Athappan et al and Patil BT et al. Hypotension is another major factor to cause ARF. Bleeding, either into tissues or externally and loss of plasma into the bitten extremity can produce hypotension and circulatory collapse.

The hypotension can be result of various factors like bleeding, disseminated intravascular coagulation, vascular endothelial damage by the toxins, which leads to plasma exudation. An early shock is probably explained by vasodilatation and late shock is precipitated by massive GI haemorrhage or acute pituitary and adrenal insufficiency.

Hypotension can be managed by early administration of ASV, timely correction of coagulopathy by administration of fresh frozen plasma or platelet concentrates as needed and optimisation of intravascular volume by crystalloids.

Intravascular haemolysis was also seen to be a major factor in causing AKI. Findings were similar to earlier studies of J. Paul and S. Dasgupta G, Athappan et al, Patil BT et al and Van holder et al.[14] Intravascular haemolysis is a well-known cause of renal injury that can be more lethal when combined with other adverse factors such as dehydration, haemorrhage or hypotension in our present study, haemolysis was identified as an independent predictor for development of ARF.

All 100% patients received IV fluids and 97.1% patients received ASV, which was comparable with study of Suma D.

Study		Management			
		ASV	FFP	IV Fluids	RCC
Suma D, RGUHS	Number of patients	40	3	50	4
	%	80%	6%	100%	8%
Present Study	Number of patients	34	4	35	5
	%	97.10%	11.4%	100%	14.30%

Table 15. Other Modes in Management in Snakebite Patients in Different Studies

The average hospital stay for survived patients from AKI group was 7.76 ± 4.45, while it was 4.08 ± 2.78 for non-AKI group. The hospitalisation duration of AKI cases was longer than non-AKI patients significantly. It was an obvious finding as they needed more intensive management and nephrotoxicity takes longer to recover than neuro or haematological toxicity.

So, at the end of comparison study of AKI patients group and non-AKI patients group, the following parameters were found to be significant statistically in this study.

- Literacy- Illiterate patients.
- Lapse of time in hospitalisation >12 hours.
- Visit to traditional healer.
- Intravascular haemolysis.
- Hypotension.
- Local toxicity.
- Neurotoxicity.
- ASV required at admission.
- Days of hospitalisation.

Furthermore, the comparison was done between the patients who survived and those who died in all AKI patients.

Out of 35 snakebite patients who developed AKI, 6 patients (17.1%) expired during their course of management in hospital and 29 patients (82.9%).

Mean age in expired AKI patients (26.83 ± 8.11 years) was lower than survived AKI patients (37.17 ± 10.95 years), which was statistically significant signifying AKI was more lethal in younger age group. This finding was similar to study of G Athappan et al and Harshavardhan L et al.

Study	Mean ± SD (Years)	
	Survived (n=29)	Expired (n=6)
Harshavardhan L et al	35.6 ± 11	40.2 ± 12
G Athappan et al	33.5 ± 14	38.3 ± 12.8
Present study	37.17 ± 10.95	26.83 ± 8.11

Table 16. Comparison of Age in Outcome of AKI in Different Studies

Male predominance was found in expired AKI patients (male:female ratio in expired AKI was 4:2 and in survived group 13:16), which was not significantly different.

Illiterates, prolonged lapse of time in hospitalisation and visit to traditional healer/quack therapy was commoner in expired AKI patients, but all those parameters were not statistically significant.

All 6 AKI patients who expired had snakebite over lower limb, while 13 of 29 patients who survived had lower limb bite. It was significant statistically.

Intravascular haemolysis, hypotension and uraemic encephalopathy were found to be significantly associated with poor prognosis and outcome in AKI patients.

Study	% Patients of Total Patients of that Group	
	Survived	Expired
Harshavardhan L. et al	9.4%	63.1%
G Athappan et al	8.1%	52.1%
Present study	27.6%	83.3%

Table 17. Comparison of Hypotension in Outcome in AKI Patients in Different Studies

Study	% Patients of Total Patients of that Group	
	Survived	Expired
Harshavardhan L. et al	17.9%	53.8%
G Athappan et al	22%	52.8%
Present study	20.7%	100%

Table 18. Comparison of Intravascular Haemolysis in Outcome in AKI Patients in Different Studies

Study	% Patients of Total Patients of that Group	
	Survived	Expired
Patil TB et al	12.5%	47.1%
Present study	24.1%	100%

Table 19. Comparison of Uraemic Encephalopathy in Outcome in AKI Patients in Different Studies

Local toxicity including cellulitis was strongly associated with poor outcome in AKI patients as all 6 expired AKI patients had local toxicity at presentation, but other toxicities, i.e. haematotoxicity and neurotoxicity were not significantly associated with poor outcome.

Haemodialysis was done in 2 out of 6 expired AKI patients, while it was done in 7 out of 29 survived AKI patients. It was not statistically significant. This finding was a doubtful in view that many expired patients were very critical since the presentation that they could not reach the point to go for haemodialysis, possibly due to factors like, hypotension, non-ambulation due to mechanical ventilation, etc.

Maximum creatinine level in expired AKI patients was 2.95 ± 2.26, while it was 3.31 ± 2.94 in survived AKI patients, which was not statistically significant.

Therefore, study of outcome in AKI patients showed a significant difference with regard to lower limb bite, IV haemolysis, hypotension, local toxicity, uraemic encephalopathy, younger age group, but not significantly associated with sex of the patient, literacy, time lapse in presentation, visit to any traditional healer, haematotoxicity, neurotoxicity and requirement of ASV or HD.

There were significant statistical differences between patients with ARF who recovered as against patients who died. Recovered cases of ARF had less bleeding manifestations as noticed by Soe et al[15] and intravascular haemolysis and elevated serum creatinine as stated by Kalantri et al.[16]

Overall mortality in snakebite patients was 9.7%, while it was 17.1% in snakebite-induced AKI patients.

Study	Mortality in Snakebite-Induced AKI Patients
G. Athappan et al	22.5%
Harshavardhan L. et al	22.2%
Patil TB et al	15.5%
Table 20. Comparison of Mortality in Snakebite-Induced AKI Patients in Different Studies	

DIC, irreversible shock and septicaemia being the immediate causes of death.

Thus, it is implied that early diagnosis and proper management of AKI (in form of appropriate antibiotics usage, early administration of ASV, early and proper management of complications like local sepsis/cellulitis, intravascular haemolysis, hypotension, proper administration of IV fluids and application of haemodialysis as and when required) can change the course of snakebite-induced acute kidney injury towards favourable outcome.

LIMITATIONS
Small sample size- Offending snake species/genus could not be identified, so species more commonly leading to AKI could not be determined by this study.

Certain investigations, e.g. complete coagulation profile for evidence of DIC, ELISA tests for D-dimer, ELISA tests to identify snake venom, renal biopsy, etc. could not be performed due to financial and technical constraints.

Outcome of AKI after peritoneal dialysis could not be studied as no AKI patient of this study underwent peritoneal dialysis.

In rural areas, many patients are initially taken to traditional healers before proper medical facility. Even those who avail medical facility, first visit Primary Healthcare Centres (PHCs) and Community Healthcare Centres (CHCs), so at the tertiary healthcare centre where this study was done, estimation of morbidity and mortality was not exact.

SUMMARY
A prospective type of study was carried out at S.S.G. Hospital, Vadodara, with the study population as patients coming to outdoor department and being admitted under Medicine Department of SSG Hospital, Vadodara, coming with definitive history of snakebite. The patients having preexisting renal disease, diabetes, hypertension and patients exposed to nephrotoxic drugs/toxins were excluded. Period of data collection was December 2013 to November 2014 (total duration of 1 year).

Total 113 patients with definitive history of snakebite were admitted during this course. Snakebite was more commonly seen in young to middle-aged outdoor working males. Most common bite site was lower limb.

12.3% patients presented after 12 hours of lapse to medical facility. 23% patients visited traditional healer and took some quack therapy prior to proper medical facility.

Primary local toxicity, haematotoxicity, neurotoxicity and nephrotoxicity was found in 37.2%, 32.7%, 31.9% and 0.9% of all snakebite patients, respectively.

102 out of 113 patients were completely cured and discharged, average days of hospitalisation for them being 5.2 ± 2.4 days.

35 out of 113 patients (30.9%) developed Acute Kidney Injury (AKI). All these patients were followed up and studied further till final outcome. They were grouped into 2 groups- AKI group (n=35) and non-AKI group (n=78). Both groups were compared for different parameters, which could be associated with occurrence of AKI statistically.

Factors which were found statistically significantly associated with occurrence of AKI in snakebite patients in this study were as follows-
- Lack of education.
- Lapse of time in seeking proper healthcare.
- Visit to any traditional healer/quack therapy prior to hospitalisation.
- Local toxicity (cellulitis, local sepsis, etc.).
- Intravascular haemolysis (in form of black/brown urination).
- Hypotension at presentation.
- Prolonged hospitalisation after neurotoxicity.
- Requirement of ASV on admission.

Factors like any particular age group, sex, addiction, any particular bite site and associated haematotoxicity were not found significantly associated with occurrence of AKI in this study.

All AKI patients were grouped according to their final outcome (survived and expired) into 2 group with favourable outcome (i.e. survived) (n=29) and group with poor outcome (i.e. expired) (n=6) and they were also compared for different parameters statistically to check for their significance.

Factors those were found to be statistically significantly associated with poor outcome in this study were as follows-

- Younger age group.
- Lower limb bites.
- Intravascular haemolysis.
- Hypotension.
- Uraemic encephalopathy.
- Local toxicity.

Mortality in snakebite-induced-AKI was found to be 17.1%.

Above-mentioned factors can be used as early predictors of AKI in snakebite patients and proper treatment in view of this can prevent occurrence of AKI or can alter the course of AKI towards favourable outcome.

CONCLUSION

From our study, we conclude that-

- Snakebites were commoner in younger outdoor working males and it was common over lower limbs than over other body sites.
- Common manifestations of snakebite include pain at local site, swelling at local site, vomiting, bleeding tendencies, giddiness, neurological symptoms like ptosis, decreased urine output, etc.
- Overall mortality due to snakebite was 9.7%.
- Incidence of AKI in snakebite was 30.9%.
- Lack of education, lapse of time in seeking proper healthcare, visit to any traditional healer/quack therapy prior to hospitalisation, local toxicity (cellulitis, local sepsis, etc.), intravascular haemolysis (in form of black/brown urination), hypotension at presentation, prolonged hospitalisation after neurotoxicity and requirement of ASV on admission were significantly associated with occurrence of AKI and so they were predictors of AKI.
- Mortality in snakebite-induced AKI patients was 17.1%.
- Factors significantly associated with poor outcome in AKI patients were younger age group, lower limb bites, intravascular haemolysis, hypotension, uraemic encephalopathy and local toxicity.

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