JKIMSU, Vol. 11, No. 2, April-June 2022 ISSN 2231-4261

ORIGINAL ARTICLE

Urinary IL-18 as an early marker for acute kidney injury in snake bite

Suram Vasanth Kumar[1], Jillla Naganna[1], Chinapaka Sangeetha[1], J. Archana[1]*

[1]Department of General Medicine, Gandhi Medical College, Musheerabad, Secunderabad-500003 (Telangana) India

Abstract

Background: Several biomarkers have been thrown into limelight to be an early predictor of Acute Kidney Injury (AKI). *Aim and Objectives:* To establish the relation between Urinary IL-18 (UIL-18) and AKI and the reliability for use as early markers in the detection of AKI compared to pre-existing surrogate markers for kidney injury such as creatinine and urea. *Material and Methods*: This is a cross-sectional study which was conducted at Gandhi Hospital, Hyderabad. Study was conducted for duration between 2018-2020 among the patients presenting with the history of snake bite. Total 80 patients with history of snake bite were included in present study after obtaining the informed consent from them all. The patients were followed up and the data were collected in proforma. *Results:* Mean age of the patients in present study was 39.32 ± 8.95 years of age, with male preponderance. Majority of the patients came with history of viper bite (45%) followed with unknown snake bite (30%), and (12.5%) each with cobra and krait bite. At 12 hr of admission, IL-18 showed a significant higher mean among AKI patients compared to urea and creatinine which were within the normal range. At 48 hr, all the three variables were significantly higher in AKI patients compared to patients without AKI. The cut-off of the 35.31 pg/ml of the UIL-18 was assessed to predict the AKI at 12th hr of follow-up with sensitivity of 48% and specificity of 93.3%. *Conclusion:* IL-18 helps to predict the occurrence of the AKI among the patients with snake bite when the urea and serum creatinine levels are well within the normal range at the 12 hr of the admission. There is a strong strength of association between the blood urea and serum creatinine with the UIL-18.

Keywords: Acute Kidney Injury, Creatinine, Interleukin (IL)-18, Snake Bite, Urea.

Introduction

Snake bite poisoning has been known to man since ancient times. Bite concentrations are highest in temperate and tropical regions where man-made farming continues to occur. In India, a significant proportion of snake bites occur while people are working barefoot in the fields or walking at night. Latest figures show between 1.2 million and 5.5 million snakebites worldwide per year, with 421,000-1,841,000 envenoms and 20,000–94,000 deaths. Several educational and preventive steps should be taken to protect farm workers who are the key victims of such accidents[1-2].

Complications linked to the kidneys are seen in majority of the patients with poisonous snake bites. Such renal failure, typically due to acute tubular necrosis, is also reversible. However, if bilateral cortical necrosis occurs, the prognosis for renal recovery is grimmer. Several biomarkers have been thrown into limelight to be an early predictor of Acute Kidney Injury (AKI). Neutrophil Gelatinase Associated Lipocalcin (NGAL), cystatin-C, Urinary IL-18 (UIL-18), Kidney Injury Molecule (KIM-I) are some of them. UIL-18 is one such marker of varying

outcomes. Previous studies have shown that UIL-18 has been increased in mouse and human AKI. However, the thresholds for predicting early AKI, sensitivity and specificity and predictive values have not been clearly established [3]. The UIL-18 research was conducted to know the usefulness of this biomarker in predicting AKI earlier than now. The forum to test this study was selected for patients admitted with snake bite and for acute kidney injury.

Material and Methods

It was a cross-sectional non-interventional study in patients admitted to Gandhi Hospital with snake bite from duration 2018-2020 were included in study. Total of 80 patients fulfilling the inclusion criteria were included in present study after obtaining institutional ethical clearance (ECR/Inst/Ap/2013/RR-16, dated 21-06-2017) and the informed consent from all the participants.

Inclusion criteria: All the patients admitted with history of snake bite

Exclusion criteria: Patients with existing renal parenchymal disease, other condition predisposing AKI: diabetes mellitus, hypertension, sepsis, shock and cardiovascular disease, infection or inflammation, nephrotoxic agent / medication.

All the patient data was collected in the proforma. The all-basic investigation and UIL-18 at 12hr and 48hr conducted in patients.

Statistical analysis

All the data were collected in pre-designed proforma and recorded in excel sheet. The demographic data of patients are presented as frequency, percentage and summarized using the mean, standard deviation. The data are represented using the pie chart and bar graphs. The mean difference between the independent continuous variable was analysed using student t-test and the mean difference between the dependent continuous variables was analysed using paired t-test. The strength of association between variables was analysed using the Pearson's correlation. The receiver operating curve was used to assess the diagnostic accuracy of IL-18 to predict AKI against the creatinine. Value of $p < 0.05$ was considered statistically significant and the statistical analysis was performed on SPSS v21 operating on windows 10.

Results

Among them, 51 were male and 29 were female patients. The mean age of the patients in present study was 39.32 ± 8.95 years of age. In present study, majority of the patients came with history of viper bite (45%) followed with unknown snake bite (30%), and (12.5%) each with cobra and krait bite (Table 1).

At 12hr of admission among the 80 patients, 50 developed AKI while remaining 30 were with no AKI. There was no significant difference in the mean level of blood urea and serum creatinine among the patients who developed AKI. There was a significant higher mean of UIL-18 in patients presented with AKI compared to normal patients ($p < 0.01$). UIL-18 was early to be elevated in urine, where the creatinine and urea were within the normal range (Table 2).

In present study, on comparison with type of snake bite, there was no significant difference in the blood urea, creatinine and the UIL-18 at the 12th hr of follow-up (Table 3).

In present study, at the 48th hr of follow-up, the mean level of the blood urea, creatinine and the IL-18 was significantly higher among the patients

with history of viper bite and unknown snake bite compared to the cobra and krait ($p < 0.01$) (Table 4).

On Pearson's correlation, at 12 hr, there was a significant weak positive association between the blood urea with the serum creatinine and the UIL-18. However, no significant association between serum creatinine with UIL-18 (Table 5).

In present study, there was significant increase in the blood level of urea, creatinine and UIL-18 at 48th hr compared to the 12th hr of measurement among the patients ($p<0.01$) (Table 6).

On Pearson's correlation, at 48 hr, we found a significant strong positive association between the blood urea, serum creatinine and the UIL-18 ($p<0.001$) (Table 7).

The ROC showed a significant higher AUC or the IL-18 (AUC=0.716) compared to the serum creatinine (AUC=0.587) and the blood urea (AUC=0.576). The cut-off of the 35.31 pg/ml of the UIL-18 was assessed to predict the AKI at 12th hr of follow-up, we results are as:

- Sensitivity = 48% (95% CI = 33.66% to 62.58%)
- Specificity = 93.3% (95% CI = 77.93% to 99.18%)
- NPV = 87.77% (95% CI = 84.40% to 90.50%)
- PPV = 64.29% (95% CI =31.39% to 87.63%)
- Accuracy = 84.27% (95% CI = 74.41% to 91.45%)
- OR = 12.93 (95% CI = 2.776 to 60.16) (Table 8)

Table 1: Distribution of type of snake bite in patients

Type of snake	Frequency	Percentage
Cobra	10	12.5
Krait	10	12.5
Unknown	24	30.0
Viper	36	45.0
Total	80	100.0

Table 2: Mean difference of blood urea, creatinine and UIL-18 at 12 hr between the groups

Parameters	Absent	Present	p
Blood urea at 12 hr mg/dl	25.49 ± 6.37	26.31 ± 4.60	0.503
Serum creatinine at 12 hr mg/dl	0.75 ± 0.10	0.78 ± 0.14	0.429
UIL-18 at 12 hr pg/ml	31.67 ± 2.90	35.23 ± 4.49	0.001**

**p<0.05 is statistically significant; p<0.001 is statistically highly significant. Values were expressed in Mean ± SD*

Table 3: Comparison of the mean level of blood urea, creatinine and UIL-18 among different type of snake bite groups at 12 hr

Parameters	Cobra	Krait	Viper	Unknown	p
Blood Urea at 12 hr mg/dl	26.31 ± 7.20	25.71 ± 5.79	26.15 ± 4.05	25.77 ± 6.20	0.987
Serum Creatinine at 12 hr mg/dl	0.77 ± 0.11	0.74 ± 0.11	0.76 ± 0.15	0.79 ± 12	0.732
UIL-18 at 12 hr pg/ml	32.1 6 ± 4.53	33.11± 2.92	34.84 ± 4.50	33.52 ± 4.31	0.281

**p<0.05 is statistically significant; p<0.001 is statistically highly significant.Values were expressed in Mean ± SD*

Table 4: Comparison of the mean level of blood urea, creatinine and UIL-18 among different snake bite group at 48 hr

Parameters	Cobra (a)	Krait (b)	Viper (c)	Unknown (d)	p
Blood Urea at 48 hr mg/dl	32.20 ± 22.71$^{*c, d}$	32.51 ± 25.32$^{* c,d}$	80.08 ± 25.52	76.95 ± 30. 64	0.001**
Serum Creatinine at 48 hr mg/dl	1.02 ± 0.73^{*c,d}	0.96 ± 0.77^{*c,d}	2.45 ± 0.79	2.29 ± 0.93	0.001**
UIL-18 at 48 hrpg/ml	41.97 ± 31.56$^{* c,d}$	43.40 ± 29.97$^{* c,d}$	105.55 ± 34. 01	97.32 ± 38.43	0.001**

**p<0.05 is statistically significant; p<0.001 is statistically highly significant. Values were expressed in Mean ± SD*

Table 5: Comparison of mean level of blood urea, creatinine and UIL-18 at 12 hr and 48 hr of follow-up

Parameters	At 12 hr	At 48 hr	p
Blood Urea in mg/dl	26.0 ± 5.31	67.20 ± 33.24	0.001**
Serum Creatinine in mg/dl	0.77 ± 0.12	2.03 ± 1.01	0.001**
UIL-18 in pg/ml	33.89 ± 4.31	87.36 ± 42.94	0.001**

**p<0.05 is statistically significant; p<0.001 is statistically highly significant. Values were expressed in Mean ± SD*

Table 6: Pearson's Correlation of Blood Urea, Creatinine and UIL-18 at 12 hr

		Blood urea at 12 hr mg/dl	Serum creatinine at 12 hr mg/dl
Serum creatinine at 12 hr mg/dl	Pearson Correlation	0.338**	-
	Sig. (2- tailed)	0.002	-
UIL-18 at 12 hr pg/ml	Pearson Correlation	0.264*	-0.044
	Sig. (2- tailed)	0.018	0.697

**Correlation is significant at the 0.05 level (2-tailed).*

Table 7: Pearson's Correlation of Blood Urea, Creatinine and UIL-18 at 48 hr

		Blood urea at 48 hr mg/dl	Serum creatinine at 48 hr mg/dl
Serum creatinine at 48 hr mg/dl	Pearson Correlation	0.986**	-
	Sig. (2-tailed)	0.000	-
UIL-18 at 48 hr pg/ml	Pearson Correlation	0.978**	0.986**
	Sig. (2-tailed)	0.000	0.000

**Correlation is significant at the 0.05 level (2-tailed).*

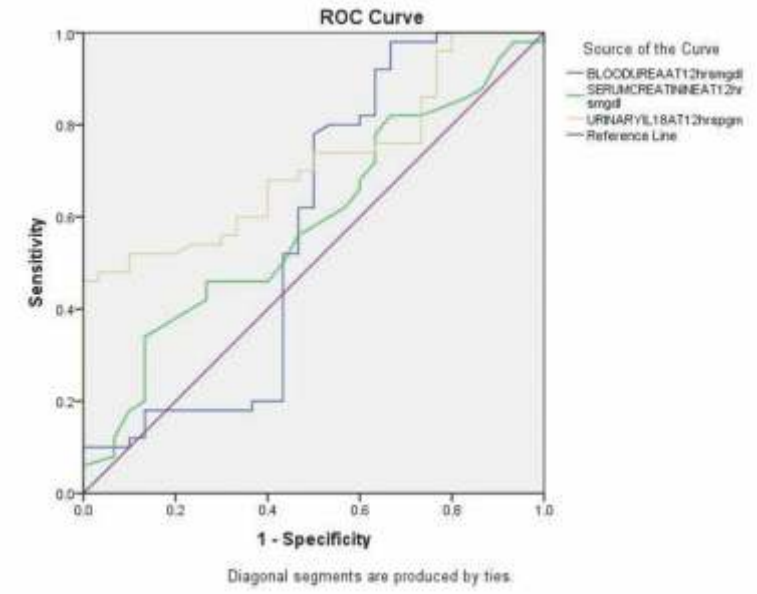

Figure 1: ROC curve of study variables to detect the AKI

Table 8: Comparison of the presence of AKI with the UIL-18 cut-off measurements

		AKI			
		Present		Absent	
		Count	Column N (%)	Count	Column N (%)
UIL-18 at 12 hr	>35.31	24	48.0	2	6.7
	<35.31	26	52.0	28	93.3

Discussion

AKI is characterised by acute increases in serum creatinine, which, for many of the reasons described above, is a late and non-specific AKI marker. AKI is emerging as a public health issue as epidemiological tests have found that a small rise in serum creatinine in hospitalised patients is linked with elevated mortality and morbidity. Several urinary biomarkers have been identified as possible candidates for AKI diagnosis prior to the spike in serum creatinine. In some animal studies, IL-18 have been shown to mediate renal ischemia–reperfusion damage, cause acute tubular necrosis, and neutrophil and monocyte infiltration of renal parenchyma [4].

More recently, a variety of clinical trials have focused on IL-18 diagnostic precision in the prediction of AKI [5-7]. Another drawback of such research is the use of SCr as the 'gold standard' for diagnosis of AKI, because sCr is not the optimal predictor for early failure of glomerular filtration or kidney injury [8]. The best approach is to use radio-labelled tracer clearances to identify AKI. However, its use in normal clinical practise is limited because it is invasive, time consuming and radioactive.

The mean age of the patients in present study was 39.32 ± 8.95 years of age, and 51 were male and 29 were female patients. Similar to present study, Azzam *et al*., documented mean age of the patients as the 33.5 ± 12.3 years. There was male preponderance in their study as compared to present study, with 60% male and 40% were female patients [9].

Snakebites have the highest incidence in Asia and are a major health problem. Clinical renal manifestations include proteinuria, hematuria, pigmenturia, and kidney failure. Nephropathy is usually caused by bites of hemotoxic or myotoxic venomous snakes [10]. Acute Renal Failure (ARF) is mainly seen after bites of the viperidae group, sea snakes, and colubridae group, but the substantial proportion of these cases is due to viper bites. The incidence of ARF following poisonous snakes varies from 13 to 22% following Echiscarinatus or Russell's viper bite [11]. Majority of the patients in presents study came with history of viper bite (45%) followed with unknown snake bite (30%), and 12.5% each with cobra and krait bite. On comparison with type of snake bite, there was no significant difference in

the blood urea, creatinine and the UIL-18 at the 12th hr of follow-up.

Ratnayake *et al*. [12] concluded that AKI was common and sometimes severe following Russell's viper bites. Three biomarkers uClu, uNGAL and sCysC, appeared to become abnormal in AKI earlier than SCr, and may be useful in early identification of envenoming.

At 12hr of admission, there was no significant difference in the mean level of blood urea and serum creatinine among the patients who developed AKI. There was a significant higher mean of UIL-18 in patients presented with AKI compared to normal patients ($p<0.01$). At 48 hr of follow-up, There was a significant increase in the mean level of blood urea, creatinine and the UIL-18 among the patients with AKI compared to patients without AKI ($p<0.01$). Similar to present study, Azzam *et al*., documented a significant higher mean of UIL-18 on both the 1st day and 3rd day in comparison to the blood urea and serum creatinine which were within the normal range on 1st day of admission [9]. The UIL-18 was found to be elevated much earlier than the creatinine could detect the impending kidney injury. The IL-18 is a sensitive marker for early detection of AKI in critically ill patients with history of snake bite in ICU.

However, at the 48th hr of follow-up, the mean level of the blood urea, creatinine and IL-18 was significantly higher among the patients with history of viper bite and unknown snake bite compared to the cobra and krait (p 0.01). There is a significant increase in the blood urea, creatinine and UIL-18 in patients at 48 hr. Similar to present study, Azzam *et al*., documented a significant increase in the blood urea and serum creatinine among the patients on 3rd day compared to the 1st day of admission [9]. In present study also, we found a significant increase the blood urea, serum creatinine and the IL-18 among the patients on 48th hr compared to 12th hour measurements ($p<0.001$). At 48 hr, we found a significant strong positive association between the blood urea, serum creatinine and the UIL-18 ($p<0.001$) whereas at 12 hr, there was a significant weak positive association between the blood urea with the serum creatinine and the UIL-18. However, no significant association between serum creatinine with UIL-18. Similar to present study, Zang *et al*., found in their study that uNGAL and uIL-18 levels increased significantly (all $p< 0.05$), while SCr levels did not change 1 day prior to the diagnosis of AKI in the AKI group ($p > 0.05$) [13].

The ROC showed a significant higher AUC or the IL-18 (AUC=0.716) compared to the serum creatinine (AUC=0.587) and the blood urea (AUC=0.576).

The cut-off of the 35.31 pg/ml of the UIL-18 was assessed to predict the AKI at 12th hr of follow-up, we found

Sensitivity = 48% (95% CI = 33.66% to 62.58%), Specificity = 93.3% (95% CI = 77.93% to 99.18%), NPV = 87.77% (95% CI = 84.40% to 90.50%), PPV = 64.29% (95% CI =31.39% to 87.63%), Accuracy = 84.27% (95% CI = 74.41% to 91.45%), OR = 12.93 (95% CI = 2.776 to 60.16), Likelihood ratio = 16.96. In study by Lin *et al*., documented a pooled diagnostic accuracy of the IL-18 in patients at different time interval. The OR was 8.18, 5.07 and 4.95 at <12 hr, 24 hr and 48 hr respectively [14]. Which was lower than that of present study at the 12th hr of time, where we found OR =12.93. In concordance to present study, Liu *et al*. (2013) documented Area under the Receiver Operating Characteristic Curve (AUROC) of

Table 9: Comparison of IL-18 with various other studies

Authors	Cut-off value (pg/ml)	Sensitivity (%)	Specificity (%)	AUC	Time of assessment (h)
Zheng *et al*. [16]	49	96.6	62.1	0.835	4
Sirotal *et al*. [7]		72	79	0.749	24
Li *et al*. [17]	1800	64	92	0.72	48
Parikh *et al*. [18]	60	54	82	0.74	48
Endre *et al*. [19]	36	34	78	0.621	0
Parikh *et al*. [20]	25	74	66	0.731	12
Present study	35.31	48	93.3	0.716	12

UIL-18 level to predict AKI was 0.70 (95% CI, 0.66-0.74). They documented that UIL-18 is a useful biomarker of AKI with moderate predictive value across all clinical settings [15] (Table 9).

The present study showed a comparable predictive result of IL-18 for detecting the AKI among the patients with snake bite prior to the elevation in the blood level of urea and creatinine.

Conclusion

The present study we conclude that, the IL-18 helps to predict the occurrence of the acute kidney injury among the patients with snake bite when the urea and serum creatinine levels are well within the normal range at the 12 hr of the admission. There is a strong strength of association between the blood urea and serum creatinine with the UIL-18. The IL-18 showed a better prediction curve for the AKI and a cut-off of 35.31pg/ml showed a sensitivity of 48%, specificity of 93.3% and accuracy of 84.27% in predicting the AKI by 12 hr of post admission when blood urea and creatinine are within the normal range. IL-18 is promising as a marker for early prediction of AKI in patients with snake bite.

Acknowledgements

The authors are thankful to the physicians who permitted us to conduct our study in their clinics. We are also thankful to the patients for extending the full cooperation to the study.

References

1. Kasturiratne A, Wickremasinghe AR, de Silva N, Gunawardena NK, Pathmeswaran A, Premaratna R, *et al*. The global burden of snakebite: a literature analysis and modelling based on regional estimates of envenoming and deaths. *PLoS Med* 2008;5(11):e218.
2. Rodrigues SL, Mendes GEF, Carlos CP, Burdmann EA. Acute kidney injury caused by bothrops snake venom. *Nephron Clin Pract* 2011; 119(2):c131-136.
3. Skowron B, Baranowska A, Dobrek L, Ciesielczyk K, Kaszuba-Zwoinska J, Wiecek G, *et al*. Urinary neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, uromodulin, and cystatin C concentrations in an experimental rat model of ascending acute kidney injury induced by pyelonephritis. *J Physiol Pharmacol* 2018;69(4).

4. Awad AS, El-Sharif AA. Curcumin immune-mediated and anti-apoptotic mechanisms protect against renal ischemia/reperfusion and distant organ induced injuries. *IntImmunopharmacol* 2011; 11(8):992-996.
5. Uo Q, Zhou F, Dong H, Wu L, Chai L, Lan K, *et al.* Implication of combined urinary biomarkers in early diagnosis of acute kidney injury following percutaneous coronary intervention. *Clin Nephrol* 2013; 79(2):85–92.
6. Zheng J, Xiao Y, Yao Y, Xu G, Li C, Zhang Q *et al.* Comparison of urinary biomarkers for early detection of acute kidney injury after cardiopulmonary bypass surgery in infants and young children. *Pediatr Cardiol* 2013; 34(4):880-886.
7. Sirota JC, Walcher A, Faubel S, Jani A, McFann K, Devarajan P, *et al.* Urine IL-18, NGAL, IL-8 and serum IL-8 are biomarkers of acute kidney injury following liver transplantation. *BMC Nephrol* 2013; 14:17.
8. Dharnidharka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. *Am J Kidney Dis* 2002; 40(2):221-226.
9. Azzam R, Mokhtar ER. Serum cystatin C and urinary interleukin 18 as early indicators of acute kidney injury in ICU patients. *Al-Azhar Assiut Med J* 2015; 13(1):180-188.
10. Kanjanabuch T, Sitprija V. Snakebite nephrotoxicity in Asia. *Semin Nephrol* 2008; 28(4):363-372.
11. Patil T, Bansod Y. Snake bite-induced acute renal failure: A study of clinical profile and predictors of poor outcome. *Ann Trop Med Public Heal* 2012; 5(4):335-339.
12. Ratnayake I, Mohamed F, Buckley NA, Gawarammana IB, Dissanayake DM, Chathuranga U, *et al*. Early identification of acute kidney injury in Russell's viper (Daboiarusselii) envenoming using renal biomarkers. *PLoS Negl Trop Dis* 2019; 13(7):e0007486.
13. Zang Z, Huang Y, Yang Y, Guo F, Qiu H. Urinary neutrophil gelatinase-associated lipocalin and urinary interleukin-18 in early diagnosis of acute kidney injury in critically ill patients. *Zhonghua Nei Ke Za Zhi* 2010;49(5):396–9.
14. Lin X, Yuan J, Zhao Y, Zha Y. Urine interleukin-18 in prediction of acute kidney injury: a systemic review and meta-analysis. *J Nephrol* 2015;28(1):7–16.
15. Liu Y, Guo W, Zhang J, Xu C, Yu S, Mao Z, *et al*. Urinary interleukin 18 for detection of acute kidney injury: a meta-analysis. *Am J Kidney Dis* 2013;62(6):1058–67.
16. Zheng J, Xiao Y, Yao Y, Xu G, Li C, Zhang Q, *et al.* Comparison of urinary biomarkers for early detection of acute kidney injury after cardiopulmonary bypass surgery in infants and young children. *Pediatr Cardiol* 2013;34(4):880-886.
17. Li Y, Fu C, Zhou X, Xiao Z, Zhu X, Jin M, *et al*. Urine interleukin-18 and cystatin-C as biomarkers of acute kidney injury in critically ill neonates. *Pediatr Nephrol* 2012; 27(5):851-860.
18. Parikh CR, Devarajan P, Zappitelli M, Sint K, Thiessen-Philbrook H, Li S, *et al.* Postoperative biomarkers predict acute kidney injury and poor outcomes after pediatric cardiac surgery. *J Am Soc Nephrol* 2011;22(9):1737–1747.
19. Endre ZH, Pickering JW, Walker RJ, Devarajan P, Edelstein CL, Bonventre JV, *et al.* Improved performance of urinary biomarkers of acute kidney injury in the critically ill by stratification for injury duration and baseline renal function. *Kidney Int* 2011;79(10):1119-1130.
20. Parikh CR, Abraham E, Ancukiewicz M, Edelstein CL. Urine IL-18 is an early diagnostic marker for acute kidney injury and predicts mortality in the intensive care unit. *J Am Soc Nephrol* 2005; 16(10):3046-3052.

***Author for Correspondence:**

Dr J. Archana, Department of General Medicine, Gandhi Medical College, Secunderabad, Telangana
Email: archanajella2k3@gmail.com
Cell: +91 96664 86665

How to cite this article:

Kumar SV, Naganna J, Sangeetha C, Archana J. Urinary Il-18 as an early marker for acute kidney injury in snake bite. *J Krishna Inst Med Sci Univ* 2022; 11(2):9-17

Submitted: *10-Feb-2022* ***Accepted:*** *17-Mar-2022* ***Published:*** *01-Apr-2022*