Section: General Medicine

Original Research Article

SERUM CYSTATIN C AS AN EARLY BIOMARKER OF ACUTE KIDNEY INJURY FOLLOWING POISONOUS SNAKEBITE: A PROSPECTIVE OBSERVATIONAL STUDY

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Received : 12/01/2026
Received in revised form : 13/02/2026
Accepted : 28/02/2026

Keywords:
Acute Kidney Injury; Biomarkers; Cystatin C; Renal Insufficiency; Snake Bites; Venomous Snakes.

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DOI: 10.47009/jamp.2026.8.2.35

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2026; 8 (2); 180-183

ABSTRACT

Background: Poisonous snakebites are a major cause of acute kidney injury (AKI) in tropical regions. Early biomarkers can improve recognition and clinical decision-making. This study aimed to assess serum Cystatin C as an early biomarker of AKI following poisonous snake bites and to compare its temporal changes with those of serum creatinine and urea. **Materials and Methods:** This prospective observational study was conducted at Rajah Muthiah Medical College, Chidambaram, between November 2018 and October 2020 over 12 months. Sixty adults with confirmed poisonous snake bites were enrolled in the study. Serum urea, creatinine, and Cystatin C were measured at admission, 24 hours, and 48 hours. AKI was defined using the AKIN criteria. **Results:** Half of the patients were aged 40–59 years (50%) and had a female predominance (53.4%). Viper bites were the most frequent (41.7%), and the lower limb was the most common bite site (76.7%). Local inflammation was observed in 76.7% of patients, whereas reduced urine output (28.4%) and urine albumin or deposits (26.7%) were less frequent. At admission, serum urea was elevated in 43.3% of patients, serum creatinine in 3.3%, and serum Cystatin C in none of the patients. At 24 h, serum Cystatin C showed the earliest and most frequent increase, elevated in 66.7% of patients, compared with creatinine (46.7%) and urea (58.3%). By 48 h, elevations in urea, creatinine, and Cystatin C were observed in an equal proportion of patients (66.7%), indicating the progression of renal involvement. **Conclusion:** Serum Cystatin C levels increase earlier than serum creatinine levels after a poisonous snakebite and may aid in the early identification of AKI.

INTRODUCTION

Snakebite envenoming is a major public health problem in tropical and subtropical regions, associated with considerable morbidity and mortality. Systemic complications, such as coagulopathy, rhabdomyolysis, and acute kidney injury (AKI), are common following envenomation. AKI is one of the most serious complications after viperid and some elapid bites and is a major cause of death and long-term renal impairment in these patients. Early detection of renal involvement is essential for appropriate fluid management, optimal antivenom administration, and timely initiation of renal replacement therapy, particularly in areas with limited access to advanced healthcare services.[1,2,3]
Serum creatinine and urine output are routinely used for the diagnosis of AKI; however, both have limitations in detecting early renal injury. Serum creatinine increases only after a significant reduction in the glomerular filtration rate and is influenced by factors such as muscle mass, dietary intake, and tubular secretion. Urine output is a nonspecific marker that can be affected by haemodynamic status, volume status, and diuretic use. These limitations are especially important in snakebite-associated AKI, where renal injury may develop rapidly following envenomation, leading to delayed diagnosis and delayed intervention in toxin-mediated kidney damage.[4,5]
Cystatin-C is a low-molecular-weight cysteine protease inhibitor produced at a constant rate by all nucleated cells. It is freely filtered by the glomerulus and is almost completely reabsorbed and metabolised by the proximal renal tubules. Its serum concentration is minimally influenced by muscle

ISSN (O): 2687-5365; ISSN (P): 2753-6556

mass, age, or diet, making it a useful endogenous marker of glomerular filtration and renal dysfunction. Due to these properties, serum Cystatin-C may rise earlier than creatinine in the setting of acute tubular injury or early reductions in glomerular filtration rate, allowing earlier identification of kidney injury.[3,6]

Evidence from clinical studies and meta-analyses in settings such as cardiac surgery, critical illness, and exposure to nephrotoxic agents suggests that serum and urinary cystatin-C can detect AKI earlier than serum creatinine. These studies also indicate improved diagnostic accuracy when cystatin-C is used alone or in combination with other biomarkers. However, the reported results vary because of differences in the study design, timing of sample collection, assay methods, and patient characteristics. Even with several incidents of AKI following snakebite envenoming, limited data are available on the use of Cystatin-C in this specific clinical setting.[3,4,7]

Snakebite-associated AKI results from multiple mechanisms, including direct venom-induced nephrotoxicity, hypotension, haemolysis, myoglobinuria, venom-related coagulopathy, and immune-mediated injury. These mechanisms can cause early tubular and vascular damage before changes in serum creatinine become noticeable.[1,2] Given the wide range of renal pathological changes after envenomation, an early and sensitive biomarker could help clinical management by enabling closer monitoring, early referral, and timely planning for renal replacement therapy.[8,9]

There is a lack of evidence regarding the early behaviour and diagnostic value of serum Cystatin-C in patients with snakebite-associated AKI. Therefore, this study aimed to assess serum cystatin-C levels within the first 24–48 h following a poisonous snakebite and to evaluate its role in the early detection of AKI in comparison with conventional renal markers.

MATERIALS AND METHODS

This was a single-centre prospective observational study conducted at Rajah Muthiah Medical College, Chidambaram, between November 2018 and October 2020. The study was approved by the ethics committee, and informed consent was obtained from all participants.

Inclusion and Exclusion Criteria

Adults aged ≥18 years presenting with clinical evidence of a poisonous snakebite, confirmed by fang marks, snake identification, or a reliable history, were included.

Patients with pre-existing kidney disease, diabetes mellitus, or hypertension with abnormal renal function, as well as those with incomplete clinical data or uncertain bite history, were excluded.

Methods

A total of 60 patients who met the eligibility criteria were included as a convenience sample based on hospital admissions during the study period. Baseline demographic information, details of the snakebite, including the identified species and site of envenomation, and clinical features such as local inflammation, bleeding, neurological signs, urine output, urine albumin or deposits, and findings of the 20-minute whole blood clotting test and other haematological investigations were documented at the time of presentation.

After admission, the patients were clinically monitored, and blood samples were obtained for renal biomarker analysis. Serum urea, creatinine, and Cystatin C were measured at admission, followed by repeat sampling at 24 hours and 48 hours. Serum CysC levels were estimated using a particle-enhanced immunoassay in accordance with standard laboratory procedures. The urine output was recorded throughout the observation period. AKI was identified based on the AKIN criteria, defined by a rise in serum creatinine of at least 0.3 mg/dL within 48 h, a 50% increase from baseline, or reduced urine output of less than 0.5 mL/kg/h for more than six hours. Statistical analysis was performed using SPSS v29. Data are presented as frequencies and percentages.

RESULTS

Most patients were aged 40–59 years (50%), with a female predominance (53.4%). Viper bites were the most commonly identified (41.7%), and the lower limb was the predominant site of envenomation (76.7%). Local inflammation was the most frequent clinical manifestation (76.7%), while reduced urine output (28.4%) and urine albumin or deposits (26.7%) were less common. [Table 1]

Table 1: Baseline demographic and clinical characteristics

Variable	Category	N (%)
Age group (years)	20–39	22 (36.6%)
	40–59	30 (50%)
	≥60	8 (13.4%)
Sex	Male	28 (46.6%)
	Female	32 (53.4%)
Snake identified	Viper	25 (41.7%)
	Cobra	7 (11.6%)
	Krait	4 (6.7%)
	Not identified	24 (40%)
Site of bite	Lower limb	46 (76.7%)
	Upper limb	14 (23.3%)

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Clinical manifestations	Local inflammation	46 (76.7%)
	Reduced urine output	17 (28.4%)
	Urine albumin/deposits	16 (26.7%)
	Neurological manifestations	6 (10%)

At admission, elevated serum urea was observed in 26 (43.3%) patients, whereas serum creatinine was elevated in only 2 (3.3%), and no patient showed raised serum Cystatin C. At 24 h, serum Cystatin C increased in 40 (66.7%) patients compared to serum creatinine in 28 (46.7%) and serum urea in 35 (58.3%). By 48 h, elevations in serum urea and creatinine were noted in 40 (66.7%) patients, whereas serum Cystatin C remained elevated in 40 (66.7%) patients. [Table 2]

Table 2: Temporal distribution of renal biomarker elevations following poisonous snakebite

Biomarker	Admission n (%)	24 hours n (%)	48 hours n (%)
Serum urea	26 (43.3%)	35 (58.3%)	40 (66.7%)
Serum creatinine	2 (3.3%)	28 (46.7%)	40 (66.7%)
Serum Cystatin C	0	40 (66.7%)	40 (66.7%)

DISCUSSION

Snakebite envenomation is a major cause of AKI in tropical regions, and delayed recognition of renal involvement causes significant morbidity and mortality. This study evaluated the temporal behaviour of serum cystatin C in comparison with conventional renal markers in patients with poisonous snakebite and its role in the early detection of AKI. The findings show that while serum urea was frequently elevated at admission and serum creatinine showed minimal early rise, serum cystatin C increased at 24 hours and identified most of the patients with renal involvement, with all biomarkers showing similar elevations by 48 hours.

In our study, half of the patients were aged 40–59 years, with a slight female predominance. Viper bites and lower limb envenomation were the most common causes, local inflammation predominated, and renal manifestations occurred less frequently. Similarly, Singh et al. found that patients with AKI were older than those without AKI (34 ± 1.64 vs. 32 ± 1.62 years; $p < 0.05$), although men predominated (84.05%).10 Mandal et al. found that from this cohort of 80 snakebite patients, viper bites were the most frequently identified, 32 cases (40%), and the lower extremity was the most common site of envenomation, involved in 66.25% of cases.[11] Kumar et al. reported that among 96 snakebite patients, viper bites occurred in 10 cases (10.4%) among the identified species, while the lower limb was the most common site of envenomation, involved in 78 cases (81.2%).[12] Satyanarayan et al. found that the lower limb was the predominant bite site, affected in 283 patients (66.27%), while poisonous bites formed a major proportion, necessitating antivenom therapy in 165 cases (38.64%).[13] These indicate the importance of protective footwear, occupational awareness, and targeted community education for the active working-age population, which may reduce exposure and improve early health-seeking behaviour.

Dasaraju reported that local inflammation was almost universal, observed in 49 patients (98%), while reduced urine output occurred in 30 (60%) and urinary involvement, such as haematuria, in 7 patients (14%).[14] Mahesh et al. found that local inflammatory complications, such as cellulitis, occurred in 54.4% of patients with AKI, while reduced urine output (oliguria 32.9%, anuria 12.7%) and proteinuria (80%) were less frequent but significant.[15] Therefore, patients presenting with local envenomation require early laboratory surveillance, strict urine output monitoring, and timely initiation of supportive therapy, even when systemic features are minimal.

Our study showed that at admission, urea was frequently elevated, creatinine was rarely elevated, and Cystatin C levels were normal. At 24 h, Cystatin C rose earliest, while by 48 h, all biomarkers showed similar elevations. Similarly, Wijewickrama et al. reported that serum creatinine showed minimal elevation at admission, while serum cystatin C rose rapidly, peaking at 16–24 h, and by 24–48 h, both creatinine and cystatin C were elevated in patients with moderate-to-severe AKI.[6] Ratnayake et al. found that at admission, serum creatinine showed poor elevation (AUC-ROC 0.58), whereas serum cystatin C levels remained normal. Serum cystatin C rose earlier, peaking at 8–16 hours (AUC-ROC 0.78), with both markers elevated by 24–48 hours.[16] Cystatin C is a more sensitive early indicator of evolving renal dysfunction following snake envenomation. Including cystatin C into the initial and early follow-up evaluation can enable earlier identification of patients at risk for AKI, closer monitoring, timely optimisation of fluid and antivenom therapy, and early nephrology referral.

Limitations

Being a single-centre study with only 60 patients, the findings may not be widely applicable. Missing baseline renal data, lack of ROC analysis, and exclusion of other biomarkers limit interpretation, although early cystatin C patterns remain informative. Biomarker measurements beyond 48 h were not available.

Clinical implications

Early serum cystatin C testing may improve the timely detection of AKI following snake bites. Larger multicentre studies with longer follow-up periods are recommended to validate its routine clinical use.

ISSN (O): 2687-5365; ISSN (P): 2753-6556

CONCLUSION

Serum Cystatin C rises earlier than serum creatinine in patients with poisonous snakebite and may help in the early detection of acute kidney injury. Early identification of renal involvement can help with timely monitoring and appropriate management. Serum creatinine levels alone may miss early renal dysfunction. Incorporating Cystatin C in the early evaluation may improve clinical assessment.

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ISSN (O): 2687-5365; ISSN (P): 2753-6556