



Role of Cystatin in Comparison to Serum Creatinine in Early Detection of Sepsis Induced Acute Kidney Injury in Emergency Department in Suez Canal University Hospital

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Abstract

Background: Sepsis remains a serious problem in critically ill patients, and the mortality rate in patients with sepsis is increased dramatically when complicated by AKI. Therefore, accurate evaluation of AKI is essential in patients with sepsis. Objective: To improve the outcome of patients with sepsis by assessment of role of Cystatin C in comparison to serum creatinine in early detection of acute kidney injury in Emergency Department. Patients and Methods: This was comparative cross-sectional study included two groups, study group included 40 patients diagnosed with sepsis-induced acute kidney injury attending to the Emergency Department (ED) at Suez Canal university Hospital during from November 2020- July 2021 and Control group included 40 healthy individuals of same age group. The Patients was clinically assessed and managed according to the ABCDE protocol. Results: a value of 0.892 IU/L was found to be the best cut-off point for prediction of sepsis-induced AKI, with sensitivity = 100%, specificity = 92.5%. Conclusions: That serum Cystatin can be used as early predictors for AKI than serum creatinine in patients presenting with sepsis.

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Introduction

Sepsis is the most important causes of Acute Kidney Injury (AKI), accounting for 50% or more of cases of AKI in ICU, and associates with a very high mortality. In adults, AKI occurs in approximately 19–23% of patients with moderate/severe sepsis, and in more than 50% in patients with septic shock.[1]

The incidence of AKI increases with the severity of sepsis and estimates are that AKI develops within the first 24 hours in 64% of patients with severe sepsis and hypotension. Strikingly, the mortality rate for septic patients with AKI is approximately doubled compared with sepsis alone.[2]

Septic acute kidney injury is a clinical diagnosis based on specific, context-dependent, and imperfect definitions with azotemia and oliguria still its key diagnostic criteria. More recently the Kidney Disease Improving Global Outcomes

produced a unified version of all key criteria of acute kidney injury.[3]

Septic acute kidney injury should describe a syndrome characterized by the simultaneous presence of both sepsis and KDIGO criteria, and still clinical judgment is required.[4]

More modern framework for rapid clinical diagnosis is evolving which is based on novel biomarkers of renal injury. Thus, definitions of AKI may soon include such biomarkers.

Biomarkers should be measured accurately and reproducibly. This is unlike medical symptoms that are restricted to indications of health or illness through the patient's perspective. Biomarkers may be used as a diagnostic tool for the identification (diagnosis) of disease or abnormal conditions, as well as for staging disease, prognosis, and response to intervention.[5]



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An ideal biomarker should be the one that is able to predict AKI and its outcomes, locate the site of injury (glomerulus vs tubule), determine the type of injury, and enable the initiation of therapeutic interventions.[6]

Several potential biomarkers have been identified and merit extensive research to establish their role in the diagnosis of AKI.

Cystatin C is a cysteine protease inhibitor that is synthesized and released into the blood at a relatively constant rate by all nucleated cells. It is freely filtered by the glomerulus, completely reabsorbed by the proximal tubule, and not secreted. As blood levels of cystatin C are not significantly affected by age, gender, race, or muscle mass, it is a better predictor of glomerular function than is serum creatinine.

Urinary excretion of cystatin C has been shown to predict the requirement for renal replacement therapy in patients with established AKI about 1 day earlier. In the intensive care setting, a 50% increase in serum cystatin C predicted AKI 1 to 2 days before the rise in serum creatinine [6,7]. So, the goal of this study was to assess of role of Cystatin C in comparison to serum creatinine in early detection of acute kidney injury in the Emergency Department.

Patients And Methods

After approval from the Research Ethics Committee of the Faculty of Medicine, Suez Canal University. All patients were informed about the trial and provided signed consent, explaining the purpose, effects, technique, and complications. This was a comparative cross-sectional study carried out in Emergency Department at Suez Canal University Hospital during the period from November 2020-July 2021. The study was conducted in accordance with the Declaration of Helsinki.

Any patient diagnosed with sepsis attending to the Emergency Department (ED) at Suez Canal university Hospital and fulfilling our inclusion

criteria; Adult (age > 18), age groups (18-45, 45-65, >65). Both sex. Diagnosed with sepsis. Exclusion criteria: Pre-existing kidney disease (ESRD, CKD, Post Renal Transplant). Patient presented to ER with sepsis and elevated serum creatinine. Any systemic illness or conditions that may elevate serum creatinine such as heart failure. History of medications that elevate serum creatinine or decrease its clearance.

Data was collected in pre-organized data sheet by the researcher. We prospectively identified patients with sepsis and after stabilizing the patient, questionnaire was filled by the researcher of the patient presented to ER by the medical team.

Demographic and clinical data were collected. Available laboratorial investigations, as complete blood count, blood typing and cross match and coagulation profile, serum creatinine, serum electrolytes and arterial blood gases were collected at baseline.

Serum Cystatin concentrations were determined using an enzyme-linked immunosorbent assay (ELISA) with a commercially available kit (Quantikine® ELISA, human cystatin C; R&D Systems, following the manufacturer’s instructions strictly. Blood samples were collected in nonheparinized tubes immediately at presentation in ED and centrifuged at 1,500 rpm for 5 minutes another sample at 24 hours and handled similarly. These samples were then stored at -80°C until assay. Samples then were transferred to private lab for assay.

Results

Table 1 summarizes the baseline characteristics of the studied groups. Study group was found to have higher age than controls (p=0.052). Meanwhile, the sex distribution was comparable in both groups (p=0.502). The source of infection of patients with sepsis. It was found that the most frequent source of infections was for GIT (27.5%), respiratory tract infection (22.5%) and UTI (20%) Figure 1.

Table 1. Baseline characteristics of the studied groups

Variables	Groups		P-value
	Study group (n= 40)	Control (n= 40)	
Age (years), mean ± SD	59.78 ± 17.36	51.30 ± 20.81	0.052a
Sex, n (%)			



Male	19 (47.5)	22 (55)	0.502b
Female	21 (52.5)	18 (45)	

a p-values are based on independent t- test. Statistical significance at P < 0.05
 b p-values are based on Chi square test. Statistical significance at P < 0.05

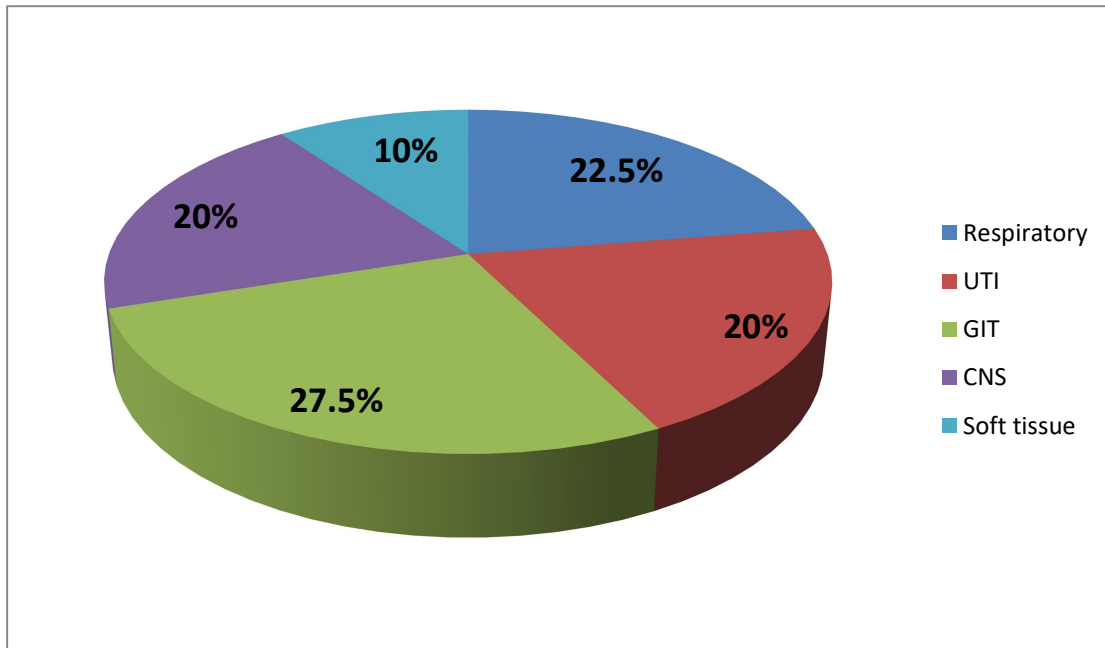


Figure 1. Source of infection of patients with sepsis

Table 2 showed; that study group had statistically significant higher serum cystatin compared to controls (1.45 ± 0.38 vs 0.52 ± 0.32) (p<0.001).

Table 2. Comparison of serum cystatin between Study group and control

Variables	Groups		p-value
	Study group (n= 40)	Control (n= 40)	
Serum cystatin mean ± SD	1.45 ± 0.38	0.52 ± 0.32	<0.001*a
median (range)	1.350 (0.90 - 2.20)	0.44 (0.4 - 1.50)	

a p-values are based on independent t-test. Statistical significance at P < 0.05

The ROC curve analysis of serum cystatin for prediction of sepsis-induced acute kidney injury, where the areas under the curve (AUC) were 0.972 (figure 2). For serum Cystatin, a value of 0.892 IU/L was found to be the best cut-off point for prediction of sepsis-induced AKI, with sensitivity = 100%, specificity = 92.5%, PPV= 93%, NPV= 100% and accuracy= 96.25% table 3.



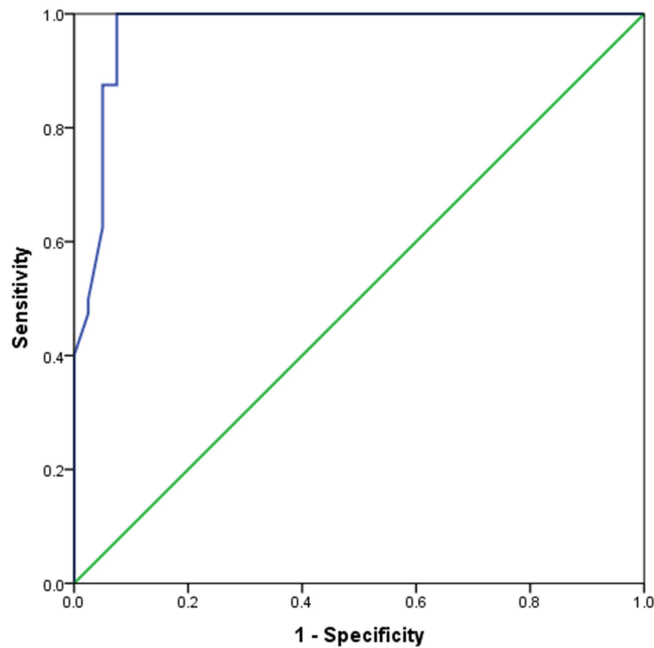


Figure 2. ROC analysis of serum cystatin at presentation for prediction of sepsis-induced AKI

Table 3. Sensitivity, specificity, PPV, NPV and diagnostic accuracy of the best cut of point of serum cystatin at presentation for prediction of sepsis-induced AKI

Cut-off points	Sensitivity	Specificity	PPV*	NPV*	accuracy
S. cystatin 0.892	100%	92.5%	93%	100%	96.25%

The ROC curve analysis of serum cystatin after 24 hours for prediction of sepsis-induced AKI, where the area under the curve (AUC) was 0.876 (figure 3).

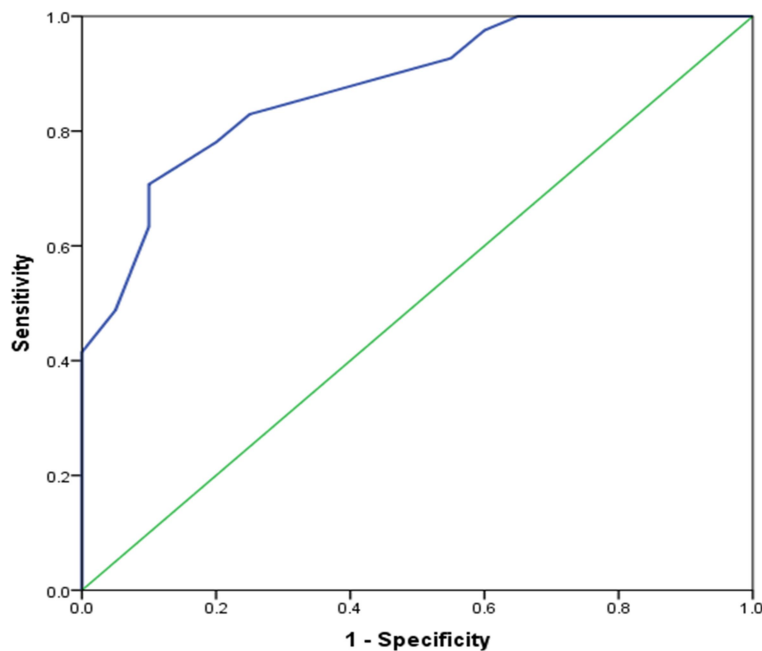


Figure 3. ROC analysis of serum Cystatin at 24 hours for prediction of sepsis induced AKI



Table 4. For serum cystatin at 24 hours, a value of 1.18 mg/ L or more was found to be the best cut-off point for prediction of sepsis-induced AKI, with sensitivity = 82.9%, specificity = 75%, PPV= 87.2%, NPV= 68.2% and accuracy= 80.3%.

Table 4. Sensitivity, specificity, PPV, NPV and diagnostic accuracy of the best cut of point of serum cystatin at 24 hours for prediction of sepsis-induced AKI

Cut-off points	Sensitivity	Specificity	PPV*	NPV*	accuracy
1.18 mg/ L	82.9%	75%	87.2%	68.2%	80.3%

Discussion

The present study showed the baseline characteristics of the studied patients, as the mean age was 59.78 ± 17.36 and 51.30 ± 20.81 in the case group and the control respectively. No statistical significance between the case group and the control group was observed in relation to gender, age.

These results were similar to the results by Feng et al, in which the mean age of the sepsis group was 51.18 ± 16.17 while in the control group was 47.57 ± 11.81 with no statistical significance between the control group and the sepsis group[8].

Regarding the source of infection in patients with sepsis, this study showed that the most frequent source of infections was GIT (27.5%), respiratory tract infection (22.5%) and UTI (20%)[8].

Liu et al., in a systematic review and meta-analysis found that there were 20 factors statistically significant that predisposing for sepsis-associated AKI, one of them included infections and their prevalence was respiratory infections in 41.22% while abdominal infection in 32.12% and UTI in 12.01% [9]. The difference in both results were due to large sample size and different population in meta-analysis done in Liu et al. and that in our sample population was collected during covid era and covid respiratory infection was not included in our study.

The current study showed that cases had statistically significant higher mean of serum cystatin compared to controls at presentation and 24 hours interval (1.45 ± 0.38 vs 0.52 ± 0.32) (p<0.001).

These results were similar to the results by Al-Amodi et al, in which the mean of cystatin C was higher in the sepsis group in comparison to control group at presentation and 24 hours interval (1.85 ± 0.48 vs 0.73 ± 0.12) with p value <0.001[10].

As shown in the present study, regarding early prediction of sepsis-induced acute kidney injury, serum cystatin was found to have a sensitivity of 100%, specificity of 92.5% and accuracy of 96.25% and AUC of 0.972 with a value of 0.892 IU/L was found to be the best cut-off point for prediction of

sepsis-induced AKI.

These results are in concordance with Azzam et al, in which they showed that serum cystatin was found to be the excellent predictor for abnormal cases whom developed AKI in critically ill patients at day 1 with sensitivity of 96%, specificity of 80% and accuracy of 93.3%[11].

In Al-Amodi et al, on ROC curve analysis of the markers for diagnosis of S-AKI, serum CysC with cut-off value of (1.18 mg/L) had a sensitivity of 92.7%, specificity of 34.5% with AUC 0.676[10].

This disagreement to our study may be related to the difference in the cut-off value between our study and AL-Amodi et al[10].

In our study, serum cystatin at 24 hours, a value of 1.18 mg/ L or more was found to be the best cut-off point for prediction of sepsis-induced AKI, with (AUC) of 0.876, sensitivity of 82.9%, specificity of 75% and accuracy of 80.3%.

In a study by Soto et al, in which they found that the serum cystatin at 24 hours of admission, a value of 0.98, it had a sensitivity of 79.5% and specificity of 77.5% with AUC of 0.86[7].

These results are close to ours as the cut-off point were close and also the study had conducted to detect discriminative abilities of biomarkers in detection on AKI in emergency department and Serial blood and urine samples were obtained at 0, 6, 12, 24, and 48 hours from presentation to the ED. Our study has some limitations. First, this cross-sectional study design was a single-center study with a relatively small sample size. However, serial follow up for biomarkers for kidney injury was carried out to potentially compensate for this weakness. Second, other new biomarkers, such as neutrophil gelatinase-associated lipocalin, were not analyzed. Third, although serum cystatin C level is less influenced by age, sex, and muscle mass, compared with serum creatinine level, it may still be affected by other unmeasured variables, such as levels of glucocorticoids, thyroid hormones, and insulin.

Conclusion

This study concluded that serum cystatin can be



used as early predictors for AKI than serum creatinine in patients presenting with sepsis.

Recommendations

Further studies with large sample size should be conducted. Availability of serum cystatin can help in early diagnosis and management of sepsis induced AKI.

Further studies to be done with focus on relation between Cystatin and chronic illness.

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