Section: General Medicine

Original Research Article

PROGNOSTIC VALUE OF ALBUMIN CREATININE RATIO (ACR) IN SEPSIS AND ITS ABILITY TO DETERMINE THE MORTALITY: A PROSPECTIVE CASE CONTROL STUDY

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Abstract

Background: The prognosis of critically ill patients helps with early therapy initiation and effective allocation of resources. To gauge the severity of the sepsis, numerous complex scoring systems have been proposed. The goal of this study was to assess the prognostic significance of the underutilized biomarker microalbuminuria. **Materials and Methods:** This was a prospective, case control, observational study conducted in SMS medical college, Jaipur, between July 2021 and July 2022. Its objectives were to measure the degree of microalbuminuria in patients with and without sepsis. Albumin/creatinine ratio (ACR), also known as ACR1, ACR2, were measured in spot urine samples that were taken at the time of admission and on the third day to determine whether it could be used to predict mortality in sepsis and evaluate its correlation to the acute physiology and chronic health evaluation II (APACHE II) score. **Observation and Results:** In total, this study comprised 60 patients with sepsis and 60 patients without sepsis. The patients involved in this study ranged in age from 18 to 86, with cases being on average 51.76 years old and controls being on average 47 years old. There were 26 males (43.33%) and 32 females (56.67%) in cases. In controls there are 32 males (53.33%) and 28 females (46.67%). The mean APACHE II score at day-1 is 30.42 and at day-3 is 29.32. Urine ACR at time of admission (ACR1) was 215.83 mg/g among survivors and 227.26 mg/g among non survivors and ACR2 (day 3) was 127.59 among survivors and 455.06 mg/g among non survivors. There is statistically no significant difference in mean Urine ACR at Day-1 (P-value 0.8586), but significant difference at day-3 (P-value 0.0008) in survivors and non- survivors among cases. There is statistically significant Pearson correlation between Urine ACR Day-1 and APACHE II score at day-1 and also between Urine ACR Day-3 and APACHE II score at day-3. **Conclusion:** Urine ACR at day-3 was the most powerful diagnostic parameter for predicting non-survivors with the sensitivity rate for correct prediction of non-survivors was 96.3%, whereas the specificity rate was 61.3%. We can conclude that the urinary albumin/creatinine ratio may be used as a simple, rapid, noninvasive, inexpensive, easy to perform and interpret test for early prognosis and prediction of mortality in septic patients.

INTRODUCTION

Sepsis is a medical condition characterized by physiological, biological, and biochemical abnormalities resulting from an uncontrolled host response to infection, often leading to ICU admission.[1] In 2017, there were an estimated 48.9 million sepsis cases and 11 million sepsis-related deaths, making it one of the leading causes of death worldwide. Septic shock, a type of sepsis, has a mortality rate of 40-50% and can be identified by the use of vasopressor therapy to increase mean arterial pressure to >65 mmHg and elevated lactate levels (>2 mmol/L) despite adequate fluid resuscitation.[2] Sepsis is an inflammatory disease caused by the activation of the innate immune system in response to microorganisms. Two key features include the recognition of pathogen-associated and damage-associated molecular patterns by cellular receptors and endothelial cells shifting to a pro-inflammatory state, producing cytokines, chemokine, and procoagulant factors. This can lead to damage to the glycocalyx and endothelial cell apoptosis, increasing permeability and causing interstitial leakage. These

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changes can result in organ failure, tissue hypo-perfusion, and decreased blood flow in the microcirculation, ultimately leading to septic shock or immunodeficiency.[3] The glycocalyx is crucial for vascular integrity and leukocyte trafficking. Insults like sepsis can cause significant changes to the glycocalyx, including decreased thickness and destruction, increasing macromolecule permeability and leukocyte adhesion. Adherens junctions can also be impaired, leading to exudation and capillary leak syndrome.[4]

Microalbuminuria, characterized by 30-300 mg/day of albumin excretion in the urine, is commonly observed in severely ill patients with sepsis. It has shown promise in predicting organ failure, vasopressor use, and mortality, outperforming traditional scoring systems like APACHE II.[5,6] Although various scoring systems like APACHE II and SAPS II are currently used to predict mortality in critically ill patients, they require numerous variables and can be cumbersome and delay the initiation of therapy. This study aimed to evaluate the predictive value of urine albumin-to-creatinine ratio (ACR) in sepsis patients and compare its prognostic value to APACHE II scoring.

MATERIALS AND METHODS

Study type: Analytical study.

Study design: Hospital based prospective type of case control study was conducted in Medicine ICU of SMS Medical College, Jaipur after approval by the research and ethical committee of SMS medical college, Jaipur.

Duration: July 2021 to July 2022

Patient Grouping

Group 1: It consists of 60 patients, aged 18 years and above diagnosed with sepsis, severe sepsis and septic shock.

Group 2: 60 Non-septicemic patients.

Inclusion Criteria

1. Adult patient: Age ≥18 years
2. Patient diagnosed with sepsis

Patients who met the criteria of the Society of Critical Care Medicine, as revised during the 2001 "International Sepsis Definition Conference," and displayed at least two of the following symptoms

(1) A body temperature above 38°C or a heart rate of more than 90 beats per minute,

(2) A respiratory rate of more than 20 breaths per minute or hyperventilation with a PaCO2 of 32 mm Hg or less,

(3) A white blood cell count of more than 12,000/μL or less than 4,000/μL, were included in the study. The presence of an infection was confirmed using the Centers for Disease Control and Prevention's clinical and microbiological criteria as the reference standard.

Exclusion Criteria:

1. Acute or Chronic kidney diseases (Glomerulonephritis or known case of CKD)
2. Neoplastic diseases (multiple myeloma)
3. Pregnancy
4. Urinary tract infection or Hematuria
5. Patient who refused to give written consent.

Upon admission, the patients' age, gender, admission date and time, clinical classification (medical or surgical), provisional diagnosis, and comorbidities such as diabetes mellitus, hypertension, and chronic kidney disease were recorded. In addition, clinical and pertinent laboratory data were gathered.

Sample Collection and Laboratory Measurement

Upon admission and 72 hours later, nursing staff collected urine samples, which were referred to as ACR1 and ACR2, respectively. The samples were sent to the biochemistry laboratory and frozen at -20°C until analysis. The urine microalbumin level was determined using the immune-turbidimetric technique, while urine creatinine was measured using a modified kinetic Jaffe reaction. The analytical range for microalbumin was 1.3 to 100 mg/L, and any results outside of this range were diluted and repeated. The MAU was defined as ACR of 300 mg/g of creatinine presented as mg/g of creatinine, with a typical cutoff value of 30 mg/g in the healthy reference group. However, the reference range for predicting death in severely ill children has yet to be established.

Statistical Analysis

SPSS for Windows, version 17.0 (SPSS, Chicago, Illinois) was used for statistical analysis. Before doing the statistical analysis, the data were examined for normality. The data was described using descriptive statistics. Using Spearman's correlation coefficient, the ACR at various time points was associated with various metrics and scores. The receiver operating characteristic (ROC) curves and area under the curve (AUC) were estimated, as well as their operational properties. To identify possible risk variables linked with the result, univariate analysis, multivariate analysis, and log transformation were utilized. A p value of less than 0.05 was deemed significant for all statistical tests.

RESULTS

Total 60 patients who were critically ill with sepsis were recruited in this study. The patients included in this study were aged between 18 and 86. The mean age of cases is 51.76 years with the majority of cases being in the age group ≥51 years (51.67%). The mean age of controls is 47 years with the majority of cases being in the age group ≥51 years (36.67%). The difference in mean age is statistically non-significant between cases and controls (P-value=0.1238).

Distribution of cases and controls according to gender: There are 43.33% females and 56.67% males in cases. In controls there are 53.33% males and 46.67% females. The difference in gender is statistically not significant (P-value 0.2370). Thirty-one patients (51.66%) died and 29 (48.33%) survived during their course of hospitalization.

Mean APACHE II score among cases: The minimum APACHE II score recorded on the first day

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of admission was 20 and maximum 41 and that of day 3 was ranging between 15 to 46.

The mean APACHE II score at day-1 is 30.27 and at day-3 is 27.39. There is a significant difference in mean APACHE II score at day-1 and day-3 in cases and controls (P-value 0.0289).

Mean Urine ACR among cases and controls: The mean Urine ACR at day-1 in cases is 221.74 and day-3 is 285.47 and in cases the difference in mean urine ACR is statistically not significant (P-value 0.5247). In controls the mean urine ACR at day-1 is 19.47 and at day-3 is 18.11. There is statistically a significant difference in urine ACR at day-1 and day-3 in cases and controls (P-value <0.0001).

Pearson correlation among Urine ACR and APACHE II score at day-1: There is statistically significant Pearson correlation between Urine ACR Day-1 (r= 0.577; p-value <0.0001) and APACHE II score at day-1.

Pearson correlation among Urine ACR and APACHE II score at day-3: There is statistically significant Pearson correlation between Urine ACR Day-3 (r= 0.417; p-value 0.0008) and APACHE II score at day-3.

APACHE-II score among non-survivors and survivors: There is statistically significant difference in mean APACHE II score at day-1 (P-value 0.0098) and day-3 (P-value 0.0001) in survivors and non-survivors among cases.

Urine ACR among non-survivors and survivors: There is statistically no significant difference in mean Urine ACR at Day-1 (P-value 0.8586), but significant difference at day-3 (P-value 0.0008) in survivors and non- survivors among cases.

Table 1: Distribution of cases and controls according to gender:

Gender	Cases		Controls		Chi-square statistic = 1.2013. P-value=0.2730
	N	%	N	%	
Male	26	43.33	32	53.33	
Female	34	56.67	28	46.67	

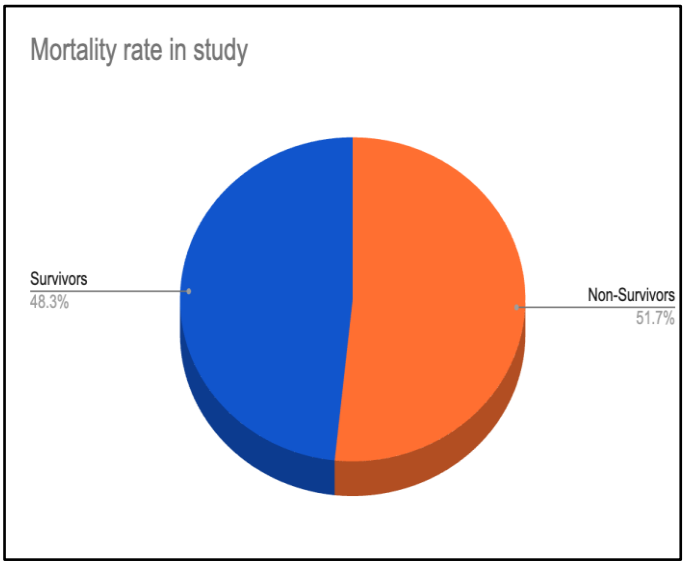

Fig 1: Distribution of cases and controls according to gender:

Table 2: Mean APACHE II score among cases

	Cases	
	Mean	SD
APACHE II score D1	30.42	5.59
APACHE II score D3	29.32	9.34
P-value	0.4353	

Table 3: Mean Urine ACR among cases and controls

	Cases		Controls		P-value
	Mean	SD	Mean	SD	
Urine ACR D1	221.74	258.29	19.47	4.88	<0.0001
Urine ACR D3	285.47	729.38	18.11	4.01	<0.0001
P-value	0.5247				

Table 4: Pearson correlation among Urine ACR and APACHE II score at day-1

	APACHE II SCORE D1	
	r	p-value
Urine ACR D1	0.577	<0.0001

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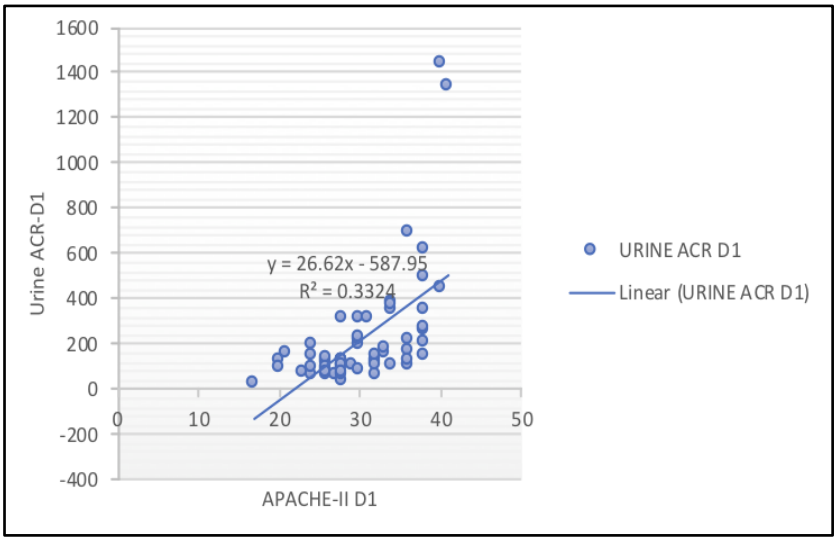

Fig 2: Pearson correlation among Urine ACR and APACHE II score at day-1

Table 5: Pearson correlation among Urine ACR and APACHE II score at day-3

	APACHE II SCORE D3	
	r	p-value
Urine ACR D3	0.417	0.0009

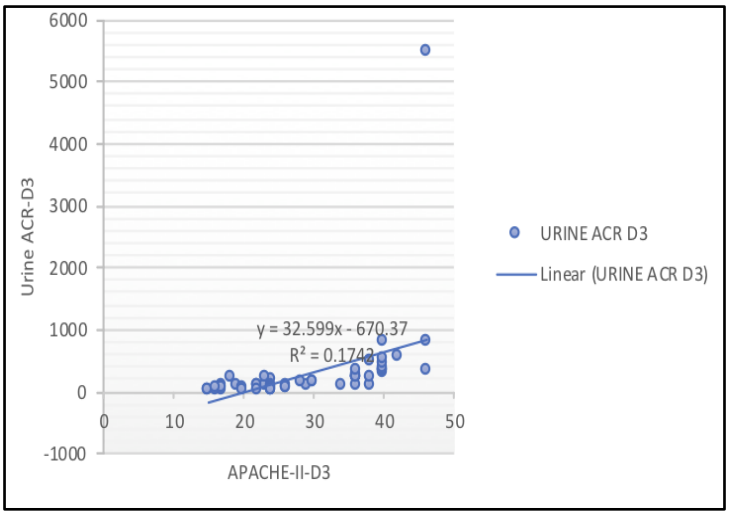

Fig 3: Pearson correlation among Urine ACR and APACHE II score at day-3

Table 6: APACHE-II score among non-survivors and survivors

	Non-survivors (N=31)		Survivors (N=29)		P-value
	Mean	SD	Mean	SD	
APACHE II score-D1	32.19	5.56	28.52	5.05	0.0098
APACHE II score-D3	35.41	12.83	23.66	7.27	0.0001

Table 7: Urine ACR among non-survivors and survivors

	Non-survivors (N=31)		Survivors (N=29)		P-value
	Mean	SD	Mean	SD	
Urine ACR D1	227.26	240.86	215.83	279.91	0.8586
Urine ACR D3	455.06	474.72	127.59	165.57	0.0008

DISCUSSION

Early diagnosis of sepsis is crucial for patient management and outcome, as early implementation of pharmacological intervention can bring significant reduction in mortality. With respect to the other available markers of sepsis PCT was found to be sensitive and specific in systemic infection. Before incorporating these tests into routine clinical practice, there are still a number of constraints that need to be taken into account. For instance, it has been illustrated that PCT serum levels can rise in individuals with non-infectious conditions such as trauma, burns, carcinomas (small cell lung, and

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bronchial carcinoid), immunomodulator therapy that raises proinflammatory cytokines etc. Therefore, it is crucial that the physician rule out the aforementioned possibilities to make sure that there are no confounding factors affecting the PCT measurements. Likewise, CRP is another marker of sepsis. Inflammation, burn injuries, cardiovascular disease, and malignancies are just a few of the ailments that can result in increased CRP levels in addition to sepsis, which all contribute to the low specificity and limited value of CRP as a sepsis biomarker.

The current study proposes to compare microalbuminuria levels with the APACHE II (Acute physiology and chronic health assessment) Score to see if the change in microalbuminuria levels in the first 24 hours might assist forecast mortality and morbidity.

The mean age of cases is 51.76 years with the majority of cases being in the age group ≥51 years (51.67%). The mean age of controls is 47 years with the majority of cases in the age group ≥51 years (36.67%). There are 43.33% females and 56.67% males in cases. In controls there are 53.33% males and 46.67% females. The difference in mean age and gender distribution is statistically non-significant between cases and controls (P-value=0.1238; 0.2730 respectively).

In our study the mean APACHE II score at day-1 is 30.42 and at day-3 is 29.32 and we do not find a significant difference in mean APACHE II score at day-1 and day-3 in cases and controls (P-value 0.4353). There is statistically significant difference in mean APACHE II score at day-1 (P-value 0.0098) and day-3 (P-value 0.0001) in survivors and non-survivors among cases.

In our study the mean Urine ACR at day-1 in cases is 221.74 and day-3 is 285.47 and in controls the mean urine ACR at day-1 is 19.47 and at day-3 is 18.11. The difference in mean urine ACR is statistically not significant (P-value 0.5247) within cases at two different days but statistically a significant difference in urine ACR at day-1 and day-3 is found in cases and controls (P-value <0.0001). In our study we did not find a significant difference in mean Urine ACR at Day-1 (P-value 0.8586), but a statistically significant difference at day-3 (P-value 0.0008) in survivors and non- survivors among cases. In Tayeh et al study Albumin/creatinine ratio (ACR) measured on admission (ACR1) was 121.3 mg/g and the 24 h ACR (ACR2) was 190.0 mg/g in non-survivors compared to 90.8 mg/g and 69.1) mg/g for survivors. They found an increase in ACR after 24 hours as compared to admission day ACR. (7)

There is statistically significant Pearson correlation between Urine ACR Day-1 (r= 0.577; p-value <0.0001) and APACHE II score at day-1 and also statistically significant Pearson correlation between Urine ACR Day-3 (r= 0.417; p-value 0.0008) and APACHE II score at day-3. In our study we found significant correlation between ACR and APACHE on both days.

Table 8: Logistic regression analysis to predict predictors of mortality

Variable	Coeff.	Std Err	p	O.R.	Low	High
APACHE II score D1	0.2735	0.0741	0.0002	1.3145	1.1369	1.5199
APACHE II score-D3	0.0627	0.031	0.0429	1.0647	1.002	1.1313
Urine ACR D1	0.0133	0.0043	0.0022	1.0134	1.0048	1.022
Urine ACR D3	0.0192	0.0052	0.0002	1.0194	1.0091	1.0298

Table 9:

	AUC	P-Value	CI95	Cut-off	Sensitivity	Specificity
Urine ACR D1	0.621	0.098	0.479-0.764	97.4	87.5	41.9
Urine ACR D3	0.823	<0.0001	0.714-0.932	80.8	96.3	61.3

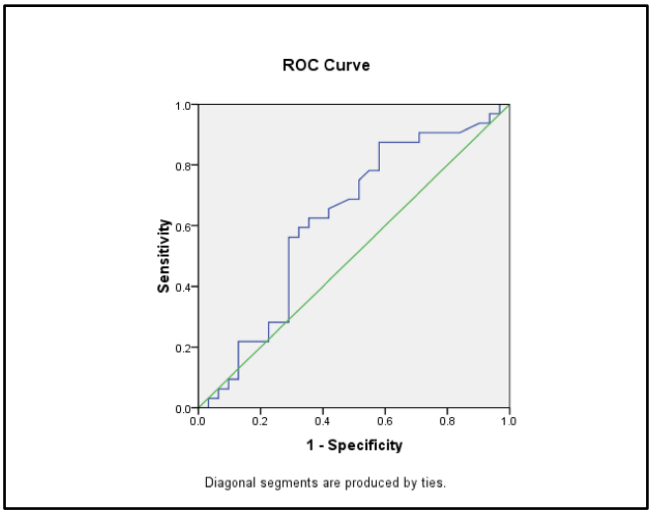

Fig 8:

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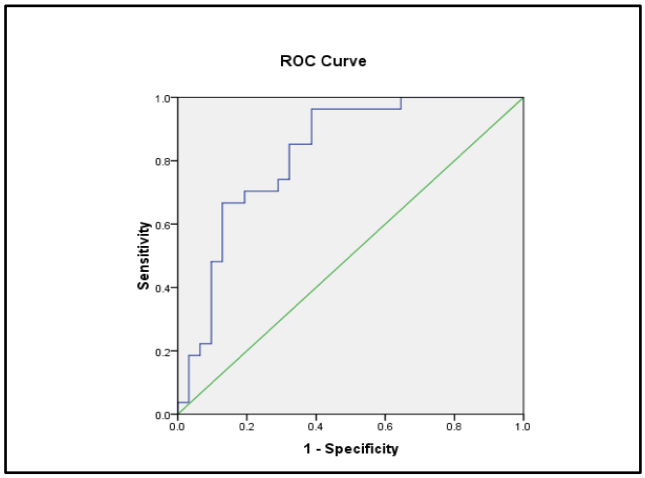

Fig 9:

On logistic regression analysis for predicting, predictors of mortality and we found that Urine ACR at day-1 (OR 1.0134; P-value 0.0022), Urine ACR at day-3 (OR 1.0194; P-value 0.0002), APACHE II score at day-1 (OR 1.3145; P-value 0.0002) and APACHE II score at day-3 (OR 1.0647; P-value 0.0429) are predictors of mortality in septicemia cases. And, to define an optimal decision threshold for Urine ACR, ROC curve analysis was performed. Urine ACR at day-3 was significantly powerful to discriminate non-survivors. Urine ACR at day-3 was the most powerful diagnostic parameter for predicting non-survivors (AUC=0.823). Optimal cut-off points for Urine ACR is 80.8. At these cut-off points, the sensitivity rate for correct prediction of non-survivors was 96.3%, whereas the specificity rate was 61.3%.

ACR and Outcome:

To define an optimal decision threshold for Urine ACR, ROC curve analysis was performed. ROC curves are demonstrated in Fig:1. Cut-off values, predictive accuracies and AUCs are shown in Table 5. Urine ACR at day-3 was significantly powerful to discriminate non-survivors. Urine ACR at day-3 was the most powerful diagnostic parameter for predicting non-survivors (AUC=0.823). Optimal cut-off points for Urine ACR is 80.8. At these cut-off point, the sensitivity rate for correct prediction of non-survivors was 96.3%, whereas the specificity rate was 61.3%.

Day 1 Day 3

Zhang et al found that in sepsis patients with normal baseline kidney function, those who developed acute renal injury had higher ACR on the second day of admission compared to those who did not. They identified that an ACR value of 143 mg/g on the second day of admission was highly sensitive (91.7%) and specific (79.2%) for predicting acute renal damage in sepsis patients.[8] Gosling et al reported that ACR on admission was associated with serum creatinine but did not assess the need for RRT. In a study of medical cases only, elevated microalbuminuria was found to be a highly sensitive and specific predictor of the onset of acute renal failure.[9] Basu et al discovered that increased ACR on admission to ICU could serve as an early warning sign for sepsis-related kidney injury.[10]

Bhadade et al found that ACR2 and change in ACR over time had the highest area under the ROC curve for predicting mortality, followed by APACHE II and ACR1.[11] Basu et al also found that ACR2 was as effective as APACHE II in predicting mortality, and an ACR value of 99.6 mg/g 24 hours after admission had a sensitivity of 85% and specificity of 68%. Lack of microalbuminuria at 24 hours was associated with a higher chance of survival. Szakmany et al reported that ACR measured at ICU admission could differentiate between survivors and non-survivors, while Gosling et al found that in both medical and surgical patients who died, ACR did not decrease significantly 6 hours after admission.[12]

CONCLUSION

In summary, based on the studies reviewed, it can be concluded that microalbuminuria, specifically the urine albumin/creatinine ratio (ACR), has the potential to serve as a predictor of disease severity and mortality in intensive care units, particularly in septic patients. ACR measured beyond 24 hours of ICU admission and the trend of ACR over time may be more valuable than early admission ACR. Moreover, ACR is found to be as closely associated with mortality as the widely used APACHE II score. Thus, measuring ACR on admission to the ICU and 24 hours later can provide additional information on patient status that can supplement traditional sickness severity ratings. Overall, the urine ACR is a simple, quick, noninvasive, low-cost, easy-to-perform, and interpret diagnostic tool for early prognosis and mortality prediction in sepsis patient.

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