The Egyptian Journal of Critical Care Medicine (2016) 4, 47–55

The Egyptian College of Critical Care Physicians

The Egyptian Journal of Critical Care Medicine

http://ees.elsevier.com/ejccm
www.sciencedirect.com

ORIGINAL ARTICLE

# Urinary albumin/creatinine ratio as an early predictor of outcome in critically-ill septic patients

Osama Tayeh [a], Khaled M. Taema [a,*], Mohamed I. Eldesouky [a], Adel A. Omara [b]

[a] Cairo University, Cairo, Egypt
[b] Electricity Hospital, Cairo, Egypt

Received 23 October 2015; revised 15 January 2016; accepted 17 March 2016
Available online 26 March 2016

KEYWORDS

Microalbuminuria;
Urinary albumin/creatinine ratio;
Sepsis;
Mortality

**Abstract** Several cumbersome scoring systems were developed for prognosis and outcome prediction in sepsis. We intended in this study to evaluate the urinary albumin/creatinine ratio (ACR) as a prognostic predictor in sepsis.

We included 40 adult septic patients in a prospective observational study. We excluded patients with preexisting chronic kidney disease or diabetes mellitus.

After clinical evaluation, urine spot samples were collected on admission and 24 h later for ACR1 and ACR2. Admission APACHE IV score and the highest recorded SOFA score of their daily estimation were considered. We also evaluated the need for mechanical ventilation, inotropic and/or vasoactive support, renal replacement therapy (RRT), and in-hospital mortality.

In a population with 63 (55–71) year old with 29 (72.5%) males, we found that the ACR2 is correlated with the SOFA score ($r = 0.4$, $P = 0.03$). SOFA was higher in patients with increasing ACR [14(4.8–16.8) vs 5(3–8), $P = 0.01$]. None of the ACR measures was correlated with APACHE IV score. ACR2 was higher in patients who needed mechanical ventilation and inotropic and/or vasoactive support [140(125–207) and 151(127–218) mg/g respectively] compared to [65(47–174) and 74(54–162) mg/g], $P = 0.01$ and 0.009. None of the measured parameters was related to the need of RRT. ACR1, ACR2, APACHE IV and increasing ACR were predictors of mortality. The AUC for mortality prediction was largest for APACHE IV (0.90) then ACR2 (0.88). ACR2 of 110.5 mg/g was 100% sensitive and 86% specific to predict mortality.

We concluded that the urinary ACR may be used as a simple test for prognosis and mortality prediction in sepsis.



* Corresponding author.

Peer review under responsibility of The Egyptian College of Critical Care Physicians.

ELSEVIER Production and hosting by Elsevier

## 1. Introduction

Sepsis occurs in 1–2% of all hospitalized patients and accounts for as much as 25% of ICU cases. In the United States, sepsis causes more than 200,000 deaths each year [1]. Sepsis is marked by a severe host defense response that involves

http://dx.doi.org/10.1016/j.ejccm.2016.03.002
2090-7303 

triggering of potent inflammatory cascades which release a plethora of pro-inflammatory and anti-inflammatory molecules into the circulation [2]. The endothelial dysfunction is a milestone in sepsis pathogenesis. An early feature of sepsis is the loss of endothelial barrier integrity leading to systemic capillary leak [3]. This enhanced capillary permeability causes increased glomerular excretion of albumin in the urine [4]. Microalbuminuria has been accordingly seen by several studies to occur early after severe inflammatory process and to persist in more severe cases [5–8].

Early prediction of mortality among critically ill sepsis patients and early institution of intensive therapy are of paramount importance. Various intensive care units scoring systems like the Acute Physiology and Chronic Health Evaluation (APACHE) II, APACHE IV, and Simplified Acute Physiology (SAPS II) scores to predict mortality are in current use. These scoring systems require a large number of variables derived from the patient's history, examination, and initial laboratory data.

Microalbuminuria was shown to be promising as a predictor of organ failure, vasopressor requirement and mortality prediction. It was shown to be even better than APACHE II and SOFA scores in some studies [9–14].

We intended in our study to evaluate the prognostic value of urinary albumin/creatinine ratio (ACR) in patients with sepsis and to compare this prognostic value with the APACHE IV and Sepsis-related Organ Failure Assessment Score (SOFA) scoring systems.

## 2. Patients and methods

This is a prospective observational study that recruited all adult critically ill patients admitted to the surgical/medical ICU department, Electricity Hospital, Cairo, Egypt from May 2013 to May 2014. We included in the study patients with diagnosis of sepsis syndrome with the presence of SIRS based on the diagnostic criteria of 1992 ACCP/SCCM [15] and its update in 2001 International Sepsis Definition Conference [16], exhibiting two or more of the following signs: (1) temperature of $>38$ °C or $<36$ °C, (2) pulse rate of $>90$ beats/min, (3) respiratory rate of $>20$ breaths/min or hyperventilation with a $PaCO_2$ of $<32$ mmHg, or (4) white blood cell (WBC) count of $>12{,}000\ \mu L^{-1}$ or $<4000\ \mu L^{-1}$, or $>10\%$ immature cells. The presence of infection was defined according to the clinical and microbiological criteria of the Centers for Disease Control and Prevention (CDC) definitions [17] and was held as a gold standard. It was determined by two independent experts who examined the patients daily for the first 48 h of admission.

We excluded from the study patients less than 18 year old, patients with anuria or hematuria, patients with preexisting chronic kidney disease, patients with diabetes mellitus, patients with proteinuria due to renal or post renal causes, patients with urinary tract infection, and patients with ICU length of stay less than 24 h.

The study protocol was approved by the institutional review board at Cairo University together with representatives of study conduction site.

All included patients were subjected for clinical evaluation including history, physical examination, routine laboratory investigations (capillary blood glucose, coagulation profile, arterial blood gases, liver function tests, kidney function tests, random blood sugar, and serum electrolytes), and cultures from suspected sources of infection including sputum, urine, ... etc. together with at least two blood cultures obtained from different venipuncture were obtained prior to antibiotic administration.

APACHE IV score was calculated in an integer score form that is web based computed by applying worst values of the measurements observed during 24 h following ICU admission, with a maximum score of 286 [18]. The score was previously validated in sepsis patients [19].

The SOFA score is a scoring system to determine the extent of organ dysfunction [20]. SOFA score was evaluated daily until ICU discharge or demise or up to a total of 28 days. The highest recorded SOFA score was considered for statistical analysis.

Other parameters of disease severity that were studied included need for mechanical ventilation, need for inotropic and/or vasoactive support and need for renal replacement therapy (RRT). Outcome was evaluated by ICU length of stay (ICU-LOS) and the in-hospital mortality.

### 2.1. Urinary albumin creatinine ratio

Urine spot samples were collected at the time of ICU admission for Albumin Creatinine Ratio 1 (ACR1) and 24 h following ICU admission for Albumin Creatinine Ratio 2 (ACR2).

Urinary microalbumin was measured by the immunoturbidimetric method and urinary creatinine by modified kinetic Jaffe reaction (Dimension RxL Max, Dade Behring Inc., U.S.A.).

Trends of microalbuminuria was assessed as the change from ACR1 to ACR2. The difference between those values represents the delta albumin/creatinine ratio ($\Delta$ ACR) and is calculated as $\Delta\ ACR = ACR2 - ACR1$. When $\Delta$ ACR is negative, it is defined as decreasing ACR and when it is positive, it is defined as increasing ACR.

### 2.2. Statistical method

Data were prospectively collected and coded prior to analysis using the statistical package of social science (SPSS version 16). Normal distribution of different dependent variables in relation to their independent variables was studied. A variable was considered normally distributed if the Shapiro–Wilk's test had a $P > 0.05$ [21,22] and with $z$-value of skewness and kurtosis between $-1.96$ and $+1.96$ [23].

Our variables were found to be non-normally distributed. Continuous variables were accordingly expressed as median (Q1–Q3). Categorical variables were expressed as frequency and proportion. Nonparametric test (Mann–Whitney $U$ test) was used for comparison between two groups as regards quantitative variable. Chi-Square Test ($x^2$) was used for comparison between two groups as regards qualitative data. Exact test was used instead when the expected frequency is less than 5. Spearman correlation coefficient test ($r$) was used to test a positive or negative relationship between two variables. Receiver operator characteristic (ROC) analysis was performed to define a cutoff value of a variable. Sensitivity was estimated as $\frac{\text{True positive}}{(\text{True positive}+\text{False negative})}$ and specificity was estimated as $\frac{\text{True negative}}{(\text{True negative}+\text{False positive})}$. Results were considered statistically significant if $P \leqslant 0.05$.

## 3. Results

During the period between May 2013 and May 2014, 65 patients with sepsis were initially recruited to our study. Twenty-five patients were subsequently excluded and the remaining 40 patients continued the study duration. Of the 25 excluded patients, 8 had preexisting chronic kidney disease, 13 had diabetes mellitus, and 4 patients died within 24 h of admission.

The 40 septic patients that included in the study had an age ranging from 28 to 87 with a median (Q1–Q2) of 63 (55–71) years old with 29 (72.5%) males and 11 (27.5%) females were included in our study.

Table 1 shows the source of infection in our patients' population.

The highest SOFA score was 7.0 (4.0–14.0) ranging from 1 to 17 and APACHE IV score recorded within first 24 h of ICU admission was 77.5 (58.8–98.0) ranging from 46 to 118.

Of the 40 patients eligible in this study, 23 (57.5%) needed ventilator support, 20 (50%) needed inotropic and/or vasoactive support to maintain hemodynamics, and only 7 (17.5%) needed RRT.

The Length of stay in our study was 7.0 (5.0:9.0) days ranging from 3 to 19 days. Eighteen patients died with a mortality rate of 45% while 22 patients (55%) survived their ICU course (Fig. 1).

### 3.1. Albumin/creatinine ratio (ACR) measurements

Albumin/creatinine ratio (ACR) measured on admission (ACR1) was 113.2 (83.7–163.5) with a range from 29 to 229 mg/g and the 24 h ACR (ACR2) was 136.4 (63.7–195.3) ranging from 21 to 255 mg/g (Fig. 2). The ACR was decreased in 17 patients (42.5%) by 30 (22.4–39.7) mg/g and it was increased in 23 (57.5%) by 37.9 (26.4–59) (Fig. 3).

### 3.2. Albumin/creatinine ratio in relation to disease severity

The ACR1 was not significantly correlated with SOFA ($r = 0.236$, $P = 0.172$) or APACHE IV ($r = 0.188$, $P = 0.28$) scores while the ACR2 was positively correlated with SOFA score ($r = 0.366$, $P = 0.031$) but not with APACHE IV score ($r = 0.286$, $P = 0.096$). The SOFA score was significantly higher in patients with increased ACR trend 14 (4.75–16.75) than in patients with stationary or declining trend 5 (3–8) ($P = 0.01$). Meanwhile, there was no significant difference in APACHE IV between patients with increased ACR trend 81.5 (58.8–101.3) and those with stationary or declining ACR trend 66 (56–86) ($P = 0.3$) (Table 2).

The ACR1 was not statistically different in patients who needed and those who didn't need mechanical ventilation [115.7 (98.5–186.4) vs 85.6 (73.5–143.4) respectively, $P = 0.09$] while ACR2 was significantly higher in patients who required mechanical ventilation compared to those who didn't need [139.7 (125.3–207.6) vs 65.0 (47.0–174.1)

**Table 1** Source of sepsis.

| Source of sepsis | Number | Percent % |
|---|---|---|
| Chest infection | 25 | 62.5 |
| Peritonitis | 7 | 17.5 |
| Infected bed sores | 3 | 7.5 |
| Wound infection | 5 | 12.5 |

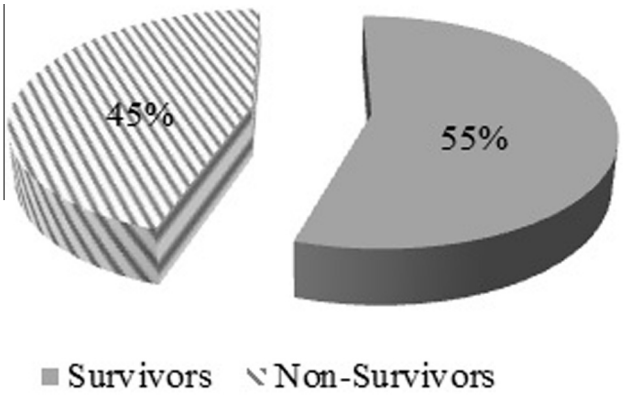


**Figure 1** Mortality rate in the study.

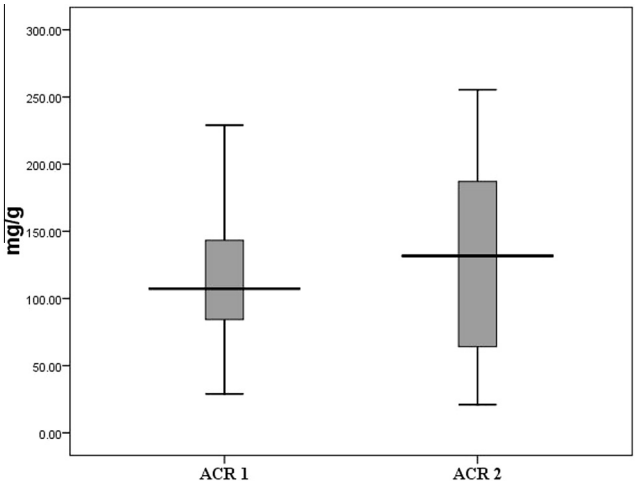


**Figure 2** ACR value on admission and 24 h later.

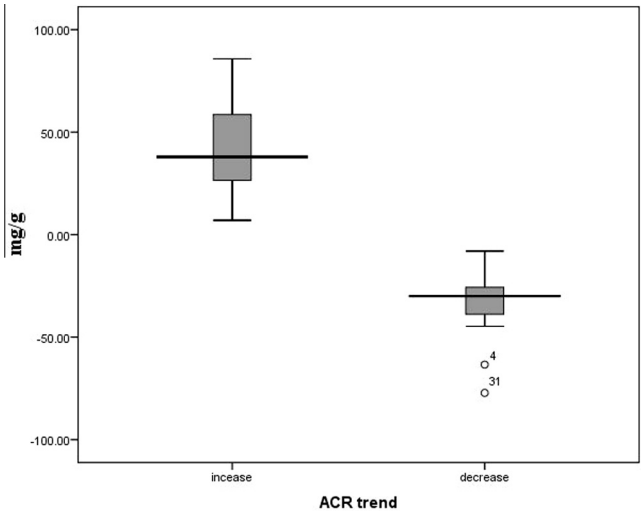


**Figure 3** ACR trend over the first 24 h.

**Table 2** Correlation between ACR1, ACR2 and SOFA and APACHE IV scores and their relation to the ACR trend.

| | | ACR1 | ACR 2 | Increasing ACR | Non-increasing ACR |
|---|---|---|---|---|---|
| SOFA | *r* | 0.236 | 0.366 | 14 (4.75–16.75) | 5 (3–8) |
| | *P*-value | 0.172 | **0.031** | **0.01** | |
| APACH IV | *r* | 0.188 | 0.286 | 81.5 (58.8–101.3) | 66 (56–86) |
| | *P*-value | 0.28 | 0.096 | 0.3 | |

The bold signify the statistically significant *P* value.

**Table 3** ACR1 and 2 in need of mechanical ventilation, inotropic and/or vasoactive support, and RRT.

| | | ACR 1 median ($Q_2$–$Q_3$) | *P* value | ACR 2 median ($Q_2$–$Q_3$) | *P* value |
|---|---|---|---|---|---|
| Mechanical ventilation | No | 85.6 (73.5–143.4) | 0.09 | 65.0 (47.0–174.1) | **0.011** |
| | Yes | 115.7 (98.5–186.4) | | 139.7 (125.3–207.6) | |
| Inotropic and/or vasoactive support | No | 99.5 (73.0–137.8) | 0.06 | 74.8 (53.9–161.8) | **0.009** |
| | Yes | 114.5 (99.8–202.7) | | 150.5 (126.9–218.2) | |
| Need for RRT | No | 115.7 (80.9–176.0) | 0.9 | 135.0 (57.4–196.0) | 0.58 |
| | Yes | 113.2 (98.5–142.0) | | 139.7 (123.7–166.7) | |

The bold signify the statistically significant *P* value.

respectively, $P = 0.011$)] (Table 3). Considering the change in ACR, we found that the increase in ACR was a predictor of need of mechanical ventilation. Of the 23 patients with increased ACR, 18 (78.3%) needed mechanical ventilation while 5 (21.7%) didn't ($P = 0.003$).

A similar relation was found between ACR1 and ACR2 and the need of inotropic and/or vasoactive support. ACR1 was not significantly different in patients who needed and those who didn't need inotropic and/or vasoactive support [114.5 (99.8–202.7) vs 99.5 (73.0–137.8) respectively, $P = 0.06$] while ACR2 was significantly higher in patients who needed inotropic and/or vasoactive support compared to those who didn't need [150.5 (126.9–218.2) vs 74.8 (53.9–161.8) respectively, $P = 0.009$] (Table 3). Considering the change in ACR, we found that the increase in ACR was a predictor of need of inotropic and/or vasoactive support. Of the 23 patients with increased ACR, 16 patients (69.6%) needed inotropic and/or vasoactive support while 7 patients (30.4%) didn't ($P = 0.01$).

Neither ACR1 nor ACR2 was significantly related to the need for RRT in our patient population. ACR1 was 113.2 (98.5–142.0) vs 115.7 (80.9–176.0) for those who needed and didn't need RRT respectively, $P = 0.9$ and ACR2 was 139.7 (123.7–166.7) vs 135.0 (57.4–196.0), $P = 0.58$ (Table 3). Even the increase in ACR over time was not significantly associated with the need for RRT. Of the 23 patients with increased ACR, 6 patients (26.1%) needed RRT while 17 patients (73.9%) didn't ($P = 0.2$).

### *3.3. Albumin/creatinine ratio and outcome*

The ACR1 and ACR2 revealed significantly positive correlation with ICU-LOS ($r = 0.5$, $P = 0.007$ for ACR1 and $r = 0.4$, $P = 0.05$ for ACR2) (Fig. 4). Both ACR1 and ACR2 was a significant predictor for mortality in our patients' population. ACR1 and ACR2 were 121.3 (103.7–189.7) mg/g and 193.0 (137.8–219.9) mg/g in non-survivors compared to 90.8 (72.3–128.4) mg/g and 69.1 (49.3–132.5) mg/g for survivors ($P = 0.009$ and $< 0.001$ for ACR1 and ACR2 respectively) (Figs. 5 and 6).

The increase in ACR after 24 h compared to admission ACR was associated with increased mortality. Sixteen of the 18 non-survivors (88.9%) had an increased ACR while only 2 (11.1%) had a stationary or decreased ACR. Of the 22 survivors, 15 (68.2%) had a stationary or decreased ACR while only 7 (31.8%) had an increased ACR ($P = 0.001$). The use of increased ACR to predict mortality had 89% sensitivity and 68% specificity.

Receiver operator characteristic (ROC) curve was examined for the use of APACHE IV and ACR concentrations as a predictor of ICU mortality (Fig. 7). The area under the ROC curve (AUC) for APACHE IV to predict ICU mortality was the highest of the examined parameters (0.90). The optimal cutoff value for APACHE IV to predict ICU mortality was 72.5 that had a sensitivity of 100% and a specificity of 80% for ICU mortality prediction while an ACR2 of 110.5 mg/g was 100% sensitive and 86.2% specific (Table 4). The different cut-off values and their sensitivity and specificity for mortality prediction are seen in Table 4.

## 4. Discussion

Sepsis is not only a great health problem but also an important socioeconomic challenge worldwide. It lowers patients' living quality and increases the mortality significantly [1]. Identification of sepsis prognosis and outcome prediction is of paramount importance.

Currently available tools for prediction of prognosis in ICU are the APACHE scores [18], which predict mortality, and the SOFA score [20], which predicts morbidity. These scoring

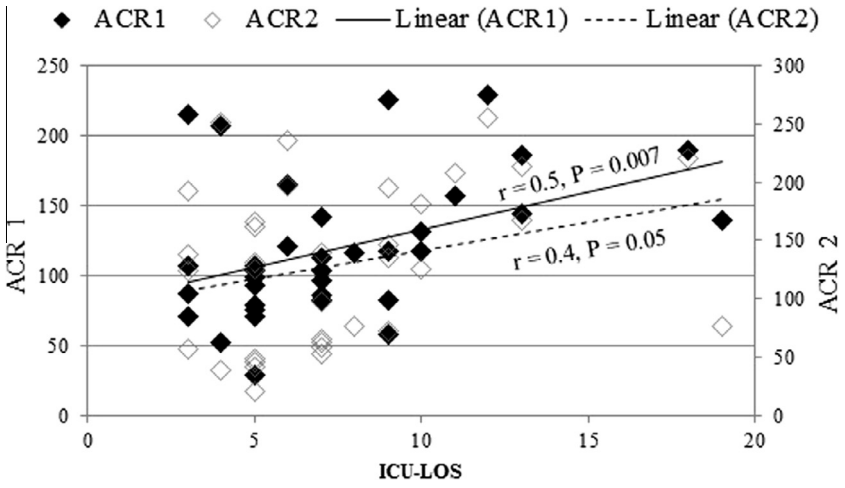


**Figure 4** Correlation between ACR and ICU-LOS.

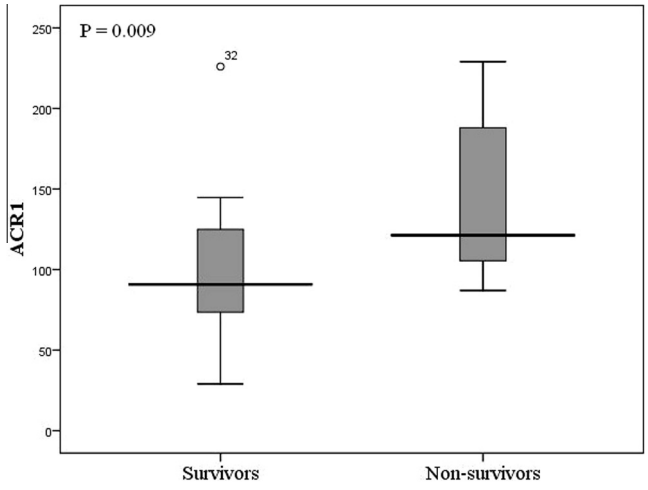


**Figure 5** ACR1 and survival.

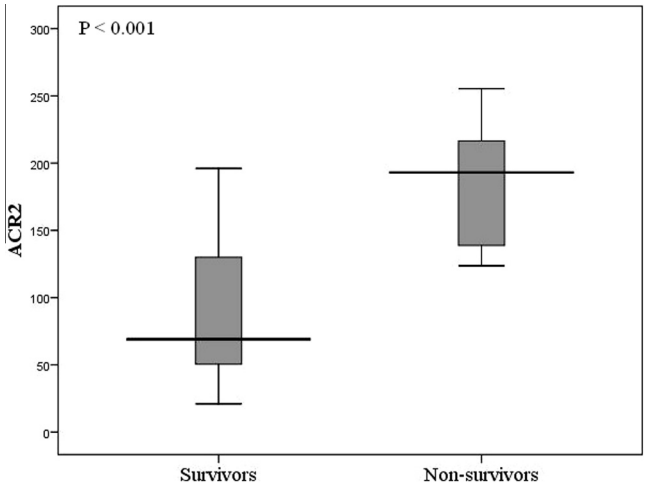


**Figure 6** ACR2 and survival.

systems are based on several physiological indices and chemical analyses. In addition to difficulty in estimation, several drawbacks and limitations have been shown to these scoring systems [24].

No laboratory biomarkers had been definitively demonstrated to correlate with severity of illness and mortality in ICU patients. Several clinical studies on critically ill patients with severe endothelial and renal involvement showed that microalbuminuria may be a beneficial marker of disease severity and mortality prediction [9,10] and it may indirectly quantify changes in systemic vascular permeability [4]. Some authors had identified microalbuminuria as a significant prognostic marker of morbidity and mortality [14]. The level of microalbuminuria starts to increase within hours of an inflammatory insult as against delayed increases in levels of many other mediators [25].

We intended in our study to evaluate the prognostic value of urinary albumin/creatinine ratio (ACR) in sepsis in the intensive care setting and to compare this prognostic value with the APACHE IV and SOFA scoring systems.

This is a prospective study involving 40 critically ill patients with sepsis syndrome admitted to medical/surgical ICU. All included patients were subjected to the measurements of urinary albumin/creatinine ratio on admission (ACR1) and 24 h later (ACR2). The recording of APACHE IV score (in the first 24 h of ICU admission) and the highest SOFA score of their daily measurements were considered.

The commonly known factors that may cause increased ACR and that might be confounding are the diabetes mellitus and chronic kidney disease; accordingly, we excluded those patients from our study.

Sepsis is characterized by widespread endothelial dysfunction arising from the effects of cytokines, and other inflammatory mediators, released during the intense inflammatory responses leading to systemic increase in capillary permeability [2]. The increased capillary permeability in the pulmonary circulation contributes into ARDS [26], in systemic circulation contributes into sepsis induced hypotension [27], and in renal circulation causes increased amounts of albumin to escape into the glomerular ultrafiltrate. The tubular reabsorptive mechanism for albumin from the ultrafiltrate is exceeded beyond its threshold capacity, leading to increased excretion of albumin in the urine [28]. As a marker of increased permeability, microalbuminuria was supposed to indicate the development

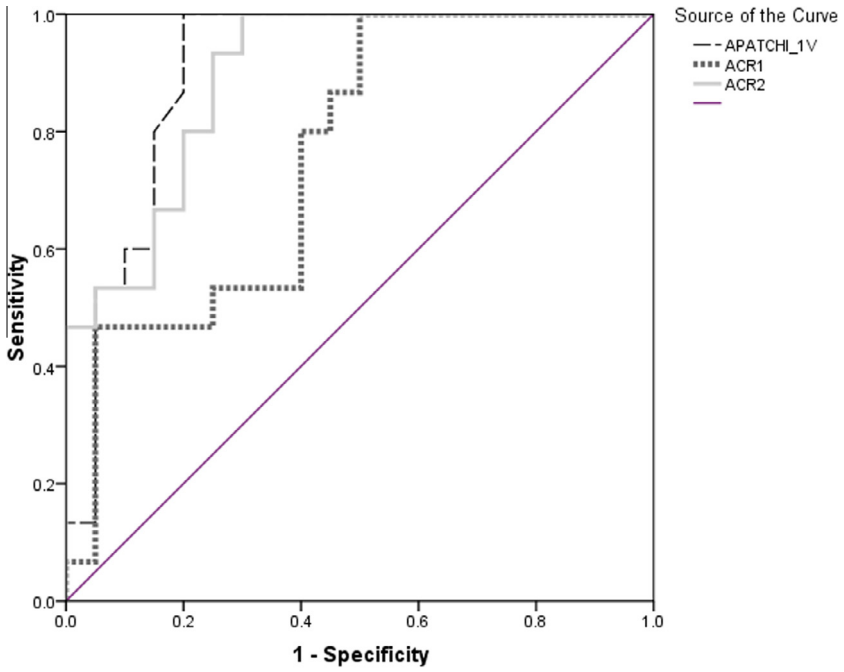


**Figure 7** ROC curve for APACHE IV, ACR1 & ACR2 for mortality prediction.

**Table 4** AUC, their significance, cut-off values and the sensitivity and specificity for mortality prediction.

| | AUC | *P* value | Cutoff value | Sensitivity (%) | Specificity (%) |
|---|---|---|---|---|---|
| APACHE IV | 0.905 | **< 0.001** | 68.5 | 100 | 75 |
| | | | 72.5 | 100 | 80 |
| | | | 75.5 | 93 | 80 |
| ACR 1 | 0.755 | **0.006** | 86.3 mg/g | 100 | 50 |
| | | | 89.8 mg/g | 94.4 | 50 |
| | | | 97.25 mg/g | 88.9 | 54 |
| ACR 2 | 0.876 | **< 0.001** | 86.9 mg/g | 100 | 63.6 |
| | | | 110.5 mg/g | 100 | 86.2 |
| | | | 124.4 mg/g | 94.6 | 86.2 |

The bold signify the statistically significant *P* value.

of ARDS, hemodynamic compromise, and acute kidney injury. The authors of this article accordingly evaluated the use of mechanical ventilation, inotropic and/or vasoactive support, and RRT as severity indicators.

We couldn't elucidate a significant correlation between ACR1 obtained on admission and either SOFA or APACHE IV scores while ACR2 obtained 24 h later significantly correlated with SOFA score and had a statistically non-significant tendency for correlation with APACHE IV score. We also found that the SOFA score while not APACHE IV score is higher in patients with an increasing trend of ACR. In a medical/surgical critically ill patients, Basu et al. found that ACR 6 and 24 h after admission were correlated with APACHE II score [29]. In a study on medical cases only, increasing microalbuminuria had a good sensitivity and specificity to predict the development of multi-organ failure. In addition, a high APACHE II score was significantly associated with increasing microalbuminuria levels [10]. They also found that APACHE II and SOFA scores were higher in patients with increasing trend of ACR over their ICU stay compared to patients with stationary or declining ACR level [10]. De Gaudio et al. [5] reported an increasing ACR to be positively correlated with an increasing SOFA score in 55 postoperative patients with sepsis. In a study of 40 trauma patients, the same authors [30] reported that the degree of increase in microalbuminuria over the first 24 h following trauma was related to the severity of the trauma.

We found that the ACR2 and the Δ ACR and not the ACR1 are associated with a higher incidence of need of mechanical ventilation and need of inotropic and/or vasoactive support. Other authors also found that ACR is inversely associated with the PaO2/FiO2 ratio in post-trauma patients and was associated with significantly more duration of mechanical ventilation in patients with initially normal lung function [31]. Pallister and colleagues [32] demonstrated that ACR done 8 h after admission was predictive of the development of ARDS. Other authors concluded that ACR on admission and 6 h later are higher in patients with vasoactive and inotropic support

and are positively correlated with ventilator days [13]. Abid et al., found that the group of patients with increasing ACR had higher incidence of acute respiratory failure and MODS compared with those with decreasing or stationary ACR [10]. Basu et al. also found an inverse relationship between the degree of change in microalbuminuria and the lowest PaO2/FiO2 ratio [29]. Another study conducted on 25 septic patients contradicted these results and showed that ACR did not correlate to extra vascular lung water and PaO2/FiO2 ratio, concluding that microalbuminuria does not reflect increased systemic capillary permeability in septic shock [33]. They considered that the pulmonary vascular permeability is not the only determinant of the extra vascular lung water. Volume status, cardiac function and severity of lung injury may also contribute to extra vascular lung water. The authors of that study criticized their conclusion by the very low serum albumin in their population that may influence urinary albumin excretion [33].

Out of the 40 patients of our study, 7 patients (17.5%) needed RRT and 33 patients (82.5%) didn't need RRT. We couldn't elucidate any relation between ACR either on admission or 24 h later or even Δ ACR and the need for RRT. In the study of Zhang and colleagues on patients with sepsis and normal initial kidney function, ACR on second day of admission was higher in patients who developed acute kidney injury [34]. They found that ACR on the second day of admission of 143 mg/g was 91.7% sensitive and 79.2% specific for predicting acute kidney injury in patients with sepsis [34]. Gosling et al. also found that ACR on admission correlated with serum creatinine but they didn't comment on need for RRT [12]. In a study on medical cases only, increasing microalbuminuria had a good sensitivity and specificity to predict the development of acute renal failure [10]. Also in study done by Basu et al. [29], they concluded that the presence of higher ACR on admission to ICU may be an early indicator of acute kidney injury in sepsis. These findings were supported by the notion that an increase in urinary albumin excretion was correlated with increases in systemic capillary leakage [35]. The kidneys receive about 25% of the cardiac output, and small changes in glomerular permeability will lead to notable changes in microalbuminuria, and thus kidneys are sensitive to permeability changes [35]. Some authors postulated the higher levels of microalbuminuria in sepsis to defects in the glycocalyx layer of the fenestrated glomerular capillaries induced by the inflammatory process. It has been shown that the glycocalyx layer acts as a barrier to protein permeability and degradation of this layer increases the passage of albumin across the glomerulus [36]. These pathologic changes related to the kidneys can explain the impairment of kidney function that occurs when ACR is increased. We supposed that the lack of relation between the ACR and need for RRT in our study was due to the small sample size and small number of patients who needed RRT (only seven patients) compared to other studies. We didn't evaluate the development of acute kidney injury that didn't reach the extent of need of RRT. We might accordingly lose an association between ACR and kidney involvement in sepsis.

The average ICU length of stay in our study was 7.0 (5.0:9.0) days. We found a positive correlation between the ACR on admission and 24 h later and the ICU-LOS. Gosling et al. and Zhang et al. found that ACR values positively correlate with ICU-LOS [13,34]. In Gosling's study, the ACR was measured on admission and 6 h later. Thorevska et al., found that among survivors of critically ill patients, those with ACR more than or equal to 100 mg/g stayed 5 days longer in the ICU [11]. This correlation between ACR and ICU-LOS represents a reflection of their association with disease severity.

APACHE IV, ACR1 and ACR2 were found to be predictors for mortality in our study. The AUC for ROC analysis was highest for APACHE IV score (0.905) followed by ACR2 (0.876) and then ACR1 (0.755). We found an APACHE IV score of 72.5 to have 100% sensitivity and 80% specificity, ACR1 of 86.3 mg/g to have 100% sensitivity and 50% specificity, and ACR2 of 110.5 mg/g to have 100% sensitivity and 86.2% specificity to predict mortality. We also found that the trend of ACR over time is a predictor of mortality with higher mortality in those with an increase in ACR2 compared to ACR1. The increase in ACR was associated with 89% sensitivity and 68% specificity for detection of mortality in sepsis patients.

In a systemic review, Gobal et al. concluded that ACR may hold promises as a predictor of mortality [14]. Bhadade et al. [37] has demonstrated that the area under the ROC curves for prediction of mortality was highest for ACR2 (0.943) and change in ACR over time (0.943) followed by APACHE II (0.835), SOFA (0.788) and ACR1 (0.725). Basu et al. concluded that ACR 2 is as good as APACHE II for mortality prediction [29,38]. They found ACR 24 h after admission of 99.6 mg/g to have sensitivity of 85% and specificity 68%. They concluded that absence of microalbuminuria at 24 h is a predictor for survival [29]. Gosling et al. found results similar to Basu et al. [29,38] in surgical, trauma, and burn patients but not in medical patients [12]. In another study also in surgical patients, ACR measured on arrival to the ICU was able to significantly differentiate survivors from nonsurvivors [6]. In the subset of surgical and trauma patients, Gosling and colleagues found that ACR more than 5.9 mg/mmol (52.2 mg/g) predict mortality with 100% sensitivity and 59% specificity however, in medical patients they didn't find any difference in ACR between survivors and non survivors [12]. Gosling et al. in another study concluded that in both medical and surgical patients who died in the ICU, median ACR failed to decrease significantly 6 h following admission [13]. In 104 mixed ICU patients, Thorevska et al. found that patients with ACR more than or equal to 100 mg/g on admission were 2.7 times as likely to die compared to those with ACR less than 100. They concluded that ACR had similar predictive characteristics of APACHE II score as an independent predictor of mortality [11]. Many other authors, like us, showed higher mortality among patients with increasing ACR levels than those with stationary or declining values [10,11,34]. However, APACHE IV score has performed better than ACR2 and Δ ACR in our study as the area under curve was higher for APACHE IV. The finding of ACR2 as a predictor of mortality could be explained by the presence of ongoing inflammatory processes among those who expired and hence the higher levels of ACR2 among them. On the other hand, a lower level of ACR2 might indicate a decrease in the inflammatory activity and explain the improved survival. This also explains the ability of Δ ACR in prediction of mortality where an increasing trend predicts a poorer outcome, whereas a decreasing trend predicts a better outcome. The decrease in levels after 24 h of ICU admission could be the result of the decrease in the inflammatory processes occurring as a result of treatment.

The initiation of early treatment might help to protect the glycocalyx layer and prevent further rise in capillary permeability [36]. On the basis of these observations, it could be said that microalbuminuria has a role in checking the effect of treatment [37]. The importance of the ACR change over time than depending on one measure was also explained by the presence of chronic microalbuminuria with some diseases as diabetic or hypertensive nephropathy, even if not previously diagnosed. We postulated the presence of a significant predictive value of APACHE IV and ACR2 while there was no correlation between them in our study to the small sample size.

Our study was limited by the small sample size. We considered only 2 measures of the ACR; on admission and 24 h later. Other measures in-between might be beneficial. We considered the need of mechanical ventilation and RRT as indicators for ARDS and acute kidney injury respectively. We didn't estimate the deterioration in PaO2/FIO2 ratio and the serum Creatinine level and accordingly we might miss an association between the ACR and some degrees of ARDS and acute kidney injury.

## 5. Conclusions

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. Late ACR after 24 h from ICU admission and ACR trend over time might be more important than the earlier admission ACR.

Thus, together with conventional illness severity scores, the measurement of ACR on admission to the ICU, and 24 h later, can provide additional information on patient outcome.

## References


[1] Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. Crit Care Med 2001;29(7):1303–10.

[2] Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. N Engl J Med 2003;348(2):138–50. http://dx.doi.org/10.1056/NEJMra021333.

[3] Aird WC. The role of the endothelium in severe sepsis and multiple organ dysfunction syndrome. Blood 2003;101(10):3765–77. http://dx.doi.org/10.1182/blood-2002-06-1887.

[4] Gosling P. Microalbuminuria: a marker of systemic disease. Br J Hosp Med 1995;54(6):285–90.

[5] De Gaudio AR, Adembri C, Grechi S, Novelli GP. Microalbuminuria as an early index of impairment of glomerular permeability in postoperative septic patients. Intensive Care Med 2000;26(9):1364–8. http://dx.doi.org/10.1007/s001340000593.

[6] Szakmany T, Molnar Z. Increased glomerular permeability and pulmonary dysfunction following major surgery: correlation of microalbuminuria and PaO/FiO ratio. Acta Anaesthesiol Scand 2004;48(6):704–10. http://dx.doi.org/10.1111/j.1399-6576.2004.00388.x.

[7] Yew WS, Pal SK. Correlation of microalbuminuria and outcome in patients with extensive burns. Br J Anaesth 2006;97(4):499–502. http://dx.doi.org/10.1093/bja/ael211.

[8] Terao Y, Takada M, Tanabe T, Ando Y, Fukusaki M, Sumikawa K. Microalbuminuria is a prognostic predictor in aneurysmal subarachnoid hemorrhage. Intensive Care Med 2007;33(6):1000–6. http://dx.doi.org/10.1007/s00134-007-0617-z.

[9] MacKinnon KL, Molnar Z, Lowe D, Watson ID, Shearer E. Use of microalbuminuria as a predictor of outcome in critically ill patients. Br J Anaesth 2000;84(2):239–41.

[10] Abid O, Sun Q, Sugimoto K, Mercan D, Vincent JL. Predictive value of microalbuminuria in medical ICU patients: results of a pilot study. Chest 2001;120(6):1984–8.

[11] Thorevska N, Sabahi R, Upadya A, Manthous C, Amoateng-Adjepong Y. Microalbuminuria in critically ill medical patients: prevalence, predictors, and prognostic significance. Crit Care Med 2003;31(4):1075–81. http://dx.doi.org/10.1097/01.CCM.0000059316.90804.0B.

[12] Gosling P, Brudney S, McGrath L, Riseboro S, Manji M. Mortality prediction at admission to intensive care: a comparison of microalbuminuria with acute physiology scores after 24 hours. Crit Care Med 2003;31(1):98–103. http://dx.doi.org/10.1097/01.CCM.0000038208.80466.E5.

[13] Gosling P, Czyz J, Nightingale P, Manji M. Microalbuminuria in the intensive care unit: clinical correlates and association with outcomes in 431 patients. Crit Care Med 2006;34(8):2158–66. http://dx.doi.org/10.1097/01.CCM.0000228914.73550.BD.

[14] Gopal S, Carr B, Nelson P. Does microalbuminuria predict illness severity in critically ill patients on the intensive care unit? A systematic review. Crit Care Med 2006;34(6):1805–10. http://dx.doi.org/10.1097/01.CCM.0000217922.75068.EA.

[15] Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. Chest 1992;101(6):1644–55. http://dx.doi.org/10.1378/chest.101.6.1644.

[16] Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Crit Care Med 2003;31(4):1250–6. http://dx.doi.org/10.1097/01.CCM.0000050454.01978.3B.

[17] Olmsted RN. Association for Professionals in Infection Control and Epidemiology. APIC Infection control and applied epidemiology: principles and practice. St. Louis, London: Mosby; 1996.

[18] Zimmerman JE, Kramer AA, McNair DS, Malila FM. Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. Crit Care Med 2006;34(5):1297–310. http://dx.doi.org/10.1097/01.CCM.0000215112.84523.F0.

[19] Dahhan T, Jamil M, Al-Tarifi A, Abouchala N, Kherallah M. Validation of the APACHE IV scoring system in patients with severe sepsis and comparison with the APACHE II system. Crit Care 2009;13(Suppl 1):P511.

[20] Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the working group on sepsis-related problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996;22(7):707–10.

[21] Shapiro SS, Wilk MB. An analysis of variance test for normality (complete samples). Biometrika 1965;52(3–4):591–611. http://dx.doi.org/10.1093/biomet/52.3-4.591.

[22] Razali NM, Wah YB. Power comparisons of Shapiro-Wilk, Kolmogorov-Smirnov, Lilliefors and Anderson-Darling tests. J Stat Model Anal 2011;2(1):21–33.

[23] Doane DP, Seward LE. Measuring skewness: a forgotten statistic? J Stat Educ 2011;19(2):1–18.

[24] Vincent J-L, Moreno R. Clinical review: scoring systems in the critically ill. Crit Care 2010;14(2):207.

[25] Molnar Z, Szakmany T, Koszegi T, Tekeres M. Microalbuminuria and serum procalcitonin levels following oesophagectomy. Eur J Anaesthesiol 2000;17(7):464–5.

[26] Ware LB. Pathophysiology of acute lung injury and the acute respiratory distress syndrome. Semin Respir Crit Care Med 2006;27(4):337–49. http://dx.doi.org/10.1055/s-2006-948288.

[27] Lee WL, Slutsky AS. Sepsis and endothelial permeability. N Engl J Med 2010;363(7):689–91. http://dx.doi.org/10.1056/NEJMcibr1007320.

[28] Adembri C, Sgambati E, Vitali L, Selmi V, Margheri M, Tani A, et al. Sepsis induces albuminuria and alterations in the glomerular filtration barrier: a morphofunctional study in the rat. Crit Care 2011;15(6):R277. http://dx.doi.org/10.1186/cc10559.

[29] Basu S, Bhattacharya M, Chatterjee TK, Chaudhuri S, Todi SK, Majumdar A. Microalbuminuria: a novel biomarker of sepsis. Indian J Crit Care Med 2010;14(1):22–8. http://dx.doi.org/10.4103/0972-5229.63034.

[30] De Gaudio AR, Spina R, Di Filippo A, Feri M. Glomerular permeability and trauma: a correlation between microalbuminuria and Injury Severity Score. Crit Care Med 1999;27(10):2105–8.

[31] Gosling P, Sanghera K, Dickson G. Generalized vascular permeability and pulmonary function in patients following serious trauma. J Trauma 1994;36(4):477–81.

[32] Pallister I, Dent C, Wise CC, Alpar EK, Gosling P. Early post-traumatic acute respiratory distress syndrome and albumin excretion rate: a prospective evaluation of a 'point-of care' predictive test. Injury 2001;32(3):177–81 (discussion 83).

[33] Molnar Z, Szakmany T, Heigl P. Microalbuminuria does not reflect increased systemic capillary permeability in septic shock. Intensive Care Med 2003;29(3):391–5. http://dx.doi.org/10.1007/s00134-003-1651-0.

[34] Zhang Z, Lu B, Ni H, Sheng X, Jin N. Microalbuminuria can predict the development of acute kidney injury in critically ill septic patients. J Nephrol 2013;26(4):724–30. http://dx.doi.org/10.5301/jn.5000231.

[35] Futrakul N, Sridama V, Futrakul P. Microalbuminuria – a biomarker of renal microvascular disease. Ren Fail 2009;31(2):140–3. http://dx.doi.org/10.1080/08860220802595948.

[36] Singh A, Satchell SC, Neal CR, McKenzie EA, Tooke JE, Mathieson PW. Glomerular endothelial glycocalyx constitutes a barrier to protein permeability. J Am Soc Nephrol 2007;18(11):2885–93. http://dx.doi.org/10.1681/ASN.2007010119.

[37] Bhadade RR, deSouza R, Harde MJ, Sridhar B. Microalbuminuria: a biomarker of sepsis and efficacy of treatment in patients admitted to a medical intensive care unit of a tertiary referral center. J Postgrad Med 2014;60(2):145–50. http://dx.doi.org/10.4103/0022-3859.132320.

[38] Basu S, Chaudhuri S, Bhattacharyya M, Chatterjee TK, Todi S, Majumdar A. Microalbuminuria: an inexpensive, non invasive bedside tool to predict outcome in critically ill patients. Indian J Clin Biochem 2010;25(2):146–52. http://dx.doi.org/10.1007/s12291-010-0027-9.