Mortality Prediction of Microalbuminuria in Septic Patients

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Abstract

BACKGROUND: Huge number of pro-inflammatory and anti-inflammatory markers is produced during the process of sepsis. Its mortality prediction value needs to be determined.

AIM: To assess the prognostic value ofAlbumin creatinine ratio (ACR) in septic patients and its ability to predict mortality in comparison with Acute physiology and chronic health evaluation II score (APACHE II).

METHODS: Seventy-five Septic patients were included within 24 hours of sepsis diagnosis and were admitted to the intensive care unit (ICU). ACR values were obtained within 6 hours of ICU admission for all patients. Prognostic scoring systems [APACHE II and Sequential organ failure assessment (SOFA) scores] were calculated.

RESULTS: Twenty percent of enrolled patients died within 28 days of hospital admission. ACR was significantly higher in non-survivor in comparison to survivors (55.1 ± 20.5 versus 30.2 ± 35.7, p = 0.006). ACR ≥ 40 (mg/gm creatinine) was the cut-off point for predicting mortality with a sensitivity of 90.7% and specificity of 71.8% with total accuracy of 66% and AUC 0.75 (CI 0.62-0.88). Mean APACHE II score was significantly higher in non-survivors than survivor groups (21.4 versus 10.8, p < 0.001). ACR was positively correlated with highest SOFA score (r = 0.3, P < 0.05).

CONCLUSION: ACR is a simple prognostic marker in septic patient and could be used as a mortality predictor, particularly in early (within 6 hours) septic patients.

Introduction

In one of four patients hospitalised at the intensive care unit, sepsis is the reason for admission [1]. It is a devastating disorder that can progress to septic shock with the development of organ dysfunction when hypotension is unresponsive to fluid resuscitation, and eventually multi-organ failure and death [1].

The endothelium is a key component in the development of macro- and microcirculatory disturbances in sepsis. Activation of the endothelium leads to a procoagulant and proinflammatory condition, a disrupted barrier and an abnormal vascular tone [2]. In sepsis, there is direct destruction of the endothelial barrier [3], and an increased amount of circulating endothelial cells has been shown in patients with septic shock [4].

Microalbuminuria is defined as the presence of albumin in urine above the normal range (currently defined as < 30 mg/d) but below the detectable range with conventional dipstick methodology (> 300 mg/day) and it is commonly presented as albumin creatinine ratio (ACR) to correct for changes in urine flow. Pathophysiological, sepsis is characterised by uncontrolled systemic inflammatory responses and widespread damage to the microvascular endothelium with increased vascular permeability to plasma protein triggered by inflammatory mediators [5].

Patients and Methods

This study was conducted on 75 patients admitted to the critical care department, Cairo university hospitals with the diagnosis of sepsis.
Inclusion Criteria: any patient admitted to intensive care unit (ICU) within 24 hours of diagnosis of sepsis fulfilling the following criteria: - Adult patient: Age ≥18 years; - Sepsis was diagnosed according to The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [6].

Exclusion Criteria: - Neoplastic diseases; - Pregnancy; - Acute or Chronic kidney diseases; - Urinary tract infection or Hematuria.

**Patient grouping**

According to 28-day mortality, patients were subsequently divided into survivors and non-survivors:
- Survivors: This included patients that discharged or transferred before a 28-day period of hospital admission or survived and stayed in the hospital beyond 28 days.
- Non-survivors: This included patients that died within 28 days of hospital admission.

**Albumin creatinine ratio (ACR) was done for all included patients**

Spot urine sample was taken once within six hours of admission for assessing the degree of microalbuminuria (defined as urinary albumin concentration of 30-300 mg/dl). It is generally expressed as urinary albumin to creatinine ratio to correct the variation in urinary flow rate.

**Prognostic scoring systems**

Acute Physiology And Chronic Health Evaluation II (APACHE II) score is the severity of disease classification system and one of several ICU scoring systems. It is applied within 24 hours of admission of a patient to ICU: an integer score from 0 to 71 is computed based on several measurements; higher scores correspond to more severe disease and a higher risk of death. The first APACHE model was presented by Knaus et al., in 1981 [7].

Sepsis-related organ failure assessment score, also known as sequential organ failure assessment score (SOFA score), is used to track a person's status during the stay in the ICU to determine the extent of a person's organ function or rate of failure. The score is based on six different scores, one each for the respiratory, cardiovascular, hepatic, coagulation, renal and neurological systems [8].

APACHE II was evaluated on the first day of ICU admission. SOFA score was evaluated on the first day and serially every day until ICU discharge or demise or up to a total of 28 days. Initial, mean and highest SOFA scores were calculated.

**Statistical methodology**

Analysis of data and results are expressed as mean ± standard deviation (SD) or median (interquartile range (IQR)), as appropriate. The Student t-test, the Wilcoxon rank-sum test, or the Wilcoxon matched-pairs signed-ranks test, was used to compare continuous or discrete variables. Fisher Exact test was used to compare categorical variables. The Spearman rank correlation coefficients (rho) were calculated between continuous variables. The receiver-operating characteristic (ROC) curves for ACR and APACHE II score measurements were compared, and the sensitivity and specificity of the optimal values were calculated. A p-value < 0.05 was considered statistically significant. All statistical analysis was performed using SPSS for Windows, version 19.0 (SPSS Inc., Chicago, IL).

**Results**

**Demographic data and clinical data of all study group**

Seventy-five sepsis patients were enrolled in the study.

| Table 1: Demographic and Clinical Comorbidities |
|-----------------------------------------------|
| Gender | Sepsis (n = 75) |
|--------|----------------|
| Males  | 36 (48%)      |
| Females| 39 (52%)      |
| Age    | 63.2 ± 14.8   |
| Comorbid conditions |               |
| Diabetes| 42 (56%)   |
| Hypertension | 9 (12%) |
| Tobacco Use | 40 (53%) |
| Dyslipidemia | 33 (44%)  |
| Vital    |               |
| Pulse    | 115.5 ± 6.8   |
| MAP      | 91.8 ± 11.4   |

MAP, mean arterial pressure.

**Survivor versus Non-Survivor group**

The sepsis group was further subdivided into 2 subgroups according to 28 days mortality (Table 2):
- Survivors: This group included 60 patients that were discharged before 28 days of hospital admission or stayed alive beyond 28 days.
- Non-survivors: This included 15 patients that died within 28 days of hospital admission.

- There was no statistically significant difference regarding sex or comorbid Conditions in both groups.
- Age was significantly lower in survivors (58.4 ± 14.5 versus 71.5 ± 11.7).
- Mean arterial blood pressures were significantly higher in survivors than in non-survivors (95.3 ± 11.2 versus 82.9 ± 9.2, p 0.005).
- There was no statistically significant difference regarding the site of infection in both groups.

Table 2: Demographic and clinical data of survivors and non-survivors

| Gender          | Survivors (n = 60) (%) | Non-survivors (n = 15) (%) | P Value |
|-----------------|------------------------|----------------------------|---------|
| Males           | 28 (47%)               | 8 (53%)                    | 0.64    |
| Females         | 32 (53%)               | 7 (47%)                    |         |

| Comorbid conditions | Survivors | Non-survivors | P Value |
|---------------------|-----------|---------------|---------|
| Diabetes            | 34 (57%)  | 8 (53%)       | 0.81    |
| Hypertension        | 7 (12%)   | 2 (13%)       | 0.9     |
| Tobacco Use         | 32 (53%)  | 8 (53%)       | 1.0     |
| Diabetes            | 26 (43%)  | 7 (47%)       | 0.81    |

| Source of sepsis   | Survivors | Non-survivors | P Value |
|---------------------|-----------|---------------|---------|
| Pulmonary           | 35 (58%)  | 8 (53%)       | 0.72    |
| Abdomen             | 15 (25%)  | 4 (26%)       | 0.78    |
| Skin/Catheter site  | 14 (23%)  | 4 (26%)       | 0.42    |
| Others              | 6 (10%)   | 2 (13%)       | 0.84    |

| Organism | Survivors | Non-survivors | P Value |
|----------|-----------|---------------|---------|
| G+ve     | 43 (71%)  | 13 (80%)      | 0.19    |
| G-ve     | 39 (65%)  | 11 (73%)      | 0.46    |
| Others   | 4 (7%)    | 1 (7%)        | 0.69    |

| Vitals  | Survivors | Non-survivors | P Value |
|---------|-----------|---------------|---------|
| Pulse   | 113.5 ± 6.3 | 117.8 ± 9.3   | 0.053 |
| MAP     | 95.3 ± 11.2 | 82.9 ± 9.2    | 0.005 |
| Temperature (C) | 38.4 ± 1.5 | 38.8 ± 1.4  | 0.7 |
| ACR (mg/gm creatinine) | 30.2 ± 35.7 | 55.1 ± 20.5 | 0.006 |

| UTI, urinary tract infection; G+ve, gram-positive; G-ve, gram-negative; MAP, mean arterial pressure. |

Assessment of ACR in Survivors and Non-Survivors

It was significantly higher in non-survivor than survivors (55.1 ± 20.5 versus 30.2 ± 35.7, p = 0.006) respectively.

ACR as a Marker for endothelial dysfunction in predicting Mortality

ACR ≥ 40 (mg/ gm creatinine) was the cut-off point for predicting mortality with a sensitivity of 90.7% and specificity of 71.8% with total accuracy of 66% and AUC 0.75 (CI 0.62- 0.88).

Figure 1: ROC curve of ACR

Evaluation of the severity of illness during ICU stay using SOFA scoring system

All SOFA scores (initial, mean and highest) were significantly elevated in non-survivors compared to survivors. Mean APACHE II score was significantly higher in non-survivors than survivor groups (21.4 versus 10.8, p < 0.001).

Table 3: SOFA and APACHE II scores of survivors and non-survivors groups

|                  | Survivors | Non-Survivors | P-value |
|------------------|-----------|---------------|---------|
| Initial SOFA     | 1.79 ± 1.38 | 8.73 ± 3.06   | < 0.001 |
| Mean SOFA        | 1.91 ± 2.15 | 10.36 ± 3.34  | < 0.001 |
| Highest SOFA     | 2 ± 2.37   | 12 ± 3.82     | < 0.001 |
| APACHE II        | 10.94 ± 7.16 | 21.4 ± 10.49  | < 0.001 |

SOFA, Sequential Organ Failure Assessment score; APACHE, Acute Physiology and Chronic Health Evaluation.

Correlation of ACR with highest SOFA values

A significant positive correlation between ACR and Highest SOFA values was observed (r = 0.30, p < 0.05).

Discussion

Endothelial dysfunction plays a major role in the pathophysiology of septic shock and organ dysfunction, and has been suggested to be a predictor of mortality in sepsis. Thus, early detection of endothelial dysfunction could be of great interest to adapt treatment in the initial stage of sepsis. Current therapeutics used in sepsis mostly aim at controlling inflammation, vascular function and coagulation [9].

Microalbuminuria may serve as a means of indirectly quantifying these changes in systemic vascular permeability. Assay of the amount of albumin excreted in a random urine sample expressed as albumin creatinine ratio (ACR), is a simple, validated and reliable test [10]. Levels of microalbuminuria increase within hours of an inflammatory insult as compared to relatively delayed inductions of procalcitonin (PCT) and C-reactive protein (CRP) [11]. Several studies in various groups of critically ill patients have unequivocally established microalbuminuria as a significant prognostic marker of morbidity and mortality in the ICU [12].

The present study included 75 patients that recently admitted to ICU with a diagnosis of sepsis with mean age 63.2 ± 14.8, 36 males (48%) and 56%
had diabetes. Fifteen patients (20%) died within 28-days of hospital stay. The mean age of non-survivors was higher than survivors. Also, the MAP was significantly lower in non-survivors than survivors who are expected for non-survivors to be more critically ill with significantly higher APACHE II and SOFA scores.

ACR values were significantly higher in non-survivor (55.1 ± 20.5 versus 30.2 ± 35.7, p = 0.006) than in survivors. The ROC curve analysis revealed the optimal ACR cut-off point for predicting mortality was 40 mg/gm creatinine with a sensitivity of 90.7% and specificity of 71.8% with total accuracy of 66%, and AUC 0.75 (CI 0.62-0.88). Also, the elevated ACR in non-survivors was positively correlated to elevation in SOFA score.

In a study by Surupa et al., [13], it was concluded that microalbuminuria is strongly predictive of ICU survival. The median albumin/creatinine ratio (ACR) [154 (IQR 114.4-395.3)] was significantly higher (P = 0.004) in non-survivors (n = 13) as compared to survivors [50.8 (IQR 21.6-144.7)]. The ROC curve analysis revealed that ACR at a cut-off of 99.6 mg/g could predict ICU mortality with the sensitivity of 85%, specificity of 68% with an NPV of 97% and PPV of 30%.

This different cut-off level of ACR in Surupa et al. could be explained by first, the timing of measuring ACR that was at 24 hours in that study while in our study it was within first 6 hours. Second, Surupa et al. included more critically ill patient as around two-thirds of patients were in severe sepsis and septic shock.

De Gaudio et al. evaluated 55 post-operative patients developed sepsis during ICU course and found that Post-operative patients developing sepsis, unlike those with an uncomplicated postoperative evolution, showed an increase in glomerular permeability which was revealed by ACR. The increase in the ACR was positively correlated to the increase in SOFA score, while it had no relation to the PaO2/FIO2 ratio (14). We found the same positive correlation between ACR and SOFA in our study that confirms the strong agreement between ACR and clinical scoring systems in septic patients.

In a study by Gosling et al., Microalbuminuria was compared with mortality, APACHE II and SAP II scores. Median (95% confidence interval) ACR at admission for survivors (n = 115) and non-survivors (n = 25) were 37.2 (31.9-57.5) and 157.5 (70.8-361.1) mg/g, respectively (p = 0.0002). For 92 surgical, trauma, and burn patients, of whom 81 survived, ACR of > 52.2 mg/gm gave a sensitivity for the death of 100%, specificity of 59%, the positive predictive value of 25%, and negative predictive value of 100%. Mortality probability receiver operator characteristic curve areas for ACR, APACHE II, and SAP II were 0.843 (p < .0001), 0.793 (p = 0.0004), and 0.770 (p = 0.0017), respectively [15]. In this study (Gosling et al.), its cut-off level is much closer to our level in spite; it was used in a different category of patients. This may indicate the widespread possible benefit of ACR in different patient categories rather than only septic patients.

In Bhadade et al., significantly higher levels of microalbuminuria were found among patients with sepsis as compared to those without sepsis. The levels decreased in survivors with sepsis after 24 hours, whereas they continued to remain almost at the same levels among those without sepsis. The change in microalbuminuria levels over 24 hours can be used to measure the effectiveness of therapy. Persistence of high levels or increasing trend of microalbuminuria levels over 24 hours was found to be a predictor of a poor outcome. A high level of microalbuminuria at 24 hours and increasing trend of microalbuminuria also predicted mortality better than APACHE II and SOFA scores [16]. The point of difference is that authors in this study measure ACR at 24 hours and not early as we did which may give earlier prognostic value in our study.

In a study by Thorevska et al., They confirmed a high prevalence of microalbuminuria in critically ill patients and suggested that an albumin- creatinine ratio ≥ 100 mg/g is an independent predictor of mortality and hospital stay [17].

Our study and other studies show that ACR is positively correlated with higher APACHE II and SOFA scores in critically ill patients, and it could be used as prognostic and mortality predictor. But at which cut-off level and when to be measured, it is different from study to another as some measure it after 24 hours while others measure it later. Also, some studies measure it in only medical cases (whether sepsis or septic patients) while others measure it in postoperative critically ill patient or even non-septic critically ill patient. Our study tried to standardise the timing and also collecting certain category of patient, to give clear data regarding prognosis in early (within 6 hours of ICU admission) diagnosis of sepsis.

In conclusion, ACR was a predictor of hospital mortality in septic patients admitted to ICU and could be used within 6 hours of admission to categorise patient with higher predicted mortality that is matched with clinical scoring systems to receive a higher level of care.

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