ORIGINAL ARTICLE

MICROALBUMINURIA: AN INEXPENSIVE, NON INVASIVE BEDSIDE TOOL TO PREDICT OUTCOME IN CRITICALLY ILL PATIENTS

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ABSTRACT

This study was conducted to evaluate whether microalbuminuria on admission and after 24 hrs of admission to intensive care unit (ICU) predicts outcome as well as the Acute Physiology and Chronic Health Evaluation (APACHE) II severity illness score, the current accepted method of doing so. The study was carried out in a 20 bed mixed medical-surgical ICU of a tertiary care hospital. Of 525 consecutive adult patients with ICU stay of more than 24 hrs, 238 were included for the study. Patients with pregnancy, menstruation, anuria, macroscopic hematuria, urinary tract infection, marked proteinuria due to renal and post-renal structural diseases, were excluded. Spot urine samples were collected on admission to ICU and 24 hrs thereafter. Urine albumin-creatinine ratio (ACR) was measured on ICU admission (ACR1) and after 24 hrs (ACR2) and expressed in mg/g. Patient demographics were noted on admission. For disease severity scoring, APACHE II scores were calculated. Each patient was followed up throughout their ICU stay for a maximum of 28 days and the following outcome data were obtained: ICU length of stay and ICU mortality. Of the 238 patients, 196 survived while 42 patients died in the ICU. Non-survivors had a significantly higher median ACR2 [162.7 mg/g (IQR 69.5 - 344.3)] in comparison to the survivors who had a median ACR2 = 54.4 mg/g (IQR 19.0 - 129.1) ($P < 0.0001$). The median ACR1 [161.0 mg/g (IQR 29.0 - 369.3)] of non-survivors was higher than the median ACR1 [80.4 mg/g (IQR 35.1 - 167.6)] of survivors but failed to reach statistical significance ($P = 0.0948$). In a receiver operating characteristic curve (ROC) analysis, ACR2 emerged as the best indicator of mortality [(area under curve (AUC) of ACR2 = 0.71 > AUC (ACR1) = 0.58 > AUC (Δ ACR) = 0.55] similar to the currently used APACHE II scores (AUC = 0.78) ($P = 0.3$). At a cutoff of 101 mg/g, ACR2 had a sensitivity of 69%, specificity of 67%, positive predictive value of 31% and a negative predictive value of 91% for predicting mortality in the critically ill patients. Absence of significant microalbuminuria at 24 hrs of ICU admission may help to predict survival in the ICU.

KEY WORDS

Microalbuminuria, Mortality, Critically ill, Severity of Illness, Intensive Care Units, Outcome.

INTRODUCTION

In critical care units, prediction of outcome of patients is of vital importance to the intensivist. It allows planning of early

aggressive therapeutic interventions, optimum resource allocation and appropriate counseling of the family and/ or patient. A number of prognostication tools have been developed for the above purpose. The two widely adopted systems to predict mortality are the Acute Physiology and Chronic Health Evaluation (APACHE) II and the Simplified Acute Physiology Score (SAP) II scores (1, 2). Though useful to evaluate outcome, these cumbersome tools are of limited use in day to day practice. Prognostication measures employed in the intensive care unit (ICU) should ideally detect short term changes in critical illnesses and also reflect the impact of early

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therapeutic interventions on the outcome of a patient. Sensitive, inexpensive and dynamic prognostic markers which generate rapid and reliable results are therefore desirable in the ICU setting.

Critical illnesses are more than often characterized by the systemic inflammatory response syndrome (SIRS) - the host response to an acute insult. SIRS is a common finding in the ICU patient which, when severe, can lead to multiple organ failure and finally death (3). A severe and sustained inflammatory reaction induces rapid and profound changes in the endothelium resulting in loss of barrier integrity leading to systemic capillary leak (4, 5). In the kidneys this manifests as altered glomerular permeability culminating in increased renal albumin excretion in the urine (6). Microalbuminuria is found to occur in several acute inflammatory states such as burns, pancreatitis, meningitis, ischemia reperfusion injury, acute myocardial infarction, and cerebral ischemia (8-13). Increased levels of microalbuminuria on admission have been shown to be associated with indicators of organ dysfunction such as pO_2/FiO_2 ratio, serum creatinine, duration of mechanical ventilation and vasopressor use and, with physiological scoring systems. (14, 19-21). Microalbuminuria has been found to be a sensitive predictor of outcome in critically ill patients early after ICU admission in several clinical situations (15-23).

Effective protocol-directed therapeutic intervention like fluid resuscitation, antibiotics, inotrope and vasopressor use and tight glycemic control, administered within the initial hours of ICU admission has been shown to attenuate endothelial dysfunction and improve survival (24). We surmised that degree of microalbuminuria after 24 hrs of ICU admission would reflect the degree of ongoing endothelial dysfunction after goal-directed therapy. It could predict mortality in critically ill patients, better than microalbuminuria at admission, as it would reflect the host response to early therapeutic interventions.

MATERIALS AND METHODS

Consecutive adult patients admitted to a 20-bed medical-surgical ICU in a private tertiary care hospital were recruited between January 2007 and May 2008. The local research and ethics committee, who waived formal informed consent, in view of the observational nature of the study, approved the study protocol. All adult patients (> 18 years old) with a stay in the ICU for more than 24 hrs were included. It was determined *a priori* that patients would be excluded if they had confounding factors such as anuria, macroscopic hematuria, or preexisting chronic kidney disease. Female patients with menstruation or

pregnancy were also excluded. Retrospectively, patients with marked proteinuria due to renal and post renal causes, for example urinary tract infection and previously undiagnosed chronic renal failure were excluded.

The study protocol was designed as per recommendations of the Standards for Reporting of Diagnostic Accuracy (STARD) steering committee (25).

Patient Demography: On admission, the following data was collected for each patient: age; gender; date and time of admission; patient's clinical classification (medical or surgical), provisional diagnosis; co-morbid conditions such as diabetes, hypertension and chronic kidney disease. For disease severity scoring, APACHE II scores were calculated from data collected during the first 24 hrs following ICU admission (1). Each patient was followed up throughout their ICU stay for a maximum of 28 days and the following outcome data were obtained: ICU length of stay and mortality.

At the time of admission and again after 24 hrs, patients were examined for vital signs and symptoms of SIRS, organ failure and/or infection. Clinical and laboratory data were collected; cultures sent and antibiotics received within 24 hrs of admission were also noted. Infection was defined by presence of clinical signs of systemic inflammatory response syndrome along with an identified source of infection and/or positive blood cultures. The American College of Chest Physicians/ Society of Critical Care Medicine (ACCP/SCCM) Consensus Conference definitions were used to identify patients with SIRS, SIRS with organ dysfunction, sepsis (SIRS with infection), severe sepsis (sepsis with organ dysfunction) and septic shock (sepsis with hypotension on vasopressor support) (26, 27).

The following therapeutic interventions that were received for the first 24 hrs of ICU admission were noted: insulin, volume of fluids received, inotropes, vasopressors, steroids, activated protein C, and antibiotics. Other clinical and laboratory data were also documented: on admission serum creatinine, mg/dl; total duration of mechanical ventilation, days; mean of capillary blood glucose recordings over the first 24 hrs of ICU admission, mg/dl. From the above data, the following were calculated: on admission estimated glomerular filtration rate (GFR) using the modified diet in renal disease (MDRD) formula, ml/min.

Sample Collection and Laboratory Measurements: Spot urine samples were collected by ICU nurses within 6 hrs of admission and again at 24 hrs, for quantification of ACR, which

were referred to as ACR1 and ACR2 respectively. Urine samples were received in the biochemistry lab and stored at -20°C till analysis. The ACR test had already been in general use in the lab before the study started. Urinary microalbumin was measured using the immunoturbidimetric method (Dimension RxL Max, Dade Behring Inc., USA). Urinary creatinine was measured using a modified kinetic Jaffe reaction (Dimension RxL Max, Dade Behring Inc., USA). The methods covered an analytical range of 1.3-100 mg/L for microalbumin and 0-20 mg/dl for creatinine. Results that fell above the analytical range were diluted appropriately and rerun. Microalbuminuria, expressed as ACR in mg/g, is defined as ACR of less than 300 mg/g. The ratio has a conventional cut off value of 30 mg/g in the healthy reference population. The reference range for mortality prediction in critically ill population is yet to be determined.

Reproducibility of urine microalbumin creatinine measurements:

The assays were validated by performing reproducibility checks using urine chemistry quality control (QC) materials from BioRad Inc., USA. Day-to-day coefficient of variation (CV %) were calculated at two significant levels of measurement, derived from QC data values obtained during each run. The mean and standard deviation (in parentheses) of microalbumin for the QC samples (two different lots) assayed during the study period were 9.4 (0.68) and 11 (1.34) mg/L at lower level and 62 (2.25) and 64 (2.69) mg/L at higher level giving satisfactory coefficients of variation (CVs) of 7.3 %, 12.0% for lower level and 4.9%, 4.2% for higher level respectively. For urine creatinine, the mean (SD) were 62.4 (1.4) and 61.9 (1.24) mg/dL at lower level and 133 (2.74) and 143 (8.7) mg/dL at higher level giving satisfactory coefficients of variation (CVs) of 2.3 %, 2.0% for lower level and 2.1%, 6.1% for higher level respectively.

Data Collection and Analysis: An intensivist who documented the clinical profile and the investigator who collated the laboratory results were blinded to each others data. Trend of microalbuminuria was assessed from the change of ACR value within 6 hrs of admission (ACR1) to the ACR value at 24 hrs (ACR2) in both groups of patients. The difference of ACR2 from ACR1 ($\Delta \text{ACR} = \text{ACR1} - \text{ACR2}$) was calculated.

The Kolmogorov-Smirnov test was used to assess sample distributions. The results are presented as the median and 25th/75th percentiles (inter quartile range, IQR) (ACR data non-normally distributed). To compare two independent samples we used the Mann-Whitney U-test (data non-normally distributed). We used the chi-square test to compare

proportions. The nonparametric Spearman ranked sign procedure was used to assess the significance of associations. The ranked Spearman statistic is presented with the 95% confidence interval and the associated *P* value. *P* < 0.05 was considered significant. Receiver operating characteristic (ROC) curves and the areas under the respective curve were calculated for ACR1, ACR2, ΔACR and APACHE II score. The discriminating powers of ACR variables (ACR1, ACR2, ΔACR) for the prediction of mortality were assessed by the area under ROC curves. From the ROC curves diagnostic accuracy of the variables were determined by calculating their respective area under the curve (AUC).

RESULTS

Of 525 patients, with an ICU stay for >24 hrs, who were recruited during the study period, a total of 238 patients were studied after exclusions (reasons for exclusion summarized in Figure 1). Patient demography, medical/surgical classification, number of patients with diabetes and hypertension, median APACHE II score, median ACR at ICU admission (ACR1) and at 24 hrs (ACR2), median change of ACR from admission to 24 hrs (ΔACR) and median duration of ICU stay, number of survivors and non survivors are summarized in Table 1.

Fig 1: Number of patients recruited and reasons for exclusion

The study population of 238 patients was screened for the presence of SIRS, organ failure, and shock. Within the first 24 hrs of ICU admission, 208 patients (87%) were found to have SIRS, of which, 63 patients had organ failure and 34 patients had organ failure with shock requiring vasopressor support. Sepsis was the most common cause of SIRS (44%) in the study population. On admission, 56 patients had ACR < 30 mg/g, 76 patients had microalbuminuria (ACR between 30 - 300 mg/g), while 106 patients had ACR > 300 mg/g. At 24

Table 1: Patient demography, medical/surgical classification, number of patients with diabetes and hypertension, median APACHE II score, median albumin-creatinine ratio within 6 hrs of ICU admission (ACR1) and at 24 hrs (ACR2), median change of albumin-creatinine ratio from admission to 24 hrs (Δ ACR), median duration of ICU stay and number of survivors and non-survivors

No. of patients	238
Median age, yrs (IQR)	62 (51 – 72)
Male (%): Female (%)	143 (60%): 95 (40%)
Medical (%): Surgical (%)	226 (95%):12 (5%)
Patients with diabetes mellitus (%)	65 (27%)
Patients with hypertension (%)	96 (40%)
Median APACHE II (IQR)	15 (10 – 21)
Median ACR1 (mg/g) (IQR)	90.4 (34.2-207.2)
Median ACR2 (mg/g) (IQR)	68.2 (22.6-150.9)
Median Δ ACR (mg/g) (IQR)	22.4 (-6.3 to 87.5)
Median duration of ICU stay, days (IQR)	4 (3 – 7)
Survivors (%)	196 (82%)
Non-survivors (%)	42 (18%)

hrs of admission, 79 patients had ACR < 30 mg/g, 128 patients had microalbuminuria while 31 patients had ACR > 300 mg/g.

A comparison between the survivors and non-survivors showed that the non-survivors had a significantly higher median APACHE II score and median duration of ICU stay as expected. ACR2 were significantly higher in the patients who died on the ICU in comparison to those who survived. There was however no significant difference in the ACR1 and Δ ACR value between the two groups (Table 2). There was a significant decrease in the median level of ACR at admission to the median level of ACR at 24 hrs in the survivors. However, the median ACR for patients who died on the ICU remained unchanged 24 hrs after ICU admission (Fig 2).

Fig 2: Change in urine albumin on intensive care unit admission (albumin-creatinine ratio [ACR] 1) and after 24 hrs (ACR 2) in survivors and non-survivors Wilcoxon's signed rank test, $p < 0.05$ was considered significant

For all patients, ACR1 and ACR2 were significantly associated with increasing age, Δ ACR also showed a positive correlation. Both ACR1 and ACR2 were positively associated with the duration of ICU stay. Duration of mechanical ventilation was strongly correlated with ACR1, ACR2 and Δ ACR. On admission serum creatinine was positively associated with ACR1 but failed to correlate with ACR2. Both ACR1 and ACR2 were negatively associated with estimated GFR (MDRD) on admission. ACR1, ACR2 and Δ ACR were strongly correlated with APACHE II scores (Table 3).

For the entire population, the area under the ROC curves for mortality was highest for APACHE II (area under the curve 0.78), then ACR 2 (0.71), followed by ACR 1 (0.58), and Δ

Table 2: Comparison of demography, median ICU stay, median APACHE II score, median levels of urine albumin-creatinine ratio (ACR) on intensive care unit admission (ACR1) and after 24 hrs (ACR2) and Δ ACR (ACR1 – ACR2) between survivors and non-survivors

	Survivors	Non survivors	*P value
Number of patients	196	42	
Median Age(IQR), years	63 (50-72)	60 (53-73)	
Male:Female ratio	122:74	21:21	
Median ICU stay (IQR), days	4 (3-6)	5 (3-9)	0.0027
Median APACHE II score (IQR)	14 (10-19)	24 (17-28)	<0.0001
Median ACR1(IQR), mg/g	80.4 (35.1 - 167.6)	161.0 (29.0 - 369.3)	0.0948
Median ACR2 (IQR), mg/g	54.4 (19.0 - 129.1)	162.7 (69.5 - 344.3)	<0.0001
Median Δ ACR (IQR), mg/g	22.5 (-1.9 to 78.3)	12.7 (-46.1 to 136.2)	0.3608

(Mann Whitney test, * P < 0.05 was considered significant)

Table 3: Associations of urine albumin with age, intensive care unit (ICU) stay, duration of mechanical ventilation, serum creatinine, estimated glomerular filtration rate (eGFR), for all patients (Spearman ranked correlations)

	ACR1, mg/g	ACR2, mg/g	Δ ACR, mg/g
Age, years	*P< 0.0001 **rs= 0.28	P= 0.0091 rs= 0.24	P=0.09 rs=0.11
Length of ICU stay, days	P=0.043 rs=0.131	P=0.034 rs=0.137	P=0.81 rs=0.015
Mechanical Ventilation, days	P< 0.0001 rs=0.28	P=0.0001 rs=0.26	P=0.04 rs=0.13
Serum creatinine, mg/dl (on admission)	P=0.036 rs=0.14	P=0.062 rs=0.12	P=0.5 rs=0.043
eGFR (MDRD), ml/min/1.73 m ² (on admission)	P=0.0032 rs= -0.20	P=0.0091 rs= -0.17	P=0.36 rs= -0.060
APACHE II Score (Day1)	P< 0.0001 rs= 0.39	P< 0.0001 rs= 0.45	P=0.03 rs=0.14

*P< 0.05 was considered significant, **rs, ranked Spearman, ACR= albumin-creatinine ratio

ACR (0.55) (Fig 3). There was no significant difference between the area under the curve for APACHE II and ACR2 (P=0.3). To estimate the diagnostic accuracy of the urine ACR in the prediction of ICU mortality, the sensitivity and specificity were determined using the conventional cut-off level of microalbuminuria at 30 mg/g. At this value, ACR2 had a sensitivity of 88% with a negative predictive value of 94% for

the prediction of ICU death. However, the positive predictive value for death was 23 %. To explore a wider clinical utility of the ACR test to include a larger subset of the population, the cut-off was increased to 101 mg/dl. At this cut-off, the negative predictive value was 91% for ICU death; however, positive predictive value was 31% (Table 4, Fig 3).

DISCUSSION

Microalbuminuria was found to be prevalent in a broad spectrum of critically ill patients studied. In these patients, 76% had ACR > 30 mg/g on ICU admission and it persisted in 67% at 24 hrs. At 24 hrs, 43% of the patients had ACR levels of more than 101 mg/g. The reason for increased incidence of microalbuminuria in critically ill patients is probably the result of widespread endothelial dysfunction arising from the effects of cytokines, and other inflammatory mediators, released during the intense inflammatory responses that are associated with critical illnesses (28). The effects of disruption of the integrity of the endothelial barrier is manifested as altered glomerular endothelial permeability in the kidneys, allowing 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. The degree of albuminuria is dependent on the intensity of the inflammatory responses, and therefore microalbuminuria reflects disease severity. This probably explains the high degree of positive association observed between microalbuminuria and APACHE II scores, both of which quantify the acute physiologic response to acute inflammation.

Fig 3: Comparison of Receiver Operating Characteristic (ROC) curves of APACHE II, ACR1, ACR2 and the change of ACR2 from ACR1 (Δ ACR) to predict mortality in patients admitted to intensive care unit. APACHE II had the highest area under the curve (0.78) followed by ACR2 (0.71), ACR1 (0.58) and Δ ACR (0.55).

Table 4: Prediction of intensive care unit (ICU) mortality after 24 hrs of admission for albumin-creatinine ratio (ACR2) at two different cutoff values

ACR2 Cut-off mg/g	Sensitivity %	Specificity %	Positive Predictive Value of Death, %	Negative Predictive Value of Death, %	% of Patients Below Cutoff
≤ 30	88	38	23	94	30
≤ 101	69	67	31	91	57

The ICU prognostic scores such as the APACHE II illness severity score, requires cumbersome data collection and employs complex statistical analyses to predict mortality. They are usually based on variables recorded within 24 hrs of ICU admission and results are collated only at the end of 24 hrs. Assay of the amount of albumin excreted in urine, expressed as ACR (29), is a simple, validated, reliable and inexpensive test that adjusts for variable urine concentrations among patients and obviates the need for a timed urine collection. Moreover it can be performed at the patient's bedside using a point-of-care device and results can be obtained as early as 15 min (21). Microalbuminuria would be an ideal tool for the early and accurate identification of patients with high risk of morbidity and mortality. This would allow the intensivist to triage and optimize aggressive and sometimes expensive therapeutic interventions in patients most likely to benefit and to curb use in those who are unlikely to do so, especially in situations of financial constraints. Measurement of ACR can guide optimum allocation of resources, counseling of family and/or patient and opportune triaging to the wards, too.

The study of Thorevska et al (20) showed that medical patients with an ACR value of more than 100 mg/g on ICU admission were 2.7 times more likely to die compared with those with ACR < 100 mg/g. A much lower cut-off value of 2.9 mg/mmol (25.6 mg/g) at 6 hrs of ICU admission was decided as optimum by Gosling et al (21) to predict mortality in a mixed medical-surgical ICU population. In our study, ROC curve analysis revealed that measurement of ACR at 24 hrs of ICU admission was a better predictor of death compared to that on admission and fared as well as the time-tested APACHE II scores. As per the conventional definition of microalbuminuria, (i.e. a cut-off of 30mg/g), ACR2 had good negative predictive value (94%) of ICU mortality. However, agreeing with the suggestions of Molnar et al (30), we too felt that a higher cut-off value is desirable in a general ICU setting, as patients do have multiple medical problems, such as age (>40 years), diabetes, hypertension, smoking, and postoperative condition, each of which could independently alter levels of microalbuminuria in the ICU (32). A value of 101 mg/g at 24 hrs of ICU admission was therefore chosen, which predicted mortality with a negative predictive value of 91%. The good negative predictive value

of the test could be utilized to identify patients who are likely to survive in the ICU.

Non survivors had higher levels of microalbuminuria on ICU admission when compared to survivors. Further, there was no significant decrease in median levels of microalbuminuria at 24 hrs of ICU admission in the non-survivors. On the contrary, the median ACR2 fell significantly in survivors. This finding corroborates with previous studies of Abid et al (18) and Gosling et al (21), indicating that failure of ACR to decline is associated with increased ICU mortality. The choice of 24 hrs as the timing for sampling was designed to assess the effects of goal directed therapy. The assessment of prognosis at 24 hrs of admission in the ICU, referred to as the 'silver day' in sepsis literature, is seemingly important to monitor the efficacy of goal directed therapy with respect to survival. APACHE scoring is also done at 24 hrs. A decreasing trend of microalbuminuria at 24 hrs of ICU admission may indicate an attenuation of endothelial dysfunction and improvement in organ function – a positive response to the initial therapy.

The study was limited by the inclusion of patients with diabetes and hypertension and/or patients on angiotensin converting enzyme (ACE) inhibitor/ angiotensin II receptor blockers (ARB) therapy, all of which could singularly confound microalbuminuria levels (31). However, these patients were included, as in studies by Gosling et al (21) and Thorevska et al (20), since their exclusion would have made the study population less representative of the real life scenario. Moreover, in acutely ill diabetic and hypertensive patients, microalbuminuria which might have been present due to underlying kidney affliction is likely to be exaggerated in the presence of acute inflammation. Secondly, critically ill patients with suspected or clinically evident confounding factors such as chronic kidney disease, diabetic nephropathy, or other renal and post renal diseases in whom urine albumin excretion could be attributed to structural changes of the glomerulus or the tubules were excluded from the study. This is a limitation one would have to keep in mind when considering the universal applicability of microalbuminuria as a prognostic indicator. Thirdly, our study cohort was predominantly medical (>90%); and therefore it would not be appropriate to extrapolate the

results to a surgical ICU population immediately. Future studies could be directed towards evaluating the use microalbuminuria in monitoring the efficacy of individual therapeutic interventions which impact survival, in critically ill patients.

Microalbuminuria at 24 hrs of ICU admission is as good a predictor of mortality as the APACHE II score, in critically ill patients. It is associated with age, length of ICU stay, duration of mechanical ventilation, and estimated glomerular filtration rate. The study indicated that microalbuminuria; a simple, noninvasive and inexpensive bedside tool could be effectively utilized to identify patients who are likely to survive in the ICU.

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