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Research Article

ANALYSIS OF MICROALBUMINURIA TO PREDICT SENSITIVITY AND OUTCOME OF TRAUMATIC INTENSIVE CARE UNIT PATIENTS

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ABSTRACT

In this prospective observational study, urine samples were collected on admission (within 06 hours) and at 24 hours in ICU. Urine albumin to creatinine ratio (ACR) was measured on ICU admission (ACR1) and at 24 hours (ACR2) along with APACHE II scores, ICU length of stay and ICU mortality. Out of 99 patients in ICU, 73 survived while 16 patients died. All the parameters like ACR1, ACR2, ACR, APACHI II score and total hospital stay were higher in non-survivors as compare to survivors and show significant difference. To estimate the diagnostic accuracy, cut-off value of ACR2, if considered below than 30 mg/g, total 03 patients are covered with 95.9% sensitivity and 100% specificity, however if considered below 100 mg/g, total 54 patients are covered with 23.3% sensitivity and 92.3% specificity. In conclusion, the absence of significant microalbuminuria at 24 hours of ICU admission may help to predict severity as well as the outcome in the ICU patients.

INTRODUCTION

Early prediction of outcome or severity of patients has the significant importance to the clinician in critical care units. It helps to plan the therapeutic interventions early, proper resource allocation and appropriate counseling of the patient as well as their family members (Godijn *et al*. 2014). Out of several number of tools to measure the outcome/severity of critically ill patients, the Acute Physiology and Chronic Health Evaluation (APACHE) II and the Simplified Acute Physiology Score (SAP) II scores are the common one (Knaus *et al*. 1985; Lemeshow *et al*. 1987). But nowadays, these tools have shown limitations of their own. Therefore a reliable fast and inexpensive prognostic marker with high sensitivity is desirable in the ICU setting. In intensive care unit (ICU), an ideal prognostic marker should ideally detect any minor changes/improvement in critical ill patients and may also reflect the therapeutic impact on the outcome of a patient early.

Systemic inflammatory response syndrome (SIRS) often characterized in critical ill patients in ICU, can lead to multiple organ failure and mortality (Davies *et al*. 1997). These severe and sustained inflammatory reactions may alter the barrier integrity of endothelium, leading to systemic capillary leak (William 2003; Fishel *et al*. 2003). In this condition, the kidney leads to increased renal albumin excretion in the urine due to altered glomerular permeability (Jensen *et al*. 1995). This abnormality also called as "Microalbuminuria" mainly occurs in several acute inflammatory states such as severely injured patient, burns, pancreatitis, ischemia reperfusion injury, meningitis, cerebral ischemia and acute myocardial infarction (Shearman *et al*. 1989; Gosling *et al*. 1991; Gosling *et al*. 1994; Roine 1993; Berton *et al*. 1997; Yew *et al*. 2006). Early indication of microalbuminuria condition on admission has been shown to be associated with organ dysfunction (Gaudio *et al*. 1999; Gosling *et al*. 2003; Thorevska *et al*. 2003; Gosling *et al*. 2006).

Few preliminary studies examined the use of albuminuria in the intensive care as a prognostic marker. In 2006, a study by Gosling suggested urine albumin to predict ICU mortality rate as well as inotrope requirement better than APACHE II and SOFA scores (Gosling *et al*. 2006). A systematic review by Gopal *et al*. (2006), describes that albuminuria may hold promise to predict the severity of illness and mortality on the intensive care. However, it was concluded that future studies need to analyze the optimal timing as well as the threshold reference value for the ACR in the adult intensive care population (Gopal *et al*. 2006). Microalbuminuria has been found to be a sensitive predictor of outcome in critically ill patients early after ICU admission (Terao *et al*. 2007). Rivers *et al*. (2001) describe that the therapeutic intervention like fluid

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resuscitation, inotrope, antibiotics, use of vasopressor and the tight glycemic control, administered initially may attenuate the endothelial dysfunction and improve survival (Rivers *et al.* 2001).

In the present study, we aim to study that whether quantification of microalbuminuria on admission (within 06 hours) and at 24 hours of admission to ICU unit predicts the disease severity and mortality outcome of the admitted patients.

MATERIALS AND METHOD

In this prospective observational study, after obtaining ethical clearance from institutional ethical review committee, total 112 patients were included in this study from November 2014 to September 2015. After the informed consent, demographic data of all enrolled patients were collected. Whole study protocol was designed as per Standards for Reporting of Diagnostic Accuracy (STARD) steering committee. This study was conducted on patients admitted in 21 beded institutional ICU unit (Trauma).

All adult patients (> 18 years old) with a stay in the ICU for more than 24 hours were included. Patients would be excluded if they had confounding factors such as anuria, macroscopic hematuria, diabetes, hypertension or pre-existing chronic kidney disease. Female patients with menstruation or pregnancy were also excluded. Patients with marked proteinuria due to renal and post renal causes also were excluded.

All the patient demographical data were collected including the provisional diagnosis & patient's clinical classification (medical or surgical) was done. 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. For disease severity scoring, APACHE II scores were calculated from data collected during the first 24 hours following ICU admission. At the time of admission and again after 24 hours, patients were examined for vital signs and symptoms of SIRS, organ failure and/or infection. All the clinical and laboratory data were collected within 24 hours of admission were also noted. Infection was defined by the presence of clinical signs of systemic inflammatory response syndrome along with an identified source of infection and/or positive reports of blood cultures. The American College of Chest Physicians (ACCP) and Society of Critical Care Medicine (SCCM) 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).

Blood samples were collected initially to quantify the serum albumin, serum ferritin, haemoglobin. For quantification of urine albumin to creatinine ratio (ACR), urine samples were collected by ICU nurses within 06 hours (ACR1) of admission and at 24 hours (ACR2). The blood and urine samples stored at -20°C till analysis. Urinary microalbumin was quantified by using immunoturbidimetric method (Dimension RxL Max, Dade Behring Inc., USA). Urinary creatinine was quantified by using modified kinetic Jaffe reaction (Dimension RxL Max, Dade Behring Inc., USA). Microalbuminuria is defined as ACR of less than 300 mg/g.

Statistical Analysis

The Kolmogorov–Smirnov test was used to assess sample distributions. The results are presented as the mean± SD and median. Mann–Whitney U-test and chi-square test are used to compare two independent samples and to compare proportions respectively. The nonparametric Spearman ranked sign test was used to assess associations at 95% confidence interval. The P value < 0.05 was considered significant. Receiver operating characteristic (ROC) curves and area under the curve (AUC) was performed for ACR1, ACR2, ACR (ACR1-ACR2) and APACHE II score.

RESULTS

Of the 112 recruited patients, with an ICU stay for more than 24 hours, a total of 99 patients were studied after exclusions [reasons for exclusion summarized in Fig-1].

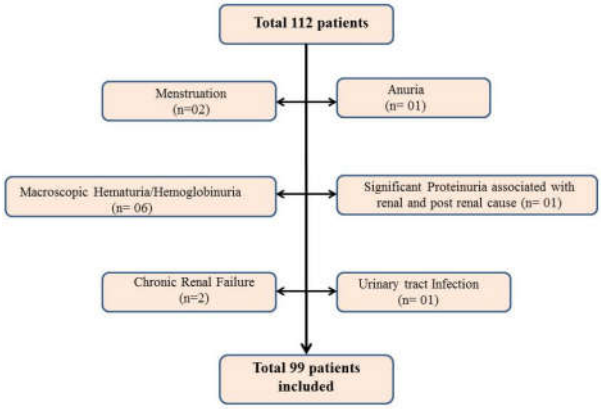

Figure-1 Total recruited patients with reasons for exclusion

All the patients demographical data are summarized in Table-1.

Table 1 Patients demographic data

Particulars	Survivors	Non-survivors	P-value
No. of patients	73	26	--
Median Age (in yrs)	35.0 (18-71)	35.5 (19-71)	---
Male : Female	44 :29	15 : 11	--
Hemoglobin Median (Mean±SD)	10.40 (10.52±1.32)	10.00 (10.41±1.40)	0.532
Serum Albumin Median (Mean±SD)	3.70(3.73±0.21)	3.70(3.75±0.20)	0.617
Serum Ferritin Median (Mean±SD)	115.00(106.59±37.10)	89.85(84.16±39.65)	0.094
ICU stay Median (Mean±SD)	4.00(4.15±1.06)	5.00(5.07±1.83)	0.038*
ACR1 Median (Mean±SD)	85.4(92.04±37.03)	193.2(186.66±120.33)	0.003*
ACR2 Median (Mean±SD)	75.3(75.41±30.95)	244.05(232.00±85.63)	<0.001*
ACR Median (Mean±SD)	21.1(16.63±45.77)	-31.05(-45.33±120.32)	0.008*
APACHI II Score Median (Mean±SD)	13(13.52±4.61)	26(27.30±4.54)	<0.001*

*Significant; Mann Whitney U test

The medical (n=92) ICU patients were higher than the surgical (n=07) ICU patients. All included patients were screened for the presence of SIRS, shock and organ failure. Within the first 24 hours of ICU admission, majority (n=62) of patients having SIRS, followed by 25 had organ failure and 12 patients had

organ failure with shock. Most common cause of SIRS (47%) was sepsis.

All the parameters like ACR1, ACR2 ACR, APACHI II Score and the total hospital stay were higher in non-survivors as compare to survivors and show the significant difference [Table 1].

Initially at the time of admission, only 10 patients had ACR < 30 mg/g followed by 14 patients had microalbuminuria (ACR between 30 - 300 mg/g) and 75 patients had ACR > 300 mg/g. Furthermore after 24 hours of admission, 59 patients had ACR < 30 mg/g, 21 patients had microalbuminuria while 19 patients had ACR > 300 mg/g. There was significant decrease in mean and median level of ACR at 06 hours to the mean and median level of ACR at 24 hours in the survivors. There was increase in mean and median ACR level at 06 hours to 24 hours for non-survivor patients; however insignificant statistical mean difference were found [Table/Fig-2].

Table 2 Change in ACR level after 24 hours between survivor and non-survivor patients admitted to ICU.

Particulars	ACR1 Median(Mean ± SD)	ACR2 Median(Mean ± SD)	P-value
Survivors	85.4(92.04±37.03)	75.3(75.41±30.95)	0.002*
Non-survivors	193.2(186.66±120.33)	244.05(232.00±85.63)	0.117

*Significant; Wilcoxon's Signed rank test

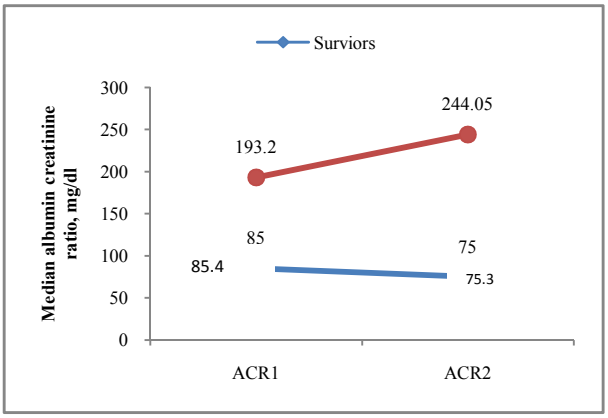

Figure-2 Change in ACR level after 24 hours between survivor and non-survivor patients admitted to ICU.

In all the patients the area under the ROC curves for mortality was highest for ACR (area under the curve 0.676*)*, then ACR 1 (0.303*)*, followed by ACR 2 (0.051), and APACHI II (0.55*)* [Fig-3]. Significant difference to all was found between the areas under the curve [Table/Fig-3].

Table 3 Area under curve (AUC) of ACR1, ACR2, ACR and APACHI II Score of patients admitted to ICU.

Particulars	Area under curve (AUC)	P-value
ACR1	0.303	0.003*
ACR2	0.051	<0.001*
ACR	0.676	0.008*
APACHI II Score	0.011	<0.001*

*Significant

The diagnostic accuracy of the urine ACR in the prediction of ICU mortality, sensitivity and specificity were determined using the conventional cut-off level of microalbuminuria at 30 mg/g. Cut-off value of ACR2, if considered below than 30 mg/g, total 03 patients are covered with 95.9% sensitivity and 100% specificity, however if considered below 100 mg/g, total 54 patients are covered with 23.3% sensitivity and 92.3% specificity[Fig-3].

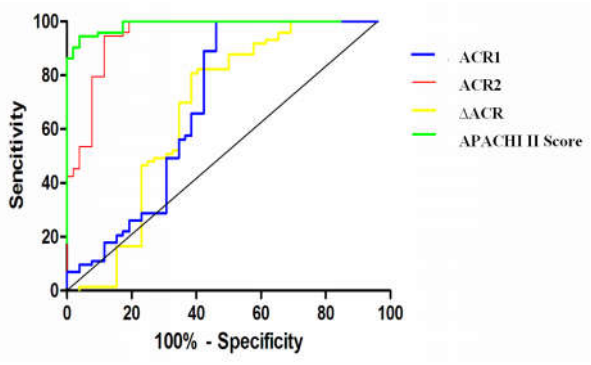

Figure-3 ROC curve of ACR1, ACR2, ACR and APACHI II Score to predict mortality in patients admitted to ICU.

The ACR1 and ACR were significantly associated with total ICU stay and show positive correlation. Both ACR1 and ACR2 were positively associated with the APACHI II Score [Table-4].

Table 4 Association of ACR with different parameters

Particulars	ACR1	ACR2	ACR
Age	P=0.990 r=-0.001	P=0.724 r=0.036	P=0.379 r=-0.089
Haemoglobin	P=0.147 r=-0.146	P=1.000 r=0.000	P=0.485 r=-0.071
Serum Albumin	P=0.991 r=0.001	P=0.271 r=0.112	P=0.400 r=-0.086
Serum Ferritin	P=0.062 r=0.189	P=0.467 r=-0.074	P=0.082 r=0.176
Total ICU stay	P<0.001* r=0.481	P=0.146 r=0.147	P=0.001* r=0.319
APACHI II Score	P<0.001* r=0.582	P<0.001* r=0.622	P=0.778 r=0.029

*Significant, Spearman ranked correlation

DISCUSSION

This study was conducted to analyse microalbuminuria to predict severity and mortality outcome of ICU patients. The effects of disruption of the endothelial integrity leads to altered glomerular endothelial permeability in the kidneys, allowing excess albumin to escape into the glomerular ultrafiltrate. This excess amount of albumin from the ultrafiltrate leading to increased excretion of albumin in the urine. The intensity of the inflammatory responses directly correlates with degree of albuminuria, and therefore microalbuminuria reflects disease severity.

Microalbuminuria was found to be prevalent in a broad spectrum of critically ill patients studied. In the present study, at the time of admission, only 10 patients had ACR < 30 mg/g followed by 14 patients had microalbuminuria and 75 patients had ACR > 300 mg/g. Furthermore after 24 hours of admission, 59 patients had ACR < 30 mg/g, 21 patients had microalbuminuria while 19 patients had ACR > 300 mg/g. This kind of observed data probably explains significant positive association between microalbuminuria and APACHE II scores, and might be able to predict the diseases severity and outcome of the patients.

Although, to predict the illness severity and mortality outcomes of ICU admitted patients by application of APACHI II score, requires huge data collection as well as complex statistical analyses, the quantification of urine albumin (ACR) is a simple, reliable and inexpensive test, can be performed at the patient's bedside (Bakker 1999). Therefore, microalbuminuria would be an ideal tool to predict the diseases severity as well as outcome mortality. Early quantification of ACR may able to decide the appropriate therapeutic interventions, optimize resource allocation, able to triaging to the wards as well as counselling of family and/or patient.,

According to Thorevska *et al*. (2003), patients with an ACR >100 mg/g on ICU were 2.7 times more chances to die compared with those with ACR < 100 mg/g. Furthermore as per Gosling *et al*. (2006), a much lower cut-off value of 25.6 mg/g at 6 hours of ICU admission able to predict mortality in a mixed medical/surgical ICU patients. Basu *et al*. (2010), in there study observed that the ROC curve analysis of ACR at 24 hours of ICU admission was a better predictor of death compared to ACR at 12 hours and the APACHE II scores. Beside the conventional definition of microalbuminuria, (i.e. a cutoff of 30 mg/g), Molnar *et al*. (2003), suggested value of 101 mg/g at 24 hours of ICU admission as better to predicted mortality with a negative predictive value of 91%. Also the microalbuminuria levels on ICU admission were higher in non survivors than the survivors. Furthermore, insignificant decrease in median levels of microalbuminuria at 24 hours of ICU admission in the non-survivors.

Our study findings shows the same finding as previously observed by Abid *et al*. (2001), Gosling *et al*. (2006) and Basu *et al*. (2010) indicating that no significant decrease in ACR at 24 hours was better predictor of high severity and mortality outcome of the critically ill patients. Also significant decrease in microalbuminuria at 24 hours of ICU admission may indicate correctness of endothelial dysfunction and improvement in organ function – that indicate a positive response to the initial therapy. However, Godijn *et al*. (2014), observed no significant difference in mean microalbuminuria at the first day between survivors versus non-survivors.

The present study indicated that microalbuminuria; a simple, non-invasive and inexpensive bedside tool could be efficiently used to identify patients who are likely to survive in the ICU. However, small sample size with predominantly medical (>90%) ICU patients are the limitation of the study.

CONCLUSION

This observational study was conducted to quantify the microalbuminuria at 06 hours and at 24 hours of ICU admitted patients. It can be concluded that the microalbuminuria was a simple, non-invasive and inexpensive bedside tool that could be efficiently used to identify mortality outcome in the ICU admitted patients. Though, the ACR in the urine is associated with severity of disease but can be used as a routine prognostic marker.

Conflict of interest

The authors have no conflict of interests in this article.

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