Microalbuminuria: As an Indicator of Sepsis and to Predict Mortality in Patients Admitted to Intensive Care Unit

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Original Article

Abstract
Background: Sepsis is an important healthcare concern in India as well as globally. This study shows how the level of microalbuminuria predict mortality of patients diagnosed with sepsis and those without sepsis.

Methods: In this study total 150 patients of which 75 patients belonging to each sepsis and non-sepsis group, with age >15 years admitted in Medical Intensive Care Unit (ICU) were enrolled. Microalbuminuria levels were analyzed at admission and after 24 hours after admission.

Results: Microalbuminuria levels were significantly high in patients with sepsis as compared to non sepsis. Microalbuminuria has highest sensitivity of 90 % and specificity of 98 % to differentiate between sepsis and non sepsis in comparison to APACHE II and SOFA scores.

Conclusion: Serial monitoring of bedside urine albumin-creatinine measurement might help in the early identification of patients with sepsis that requires early targeted therapy. The 24-hour ACR assessment predicts ICU survival and may have the potential to monitor the efficacy of therapeutic interventions delivered, such as fluid resuscitation, appropriate antibiotics, vasopressors, and ionotropes that affect the endothelium.

Introduction
Sepsis is still an important healthcare concern in India as well as globally, despite all the advances that have been made in medical therapeutics.1,2 Because of frequent delay in diagnosis, targeted therapies do not remain as effective.3,4 There is no standard method to diagnose sepsis early in patients who are critically ill. Sepsis is characterized by host defense response in which a variety of inflammatory mediators are released in the circulation.5 Increased capillary permeability leading to loss of barrier function is an important early event.6 In the kidneys, this is manifested by the glomeruli in the form of increased albuminuria.7 This study was conducted with the objective of assessing the difference between levels of microalbuminuria in sepsis and non sepsis patients. The change in the levels in the first 24 hours were also compared with two scores of sepsis i.e. APACHE II (Acute physiology and chronic health evaluation) and SOFA (Sequential Organ Failure Assessment) scores for the prediction of morbidity and mortality.

Material and Methods
75 patients of sepsis and 75 patients of non-sepsis admitted in ICU of SMS hospital were taken for study after applying inclusion and exclusion criteria.

Inclusion Criteria
• Patient admitted in Medical Intensive Care Unit (ICU) with age >15 years.

Exclusion Criteria
• Patient with anuria, macroscopic hematuria
• History of preexisting Chronic Kidney Disease (CKD) (patients on long-term renal replacement therapy, and/or sonologic features of chronic damage and/or history of glomerular filtration rate of <30 ml/min)
• Female patients with menstruation or pregnancy
• Patients with macroalbuminuria [more than 1+ protein on dipstick] due to renal and post renal causes, for example urinary tract infection
• New infection after 48 hours of ICU admission, i.e., nosocomial infection will be excluded.
• Known case of diabetes and hypertension

Comparison of SOFA score and APACHE score with Microalbuminuria within 6 hour of admission (ACR1), Micro albuminuria at 24 hour of admission (ACR2) and ∆ACR (ACR1-ACR2) was done between sepsis and non-sepsis group.

Results
We enrolled total 150 patients of which 75 patients belonged to sepsis group (Group A) and 75 in non-sepsis group (Group B). Mean age of group A was 50.90 ± 13.32 year and mean age of group B was 47.37 ± 14.37 year. In group A, there were 28 female and 47 male patients, mean SOFA score and mean APACHE II was 7.97 ± 3.802 and 14.53 ± 6.98 respectively. In group B, there were 24 females and 51 male patients and mean SOFA score and mean APACHE II was 5.23 ± 2.84 and 8.71 ± 5.18 respectively (Table 1).

Regarding mortality, out of 75 patients, 24 died in group A comparing with group B in which only 15 patients were succumbed to
As compared to PCT, levels of microalbuminuria increase within hours of inflammatory injury.\(^{13}\)

In our study, patients were divided into two groups: Patients without sepsis and patients with sepsis. In both groups, patients were comparable with respect to their demographic parameters.

In our study, in sepsis group 24 out of 75 patients died. Low mortality and low median APACHE II score in sepsis group in our study as compared to C Grion et al (32% vs 71% mortality, mean APACHE II score 14.53 ± 6.98 vs 24.4 ± 7.7) (Table 1).\(^{14}\) Bhadade RR et al had mortality and APACHE II score similar to our study.\(^{15}\)

In the current study, the mean levels for ACR1 in sepsis group was 152.01 ± 25.62 mg/g with standard deviation (SD) of 25.62 and in non-sepsis group mean level of ACR1 was 81.4 ± 18.63 mg/g with SD of 18.63. The levels of microalbuminuria were significantly high among the patients with sepsis at admission as compared to those without sepsis.

In our study, the microalbuminuria levels after 24 hours (ACR 2) and mean ∆ACR levels were found to decrease significantly among the patients with sepsis [ACR2=156.77 ± 58.64 mg/g, ∆ACR= -4.76 ± 36.68 mg/g] as compared to the patients without sepsis [ACR2=71.13 ± 28.60, ∆ACR= 10.26 ± 14.34]. After 24 hours, the decline in microalbuminuria could be attributed to the effect of treatment, protecting the glycocalyx layer and preventing rise in capillary permeability. From these observations one could infer that microalbuminuria can be used as a diagnostic tool as well as to check the efficacy of treatment. Singh A et al used microalbuminuria to document the ability to distinguish between sepsis and non-sepsis. In this current study, the area under curve (AUC) of Receiver Operating Characteristics (ROC) curve for differentiating sepsis and non-sepsis was highest for ACR1 (0.994) followed by ACR2 (0.919) and ∆ACR (0.553) (Figure 1).

ACR1 was found to have a differentiating value between sepsis and non-sepsis. In this current study, based on the area under ROC curve, the ability to distinguish between sepsis and non-sepsis was highest for ACR1 at a cutoff of >118.5 mg/g with a sensitivity of 90 % and specificity of 98 %. In our sepsis group the survivors had a mean ACR1 of 138.41 ± 17.65 mg/g which decreased to a value of 121.86 ± 28.34 mg/g after 24 hours with a mean ∆ACR value of 16.55 ± 16.83 mg/g. On the other hand, those who expired had a mean ACR1 of 180.92 ± 12.38 mg/g which increased to 230.96 ± 28.73 mg/g after 24 hours with a mean ∆ACR value of -50.04 ± 23.84 mg/g (Figure 2). Similar findings were found in studies done in past by Basu et al\(^{18,19}\) and Bhadade RR et al.\(^{15}\)

Our study has demonstrated using the area under the ROC curves for death. Microalbuminuria at 24 hour of admission (ACR2) and ∆ACR (ACR1-ACR2) between sepsis and non-sepsis group. In sepsis group mean SOFA score was 7.97 ± 3.802 and in non-sepsis group was 5.23 ± 2.84 and it was statistically significant (p value = 0.0001). In sepsis group mean APACHE II score was 14.53 ± 6.98 and in non-sepsis group was 8.71 ± 5.18 and it was statistically significant (p value = 0.0001).

In sepsis group initial level of microalbuminuria (ACR1) was 152.01 ± 25.62 mg/g which increased to 156.77 ± 58.64 mg/g (ACR2) after 24 hours of admission. Mean ∆ACR was -4.76 ± 36.69 mg/g in sepsis group. In non-sepsis group initial level of microalbuminuria (ACR1) was 81.4 ± 18.63 mg/g which decreased to 71.13 ± 28.60 mg/g (ACR2) after 24 hours of admission. Mean ∆ACR was 10.27 ± 14.35 mg/g in non-sepsis group. This difference of ACR1, ACR2 and ∆ACR was statistically significant (p value = 0.0001, 0.0001, 0.0012 respectively) (Table 2).

### Discussion

It is important to diagnose sepsis early for optimum patient management and early initiation of appropriate lifesaving therapy. There are several markers that have been used conventionally to identify sepsis. Procalcitonin (PCT) has been used as a sensitive and specific marker for systemic infections, but it is also known to increase in other non-infectious inflammatory conditions and may remain normal in localized infections.\(^{5,6}\) C-Reactive Protein (CRP) is another marker which is used but it is nonspecific, takes time to rise and does not correlate with the severity of the disease.\(^{6,15}\) As compared to PCT and CRP, levels of microalbuminuria increase within hours of inflammatory injury.\(^{13}\)

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In the current study, the area under curve (AUC) of Receiver Operating Characteristics (ROC) curve for differentiating sepsis and non-sepsis was highest for ACR1 (0.994) followed by ACR2 (0.919) and ∆ACR (0.553) (Figure 1).

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### Table 1: Comparison of SOFA and APACHE score with ACR1, ACR2 and ∆ACR

<table>
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<th>Groups</th>
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<th>Std. Deviation</th>
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<td></td>
<td>Non-seps</td>
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<td>25.62</td>
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Above table shows comparison of SOFA score, APACHE score, Microalbuminuria within 6 hour of admission (ACR1), Microalbuminuria at 24 hour of admission (ACR2) and ∆ACR (ACR1-ACR2) between sepsis and non-sepsis group.
prediction of mortality in sepsis group was highest for APACHE II score (0.993) and ACR2 (0.983) followed by ACR1 (0.969), ∆ACR (0.961) and SOFA score (0.957) (Figure 2). Bhadade RR et al found ACR2 significantly better than APACHE II score for mortality prediction.15 Basu et al had found that ACR2 was as good as APACHE II for mortality prediction.15,19 Gosling et al had found ACR1 as good a predictor of mortality as APACHE II among surgical patients but not medical patients.20

In our study, APACHE II has the highest value among all for predicting mortality. In our study, comparison of ROC of ACR2 APACHE II in sepsis group demonstrate that difference in AUC is 0.0102, Standard error-0.0179 with 95 % confidence interval = -0.0249 to 0.0453, Z value = 0.570 and P value = 0.5689. This finding suggest that there is no significant difference in predicting mortality by ACR2 and APACHE II score and ACR2 is as good as APACHE II score for prediction of mortality in patient of sepsis group.

This can 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 decrease in the inflammatory activity and explain the improved survival.

In our study for mortality prediction of sepsis group, ∆ACR performed better than SOFA score but not better than APACHE II score. Still, there is no significant difference observed between mortality prediction by APACHE score, SOFA score and ∆ACR (Figure 2).

A similar logic explains the better ability of ∆ACR in prediction of mortality where an increasing trend predicts a poorer outcome, whereas a decreasing trend predicts a better outcome. Abid ET al and Bhadade RR ET al had also found a higher mortality among patients with increasing microalbuminuria levels.15,21

In the past, studies done by Gosling, Gopal and Bhadade RR et al found microalbuminuria as a good marker in the prediction of mortality in sepsis patients.15,22-23

Limitation of study

We have excluded diabetic and hypertensive patient because they have pre-existing microalbuminuria. So our study population is less representative of real life scenario. Further studies will be required to determine effects of illness on pre-existing microalbuminuria. Critically ill patients with urinary tract infections and chronic renal insufficiency were excluded from the study, which may be a limitation to the universal applicability of microalbuminuria as a diagnostic tool.

Many conditions such as age (>40 years), smoking, alcohol, BMI (Body mass index) are independent causes of microalbuminuria in the general population, these patients were included in our study. During the course of treatment, certain nephrotoxic antibiotics were used within creatinine clearance range, thereby limiting kidney injury and ACR levels.

Conclusion

Several potential applications of microalbuminuria measurement in the critically ill are suggested by this study. Urine ACR is significantly higher in the sepsis group in comparison to non-sepsis group. Serial monitoring of bedside urine albumin-creatinine measurement might help in the early identification of patients with sepsis that requires early targeted therapy. The 24-hour ACR assessment predicts ICU survival and may have the potential to monitor the efficacy of therapeutic interventions delivered, such as fluid resuscitation, appropriate antibiotics, vasopressors, and inotropes that affect the endothelium.

References