Section: Medicine

Microalbuminuria as a Marker of Sepsis - A Prospective Study in a Tertiary Care Hospital.

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ABSTRACT

Background: Diffused endothelial dysfunction in sepsis leads to an increase in systemic capillary permeability, the renal component manifesting as microalbuminuria. The degree of microalbuminuria correlates with the severity of the acute insult, the quantification of which may serve to predict sepsis and mortality in critically ill patients. Aim: To study the trend of microalbuminuria in sepsis patient, to evaluate microalbuminuria as novel biomarker of sepsis, To evaluate the capability of microalbuminuria for the prediction of ICU mortality. **Methods:** After exclusions, between November 2014 to May 2015, 50 consecutive adult patients were found eligible. Urine spot samples was collected at the time of ICU admission for Albumin Creatinine Ratio 1 and Albumin Creatinine Ratio 2 at 24hrs of ICU admission and Albumin creatinine Ratio 3. **Results:** Total of 50 patients were included into the study. The study included 56% of the patients as males and 44% as females. Out of 50 patients 78% of the patients had microalbuminuria, 66% of the patient were culture positive, out of which 79.49% of the patient had microalbuminuria. Majority of the patient (87.18%) with microalbuminuria require mechanical ventilation and the ICU stay was prolonged in survivor patients. Mortality rate was 61.54%. Microalbuminuria levels at 24 hours of admission among survivors and non survivors indicates its prognostic significance in ICU mortality. **Conclusion:** Microalbuminuria is a reliable marker of sepsis, At 48 hours of admission, increased levels of microalbuminuria compared to microalbuminuria levels at admission and 24 hour, indicates its prognostic significance among survivors and non survivors in critically ill patients.

Keywords: Microalbuminuria, Sepsis.

INTRODUCTION

Sepsis remains a major global healthcare concern, owing to high morbidity and mortality, despite the advances in medical therapeutics.[1,2] Targeted therapies probably lose their efficacy due to late administration.[3,4] Till date, there is no reliable method of diagnosing sepsis early in the critically ill. Sepsis is marked by a severe host defense response that involves triggering of potent inflammatory cascades which release a plethora of pro-inflammatory molecules into the circulation.[5] The endothelium becomes dysfunctional due to the sustained onslaught of the inflammatory molecules and the simultaneous oxidative stress. An early event is the loss of barrier integrity leading to systemic capillary leak.[6] The glomerular manifestation of this enhanced capillary permeability is increased excretion of albumin in the urine.[7]

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Microalbuminuria, defined as 30–300 mg/day of albumin excretion in the urine, occurs rapidly after an acute inflammatory insult such as sepsis and persists in patients with complications.[8–13] It is a common finding in critically ill patients, where it has shown promise not only as a predictor of organ failure and vasopressor requirement but of mortality, faring better than Acute Physiological and Chronic Health Evaluation (APACHE) II score and Sequential Organ Function Assessment (SOFA) scores.[14-19]

Similar endothelial dysfunction may occur in non-septic inflammatory states. But, it is not known whether the degree of microalbuminuria is different after a septic insult when compared to noninfectious ones such as pancreatitis, burns, trauma etc. and, whether it could delineate sepsis in a heterogeneous population of critically ill patients. By drawing an analogy with current biomarkers of sepsis such as procalcitonin (PCT), C-reactive protein (CRP) and the markers of endothelial damage such as the adhesion molecules, which are relatively elevated in sepsis;[20,21] we surmised a similar occurrence for microalbuminuria. To test this hypothesis, our study endeavored to explore a diagnostic role of microalbuminuria, by quantifying its level in patients with and without sepsis. A

secondary aim was to evaluate the ability of microalbuminuria to predict mortality in the ICU.

MATERIALS AND METHODS

The present study was a Prospective, non-interventional study conducted on patients admitted to Medicine ICU/ Central ICU, Teerthanker Mahaveer Medical College & Hospital, Moradabad from Nov 2014 to May 2015. Patients of age 18-80 from both sexes with 2 or more features of SIRS (systemic inflammatory response syndrome) and suspected infection were included in the study. Patients receiving nephrotoxic drugs, with preexisting urinary tract infection, with urologic trauma resulting in frank hematuria or urinary infection, with preexisting chronic kidney disease (serum creatinine level $\geq$ 2.0mg/dL), pregnancy, and anuria were excluded from the study.

Collected spot urine sample, 24 hours and after 48 hour of admission to medical ICU. Samples were tested for urine microalbumin by immunoturbidometric method and for urine creatinine by Jaffe method and urine microalbumin: creatinine ratio was calculated. All the investigations like Hemoglobin, Serum Electrolytes, Blood urea and serum creatinine, RBS (Random Blood Sugar), LFT (Liver Function Test), White blood cell count, ABG (Arterial Blood Gas) if patient was on mechanical ventilator were sent and noted. Urine microalbumin: urine creatinine ratio was calculated at spot (Urine ACR1), 24 hour (Urine ACR2) and 48 hour (Urine ACR3) of admission to the ICU

Two or more of the following if present: SIRS.[2]

1. Fever(>38 C) /Hypothermia(<36)
2. Tachypnea (Respiratory rate >24/min)
3. Tachycardia (Heart rate >90/min)
4. Leukocytosis (>12000/microliter) or
5. Leukopenia (<4000/microliter) or >10% bands.

Data were collected using a pretested proforma meeting the objectives of the study. Detailed history, physical examination and necessary investigation was undertaken. The purpose of the study was explained to the patient and informed consent were obtained. Patients were followed up during the course of the hospital stay and the outcome of the patient (i.e. Death/Survival) were recorded

RESULTS

Table 1: Distribution of patients according to their Urine ACR1

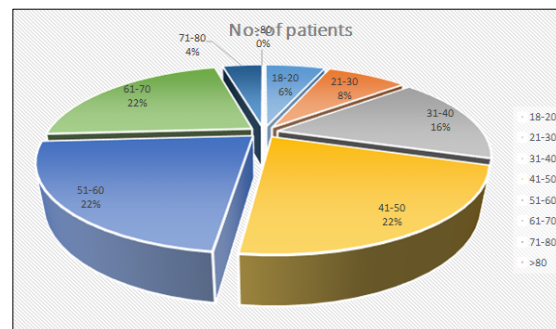| No. of patient (n=50)	Non survivor		Survivor		Total	
	No.	%	No.	%	No.	%
30-90	0	0	22	44	22	44
91-150	8	16	4	8	12	24
>150	16	32	0	0	16	32
Mean±S.D	161.46±36.287		66.42±23.374		95.042±48.140	
Range	32-216					
P value	<0.0001		<0.0001		<0.0001	

Figure 1: Most of the patients in the study were in the age group of 41-70years.

Table 2: Distribution of patients according to their Urine ACR2

Urine ACR2 (µg/mg)	Non survived		Survived		Total	
	No	%	No	%	No.	%
0-90	0	0	26	52	26	52
91-150	11	22	0	0	11	22
>150	13	26	0	0	13	26
Mean ± SD	205.46±77.000		54.42±14.856		150.042±85.097	
Range	33-389					
P value	<0.0001		<0.0001		<0.0001	

Table 3: Distribution of patients according to their Urine ACR3

Urine ACR3 (µg/mg)	Non survival		Survival		Total	
	No.	%	No.	%	No	%
0-90	0	0	26	52	26	52
90-150	4	8	0	0	4	8
>150	20	40	0	0	20	40
Mean ± SD	296.25±111.352		51.25±11.678		245.00±117.284	
Range	59-486					
P value	<0.0001		<0.0001		<0.0001	

Urine ACR 1 (albumin creatinine ratio) was 66.42µg/mg among survivors and 161.46µg/mg among non survivors, Urine ACR 2 were 55.42among survivors and 205.46 among non survivors and for Urine ACR 3 were 51.25 µg/mg among survivors and 296.25 µg/mg among non survivors. All were statistically significant with p value of <0.0001

Table 4: Correlation of ACR at admission 24 hours and 48 hour of admission.

	Mortality		P value
	Survived	Non survived	
ACR 1	66.42±23.374	161.46±36.287	<0.001**
ACR 2	55.42±14.856	205.46±77.000	<0.001**
ACR 3	51.25±11.678	296.25±111.357	<0.001**

ACR has been significantly been increased in non-survivors patients

DISCUSSION

Earliest analysis of sepsis is necessary to manage patients. The cultures of the body fluids as

considered gold standard, do not come positive regularly and the results are often delayed by 48 hours, because of late result, cannot administering targeted therapies to the patient.

Microalbuminuria serves as a method for quantification of alteration in systemic vascular permeability. Measurement of albumin excreted in urine sample randomly collected, known as Albumin/ creatinine. Microalbuminuria levels as a result of inflammatory insult. Various studies in several groups of critically ill patients with microalbuminuria acts as a important prognostic marker of morbidity and mortality in Intensive Care Units.

This prospective study was done in Teerthanker Mahaveer Medical College and Research Centre Moradabad (U.P).

In this study mostly patients belonged to the age group of 40-70 years (66%). Mean age of the patient was 50.32±17.89. In a study done by Basu et al mean age of the patient came out to be 61.522. Grion et al the mean age was 65.8 ± 15 years23. Bhavita et al, mean age showed as 5224. Mackinnon showed mean age as 6314

In our study most of the participant were males (56%). Basu et al showed majority as males (66.7%).[22] Grion et al too showed males as majority (63.3%).[23] Bhavita et al majority of the patients was males (53%).[24]

In our study, Microalbuminuria occurred in 68% of the patient .Thoreveska et al showed occurrence of microalbuminuria in 69% patient.[17] Basu et al showed microalbuminuria occurred in 87% of the patient.[22] In a study by Bhavita et al microalbuminuria occurred in 71% of the patient.[24]

In our study mortality rate was 61.54%. In a study conducted by Thoreveska et al mortality rate was 26.9%.[17] In a study conducted by Abid et al mortality rate was 43%15. In a study conducted by Basu et al mortality was 26.7%.[22] In a study done by Grion et al mortality rate was 71.4%.[23] In a study conducted by a Bhavita et al mortality rate was 18%.[24]

In our study median ACR1 was 66.42 among survivors and ACR 1 among non-survivors was 161.46, p value was <0.001 which was statistically significant. In a study done by Basu et al median ACR1 was 108.3 among survivors and ACR 1 was 156.5 among non-survivors, p value was 0.41 which was not statistically significant.[22] In a study conducted by Groin et al median ACR1 among survivors was 61.88 and ACR1 among non-survivors was 137.0223. In a study conducted by Bhavita et al median ACR1 among survivors was 89.8 and ACR1 was 161.5 among non-survivors, p value was <0.001 which was statistically significant.[24]

In a study done by Gosling et al median ACR1 among survivors was 37.2 and ACR1 among non-survivors was 161.8, p value was <.0002 which was statistically significant.[16]

In our study median ACR2 among survivors was 55.42 and ACR2 among non survivors was 205.46, p value was < 0.001 which was statiscally significant, indicating ACR2 can be taken as prognostic signicance in ICU mortality. In a study by Thorveska et al concluded ACR of >100 were 2.7 times more likely to die than those with an ACR <100,p value was 0.0007 which was statistically significant, indicating its prognostic significance.[17]

A systematic review conducted by Gopal et al, concluded that microalbuminuria can be a promising predictor of severity of illness and mortality in the icu setups 19. In a study conducted by Abid et al, group 1 -14 patients who had increased microalbuminuria median range from 45.96 to 167.96 had mortality rate was 43% and group 2 – 26 patients who had decreasing value of microalbuminuria median range from 144.97 to 68.95 had mortality rate was 15%, p value was <0.05 which was statistically significant, indicating its prognostic significance in ICU mortality.[15]

Basu et al, showed median ACR2 in survivors was 50.8 and median ACR 2 among non survivors was 154, p value was <0.004 which was statically significant, indicating its prognostic significance.[6]

In a study done by Grion et al, median ACR at 3rd day of admission was 61.8 among survivors and median ACR at 3rd of admission was 137.02 among non survivors, indicating its prognostic significance.[23]

In a study done by Bhavita et al, median ACR2 at 24 hours of admission was 46 among survivors and median ACR2 at 24 hours of admission was 164.5, p value was <0.0001 which was statistically significant, indicating its prognostic significance.[24]

In a study conducted by Mackinnon et al, concluded ACR measured 6hour after post admission to ICU showed a significant difference (p =0.01) among survivors & non survivors, permitting identification of patients at Increased risk of development of organ failure and death.[14]

CONCLUSION

- ❖ Microalbuminuria is a common occurrence in critically ill patients.
- ❖ Microalbuminuria is a reliable marker of sepsis
- ❖ At 48 hours of admission, increased levels of microalbuminuria compared to microalbuminuria levels at admission and 24 hour, indicates its prognostic significance among survivors and non survivors in critically ill patients.
- ❖ Microalbuminuria is an inexpensive and rapid diagnostic bedside tool, could be efficiently utilized for identification of patient survival in ICU.
- ❖ Serial measurements of microalbuminuria may serves a helpful measure in the clinical assessment of critically ill patients at risk of worse prognosis.

REFERENCES

1. Angus DC, Linde-Zwirble WT, Lidicker J. Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. Crit Care Med 2001;29:1303-10.
2. Todi S, Chatterjee S, Bhattacharyya M. Epidemiology of severe sepsis in India. Crit Care 2007;11:65.
3. Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. N Engl J Med 2001;345:1368-77.
4. Wheeler AP, Steingrub J, Linde-Zwirble W, McCollam JS, Zeckel M. Prompt administration of drotrecogin alfa (activated) is associated with improved survival. Crit Care Med 2003;12:A120.
5. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis.N Engl J Med 2003;348:138-50.
6. Aird William C. The role of the endothelium in severe sepsis and multiple organ dysfunction syndrome. Blood 2003;101:3765-77.
7. Gosling P. Microalbuminuria: A marker of systemic disease. Br J HospMed 1995;54:285-90.
8. Berton G, Citro T, Palmieri R, Petucco S, De Toni R, Palatini P. Albumin excretion rate increases during acute myocardial infarction and strongly predicts early mortality. Circulation 1997;96:3338-45.
9. 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;27:2105-8.
10. 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;26:1364-8.
11. Szakmany T, Molnar Z. Increased glomerular permeability and pulmonary dysfunction following major surgery: Correlation of microalbuminuria and PaO2/FiO2 ratio. Acta Anaesthesiol Scand 2004;48:704-10.
12. Yew WS, Pal SK. Correlation of microalbuminuria and outcome in patients with extensive burns. Br J Anaesth 2006;97:499-502.
13. 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;33:1000-6.
14. 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;84:239-41.
15. 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;120:1984-8.
16. Gosling P, Brudney S, McGrath L, Riseboro S, Manji M. Mortality prediction at admission to intensive care: A comparison ofmicroalbuminuria with acute physiology scores after 24 hours. Crit Care Med 2003;31:98-103.
17. 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;31:1075-81.
18. 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;34:2158-66.
19. 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;34:1805-10.
20. Reinhart K, Meisner M, Brunkhorst FM. Markers for sepsis diagnosis: What is useful? Crit Care Med 2006;22:503-19.
21. Boldt J, Muller M, Kuhn D, Linke LC, Hempelmann G. Circulating adhesion molecules in the critically ill: A comparison between trauma
22. Basu S, Bhattacharya M, Chatterjee TK, Chaudhuri S, Todi S, Majumdar A et al. Microalbuminuria: a novel biomarker of sepsis. Indian journal of Critical Care Medicine 2010;14(1):22-28.
23. Grion C, Cardoso L, Carrilho C, Altafin J, Barros S, Carvalho L et al. Microalbuminuria evaluated as a biomarker in patients with septic shock. Critical care 2010;14:30 24.
24. Bhavita Patel, Sirajwala H B, Dilip Taviad, Shah R M, Rinku Makadiya Microalbuminuria : A marker of critically ill patients. International journal of biomedical and advance research. 2013