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Microalbuminuria in sepsis with reference to apache II score, in an intensive care tertiary care setting

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Abstract:
Background: *Sepsis remains a major healthcare concern .Systemic inflammatory response is usually severe in patients with critical illnesses.ICU scoring systems like APACHE and SAPSII to predict mortality are done at 24 hour of admission during which precious time is lost in administering therapy. Microalbuminuria has shown as a predictor of organ failure and also mortality. Our study evaluates the role of microalbuminuria in predicting the mortality among critically ill patients.*
Methods: *In a prospective, non-interventional study conducted on patients admitted to ICU of Institute of medical sciences madras medical college .A total of*
50 adult patients (>18 years) with a stay in the ICU for more than 24 h were included. Spot urine samples were collected at 6 and 24 hours of admission and were tested for urine micro albumin by immunoturbidometric method and for urine creatinine by Jaffe method and urine micro albumin: creatinine (Urine ACR) ratio was calculated. T For disease severity scoring, urinary micro albumin will be measured using the immunoturbidimetric method with an albumin creatinine ratio cut off of 30-300 mg/ L. The urine ACR Wasco-related with SAPSII score and mortality of the patients.
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 was61.54%.. Microalbuminuria levels at 24 hours of admission among survivors and non survivors indicates its prognostic significance in ICU mortality*
Conclusion: *Presence of significant microalbuminuria at admission and persistence of microalbuminuria at 24 hrs of admission correlated well with mortality as comparable to APACHE II score. Survival rate in patients with severe*
Sepsis can be improved by early institution of intensive therapy. Microalbuminuria is an inexpensive rapid diagnostic as well as prognostic test. Hence microalbuminuria can be used as dynamic marker of sepsis
Keywords: *Sepsis Microalbuminuria, the APACHE II score.*

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I. Introduction

Sepsis has very high morbidity and mortality leading to major healthcare burden in the world (1). It is marked by a severe host defense response that involves triggering of potent inflammatory cascades. The systemic inflammatory response is usually widespread. There is a release plethora of proinflammatory molecules into the circulation (2, 3). It is severe in patients with critical illnesses, sometimes in advanced cases may result in multiple organ failures and eventually death (4). Systemic inflammatory response syndrome (SIRS) is a consequence to a variety of acute pathological conditions such as hemorrhagic shock, sepsis, multiple trauma, or pancreatitis (5). Invasive bacterial infections like Non-typhoid salmonella species, Streptococcus pneumonia, Hemophilus influenza, and Escherichia coli were the most commonly isolated bacteria(6) and the prominent causes of death around the world. Microalbuminuria, defined as30– 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(7). 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 also of mortality. (7, 8, 9).

Though there is far advancement in the therapeutic options, the mortality rate remains high due to the delay in the diagnosis because of lack of availability of reliable diagnostic methods (10).But there is significant improvement in the outcome of the patients in early goal directed therapy in severe sepsis and septic shock. Various ICU scoring systems to predict mortality are in current use like the APACHE II and SAPSII score (9, 10). These scoring systems have many variables and are cumbersome and are done at 24 hours of admission during which precious time is lost in administering therapy. Microalbuminuria is a common consequence to numerous inflammatory conditions such as burns, meningitis, pancreatitis, myocardial infarction, and cerebral ischemia. 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 (11). The glomerular manifestation of this enhanced capillary permeability is increased excretion of albumin in the urine. Studies have consistently shown that microalbuminuria is a simple, suitable, non-invasive, and inexpensive predictor of mortality, which can be used as a bedside tool in critically ill patients (12, 13). In fact, its utility and efficiency are found to be equal to APACHE II score, a standard but complex tool in predicting the ICU patient mortality (10, 12). In This study is an attempt. In resource poor and increased patient load, where the sophisticated and cost demanding therapeutic interventions are scarce, effective determination, and monitoring of optimal treatment procedures and patient mortality is of utmost importance. Hence, low-cost reliable markers like microalbuminuria can be utilized in such situations; hence, the present study intends to assess the role of microalbuminuria in predicting the mortality among critically ill patients and to understand the usefulness of Urine Micro albumin and creatinine ratio in predicting the mortality of the patient and to compare it with validated ICU scoring systems such as SAPS II. [8]

II. Materials And Methods

Study design and population the present study was a Prospective, non-interventional study conducted on patients for a period of 6 months in Medicine ICU, Institute of Internal Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai, India for 6 months. Sample size and Sampling method: A total of 50 study participants were included in the study. All the eligible subjects were included sequentially into the study, hence no sampling was done. 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. Data collection and clinical examination, We used a structured questionnaire to collect data regarding sociodemographic details, behavioral risk factors, 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. We reviewed the clinical records and prescription for drugs and diagnostic tests. We measured the height and weight of all the patients. The basic vital parameters measured at the time of admission and after 24hoursof admission were recorded. At the time of admission, patients were examined for vital signs and symptoms of SIRS, organ failure, and/or infection Culture samples sent and antibiotics received within 24 h of admission to be noted. Infection is defined by the presence of clinical signs of SIRS along with any identified source of infection and/or positive blood cultures for disease. Severity scoring, APACHE II score was calculated from data collected during the first 24 h following ICU admission. Each patient were followed up throughout their ICU stay and the following and the outcome of the patient (i.e. Death/Survival) is recorded.

Biochemical measurements:

Collected spot urine sample, 24 hours and after 48 hour of admission to medical ICU. Samples were tested for urine micro albumin by immunotubidometric 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 micro albumin: urine creatinine ratio was calculated at spot (Urine ACR1), 24 hour (Urine ACR2) and 48 hour (Urine ACR3) of admission to the ICU.

Operational definitions:

The American College of Chest Physicians/ Society of Critical Care Medicine Consensus Conference definitions issued to identify patients with SIRS, sepsis(SIRS with infection), septic shock (sepsis with hypotension on vasopressor support), and multiorgan dysfunction syndrome.

Two or more of the following if present: SIRS

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

III. Statistical Analysis

Various sociodemographic, clinical, and laboratory parameters were considered as other explanatory variables. Descriptive analysis of the explanatory and outcome variables was done using mean and standard deviation for quantitative variables, frequency, and percentages for categorical variables. Mortality was the primary outcome variable in the study. Urine albumin levels and APACHE II score were considered as primary explanatory variables... The correlation between microalbumin levels and APACHE II score was assessed by Spearman rank correlation and its value. Receiver operating characteristic (ROC) analysis was done to assess the validity of microalbumin predicting mortality. The sensitivity, specificity, and predictive values for various cut off levels of micro albumin were Calculated. IBM SPSS version 21 was used for statistical analysis. Protection of human subjects. The study was approved by Institutional Human Ethics

Committee of the Institute of Internal Medicine, Madras Medical College, Chennai, and Tamil Nadu. Informed written consent was obtained from the legal guardian of the study participants after explaining The purpose of the study, risks, and benefits involved. The personal data of the participants were kept confidential throughout the study period.

IV. Results

Characteristics of the study population:

We screened a total of 50 persons but excluded 5 persons because of lack of medical records confirming the diagnosis the mean age of the study group was 43.5(±15).The were 19 female (38%) as compared to 31 male (62%).Among the 19. Non Survivors5 were female (26.21 %) and 14 were male (73.68%).

Among the 31 survivors14 were female (Table1).Based on SIRS criteria 27(54%) patients had all the four criteria for SIRS And 19 patients (38%) had three criteria of SIRS and 4 patients (8%) had only two criteria. The mortality rate for the patients who were having four criteria of SIRS was 33.33%. And who were having three criteria of SIRS were 42.1 %(Table2).When looking at the outcome about 38% died and 62% survived (Figure.1). The APACHE II score ranged from 6 to 37 with a mean value of 19.82(SD±8.11). Out of 36 patients who had APACHE II score of more than 18.5, 15 patients died (55.55%), when compared to patients who had APACHE II score of less than 18.5, Four patients died (17.39%) (Table 3). The mean APACHE II score among the survivors was16.35 with Standard Deviation of 6.78, when compared to the mean value of non survivors was25.47 with Standard Deviation of 6.93 .As the P value was<0.0001, hence it was statistically significant. Urine Micro Albumin Creatinine Ratio done on admission ranged 33 to 245 microgram/mg .Out of 16 patients (32%) who had ACR 1 value more than 109.5, all the 16 patients died. Out of 34 patients(68%) who had ACR 1 value less than 109.5, three patients died (8.82%).There is statistically significant P value of <0.0001. (Table 4).The Urine Micro Albumin Creatinine Ratio done at 24 hours of admission ranged 15 to 221microgram/mg. Out of 16 patients (32%) who had ACR

2 value more than 118.5, all the 16 patients died. Out of 34 patients (68%) who had ACR 2 value less than 118.5, three patients died (8.82%).There is Statistically significant P value (Table5). Urine ACR 1 WAS74.06 µgm/mg among survivors and 164µg/ mg among non survivors and ACR 2 was45.81 µg/ mg among survivors and 157 µg/ mg among non survivors. Both were statistically significant with p value <0.0001(Figure 2). There is good co-relation between Urine ACR 1 and APACHE II score. The P value is<0.0001, which is statistically significant. (Table 5).The area under curve was Larger for Urine ACR 2 (92%), when compared to APACHE II score (70%). Urine ACR 1 (AUC 90.5%) also has comparable value with ACR 1 value. This implies, ACR 2 and ACR 1 had better correlation with the mortality of the patients when compared to APACHE II score (Figure 3)

V. Discussion

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 an important prognostic marker of morbidity and mortality in Intensive Care Units.

Mortality percentage in this study was38%.Thisisconsistent with various studies by Rangel-Frausto MS et al which showed mortality ranging from 20-35% and study conducted by Greg Set al 2006 which showed case fatality increased linearly with age and age was an independent predictor of mortality (15,16). In this study mortality rate is higher in males than females. This is contary to the study done by by AngusDC et al showed that women had less age specific incidence and Mortality rates compared to men (17).Among the who died majority have shown had an infectious source in the lung. Other causes included localized infection in the form of cellulitis or abscess or an abdominal source of infection. Urinary tract infections were excluded from the study as it was an exclusion criteria of the study. This is similar study to other studies which showed that most common primary sources of infection resulting in sepsis are the lungs, the abdomen, and the urinary tract (17, 18). Urine microalbumin was significantly elevated among those with organ dysfunction than those without organ dysfunction and the degree of elevation was more in those with multiorgan dysfunction than those with single organ dysfunction. Absence of significant microalbuminuria among sepsis patients at admission is predictive of survival and significant microalbuminuria At admission is predictive of mortality which is equivalent to the time Tested SAPSII score. Early institution of intensive therapy to these patients can Improve survival rates. One of the limitations of the study was its smaller sample size, which may explain the weaker mortality predictively of microalbuminuria. There is some evidence suggesting the appreciable role of using microalbuminuria as a simple, rapid, inexpensive biochemical tool. Smoking and Hypertension could be independent cause of microalbuminuria Patients with urological causes of sepsis were not included in the study group. Sepsis with pre-existing chronic kidney disease could not be included in the study. In systematic review on the ability of urinary micro albumin in predicting the severity of illness among critically ill patients

VI. Conclusion

Microalbuminuria can be a promising predictor of severity of illness and mortality in the ICU setups and that there was a need to assess the optimal timing and threshold reference value for the urine ACR in diverse, heterogeneous ICU patients. (19, 20) In summary Presence of significant microalbuminuria at admission and persistence of microalbuminuria at

24 hrs of admission correlated well with mortality as comparable to APACHE II score. Survival rate in patients with severe sepsis can be improved by early institution of intensive therapy. Microalbuminuria is an inexpensive rapid diagnostic as well as prognostic. Hence microalbuminuria can be used as dynamic marker of sepsis

VII. Tables And Figures

Table1 Distribution of patients according to age group

AGE IN YEARS	DEATH		SURVIVED		TOTAL	
	No.	%	No.	%	No.	%
< 20	1	2	4	8	5	10
21-40	10	20	6	12	16	32
41-60	7	14	18	36	25	50
> 60	1	2	3	6	4	8
TOTAL	19	38	31	62	50	100
MEAN	43.5 ±15.8					
RANGE	16-85					

Table2. Distribution of patients according to no of SIRS criteria

NO OF SIRS CRITERIA	DEATH		SURVIVED		TOTAL	
	No.	%	No.	%	No.	%
2	2	4	2	4	4	8
3	8	16	11	22	19	38
4	9	18	18	36	27	54
TOTAL	19	38	31	62	50	100

Figure1. Distribution of patients according to coutcome

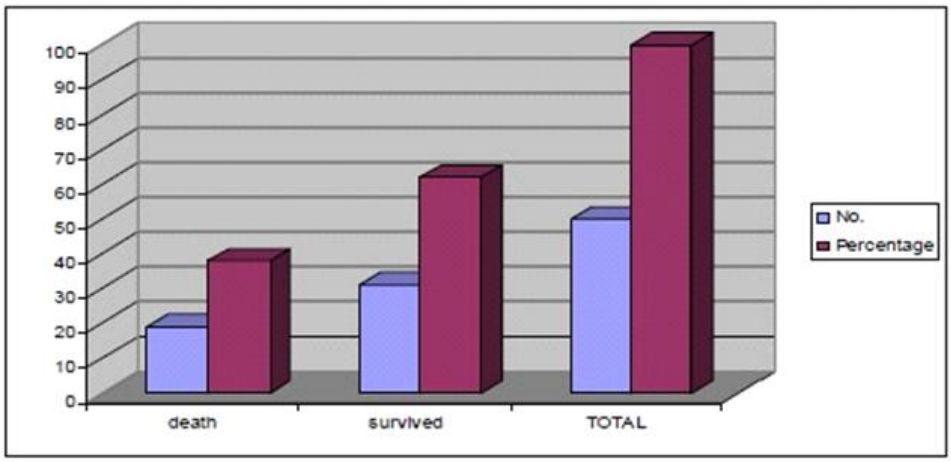


Table 3: Distribution of patients according to APACHE II score

APACHE II	DEATH		SURVIVED		TOTAL	
	No.	%	No.	%	No.	%
< 18.5	4	8	19	38	23	46
>18.5	15	30	12	24	27	54
TOTAL	19	38	12	62	31	62
MEAN	25.47±6.93		16.35±6.78		19.82±8.11	
RANGE	6 – 37					
P Value	<0.0001					

Table4. Distribution of patients according to urine ACR 1

ACR 1	DEATH		SURVIVED		TOTAL	
	No.	%	No.	%	No.	%
< 109.5	3	6	31	62	34	68
>109.5	16	32	0	0	16	32
TOTAL	19	38	31	62	50	100
Mean	164.53±46.61		74.06±20.83		108.44 ± 55.05	
Range	33 – 245					
P Value	< 0.001					

Table5. Distribution of patients according to urine ACR 2

ACR 2	DEATH		SURVIVED		TOTAL	
	No.	%	No.	%	No.	%
< 118.5	3	6	31	62	34	68
>118.5	16	32	0	0	16	32
TOTAL	19	38	31	62	50	100
Mean	157.84±36.96		45.81±17.92		88.38±60.96	
Range	15 – 221					
P Value	< 0.001					

Table6. Co-relation between Micro-Albuminuria and APACHE II Score

Co-relation	Co-relation Co-efficient	P value
Urine ACR 1 and APACHE II score	0.809	<0.0001
Urine ACR 2 and APACHE II score	0.726	<0.0001
Urine ACR 1 and Urine ACR 2	0.912	<0.0001

Figure 2 Comparison of urine ACR 1 AND urine ACR 2 among survivors and non-survivors.

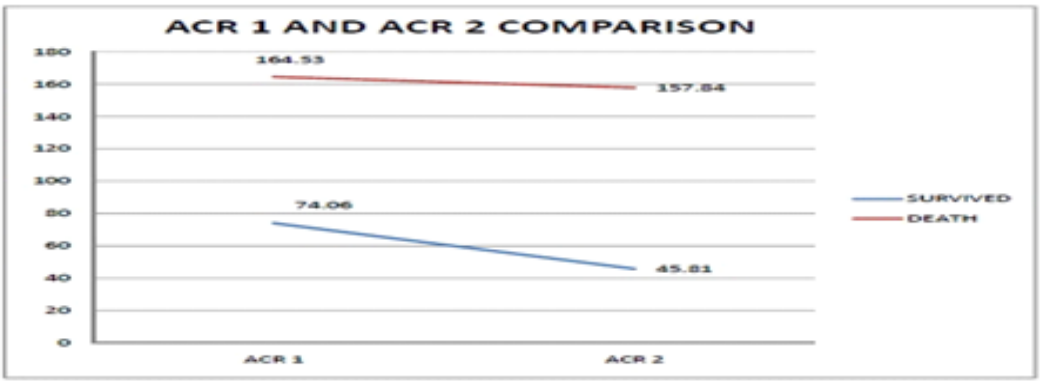
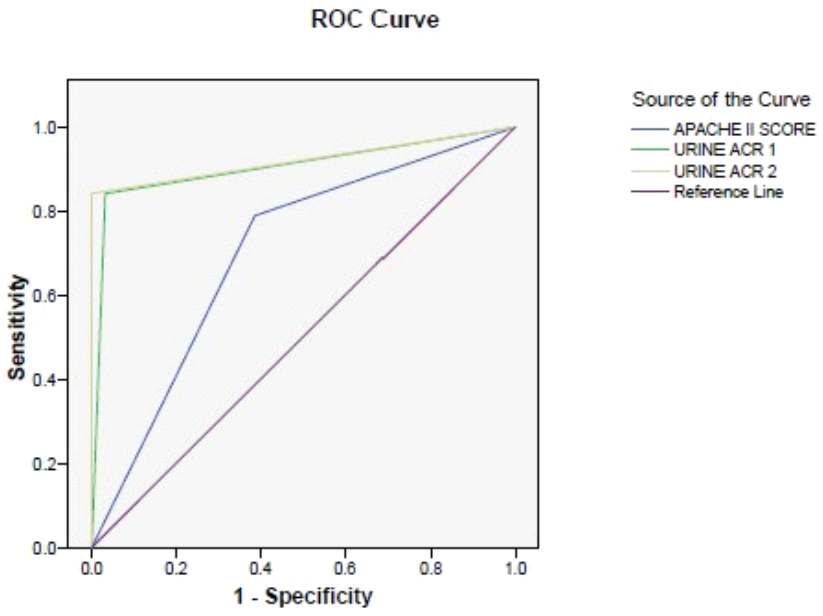


Figure 3 . Comparison of Area under curve for APACHE II Score, ACR1 and ACR 2 in predicting mortality



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