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General Medicine

STUDY OF MICROALBUMINURIA IN SEPSIS WITH REFERENCE TO APACHE II SCORE

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ABSTRACT

Sepsis has very high morbidity and mortality, which leads to major healthcare burden in the world. Though there is far from 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. In sepsis there is potent activation of inflammatory cascade leads to endothelial dysfunction and increase in systemic capillary permeability. In kidney there is loss of barrier integrity and capillary leak in the glomerulus results in increased excretion of albumin in the urine. This study was done to evaluate the degree of microalbuminuria in sepsis in correlation with APACHE II score and to test whether the degree of microalbuminuria could predict the mortality in critically ill sepsis patients.

Methodology: The present study was conducted on 50 patients admitted to medical emergency/ Medical ICU in Kamineni Institute of Medical Sciences Narketpally. Spot urine sample was collected within 6 hours and at 24 hours of admission to medical emergency/ICU /ward. Sample tested for urine micro albumin by using immunoturbidometric method and for urine creatinine by Jaffee method.

Urine albumin: creatinine ratio was calculated. (At 6 hours ACR-1 and at 24 hours ACR-2). APACHE II scoring was done at 24 hours of admission.

Patients was followed up during hospital stay and the outcome of the patient (i.e., Death/Survival) is recorded.

RESULTS: The present study included 50 patients, among which 31 were males and 19 were females. Mean age was 43.5 years. Mortality was 38%. Mortality was more among male patients than in female. APACHE II score ranges from 6 - 37, mean APACHE II among survivors were 16.35 with Standard Deviation of 6.78 and among non survivors were 25.47 with Standard Deviation of 6.93 with p value of < 0.0001 for predicting mortality. Urine ACR 1 was $74.06 \pm 20.83 \,\mu$ gm/mg among survivors and 164.53 ± 46.61 μ gm /mg among non survivors and ACR 2 was $45.81 \pm 17.92 \mu$ gm/mg among survivors and $157.84 \pm 36.96 \mu$ gm/mg among non survivors. Both were statistically significant with p value of 0.0001 for predicting mortality. The degree of microalbuminuria correlates with disease severity.

CONCLUSION: Significant microalbuminuria is predictive of mortality which is equivalent to APACHE II score. Microalbuminuria is an inexpensive and rapid diagnostic tool. Serial measurements may help in the clinical assessment of critically ill patients at risk of worse prognosis, even in resource poor areas.

KEYWORDS : Sepsis; microalbuminuria; APACHE II score; urine albumin creatinine ratio.

INTRODUCTION

SEPSIS is defined as SIRS (systemic inflammatory response syndrome) that has a proven or suspected microbial etiology. 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.¹ The endothelium becomes dysfunctional due to the sustained on slaught of the inflammatory molecules and the simultaneous oxidative stress. An early event is the loss of barrier integrity leading to systemic capillary leak. Increased capillary permeability is an early feature of Systemic Inflammatory Response Syndrome (SIRS).^{1,2}

The glomerular manifestation of this enhanced capillary permeability is increased excretion of albumin in the urine. In various studies microalbuminuria has been correlated with rapid changes in vascular integrity. Early prediction of mortality among critically ill sepsis patients and early institution of intensive therapy is of paramount importance which has significant implications on survival of the patient.²

Various ICU scoring systems to predict mortality are in current use like the APACHE II and SAPS II score. These scoring systems are cumbersome and are done at 24 hours of admission during which precious time is lost in administering therapy³.

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. 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.^{3,4}. This study is an attempt to understand the usefulness of Urine Micro albumin and creatinine ratio in predicting scoring the mortality of the patient and to compare it with validated systems such as APACHE II.

AIM AND OBJECTIVES:

- 1) To study the correlation between the degree of micro albuminuria and severity of sepsis.
- 2) To evaluate whether the degree of micro albuminuria could predict mortality in sepsis.
- To develop a simple, inexpensive and dynamic marker of 3) critical illness.

Method of data collection:

- a) Study design: Prospective study in a tertiary care hospital.
- b) Sample size: 50
- c) Duration of study: 6 months.
- d) Method of collection of specimens and processing:
- Spot urine sample was collected within 6 hours and at 24 hours of admission to medical emergency/ICU ward. Sample tested for urine micro albumin by using immunoturbidometric method and for urine creatinine by Jaffee method. Urine albumin: creatinine ratio was calculated. (At 6 hours ACR-1 and at 24 hours ACR-2).
- APACHE II scoring was done at 24 hours of admission.

Patients were followed up during the course of hospital stay and the outcome of the patient (i.e. Death/Survival) is recorded.

| Physiologic Variable | | Hig | h Abnorm | al Range | | | Lo | w Abnorm | al Range | |
|--|--------------|---------------------------------|---------------|---------------------------------|----------------------------------|--------------------|-------------------------------------|-------------------------------------|----------------|----------|
| 500 500 C | +4 | +3 | +2 | +1 | 0 | +1 | +2 | +3 | +4 | Points |
| Temperature - rectal (°C) | <u>≥</u> 41° | 39 to 40.9° | | 38.5 to 38.9° | 36 to 38.4° | 34 to 35.9° | 32 to 33.9° | 30 to 31.9° | <u>≤</u> 29.9° | |
| Mean Arterial Pressure - mm Hg | <u>≥</u> 160 | 130 to 159 | 110 to 129 | | 70 to 109 | | 50 to 69 | | <u><</u> 49 | |
| Heart Rate (ventricular response) | ≥180 | 140 to 179 | 110 to 139 | | 70 to 109 | | 55 to 69 | 40 to 54 | ≤39 | |
| Respiratory Rate (non-ventilated or ventilated) | ≥50 | 35 to 49 | | 25 to 34 | 12 to 24 | 10 to 11 | 6 to 9 | | _≤5 | |
| Oxygenation: A-aDO2 or PaO2 (mm Hg) a. FIO2 ≥0.5 record A-aDO2 b. FIO2 <0.5 record PaO2 | ≥500 | 350 to 499 | 200 to 349 | | <200 PO2>70 | PO2 61 to 70 | | PO2 55 to 60 | P02<55 | |
| Arterial pH (preferred) Serum HCO3 (venous mEq/l) (not preferred, but may use if no ABGs) | ≥7.7 ≥52 | 7.6 to 7.69 41 to 51.9 | | 7.5 to 7.59 32 to 40.9 | 7.33 to 7.49 22 to 31.9 | | 7.25 to 7.32 18 to 21.9 | 7.15 to 7.24 15 to 17.9 | <7.15 | |
| Serum Sodium (mEq/l) | ≥180 | 160 to 179 | 155 to 159 | 150 to 154 | 130 to 149 | | 120 to 129 | 111 to 119 | ≤110 | |
| Serum Potassium (mEq/l) | ≥7 | 6 to 6.9 | | 5.5 to 5.9 | 3.5 to 5.4 | 3 to 3.4 | 2.5 to 2.9 | | <2.5 | |
| Serum Creatinine (mg/dl) Double point score for acute renal failure | ≥3.5 | 2 to 3.4 | 1.5 to 1.9 | | 0.6 to 1.4 | | <0.6 | | | |
| Hematocrit (%) | <u>≥</u> 60 | | 50 to 59.9 | 46 to 49.9 | 30 to 45.9 | | 20 to 29.9 | | <20 | |
| White Blood Count (total/mm3) (in 1000s) | ≥40 | | 20 to 39.9 | 15 to 19.9 | 3 to 14.9 | | 1 to 2.9 | | <1 | |
| Glasgow Coma Score (GCS) Score = 15 minus actual GCS | | | | | | | | | | |
| A. Total Acute Physiolog | y Score | (sum of 1 | 2 above p | points) | 24-5-525 | _/ | | | | |
| b. Age points (years) < C. Chronic Health Points | (see he | to 54=2 | ; 33 10 64 | =3; 65 t0 | /4=0) <u>2</u> /5 | -6 | | | | - |
| Total ADACHE II Score (| add tone | ther the | points from | m 4+8+C) | | | | | | <u> </u> |

INCLUSION CRITERIA:

Patients admitted to medical emergency ward/medical ICU/ward in Kamineni Institute of Medical Sciences, Narketpally with features of SIRS (systemic inflammatory response syndrome) and suspected infection.

Systemic inflammatory response syndrome (SIRS): Presence of two or more of the following:

- Fever (oral temperature more than 38°C) or hypothermia (less than 36°C).
- Tachycardia (heart rate more than 90 beats per min).
- Tachypnea (more than 24 beats per min).
- Leukocytosis (more than 12,000/ μ L), leukopenia (less than $4.000/\mu$ L) or presence of more than 10 percent bands.

EXCLUSION CRITERIA:

- Patients with preexisting chronic kidney disease
- · Patients with proteinuria due to renal/post renal causes
- Patients with preexisting urinary tract infection
- Patients receiving nephrotoxic drugs
- Patients with urologic trauma resulting in frank hematuria or urinary tract infection
- Anuria
- Patients less than 16 yrs

Investigations:

Hemogram Blood urea serum creatinine Serum electrolytes Random blood sugar Liver function test Urine culture sensitivity Blood culture sensitivity Sputum culture sensitivity (if needed) Arterial blood gas analysis Chest X ray ECG/USG KUB/Abdomen (if needed) CSF analysis (in suspected meningitis)

Data was 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 obtained. Patient was followed up during the hospital stay and the outcome of the patient (i.e., Death/survival) is recorded.

Data Analysis and interpretation:

Data was entered into Microsoft excel and analysis were done using the statistical Package for Social Sciences (SPSS) for windows software (version 18.0; SPSS Inc, Chicago). The chisquare test and fisher's exact test was used to show the associations between predictor and outcome variables. The level of significance was set at 0.05.

OBSERVATION AND RESULTS

Table 1: Distribution of patients according to age group and outcome.

| AGE IN YEARS | DE | ATH | 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 | | | 10 | 6-85 | | |

In this study the lowest age in this group of patients was 16 Years and the highest age in this group was 85 Years. The mean age of the study group was 43.5 with the SD of 15.8.



Table 2: Distribution of patients according to gender and outcome.

| GENDER | DEATH | | SURV | IVED | TOTAL | | |
|--------|-------|----|------|------|-------|-----|--|
| | No. | % | No. | % | No. | % | |
| MALE | 14 | 28 | 17 | 34 | 31 | 62 | |
| FEMALE | 5 | 10 | 14 | 28 | 19 | 38 | |
| TOTAL | 19 | 38 | 31 | 62 | 50 | 100 | |

In this study out of 50 patients, 19 were female (38%) as compared to 31 male (62%).Among the 19 Non Survivors 5 were female (26.21 %) and 14 were male (73.68%). Among the 31 survivors 14 were female.



| Table 3: E | Distribution | of patients | according | to SIRS | criteria |
|------------|--------------|-------------|-----------|---------|----------|
| and outco | me. | | | | |

| 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 |

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In this study out of 50 patients 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%.



Table 4: Distribution of patients according to APACHEII Score and outcome.

| APACHE II | DEATH | | SURVI | 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 – 3 | 57 | | |
| p Value | | | < 0.00 | 01 | | |

In this study out of 50 patients APACHE II score ranged from 6 to 37 with a mean value of $19.82(SD\pm8.11)$. 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%)

The mean APACHE II score among the survivors was 16.35 with Standard Deviation of 6.78, when compared to the mean value of non survivors was 25.47 with Standard Deviation of 6.93 .As the P value was <0.0001, hence it was statistically significant.



| Table 5: Distribution of | f patients accord | ding to ACR1 | (Albumin |
|--------------------------|-------------------|--------------|----------|
| Creatinine Ratio) and | outcome. | | |

| ACR 1 | DEA | 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 | 164.5 | 53±46.61 | 74.00 | 6±20.83 | 108 | .44 ± 55.05 | |
| Range | | | 33 – | 245 | | | |
| p Value | | | < 0.0 | 001 | | | |

In this study out of 50 patients Urine Micro Albumin Creatinine Ratio done on admission ranged 33 to 245 microgram/mg.

Out of 16 patients (32%) who had ACR l value more than 109.5, all the 16 patients died. Out of 34 patients (68%) who had ACR l value less than 109.5, three patients died (8.82%). There is statistically significant P value of < 0.0001.

Table 6: Distribution of patients according to ACR2 (Albumin Creatinine Ratio) and outcome.

| 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 | | |

In this study out of 50 patients 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 < 0.001.

Table 7: Co-relation between Microalbuminuria and APACHEII Score.

| | Mean | | Standard Deviation | | |
|------------------------------------|------------------------------------|---------|--------------------|-----|----------|
| APACHE II SCORE | 19. | 82 | 8.113 | | |
| URINE ACR 1 | 88. | 38 | 60.960 | | |
| URINE ACR 2 | 108 | 3.44 | 55.055 | | |
| Co-relation | | Co-rela | tion efficient | Co- | p value |
| Urine ACR 1 and APACHE II score | Urine ACR 1 and APACHE II score | | | | <0.0001 |
| Urine ACR 2 and APACHE II score | | 0.726 | | | < 0.0001 |
| Urine ACR 1 and Uri ACR 2 | Urine ACR 1 and Urine ACR 2 | | | | < 0.0001 |

There is good co-relation between Urine ACR and APACHE II score. The p value is $<\!0.0001$, which is statistically significant

DISCUSSION

1)AGE

Patients were distributed from age 15 to 85 years with age >60 years constituting 8%. Mean age of the study population was 43.5 years (SD 15.8).

A study conducted by S Todi et al (2010) showed mean age of 58.17 years (SD 18.66) and a study done by Angus DC et al showed mean age of 57.Patients with age > 60 years constituted 34.8% of the study population.⁵

2) SEX

In the present study 19 patients (38%) were female and 31 patients were male (62%). In a study conducted by S Todi et al in India which studied epidemiology of sepsis in which male patients constituting 57.71%.⁵ study done by Angus DC et al⁶

showed male patients constituted 51.9%. This study shows that sepsis is more common among males compared to females.

Comparision of Gender distribution of patients with other studies

| Study | Āngus DC et [°] αl | S todi et αl ⁵ | Present study |
|---------|-----------------------------|----------------|---------------|
| % male | 51.9% | 57.71% | 57.81% |
| %female | 48.1% | 42.29% | 38% |

3) SIRS CRITERIA

In the present study 27 patients (54%) had all the 4 criteria for SIRS, 19 patients (38%) had 3 criteria and 4 patients (8%) had 2 criteria.

4) ORGAN DYSFUNCTION

Cardiovascular system: 33 Patients (66 %) had cardiovascular system dysfunction in the form of MAP < 70 mmHg, mean

ACR1 and ACR2 were 116.45 g/mg and 101.09 μ g/mg among patients with cardiovascular dysfunction and 92.88 μ g/mg and 63.7 μ g/mg among patients with no cardiovascular dysfunction.

P value was statistically significant.

Renal system: 19 patients (38%) had renal dysfunction in the form of urine output <0.5L/24 hr. Median ACR1 and ACR2 were 102 μ g/mg and 84 μ g/mg among patients with renal dysfunction and 88 μ g/mg and 53 μ g/mg among patients with no renal dysfunction. P value was statistically significant.

Hematologic system: 7 patients (14 %) had hematologic dysfunction in the form of platelet count <80000/cumm.

5) MORTALITY

Mortality percentage in this study was 38%. This is consistent with various studies including study done by Rangel-Frausto MS et al ⁷which showed mortality ranging from 20-35% and study conducted by Greg S et al 2006 which showed case fatality increased linearly with age and age was an independent predictor of mortality.⁸

A study done by Angus DC⁶ et al showed that women had less age specific incidence and mortality rates compared to men. In this study out of 50 patients, among the 19 Non Survivors 5 were female (26.2.1 %) and 14 were male (73.68%). In this study mortality rate is higher in males than females. Among the 19 patients who died 7 (36.84%) 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 criterion of the study.

A study done by Angus DC et al ⁶ showed that 44% of the cause of mortality had a respiratory source of infection, 17.3 % had bacteremia from an unidentified source and 8.6 % had an abdominal source and 6.6 % had local wound as a source of infection.

Similar study done by dolin et al⁹ showed that most common primary sources of infection resulting in sepsis are the lungs, the abdomen, and the urinary tract. Of the 19 patients who died 4 patients (8%) were immunocompromised.

6) APACHE II SCORE

In this study out of 50 patients APACHE II score ranged from 6 to 37 with a mean value of $19.82(SD\pm8.11)$. 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%)

The mean APACHE II score among the survivors was 16.35 with Standard Deviation of 6.78, when compared to the mean value of non survivors was 25.47 with Standard Deviation of 6.93 .As the P value was <0.0001, hence it was statistically significant.

7) URINE ACR 1 (Albumin Creatinine Ratio):

Urine for ACR (Urine Albumin Creatinine Ratio) collected on admission (Urine ACR1) and within 24 hour of admission (Urine ACR2). In this study out of 50 patients Urine Micro Albumin Creatinine Ratio done on admission ranged 33 to 245 microgram/mg with mean value of 108.44 ± 55.05 . Urine ACR1 differed significantly among survivors and non survivors. Patients who survived had mean ACR1 of $74.06 \pm 20.83 \mu g/mg$ and patients who died had mean ACR1 of $164.53 \pm 46.61 \mu g/mg$.

| ACR 1 | Gosling et al ³ | S Basu et al 10 | Present study |
|--------------|----------------------------|-----------------|---------------|
| Survivor | 70.4 | 108 | 84 |
| Non survivor | 168.6 | 156.6 | 158 |
| p value | 0.0002 | 0.0004 | 0.0001 |

Out of 16 patients (32%) who had ACR value more than 109.5, all the 16 patients died. Out of 34 patients (68%) who had ACR value less than 109.5, three patients died (8.82%).There is statistically significant P value of < 0.0001 for survivor and non survivor.

8) URINE ACR 2 (Albumin Creatinine Ratio):

In this study out of 50 patients Urine Micro Albumin Creatinine Ratio done on admission ranged 15 to 221 microgram/mg with mean value of 88.38 ± 60.96 . 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 value less than 118.5, three patients died (8.82%). Urine ACR 2 differed significantly among survivors and non survivors. Patients who survived had mean ACR2 of $45.81 \pm 17.92\mu$ g/mg and patients who died had mean ACR2 of $157.84 \pm 36.96\mu$ g/mg. There is statistically significant P value of < 0.0001 for survivor and non-survivor. A study done by gosling et al showed that Urine ACR at 24 hours was 36.96μ g/mg among survivors and 156.64μ g/mg among mon-survivors with significant p value of 0.0002(Mann Whitney test).

Comparison of median Urine ACR2 with other studies ACR2

| ACR 2 | Gosling et al ³ | S Basu et al ¹⁰ | Present study |
|--------------|----------------------------|----------------------------|---------------|
| Survivor | 36.96 | 50.8 | 46 |
| Non surviour | 156.64 | 154 | 155 |
| P value | 0.0002 | 0.0004 | 0.0001 |

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 tool.

Hence microalbuminuria can be used as dynamic marker of sepsis.

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