Print ISSN: 2321-6379
Online ISSN: 2321-595X

Original Article

Clinical Study using Urinary Albumin/Creatinine Ratio as an Early Predictor of Prognosis in Critically Ill Septic Patients

Anesh Ashok[1], P Muhammed Mushtaque[2]

[1]Assistant Professor, Department of Medicine, Kannur Medical College, Kannur, Kerala, India, [2]Associate Professor, Department of Medicine, Kannur Medical College, Kannur, Kerala, India

Abstract

Background: Sepsis following surgery or trauma remains one of the leading causes of morbidity and mortality in hospital populations, especially in populations in intensive care units (ICUs). The key to successful control of sepsis-associated infections is early prediction and rapid treatment of the disease. Standard clinical and laboratory parameter testing estimate the levels of expression of interleukin-1 β (IL-1 β), IL-6, IL-8, and IL-10, tumor necrosis factor-α, FasL (Fas ligand is a type-II transmembrane protein), and CCL2 (C-C Motif Chemokines Ligand 2) mRNA and growth differentiation factor-15. These are a few measured by real- time reverse transcriptase polymerase chain reaction.

Aim of the Study: In this study, evaluation of the urinary albumin/creatinine ratio (ACR) was used as a prognostic predictor in critically ill sepsis patients.

Materials and Methods: In a prospective observational study, 365 adult critically septic patients were included. After clinical evaluation, urine spot samples were collected on admission and 24 h later for ACR1 and ACR2. Admission Acute Physiology and Chronic Health Evaluation (APACHE) IV score and the highest recorded Sepsis-related Organ Failure Assessment (SOFA) score of their daily estimation were considered. The need for mechanical ventilation was assessed in addition to inotropic and/or vasoactive support, renal replacement therapy (RRT), and in-hospital mortality.

Observations and Results: A total of 365 patients who were critically ill with sepsis were initially recruited to this study. The patients included in this study were aged between 28 and 87 with a mean age of 62.37 ± 9.15 years. There were 235 (64.38%) males and 130 females (35.61%). The highest SOFA score was 7.4 (4.0–14.0) ranging from 1 to 17 and APACHE IV score recorded within the first 24 h of ICU admission was 76.8 (58.8–98.0) ranging from 46 to 118. Of 365 patients, 191 (52.32%) required ventilator support, 201 (55.06%) needed inotropic and/or vasoactive support to maintain hemodynamics, and 71 (19.45%) needed RRT. The mean length of hospital stay in the present study was 17.65 ± 8.60 days.

Conclusions: Evaluating the urinary ACR values regularly in all critically ill sepsis patients was a simple, rapid, non-invasive, inexpensive, easy to perform, and interpret test for early prognosis and prediction of mortality.

Key words: Microalbuminuria, Mortality, Sepsis, Urinary albumin/creatinine ratio

INTRODUCTION

Sepsis occurs in 1%–2% of all hospitalized patients and sepsis is a major cause of morbidity and mortality and the second leading cause of death worldwide.[1] Epidemiological studies are based on community or hospital studies, and the nature of data collection such as retrospective chart review, discharge diagnoses, diagnosis in death certificates, or prospective observational studies gives different figures. A robust epidemiological study methodology should be prospective in nature conducted over a prolonged period and should include heterogeneous case mix representative of the disease, thus allowing scope for generalizing the observed data. Epidemiological data on sepsis come mostly from western literature.[1-6] Data from India are sparse and in the form of epidemiology of infection

Access this article online

www.ijss-sn.com

Month of Submission : 04-0000
Month of Peer Review : 05-0000
Month of Acceptance : 05-0000
Month of Publishing : 06-0000

Corresponding Author: Dr. P Muhammed Mushtaque, Department of Medicine, Kannur Medical College, Anjarakandy, Kannur, Kerala, India.

(both community and hospital acquired) rather than sepsis which is a host response to infection.[7-10] Moreover, literature and surveys conducted in India concentrate on the microbiological profile, resistance pattern, antibiotic usage, and outcome rather than sepsis epidemiology. In the United States, sepsis causes more than 200,000 deaths each year.[2] Sepsis is characterized by a severe host defense response that involves triggering of potent inflammatory cascades which release a plethora of pro-inflammatory and anti-inflammatory molecules into the circulation.[11] The endothelial dysfunction is a milestone in sepsis pathogenesis. An early feature of sepsis is the loss of endothelial barrier integrity, leading to systemic capillary leak.[12] This enhanced capillary permeability causes increased glomerular excretion of albumin in the urine.[13] Microalbuminuria has been accordingly seen by several studies to occur early after severe inflammatory process and to persist in more severe cases.[14-17] Early prediction of mortality among critically ill sepsis patients and early institution of intensive therapy are of paramount importance. Various ICUs scoring systems such as the APACHE II, APACHE IV, and Simplified Acute Physiology II scores to predict mortality are in current use. These scoring systems require a large number of variables derived from the patient's history, examination, and initial laboratory data. Microalbuminuria was shown to be promising as a predictor of organ failure, vasopressors requirement, and mortality prediction. It was shown to be even better than APACHE II and SOFA scores in some studies.[18-20] In the present study, an attempt was made to evaluate the prognostic value of urinary ACR in patients with sepsis and to compare this prognostic value with the APACHE IV and SOFA scoring systems.

Type of Study

This was a prospective, cross-sectional, and observational and analytical study.

Institute of Study

This study was conducted at Kannur Medical College, Anjarakandy, Kannur, Kerala, India.

Period of Study

The study duration was from May 2017 to April 2019.

MATERIALS AND METHODS

In this prospective observational and analytical study, 365 critically ill patients with sepsis who were admitted to surgical/medical ICUs were included. Kannur Medical College Hospital was a 750-bed tertiary care hospital attaché to a teaching institute. An ethical committee clearance was obtained before the commencement of the study. An ethical committee approved consent form signed by the patient or his/her attendant was obtained before collecting the data.

Inclusion Criteria

1. Patients with diagnosis of sepsis syndrome with the presence of systemic inflammatory response syndrome based on the diagnostic criteria of 1992 ACCP[21] were included
2. Patients with[22] Society of Critical Care Medicine criteria with its update in 2001 "International Sepsis Definition Conference," exhibiting two or more of the following signs: (1) Temperature of >38°C or 90 beats/min, (3) respiratory rate of >20 breaths/min or hyperventilation with a PaCO2 of 12,000 lL1, or 10% immature cells were included. The presence of infection was defined according to the clinical and microbiological criteria of the Centers for Disease Control and Prevention definitions[23] and was held as a gold standard.

Exclusion Criteria

1. Patients aged <18-year-old, patients with anuria or hematuria, patients with preexisting chronic kidney disease, patients with diabetes mellitus, patients with proteinuria due to renal or post-renal causes, patients with urinary tract infection, and patients with ICU length of stay (LOS) <24 h were excluded. All the patients were examined and determined by two independent experts who examined the patients daily for the first 48 h of admission. All the patients included in the study were subjected for clinical evaluation including history, physical examination, routine laboratory investigations (capillary blood glucose, coagulation profile, arterial blood gases, liver function tests, kidney function tests, random blood sugar, and serum electrolytes), and cultures from suspected sources of infection including sputum and urine. For all the patients at least two blood cultures obtained from different venipunctures were obtained before antibiotic administration. APACHE IV score was calculated in an integer score form that is web-based computed by applying worst values of the measurements observed during 24 h following ICU admission, with a maximum score of 286. Other parameters of disease severity that were studied included need for mechanical ventilation, need for inotropic and/or vasoactive support, and need for RRT. Outcome was evaluated by ICU-LOS and the in-hospital mortality. Urinary ACR urine spot samples were collected at the time of ICU admission for ACR1 and 24 h following ICU admission for ACR2. Urinary microalbumin was measured by the immunoturbidimetric method and urinary creatinine by modified kinetic Jaffe reaction (Dimension RxL Max, Dade Behring Inc., U. S. A.). A trend of microalbuminuria was assessed as the change from ACR1 to ACR2. The difference between those values represents the delta ACR

(D ACR) and is calculated as D ACR = ACR2 ACR1. When D ACR is negative, it is defined as decreasing ACR and when it is positive, it is defined as increasing ACR. SOFA score was calculated in all the patients right from the admission to the time of discharge or demise. All the data were analyzed using standard statistical methods.

OBSERVATIONS AND RESULTS

A total of 365 patients who were critically ill with sepsis were initially recruited to this study. The patients included in this study were aged between 28 and 87 with a mean age of 62.37 ± 9.15 years. There were 235 (64.38%) males and 130 females (35.61%). Table 1 shows the various causes and sources of infection in the present study subjects. The highest SOFA score was 7.4 (4.0–14.0) ranging from 1 to 17 and APACHE IV score recorded within the first 24 h of ICU admission was 76.8 (58.8–98.0) ranging from 46 to 118. Of 365 patients, 191 (52.32%) required ventilator support, 201 (55.06%) needed inotropic and/or vasoactive support to maintain hemodynamics, and 71 (19.45%) needed RRT. The mean length of hospital stay in the present study was 17.65 ± 8.60 days. One hundred and thirty-seven (37.53%) patients died and the remaining survived their ICU course (Figure 1). ACR measurements: ACR measured on admission (ACR1) was 116.7 (79.1–153.9) with a range from 27 to 221 mg/g and the 24 h ACR (ACR2) was 138.3 (65.2–193.2) ranging from 23 to 245 mg/g. The ACR was decreased in 160 patients (43.83%) by 31 (24.1–38.9) mg/g and it was increased in 205 (56.16%) by 36.7 (25.7–58.95) mg/g. ACR in relation to disease severity, the ACR1 was not significantly correlated with SOFA (r = 0.216, P = 0.143) or APACHE IV (r = 0.178, P = 0.301) scores while the ACR2 was positively correlated with SOFA score (r = 0.315, P = 0.023) but not with APACHE IV score (r = 0.277, P = 0.076), (p significant at < 0.05). The SOFA score was significantly higher in patients with increased ACR trend 13 (4.15–15.35) than in patients with stationary or declining trend 5.2 (3–8) (P = 0.01). Meanwhile, there was no significant difference in APACHE IV between patients with increased ACR trend 89.15 (57.7–99.03) and those with stationary or declining ACR trend 64 (53–81) (P = 0.201). The ACR1 was not statistically different in patients who needed and those who did not need mechanical ventilation; 113.8 (96.25–184.14) versus 83.40 (71.8–140.70), respectively (P = 0.09), while ACR2 was significantly higher in patients who required mechanical ventilation compared to those who did not need 137.40 (122.80–201.3) versus 64.05 (46.03–171.15).

Table 1: The different sources of infection in the study group (*n*=365)

Source of sepsis	*n* (%)
Chest infection	220 (60.27)
Peritonitis	072 (19.72)
Infected bed sores	027 (07.39)
Wound infection	046 (12.60)

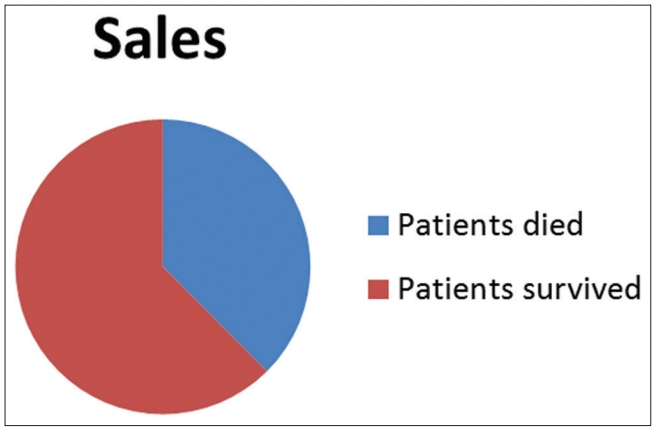

Figure 1: The mortality rate in the study (Blue: 37.53, Pink: 62.46%)

Considering the change in ACR, it was observed in this study that the increase in ACR was a predictor of the need of mechanical ventilation. Of the 205 patients with increased ACR, 155 (75.60%) needed mechanical ventilation while 50 (24.39%) did not (P = 0.010). A similar relation was found between ACR1 and ACR2 and the need of inotropic and/or vasoactive support. ACR1 was not significantly different in patients who needed and those who did not need inotropic and/or vasoactive support (112.65 [96.3–200.80] vs. 98.5 [72.0–135.6], respectively, P = 0.040) while ACR2 was significantly higher in patients who needed inotropic and/or vasoactive support compared to those who did not need (151.15 [125.85–218.2] vs. 73.3 [51.7–159.5], respectively, P = 0.018). Considering the change in ACR, we found that the increase in ACR was a predictor of need of inotropic and/or vasoactive support. Of the 205 patients with increased ACR, 136 patients (66.34%) needed inotropic and/or vasoactive support while 69 patients (33.65%) did not (P = 0.015). Neither ACR1 nor ACR2 was significantly related to the need for RRT in this study. ACR1 was 111.05 (96.4–140.70) versus 113.2 (83.09–171.60) for those who needed and did not need RRT, respectively, P = 0.712 and ACR2 was 137.40 (121.3–163.8) versus 133.05 (55.24–193.0), P = 0.431. Even the increase in ACR overtime was not significantly associated with the need for RRT. Of the 205 patients with increased ACR, 56 patients (27.31%) needed RRT while 149 patients (72.68%) did not (P = 0.340).

ACR and Outcome

The ACR1 and ACR2 revealed significantly positive correlation with ICU-LOS (r = 0.5, P = 0.007 for ACR1 and r = 0.4, P = 0.05 for ACR2). Both ACR1 and ACR2

were a significant predictor for mortality in our patients' population. ACR1 and ACR2 were 120.83 (101.3–184.31) mg/g and 191.0 (136.4–216.8) mg/g in non-survivors compared to 90.8 (72.3–128.4) mg/g and 69.1 (49.3–132.5) mg/g for survivors ($P = 0.009$ and <0.001 for ACR1 and ACR2, respectively).

DISCUSSION

Sepsis is not only a great health problem but also an important socioeconomic challenge worldwide. It lowers patients' living quality and increases the mortality significantly.[1] Identification of sepsis, its prognosis, and outcome prediction are of paramount importance in medical practice. At present, available tools for prediction of prognosis in ICU are the APACHE scores,[24] which predict mortality, and the SOFA score,[25] which predicts morbidity. These scoring systems rely on several physiological indices and chemical analyses. In addition to difficulty in estimation, several drawbacks and limitations have been shown to these scoring systems.[26] No definite laboratory biomarkers had been definitively demonstrated to correlate with severity of illness and mortality in ICU patients. Several clinical studies on critically ill patients with severe endothelial and renal involvement showed that microalbuminuria may be a beneficial marker of disease severity and mortality prediction[18,19] and it may indirectly quantify changes in systemic vascular permeability.[13] Few authors had identified microalbuminuria as a significant prognostic marker of morbidity and mortality.[23] The level of microalbuminuria starts to increase within hours of an inflammatory insult as against delayed increases in levels of many other mediators.[27] In the present study, an attempt was made to evaluate the prognostic value of urinary ACR in sepsis in the intensive care setting and to compare this prognostic value with the APACHE IV and SOFA scoring systems. The commonly known factors that may cause increased ACR and that might be confounding are the diabetes mellitus and chronic kidney disease; accordingly, hence, these conditions were excluded. Sepsis is characterized by widespread endothelial dysfunction arising from the effects of cytokines, and other inflammatory mediators released during the intense inflammatory responses, leading to systemic increase in capillary permeability.[11] The increased capillary permeability in the pulmonary circulation contributes into ARDS,[26] in systemic circulation contributes into sepsis-induced hypotension,[27] and in renal circulation causes increased amounts of albumin to escape into the glomerular ultrafiltrate. The tubular reabsorptive mechanism for albumin from the ultrafiltrate is exceeded beyond its threshold capacity, leading to increased excretion of albumin in the urine.[28] As a marker of increased permeability, microalbuminuria was supposed to indicate the development of ARDS, hemodynamic compromise, and acute kidney injury. Accordingly, in this study, observation of the use of mechanical ventilation, inotropic and/or vasoactive support, and RRT as severity indicators were done. Here was no significant correlation between ACR1 obtained on admission and either SOFA or APACHE IV scores while ACR2 obtained 24 h later significantly correlated with SOFA score and had a statistically non-significant tendency for correlation with APACHE IV score. It was also found that the SOFA score while not APACHE IV score is higher in patients with an increasing trend of ACR. In a medical/surgical critically ill patients, Basu *et al.* found that ACR 6 and 24 h after admission were correlated with APACHE II score.[28] De Gaudio *et al.*[14] reported an increasing ACR to be positively correlated with an increasing SOFA score in 55 post-operative patients with sepsis. It was observed in this study that the ACR2 and the Δ ACR and not the ACR1 are associated with a higher incidence of need of mechanical ventilation and need of inotropic and/or vasoactive support. Other authors also found that ACR is inversely associated with the PaO2/FiO2 ratio in post-trauma patients and was associated with significantly more duration of mechanical ventilation in patients with initially normal lung function.[29] The mean length of hospital stay in the present study was 17.65 ± 8.60 days. There was a positive correlation between the ACR on admission and 24 h later and the ICU-LOS. Gosling *et al.* found that ACR values positively correlate with ICU-LOS.[29] In Gosling's study, the ACR was measured on admission and 6 h later. APACHE IV, ACR1, and ACR2 were found to be predictors for mortality in this study. The AUC for ROC analysis was highest for APACHE IV score (0.905) followed by ACR2 (0.876) and then ACR1 (0.755). We found an APACHE IV score of 72.5 to have 100% sensitivity and 80% specificity, ACR1 of 86.3 mg/g to have 100% sensitivity and 50% specificity, and ACR2 of 110.5 mg/g to have 100% sensitivity and 86.2% specificity to predict mortality. It was also observed that the trend of ACR overtime is a predictor of mortality with higher mortality in those with an increase in ACR2 compared to ACR1. The increase in ACR was associated with 89% sensitivity and 68% specificity for detection of mortality in sepsis patients.

CONCLUSIONS

Evaluating the urinary ACR values regularly in all critically ill sepsis patients was a simple, rapid, non-invasive, inexpensive, easy to perform, and interpret test for early prognosis and prediction of mortality. Late ACR after 24 h from ICU admission and ACR trend overtime might be more important than the earlier admission ACR. Thus,

together with conventional illness severity scores, the measurement of ACR on admission to the ICU, and 24 h later, can provide additional information on patient outcome.

REFERENCES

1. Linde-Zwirble WT, Angus DC. Severe sepsis epidemiology: Sampling, selection, and society. Crit Care 2004;8:222-6.
2. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. Crit Care Med 2001; 29:1303-10.
3. Finfer S, Bellomo R, Lipman J, French C, Dobb G, Myburgh J. Adult-population incidence of severe sepsis in Australian and New Zealand intensive care units. Intensive Care Med 2004;30:589-96.
4. Alberti C, Brun-Buisson C, Burchardi H, Martin C, Goodman S, Artigas A, *et al.* Epidemiology of sepsis and infection in ICU patients from an international multicentre cohort study. Intensive Care Med 2002; 28:108-21.
5. Harrison DA, Welch CA, Eddleston JM. The epidemiology of severe sepsis in England, Wales and Northern Ireland, 1996 to 2004: Secondary analysis of a high quality clinical database, the ICNARC case mix programme database. Crit Care 2006;10:R42.
6. Vincent JL, Sakr Y, Sprung CL, Ranieri VM, Reinhart K, Gerlach H, *et al.* Sepsis in European intensive care units: Results of the SOAP study. Crit Care Med 2006;34:344-53.
7. Ghanshani RV, Gupta R, Sood S, Bansal A, Joad SH, Khedar RS. Epidemiology of infections in a medical ICU in India. Intensive Care Med 2014;40:456-7.
8. Agarwal R, Gupta D, Ray P, Aggarwal AN, Jindal SK. Epidemiology, risk factors and outcome of nosocomial infections in a respiratory intensive care unit in North India. J Infect 2006;53:98-105.
9. Ghanshani R, Gupta R, Gupta BS, Kalra S, Khedar RS, Sood S. Epidemiological study of prevalence, determinants, and outcomes of infections in medical ICU at a tertiary care hospital in India. Lung India 2015;32:441-8.
10. Pradhan NP, Bhat SM, Ghadage DP. Nosocomial infections in the medical ICU: A retrospective study highlighting their prevalence, microbiological profile and impact on ICU stay and mortality. J Assoc Physicians India 2014;62:18-21.
11. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. N Engl J Med 2003;348:138-50.
12. Aird WC. The role of the endothelium in severe sepsis and multiple organ dysfunction syndrome. Blood 2003;101:3765-77.
13. Gosling P. Microalbuminuria: A marker of systemic disease. Br J Hosp Med 1995;54:285-90.
14. 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.
15. Szakmány T, Molnár Z. Increased glomerular permeability and pulmonary dysfunction following major surgery: Correlation of microalbuminuria and paO/FiO ratio. Acta Anaesthesiol Scand 2004;48:704-10.
16. Yew WS, Pal SK. Correlation of microalbuminuria and outcome in patients with extensive burns. Br J Anaesth 2006;97:499-502.
17. 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.
18. 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.
19. 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.
20. 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.
21. Bone RC, Balk RA, Cerra FB, Dellinger RP, Fein AM, Knaus WA, *et al.* Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM consensus conference committee. American college of chest physicians/Society of critical care medicine. Chest 1992;101:1644-55.
22. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, *et al.* 2001 SCCM/ESICM/ACCP/ATS/SIS international sepsis definitions conference. Crit Care Med 2003;31:1250-6.
23. 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.
24. Zimmerman JE, Kramer AA, McNair DS, Malila FM. Acute physiology and chronic health evaluation (APACHE) IV: Hospital mortality assessment for today's critically ill patients. Crit Care Med 2006;34:1297-310.
25. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonça A, Bruining H, *et al.* The SOFA (Sepsis-related organ failure assessment) score to describe organ dysfunction/failure. On behalf of the working group on sepsis-related problems of the European society of intensive care medicine. Intensive Care Med 1996;22:707-10.
26. Vincent JL, Moreno R. Clinical review: Scoring systems in the critically ill. Crit Care 2010;14:207.
27. Molnár Z, Szakmány T, Köszegi T, Tekeres M. Microalbuminuria and serum procalcitonin levels following oesophagectomy. Eur J Anaesthesiol 2000;17:464-5.
28. Basu S, Bhattacharya M, Chatterjee TK, Chaudhuri S, Todi SK, Majumdar A. Microalbuminuria: A novel biomarker of sepsis. Indian J Crit Care Med 2010;14:22-8.
29. Gosling P, Sanghera K, Dickson G. Generalized vascular permeability and pulmonary function in patients following serious trauma. J Trauma 1994;36:477-81.

How to cite this article: Ashok A, Mushtaque PM. Clinical Study Using Urinary Albumin/Creatinine Ratio as an Early Predictor of Prognosis in Critically Ill Septic Patients. Int J Sci Stud 2019;7(3):9-13.

Source of Support: Nil, **Conflict of Interest:** None declared.