ORIGINAL ARTICLE

Comparison of Epidemiology and Outcomes of Acute Kidney Injury in Critically Ill Patients with and without Sepsis

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Abstract

Objectives: In critically ill patients, acute kidney injury (AKI) and sepsis often coexist. This confounds the assessment of outcomes of both sepsis and AKI in these patients. Hence, in this study, we compare the outcomes of AKI with sepsis, AKI without sepsis, and sepsis without AKI against a control cohort comprising patients with neither AKI nor sepsis.

Materials and methods: Prospective observational study conducted in our critical care unit (CCU) between January and July 2009. Data including demographic details, acute physiology and chronic health evaluation (APACHE) III score, presence of AKI, presence of sepsis, intensive care unit (ICU) length of stay (LOS), and outcomes were collected for all patients. Acute Kidney Injury Network (AKIN) criteria were used to define the presence of AKI and American College of Critical Care Medicine 2001 definition was used to define the presence of sepsis.

Results: A total of 250 patients were included in the study and 8 patients were excluded from analysis as they were discharged from hospital against medical advice. The remaining 242 patients (mean age 52.8 $\pm$ 17 years; 61.6% male; APACHE III score: 48.2 $\pm$ 24.1) were analyzed, and AKI was seen in 111 patients (45.8%). Among the patients with AKI, 55.8% (62/111) had sepsis and 44.2% (49/111) had nonseptic AKI. There was a higher need for renal replacement therapy (RRT) among patients with septic AKI in comparison to those with nonseptic AKI (19.3% vs 6.1%; $p = 0.04$), but no mortality difference was seen between the two groups (25.8% vs 20.4%, $p = 0.5$). Patients with sepsis and AKI had a significantly higher mortality (25.8%) compared to the patients with sepsis alone (5.6%; $p < 0.01$).

Conclusion: Patients with septic AKI had a higher RRT requirement compared to patients with nonseptic AKI, but no significant differences in mortality were seen between the groups. Occurrence of AKI in septic patients substantially increases their mortality.

Keywords: Acute kidney injury, Acute kidney injury network, Sepsis.

Indian Journal of Critical Care Medicine (2020): 10.5005/jp-journals-10071-23386

Introduction

Acute kidney injury (AKI) is a common manifestation of critical illness that compounds the burden of the existing clinical problem.[1] Acute kidney injury independently predicts higher mortality and consumes considerable financial and healthcare resources.[2–5] The etiology of AKI in critically ill patients is often multifactorial with diverse epidemiology. Sepsis, a dysregulated cacophonic inflammatory response syndrome to infection, is the most common cause of AKI in critically ill patients.[1,6,7] Moreover, AKI and sepsis often coexist in a critically ill patient, confounding the prediction of prognosis and the assessment of outcomes of both sepsis and AKI.

The incidence of AKI among critically ill patients with sepsis ranges from 40 to 70% across various studies.[1,7–11] This wide variability could be due to the differences in diagnostic criteria used to define AKI and the population studied. Furthermore, recent evidence suggests that AKI associated with sepsis may have a distinct pathophysiology, course, and outcome compared to nonseptic AKI.[12,13] Most of the studies on AKI and sepsis have been reported from the developed world,[1,6–9,14] and similar data from India is sparse. A few Indian studies that have examined the entity of septic AKI either have been retrospective analyzes[15,16] or the study population was not representative of critically ill patients alone,[15] in whom the disease burden is the most severe and the prognosis grave. Two studies from India have analyzed AKI in sepsis among critically ill patients, but their study sample size was small.[17,18]

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How to cite this article: Nandagopal N, Reddy PK, Ranganathan L, Ramakrishnan N, Annigeri R, Venkataraman R. Comparison of Epidemiology and Outcomes of Acute Kidney Injury in Critically Ill Patients with and without Sepsis. Indian J Crit Care Med 2020;24(4): 258–262.

Source of support: Nil

Conflict of interest: None

We prospectively evaluated the clinical characteristics and outcomes of critically ill patients in the following groups: (a) AKI with sepsis, (b) AKI alone, (c) sepsis alone, and (d) the group without AKI and sepsis that formed the control cohort.

Materials and Methods

Study Population

This is a prospective observational study conducted in a multidisciplinary ICU of a tertiary hospital in South India between January 1, 2009 and July 31, 2009.

Definitions

The AKIN criteria[19] was used to define the presence of AKI, and American College of Critical Care Medicine 2001 definition was used to define the presence of sepsis.[20] Distinction was not made between sepsis, severe sepsis, and septic shock. Preexisting renal disease was defined as baseline serum creatinine >1.3 mg/dL in men and >1.2 mg/dL in women when available or was diagnosed by the attending nephrologist based on the available clinical information such as patient comorbidities, urine analysis, and ultrasound findings.

Inclusion Criteria

The patients admitted to the ICU with an ICU stay of more than 48 hours.

Exclusion Criteria

The patients admitted to coronary care unit, those readmitted to ICU within a single hospital admission, and those with any known preexisting renal disease were excluded from the study.

Methods and Data collection

We categorized patients according to the maximum AKIN class: stage 1, stage 2, or stage 3 reached during their hospital stay. Determination of the AKI class was done based on the worst of either serum creatinine or urine criteria. We calculated a serum creatinine level using the modified diet in renal disease (MDRD) equation (Cr MDRD) as recommended by the acute dialysis quality initiative (ADQI)[21] by solving the MDRD equation for serum creatinine, assuming a glomerular filtration rate of 75 mL/minute/1.73 m^2. We then used the lowest creatinine value among the hospital admission, the ICU admission, or the MDRD creatinine, as the baseline value. We used the change in this baseline serum creatinine level and urine output to classify patients according to the AKIN criteria. Patients who met any of the criteria in the AKIN classification were categorized as AKI patients.

Data including demographics, APACHE III score, presence of sepsis, need for mechanical ventilation, need for dialysis and dialysis modality, ICU LOS, and ICU and 28-day hospital mortality were collected. As this was an observational study, the institutional ethics committee waived approval.

Statistical Analysis

Student *t* test for quantitative variables and χ^2 test for qualitative variables were used for comparison. Kruskal–Wallis one-way analysis of variance was used to compare mortality rates between groups. Survival analysis was performed using Kaplan–Meier curves. Logistic regression was performed to determine the factors associated with ICU mortality. The variables which have been known to affect the mortality in AKI and those with a $p < 0.1$ on univariate analysis were included in the multivariate regression analysis to predict mortality. Receiver–operative characteristic (ROC) curves were plotted and area under the curve (AUC) was calculated for maximum AKIN, sepsis, and APACHE III score to test their validity in predicting mortality. A $p < 0.05$ was selected as the level of significance. Statistical analysis was done using the Statistical Package for Social Science (SPSS) version 17.0 (SPSS Inc., Chicago, IL).

Results

A total of 250 patients were included in the study and 8 patients were excluded from analysis since they were discharged from hospital against medical advice. The remaining 242 patients were analyzed. The mean age of the study population was 52.8 ± 17 years and 61.6% were male. The demographic data of the overall patient populations is shown in Table 1. Flowchart 1 shows the incidence of sepsis and AKI and their impact on mortality. Acute kidney injury was seen in 111 patients (45.8%) with 16 (6.6%) receiving RRT. The overall mortality in our study population was 12% (Table 1). Mortality among patients who received RRT was 50%. Table 2 shows the comparison of demographic data and outcomes in patients with and without sepsis and AKI. Patients with AKI had higher ICU LOS (8.4 ± 5.6 vs 6.4 ± 4 days, $p = 0.001$) and mortality (23.4 vs 3%, $p = 0.001$) compared to those without AKI.

Sepsis was the cause of AKI in 62 (55.8%) and remaining 49 (44.2%) had nonseptic AKI (Flowchart 1). No significant differences in age, APACHE III score, and ICU LOS were found between patients with septic AKI and nonseptic AKI (Table 2). There was a higher need for RRT among patients with septic AKI in comparison to those with nonseptic AKI (19.3% vs 6.1%; $p = 0.04$), but no mortality difference was seen between the two groups (25.8% vs 20.4%, $p = 0.5$) (Table 2). One patient with neither sepsis nor AKI needed RRT for phenobarbitone/benzodiazepine poisoning.

The patients with sepsis and AKI were older (56 ± 17.1 vs 48.8 ± 16.6, $p = 0.04$) and had significantly higher APACHE III score (62.6 ± 26.3 vs 44.1 ± 19.1, $p = 0.001$) compared to those with sepsis alone (Table 2). The presence of AKI among patients with sepsis had significantly higher mortality compared to sepsis alone (25.8% vs 5.6%, $p = 0.01$) (Table 2).

On multivariate analysis, APACHE III score ($p = 0.001$) and AKI ($p = 0.01$), but not sepsis, were the independent predictors of ICU mortality. The Kaplan–Meir survival curves for four groups classified based on the presence of AKI and sepsis is shown in Figure 1. Acute kidney injury with or without sepsis had similar and poor outcomes, whereas sepsis without AKI had similar outcome as patients with no sepsis and no AKI. The mortality increased with increase in the severity of AKI. Both APACHE III and AKI predicted mortality much better than the presence of sepsis, with the AUC of ROC of 0.815 for APACHE III, 0.809 for AKI, and 0.611 for sepsis, as shown in Figure 2.

Table 1: Baseline demographic characteristics and outcomes of the overall study population

Parameters	*Mean ± SD and percentage*
Total number of patients	250
Patients left against medical advice	8
Patients included in study	242
Age (years)	52.8 ± 17
Sex (male/female)	(149/93) (61.6%/38.4%)
APACHE III score	48.2 ± 24.1
AKI	111 (45%)
Renal replacement therapy	16 (6.6%)
CCU length of stay	7.4 ± 4.9
Mortality	30 (12%)

AKI, acute kidney injury; APACHE, acute physiology and chronic health evaluation; CCU, critical care unit

Flowchart 1: Interaction of acute kidney injury and sepsis and their outcomes in our study population

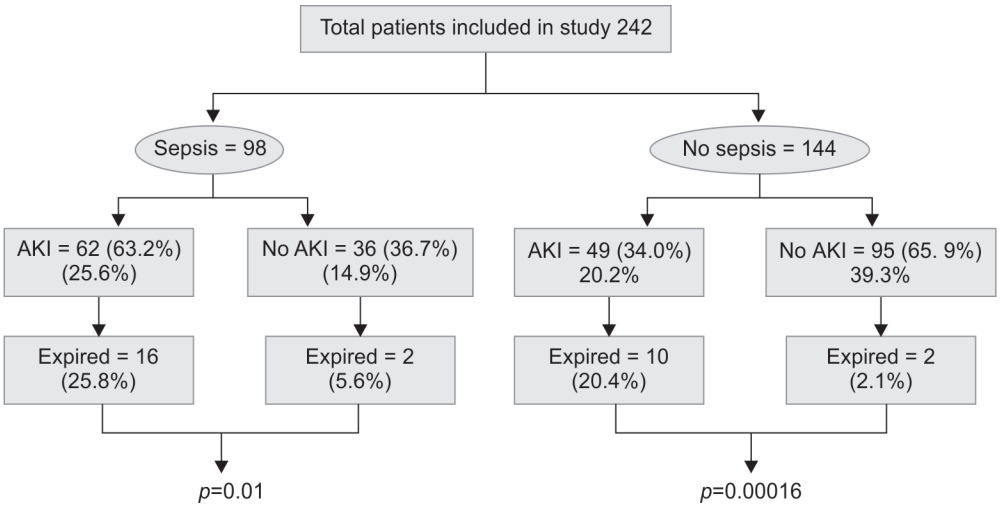

Table 2: Baseline characteristics and outcomes of patients AKIN with and without sepsis

Variables	*Group I, AKI with sepsis*	*Group II, AKI without sepsis*	*Group III, sepsis without AKI*	*Group IV, no sepsis no AKI*
No. of patients (242)	62 (25.6%)	49 (20.2%)	36 (14.9%)	95 (39.3%)
Gender (male/female)	39/23 (62.9%/37.1%)	36/13 (73.5%/26.5%)	22/14 (61.1%/38.9%)	52/43 (54.7%/45.3%)
Age	56 ± 17.1	54.3 ± 17.3	48.8 ± 16.6	51.4 ± 16.8
APACHE III score	62.6 ± 26.3	55.0 ± 23.9	44.1 ± 19.1	36.8 ± 17.6
CCU LOS	8.9 ± 5.9	7.9 ± 5.2	7.0 ± 4.04	6.2 ± 4.0
RRT	12 (19.3%)	3 (6.1%)	0	1 (1%)[±]
Mortality	16 (25.8%)	10 (20.4%)	2 (5.6%)	2 (2.1%)

AKI, acute kidney injury; APACHE, acute physiology and chronic health evaluation; CCU LOS, critical care unit length of stay
No significant difference in age, APACHE III score, CCU LOS, and mortality between those with septic AKI and nonseptic AKI.
AKI with sepsis had higher RRT requirement compared to AKI without sepsis (19.3 vs 6.1%, respectively, $p = 0.04$).
Among septic patients, those with AKI were older (mean age: 56 ± 17.1 vs 48.8 ± 16.6, $p = 0.04$), had higher severity of illness score (APACHE III: 62.6 ± 26.3 vs 44.1 ± 19.1, $p < 0.01$), and had higher mortality (25.8% vs 5.6%, $p = 0.01$) compared to those without AKI
Those with AKI had longer CCU LOS (8.4 ± 5.6 vs 6.4 ± 4 days, $p = 0.001$) and higher mortality (23.4 vs 3%, $p = 0.001$) as compared to those without AKI
[±]Patient did not have AKI; underwent RRT for phenobarbitone/benzodiazepine poisoning

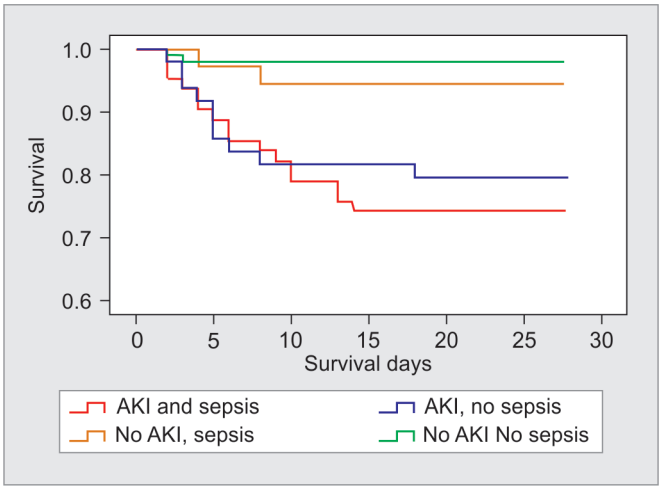

Fig. 1: Kaplan–Meier survival curves for patients with sepsis and acute kidney injury

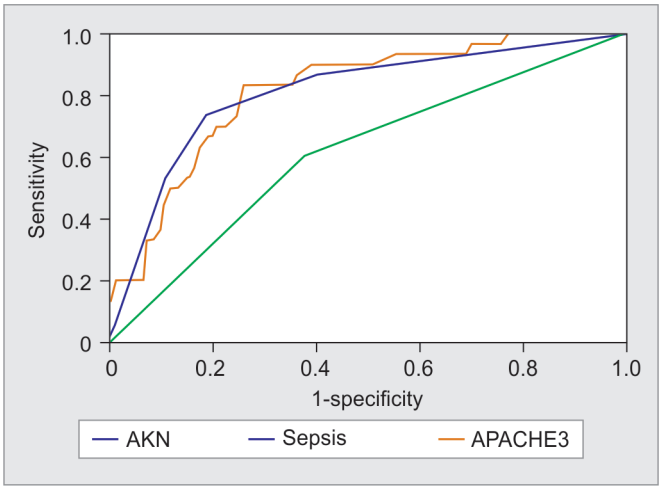

Fig. 2: Receiver–operating characteristics curves for prediction of mortality. *Area under the curve of ROC for APACHE III score was 0.815, for sepsis was 0.611, and for acute kidney injury was 0.809

Discussion

We conducted this study to investigate the effect of interaction of sepsis and AKI on the outcome of patients admitted to ICU. The incidence of AKI in our study population was 45.8%, which was similar to AKI incidences observed in several earlier studies from the developed world.[6–10] More than half of the patients with AKI had sepsis (55.9%), which was slightly higher, when compared to a large multicenter study by Neveu et al.[7] who found that AKI had a septic origin in 45.5% of patients. In patients with septic AKI, the mean age of patients was 56 ± 17.1 years and previous studies have reported an older mean age of 66 years.[22,23] However, we found that among septic patients, those with AKI were significantly older compared to those without AKI (56 ± 17.1 vs 48.8 ± 16.6, $p = 0.04$), a finding similar to earlier studies,[22,23] indicating an increased susceptibility of older population to AKI. Our study, however, differs from a prospective Indian study, which reported a much lower mean age of 38.6 years in patients with AKI due to sepsis.[17] Among patients with AKI, we found no difference in the age of septic AKI and nonseptic AKI patients (56 ± 17.1 vs 54.3 ± 17.3 years, $p = 0.59$), which is in concordance with the study by Bagshaw et al.[6]

A majority of our patients were males, similar to that reported by Bagshaw et al.[6] and a previous retrospective study of critically ill patients with AKI in the Indian setting.[16] However, Plataki et al.[24] found no sex predilection for AKI. Our observation that those with sepsis and AKI have a higher burden of disease as demonstrated by the severity of illness scores compared to sepsis alone is a finding consistent with previous studies.[8,22,23] As expected, patients without AKI had a significantly better survival than those with AKI (3% vs 23.4%, $p = 0.001$). Suh et al.[22] in a single-center study from Korea reported a similar finding of a significantly lower hospital mortality among those without AKI (2.9% vs 16.4%).

The overall hospital mortality of approximately 12% in our study is lower than the outcome observed by the beginning and ending supportive therapy for the kidney (BEST kidney) study investigators.[1] In their multinational, multicenter observational study of AKI in critically ill patients, BEST study investigators reported a very high mortality of 60% in patients with AKI.[1] This high mortality among AKI patients in their study could be explained by large proportion of patients requiring RRT (1,260/1,738, 72.5%) in comparison to only 15 (13.5%) patients with AKI (15/111 patients) needing RRT in our study. We also found that AKI was an independent predictor of the 28-day mortality based on the multiple regression analysis, a finding similar to that reported by Oppert et al.[25] The mortality in septic AKI, AKI without sepsis, and sepsis without AKI was 25.8%, 20.4%, and 5.6%, respectively. A large multicenter study[23] compared hospital mortality between the same three groups as in our study and found similar mortality rates of 29.7%, 21.6%, and 12.6% in the septic AKI, nonseptic AKI, and sepsis-only groups, respectively. In our study, among the patients with sepsis, we found significantly higher 28-day mortality and length of CCU stay in patients with AKI compared to those without AKI. This finding is similar to that of previous studies by Hoste et al.[8] and Suh et al.[22] We found no significant difference in mortality between patients with septic and nonseptic AKI. This is in contrast to previous studies[6,7,23] which have consistently reported that septic AKI portends a poorer prognosis when compared to nonseptic AKI. The reason for our discordant finding is likely to be due to the small size of our study population and a similar degree of acute illness assessed by APACHE III score in the two groups. The previous large studies have consistently shown a higher acute illness scores in patients with septic AKI compared to AKI without sepsis.[6,7,23]

Among all our study patients, 6.1% (15/242) received RRT, which is similar to the multinational study reported by BEST Kidney investigators who reported an incidence of RRT in 4.3% (1,260/29,269) among their study patients.[1] We found that the need for RRT was significantly higher in AKI patients with sepsis compared to those who did not have sepsis (19.3 vs 6.1%, $p = 0.04$). In a subgroup of AKI patients who received RRT, the mortality was high compared to AKI patients who did not require RRT (53.3 vs 18.8%) ($p = 0.003$). An Indian study that analyzed hospital-acquired AKI in the medical and surgical intensive care setting reported dialysis requirement in 20.6% of patients in the ICU.[26] The lower rate of RRT use in our study could be multifactorial. First, it could be due to heterogeneity of our patient population. Second, the lower incidence of severe degree of AKI in our study population could have limited patients needing RRT. Third, the lower RRT rates may be due to the differences in the criteria to initiate RRT.

Our study showed that sepsis was the most common cause of AKI in ICU, and the development of AKI in patients with sepsis markedly increased the 28-day hospital mortality. Hence, the effort on identifying sepsis early and preventing AKI progression in septic patients should be the focus among the physicians involved in the care of patients in ICU. Several strategies such as incorporation of biomarkers, careful fluid therapy after assessment of fluid responsiveness and tolerance minimizing both hypovolemia and fluid overload, maintenance of adequate perfusion pressure, avoidance of nephrotoxic drugs when feasible, and appropriate dosing of drugs should be routinely implemented to recognize and minimize AKI progression.

Our study has several strengths. First, this is the largest prospective study reviewing in detail the epidemiology and outcome of septic AKI in the Indian critical care setting. Second, our patient population is representative of most of the tertiary care multidisciplinary ICUs. Third, we used the validated AKIN criteria to evaluate epidemiology and outcomes of AKI with sepsis in a heterogeneous population in the ICU. Finally, ours is the only study in India that has compared the outcomes in the following groups: septic AKI, nonseptic AKI, and sepsis only. Our study has certain limitations. First, our study is not a multicenter study. Hence, the generalizability of our study is weakened by the lack of data from various centers and across different types of hospitals. Second, the patients with septic AKI were not further subgrouped based on the presence or absence of shock. Hence, the outcome of septic AKI in the subgroup of severe sepsis vs septic shock was not assessed. This might have given a better insight into the attributable mortality in the subgroup of patients with AKI and severe sepsis/septic shock. Third, ours was an observational study and initiation of RRT was not standardized. This could have led to lower RRT rates among our study patients.

Conclusion

Septic AKI was more common than nonseptic AKI in critically ill patients. The presence of AKI predicted a significantly higher mortality compared to no AKI in critically ill patients with sepsis. Thus, detecting AKI early and initiating treatment promptly may improve outcomes in this subset of patients. The mortality between septic and nonseptic AKI was similar, but the requirement of RRT was significantly higher in AKI due to sepsis compared to nonseptic AKI.

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