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A RETROSPECTIVE STUDY OF FACTORS AFFECTING MORTALITY IN PATIENTS WITH SEPSIS-ASSOCIATED ACUTE KIDNEY INJURY ADMITTED TO INTENSIVE CARE UNITS

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ABSTRACT **Objective:** This study aimed to identify the factors contributing to the death of patients with sepsis-associated acute kidney injury (SA-AKI) admitted to intensive care unit (ICU). **Methods:** A retrospective study was conducted in 128 patients with SA-AKI in a mixed medical- surgical ICU over a period of 14 months. The patients were divided into those who survived and those who died on the basis of whether they survived to hospital discharge. Demographic, clinical and laboratory parameters were collected. Uni- and Multi- variate logistic regression was performed. **Results:** Forty seven (36.71%) patients died during hospital stay after admission to the ICU. Multivariate logistic regression analysis showed that age (odds ratio [OR]: 0.054, p<0.001), vasopressor use (OR:0.061, p<0.001), and MV (OR: 0.55, p<0.001) were significantly associated with mortality at hospital discharge in patients with SA-AKI. **Conclusions:** Patients with SA-AKI have a high mortality rate. Older patients, those with shock requiring vasopressor use and those requiring mechanical ventilationare independent risk factors for mortality in patients with SA-AKI.

KEYWORDS : Acute Physiology and Chronic Health Evaluation II (APACHE II) Score, Sepsis, Acute Kidney Injury, Norepinephrine, Vasopressors, Mortality

INTRODUCTION

Sepsis is a severe condition in which the body's response to an infection becomes dangerously unbalanced, leading to critical organ dysfunction. One common and serious complication of sepsis is acute kidney injury (AKI), which happens in 45–70% of all cases of AKI in critically ill patients. When sepsis triggers AKI, the resulting sepsis-associated AKI (SA-AKI) has worse outcomes compared to either condition on its own. Patients with SA-AKI typically face longer stays in the intensive care unit (ICU) and hospital, higher rates of mortality, and an increased likelihood of long-term disability and reduced quality of life.[1] The challenge in preventing SA-AKI lies in the fact that many patients are already experiencing acute kidney injury by the time they seek medical attention. As a result, early detection becomes essential to start supportive treatment and prevent further damage.

However, the risk factors for death in patients with sepsis-associated acute kidney injury are not completely clear. Therefore, this study was performed to enumerate the risk factors affecting the prognosis of patients with sepsis associatedkidney injury.

MATERIAL AND METHODS

Clinical Data

This retrospective analysis was done of patients with SA-AKI who were admitted to our academic centre tertiary care hospital from January 2023 to April 2024. The study was approved by the institutional ethical committee. Need for informed consent was waiveddue to the retrospective nature of the study.

Inclusion Criteria

(1) Patients admitted to ICU with diagnosis of sepsis according to the sepsis-3 definition.
(2) Patients with acute kidney injury according to the KDIGO criteria, either on admission to ICU or develop AKI during the course of ICU stay.
(3) Age ≥18years.

Exclusion Criteria

(1) Patients on renal replacement therapy prior to ICU admission,
(2) Patients on palliative care
(3) Pregnant women.

Data Collection

Demographic characteristics (age, gender), previous medical history and pharmacological treatments, clinical parameters (pulse, blood pressure including mean arterial pressure, respiratory rate, urinary output, central venous pressure), laboratory tests (blood urea and blood urea nitrogen levels, serum creatinine, electrolytes, lipid profile, thyroid function tests, blood sugar levels, procalcitonin/ lactate when done), and causes of sepsis infection were collected.The sequential organ failure assessment (SOFA) score and Acute Physiology and Chronic Health Evaluation II (APACHE II) score were recorded for 24 hours after admission to the ICU. The use of mechanical ventilation, occurrence of acute myocardial injury, use of continuous renal replacement therapy, and use and dose of vasopressors (norepinephrine, vasopressin, dopamine, dobutamine, and adrenaline) during the ICU stay were recorded. Liquid intake and urinary output was measured and cumulative fluid balance was calculated for all days of ICU stay.The patients were divided into survivors and non-survivors groups on the basis of whether death occurred during hospital stay.

Statistical Analysis

Means and standard deviations are reported for continuous variables and the independent- sample t test was used for comparison. Comparison between groups was performed using the rank-sum test. Categorical data are presented as the percentage and the chi-square test was performed for comparisons ($p < 0.05$ was significant). Uni-variate and multi-variate logistic regression analyses were performed to analyze the independent risk factors associated with mortality. Variables with $p < 0.1$ in uni-variate analysis were involved in multi-variate analysis.IBM SPSS version 25.0software (IBM Corp., Armonk, NY, USA) was used to perform statistical analysis.

RESULTS

128 patients were included in the study. 81patients were in the survivor group while47patients were in the non-survivor group. Clinical characteristics of all the patients in the study as well as those in survivor and non-survivor groups are shown in Table 1. Overall, 69.53% of the patients were men and 30.46% were women. 9 females were found to be pregnant. All were in the second trimester of gestation and all survived. The age of the patients ranged from 27 to 89 years, with a mean age of 60.88 years. Pulmonary infections (70.32) were the most common, followed by the urinary tract infections& skin and soft tissue infections (7.81% each).

Patients in the non-survivor group had a significantly higher rate of lung infections($p < 0.001$), renal replacement therapy ($p < 0.001$), and

more septic shock as shown by greater number of patients requiring noradrenaline administration(p< 0.001) than those in the survival group.

More than half of the patients had hypertension and dyslipidemia while a third of patients had coronary artery disease. Diabetes mellitus was a common co-morbidity and was seen in 60% of the study population. The median SOFA score was 9 (interquartile range [IQR]: 0–20) in the study population and 10(IQR: 3–20) in the survivor and 7 (IQR:0-18) in the non-survivor groups, respectively, within 24 hours after admission to the ICU. The median APACHE score was 26 (IQR: 0-40) in the study population, 31 (IQR: 0, 40) in the non-survivor group and 24 (IQR: 0, 38) in the survivor group. The difference for both the scores was statistically significant.

Logistic Regression Analyses for Identifying Prognostic Factors

Uni-variate logistic regression analyses showed that the following factors were associated with mortality on hospital discharge (P < 0.1): age(p< 0.001), pulse (p =0.001), mean arterial pressure (p=0.001), mechanical ventilation rate (p = 0.003), renal replacement therapy (p= 0.006), vasopressor use(p= 0.001), hypertension (p= 0.001), lung as site of infection (p<0.001), SOFA score (p= 0.006), and APACHE II score (p= 0.006) (Table 2).

A multivariable regression model further showed that age (odds ratio [OR]: 0.54, p< 0.001), vasopressor use (OR: 0.61, p< 0.001), and MV(OR:0.55, p<0.001) were independent factors for mortality at hospital discharge in patients with sepsis-related acute kidney injury.

DISCUSSION

In India, data on acute kidney injury (AKI) is fragmented, with no comprehensive national database. According to available information, while sepsis is a major cause of AKI, which aligns with global trends, there is also a significant role played by tropical infections. These infections, which are more common in India, may be a leading cause of AKI in the country.[2] Studies provide some insights into AKI in the ICU context, there are no specific datasets or research focused on septic AKI in critically ill patients.[3,4] In Indian patients, sepsis-associated acute kidney injury (septic AKI) is both common and has a high mortality rate. Several factors are significant predictors of mortality. These include age, the severity of illness as measured by the number of organ failures outside of the kidneys, and the APACHE II score, a widely used tool for assessing the severity of disease in critically ill patients.[5]

In our study, patients with SA-AKI had mean age of 60.88 years. The mean age in studies done in SA-AKI patients admitted to predominantly mixed medical surgical ICU has ranged from 40 -60 years.[3-5] In a study of patients with predominant post-cardiovascular and post- gastrointestinal surgical patients, the mean age was 28.6 years.[4] Patients were younger in this study as the majority of patients underwent surgeries electively.

In a multicentric prospective study conducted in ICUs of tertiary care centers from India, the site of infection was predominantly skin and soft tissue infections.[6] The sites of infections in our study were predominantly the lungs (70.32%) followed by the urinary tract (7.81). The lung followed by intra-abdominal infections as major site of infections were seen in a single center retrospective trial in a north Indian ICU.[4] This was also the case in another study.[7]

Renal replacement therapy was required in one third of all patients in the multi-centric prospective study conducted in ICUs of Indian tertiary care centers. Our requirement for RRT was in one half of all patients. The percentage of patients needing RRT varies in various studies from 33% to more than 75%.[3,4,7] The requirement of RRT depends on severity of the AKI as demonstrated by the grades of AKI as well of time to presentation from symptom onset and the etiology of the AKI.[1,2]

The mortality in patients with SA-AKI in our study was 36.71%. Mortality in some studies has been found to be 50% or even more in some studies.[3,5-8] On uni-variate analysis of factors determining whether a patient will or will not survive, Age, MAP, presence of hypertension as co-morbidity, need for mechanical ventilation, RRT, vasopressor and APACHE and SOFA scores were significantly associated with mortality. On multi-variate analysis this was narrowed down to age, vasopressor and mechanical ventilation use as significant determinants of death in our patients. These were also the determinants of death in the retrospective study in north Indian ICU.[5] Acute respiratory failure (ARDS) in patients with SA-AKI increases likelihood of death as the number of non-renal organ failure is associated with increased mortality.[5] As age increases mortality in patients with SA-AKI increases. This has been shown in a number of studies.[5,6] Inotropic use demonstrating presence of septic shock was also shown to be significantly associated with mortality in a south African study of critically ill patients with AKI (including SA-AKI).[9]

One of the strengths of our study is the presence of 9 pregnant patients with SA-AKI. All these pregnant patients survived. A Brazilian study in pregnancy related AKI (including SA-AKI) had a mortality rate of 8.7%. Use of noradrenaline and RRT were independent factors associated with maternal mortality.[10]

CONCLUSION

SA-AKI is common in critically-ill patients, has unique pathological mechanisms, and carries significant prognostic implications. Early identification and treatment of SA-AKI may improve its incidence or outcomes. Our study found that elderly patients and those with vasopressor and mechanical ventilation use had higher mortality. Recognition of factors affecting prognosis in SA-AKI patients, may likely help in developing strategies which may reduce its heavy toll on septic patients.

Table No. 1. Comparison of Clinical Characteristics Between the Survival and Nonsurvival Groups.

Parameters	All patients (n=128)	Non-survivors (n=47)	Survivors (n=81)	P value
Age, years, mean+- SD	60.88+-10.33	71.33+-9.08	62.94+-7.10	<0.05
Males, n (%)	89 (69.53)	32 (68.08)	57 (70.37)	0.843
Pulse (beats per minute)	106 (20, 198)	111 (50, 196)	108 (33, 220)	0.035
MAP, mmHg	79 (40, 198)	73 (39, 200)	89 (45, 220)	0.044
Mechanical ventilation, n (%)	99 (77.34)	35 (74.46)	64 (79.01)	0.008
RRT, n (%)	51 (39.84)	30 (63.82)	21 (25.92)	<0.001
Vasopressors, n (%)				
Noradrenaline,	87 (67.96)	40 (85.10)	37 (45.67)	<0.001
Vasopressin,	30 (23.43)	12 (25.53)	18 (22.22)	0.544
Comorbidities, n (%)				
Hypertension	76 (59.375)	26 (55.31)	50 (61.72)	0.031
Coronary artery disease	35 (27.34)	15 (31.91)	20 (24.69)	0.631
Diabetes mellitus	80 (62.5)	28 (59.57)	52 (64.19)	0.848
Chronic kidney disease	15 (11.71)	6 (12.76)	9 (11.11)	0.755
Dyslipidemia	66 (51.56)	23 (48.93)	43 (53.08)	0.655
History of smoking	56 (43.75)	18 (38.29)	38 (46.91)	0.691
History of Alcohol intake	44 (34.37)	15 (31.91)	29 (35.80)	0.545
Infection site, n (%)				
Pulmonary	90 (70.32)	40 (85.10)	50 (61.72)	<0.001
Urinary tract	10 (7.81)	4 (8.51)	6 (7.40)	0.766
Biliary tract	8 (6.25)	3 (6.38)	5 (6.17)	0.712
SSI	10 (7.82)	5 (10.63)	5 (6.17)	0.006
Abdomino-pelvic cavity	3 (2.34)	1 (2.12)	2 (2.47)	0.651
Others	7 (5.46)	2 (4.25)	5 (6.17)	0.056
Laboratory Investigations				
Hemoglobin (mg/dl)	9.6 (5.4, 16.7)	8.4 (4.9, 16)	10.9 (6.7, 17.9)	0.871
Total Leucocyte Count	11450 (2015, 24600)	14004 (3511, 22430)	11054 (4515, 18677)	0.966
Creatinine, mg/dl	5 (2.1, 8.9)	4.9 (2.3, 9.45)	5.3 (1.9, 8.67)	0.762
Cumulative fluid balance, ml/day				
1st Day	1248 (-6540, 6950)	1098 (-6540, 6800)	1310 (-6000, 6950)	0.774

2nd Day	2005 (-10110, 8950)	2200 (-5156, 10018)	1765 (-6543, 1367)	0.546
3rd Day	1655 (-1650, 5070)	1900 (-2456, 6798)	1523 (-3145, 8754)	0.943
5th Day	850 (-3015, 8060)	1213 (-0455, 7658)	710 (-359, 8723)	0.028
7th Day	440 (-1850, 15100)	400 (-1448, 13445)	610 (-1871, 15677)	0.156
Serum potassium, mg/dl	5.2 (3.3, 7.5)	4.9 (3.5, 7.1)	5.5 (3.9, 8.2)	0.388
Procalcitonin pg/ml	20.12 (0, 67)	19 (0, 55)	22 (0, 67)	0.444
Serum lactate	2.0 (0,15)	2.1 (0,15)	2.0 (0,15)	0.468
SOFA score	9 (0, 20)	10(3, 20)	7 (0, 18)	0.045
APACHE II	26 (0, 40)	31 (0,40)	24 (0, 38)	0.036

Data are median (25th percentile, 75th percentile) SSI, Skin and soft tissue infections; RRT, Renal recruitment therapy;CVP, Central venous pressure; MAP, Mean arterial pressure; SOFA, Sepsis-related Organ Failure Assessment; APACHE II, Acute Physiology and Chronic Health Evaluation II.

Table no. 2 Univariate and Multivariate Analysis of Factors Associated with Mortality

Variable	Univariate analysis		Multivariate analysis	
	Odds ratio	P value	Odds ratio	P value
Age	0.31	<0.001	0.54	<0.001
Pulse	0.77	0.001		
MAP	0.69	0.001		
MV	0.41	0.003	0.61	<0.001
RRT	0.85	0.006		
Vasopressure use	0.44	0.001	0.55	<0.001
HTN	0.56	0.001		
Lung infection	0.68	<0.001		
SOFA score	0.78	0.006		
APACHE score	0.86	0.006		
Cumulative fluid balance on 5th day	0.97	<0.001		

MAP- mean arterial pressure, MV- Mechanical ventilation, RRT-Renal replacement therapy, HTN- Hypertension, SOFA score-sequential organ failure assessment score, APACHE score- Acute physiology and chronic health evaluation,

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