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Original Research Article

Assessment of Sepsis and Acute Kidney Failure Outcomes: An Observational Study

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Abstract

Aim: The aim of the present study was to assess sepsis and acute kidney failure outcomes investigated in Bihar region.

Material & Methods: The present study was conducted in AIIMS, Patna, Bihar, India. Among 300 patients with sepsis and septic shock, 200 patients developed AKI. We retrospectively analyzed the data of all the adult patients (>18 years of age) who visited the Emergency Department

Results: The mean age of patients with septic AKI was significantly higher than that of patients without AKI ($p<0.001$). Patients with AKI were more likely male ($p=0.017$). DM ($p=0.004$) and HTN ($p<0.001$) were more frequently associated with the development of septic AKI, whereas there were no significant differences in BMI and history of smoking and alcohol consumption. Those who developed AKI had higher baseline serum creatinine levels ($p<0.001$) and lower GFR ($p=0.002$) than those who did not developed AKI. Among medications that might affect the renal function, ACEI/ARB ($p<0.001$) and statins ($p=0.004$) were more frequently used in AKI group. Although the percentage of patients who used aminoglycosides and NSAIDs was higher in AKI group, there was no statistical significance. The frequency of septic shock was significantly higher in the patients with AKI than were those without AKI ($p<0.001$). Accordingly, MAP was lower in the AKI group ($p<0.001$). Patients with AKI had a more severe illness with higher APACHE III scores than patients without AKI had ($p<0.001$). White blood cell (WBC) ($p=0.025$) and platelet ($p=0.004$) counts were significantly lower in AKI group. The other physio- logic and laboratory data collected in this study indicated the tendency of more evident clinical deterioration among patients who developed AKI, although this was not statistically significant.

Conclusion: AKI developed in more than half of patients with sepsis and septic shock. Old age, pre-existing CKD, presence of shock, positive blood culture results, use of ACEI/ARB, and low WBC and platelet counts were associated with an increased risk for the development of septic AKI.

Keywords: Sepsis; Renal Failure; Acute Kidney Injury.

Introduction

Sepsis is the systemic inflammatory response to infection, and one of the most common contributing factors in AKI of critical illness. [1] Acute kidney injury (AKI) is a common clinical problem in intensive care unit (ICU) patients and independently predicts poor outcome [4] and known to be associated with increased mortality. [2,3] AKI is defined by serum creatinine levels and urine output. Although small changes in serum creatinine or acute reduction in urine output can be used in the diagnosis of AKI, these changes are often evident after the chance of effective management for renal protection has already passed. A previous prospective multicenter study reported the delayed onset of AKI of septic origin compared with AKI of non-septic origin. [5] The recognition of high-risk patients for development of septic AKI is important because early interventions may improve the clinical course.

A plethora of comorbidities associated with sepsis can negatively affect both short-term and long-term patient outcomes. As individual syndromes, sepsis and acute kidney injury (AKI) render the host susceptible to each other. Although sepsis is the most common contributing factor for developing AKI, AKI of any origin is associated with higher risk of developing sepsis. [6] Perhaps the most common secondary diagnosis confronting sepsis patients is acute kidney injury (AKI) leading to kidney failure. Up to half of all cases of acute renal failure are associated with sepsis, and up to 60% of patients with sepsis have AKIs. [7] It would be

reasonable to assume that as comorbidities multiply, mortality rates would increase, especially with complications as severe as organ failure. Because AKI and renal failure are the most common comorbidities associated with sepsis, it is essential to understand to what extent they contribute to increases in patient mortality. Sepsis has a complex and unique pathophysiology, which makes S-AKI a distinct syndrome from any other phenotype of AKI.

Sepsis-associated AKI (SA-AKI) is associated with such a high mortality rate that it is sometimes used as a "biomarker" in predicting poor prognosis.[7] Even when mortality is not the outcome, AKI from sepsis can result in long lasting decrease in quality of life and high economic costs. Sepsis is the dominant cause of AKI in intensive care unit (ICU) patients, and frequently requires patients to utilize continuous renal replacement therapy (CRRT), which improves outcomes but at a large economic and quality of life burden. [8,9] If the damage is severe enough to both kidneys, sepsis may cause permanent hypoxic damage requiring donor transplantation. The cost for patient treatment is high, and quality of life is greatly diminished. Prevention of permanent kidney damage via early sepsis detection and bundle therapy is the current standard treatment of care. [10] Efficiency in triaging using biomarkers or secondary comorbidities has the potential to reduce the mortality rate in septic patients. AKI could be a critical piece to treating sepsis efficiently due to required fluid bolus intake. [11,12]

The aim of the present study was to assess sepsis and acute kidney failure outcomes investigated in Bihar region.

Materials & Methods

The present study was conducted in AIIMS, Patna, Bihar, India. Among 300 patients with sepsis and septic shock, 200 patients developed AKI. We retrospectively analyzed the data of all the adult patients (>18 years of age) who visited the Emergency Department of AIIMS, Patna, Bihar, India. Informed consent was exempted by the board because this was a retrospective study of collected data. In the event of multiple admissions, only the initial admission was considered to avoid bias. Those with end stage renal disease (ESRD) on chronic renal replacement therapy were also excluded.

We recorded pulse rate (PR), mean arterial pressure (MAP), and laboratory findings at the diagnosis of sepsis or septic shock. Other variables included age, gender, body mass index (BMI), length of stay in intensive care unit (ICU) and hospital, and source of infection. To investigate the underlying condition that might affect the development of AKI, history of smoking and/or alcohol consumption, and pre- existing diabetes mellitus (DM), hypertension (HTN), and chronic kidney disease (CKD), which was defined as estimated glomerular filtration rate (GFR) <60 milliliters per minute per 1.73 m2 for more than 3 months, were checked. The abbreviated Modification of Diet in Renal Disease formula was used to estimate GFR in milliliters per minute per 1.73 m2 from the baseline serum creatinine level. [13]

The use of agents that may alter renal function were re- viewed, which included angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), statins, aminoglycosides, non-steroidal anti-inflammatory drugs (NSAIDs), and intravenous contrast media. Acute Physio-logic and Chronic Health Evaluation (APACHE) III scores [14] at the diagnosis of sepsis or septic shock were calculated to assess the severity of illness.

Sepsis and septic shock was defined according to the American College of Chest Physicians/Society of Critical Care Medicine consensus conference criteria. [15] Among patient's with a proven or suspected infection, those with the two or more systemic inflammatory response syndrome (SIRS) criteria were classified as having sepsis. Briefly, SIRS is manifested by the following features: 1) body temperature >38°C or <36°C; 2) PR >90 beats per minute; 3) respiratory rate >20 breaths per minute or PaCO2 <32 mm Hg; and 4) white blood cell count >12000/mm3, <4000 mm3 or >10% band forms. Among patients with sepsis, septic shock was defined as a systolic blood pressure <90 mm Hg or a reduc- tion of ≥40 mm Hg from the baseline despite adequate fluid resuscitation.

Definition and sStaging of AKI

Definition and staging of AKI was determined based on the worst of either creatinine or urine output criterion during hospital stay. Urine output was hourly measured during ICU stay. The cutoffs for AKI were based on the RIFLE criteria as meeting one of the following criteria: a decrease in GFR ≥25% or an increase in creatinine ≥50% (1.5 times) from baseline in a 48-hour time frame, or a reduction in urine output with documented oliguria of ≤0.5 mL/kg per hour for ≥6 hours. Patients were divided into three groups according to the RIFLE criteria (stage-1, -2 and -3). [16] When a patient's condition met the aforementioned criteria, the patient was classified as stage 1 AKI. In the case of more severe derangement, i.e., a decrease in GFR ≥50% or an in- crease in creatinine ≥100% (2 times) from baseline in a 48- hour time frame, or a reduction in urine output with documented oliguria of ≤0.5 mL/kg per hour for ≥12 hours, stage 2 AKI was defined. Stage 3 AKI was defined as follows: a decrease in GFR ≥75% or an increase in creatinine

≥200% (3 times) from baseline in a 48-hour time frame, or a reduction in urine output with documented oliguria of ≤0.3 mL/kg per hour for ≥24 hours or anuria for ≥12 hours. Serum creatinine ≥4.0 mg/dL with acute increase of ≥0.5 mg/dL was also defined as stage 3 AKI.

Statistical Analysis

Analyses were performed using SPSS 18.0.0 (SPSS Inc., Chicago, IL, USA). In the event of missing data values, data were not replaced. Normally or near normally distributed variables are reported as mean with standard deviations and compared using Student's t-test, analysis of variance. Non-normally distributed continuous data are reported as medians with interquartile ranges and compared using Mann-Whitney U test and Kruskal-Wallis test. Categorical data were reported as proportions and compared using Fisher's extact test or chi-square test where appropriate. Multi- variable logistic regression was used to assess the risk factors for the development of septic AKI. Calibration of the model was assessed by the Hosmer-Lemeshow goodness of fit statistic for significance (p>0.05). Odds ratios (OR) and 95% confidence intervals (CI) were calculated. A p value <0.05 was considered statistically significant.

Results

Table 1: Demographic Data and Characteristics of Sepsis and Septic Shock Patients

	No AKI (n=80, 40%)	AKI (n=120, 60%)	*p* value
Age (yrs)	56.64±16.34	64.76±12.38	<0.001
Male gender	90 (45)	175 (58.33)	0.017
BMI, kg/m^2	23.87±3.87	21.89±4.16	0.912
Smoking history	72 (36)	120 (40)	0.149
Chronic alcohol consumption	50 (25)	90 (30)	0.136
DM	44 (22)	161 (28.3)	0.004
HTN	50 (25)	118 (39.33)	<0.001
Baseline creatinine, mg/dL	0.72±0.28	0.82±0.48	<0.001
Baseline GFR, mL/min/1.73 m^2	116.54±36.74	106.54±48.02	0.002
Previous CKD	4	15	<0.001
Medications			
Intravenous contrast use	72	86	<0.001
Aminoglycosides	2	6	0.445
NSAIDs	2	4	0.630
Statins	6	24	0.004
ACEI or ARB	10	48	<0.001

The mean age of patients with septic AKI was significantly higher than that of patients without AKI (p<0.001). Patients with AKI were more likely male (p=0.017). DM (p=0.004) and HTN (p<0.001) were more frequently associated with the development of septic AKI, whereas there were no significant differences in BMI and history of smoking and alcohol consumption. Those who developed AKI had higher baseline serum creatinine levels (p<0.001) and lower GFR (p=0.002) than those who did not developed AKI. Among medications that might affect the renal function, ACEI/ARB (p<0.001) and statins (p=0.004) were more frequently used in AKI group. Although the percentage of patients who used aminoglycosides and NSAIDs was higher in AKI group, there was no statistical significance.

Table 2: Physiologic and Laboratory Data on Admission

	No AKI	AKI	*p* value
Presence of shock	6	40	<0.001
APACHE III	46 (32-66)	56 (43-70)	<0.001
MAP, mm Hg	91.00 (83.33-96.67)	83.33 (73.33-96.67)	<0.001
Heart rate, bpm	81 (76-96)	86 (76-98)	0.414
pH	7.43 (7.41-7.49)	7.43 (7.41-7.49)	0.096
PaO2, mm Hg	82.68 (68.22-104.90)	83.67 (69.25-106.20)	0.713
PaCO2, mm Hg	32.4 (27.3-35.4)	31.4 (27.4-36.3)	0.750
Bicarbonate, mmol/L	21.9 (18.9-24.8)	22.0 (18.9-24.6)	0.505
WBC count per mm^3	11352 (7.70-16.90)	11100 (7.40-15.00)	0.025
Hematocrit, %	35.2 (30.2-38.8)	35.0 (30.7-38.7)	0.670
Platelets count per mm^3	196000 (124-275)	176000 (109-253)	0.007

Glucose, mg/dL	135 (105-173)	127 (105-158)	0.090
BUN, mg/dL	19.2 (12.5-31.9)	19.4 (12.5-29.1)	0.692
Total bilirubin, mg/dL	0.90 (0.66-1.32)	0.94 (0.66-1.42)	0.712
Positive blood cultures	8	24	<0.001
Gram negative bacilli	4	26	<0.001
Gram positive cocci	2	8	0.092
Fungi	0 (0)	2	0.024

The frequency of septic shock was significantly higher in the patients with AKI than were those without AKI (p<0.001). Accordingly, MAP was lower in the AKI group (p<0.001). Patients with AKI had a more severe illness with higher APACHE III scores than patients without AKI had (p<0.001). White blood cell (WBC) (p=0.025) and platelet (p=0.007) counts were significantly lower in AKI group. The other physio- logic and laboratory data collected in this study indicated the tendency of more evident clinical deterioration among patients who developed AKI, although this was not statistically significant.

Table 3: Risk Factors for Development of AKI in Patients with Sepsis and Septic Shock

	OR	95% CI	*p* value
Age (for every yr)	1.025	1.016-1.041	<0.001
Male sex	1.316	0.955-1.800	0.094
BMI	0.990	0.954-1.034	0.749
Presence of CKD	2.392	1.301-4.420	0.005
Presence of DM	1.086	0.743-1.576	0.679
Presence of HTN	1.132	0.760-1.685	0.544
Use of ACEI or ARB	2.068	1.214-3.510	0.007
Use of statins	0.732	0.394-1.357	0.321
Presence of shock	8.202	4.678-14.400	<0.001
Positive blood culture result	1.778	1.123-2.812	0.014
WBC counts per mm^3	0.970	0.949-0.993	0.011
Platelet counts per mm^3	0.995	0.997-1.000	0.016
APACHE III score	0.990	0.986-1.003	0.207

Variables, which were associated with p<0.1 in the univariate analysis and/or clinically plausible, were included in this model. After adjustment of confounders, the development of septic AKI was independently associated with age, pre-existing CKD, use of ACEI or ARB, presence of septic shock, positive blood culture result and lower WBC and platelet counts. Other variables included in multivariate analysis, such as BMI, male sex, previous history of diabetes or hypertension, and medication history of statins were not independently associated with the development of septic AKI. Unexpectedly, APACHE III score was not statistically significant with septic AKI in this study.

Table 4: Clinical Outcomes

	No AKI	AKI	*p* value
Hospital mortality	2	18	<0.001
Hospital LOS, days	9.71±7.93	15.25±18.62	<0.001
ICU LOS, days	0.52±2.92	2.96±8.22	<0.001

Hospital mortality was significantly higher in patients with AKI (p<0.001). Length of stay in the hospital and ICU was longer for patients who suffered AKI (p<0.001).

Discussion

Previous studies of septic AKI noted that about 60% patients with septic shock developed AKI and found a higher mortality and longer duration of hospital stay in patients with AKI compared with patients without AKI. [17,18] According to the risk, injury, failure, loss of function, and end-stage renal disease (RIFLE) criteria, [19] AKI is defined by serum creatinine levels and urine output. Although small changes in serum creatinine or acute reduction in urine output can be used in the diagnosis of AKI, these changes are often evident after the chance of effective management for renal protection has already passed. A previous prospective multicenter study reported the delayed onset of AKI of septic origin compared with AKI of non-septic origin. [20] The recognition of high-

risk patients for development of septic AKI is important because early interventions may improve the clinical course.

The mean age of patients with septic AKI was significantly higher than that of patients without AKI ($p<0.001$). Patients with AKI were more likely male ($p=0.017$). DM ($p=0.004$) and HTN ($p<0.001$) were more frequently associated with the development of septic AKI, whereas there were no significant differences in BMI and history of smoking and alcohol consumption. An observational cohort study of 390 patients with septic shock in a single center ICU for about 2 years reported nearly 2 out of 3 patients experiencing AKI. [17] In a recent retrospective multicenter study of 4532 patients with septic shock, a similar percentage of patients (64.4%) developed AKI. [18] Those who developed AKI had higher baseline serum creatinine levels ($p<0.001$) and lower GFR ($p=0.002$) than those who did not developed AKI. Among medications that might affect the renal function, ACEI/ARB ($p<0.001$) and statins ($p=0.004$) were more frequently used in AKI group. Although the percentage of patients who used aminoglycosides and NSAIDs was higher in AKI group, there was no statistical significance. The frequency of septic shock was significantly higher in the patients with AKI than were those without AKI ($p<0.001$). Accordingly, MAP was lower in the AKI group ($p<0.001$). Patients with AKI had a more severe illness with higher APACHE III scores than patients without AKI had ($p<0.001$). White blood cell (WBC) ($p=0.025$) and platelet ($p=0.004$) counts were significantly lower in AKI group. The other physio- logic and laboratory data collected in this study indicated the tendency of more evident clinical deterioration among patients who developed AKI, although this was not statistically significant. In 2004, the SSC published guidelines for two clinical approaches in combating sepsis: "resuscitation" and "management" bundles. [21] The bundles are sets of standardized intervention protocols to be completed during certain timeframes throughout the progression of sepsis. Although there is still plenty of room for improvement in bundle development and compliance protocols, studies show encouraging results regarding their effectiveness. [22,23]

Variables, which were associated with $p<0.1$ in the univariate analysis and/or clinically plausible, were included in this model. After adjustment of confounders, the development of septic AKI was independently associated with age, pre-existing CKD, use of ACEI or ARB, presence of septic shock, positive blood culture result and lower WBC and platelet counts. Other variables included in multivariate analysis, such as BMI, male sex, previous history of diabetes or hypertension, and medication history of statins were not independently associated with the development of septic AKI. Unexpectedly, APACHE III score was not statistically significant with septic AKI in this study. Hospital mortality was significantly higher in patients with AKI ($p<0.001$). Length of stay in the hospital and ICU was longer for patients who suffered AKI ($p<0.001$). Langenberg, et al [24] found AKI in septic shock mainly affected by dysfunction of the renal vascular bed rather than systemic hypotension and renal hypoperfusion. In their study, fluid resuscitation and maintenance of renal perfusion did not prevent the deterioration of GFR. In contrast, recovery from sepsis resulted in the normalization of GFR. This implies the development of AKI involves inflammatory/ immunologic mechanisms.

Conclusion

AKI developed in more than half of patients with sepsis and septic shock. Old age, pre-existing CKD, presence of shock, positive blood culture results, use of ACEI/ARB, and low WBC and platelet counts were associated with an increased risk for the development of septic AKI. The development of septic AKI adversely affected clinical outcomes. Moreover, the severity of AKI was associated with increased short-term mortality.

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