ACUTE KIDNEY INJURY IN SEPSIS PATIENTS- AN OBSERVATIONAL STUDY

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ABSTRACT

BACKGROUND

Severe sepsis and acute kidney injury (AKI) are both common syndromes that are encountered in the emergency settings. The proportion of patients presenting with severe sepsis upon admission has been reported to be approximately 9% to 12%. An increasing trend in the presence of severe sepsis in ICU-treated patients has been observed. Discriminating between AKI of septic and non-septic origin may have clinical relevance. Evolving data suggests that septic AKI may be characterized by a distinct pathophysiology. For that reason, septic AKI may be associated with important differences in terms of patient characteristics, response to interventions and clinical outcomes when compared with non-septic precipitants of AKI.

The objective of the study is to evaluate the occurrence of Acute Kidney Injury in patients with Sepsis attending the Emergency Medicine Department at the Government Medical College, Kozhikode during the study period.

MATERIALS AND METHODS

Study Design- Single Cohort Study.
Study Setting- Department of Emergency Medicine, Govt. Medical College, Kozhikode.
Study Period- 1 year.
Study Population- Both males and females with sepsis between 30 and 70 years of age.
Sample Size- 200
Study Procedure- Patients attending emergency medicine department and satisfying inclusion criteria are enrolled in the study. Medical records will be examined for 2 days from the date of admission, including laboratory data. Glomerular filtration was calculated according to the MDRD equation. AKI was defined according to the Acute Kidney Injury Network (AKIN criteria) based on serum creatinine. Briefly, AKI was defined as an absolute difference of 50%, taking into consideration the peak and admission serum creatinine values during hospitalization.

Moreover, AKI was classified into 3 stages based on an increase of 50% to 100% in terms of admission serum creatinine (stage 1); 100% to 200% (stage 2); or greater than 300% or an increment of 0.5 mg/dL, if admission serum creatinine was higher than 4 mg/ dL (Stage 3), within 48 hours. The following parameters were collected in the ED: age, gender, temperature, respiratory rate, heart rate, mean blood pressure, leukocyte count, platelet count, vasopressor administration, urine output, serum creatinine, baseline GFR, AKIN stage and blood culture.

RESULTS

AKI was noticed in 27% of the patients with sepsis. There was no gender difference in the prevalence of AKI. Old age, presence of comorbidities like hypertension and diabetes mellitus were more common in the AKI group. Laboratory and clinical findings were also abnormal in the AKI group compared with non-AKI group.

CONCLUSION

Around one third of patients presenting with sepsis have features of AKI. AKI was associated with increased morbidity and mortality in patients with AKI. Multiple risk factors were noticed to have a role in the development of AKI and further studies in this regard is needed

KEYWORDS

Sepsis, Acute Kidney Injury, AKIN Criteria, Hypertension, Diabetes Mellitus.

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BACKGROUND

Sepsis, a commonly encountered scenario in an emergency department, often leads to multi-organ dysfunction and kidney is one of the organs frequently afflicted. In blood culture positive cases Acute Kidney Injury (AKI) occurs in about 19%, 23% and 51% of patients with moderate, severe and septic shock, respectively.[1]

Septic AKI had a higher in- hospital mortality rate, compared with non-septic AKI (70.2 vs. 51.8%; p <0.001). Median duration of ICU and hospital stay for survivors (37 vs.

21d; P <0.0001), was longer for septic AKI.[2] Gram-negative sepsis, which is more common in India, is also independently associated with AKI.[3]

The current study was conducted to understand the prevalence of AKI and the various factors affecting the development of AKI in patients with sepsis

Aims and Objectives

To study the occurrence of Acute Kidney Injury in patients with Sepsis attending the Emergency Medicine Department at the Government Medical College, Kozhikode during the study period.

Background and Review of Literature

Sepsis is defined as a host's response to proven or suspected infection with at least two out of 4 systemic inflammatory response syndrome (SIRS) criteria.[4] The SIRS criteria are alterations in body temperature, heart rate, respiratory rate and leukocytes. Sepsis with organ dysfunction is severe sepsis and Septic shock is severe sepsis with hypotension or hypo perfusion, which is not reversed with adequate fluid resuscitation.

MATERIALS AND METHODS

Estimations of GFR

Serum creatinine and urine output are the most common parameters to detect and diagnose AKI in daily clinical practice.

Cockroft-Gault Equation	CrCl (ml/min) = (140-Age) x Weight (x 0.85 if female)72 x Cr
MDRD Equation	GFR (ml/min/1.73m^2) = 186 x Cr $^{(-1.154)}$ x Age$^{(-0.203)}$ x (0.742 if female) x (1.212 if Afro-Americans)
CKD-EPI Equation	GFR (ml/min/1.73m^2) = 141 x min (Cr/κ, 1)$^{\alpha}$ x max(Cr/κ, 1$^{)-1.209}$ x
	0.993^{age} x (1.018 if female) x 1.159 if Afro-Americans)

Table 1. Equations of the Glomerular Filtration Rate (GFR)

Cr = S.Cr (mg/ml); κ = 0.9 for male / 0.7 for female; α = -0.411 for male / -0.329 for female; min= minimum S.Cr / κ or 1; max = maximum S.Cr / κ or 1

Incidence of Septic AKI and Severe sepsis

In general ICU patients, the incidence of AKI varies from 6% to 67% and in critically ill patients. The AKI is multifactorial. Most common contributing factor for AKI is severe sepsis. The incidence of severe sepsis associated AKI treated in the ICU has varied from 13% upto 78% depending on the severity of sepsis and definition of AKI.[5-8] In the FINNSEPSIS study, acute renal failure (renal SOFA points ≥3 was present in 23% of patients with severe sepsis and in the soaps study in 51%.[9]

The proportion of patients with severe sepsis in ICU admissions has been approximately[10-14] 9% to 12% and the population-based incidence of severe sepsis has varied from 0.46 to 3.00 /1000 adults/year. Globally the sepsis patients have shown to increase. The annual increment of 8.2% (between 1993 and 2003) and 17.8% (between 2000- 2007)[15] in hospitalized patients with severe sepsis has been reported in the U.S.

Biomarkers of Septic AKI

Both plasma and urine NGAL has been shown to increase in acute tubular injury and in sepsis. Significantly higher NGAL levels (plasma and urine) have been found in adults and children with sepsis associated AKI than in patients without sepsis associated AKI.[16-18] Interleukin-18 (IL-18) is a pro-inflammatory cytokine, which is produced by mononuclear cells, macrophages, and non-immune cells, including renal tubular injury.[19-23] Increased plasma IL-18 has been observed in sepsis and in numerous inflammatory diseases, such as arthritis, inflammatory bowel diseases, psoriasis, and multiple sclerosis. Higher urinary IL-18 levels have been found in patients with septic AKI than in patients with non-septic AKI.[24] Cystatin-C is a surrogate of GFR.

Treatment of Septic AKI

Guidelines for management of severe sepsis and septic shock (SSC guidelines) were initially published in 2004,[25] and have been revised in 2008[26] and 2013.[6] Regarding the treatment of septic AKI guidelines reveals detailed recommendations on the administration of adequate antimicrobial treatment, of early resuscitation of hemodynamic, and of supportive therapies.[6] Up to date, no curative therapy for septic AKI exists and the treatment is mainly supportive.

Renal Replacement Therapy (RRT)

Of the patients with septic AKI, 4% to 70% of patients receive RRT.[6,7,8,19,20,27,28,29,30] excluding the absolute indications for RRT such as hyperkalaemia, severe metabolic acidosis, overt uraemia, fluid overload with pulmonary oedema, and specific drug intoxications[31-32] the decision to initiate RRT is mainly based on clinical judgment. The B.E.S.T. (Beginning and Ending Supportive Therapy for the Kidney) - study reported marked practice variation for RRT world widely and corresponding results have been found among European intensivists. In these studies, oliguria[31-32] high serum or plasma urea or creatinine,[31-32] fluid overload,[32-33] metabolic and hyperkalaemia[32] were the main indications for initiation of RRT. However, patients with sepsis associated AKI treated with early RRT (defined as urea <35.7 mmol/l, inception of CRRT ≤24 hours after diagnosing sepsis, or by time from ICU admission/initiation of vasopressor infusion to initiation of RRT) have survived

better. Recent reviews[33-34] and a meta-analysis[35] concluded that critically ill patients may benefit from early RRT. Instead of single laboratory values or timeframes, the decision to initiate RRT is advocated to be based on wider clinical evaluation of the patient with concern for fluid balance and nutrition, severity of underlying diseases, degree of other organ dysfunction, and likelihood of renal recovery.[19]

Studies from the 1990s reported greater haemodynamic stability and suggested favorable survival with CRRT compared to intermittent haemodialysis (IHD) in critically ill patients.[36] Recent studies have not supported this theory, however, patients with unstable haemodynamics have been converted from IHD groups to CRRT, leading to a significant bias. Better achievements of fluid balance targets have been shown with CRRT than IHD. As CRRT is suggested for haemo dynamically unstable patients,[19] it is a reasonable modality of patients with severe sepsis or septic shock. Of the prescribed RRT, European intensivists administered CRRT to patients in 88% of cases Uncertainty of the optimal dose of RRT for patients with severe sepsis associated AKI persists. Some important studies showed no reduction in mortality even by intensive RRT. Thus, a CRRT dose of 20-25 ml/kg/h is recommended by KDIGO and other reviews regarding AKI or CRRT.

It has been theorized that high-volume hemofiltration (HVHF) could be beneficial in septic AKI by purifying inflammatory mediators from the bloodstream. Previous small, single centre studies reported decreased vasopressor doses and improvements in haemo dynamics in patients treated with HVHF.

Relevance

Sepsis, a commonly encountered scenario in an emergency department, often leads to multi-organ dysfunction and the kidney is one of the organs frequently afflicted. The factors leading to AKI in patients with sepsis is an area of growing interest in emergency settings. The current study will add more evidence to this area under research.

RESULTS

Sepsis and Acute Kidney Injury (AKI)

AKI	Frequency	Percentage
Present	54	27
Absent	146	73
Total	200	100

Table 2. Frequency Distribution of AKI in Patients with Sepsis

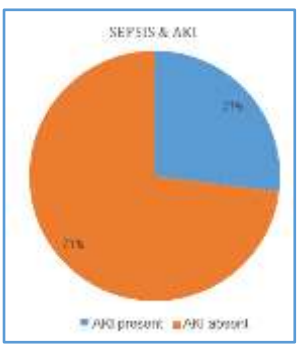

Figure 1. Prevalence of AKI

AKI was present in 27% of patients who were diagnosed with sepsis.

Gender	Frequency	Percentage
Male	106	53
Female	94	47
Total	200	100

Table 3. Frequency Distribution of Gender

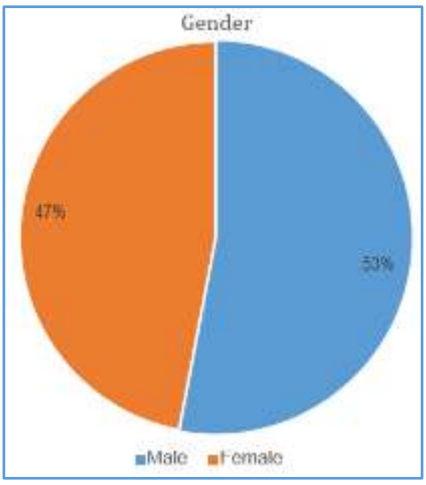

Figure 2. Gender Distribution

Gender	AKI	No AKI
Male	76	70
Female	30	24
Total	106	94

Table 4. Gender Distribution of Patients with and without AKI

There were more males than females in the sample but there was no significant difference in gender distribution among the patients with acute kidney injury and others.

Age	AKI Present	AKI Absent
<60 years	30	98
>60 years	24	48
Total	146	54

Table 5. Age Distribution of Patients with and without AKI

There was no significant difference in the age distribution patients having sepsis with or without AKI.

Co- Morbidities		AKI Present	AKI Absent	P Value
Smoking	Present	23	47	0.18
	Absent	31	99	
Hypertension*	Present	21	43	0.03*
	Absent	33	113	
Diabetes Mellitus*	Present	16	24	0.04*
	Absent	38	122	
CAD	Present	7	14	0.60
	Absent	47	132	

Table 6. Frequency Distribution of Comorbidities in Patients with and without AKI

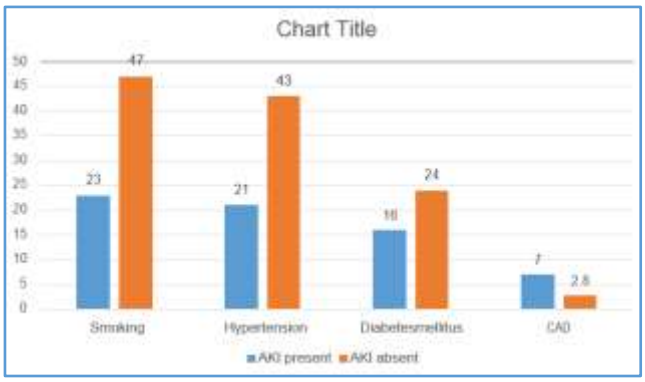

Figure 3. Frequency Distribution of Comorbidities in Patients with and without AKI

Significant difference (p value <0.05) was noticed in the incidence of hypertension and diabetes mellitus in patients with AKI compared with that of patients without AKI.

	AKI Present	AKI Absent	Total
Abdomen (Gastro Intestinal)	21	39	60
Respiratory	15	36	51
Kidney	5	30	35
Skin	4	17	21
Others	4	18	22
Unknown	5	6	11

Table 7. Source of Infection

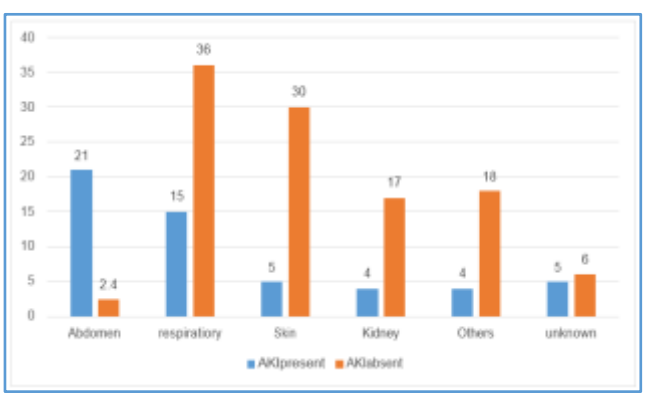

Figure 4. Source of Infection

Blood Culture	AKI Present	AKI Absent
Positive	11	43
Negative	14	132
Total	54	146

Table 8. Blood Culture

Organism	AKI Present	AKI Negative
No organism found	43	133
Gram positive cocci	4	5
Gram negative bacilli	7	8
Total	54	146

Table 9. Organism Present in Blood

Positive blood culture results were significantly more in patients having sepsis with AKI compared with without AKI.

Other Clinical & Lab Parameters	AKI	Total	Mean	S.D.	*
Baseline S. Creatinine	AKI absent	146	1.4000	.01661	0.90
	AKI present	54	1.4000	.02747	
Temperature *	AKI absent	146	36.8000	.01661	0.001
	AKI present	54	36.9000	.02747	
Respiratory Rate*	AKI absent	146	20.00	.166	0.001
	AKI present	54	23.00	.275	
Heart Rate*	AKI absent	146	96.00	.664	0.001
	AKI present	54	103.93	.544	
Mean Blood Pressure*	AKI absent	146	86.5000	.00000	0.001
	AKI present	54	76.5000	.13736	
Leucocyte Count*	AKI absent	146	14.2000	.13287	0.001
	AKI present	54	16.2000	.05494	
Platelet Count*	AKI absent	146	1.3000E2	.66436	0.001
	AKI present	54	1.2644E2	1.67857	
Urine Output*	AKI absent	146	2.0497	.00928	0.001
	AKI present	54	1.3900	.03297	
S. Creatinine at Day 1*	AKI absent	146	1.6144	.17380	0.001
	AKI present	54	3.0815	.72008	

Table 10. Other Clinical and Laboratory Findings

There was significant difference in the clinical and lab parameters in patients with AKI and without AKI. Temperature, Respiratory rate and Heart rate were higher while Mean blood pressure and urine output were lower in the AKI group compared with non-AKI group. Platelet count and serum creatinine were high, and leucocyte count lower in patients with AKI. The results were significant at a P value of <0.05.

AKIN Stage	Frequency	Percentage
Stage 1	14	26
Stage 2	12	22
Stage 3	28	52
Total	54	100

Table 11. AKIN Stage

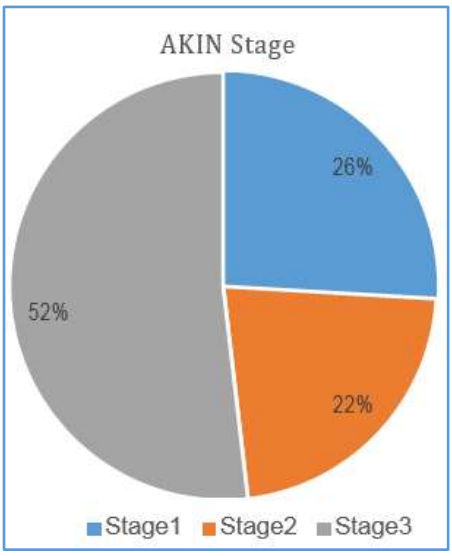

Figure 6. AKIN Stage

Mortality

Mortality	Present	Absent
Present	11	20
Absent	43	126
Total	54	146

Table 12. Difference in Mortality Rate in Patients with and without AKI

There was higher incidence of mortality in patients with sepsis and AKI (20.3%) than in patients with sepsis (15.8%) alone.

DISCUSSION

AKI and Sepsis.

Incidence of AKI

AKI was noticed in 27 % of the patients admitted with sepsis. The findings were similar to that of Lopes and colleagues. In a study of 186 patients they found that nearly one-third of septic patients developed AKI. In a Belgian single-center study, AKI was identified in 16% of septic patients hospitalized in a surgical ICU.[37] Conversely, in a German multicenter study, 41.4% of ICU patients with severe sepsis and septic shock had AKI.[38] Wide variations in patient populations and definitions of AKI could explain discrepancies in terms of AKI incidence.

Age and Gender

AKI was more frequently accompanied by older age, and no significant male or female predominance in incidence was observed. It is controversial whether these demographic differences actually affect the development of septic AKI. In a previous study conducted in Australia[39] septic AKI was more prevalent in the older patients. Another study of AKI in septic shock by Bagshaw SM et al,[2] however, conducted in Germany, showed male dominance in the development of AKI in patients with severe sepsis and septic shock, where older patients were more likely to experience AKI in this study. In contrast, no significant differences were observed in the age and frequency of male sex between the patient groups with or without AKI in a study conducted by Plataki et al Despite some discrepancies among studies, more careful approaches to kidney protection are required in the management of older aged patients with sepsis and septic shock.

Source of infection and blood culture

Most common source of infection for septic AKI was intra-abdominal followed by respiratory and urinary tract. The results reflected the findings of Bagshaw and colleagues[2] who reported a higher incidence of intrabdominal and respiratory source of infection for patients with sepsis and AKI.

Positive blood culture (20%) was present significantly more in patients with AKI. The most common organisms identified were gram negative bacilli (12.9). Sangh Heon Suh reported a higher incidence of positive blood culture (9.4%) in Patients with AKI. Gram negative bacilli were more common (6%) reflecting the findings of the current study

Co-morbidities

We identified that the co morbidities were more common in patients with acute kidney injury than the control group. Presence of hypertension (38.8%) and diabetes mellitus (29.6%) were significantly higher in patients with AKI. A retrospective data analysis of 992 patients by Sang Heon Suh et al found that the incidence of hypertension (39.9%) and diabetes mellitus (28.3%) in patients with AKI and sepsis was higher compared with that of patients with sepsis but no AKI. The FINNAKI study[29] which was a prospective, observational, multicentre study in which 17 Finnish ICUs participated with a total of 2901 patients. They reported a higher incidence of hypertension (50.5%) but the incidence of diabetes mellitus was similar (30%).

Laboratory Findings

Increased WBC count and low platelet count was noticed in patients with AKI Bagshaw et al[2] reported a higher WBC count in the septic AKI group when compared the patients with septic non-AKI group. Low platelet counts in septic AKI patients are consistently observed in the previous studies on septic AKI.[27,40,41] A possible explanation is a more severe inflammatory response might contribute to the development of AKI. It is known that the secretion of pro-inflammatory cytokines, such as IL-1β, TNF-α, and IL-6, is increased in the initial stage of sepsis, followed by activation of anti- inflammatory mechanisms.

AKIN Stage and Mortality

Most of the patients with AKI were in the AKIN Stage 3 (56%) followed by stage 1(26%). These findings were similar to the reports of Lopes et al where most of the patients were in stage 3(53.6%).

ICU mortality was higher for patients having sepsis with AKI (20%) compared with patients without AKI

(13.69%). Positive blood culture (20%) was present significantly more in patients with AKI. The most common organisms identified were gram negative bacilli (12.9). Sangh Heon Suh reported a higher incidence of positive blood culture (9.4%) in Patients with AKI. Gram negative bacilli were more common (6%) reflecting the findings of the current study

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CONCLUSION

AKI was noticed in 27% of the patients with sepsis. There was no gender difference in the prevalence of AKI. Old age, presence of co morbidities like hypertension and diabetes mellitus were more common in the AKI group. Laboratory and clinical findings were also abnormal in the AKI group compared with non-AKI group. AKI was associated with increased morbidity and mortality in patients with AKI. Multiple risk factors were noticed to have a role in the development of AKI and further studies in this regard are needed.

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