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Original Research Article

Acute Kidney Injury in Covid-19 Patients Hospitalised in Intensive Care Unit

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Abstract

Introduction: The incidence of AKI with COVID-19 has been reported varying from 3%–9%. A large prospective study has reported the overall incidence of 5.1%.17 In a study of 59 COVID-19 patients with 28 severe cases and 3 deaths, Li *et al* found that 34% of patients had proteinuria on the first day of admission, and 63% developed proteinuria during the hospital stay. Nineteen percent of people showed an elevated level of serum creatinine. Blood urea nitrogen (BUN) was elevated in 27% patients and in two-thirds of patients who died. The study also emphasized that renal impairment may be an independent factor of mortality. There is a dearth of data in India, especially among critically ill patients in the ICU. Little to date has been published on AKI in COVID-19 beyond rate; for example, wider descriptions of the timing, urine studies, relationship to respiratory failure, detailed analysis of renal replacement therapy (RRT) requirements, risk factors, and outcomes post-AKI are lacking.

Settings and Design: We conducted a cross sectional observational study at a tertiary health care centre in Mysuru, India. Data for this study was obtained from the Intensive Care Unit (ICU) admitted patients who were confirmed positive by polymerase chain reaction testing of a nasopharyngeal sample for COVID-19 and those who were hospitalized from October 1, 2020 to December 31, 2020 were included.

Methods and Material: Patients aged above 18 years; ICU admitted with COVID 19 infection patients. The definition of AKI was considered according to Kidney Disease - Improving Global Outcomes (KDIGO) criteria. The primary outcome was Acute Kidney Injury in ICU set-up. Secondary outcomes was requirement for discharge, death . The RRT facility provided to our patients were in the form of intermittent haemodialysis, sustained low efficacy dialysis or CRRT (Continuous Renal Replacement Therapy).

Statistical analysis: The data was collected using a pre-tested structured questionnaire. The data was entered into Microsoft excel spread sheet. The qualitative variables were coded.The collected data was summarized and presented as frequencies, proportion, mean and standard deviation, depending on the quantitative or qualitative variables. Analysis was performed using SPSS 22 version.

Results: Among patients hospitalized with COVID-19, we found that 33.8% developed AKI during their hospitalization. In addition, the respiratory disease severity appeared to be less, as only 13.4% of their patients required mechanical ventilation compared with 21.5% among our patients. We also found that the development of AKI among our patients was associated with poor prognosis. Of 176 who developed AKI, 17 % of them died.

Conclusions: In conclusion, we found that AKI was a relatively common finding among patients hospitalized with COVID-19. It was strongly linked to the occurrence of respiratory failure and was rarely a severe disease among patients who did not require ventilation. The development of AKI in patients hospitalized for COVID-19 conferred a poor prognosis.

Key-words: AKI, COVID 19, ICU, Morbidity, Mortality

Key Messages: In our analysis, the clearest risk factors for the development of AKI were indicators of severe COVID-19, specifically the need for ventilator support or treatment with inotropes. Reported risk factors for generally poor outcomes of COVID- 19, such as increased age and male sex12,18–21 also contributed to AKI risk. Older individuals and men were at greater risk. The prothrombotic state that has been observed among patients with COVID-19 suggests other renal pathogenic factors.

Introduction

Since late 2019, when the severe acute respiratory coronavirus 2, and the resulting illness, acute respiratory syndrome with coronavirus 2 [COVID-19], developed in Wuhan, China, [1] COVID-19 has become a worldwide pandemic, with 47.6 million cases reported as of November 4, 2020. [2] The first indigenous case of COVID-19 in India was reported on January 30, 2020 in Thrissur district of Kerala and the patient, a student of Wuhan University, China. [3]

As had been observed in China and Italy, the disease resulted in a large number of hospitalizations, respiratory failure, and intensive care unit (ICU) admissions. [4,5] Along with the rise in patients with COVID-19, we noticed an alarming number of patients who developed acute kidney injury (AKI), at rates higher than had been reported from China.Though COVID-19 manifests primarily as diffuse alveolar damage, interstitial pneumonia, and acute respiratory failure, the involvement of other organs such as the kidney, heart, digestive tract, blood, and nervous system is potentially possible. [6,7,8] Early reports from China and Italy found the rate of AKI to range widely from 0.5% to 29%, with most estimates on the lower end. [7-13]

In the previous reports of SARS and MERS-CoV infections, acute kidney injury (AKI) developed in 5% to 15% cases and carried a high (60%–90%) mortality rate. [11] A study reported that although AKI was uncommon in SARS but accounted for the fiercely high mortality of 91.7%, notably 33 out of 36 cases died. [12] Kidney involvement was a strong and independent predictor of mortality during the SARS and MERS outbreak, suggesting the similar situation for the kidney involvement with COVID-19 infection as well.

The incidence of AKI with COVID-19 has been reported varying from 3%–9%. [12,13,14,15] A large prospective study has reported the overall incidence of 5.1%. [16, 17] In a study of 59 COVID-19 patients with 28 severe cases and 3 deaths, Li *et al*found that 34% of patients had proteinuria on the first day of admission, and 63% developed proteinuria during the hospital stay. [18] Nineteen percent of people showed an elevated level of serum creatinine. Blood urea nitrogen (BUN) was elevated in 27% patients andin two-thirds of patients who died. The study also emphasized that renal impairment may be an independent factor of mortality.

In this regard, there is a dearth of data in India, especially among critically ill patients in the ICU. Little to date has been published on AKI in COVID-19 beyond rate; for example, wider descriptions of the timing, urine studies, relationship to respiratory failure, detailed analysis of renal replacement therapy (RRT) requirements, risk factors, and outcomes post-AKI are lacking.

Hence our study aims to determine the overall prevalence of AKI among ICU hospitalised COVID 19 patients and also to assess the mortality pattern and its relation to the above mentioned contributory factors.

Objectives

1. To determine the prevalence of AKI in patients hospitalized with COVID 19 infection.

2. To assess the morbidity and its risk factors among ICU hospitalised COVID 19 patients with AKI.

Subjects and Methods:

Study design

This was a cross sectional observational study of a tertiary health care centre in South India. Data for this study was obtained from the Intensive Care Unit (ICU) admitted patients who were confirmed positive by polymerase chain reaction testing of a nasopharyngeal sample for COVID-19 and those who were hospitalized from October 1, 2020 to December 31, 2020 were included.

Patients were excluded if they had End Stage Kidney Disease (ESKD), or were dialysis dependent or had prior Kidney transplant. The Institutional Review Board of JSS Medical College approved the study protocol before the commencement of the study.

Definitions and measurements

The definition of AKI was considered according to Kidney Disease - Improving Global Outcomes (KDIGO) criteria, it is as follows, stage 1: Increase in serum creatinine by 0.3 mg/dl within 48 hours or a 1.5 to 1.9 times increase in serum creatinine from baseline within 7 days; stage 2: 2.9 times increase in serum creatinine within 7 days; stage 3: 3 times or more increase in serum creatinine within 7 days or initiation of RRT. [19]

Inclusion Criteria:

Age above 18 years, ICU admitted with COVID 19 infection patients

Exclusion Criteria:

Transplant recipients, End stage kidney disease

Patients were classified as per the stages of AKI gained during their stay in the hospital.

We defined baseline renal function from the pre-hospitalization or at hospitalisation serum creatinine values to determine AKI based on the above mentioned KDIGO criteria.

The baseline creatinine was defined as the median serum creatinine within a week to 52 weeks before hospitalization. When there was no previous serum creatinine record available, the serum creatinine at the time of admission was used as the baseline serum creatinine.

As the serum creatinine values were available only for10% of patients prior to admission, we adjusted the baseline value to the median value of serum creatinine from the total period of hospitalization. A ratio of more than 1.5 from peak to median was classified as AKI.

A patient who required Renal Replacement Therapy (RRT) was defined as stage 3 of AKI, according to KDIGO guidelines.

We used the urine output criteria in defining AKI as the Information regarding indwelling urethral catheter was alsoavailable.

The Chronic Kidney Disease Epidemiology Collaboration creatinine equation was used to calculate the estimated (e) glomerular filtration rate. [20]

In addition to this, urinalysis using automated microscopy which was obtained after the initial development of AKI.

Outcomes

The primary outcome was Acute Kidney Injury in ICU set-up. Secondary outcomes were requirement for discharge, death. The RRT facility provided to our patients were in the form of intermittent haemodialysis, sustained low efficacy dialysis or CRRT (Continuous Renal Replacement Therapy).

Statistical Analysis:

The data was collected using a pre-tested structured questionnaire. The data was entered into Microsoft excel spread sheet. The qualitative variables were coded.

The collected data was summarized and presented as frequencies, proportion, mean and standard deviation, depending on the quantitative or qualitative variables. Analysis was performed using SPSS 22 version. Chi square was the test of significance for qualitative data. Independent t-test/Z-test was the test of significance for quantitative data between two groups. Analysis of variance(ANOVA) was the test of significance for quantitative data between three or more groups. Post Hoc Bonferroni was used to find the difference between the groups after ANOVA, p value less than 0.05 was considered as statistically significant.

Ethical Consideration

The study received approval by the Institutional research review board.

Results

From October 1, 2020 to December 31, 2020,520 patients were admitted to JSS hospital with a diagnosis of COVID-19 present on admission or made during the hospitalization. The baseline characteristics of patients at hospital admission are provided in Table 1. A total of 112 patients (21.5%) were treated with mechanical ventilation at some point during the hospitalization. Among the 520 patients, 52 (10%) died, 61 (11.7%) were discharged to home or to a rehabilitation facility, and 85 (16.3%) were still in treatment.

Table 1: Demographic characteristics of study participants

Variables		N (%)
Age Mean-58.84 Median-60 Min=18 Max-91	18-40 years	76(14.6)
	41-60 years	196(37.7)
	>60 years	248(47.7)
Gender	Male	368(70.8)
	Female	152(29.2)
Co-morbid condition	Diabetes	292(56.2)
	HTN	268(51.5)
	Heart disease	96(18.5)
	Chronic lung disease	32(6.2)
	CKD	38(9.2)
	Autoimmune disease	12(2.3)
	Malignancy	12(2.3)
	Transplant recipient	4(0.8)
	CVA	4(0.8)
	Recent surgery(in last 4 weeks)	4(0.8)
Mechanical ventilator		112(21.5)
Inotropes		116(22.4)
Mortality among COVID with AKI patients in ICU		286(55)
Mean length of stay in ICU		7.2 days
Disposition from ICU:		

Death		52(10)
Discharge		61(11.7)
ICU Shift out		85(16.3)
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Overall, 176 of 520 patients (33.8%) developed AKI during their hospitalization. The peak stages of AKI were stage 1 in 45.5%, stage 2 in 11.4%, and stage 3 in 43.2.1% (Table 2).

Table 2: Baseline characteristics of study cohort, by AKI stages

	AKI stages								p value
	No AKI		Stage 1		Stage 2		Stage 3		
	Count	%	Count	%	Count	%	Count	%	
AGE GROUP									
18-40y	64	84.2	0	0	4	5.3	8	10.5	0.001
41-60y	152	77.6	28	14.3	0	0	16	8.2	
>60y	128	51.6	52	21	16	6.5	52	21	
Sex									
Male	232	62.4	72	19.4	20	5.4	48	12.9	0.001
Female	112	75.7	8	5.4	0	0	28	18.9	
Co-morbidities									
Diabetes	200	68.5	40	17.5	12	5.3	32	14	0.262
Hypertension	168	62.7	48	17.9	8	3	44	16.4	0.133
Heart disease	40	41.7	24	25	4	4.2	28	29.2	0.001
Autoimmune disease	8	66.7	0	0	0	0	4	33.3	0.151
Transplant recipient	4	100	0	0	0	0	0	0	0.560
Malignancy	8	66.7	4	33.3	0	0	0	0	0.184
Chronic liver disease	4	100	0	0	0	0	0	0	0.560
Chronic lung disease	16	50	8	25	0	0	8	25	0.065
CVA	0	0	4	100	0	0	0	0	0.001
Recent surgery in last 4 weeks	4	100	0	0	0	0	0	0	0.560
CKD	20	41.7	4	8.3	0	0	24	50	0.001
Mechanical ventilator	0	0	35	31.2	20	17.9	57	50.9	0.001
Inotropes	0	0	20	17.2	20	17.2	76	65.5	0.001
DISPOSITION									
Death	22	42.3	12	23.1	3	5.8	15	28.8	0.001
Discharge	28	45.9	15	24.6	3	4.9	15	24.6	0.005
Shift out	67	78.8	10	11.8	2	2.4	6	7.1	0.048

The relationship between respiratory failure and development of AKI was substantial and is displayed in Table 3.Among 176 patients who developed AKI, 112 required mechanical ventilation, 64 of 176 AKI patients did not require mechanical ventilation. The majority of severe (stage 3) AKI (57 of 112 [50.9%) and most patients requiring dialytic support (26 of 112 [23.2%]) occurred in patients on mechanical ventilation and was found to be statistically significant. RRT was required in 3 of 64 non-ventilated patients (4.6%) compared with 26 of 112 patients on ventilators (23.2%)

Table 3: Baseline characteristics of study cohort, by AKI status

	AKI status				
	No AKI		AKI		p value
	Count	%	Count	%	
AGE GROUP					
18-40y	64	84.2	12	15.8	0.001
41-60y	152	77.6	44	22.4	
>60y	128	51.6	120	48.4	
Sex					
Male	232	62.4	140	37.6	0.004
Female	112	75.7	36	24.3	
Co-morbidities					
Diabetes	200	68.5	92	31.5	0.202
Hypertension	168	62.7	100	37.3	0.085
Heart disease	40	41.7	56	58.3	0.001
Autoimmune disease	8	66.7	4	33.3	0.970
Transplant recipient	4	100	0	0	0.151
Malignancy	8	66.7	4	33.3	0.970
Chronic liver disease	4	100	0	0	0.151
Chronic lung disease	16	50	15	50	0.046
CVA	0	0	4	100	0.005
Recent surgery in last 4 weeks	4	100	0	0	0.151
CKD	20	41.7	28	58.3	0.001
Mechanical ventilator	0	0	112	100	0.001
Inotropes	0	0	116	100	0.001
DISPOSITION					
Death	22	42.3	30	57.7	0.001
Discharge	28	45.9	33	54.1	0.001
Shift out	67	78.8	18	21.2	0.007

Table 4 : The proportion of patients with AKI, by requirement for invasive mechanical ventilation

	No use of Invasive mechanical ventilation (n = 64)	Required Invasive mechanical Ventilation (n =112)	P valuea
Stage 1	45(15)	35(31.2)	<0.001
Stage 2	0(0)	20(17.9)	<0.001
Stage 3	19(29.6)	57(50.9)	<0.001
Required renal replacement therapy	3(4.6)	26(23.2)	<0.001

Among 112 patients who developed AKI during the hospitalization, a total of 31 (27.6%) were still hospitalized, 33 patients (29.4%) were discharged and 30 (26.7%) died. Among those who died, 40% had stage 1, 10% stage 2, and 50% stage 3 (Figure 1).

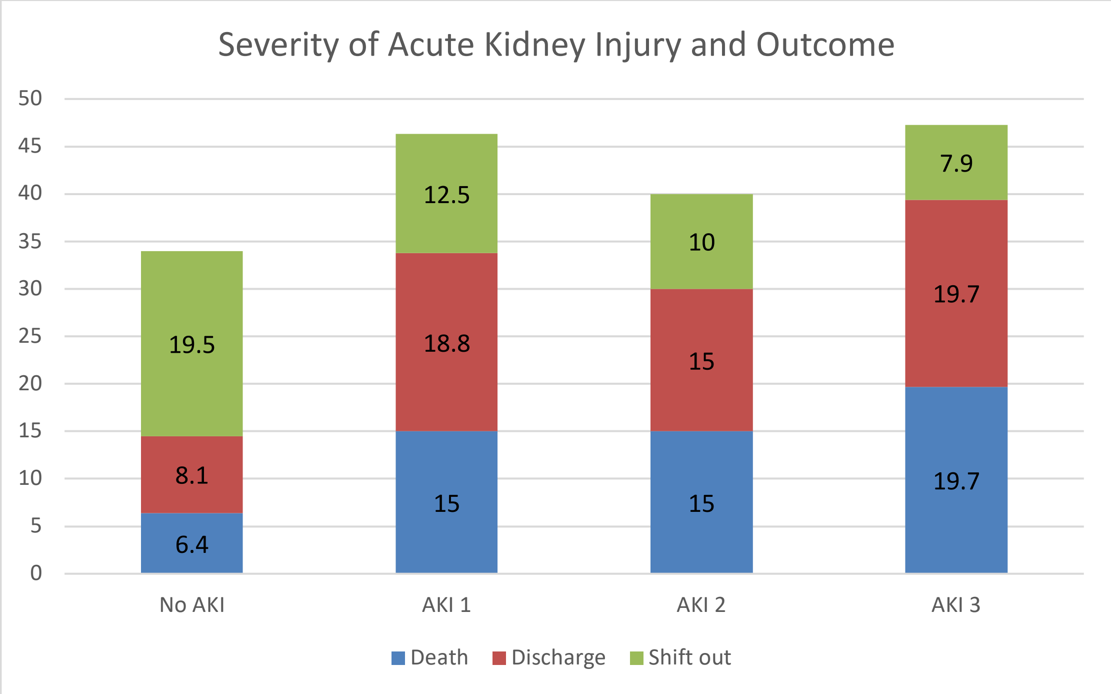

Figure 1: The proportion of disposition type, by stages (1–3) of acute kidney injury (AKI)

Discussion:

COVID-19 infection is basically a respiratory illness, but organs like kidneys are also often affected. [21] Development of AKI is commonly seen as a complication among patients hospitalized for a wide range of diagnoses. Among patients hospitalized with COVID-19, we found that 33.8% developed AKI during their hospitalization. This is a higher rate and similar incidence has been reported previously from China and other areas, from smaller studies, and including various stages of disease. The rate of AKI reported among these studies has ranged from 0.5% to 29%. [21-23]

Cheng et al. [24] reported from Wuhan, China, a rate of AKI of only 5.1% of 701 patients.

This difference cannot be explained completely, but amongst these studies, significantly lower rates of comorbidities such as diabetes and hypertension were reported in their patients.

In addition, the respiratory disease severity appeared to be less, as only 13.4% of their patients required mechanical ventilation compared with 21.5% among our patients. This greater rate reported in our study is found to be consistent with the reports of the hospitals in the United States.

In our analysis, the clearest risk factors for the development of AKI were indicators of severe COVID-19, specifically the need for ventilator support or treatment with inotropes. Reported risk factors for generally poor outcomes of COVID- 19, such as increased age and male sex [25] also contributed to AKI risk. Older individuals and men were at greater risk.

The close temporal relationship between AKI and respiratory failure occurrence is suggestive of ischemic acute tubular necrosis, which usually occurs in association with systemic collapse. However, other aetiologies should be continued to be considered.

The prothrombotic state that has been observed among patients with COVID-19 suggests other renal pathogenic factors.

Our urinary results are provocative.

We found a high median majority of patients with urinary sodium <35 mEq/l at the time of development of AKI. Traditionally these findings are most indicative of prerenal states, but they may also be found with glomerulonephritis and even certain forms of acute tubular necrosis. Because a cytokine storm often occurs in close temporal proximity to respiratory failure, it is possible that circulating substances or other related factors could contribute to AKI.

In addition, our findings of fairly high rates of proteinuria and haematuria are noteworthy, but inferences are limited as we were unable to ascertain indwelling urethral catheter status at the time of urine collection. It should be noted that, Su et al.,28 in a study from Wuhan, China, determined autopsy findings among 26 patients, with tubular injury as the primary renal finding.

We also found that the development of AKI among our patients was associated with poor prognosis. Of 176 who developed AKI, 17 % of them died.

Our study has certain strengths. Our definition and identification of AKI is consistent with national and international guidelines, is well validated, and has been automatically calculated in real time for almost 1 year. The present study has may be different if we had included other health system hospitals in the area.

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