



High mortality and residual kidney damage with Coronavirus disease-19-associated acute kidney injury in northern India

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Received: 2 April 2022 / Accepted: 17 June 2022 / Published online: 8 July 2022
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Abstract

Background Acute kidney injury (AKI) is associated with morbidity and mortality in COVID-19 patients. The incidence of AKI and its outcomes vary in different parts of the world. We aimed to analyze the AKI incidence, predictors of AKI, mortality, and renal function outcomes on follow-up in hospitalized patients with COVID-19.

Materials and methods The study was designed as a retrospective, observational study of electronically captured data on the hospital information system of laboratory-confirmed COVID-19 patients, with and without AKI, between March 2020 to June 2021. The predictor of AKI and mortality and residual damage in recovered AKI patients were analyzed.

Results Of the 3395 patients, 3010 COVID-19 patients were eligible. AKI occurred in 951 (31.5%); with stages 1, 2, and 3 in 605 (63.7%), 138 (14.5%), and 208 (21.8%) patients, respectively. AKI severity increased with COVID-19 severity. Of 951 AKI patients, 403 died, and 548 were discharged. AKI group had higher mortality (42.3%) than the non-AKI (6.6%). At discharge, complete recovery was noticed in 370 (67.5%), while 178 (32.5%) had residual damage. At three months of follow-up, 108 (69.6%) of 155 patients showed complete recovery. Residual damage was observed in 47 (30.3%). In 14 (9%) patients, serum creatinine remained elevated above the baseline. Thirty-three (21.2%) patients showed proteinuria ($n = 24$) and microscopic hematuria ($n = 9$).

Conclusions AKI is common among patients hospitalized with COVID-19 and is associated with high mortality. Residual kidney damage post-COVID-19 in recovered AKI patients may increase the CKD burden.

Keywords Coronavirus disease-19 · Acute kidney injury · Outcomes · Residual kidney damage

Abbreviations

COVID-19	Coronavirus disease-19
AKI	Acute kidney injury
CKD	Chronic kidney disease
SIRS	Systemic inflammatory response syndrome
MDRD	Modification of diet in renal disease
KIDGO	Kidney disease improving global outcomes
CCI	Charlson comorbidity index
qSOFA	Quick sequential organ failure assessment
CRP	C-reactive protein
NIV	Non-invasive ventilation
ESR	Erythrocyte sedimentation rate

Introduction

Coronavirus disease-19 (COVID-19) primarily affects the respiratory tract, may manifest with systemic inflammatory response syndrome (SIRS), acute kidney injury (AKI), and multiorgan dysfunction. SARS-CoV-2 has a 10–20-fold higher binding affinity for ACE2 receptors expressed in the respiratory tract, kidneys, gastrointestinal tract, and many other organs [1–3]. The SARS-CoV-2 enters the lungs by binding through ACE2 receptors and causes pneumonia. ACE2 receptors are manifold high in kidneys, and the virus has a tropism for renal cells, which express ACE2 receptors, particularly on proximal tubules and podocytes. The virus affects kidneys through direct cytotoxicity, acute tubular and interstitial injuries, systemic inflammatory response syndrome, and associated complications [1]. (1) Limited histological studies have shown tubulointerstitial injuries are more common than glomerular injuries with SARS-CoV-2 [2].

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The incidence of AKI associated with COVID-19 reportedly varied in different parts of the world. Data are limited on outcomes of AKI associated with COVID-19 from this part of the world. Several studies showed an association in mortality between AKI and COVID-19. A recent systematic analysis revealed higher mortality in COVID-19 patients with AKI [3]. Along with agent, host factors, and comorbidities, several other factors such as infrastructure, timely admission, and the availability of beds for severe COVID patients also affected mortality. During the pandemic, India, particularly Uttar Pradesh, a resource-limited state, was severely affected by COVID-19. Rajdhani Corona Hospital at Lucknow is one of the largest referral centers for COVID-19 in Uttar Pradesh, India. Since the declaration of the pandemic in March 2020, this hospital has been repurposed to tackle COVID-19 patients exclusively. This hospital accommodated all patients infected with COVID-19 from March 2020 to June 2021. We aimed to analyze the

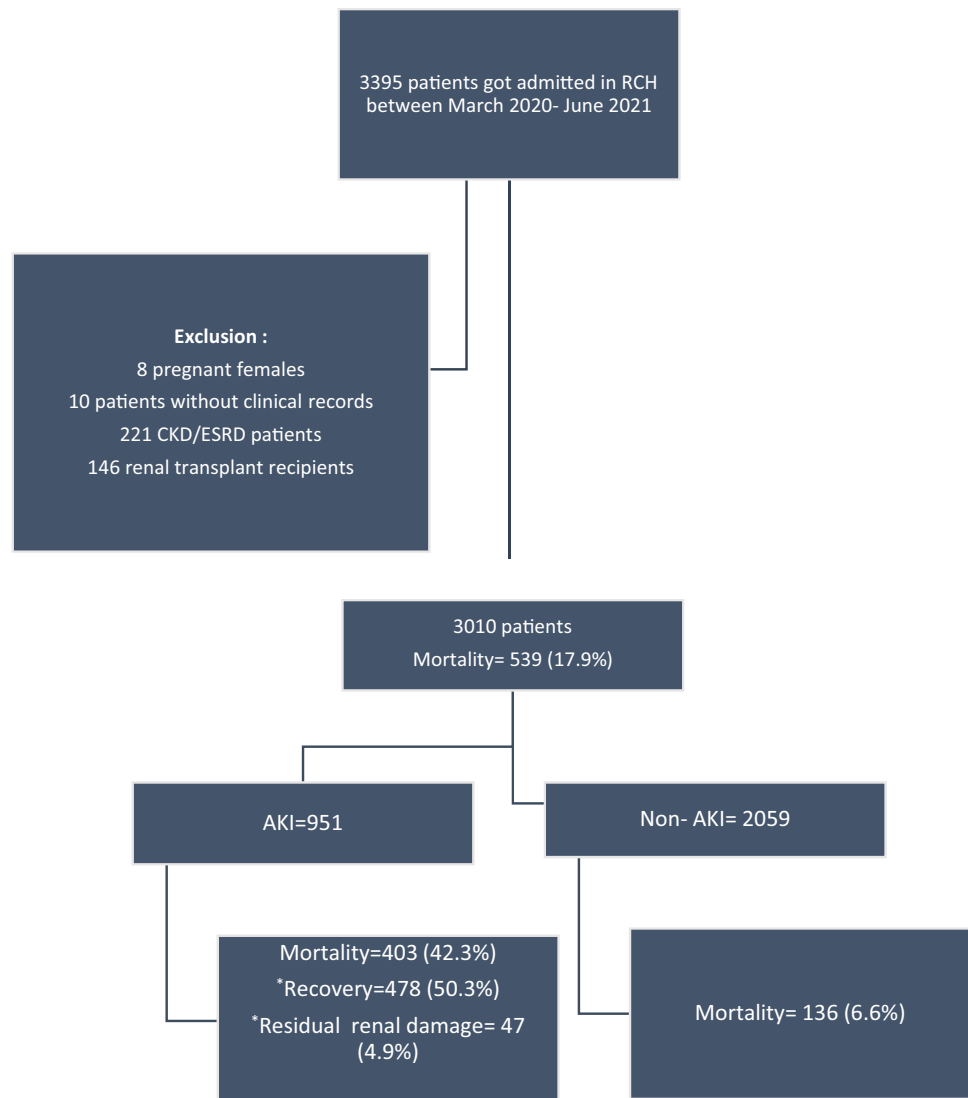
factors associated with the development of AKI and explore the relation between AKI, mortality, and renal outcomes in the North Indian population with COVID-19.

Methods

Study population

The flow diagram of the study of COVID-19 patients with AKI and their outcomes is shown in Fig. 1. The study was conducted at Rajdhani Corona Hospital of this tertiary care institute, a 210 bedded hospital dedicated to the care of COVID-19 patients. We retrospectively reviewed the medical records of each patient admitted with COVID-19 between March 2020 and June 2021. The hospital had an electronic hospital information system that captured each patient's demographic, clinical, laboratory parameters,

Fig. 1 Flow diagram of the COVID-19 patients with AKI and their outcomes



death, and discharge summary. The daily progress records of each patient from admission to discharge were retrieved. The patients were categorized into the AKI group and the Non-AKI group. The demographic profiles, clinical details, biochemical, and outcome parameters were retrieved to analyze AKI incidence, risk factors associated with AKI development, and mortality of the patients. The clinical and laboratory parameters change over the first 48 h to define AKI for the analysis. The study was carried out per the code of ethics of the World Medical Association, Declaration of Helsinki. The Institute's ethics committee has approved the study.

Inclusion and exclusion criteria

We included patients of 18 years of age or older who had a laboratory-confirmed SARS-CoV-2 infection with reverse transcriptase–polymerase chain reaction (RT–PCR) on two specimens collected from two oropharyngeal and nasopharyngeal swabs. The study did not include pregnant women, chronic kidney disease (CKD) patients, patients with evidence of CKD on radio imaging, known end-stage renal disease, renal allograft recipients, and individuals with incomplete medical records.

Definitions

- (1) The severity of COVID-19 was categorized as per the guideline of the Indian Council of Medical Research, Ministry of Health & Family Welfare, Government of India [4, 5]. The disease was classified as mild when symptoms were present without features of viral pneumonia on imaging (X-ray chest or high-resolution computed tomography [HRCT] scans), moderate if manifestations were present, while severe disease refers to the presence of hypoxia with respiratory rate > 30 breaths/min, severe respiratory distress, SpO₂ < 90% on room air including acute respiratory distress syndrome (ARDS).
- (2) AKI, the primary endpoint, was defined as per Kidney Disease Improving Global Outcomes (KDIGO) criteria: a change in the serum creatinine of 0.3 mg/dl over 48 h or a 50% increase from baseline creatinine. For patients with previous serum creatinine before admission, the most recent serum creatinine value was the baseline creatinine. For patients without a baseline creatinine in the 7–365 days prior to admission, the admission creatinine was imputed based on a Modification of Diet in Renal Disease (MDRD) eGFR of 75 ml/min per 1.73 m² as per the KDIGO AKI guidelines [6, 7]. The clinical and laboratory parameters change over the first 48 h after admission were taken for AKI staging. AKI staging was performed using the KDIGO AKI stage creatinine definitions: stage 1 as an increase in serum creatinine of ≥ 0.3 mg/dl or an increase to ≥ 1.5–1.9 times baseline serum creatinine. Stage 2 was defined as an increase to > 2–2.9 times from baseline serum creatinine, and stage 3 as an increase of creatinine more than three times baseline serum creatinine or a peak serum creatinine ≥ 4.0 mg/dl or if the patient received RRT during admission. Proteinuria had been considered if the patient had a protein–creatinine ratio of ≥ 0.5, 1+ proteinuria or higher on the dipstick. The presence of trace was not counted as proteinuria. Leukocyturia was defined as more than five white blood cells per high-power field. Hematuria was defined as 1+ or higher on dipstick or urinalysis [6].
- (3) Charlson Comorbidity Index (CCI) was assessed as performed in the study reference-8 of the manuscript.
- (4) The quick sequential organ failure assessment (qSOFA) was calculated from the details collected from the patients' records as per reference-9 of the manuscript.
- (5) Recovery of kidney function was defined as mentioned in reference[10]. Full recovery from AKI was defined by the absence of AKI criteria over three months on subsequent follow-up. Partial recovery was defined as a fall in the AKI stage over three months, i.e., the patient recovered; however, there was evidence of persisting residual damage. No recovery is no change in the AKI stage over three months.

For all surviving patients with AKI, renal function was followed at the time of discharge. At three months after discharge, each patient was contacted for a repeat laboratory test for serum creatinine value and urinalysis. The Institute has a facility for serum creatinine estimation that has calibration traceable to an isotope dilution mass spectrometry (IDMS) reference measurement.

Statistical analysis

Kolmogorov–Smirnov test was performed to test the normality of data distribution. The values are expressed in terms of mean and standard deviation for normally distributed continuous variables and in the form of the medians and interquartile ranges for non-parametric distributions. The categorical values were expressed in the form of percentages and proportions. The student's *t* test was used to compare the mean values between the two groups. Mann–Whitey *U* test was used to compare the median values between two independent groups. Pearson's Chi-square test was used to compare the significant differences of proportion between the severity of the COVID-19 and AKI staging. Two proportion *z* test was used to compare the pair wise proportion between groups.

Univariate and multivariate logistic regression analysis was used to predict AKI development of patients in the cohort. Those who developed AKI or not were considered dependent variables in AKI development prediction analysis. Univariate and multivariate cox-regression analysis was used to predict mortality. The death of the patient was considered as an event in the analysis. A P value < 0.05 was considered statistically significant. Statistical analysis was performed using IBM. SPSS software version 25.

Results

Characteristics of the study population

The flow diagram of the study is shown in Fig. 1. A total of 3395 COVID-19 patients were admitted to the RCH during the study period. Eight pregnant females, 221 CKD/ESRD patients, 146 renal transplant recipients, and ten patients without clinical records were excluded. Finally, we analyzed the data of 3010 (median age 55 (IQR = 42–64) years, and males 2091 (69.4%) COVID-19 patients. The demographic and clinical parameters of the cohort, patients with and without AKI, are shown in Table 1. Patients with AKI were older and predominantly male. The median duration of onset of AKI was 4 days (IQR 1–9 days). A higher percentage of patients with AKI had a fever, cough, upper respiratory tract infection, and dyspnoea than non-AKI patients. However, diarrhea and other symptoms such as loss of smell and taste were similar.

Comorbidities and inflammatory markers in AKI

On the evaluation of inflammatory markers, we observed that AKI patients had higher serum ferritin levels, C-reactive protein levels, erythrocyte sedimentation rates, and LDH than non-AKI (Table 1). The Charlson's Comorbidity Index in AKI patients (2.76 vs. 1.54, $P = 0.001$) was higher than in non-AKI patients (Table 1). The qSOFA score was also significantly higher in the AKI group than in the non-AKI group (0.99 vs. 0.34; $P = 0.001$). A higher proportion of patients with AKI had hypertension, diabetes, coronary artery disease, cerebrovascular accident, and chronic liver disease than non-AKI patients (Table 2). The proportion of patients with obesity and pulmonary disease was similar between AKI and non-AKI patients.

Association between severity of AKI and COVID-19

The association between the severity of AKI and COVID-19 is depicted in Fig. 2A, B. Of all the patients, mild COVID was observed in 1878, moderate in 409, and severe COVID in 723 patients. Overall AKI was observed in 951 (31.5%)

patients with stages 1, 2, and 3 in 605 (63.7%), 138 (14.5%), and 208 (21.8%) patients, respectively. The stage 1, 2, and 3 AKI in mild COVID were observed in 15.2%, 1.8%, and 1.2% of patients, respectively. The stage 1, 2 and 3 in the moderate COVID was 27.6%, 5.6%, and 5.6%, and in severe COVID was 28.8%, 11.4%, and 22.3%, respectively. Stage 3 AKI increased from 1.2% in mild COVID-19 to 5.6% in moderate and 22.3% in severe COVID-19 ($P = 0.0001$) (Fig. 2A). On clubbing stage 2 and 3 AKI together and pairwise comparison (Fig. 2B), we again found that the stage 2 and 3 AKI increased significantly with the severity of AKI. Out of all the patients with AKI, the percentage of stage 1 AKI decreased from 83.5% in mild COVID-19 to 71% in moderate COVID-19 and 46% in severe COVID-19 patients, while the combination of stage II and III AKI significantly increased from 16.5% in mild COVID-19 to 29% in moderate COVID-19 and 54% in severe COVID-19 patients. Stage III AKI was seen in only 1.2% of mild COVID-19, 5.6% of moderate COVID-19 and 22.3% of severe COVID-19.

A total of 178 (18.7%) of the AKI stage 3 patients required dialysis. Of the 178 patients who required dialysis, 162 patients had severe COVID-19, and 16 had moderate COVID-19. We observed that the severity of AKI increased with COVID-19 severity. Out of 723 patients who had severe COVID-19, 453 (62.5%) patients had AKI. In the AKI group, a total of 76% had proteinuria, 67% had hematuria, and 48% had leukocyturia. In the non-AKI group, 4% had proteinuria, 2% had hematuria, and 22% of patients had leukocyturia.

Predictors of development of AKI

The details of the independent variables associated with the prediction of AKI development on univariate and multivariate logistic regression analysis are shown in Table 3. On multivariate analysis, we observed that hypertensives (OR = 1.40; 95% CI 1.08–1.82) and males (OR = 1.55, 95% CI 1.17–2.05) were at 40% and 55% higher risk of having AKI, respectively. Other factors such as Charlson Comorbidity Index (OR = 1.22; 95% CI 1.11–1.32), qSOFA (OR = 1.48, 95% CI 1.22–1.79), oxygen requirement during hospitalisation (OR = 1.59, 95% CI 1.19–2.13), ESR (OR = 1.004, 95% CI 1.001–1.008), antifungal usage (OR = 2.54, 95% CI 1.88–3.43), vasopressors requirement (OR = 8.60, 95% CI 7.81–9.42), requirement of invasive ventilation (OR = 3.50, 95% CI 1.68–7.26) were significantly associated with the development of AKI. However, age, SGPT level, chronic liver disease, CRP level, and NIV lost significance on multivariate analysis.

Predictors of mortality

The univariate and multivariate cox-regression analysis showing predictors of mortality is shown in Table 4. A total

Table 1 Patient characteristics of COVID-19 patients with acute kidney injury and non-acute kidney injury

Patient characteristics	All, <i>n</i> = 3010	AKI, <i>n</i> = 951	No AKI, <i>n</i> = 2059	<i>P</i> value
Age, median (IQR) Y	55 (42–64)	59 (49–68)	53 (40–61)	0.001
Sex, <i>n</i> (%) Male	2091 (69.4%)	709 (74.5%)	1382 (67.1%)	0.001
CCI, mean ± SD	1.93 ± 1.8	2.76 ± 2.1	1.54 ± 1.6	0.001
qSOFA, mean ± SD	0.55 ± 0.77	0.99 ± 0.89	0.34 ± 0.61	0.001
<i>Laboratory values, median (IQR)</i>				
Hemoglobin, g/dl (<i>n</i> = 2942)	12(11–14)	12(10–13)	12(11–14)	0.198
TLC, 10 ³ /μl (<i>n</i> = 2943)	8 (6–11)	9 (6–14)	7(5–10)	0.002
Platelet, 10 ³ /μl (<i>n</i> = 2934)	158 (120–213)	162 (120–217)	155 (120.2–212)	0.592
ESR, mm/h (<i>n</i> = 2956)	54(23–82)	68 (33.5–88)	46 (19–77)	0.001
CRP, mg/L (<i>n</i> = 2871)	22 (6–75)	48 (14–120)	14 (4–55)	0.001
Ferritin, μg/L (<i>n</i> = 2734)	418 (177–919)	619.5 (275–1341)	347.5 (142–753.2)	0.001
LDH, U/L (<i>n</i> = 2989)	318 (230–451)	463 (308–696)	352 (245–521)	0.001
AST, U/L (<i>n</i> = 2990)	35(24–54)	46 (29–74.5)	38 (25–60)	0.001
ALT, U/L (<i>n</i> = 2897)	39 (24–66)	42 (25–72)	40(25–68)	0.020
Albumin, g/dl (<i>n</i> = 2989)	3.9 (3.5–4.3)	3.51 (3.1–3.9)	3.8 (3.4–4.2)	0.167
BUN, mg/dl (<i>n</i> = 2979)	18 (13–28)	35 (26–50)	25 (17–40)	0.001
Creatinine, mg/dl (<i>n</i> = 2994)	0.95 (0.8–1.17)	1.87(1.36–2.87)	1.2(0.8–1.4)	0.001
Proteinuria (1 + or more)	380 (28%)	344 (76%)	36 (4%)	0.001
Hematuria	322 (23.7%)	304 (67%)	18(2%)	0.004
Leucocyturia	415 (30.6%)	217 (48%)	198 (22%)	0.02
<i>Vital signs, median (IQR)</i>				
MAP, mm Hg (<i>n</i> = 3005)	94.6 (86.6–102)	88.3 (80–96.6)	96.6 (90–103.3)	0.001
Heart rate, BPM (<i>n</i> = 3005)	96 (84–110)	106 (76–120)	90 (80–102)	0.001
Respiratory rate, per min (<i>n</i> = 3004)	19(17–22)	24 (20–30)	20(18–22)	0.001
Oxygen saturation, % (<i>n</i> = 3004)	97 (91–98)	91(85–98)	98(95–99)	0.001
<i>Symptoms, n = 3010 (%)</i>				
Fever	2515 (83.6%)	843 (88.6%)	1672 (81.2%)	0.001
Cough	1835 (61%)	644 (67.7%)	1191 (57.8%)	0.001
Sore throat	1524 (50.6%)	510 (53.6%)	101(49.2%)	0.024
Dyspnoea	1192 (39.6%)	564 (59.3%)	628(30.5%)	0.001
Diarrhoea	131 (4.4%)	40 (4.2%)	91 (4.4%)	0.798
Loss of smell, taste and others	510(16.9%)	87(9.1%)	423(20.5%)	0.897
<i>Severity of COVID, n (%)</i>				
Mild	1878 (62.4%)	340 (35.8%)	1538 (74.7%)	0.012
Moderate	409 (13.6%)	159 (16.7%)	250 (12.1%)	0.564
Severe	723 (24%)	452 (47.5%)	271 (13.2%)	0.002
<i>Organ support</i>				
Vasopressor, <i>n</i> (%)	483(16%)	365(38.3%)	118(5.7%)	0.002
Ventilator, <i>n</i> (%)	512 (17%)	382 (40.2%)	130 (6.3%)	0.002
NIV, <i>n</i> (%)	508 (16.9%)	317 (33.3%)	191 (9.3%)	0.001
Mortality, <i>n</i> (%)	539 (17.9%)	403 (42.3%)	136 (6.6%)	0.001

CCI Charlson comorbidity index, qSOFA quick sequential organ failure assessment, ESR erythrocyte sedimentation rate, CRP C-reactive protein, AST aspartate aminotransferase, ALT alanine aminotransferase, LDH lactate dehydrogenase, MAP mean arterial blood pressure, NIV non-invasive ventilation

of 539 (17.9%), patients died during hospitalization. We observed 403(42.3%) mortality in the AKI group and 136 (6.6%) patients in the non-AKI group. Of the 403 patients who died in the AKI group, the causes of death had been attributed to severe ARDS with multiorgan failure(*n* = 298),

COVID-19 pneumonia associated with secondary bacterial sepsis (*n* = 57), associated fungal infection (*n* = 16), cerebrovascular accident (*n* = 12), acute coronary syndrome (*n* = 14) and sudden death (*n* = 6). In non-AKI group, the cause of death were attributed to severe COVID pneumonia (*n* = 98),

Table 2 Comorbidities in COVID-19 patients with AKI and without AKI

Comorbidity	Total (n=3010)	AKI (n=951)	Non-AKI (n=2059)	P value
Hypertension	1177 (39.1%)	495 (52%)	682 (33.1%)	0.001
Diabetes Mellitus	1129 (37.5%)	480 (50.4%)	649 (31.5%)	0.001
Coronary Artery disease	262 (8.7%)	129 (13.5%)	133 (6.5%)	0.001
Cerebrovascular accident	68 (2.3%)	38 (4%)	30 (1.5%)	0.001
Chronic liver disease	41 (1.4%)	26 (2.7%)	15 (0.7%)	0.001
Obesity	51 (1.7%)	22 (2.3%)	29 (1.4%)	0.074
Pulmonary diseases	143 (4.8%)	56 (5.9%)	87 (4.3%)	0.065

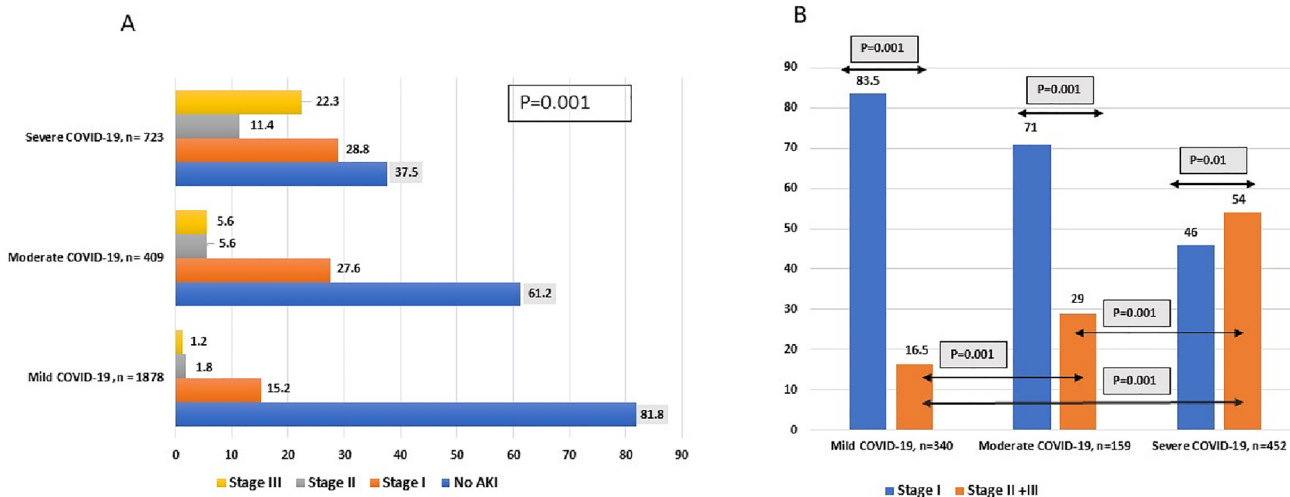


Fig. 2 A Overall association between the severity of the COVID-19 and AKI staging was statistically significant on Pearson Chi square test for multiple comparison ($P=0.001$). It shows that with increasing severity of COVID-19, the percentage of patients with stage I AKI decreased, and stage II, and stage III AKI increased. Further-

more, **B** shows that stage II and III AKI clubbed together significantly increased with severity of COVID-19 on pairwise comparison with two proportion z test between the groups. AKI staging data are expressed in percentages

bacterial sepsis($n=15$), acute coronary syndrome($n=11$), cerebrovascular accident ($n=8$) and sudden death($n=4$). On multivariate analysis, AKI patients had 4.2 times higher mortality risk (OR=4.20; 95% CI 2.80–6.31) than non-AKI patients. Amongst other independent variables, each unit increase in Charlson Comorbidity Index (OR=1.25, 95% CI 1.10–1.42), and qSOFA score (OR=5.14, 95% CI 3.66–7.21) were associated with a high odds ratio of mortality. The antifungal usage (OR=3.81, 95% CI 2.53–5.73), non-invasive ventilation (OR=1.66; 95% CI,1.03–2.68), and invasive ventilation (OR=21.8, 95% CI 8.83–54.2) and vasopressor use (OR=17.66, 95% CI 7.47–41.74) were associated with high odds ratio of mortality. Each gram increase in hemoglobin (OR=0.9, 95% CI 0.82–0.99), was associated with a 10% lower mortality risk.

Residual damage post-COVID AKI

The mean duration of hospitalization was higher in patients with residual damage (23.45 ± 11.23 days) compared to patients without residual damage (16.26 ± 10.41 days)

($P=0.04$). Of the 951 AKI patients, 403 died, and 548 were discharged. At discharge, 370 (67.5%) patients showed complete recovery, and 178 (32.5%) had persistent residual with elevated serum creatinine from baseline, haematuria, and or proteinuria. Out of 178 (32.5%) patients with AKI, 155 patients were followed for three months. They were contacted telephonically and advised to a repeat laboratory test. Twenty-three patients could not be followed up because of incorrect details in the hospital's electronic record. Of the 155 patients on 3-month follow-up, 108 (69.6%) patients showed complete recovery, and 47 (30.3%) patients had residual damage. A total of 14 (9%) patients had elevated serum creatinine above the documented baseline and the mean eGFR of 47.15 ± 11.38 ml/min/1.73m². A total of 44 out of 47 patients required renal replacement therapy during hospitalization. Thirty-three 33 (21.2%) patients showed residual damage in the form of proteinuria ($n=24$) and microscopic hematuria ($n=9$). To note, all patients with residual damage had severe COVID-19 and had at least one or more comorbidities; 26 had a vasopressor requirement, and 34 of them had a need for non-invasive or invasive ventilation.

Table 3 Univariate and multivariate logistic regression analysis showing predictor of development of AKI in patients with COVID-19

Variable	OR (95% CI)	P value
<i>Univariate analysis</i>		
Age, years	1.031 (1.025–1.036)	0.001
Gender (males vs. females)	1.43 (1.20–1.70)	0.001
Diabetes mellitus (yes vs. no)	1.03 (0.76–1.41)	0.811
Hypertension (yes vs. no)	1.59 (1.19–2.13)	0.002
Coronary artery disease (yes vs. no)	0.88 (0.55–1.42)	0.618
Chronic liver disease (yes vs. no)	4.61 (1.46–14.47)	0.009
Charlson comorbidity index (increase by 1)	1.22 (1.11–1.33)	0.001
qSOFA (increase by 1)	1.94 (1.13–2.21)	0.001
Hemoglobin, g/dl (increase by 1)	0.99 (0.96–1.02)	0.707
Total Leucocyte Count, 10 ³ /μl	1.002 (0.991–1.004)	0.664
ESR, mm/h (increase by 1)	1.005 (1.001–1.010)	0.021
CRP, mg/L (increase by 1)	1.004 (1.001–1.009)	0.045
Ferritin, μg/L	1.002 (0.995–1.011)	0.345
SGOT, U/L	1.003 (0.999–1.006)	0.105
SGPT, U/L (increase by 1)	0.997 (0.994–0.999)	0.007
Serum albumin, g/dl (decrease by 1)	1.016 (0.988–1.044)	0.278
Oxygen requirement during hospitalisation (yes vs. no)	2.74 (1.80–4.16)	0.001
Oxygen requirement at the time of admission (yes vs. no)	0.76 (0.50–1.18)	0.232
NIV (yes vs. no)	4.89 (1.00–5.98)	0.002
Invasive ventilation (yes vs. no)	3.57 (1.63–7.81)	0.001
Vasopressors (yes vs. no)	1.69 (0.76–3.76)	0.006
Remdesivir (yes vs. no)	1.05 (0.78–1.40)	0.732
Antifungal usage (yes vs. no)	4.96 (4.05–6.07)	0.001
<i>Multivariate analysis</i>		
Age, years	1.01 (0.98–1.136)	0.532
Gender (males vs. females)	1.55 (1.17–2.05)	0.002
Hypertension (yes vs. no)	1.40 (1.08–1.82)	0.010
Chronic liver disease (yes vs. no)	1.03 (0.93–1.13)	0.342
ESR, mm/h (increase by 1)	1.004 (1.001–1.008)	0.025
CRP, mg/L	1.001 (1.000–1.002)	0.078
ALT, U/L	1.000 (1.000–1.002)	0.368
Charlson Comorbidity Index (per unit increase)	1.22 (1.11–1.32)	0.001
qSOFA (per unit increase)	1.48 (1.22–1.79)	0.002
Oxygen requirement during hospitalisation (yes vs. no)	1.59 (1.19–2.13)	0.002
NIV (yes vs. no)	1.027 (0.732–1.441)	0.877
Invasive ventilation (yes vs. no)	3.503 (1.689–7.264)	0.001
Vasopressors (yes vs. no)	8.60 (7.81–9.42)	0.003
Antifungal usage (yes vs. no)	2.54 (1.88–3.43)	0.001

CCI Charlson comorbidity index, qSOFA quick sequential organ failure assessment, ESR erythrocyte sedimentation rate, CRP C-reactive protein, AST aspartate aminotransferase, ALT alanine aminotransferase, LDH lactate dehydrogenase, MAP mean arterial blood pressure, NIV non-invasive ventilation

Table 4 Univariate and multivariate cox-regression analysis showing predictor of mortality in patients with COVID-19

Variable	OR (95% CI)	P value
<i>Univariate analysis</i>		
Age, year	0.970 (0.965–0.975)	0.001
Gender (males vs. females)	1.11 (0.90–1.36)	0.322
Diabetes mellitus (yes vs. no)	2.14 (1.76–2.59)	0.001
Hypertension (yes vs. no)	2.02 (1.67–2.44)	0.001
Coronary artery disease (yes vs. no)	2.40 (1.82–3.18)	0.001
Chronic liver disease (yes vs. no)	4.26 (2.29–7.93)	0.001
Charlson comorbidity index (increase by 1)	0.706 (0.675–0.737)	0.001
qSOFA (increase by 1)	0.332 (0.29–0.37)	0.001
Hemoglobin (g/dl)	1.11 (1.07–1.15)	0.001
Serum albumin (g/dl) (decrease by 1)	3.27 (2.76–3.87)	0.001
ESR, mm/h (increase by 1)	0.984 (0.982–0.987)	0.001
CRP, mg/L (increase by 1)	0.992 (0.990–0.999)	0.001
Oxygen requirement at the time of admission (yes vs. no)	7.46 (6.04–9.27)	0.001
Oxygen requirement during hospitalisation (yes vs. no)	10.14 (8.05–12.77)	0.001
NIV (yes vs. no)	8.77 (6.86–11.20)	0.001
Invasive ventilation (yes vs. no)	39.35 (25.40–60.95)	0.001
Vasopressors (yes vs. no)	328.9 (223–485)	0.001
Remdesivir (yes vs. no)	1.89 (1.54–2.31)	0.001
Antifungal usage (yes vs. no)	9.75 (7.84–12.12)	0.001
AKI (yes vs. no)	9.53 (7.65–11.84)	0.001
<i>Multivariate analysis</i>		
Age, year	1.011 (0.995–1.027)	0.417
Diabetes mellitus (yes vs. no)	0.749(0.48–1.169)	0.203
Hypertension (yes vs. no)	0.805 (0.526–1.230)	0.316
Coronary artery disease (yes vs. no)	1.001 (0.892–1.108)	0.208
Chronic liver disease (yes vs. no)	0.768 (0.671–1.023)	0.256
Hemoglobin, g/dl (increase by 1)	0.90 (0.82–0.99)	0.030
S albumin (g/dl) (decrease by 1)	0.825 (0.612–1.112)	0.206
ESR, mm/hr (increase by 1)	0.998 (0.993–1.004)	0.553
CRP, mg/L (increase by 1)	1.001 (0.987–1.003)	0.352
Charlson comorbidity index (increase by 1)	1.25 (1.10–1.42)	0.001
qSOFA (increase by 1)	5.14 (3.66–7.21)	0.001
NIV (yes vs. no)	1.66 (1.03–2.68)	0.037
Oxygen requirement at the time of admission (yes vs. no)	1.074(0.662–1.744)	0.771
Oxygen requirement during hospitalisation (yes vs. no)	1.014 (0.891–1.277)	0.548
Vasopressor (yes vs. no)	17.66 (7.47–41.74)	0.001
Invasive ventilation (yes vs. no)	21.82 (8.83–54.2)	0.001
Remdesivir (yes vs. no)	1.020 (0.639–1.627)	0.935
Antifungal usage (yes vs. no)	3.81 (2.53–5.73)	0.002
AKI (yes vs. no)	4.20 (2.80–6.31)	0.001

CCI Charlson comorbidity index, qSOFA quick sequential organ failure assessment, ESR erythrocyte sedimentation rate, CRP C-reactive protein, AST aspartate aminotransferase, ALT alanine aminotransferase, LDH lactate dehydrogenase, MAP mean arterial blood pressure, NIV non-invasive ventilation

Discussion

In this large cohort of COVID-19 patients admitted to a tertiary care COVID hospital, we observed that 31.5% of the patients had AKI as per KDIGO criteria. The incidence is almost similar to the incidence reported from different

centers of the developed [11] and the developing world [3, 12, 13]. The high incidence of AKI compared to other centers in India at our Institute was primarily because our hospital was a level 3 referral center for COVID care, accommodating mainly sicker patients [11, 14]. The temporal and geographical heterogeneity in AKI has been observed in the

literature. It may be because of differences in hospitalization criteria, differences in the healthcare system, risk factors, socio-economic disparity, ethnicities, and differences in the population studied with comorbidity burden varying government approaches for managing COVID-19.

We have also observed that the severity of AKI increases with the severity of COVID-19. Stage 3 AKI was observed in 1.2% mild, 5.6% moderate, and 22.3% severe COVID-19. The association between the severity of AKI and COVID-19 may be attributed to high viral loads and associated comorbidities [15]. Almost 1 in every 4 cases (162/723) of severe COVID-19 was noted to require dialysis in our cohort. AKI patients had a higher Charlson Co-morbidity Index and qSOFA score than patients in the non-AKI group. The predictors of AKI associated with COVID-19 (Table 2) are similar to any critically ill patients developing AKI [16]. The high incidence of AKI indicates that besides the lung, the kidney is one of the most commonly involved organs with SARS-CoV-2 infection.

Besides direct viral cytotoxicity, hemodynamic instability may be a major risk factor for AKI. Microcirculatory dysfunction, renal congestion, microvascular thrombi, endothelial dysfunction, and tubular injury, were also associated with AKI development [17]. The abundance of ACE2 on proximal tubules and podocytes makes kidneys susceptible to injury by SARS-CoV [1]. Proteinuria and microscopic hematuria indicate glomerular injury with podocytopathy in these patients [18]. The urinary findings indicate that proteinuria is more common than hematuria, implying direct tubules injury [19].

Similar to other studies, we have also observed that hypertensives and diabetics with COVID-19 risk having AKI. Hypertension (52%) and diabetes (50%) are the most common comorbidities in the AKI cohort. In our cohort, hypertensives had a 40% higher risk of developing AKI. Hypertensive patients are prone for an imbalance between renin–angiotensin–aldosterone system activity, chronic low-grade inflammation, and elevated dipeptidyl peptidase activity [19]. The dysregulation of these biological processes may be aggravated by the SARS-CoV-2 infection, giving rise to an exacerbated immune response. It may culminate in tissue damage/dysfunction leading to multiorgan failure with myocardial injury and ischemia, acute lung injury, thrombosis, acute kidney injury, ventricular arrhythmias, and death [18]. Similarly, people with diabetes with COVID-19 were also at higher risk of AKI. It may be because of the baseline upregulation of the ACE and downregulation of ACE2, a combination that primes a proinflammatory state, along with complement activation and pro-fibrotic state in the kidneys [15].

Similar to other studies [19, 20] we also observed that AKI is an independent predictor of mortality in patients with COVID-19. After adjusting different parameters, AKI

patients had almost 4.2 times higher mortality risk than the non-AKI group. Males were at 55% higher risk of developing AKI, consistent with the existing literature [21]. Oxygen requirement, vasopressors, high values of inflammatory markers such as serum ferritin, ESR, and CRP are severe COVID-19 and AKI markers. We did not have facilities to measure IL-6 levels. Our cohort has a mortality of 17.9%, among which the AKI group had a mortality of 42.3%, while 83.2% of patients with stage III AKI succumbed to the illness.

One of the remarkable findings in our study was antifungal usage in 298 (41.2%) patients with severe COVID-19. Antifungal use was associated with 3.8 times higher risk of mortality and 2.5 times higher risk of AKI. Antifungals in viral disease are unusual, but bacterial and fungal infections are not uncommon complications of viral pneumonia, especially in critically ill patients [21]. However, it can be difficult to distinguish bacterial or fungal infection and existing viral pneumonia based on clinical and radiological appearance. However, a microbiological examination can add tremendous value to diagnosis, especially sputum culture, which is not always feasible. Antibacterials and antifungal agents were used at the discretion of intensivists looking after these patients. Moreover, it may be attributed to the super-added infections in a viral disease leading to higher mortality and complication [22].

The risk of mortality and AKI increases by 25% and 22% for each increase in CCI, respectively. For each unit increase in qSOFA score, the risk of AKI increases by 48% and is associated with a 5.14 times higher mortality risk. Compared to other centers in the country, the high mortality rate at our center may be due to the referral preference of severe COVID-19 patients to this center, which was designed as a level 3 hospital to tackle COVID-19 patients. The majority of patients having severe covid pneumonia (62.5%) had AKI, which increases the risk of mortality by 4.2 times.

The most important observation in the study is the residual damage in surviving AKI patients with COVID-19. We studied the trend of AKI recovery at discharge and three months after discharge. We observed that a total of 1.4% of AKI patients (14/951) did not achieve the baseline values, and 3.4% of patients (33/951) had persistent proteinuria and/or, microscopic hematuria. This is the first study to follow up the surviving cohort of AKI at three months. The association of residual damage with comorbidity is known. However, the study highlights that severe episodes of AKI with COVID-19 will pose the risk of developing new CKD on top of the existing CKD, burdening the already overwhelmed health care system. AKI patients need a special mention for hospitalized COVID-19 patients as it affects the course of the disease and allocation of resources and may add a burden to the CKD cohort. This may bring post-COVID implications that COVID-19 has increased a significant number of patients

to the CKD pool, which needs care and regular follow-up. Post-COVID CKD needs a mention here as 4.9% of patients (47/951) did not show the recovery of renal function; hence need care and follow-up under nephrologists. Thus, renal involvement in COVID-19 has huge prognostic implications and is a challenge for the healthcare system, especially for resource-constraint countries such as India.

Strengths and Limitations of the study

This is one of the most extensive studies from the developing world with limited resources to deal with the COVID-19 pandemic. It conclusively highlights the high mortality associated with AKI in patients with COVID-19. The findings may help healthcare providers to allocate the resources to deal with AKI in COVID-19 patients. Another major strength is outcomes of AKI three months after discharge of the patients and assessment of the residual damage in the surviving patients. The study is limited to a single-center experience.

Conclusions

The comorbidities associated with patients predispose them to develop AKI and high mortality risk. AKI in patients with COVID-19 increases the risk of mortality. The residual kidney damage at the end of three months of discharge in surviving patients alarms the nephrologists for regular follow-up of the patients for CKD development.

Acknowledgements We acknowledge the health care professional in assisting the collection of data. We acknowledge the contribution of Dr Prabhakar Mishra, the biostatistician of the institute for guiding with the statistical analysis of data.

Data availability The data that support the findings of this study are available on reasonable request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declarations

Conflict of interest The authors declare no conflict of interests.

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