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ORIGINAL ARTICLE

Factors associated with unfavourable outcomes in COVID-19 patients with acute kidney injury: A single-centre retrospective observational study

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ABSTRACT

Background: COVID-19 infection adversely affects all nephron segments to cause acute kidney injury (AKI), leading to greater mortality.

Methods: A retrospective analysis was conducted of patients (age >18 years) with COVID-19-related AKI admitted at a quaternary-level multispeciality hospital between September 2020 and April 2021. Data regarding various clinical, radiological, biochemical and haematological parameters were analysed and their association with clinical outcomes concerning mortality or survival was determined.

Results: We included 67 patients (46 males) with a mean age of 68.2 ± 12.17 years, of whom 45 patients were haemodynamically unstable, and 52 had hypoxaemia at the time of presentation. Overall, 53% of the cases were discharged from the hospital and 46% succumbed to the illness; females had higher mortality (67%, P = 0.024). The mean neutrophil/lymphocyte ratio (P = 0.014), HbA1c (P = 0.011), LDH (P = 0.002), D-dimer (P = 0.034) and C-reactive protein (P = 0.001) levels at admission were higher in patients with unfavourable outcomes. Increased mortality was present in patients who had a higher clinical category of illness (P = 0.014), advanced AKI stage (P = 0.001), haemodynamic instability at presentation (P < 0.001), required some form of KRT (P = 0.009), oxygen (P = 0.047), ventilatory (P = 0.028) or inotropic support (P = <0.001), were on calcium channel blockers at the time of admission (P = 0.024) or required antifungal agents (P = 0.003) or insulin therapy (P = 0.041).

Conclusions: Female COVID-19 patients with AKI, presenting with advanced disease and chest pain, having pre-existing comorbidities, had increased mortality.

Keywords: COVID-19 with acute kidney injury, acute kidney injury, severe acute respiratory syndrome coronavirus-2.

INTRODUCTION

The novel severe acute respiratory syndrome caused by coronavirus-2 (SARS-CoV-2), which induces SARS-like symptoms, is genetically similar to the bat coronavirus; presumably, it emerged from bats and was transmitted to humans by an unknown animal. The first case of the coronavirus disease-2019 (COVID-19) was reported in the city of Wuhan, China, in December 2019 [1]; eventually, the World Health Organization (WHO) declared the disease outbreak a public health emergency of international concern on 30 January, 2020, and later as a pandemic on 11 March, 2020 [2]. The acute clinical manifestations of COVID-19 may vary from a mild flu-like illness to life-threatening viral pneumonia, severe acute respiratory distress syndrome (ARDS), sepsis, or even septic shock [3-6]. Acute kidney injury (AKI) is one of the most serious health concerns in COVID-19 patients because of the associated high fatality, morbidity, and economic burden of treatment. AKI is highly prevalent in COVID-19 intensive care units (C-19 ICUs) and is the chief precipitating factor for mortality in COVID-19

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patients, especially in those requiring some form of kidney replacement therapy (KRT) [7-9]. A multicentre longitudinal study reported a significant decline in the estimated glomerular filtration rate (eGFR) in AKI due to COVID-19 as compared to other causes of kidney injury [10]. A high mortality rate was noted in COVID-19 patients with severe AKI but long-term survival rates and predictors of mortality in COVID-19 patients with AKI are uncertain [7]. There are few studies in the literature which have determined the factors associated with unfavourable outcomes of AKI in COVID-19 patients. We therefore conducted the study reported here to characterise the association between COVID-19 and various conditions that may predict the outcomes of AKI patients.

METHODS

This retrospective observational analytical study included COVID-19 patients with AKI admitted at the B.M.H. Gimcare hospital, Kannur, Kerala, India – a quaternary-care centre in South India catering to nearly 1000 outpatients and 250 inpatients daily with an average COVID-19 ICU load of 100 patients/month during the study period. All patients above the age of 18 years admitted to the centre between September 2020 and April 2021, diagnosed with COVID-19 and AKI during their hospital stay, were included in the study. AKI was identified and classified based on the serum creatinine level as recommended by the Kidney Disease Improving Global Outcomes (KDIGO) guidelines defined as either a 0.3 mg/dL rise from the lowest creatinine value within 48 hours or a 50% increase in creatinine from baseline [11]; however, urine information, a prominent criterion, was inappropriately documented in some of the records and hence was not used for the AKI classification of cases. A patient self-discharged against medical advice or transferred to another centre was labelled as an unknown outcome and excluded from the study. All established chronic kidney disease (CKD) patients and those who underwent renal transplantation were also excluded from the study.

All patients were assigned a quick sequential organ failure assessment (qSOFA) score based on their admission parameters used to describe the baseline severity of illness. The qSOFA uses three criteria, assigning one point for high respiratory rate (≥22 breaths per min), low systolic blood pressure (SBP ≤100 mmHg), or altered mentation (Glasgow coma scale <15). Data about the patients' demographic status and serum biochemical and haematological parameters were collected. Additionally, systolic and diastolic blood pressure, vasopressor requirements and clinical outcomes in terms of mortality (unfavourable) or survival (favourable) were recorded. Clinical categorisation of the patients was also performed at admission (supplementary Table 1), as per the state government directives [12].

A patient was considered haemodynamically unstable if there was perfusion failure as evident from the symptoms of circulatory shock and/or severe heart failure, or one or more vital sign measurements that were abnormal at the time of presentation. A patient with oxygen saturation (SpO_2) of less than 93% on room air at the time of presentation was considered to have hypoxaemia.

The data collected were statistically analysed to determine the association of various parameters on the outcome of patients with AKI and COVID-19. All the data collected were coded and entered in a Microsoft Excel sheet, which was re-checked and analysed using SPSS statistical software version 22. Quantitative variables were summarised using mean and standard deviation or in terms of median and interquartile range. Categorical variables were represented using frequency and percentage. Independent sample t-test and Mann–Whitney test were used to compare continuous variables between groups, depending on the normality of distribution. Pearson's chi-squared test and Fisher's exact test were used to compare categorical variables between groups. A P value of <0.05 was considered statistically significant.

Ethical approval

This study was approved by the Research and Scientific Committee, Institutional Human Ethics Committee (EC/GIMCARE/NEPRO/OBSV/03.21/001), and the approval for publication was granted by the Medical Director, B.M.H. Gimcare Hospital, Kannur, Kerala, India.

RESULTS

Sixty-seven cases (46 men and 21 women) were included in the final analysis of 74 patients enrolled in our study. Seven cases were excluded due to unknown outcomes. The most common presenting complaints were fever (85%), cough (58%), shortness of breath (56%), myalgia (57%), vomiting (16%), chest pain (9%), diarrhoea (6%), insomnia (4.5%) and headache (4.5%). As compared to patients without complaints of chest pain, all those who reported chest pain at the time of admission succumbed to the illness (P = 0.007). Most (n = 55; 82%) of the patients belonged to clinical category C and 16% (11) were in category B. The overall mean qSOFA score at admission was 0.88 ± 0.66 and was higher among the female population than the males (0.90 ± 0.53 versus 0.87 + 0.71).

Forty-five (67%) of the patients were haemodynamically unstable and 52 (78%) subjects had hypoxaemia at the

time of presentation. Inotropic support was required in 43% (29) of the cases. Fourteen patients (21%) needed invasive ventilation, 41 (62%) were treated with non-invasive ventilation (NIV), 55 (83%) required some form of oxygen support via a nasal cannula or non-rebreather mask (NRBM), and 50 patients (75%) needed ICU care at some point during their hospital stay. The average length of hospital stay was 11.5 ± 8.7 days (Table 1).

We identified various comorbidities, such as diabetes mellitus (DM) (n = 52; 78%), hypertension (n = 49; 73%), coronary artery disease, CAD (n = 26; 39%), cerebrovascular accident, CVA (n = 12; 18%), dyslipidaemia, DLP (n = 9; 13%), chronic obstructive pulmonary disease, COPD (n = 7; 10%), thyroid disorders (n = 5; 7.5%), and cancer in two patients (3%); none of these comorbidities had a significant impact on the disease's outcome.

Table 1. Clinical and laboratory features of the study population (N = 67).

Parameter	Median (IQR) value
Pulse rate (beats per minute)	90 (77–106)
Respiratory rate (breaths per minute)	24 (20–28)
SPO_2 in room air (%)	93 (87–96)
SBP (mmHg)	140 (130–150)
DBP (mmHg)	80 (70–90)
Neutrophil /Lymphocyte ratio	3.17 (2.43–7.08)
Platelet count (cells/µL) x10^3	181 (138–227)
Haemoglobin (g/dL)	12 (10.5–13.5)
RBS (mg/dL)	320 (243–393)
HbA1C (%)	7.91 (6.87–8.85)
CRP at admission (mg/L)	61.43 (23.9–113.78)
Peak CRP attained during the period of hospital stay (mg/L)	108.41 (60.98–202.89)
Creatinine at admission (mg/dL)	1 (0.7–2)
Peak creatinine (mg/dL)	2.3 (1.5–4.3)
Urea (mg/dL)	60.46 ± 40.73
Uric acid (mg/dL)	5.96 ± 2.14
Sodium (mmol/L)	132.48 ± 5
Potassium (mmol/L)	4.41 ± 0.78
Calcium (mg/dL)	8.38 ± 0.98
Peak LDH (U/L)	468.3 ± 285.0
Peak D dimer (ng/mL)	3547.8 ± 3161.7
Time taken to attain RAT negativity (days)	11.96 ± 7.17

Abbreviations: RBS, Random blood sugar; FBS, fasting blood sugar; HbA1C, glycated haemoglobin; CRP, C reactive protein; LDH, lactate dehydrogenase; RAT, rapid antigen test.

The mean D-dimer level was 2,249 ± 2,565 ng/mL, total leukocyte count (TLC) was 9.59 ± 5.81 x 10^3 cells/µL, and the eGFR at admission was 49.7 ± 32.51 mL/min/1.73 m^2. Trace proteinuria was seen in nine patients (13%), 1+ protein in six patients (9%), 2+ in eight (12%), and 3+ in five patients (7.5%). Compared to those with favourable outcomes, the subjects who succumbed to the illness had higher levels of mean neutrophil/lymphocyte ratio (3.91 ± 3.09 versus 6.68 ± 5.17 , P = 0.014), HbA1c (7.54 ± 1.42% versus 8.66 ± 2.01% , P = 0.011), lactate dehydrogenase (LDH)(374.25 ± 208.06 U/L versus 577.61 ± 324.47 U/L, P = 0.002), D-dimer (1851.02 ± 2248.98 ng/mL vs 2711.34 ± 2857.84 ng/mL, P = 0.034), and C-reactive protein (CRP)(58.82 ± 61.09 mg/L versus 102.60 ± 64.27 mg/ L, P = 0,001) at the time of admission (Table 2). Furthermore, 18 patients (27%) were found to have microscopic haematuria.

According to the computerised tomography (CT) scan at the time of admission, 37 patients (55%) belonged to the COVID-19 Reporting and Data System (CO-RADS) grade 6, whereas 27 patients (40%) were in the grade 5 category.

Nearly 34% (n = 23) of the cases reached stage 3 AKI, while 15% (n = 10) progressed to stage 2 AKI during their inpatient care. Nine patients required some form of KRT, such as sustained low-efficiency daily dialysis (SLEDD) or intermittent haemodialysis (IHD), with an interquartile range (IQR) of 2–3 sessions of dialytic therapy. The mortality rate proportionately increased with the stages of AKI, that is, 23% for stage 1, 60% for stage 2, and the highest mortality (74%) in stage 3 patients (P = 0.001).

Fifty-three percent of the patients (n = 36) were discharged from the hospital and 46% (n = 31) succumbed to the illness, with significantly higher mortality among the female population (67%, P = 0.024). The outcome was unfavourable in patients who had a higher category of clinical illness category C (P = 0.014), advanced stage AKI (P = 0.001), were haemodynamically unstable at the time of presentation to the hospital (P < 0.001), or required some form of KRT (P = 0.009), oxygen (P = 0.047), ventilatory support (P = 0.028), or inotropic support (P < 0.001) during the period of inpatient care.

Regarding medications, most patients (n = 61; 91%) were treated with some form of steroids, such as dexamethasone (n = 3; 4.5%), hydrocortisone (n = 4; 6%), and methylprednisolone (n = 54; 81%). More than half (n = 56; 84%) required insulin therapy either due to underlying DM, for hyperglycaemia induced by steroids, or the disease per se. Ten patients were on oral antidiabetic drugs (OADs), nine were on angiotensin receptor blockers (ARBs), and 27 patients were on calcium channel blockers (CCBs) at the time of admission. Remdesivir was administered in 12

Table 2. Association of various clinical, haematological, biochemical, radiological, and therapeutic parameters with patient outcome.

Factors	Outcome [n (%)] Discharged (n = 36)	Deceased (n = 31)	P value
Age (years)	65.69 ± 12.49	71.16 ± 11.27	0.066
Sex			
Male	29 (63)	17 (37)	0.024
Female	7 (33)	14 (67)	
Hypoxaemia at admission	26 (50)	26 (50)	0.254
Hypotension at admission	5 (63)	3 (38)	0.716
CVA	8 (67)	4 (33)	0.321
CAD	13 (50)	13 (50)	0.626
Diabetes mellitus	25 (48)	27 (52)	0.084
Thyroid disease	2 (40)	3 (60)	0.656
Hypertension	25 (51)	24 (49)	0.463
Dyslipidaemia	6 (67)	3 (33)	0.488
COPD	5 (71)	2 (29)	0.437
Cancer	2 (100)	0 (0)	0.495
Clinical category at admission			
A	1 (100)	0 (0)	
B	10 (90.9)	1 (9.1)	0.014
C	25 (45.5)	30 (54.5)	
N/L ratio	3.91 ± 3.09	6.68 ± 5.17	0.014
Haemoglobin (g/dL)	12.07 ± 1.92	11.85 ± 2.44	0.674
HbA1C (%)	7.54 ±1.42	8.66 ± 2.01	0.011
CRP at admission (mg/L)	58.82 ± 61.09	102.60 ± 64.27	0.001
Peak CRP (mg/L)	107.32 ± 71.79	162.26 ± 95.5	0.001
Peak creatinine (mg/dL)	2.35 ± 1.54	4.04 ± 2.5	0.004
AKI stage			
Stage 1	26 (76.5)	8 (23.5)	0.001
Stage 2	4 (40)	6 (60)	
Stage 3	6 (26.1)	17 (73.9)	
eGFR at admission (mL/min/1.73 m^2)	52.31 ± 31.99	46.66 ± 33.37	0.399
LDH (U/L)	374.25 ± 208.06	577.61 ± 324.47	0.002
D dimer at admission (ng/mL)	1851.02 ± 2248.98	2711.34 ± 2857.84	0.034
Chest pain	0 (0)	6 (100)	0.007
Haemodynamic stability	21 (95.5)	1 (4.5)	<0.001
KRT initiation	1 (11.1)	8 (88.9)	0.009
Ventilation	4 (28.6)	10 (71.4)	0.028
Oxygen requirement	27 (49.1)	28 (50.9)	0.047
NIV	17 (41.5)	24 (58.5)	0.006
ICU stay	23 (46)	27 (54)	0.030
Inotropes	5 (17.2)	24 (82.8)	<0.001

Table 2. Association of various clinical, haematological, biochemical, radiological, and therapeutic parameters with patient outcome continued.

Factors	Outcome [n (%)] Discharged (n = 36)	Deceased (n = 31)	P value
Oral hypoglycaemic drugs	7 (70)	3 (30)	0.320
Insulin	27 (48.2)	29 (51.8)	0.041
Angiotensin receptor blockers at time of admission	4 (44.4)	5 (55.6)	0.723
Angiotensin-converting enzyme inhibitors at time of admission	1 (100)	0 (0)	1.000
Calcium channel blockers at time of admission	10 (37)	17 (63)	0.024
Remdesivir	8 (66.7)	4 (33.3)	0.321
Antifungals	3 (20)	12 (80)	0.003
Steroids			
Dexamethasone	2 (66.7)	1 (33.3)	
Hydrocortisone	1 (25)	3 (75)	0.586
Methylprednisolone	29 (53.7)	25 (46.3)	

Abbreviations: CVA, Cardiovascular accidents; CAD, coronary artery disease; N/L ratio, neutrophil/ lymphocyte ratio; HBA1C, glycated haemoglobin; CRP, C reactive protein; LDH, lactate dehydrogenase; KRT, kidney replacement therapy; NIV, non-invasive ventilation; ICU, intensive care unit; n, number.

patients (18%) and antifungal therapy was clinically indicated in 15 cases (22%). Heparin was required in 77% (n = 52), aspirin in 43% (n = 29), clopidogrel in 40% (n = 27) and statins in 52% (n = 32) of the study population. Higher mortality was observed among patients who were on CCBs at the time of presentation (P = 0.024) and who required antifungal agents (P = 0.003) or insulin therapy (P = 0.041).

DISCUSSION

In this study, we observed higher mortality among female COVID-19 patients with AKI who were on CCBs and presenting with chest pain. This may have been due to the severity of illness at the time of admission, as reflected in the higher qSOFA scores, or due to Berkson's bias as women are less likely to be admitted to the hospital than men in the Indian scenario [13]. Previous studies have demonstrated a higher case fatality rate, respiratory intubation, and longer length of hospital stay among men across all age groups, races and ethnicities [14,5]. In contrast, in the Indian scenario, the mortality rate among women was noted to be 3.3% and 2.9% for men [16]. These disparities could be attributed to gender bias in case identification, insufficient COVID-19 data across geographies or higher risks for women in some countries due to demographic circumstances [17].

The reported incidence of AKI in COVID-19 patients varies from 38% to 57%, which leads to a greater requirement for KRT and mechanical ventilation, as well as higher in-hospital mortality and complication rates in this group [18,19]. The pathogenesis of COVID-19-related AKI is multidimensional. The typical and most frequent pathological features recorded in the kidney biopsies of COVID-19 patients were acute tubular injury, collapsing glomerulopathy, membranous glomerulopathy, and thrombotic microangiopathy. These features indicate complex mechanisms underlying the development of AKI associated with COVID-19, secondary to haemodynamic instability, ARDS, sepsis, use of redundant diuretics/nephrotoxic medications, hypothermia, hypoxia, cytokine storm, or the prothrombotic nature of the disease per se [20-22]. The aetiology of AKI in COVID-19 patients is a discrete entity compared with AKI developing in other hospitalised patients because of the potential role of angiotensin-converting enzyme 2 (ACE2) receptor-mediated pathogenesis of the disease. Additionally, renal tissue has the maximum number of ACE2 receptors in the body, which facilitates the entry of the virus into the kidney cells, making it a viral reservoir [23]. This may explain the statistically significant and higher mortality among patients on CCBs than on ACE inhibitors (ACEi); the ARB class of antihypertensives, such as ACEi/ARB, may prevent the entry of the virus to these cells and reduce the incidence of AKI.

Only a few studies have demonstrated reduced mortality in hypertensive COVID-19 patients on CCBs [24,25]. Interestingly, a meta-analysis revealed that the use of CCBs

was not associated with reduced mortality; in contrast, a subgroup analysis of hypertensive patients in our study revealed significantly higher mortality with CCBs [26]. Reynolds et al. analysed 634 patients with hypertension who had developed severe COVID-19 disease, to demonstrate that previous use of CCBs was linked to a "slightly greater" (4%) incidence of severe illness, although this difference was not clinically significant [27]. Another large observational study suggested that ARBs were linked to a lower risk of COVID-19-related hospitalisation as compared to CCBs [28]. Therefore, it can be deduced that the data regarding the efficacy of various medications on the outcome of COVID-19 patients with AKI are inconclusive. Some studies have demonstrated favourable effects of CCBs and hypocalcaemia in COVID-19 patients as it may alter calcium influx to the virus, preventing its replication [24-26]; however, our study found that patients with COVID-19-related AKI had poor outcomes, which needs to be verified by larger, randomised control studies. The exact mechanism by which CCBs increase mortality, as noted in our study, needs to be re-examined.

Most of the patients in our investigation were older than 65 years, which represents the population most vulnerable to COVID-19 [29]. The preponderance of males (n = 46) in our sample could have been due to greater outdoor movement and socialisation among males than females, making them susceptible to COVID-19. Most clinical category A cases improved with outpatient care and did not require admission; however, they constituted <2% of our study population.

Comorbidities observed in our study sample included chronic, hereditary, or non-communicable disorders, such as DM, hypertension, dyslipidaemia, CAD, chronic kidney disease, CVA, cancer, and lifestyle habits or addictions such as smoking, drinking, and tobacco consumption; these comorbidities affect the patient's immunity level. Most patients in the study had multiple comorbidities, resulting in frailty, which often restricted aggressive curative treatment options.

We also observed that patients with pre-existing comorbidities, such as COPD, CAD, DM, and blood pressure-related issues, had a higher incidence of severe AKI with COVID-19. Of eight significant comorbidities analysed, patients with uncontrolled DM were most vulnerable as these cases experienced a higher mortality rate. The mortality rate in our study was 49% in patients with hypertension, 60% in those suffering from thyroid disorders, 52% in uncontrolled DM patients, and 50% in CAD cases. AKI develops in a considerable percentage of COVID-19 patients, particularly in diabetics, and is significantly associated with mortality [30]. However, in our study, a history of DM did not attain statistical significance as a risk factor for mortality, which may have been due to the small sample size. Higher mean HbA1C values at the time of admission and the requirement for insulin during the illness period showed a statistically significant association with mortality, suggesting that poor pre-illness glycaemic control may lead to an unfavourable outcome. The severity of illness at the time of presentation as reflected by haemodynamic instability, higher clinical categorisation, the requirement of inotropic support, ventilation, and ICU admission, also led to an unfavourable outcome. Moreover, the presence of central chest pain, high neutrophil/lymphocyte ratio, uncontrolled DM as suggested by raised HbA1c values, and elevated inflammatory and pro-thrombotic markers, such as CRP, D-dimer, and LDH at the time of admission, were associated with an adverse outcome. Chest pain may occur due to the virus affecting the lungs or secondary to micro thrombus formation in coronary or pulmonary circulations.

Advanced AKI stages, due to worsening kidney function requiring urgent KRT support, adversely affect patient outcomes. In the advanced stages of renal dysfunction associated with COVID-19, early initiation of dialytic therapies may be the only intervention that can reliably enhance survival [31]. Additionally, antifungals were used for advanced COVID-19 disease when the patient suffered from secondary fungal infections either due to immunocompromised status or exposure to steroids, thus leading to death.

Our results are limited by the retrospective observational nature of the study involving a limited sample size, as it was conducted at a time when the entire healthcare personnel and resources of the nation were re-routed for patient care and research was at a standstill. These findings need to be verified with larger randomised trials; nevertheless, the study contributes to the ever-expanding literature on this novel disease that is spreading at an alarming pace, with far-reaching economic implications globally.

CONCLUSIONS

We found that the female gender, clinical severity of illness, use of CCBs, presence of chest pain, uncontrolled DM, and haemodynamic instability were the factors that led to poor outcomes in COVID-19 patients with AKI. Additionally, those who required some form of ventilation or inotropic support, had raised neutrophil/lymphocyte ratio and D-dimer and CRP levels, and required KRT or antifungal medications during the period of hospital stay had a poor prognosis. Larger randomised control studies are warranted to corroborate these findings.

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Competing Interest

There are no competing interests to declare.

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APPENDIX

Supplementary Table 1. Clinical categorisation of patients based on their presenting complaints.	
A	Mild symptoms: sore throat, cough, rhinitis, diarrhoea without dehydration or electrolyte disturbances.
B	Category A + two or more of the following: 1. Lung/heart/liver/neurological disease? Hypertension/haematological disorders/uncontrolled diabetes/cancer/ HIV-AIDS. 2. On long-term steroids or immunosuppressive drugs. 3. Pregnant female. 4. Age >60 years. OR Category A + cardiovascular disease.
C	Breathlessness, chest pain, fall in blood pressure, haemoptysis, cyanosis, worsening of underlying chronic disease.