

Renal Involvement and Outcomes in Patients Hospitalized with COVID-19 Infection in A Tertiary Hospital

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ABSTRACT

Background Kidney involvement is seen frequently in COVID-19 patients and is essential to the prognosis. This study is undertaken to describe the clinical presentation of renal involvement in COVID-19 patients concerning acute kidney injury (AKI), chronic kidney disease (CKD) and urinary abnormalities and to correlate with the severity of COVID-19 illness and its outcome.

Material and Methods A retrospective cross-sectional study reviewed the medical records of patients admitted with COVID-19 infection who had pre-existing renal conditions or renal manifestations in the form of deranged renal function tests or abnormal urinary findings. All the relevant clinical and laboratory parameters, including the treatment details and outcome, were noted, and statistical analysis was done.

Results A total of 72 out of 1,544 patients satisfied the inclusion criteria. Hypertension (72%) and Diabetes (62%) were the commonest co-morbidities noted. CKD was seen in 51 (70%) patients, and 21 patients (29%) were on maintenance dialysis. 39 (76%) patients with CKD were diagnosed with severe COVID-19, 25 (49%) of the patients developed acute worsening of CKD, and 45% had mortality. AKI was seen in 19 patients (26%). Urinary abnormality was seen in 34 (47%) patients, out of which 27 (37%) had proteinuria of more than 1+. Haematuria was seen in 27 (37.5%) patients, of which 12(17%) had gross haematuria. Dialysis was required in 24 patients (33%) additionally. Mechanical ventilation was required in 32(44%) patients, and inotropes in 41(56%). 21 (29%) patients developed acute respiratory distress syndrome, 39 (54%) had sepsis, with six patients developing multiorgan dysfunction syndrome. 62.5% of patients had mortality. The presence of other comorbid conditions, thrombocytopenia, coagulopathy, abnormality in arterial blood gases and usage of inotropes were found to be significantly associated with adverse outcomes.

Conclusions Most cases had severe renal system involvement, with an AKI prevalence rate of 1.2% and a case-specific mortality rate of 62.5%.

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INTRODUCTION

Coronavirus disease 19 (COVID-19), caused by severe acute respiratory syndrome-coronavirus (SARS-CoV-2), a beta coronavirus, mainly involves the respiratory tract and other systems like the cardiovascular, nervous system, haemopoietic, digestive system and renal system. Kidney involvement is seen frequently and plays an important role in the prognosis of severely affected patients, especially the development of acute kidney injury (AKI).¹ The overall incidence of AKI varies between 5% to 15%², and it is an independent risk factor for mortality. Other renal manifestations noted are the presence of proteinuria and haematuria, proteinuria being more common.³ COVID-19 patients suffering from chronic kidney disease (CKD) and dialysis-dependent patients are reported to be at higher risk of a severe form of the disease. They are advised to take extra preventive measures to avoid exposure to SARS-CoV-2. Kidney involvement is more likely in the presence of additional comorbidities.⁴

The coronavirus or a cytokine storm could directly attack renal impairment due to abnormal immunity.⁵ Hypotension or dehydration, hypoxemia, sepsis, and nephrotoxic drugs could also be involved in developing AKI. ACE2 is considered a functional receptor of SARS-CoV-2. It is expressed in lung tissue and can also be detected in the kidneys, mainly in proximal tubules, afferent arterioles and collecting ducts. In addition, viral nucleic acid could also be found in the urine, suggesting that the kidneys might be the target of this novel coronavirus. Tubular epithelial cell necrosis, degeneration, interstitial hyperemia, microthrombus, or focal fibrosis were the main pathological features, while glomerular lesions are uncommon.

The management strategies for COVID-19-related kidney issues are largely supportive.⁶ Renal replacement therapy (RRT) may be required in many critically ill patients with AKI. However, in a developing country like India with limited resources and health infrastructure, it may be challenging to combat the situation of patients with multiorgan failure. The impact of COVID-19 on patients' long-term kidney function is unclear. SARS-CoV-2's effects on the kidney and in patients with underlying kidney disease are not well-characterized. Therefore, this study aimed to describe the clinical presentation of kidney involvement in COVID-19 patients, examine the laboratory profile and treatment modality of kidney disorders, correlate the severity of COVID-19 disease with renal system involvement and know the outcome of

pre-existing kidney disease.

MATERIAL AND METHODS

This retrospective study was conducted on patients admitted to a tertiary care hospital from coastal Karnataka after obtaining ethical approval from an institutional committee. All patients, including children with pre-existing kidney disease, impaired renal function tests (RFT), or abnormal urine findings at admission, diagnosed with COVID-19 by RT-PCR or rapid antigen testing between March 2020 and October 2020, were included in the study. Case files that did not have urinalysis and kidney function evaluation reports were excluded from the study.

Data regarding history, particularly the presence of the chronic renal condition and other comorbid conditions, present clinical manifestations, laboratory investigations including blood and urine examination and management of the patients, and the dialysis requirement during their hospital stay were noted. KDIGO definitions were used to define AKI based on serum creatinine and urine output. CKD was defined as eGFR <60 mL/min per 1.73 m² or proteinuria at urinalysis within 180 days before hospital admission. Proteinuria was defined by the presence of $\geq 1+$ protein in urine analysis. Hematuria was defined as more than five red blood cells per high-power field on centrifuged urine sample. A correlation between the severity and outcome of COVID-19 and pre-existing renal diseases, along with other comorbid conditions, was done. Development of AKI, factors leading to developing AKI and outcome with respect to the disease's mortality was noted.

Statistical Analysis

Descriptive statistics were performed using SPSS software 27.0. A chi-square test was performed to correlate the severity of COVID-19 disease with kidney symptoms. Logistic regression was used to analyse the outcome with various confounding factors.

RESULTS

A total of 1,544 patients were admitted with COVID-19 infection during the study period at our hospital. Out of these, 72 patients had renal manifestations or were known cases of renal disorders diagnosed with COVID-19 infection. The mean age in adults was 52.2 years. 2 were paediatric patients aged 11 and 15 years, respectively. Of 72, 46 (63%) were

Table 1. The frequency of symptoms and signs.

Variables	n (%)
Symptoms	
Cough	26 (36.1%)
Fever	35 (48.6%)
Reduced urine output	7 (9.7%)
Haematuria	2 (2.8%)
Breathlessness	40 (55.6%)
Edema	12 (16.7%)
Co-morbidities	
Diabetes mellitus	45 (62.5%)
Hypertension	52 (72.2%)
Ischemic heart disease	20 (27.8%)
Neurological disease	5 (6.9%)
Chronic kidney disease	50 (69%)
Other renal disease	2 (2.8%)
Maintenance haemodialysis	22 (30.6%)
Signs	
Impaired consciousness	44 (61.1%)
Tachypnea	52 (72.2%)
Tachycardia	45 (62.5%)
Reduced SPO ₂	36 (50.0%)
Respiratory distress	57 (79.2%)
CVS (congestive cardiac failure)	12 (16.7%)
Per abdomen (ascites)	6 (8.3%)
Central nervous system (encephalopathy)	17 (23.6%)
High blood pressure on admission	11 (15.3%)
Shock	22 (30.6%)

male patients, and 26 (36%) were females. Out of 72 patients, four were mild, eight were moderate, and 60 (83%) were of severe category. Details of their presenting symptoms and signs and the common co-morbid condition were given in Table 1. Most of the patients presented with cough, fever and breathlessness, but common symptoms related to the renal system were oedema, reduced urine output and haematuria. Other symptoms like abdominal pain, vomiting, loose

Table 2. Laboratory parameters.

Variables	Mean value
Haemoglobin	9.6 g/dL
Total leukocyte count	11,531.92 cells/ μ L
Neutrophil/lymphocyte ratio	5:1
Platelet count	222,333.35/ μ L
Erythrocyte sedimentation rate	64.57 mm/hour
C-reactive protein	72.029 mg/L
Urea	140.79 mg/dL
Creatinine	6.992 mg/dL
Uric acid	8.418 mg/dL
Lactate dehydrogenase	1005.96 U/L
D-dimer	4149.14 ng/mL
Ferritin	741.19 μ g/L

stools, headache, myalgia, generalised weakness, seizures, and altered sensorium were noted in 36 (50.0%) patients. Hypertension was noticed in 72% (52) of the patients. In contrast, diabetes was seen in 62% (45), ischemic heart disease (IHD) in 20 (27%) and neurological conditions in 5 (6.9%) of the patients. Other co-morbid conditions noted in 23 (31.9%) patients were hypothyroidism, anaemia, connective tissue disorders, chronic obstructive pulmonary disorders (COPD), asthma, obesity, chronic liver disorders, pancreatitis, peripheral vascular diseases, arrhythmias, malignancies.

AKI was seen in 19 patients (26%). Twelve patients had stage 3 AKI, 5 had stage 2 AKI, and 2 had stage 1 AKI. Of 72 patients, 51 (70%) were already diagnosed with chronic kidney disease, and 21 (29%) were on maintenance dialysis. 25 (49%) of the patients developed acute worsening of chronic kidney disease. Out of 51 cases of chronic kidney disease, 39 (76%) patients were diagnosed with severe COVID-19. Out of the two paediatric patients, one patient had AKI, and the other was a CKD case on maintenance dialysis. Other renal diseases noted were renal calculi, bilateral hydronephrosis, polycystic kidney disease, single kidney, pyelonephritis, IgA nephropathy and atypical haemolytic uraemic syndrome. One patient was the recipient of a kidney transplant.

Details of the investigation report were given in Table 2. Abnormal serum electrolyte levels were seen in 61 patients (84%). 14 (19%) of them had sodium abnormality, hyponatremia being more common. 40 (55%) patients had hyperkalemia, and 6 had hypokalemia. Arterial blood gas (ABG) was abnormal in 45 patients, out of which 21 (29%) had metabolic acidosis, whereas 13 patients had both hypoxia and metabolic acidosis (18%), and only 11 patients had isolated hypoxia (6.9%). 24 (33%) patients had abnormal liver function tests, and 12 (16%) had coagulopathy. Urinary abnormalities were observed in 34 (47%) patients, and 27 (37%) had proteinuria greater than +1. 27 (37.5%) patients had hematuria, and 12 (17%) had gross hematuria. On the statistical analysis of laboratory parameters with the risk of development of AKI, none of the parameters was found to be associated with the development of AKI (Table 3).

Remdesivir was used in 9 (12.5%) patients. Anti-inflammatory agents were used in 41(56) % of patients. Anticoagulants were used in 40 (55%) patients, with regular heparin (unfractionated) commonly used. Dialysis was required in 24 patients (33%), apart

Table 3. The risk of acute kidney injury with the laboratory parameters.

Acute kidney injury	N	Mean ± SD	95% CI for mean		Median (IQR)	P value
			Lower bound	Upper bound		
Neutrophil (cells/μL)	6	69.5000±22.49222	45.8959	93.1041	80.00 (73.25, 86.00)	0.513
	11	74.9391±26.61532	57.0587	92.8195	83.00 (70.00, 93.00)	
Lymphocyte (cells/μL)	6	20.1000±19.89321	-.7766	40.9766	11.00 (8.425, 18.250)	0.339
	11	9.9264±8.46863	4.2371	15.6157	9.00 (1.700, 15.00)	
CRP (mg/L)	6	50.300±37.9401	10.484	90.116	90.00 (61.675, 90.00)	0.218
	11	76.727±19.6728	63.511	89.944	81.00 (60.00, 90.00)	
LDH (U/L)	6	518.17±271.806	232.92	803.41	465.50 (302.75, 681.75)	0.421
	11	1047.36±1607.228	-32.39	2127.11	632.00 (345.00, 900.00)	
D-dimer (ng/mL)	6	3062.67±1789.710	1184.48	4940.85	3460.00 (1559.25, 5521.75)	0.087
	11	5779.18±3433.313	3472.65	8085.71	4703.00 (2000.00, 9732.00)	
Ferritin (μg/L)	6	463.00±446.152	-5.21	931.21	1000.00 (594.00, 1000.00)	0.137
	11	783.64±339.815	555.35	1011.93	1000.00 (648.00, 1000.00)	

CI: confidence interval, CRP: C-reactive protein, LDH: lactate dehydrogenase.

from those on maintenance dialysis, including both 6 AKI patients and the other 18 patients who had acute worsening of a pre-existing CKD. In another ten patients, dialysis was indicated, but it could not be done due to very poor general condition (3 AKI patients). Oxygen was required in all patients except mild cases, venturi mask being used commonly to deliver oxygen. A high-flow nasal cannula (HFNC) was used in 8 patients, and non-invasive ventilation was used in 11 patients. Mechanical ventilation was required in 32 (44%) patients. Inotropes were used in 41 (56%) patients. 54 (75%) patients had bilateral pneumonia, out of which 21 (29%) patients developed acute respiratory distress syndrome (ARDS), 39 (54%) had sepsis, with six patients developing multiorgan dysfunction syndrome (MODS). 62.5% of patients had mortality. Among AKI patients, 57.8% had mortality, and 45% had mortality among CKD patients.

The results of logistic regression used to examine clinical signs and symptoms, laboratory parameters, and treatment of kidney disorders are shown in Table 3. All variables were entered into the model. The presence of other comorbid conditions, thrombocytopenia, coagulopathy, ABG abnormality, and use of inotropes was significantly associated with adverse outcomes (Table 4).

DISCUSSION

There were 72 patients in our hospital, including both paediatric and adult patients who had, for the first-time renal manifestations due to COVID-19 or were known cases of renal disorders diagnosed with COVID-19 infection. Our study's mean age at presentation was 52 years, with male predominance. A

similar finding was noticed by Allemailem *et al.*⁷, where most patients were males older than 50. Breathlessness (55.6%) and fever (48.6%) were the common presenting symptoms similar to the study mentioned above⁷, as the majority of the cases were severe to the moderate category in both the study groups. Underlying CKD also might have contributed to the increased prevalence of breathlessness among the study group. More than 80% were classified as having severe disease and had renal involvement, either pre-existing or newly developed renal manifestations. But its significance is not measured statistically as we had not taken the COVID-19 cases without renal involvement. Apart from a kidney involvement, the most common associated co-morbidities were hypertension and diabetes mellitus, followed by ischemic heart disease. None of the above factors was independently associated with an increased risk of mortality which is in contrast to other studies.⁸ Still, it was noticed that additional other co-morbid conditions increased the chances of mortality, like malignancy and COPD ($p = 0.02$).

In a systematic review done by Chen *et al.*⁹, the incidence of COVID-19 in haemodialysis patients was 7.7%, and the overall mortality rate was 22.4% in these patients with COVID-19. Similarly, our study's mortality rate was 28% with patients on haemodialysis. So both the incidence and mortality of COVID-19 infection were higher in haemodialysis patients. Among CKD patients without dialysis, 76% had severe disease, and 45% had mortality. There was a decline in the number of patients who underwent kidney transplantation initially when the COVID-19 pandemic began. A study done by Akalin *et al.*¹⁰ noted a very high mortality rate in kidney transplant patients, 28% at the end of 3 weeks. We had one patient with kidney

Table 4. The logistic regression studying the clinical symptoms and signs, laboratory parameters along with the mode of treatment for renal conditions with the outcome (Significance was decided at 5%).

Variables	B	S.E.	Wald	Df	Significance	Exp (B)
Symptoms and co-morbid conditions						
Decreased urine output	-1.728	1.210	2.042	1	0.153	0.178
Haematuria	0.397	1.807	0.048	1	0.826	1.487
Chronic kidney disease	-0.090	0.537	0.028	1	0.867	0.914
Co-morbid conditions	0.739	1.258	0.345	1	0.557	2.093
Hypertension	-0.201	0.542	0.137	1	0.711	0.818
Diabetes mellitus	-0.795	0.507	2.454	1	0.117	0.452
Neurological disease	1.552	1.182	1.726	1	0.189	4.723
Ischemic heart disease	-0.961	0.729	1.739	1	0.187	0.382
Maintenance haemodialysis	0.363	0.665	0.298	1	0.585	1.438
Other renal diseases	-0.902	1.339	0.454	1	0.501	0.406
Other co-morbidities	-2.645	1.149	5.295	1	0.021	0.071
Signs						
Conscious level	-0.194	0.873	0.049	1	0.824	0.824
Blood pressure	-0.274	0.480	0.325	1	0.569	0.760
SPO ₂	-0.367	0.820	0.200	1	0.655	0.693
Respiratory system	-1.939	1.100	3.109	1	0.078	0.144
Per abdomen	2.113	1.639	1.663	1	0.197	8.276
Cardiovascular system	-1.311	1.074	1.489	1	0.222	0.270
Central nervous system	-2.019	1.081	3.487	1	0.062	0.133
Laboratory investigations						
Haemoglobin	-0.003	0.165	0.000	1	0.984	0.997
Total count	0.000	0.000	1.256	1	0.262	1.000
Erythrocyte sedimentation rate	-0.004	0.015	0.064	1	0.800	0.996
Urea	0.001	0.006	0.020	1	0.887	1.001
Creatinine	-0.107	0.087	1.506	1	0.220	0.898
Liver function test	-0.310	0.801	0.150	1	0.699	0.733
C-reactive protein	-0.027	0.014	3.809	1	0.051	0.973
Coagulopathy	-2.574	1.309	3.865	1	0.049	0.076
Urine abnormality	2.158	2.603	0.687	1	0.407	8.652
Proteinuria	-1.457	0.825	3.119	1	0.077	0.233
Haematuria	-0.368	1.363	0.073	1	0.787	0.692
Lactate dehydrogenase	0.000	0.000	0.257	1	0.612	1.000
D-dimer	0.000	0.000	2.625	1	0.105	1.000
Arterial blood gas analysis	-0.510	0.255	4.002	1	0.045	0.601
Acute kidney injury	0.548	0.793	0.478	1	0.489	1.730
Ferritin	-0.003	0.002	3.079	1	0.079	0.997
Sodium	0.050	0.040	1.543	1	0.214	1.051
Potassium	0.061	0.118	0.270	1	0.604	1.063
Thrombocytopenia	0.051	0.017	9.215	1	0.002	1.052
Treatments						
Anti-inflammatory	-1.474	1.344	1.202	1	0.273	0.229
Anticoagulants	0.991	1.310	0.573	1	0.449	2.694
Inotropes	-3.459	1.037	11.122	1	0.001	0.031
Severity	-19.946	8589.258	0.000	1	0.998	0.000
Dialysis	-1.061	0.551	3.709	1	0.054	0.346
Ventilation	-0.349	0.238	2.159	1	0.142	0.705

transplantation who had expired.

In our study, 27 (37%) patients had proteinuria of more than 1+ and haematuria was seen in 27 (37.5%) patients. Still, in a study by Vasist *et al.*¹¹, proteinuria was positive in 75 patients (17.6%) and haematuria in 39 patients (9.15%), which is lower than our study. They also noticed that patients with proteinuria and/or haematuria were more likely to have severe COVID-19 illness. More than 80% of cases were severe COVID-19 cases in our study, which may explain the higher incidence of proteinuria and haematuria.

AKI was seen in 19 patients, which accounts for 1.2% of the total admissions with COVID-19 during the same period, which is lower compared to 39.9% of AKI in COVID-19 hospitalised patients as observed by Jia *et al.*¹². They also noticed that among AKI cases which required dialysis, 79.3% patients expired with 30.6% of survivors remaining on dialysis at the time of discharge. In contrast, in our study, it was around 57% of mortality, which is slightly lower. Smarz *et al.*¹³ observed that elevated leukocytes with neutrophil predominance and elevated D-dimers were associated with an increased risk of AKI, which correlates with the severity of COVID-19. However, in our study, none of the parameters was significantly associated with AKI. Remdesivir was used in a low percentage of cases due to renal impairment, which limits its use. Similarly, regular heparin was used as fractionated heparin usage is avoided with renal dysfunction. Głowacka *et al.*¹⁴ reviewed articles on AKI and COVID-19 and noticed that 64% of critically ill COVID-19 patients required dialysis who had AKI. Still, in our study, additional dialysis was required in 24% of patients, including AKI and acute on CKD.

We observed increased mortality with thrombocytopenia and coagulation abnormalities; similar findings were noticed in other studies.^{15,16} Metabolic acidosis (29%) is the predominant ABG finding noted in our research, contributed by kidney disease. In a study by Alfano *et al.*¹⁷, metabolic acidosis was noticed in 2.8% of all COVID-19 patients, which is much lower than our study. Still, all of them had mortality, and the authors noted that they had high SOFA scores with kidney impairment.

In a study done by Sindhu *et al.*¹⁸, it was noticed that inotropes usage and mechanical ventilation were associated with an increased risk of poor outcomes. In contrast, as in our study, only inotropes were noted to be significant on logistic regression. Though the statistical presence of AKI, CKD or mechanical ven-

tilation has not come significant on logistic regression analysis due to the interrelation of confounding factors, and the majority of cases were of severe category, which might have led to an inconclusive picture in the end, it gives the scope for further exploration, as their clinical significance can not be undetermined. Also, long-term effects, particularly on kidney function and persistence of proteinuria or haematuria, should be investigated further. In case of persistent proteinuria or haematuria at intensive care unit discharge, COVID-19 patients should be advised for follow-up by a nephrologist, as the course of the long-term kidney involvement is still unclear.

CONCLUSIONS

Most of the cases were in a severe category, with 62.5% case-specific renal system involvement and mortality. The development of AKI and the presence of CKD were responsible for increased mortality and morbidity.

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Ethical Approval

The protocol of the study was approved by the Yenepoya Ethics Committee-1, University Road, Deralakatte, Mangalore-575018 India, (Decision number: YEC-1/2020/071, date: November 2020).

Authors' Contribution

Study Conception: SKS, SPBH,; Study Design: SKS, RG,; Supervision: SKS, SPBH,; Literature Review: SKS, RG,; Critical Review: SKS, SPBH,; Data Collection and/or Processing: SKS, RG,; Statistical Analysis and/or Data Interpretation: SKS, SPBH,; Manuscript preparing: SKS, SPBH, RG.

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