

Nephrology Referral Pattern and Short-Term Outcomes in COVID-19 Positive Patients

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Abstract

Introduction: Coronavirus disease is considered a pandemic by the WHO. Studies which have described the pattern and outcomes of kidney disease in COVID patients are scarce. Kidney involvement can be a decisive factor which can lead to negative outcomes in these patients.

Aim: To study the clinical presentation, laboratory profile and short-term outcomes of COVID patients who already have or who newly develop kidney disease.

Materials and Methods: All COVID-19 positive patients who sought nephrology referral were included in the study. Laboratory parameters were measured serially during the admitted period and at discharge or before death.

Results: Among a total of 885 patients, 38.2% (n=338) were previously diagnosed Chronic Kidney Disease (CKD) patients of which 45.9% (n=155) were Chronic Kidney Disease Stage 5 on Dialysis (CKD 5D) and 5.5% (n=50) were Kidney Transplant Recipients (KTR). Acute deterioration of renal function was noted in 83.6%, with 9.3% warranting renal replacement therapy. There was a significant difference ($p=0.002$) in death rates between COVID waves 1 and 2 (16.1% vs. 25.4%). Mortality was highest among the CKD 5D patients (31.3%) followed by KTR (28.6%) followed by CKD ND (Non-Dialysis). Hypotension at admission ($p=0.00$), dialysis-requiring renal failure ($p<0.05$) and requirement for mechanical ventilation ($p=0.00$) were factors which predicted higher mortality. In 18.1% of patients (n=159), baseline CKD was detected for the first-time during hospitalisation.

Conclusion: Among the COVID patients, mortality was higher in those patients who had kidney disease (especially CKD 5D and KTR). Compared to the first wave, second COVID wave had higher mortality.

Keywords: COVID-19; Renal replacement therapy; Mortality; Chronic kidney disease; Transplant recipients.

Introduction

December 2019 witnessed the upsurge of cases of viral pneumonia which began in the city of Wuhan located in the providence of Hubii, China. In March 2020, the World Health Organization described the outbreak as a pandemic [1]. The causative virus was identified as SARS-CoV2, an RNA virus from the coronaviridae family. The same family of viruses caused the Severe Acute Respiratory Syndrome (SARS) in 2002 and Middle East Respiratory Syndrome (MERS) in 2012 [2]. What makes the current virus more dreaded than SARS and MERS? Although the basic number of reproductions are high (2-3.5), the most crucial factor in transmission is the high level of viral colonisation in the upper respiratory tract [3].

While SARS-CoV2 is known to cause predominant pulmonary disease, clinicians have observed many other systemic manifestations of COVID-19 such as hematological, hepatobiliary, neurological, ophthalmic, dermatological and renal [4,5]. The effects of COVID-19 pandemic has been felt in all spectrum of kidney ailments. Even though the pandemic has taken a backfoot currently, many questions still remain unanswered. How to best manage patients with ESRD (End Stage Renal Disease) receiving out-patient in-centre dialysis or patients hospitalised with COVID-19 and ESRD or AKI requiring RRT (Renal Replacement Therapy)?

As the pandemic spread in the country, our tertiary care hospital was converted to a predominantly COVID referral centre with huge inflow of cases from the peripheral care centres. Currently, little is known about the outcomes of COVID-19 in Chronic Kidney Disease (CKD), Hemodialysis (HD) patients and Kidney Transplant Recipients (KTRs) esp. from our part of the world. For this purpose, we studied the nephrology referral pattern from the COVID unit for an analysis of the clinical outcomes and short-term prognosis.

Materials and Methods

Subjects and methods

This study was a single centre, descriptive study conducted at our tertiary care hospital from March to November 2020 (first COVID wave) and from April to June 2021 (second COVID wave).

Patient selection and data collection

All COVID positive patients who sought nephrology referral during the period were included in the study. The patients were grouped into different groups according to their renal syndromes as AKI/Acute on Chronic Kidney disease (ACKD), CKD ND, CKD 5D, KTRs. RT-PCR of nasopharyngeal swab was used to diagnose COVID infection. Complete blood count and renal function tests was done at admission, serially and at discharge. Data on demography, etiology, clinical features related to renal failure, comorbidities, biochemical parameters, treatment provided, renal replacement therapy and short-term outcomes were collected from patients using a standardized data form.

We have divided the patients into three categories according to COVID severity, which are defined by the Ministry of Health and Family Welfare, India. Mild disease, positive for COVID-19 but no pneumonia or hypoxia. Moderate disease, patients with pneumonia with $\text{SpO}_2 > 90\%$ on room air. Severe disease, pneumonia plus any one of the following: $\text{SpO}_2 < 90\%$ on room air, respiratory rate $> 30/\text{min}$ or severe respiratory distress.

Those patients who were previously known to have kidney disease and those whose in-hospital evaluation showed evidence of chronicity like USG showing contracted kidneys/lost corticomedullary differentiation were included under the CKD category. All others with normal ultrasound findings and unresolving renal failure at discharge were included under the acute kidney disease category.

Outcome

The data was analysed regarding the demographic, clinical and laboratory parameters. The primary outcome of in-hospital mortality was assessed in the whole study population as well as all the subgroups in the study population. Patients with AKI

alone were not included in the subgroup analysis though they were included in the overall analysis.

Statistical methods

For categorical variables, descriptive statistics, frequency analysis and percentage analysis were used and for continuous variables, mean with Standard Deviation (SD) or median with Interquartile Range (IQR) were used. Chi-square, fisher exact and student t tests were used wherever appropriate. The risk factors for primary outcome were identified with univariate analysis using chi-square test. P value <0.05 was considered as statistically significant. Statistical analysis was done using IBM SPSS statistics software 26.0 Version.

Results

Of the total 885 patients, 653 (73.8%) were from COVID wave 1 and 232 (26.2%) were from COVID wave 2. Among these, 674 patients had an acute worsening of renal function (either AKI or ACKD); 155 were CKD 5D; 49 were KTRs.

Demographic and clinical characteristics

Mean age of the study population was 58.09 ± 12.90 years; 609 (68.8%) were males and 276 (31.1%) were females with a Male: Female ratio of 2.20:1.

Diabetes mellitus (n=432; 48.81%) was the most common comorbidity followed by hypertension (n=411; 46.4%), known CKD (n=183; 20.67%), coronary artery disease (n=83; 9.37%). Severity of COVID was found to be mild in 41.6% (n=368); moderate in 28.2% (n=250) and severe in 30.2% (n=267). **Table 1** summarises the demographic characteristics and comorbidities in the study population.

Table 1: Baseline patient characteristics according to patient groups.

Parameter		All	CKD-ND	CKD 5D	KTR
N		885	183	155	49
COVID wave	Wave 1	653	126	92	29
	Wave 2	232	57	63	20
Age (years (mean \pm SD))		58.09 ± 12.90	57.51 ± 11.47	51.14 ± 11.72	42.61 ± 9.71
Gender	Male (n, %)	607 (68.8)	116 (63.4)	121 (78.1)	42 (85.7)
	Female (n, %)	276 (31.2)	67 (36.6)	34 (21.9)	7 (14.3)
Comorbidities (n,%)	DM	432 (48.8)	107 (58.5)	51 (32.9)	5 (10.2)
	HTN	411 (46.4)	110 (60.1)	79 (51.0)	9 (18.4)

	CAD	83 (9.4)	22 (12.0)	4 (2.6)	0 (0.0)
	CKD 1-4	127 (14.4)	127 (69.4)	-	-
	CKD 5	56 (6.3)	56 (30.6)	-	-
	COPD	3 (0.3)	2 (1.1)	0 (0.0)	0 (0.0)
Addictions (n, %)	Smoking	356 (40.2)	112 (61.2)	67 (43.2)	39 (79.6)
	Alcohol	198 (22.4)	137 (74.9)	125 (80.6)	3 (6.1)

Note: CKD: Chronic Kidney Disease; CKD-ND: Chronic Kidney disease Not on Dialysis; CKD 5D: Chronic Kidney Disease Stage 5 on dialysis; KTR: Kidney Transplant Recipient; DM: Diabetes Mellitus; HTN: Hypertension; CAD: Coronary Artery Disease; COPD: Chronic Obstructive Pulmonary Disease.

Among the CKD stages 1-5 (not on dialysis), 83.6% (n=153) had an acute worsening of renal function during the COVID admission of which 25.4% (n=39/154) required Renal Replacement Therapy (RRT).

Mortality was 15.7% in CKD stages 1-4 whereas in CKD 5 (not on dialysis), mortality was 33.9 % (p=0.006) (**Table 2**).

Table 2: Clinical, laboratory parameters and outcomes characteristics according to patient groups.

Parameter		All	CKD-ND	CKD 5D	KTR
Blood pressure (n, %)	Hypotension	105 (11.9)	15 (8.2)	30 (19.4)	0 (0.0)
	Normotension	546 (61.7)	104 (56.8)	51 (32.9)	33 (67.3)
	Hypertension	234 (26.4)	64 (35.0)	74 (47.7)	16 (32.7)
CBC Median (Q1-Q3)	Haemoglobin (g/dl)	11 (9.4-12.0)	9.7 (9.1-11.3)	9.2 (8.9-10.4)	11 (9.4-12.0)
	Total WBC count (cells/mm ³)	8700 (6700-11650)	8800 (6700-12300)	8700 (6600-10450)	8700 (5600-9800)
	Platelet count (lakhs/mm ³)	2.4 (2.1-2.8)	2.3 (2.1-2.8)	2.4 (2.2-2.8)	2.4 (2.1-2.8)
Peak serum creatinine (mg/dl) Median (Q1- Q3)		2.6 (1.9-4.7)	4.4 (2.5-7.0)	-	2.5 (1.8-4.4)
AKI (n, %)		674 (76.2)	153 (83.6)	-	33 (67.3)
AKI stages (n, %)	KDIGO 1	322 (47.8)	59 (38.6)	-	18 (54.5)
	KDIGO 2	185 (27.4)	38 (24.8)	-	7 (21.2)
	KDIGO 3	167 (24.8)	56 (36.6)	-	8 (24.2)
COVID severity (n, %)	Mild	368 (41.6)	81 (44.3)	40 (25.8)	22 (44.9)
	Moderate	250 (21.2)	49 (26.8)	63 (40.6)	8 (16.3)
	Severe	267 (30.2)	53 (29.0)	52 (33.5)	19 (38.8)
Dialysis-requiring renal failure (n, %)		222 (25.0)	39 (21.4)	155 (100.0)	7 (14.3)

Oxygen/ventilator requirement (n, %)	NIV/Face mask	266 (30.1)	53 (29.0)	64 (41.3)	9 (18.4)
	Mechanical ventilation	251 (28.4)	49 (26.8)	51 (32.9)	18 (36.7)
Death (n, %)		164 (18.5)	39 (21.3)	50 (32.3)	14 (28.6)
AKI resolution (n/N, %)		344/674 (51.0)	13/153 (8.5)	-	19/33 (57.6)
Treatment given (n, %)	Hydroxychloroquine	56 (6.3)	6 (3.3)	4 (2.6)	0 (0.0)
	Azithromycin	885 (100.0)	183 (100.0)	155 (100.0)	49 (100.0)
	Oseltamivir	53 (6.0)	7 (3.8)	3 (1.9)	0 (0.0)
	Methylprednisolone	277 (31.3)	55 (30.1)	54 (34.8)	20 (40.8)
	Heparin	277 (31.3)	55 (30.1)	54 (34.8)	20 (40.8)
	Remdesivir	277 (31.3)	57 (31.1)	52 (33.5)	13 (26.5)

Note: CBC: Complete Blood Count; WBC: White Blood Cells; AKI: Acute Kidney Injury; KDIGO: Kidney Disease Improving Global Outcomes; NIV: Non Invasive Ventilation.

Among the CKD 5D, the mean age was 51.23 ± 11.69 years. There were a total of 155 patients in the group among which 32.9% had severe COVID; 72.3% (n=112) were oxygen dependent and 31.5% (n=49) expired.

Considering the KTRs (n=49), the mean age was 42.6 ± 9.71 years; median age after transplant was 5.0 (IQR 3.00-7.75 years). Among these, 67.3% (n=33) developed AKI of whom 8.2% (n=4) required RRT; 3 patients expired (75%). 57.5% (n=19) recovered from AKI before discharge from hospital.

Outcome and associated risk factors

The primary outcome of mortality among the CKD ND was 21.3%, 31.3% among the CKD 5D and 28.6% among the KTRs. The mortality among hospitalised patients in COVID wave 1 without renal involvement was 2.3% while among those with renal involvement was 16.1%; in COVID wave 2, mortality among those without renal involvement was 6.1% while it was 25.4% among those with renal involvement. 18.1% (n=159) of the patients were found to have underlying CKD which was first detected during COVID admission. **Table 3** summarises the outcomes and associated factors.

Table 3: Comparative analysis of baseline patient characteristics according to survival.

Parameter		ALL	Dead	Discharged	P-value
N		885	164	721	-
COVID wave	Wave 1	653	105 (64.0)	548 (76.0)	-
	Wave 2	232	59 (36.0)	173 (24.0)	P<0.05
Age (years (mean \pm SD))		58.09 ± 12.90	58.7 ± 12.87	57.95 ± 12.91	P=0.82
Gender	Male (n, %)	607 (68.8)	122 (74.4)	487 (67.5)	P= 0.08
	Female (n, %)	276 (31.2)	42 (25.6)	234 (32.5)	-
Comorbidities (n, %)	DM	432 (48.8)	84 (51.2)	348 (48.3)	P= 0.49
	HTN	411 (46.4)	82 (50.0)	329 (45.6)	P= 0.31
	CAD	83 (9.4)	11 (6.7)	72 (10.0)	P= 0.19

	CKD 1-4	127 (14.4)	20 (12.2)	107 (14.8)	-
	CKD 5	56 (6.3)	19 (11.6)	37 (5.1)	-
	COPD	3 (0.3)	0 (0.0)	3 (0.4)	P= 0.40
Addictions (n, %)	Smoking	356 (40.2)	67 (40.9)	289 (40.1)	P= 0.85
	Alcohol	198 (22.4)	39 (23.8)	159 (22.1)	P= 0.63

The mean Haemoglobin (Hb) in the CKD ND group had a significant difference ($p=0.007$) between the survivors (9.53 ± 1.28) and non-survivors (10.29 ± 1.60) whereas this difference was not statistically significant among the CKD 5D group between the survivors (9.73 ± 1.53) and non-survivors (9.68 ± 1.59). 70.5% of patients who had hypotension at admission

expired whereas only 10.8% and 13.8% among the normotensive and hypertensive group respectively expired ($p=0.001$). 56.2% of patients who required mechanical ventilation expired whereas only 3.6% of patients who did not require mechanical ventilation expired ($p=0.001$) (**Table 4**).

Table 4: Clinical, laboratory parameters and outcomes characteristics according to survival.

Parameter		All (N=885)	Dead (N=164)	Discharged (N=721)	P-value
Blood pressure (n, %)	Hypotension	105 (11.9)	74 (45.1)	31 (4.3)	P<0.05
	Normotension	546 (61.7)	59 (36.0)	487 (67.5)	-
	Hypertension	234 (26.4)	31 (18.9)	203 (28.2)	-
CBC Mean (Q1-Q3)	Haemoglobin (g/dl)	10.80 ± 1.61	10.10 ± 1.54	10.96 ± 1.58	P<0.05
	Total WBC count (cells/mm ³)	9510.5 ± 4290.1	12555.3 ± 5426.8	8817.9 ± 3652.0	P<0.05
	Platelet count (lakhs/mm ³)	2.44 ± 0.49	2.41 ± 0.60	2.44 ± 0.47	P=0.44
Peak serum creatinine (mg/dl) Mean \pm SD		3.79 ± 2.96	5.55 ± 4.20	3.46 ± 2.54	P<0.05
AKI (n, %)		674 (76.2)	106 (64.6)	568 (78.8)	P<0.05
AKI stages (n, %)	KDIGO 1	322 (47.8)	24 (22.6)	298 (52.5)	-
	KDIGO 2	185 (27.4)	18 (17.0)	167 (29.4)	-
	KDIGO 3	167 (24.8)	64 (60.4)	103 (18.1)	P<0.05
COVID severity (n, %)	Mild	368 (41.6)	5 (3.0)	363 (50.3)	-
	Moderate	250 (21.2)	15 (9.1)	235 (32.6)	-
	Severe	267 (30.2)	144 (87.8)	123 (17.1)	P<0.05
Dialysis-requiring renal failure (n, %)		222 (25.0)	90 (54.9)	132 (18.3)	P<0.05
Oxygen/ventilator requirement (n, %)	NIV/Face mask	266 (30.1)	18 (11.0)	248 (34.4)	-
	Mechanical ventilation	251 (28.4)	141 (86.0)	110 (15.3)	P<0.05

AKI resolution (n/N, %)		344/674 (51.0)	4/111 (3.6)	340/608 (55.9)	P<0.05
Treatment given (n, %)	Hydroxychloroquine	56 (6.3)	5 (3.0)	51 (7.1)	P= 0.06
	Azithromycin	885 (100.0)	164 (100.0)	721 (100.0)	-
	Oseltamivir	53 (6.0)	6 (3.7)	47 (6.5)	P= 0.16
	Methylprednisolone	277 (31.3)	146 (89.0)	131 (18.2)	P<0.05
	Heparin	344 (38.9)	69 (42.1)	275 (38.1)	P= 0.35
	Remdesivir	277 (31.3)	88 (53.7)	189 (26.2)	P<0.05

Discussion

In our study, among the CKD stages 1-5 (not on dialysis), 83.6% had acute worsening. This is in concordance with other reported studies from the country. In a study by Pawar et al. 83.3% had developed acute on CKD [6]. The aetiology of acute worsening is multifactorial. Firstly, may be due to direct cytopathic effect of the virus, in which the novel corona virus uses ACE2 as a cell entry receptor [5]. Second, immune complex deposition comprising of viral antigen may damage the kidney. Third is the indirect effects of virus-induced cytokines or mediators on renal tissue, such as shock, hypoxia and rhabdomyolysis. Our study also showed that mortality increases with higher stages of CKD. Studies by Ramamurthy and Williamson have yielded the same results [7,8].

Considering the CKD on dialysis, the mean age of our study population was 51.23 ± 11.69 years. This is comparable to that of the mean age in other studies reported from India. Trivedi et al. (median age of 48 (20-77)) and Banerjee et al. (mean age 47.7 ± 16.9) reported similar age involvement whereas reports from Spain by Goicoechea et al. shows that higher age groups (71 ± 12) were involved [9-11]. The percentage of patients who had severe COVID disease was higher in the dialysis group (32.9%) compared to the entire study group. Study by Banerjee et al. also showed similar results (32.7% had severe disease) [10]. The mortality rate among dialysis patients was also similar in other studies. Study from Italy by Scarpioni et al. had a mortality of 41%, while another study by Alberici et al. showed a mortality of 25% in the dialysis population [12,13].

An analysis of the Kidney Transplant Recipients (KTR) shows that AKI has developed in 67.3% of our recipients (n=33). Many prior studies among KTRs also reported high rates of AKI. Banerjee et al. reported an AKI rate of 57%, while Nair et al. reported AKI rates of 50% in KTRs [14,15]. Study from Turkey by Yilmaz et al. reported lower AKI rates of 34% [16]. The mortality among our KTRs was found to be 28.6%. In a study by Alberici et al., the mortality was 25% [13]. Another report by Akalin et al. reported a mortality of 28 % among KTRs whereas Rahimzadeh et al. reported a slightly higher mortality of 33% (probably due to a low sample size (n=6) [17,18]. In our study, there was no statistically significant difference between mortality in KTRs who developed AKI vs no AKI (31.3% vs. 27.3%; p=0.77). This might be because of the fact that majority of our KTRs developed only

stage 1 AKI (54.5%) in contrast to other studies which report a higher mortality in AKI [16]. But another thing to be noted is that we had a mortality of 75% (n=3) among those KTRs who required RRT. Study by Yilmaz et al. also yielded mortality of 50% (n=2) in those KTRs who required RRT. However, the number of patients who required RRT is too low in both studies. Another notable finding in our KTR group was that 57.5% (n=19) of those KTRs who developed AKI reverted back to their baseline renal function at the time of discharge. Comparable data for AKI recovery was not available from any of the published data.

Taking the overall study population, our study showed that the highest mortality occurred in the CKD HD (Haemodialysis) group followed by Kidney Transplant Recipients (KTR) followed by CKD non-dialysis group. The reason for the high mortality in CKD 5D group may be due to uremia which is a state of chronic immunosuppression and uremic patients are at an increased risk of infection as they have a disordered natural as well as adaptive immunity [19]. Higher production and reduced clearance of proinflammatory cytokines can lead to inflammation along with deranged extracellular volume can cause high mortality in these patients [20]. These patients may require many additional medical treatments and invasive interventions which may be less applicable during COVID times [21]. Moreover, dialysis population had a high risk of exposure to the virus at their HD centre even if maximum precautions were taken [12]. Also, many patients on maintenance HD missed their HD sessions either due to non-availability/denial of HD at their native centre or due to lack of transportation facilities imposed by the nationwide lockdown [22].

The mortality among KTRs was slightly lower than HD patients in our study. This may be due to a “possibility of the anti-inflammatory and immune-balancing effects of immunosuppressives that could diminish the severity of COVID” [23,24]. The higher mortality rate of the HD patients compared with KTRs should be a point of concern for the authorities. This point should be considered esp. with regard to those HD patients with a suitable living donor, because of the suspension of transplant programmes due to the ongoing pandemic. Massie et al. developed a tool to determine the benefit vs harm of kidney transplantation during COVID times and found that, “in 72% of simulated scenarios, immediate transplantation provided a survival benefit to deferring transplantation and remaining on waiting list” [25].

Anaemia as a risk-factor for mortality in COVID has been well established in other studies [26]. However, no particular data could be obtained from the available literature regarding anaemia, COVID and renal disease. CKD patients on HD would be having more of a chronic compensated anaemia compared to the CKD not on dialysis. That might be the reason why we could not identify anaemia as a risk factor in dialysis population. Anaemia could also be a sign of poor nutritional status [27]. So it may reflect a fragile patient with greater burden on chronic comorbidities and hence the higher mortality.

Our study showed that mortality was higher in patients with kidney disease compared to those without kidney disease, with a higher mortality rate in the second wave compared to the first wave. Reasons for the higher mortality in the second wave could be numerous. Circulating double-mutant and triple-mutant strain of SARS-CoV-2 which has more effective transmission capability and lesser incubation period, overwhelming burden on the already frail healthcare system, reduced supply of essential treatments could be some of the reasons [28]. Increased mortality among younger age groups have been reported in second wave [29]. We also noticed a higher percentage of deaths in younger age group (20-40 years) in COVID wave 2 (25.9%) compared to COVID wave 1 (14.1%) though it did not reach statistical significance.

Our study has its limitations. Firstly, urinalysis was not routinely done in our COVID unit due to logistic reasons. Detailed data regarding the symptomatology, inflammatory parameters and radiological data could not be obtained due to the lack of electronic data as well as due to the huge case load. Another limitation is that being a referral centre, the incidence of COVID among patients with kidney disease and their follow-up data are not available. The strength of our study is that it has a large sample size which analyses the impact of first and second covid wave separately on patients with kidney disease.

Conclusion

Second COVID wave which spanned during a short time period had higher mortality compared to the first COVID wave. Mortality among COVID patients with kidney disease was higher (esp. the ESRD and KTR population). Thus, the presence of kidney disease should be an important factor in risk stratification of COVID patients which requires close monitoring and timely management. Hypotension at admission, dialysis-requiring renal failure and requirement of mechanical ventilation predicted mortality.

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