Original Article

COVID-19 in Hemodialysis Patients: Experience from a Western Indian Center

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Abstract

Introduction: Chronic kidney disease patients on hemodialysis (CKD-5D) are among the worst hit by the coronavirus disease 2019 (COVID-19) pandemic. Need to travel for dialysis, comorbidities, and immunosuppressive state put them at risk of severe disease and poor outcomes. We report our experience of COVID-19 in a cohort of CKD-5D from a public sector tertiary-care center from western India. **Material and Methods:** We retrospectively analyzed the records of 58 CKD-5D patients with confirmed COVID-19 admitted to our COVID-19 hospital. Suspected COVID-19, acute kidney injury (AKI), or AKI on CKD were excluded. We studied the clinical, demographic, radiological, and laboratory profiles; treatment; and outcomes of the patients. We assessed the potential clinical and laboratory parameters to predict mortality. **Results:** The mean age of the patients was 48.7 ± 16.9 years, with 55% males. Comorbidities included hypertension (65%), diabetes (19%), and cardiovascular disease (15.5%). The presenting features included fever (69%), respiratory distress (50%), upper respiratory symptoms (36%), and diarrhea (13%). Five (8.6%) were asymptomatic. Bilateral infiltrates on chest imaging were the commonest radiological pattern. The patients were managed with oxygenation, hydroxychloroquine, steroids, anticoagulation, remdesivir, and favipiravir. Twenty-two (37.9%) patients died, predominantly due to respiratory failure. Disease severity and C-reactive protein (CRP) above 175 mg/L at admission were the only parameters predictive of mortality. **Conclusion:** CKD-5D patients with COVID-19 were less likely to present with the classical syndrome of fever and respiratory distress compared with reports from the general population and had higher mortality. Only disease severity and high CRP (>175 mg/L) were predictive of mortality in our cohort.

Keywords: *Coronavirus, COVID-19, dialysis, ESRD, mortality, outcomes*

Background

The novel coronavirus disease 2019 (COVID-19) pandemic is ongoing since December 2019, affecting lives around the world. More than 46 million cases and 1.1 million deaths have been reported worldwide, and India has reported 8 million cases and more than 120,000 deaths as on November 1, 2020[1,2] The epidemic is not over yet, with several parts of the world reporting second surges, and continued preparedness of the health care system is important.

Most deaths from COVID-19 have been reported in the elderly and in those with comorbidities or an immunosuppressed state. Hypertension, diabetes, and chronic pulmonary, cardiovascular, and cerebrovascular diseases have been reported as major risk factors for patients with COVID-19. Chronic kidney disease (CKD) and hemodialysis (HD) have been associated with worse outcomes in some but not all previous reports.[3,4] In this single-center hospital-based study from western India, we retrospectively evaluated the clinico-demographic variables, laboratory parameters, and outcomes of CKD-5D patients with COIVD-19. We sought to identify the important predictors of mortality in this cohort.

Material and Methods

Setting

When the pandemic hit India, the western Indian state of Gujarat was affected early and reported high death rates (about 5% against a national average of 3.27% as of May 1, 2020). In mid-May 2020, the patient numbers continued to spike, and public sector subspecialty hospitals (like our kidney institute) were made COVID-19

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hospitals. Adoption of home quarantine policy meant only the sick patients got hospitalized. Our 190-bed COVID-19 facility had 50 intensive care unit beds and 70 beds with oxygen facility. The management was headed by nephrologists and intensivists. Only emergency nephrology and urology services remained functional as per government advisory. Our facility provided bedside dialysis for 100 + beds and created an outpatient dialysis unit for COVID-19 suspected patients, and asymptomatic COVID-19 cases were advised home quarantine. In the first week of July, when the epidemic plateaued, the institute ceased to be a COVID-19 hospital and admitted only patients with COVID-19 and renal disease (primarily post kidney transplant cases).

Case definition and management protocols

A case was defined as a person with real-time reverse transcriptase–polymerase chain reaction (RT-PCR)– confirmed COVID-19 infection, irrespective of signs and symptoms. Cases were labeled as mild when patients had oxygen saturation (SpO_2) above 94%, moderate when SpO_2 was 90% to 94%, and severe when SpO_2 was below 90%.[5] The patients underwent basic investigations and investigations to determine prognosis. Most patients received hydroxychloroquine (HCQ), azithromycin, ascorbic acid, and symptomatic treatment as per the government guidelines.[6,7] Unfractionated heparin was used as 5,000 units subcutaneously twice a day in high-risk patients and thrice a day in those with severe disease, unless contraindicated. Patients requiring oxygen support were given intravenous methylprednisolone sodium succinate (MPSS, 1 mg/kg in two divided doses). At the end of May 2020, tocilizumab became available and was used based on laboratory features suggesting cytokine storm (given as 400 mg single-dose infusion over 1 hour).[6] Favipiravir became available in the third week of June. It was used as 1,800 mg twice a day on the first day and 800 mg twice a day for the next 6 days. Remdesivir (200 mg on Day 1 and 100 mg daily for 5–10 days) and convalescent plasma were used starting from mid-July. Other agents such as ivermectin and doxycycline were not used.

Records of all the patients admitted with COVID-19 infection were screened. Patients who were known to have chronic kidney disease on hemodialysis (CKD-5D) for at least 1 month before admission were included in the study. COVID-19-suspect patients, those with AKI or AKI superimposed on CKD, and those with incomplete information were excluded. The primary aim was to study the clinical outcomes of such patients. We also attempted to identify the prognostic epidemiological and laboratory markers in our cohort.

Based on the previous studies, we studied age, dialysis vintage, saturation on room air at presentation, absolute neutrophil and lymphocyte counts, D-dimer levels, Serum ferritin, C-reactive protein (CRP), lactate dehydrogenase (LDH), and length of hospital stay as potential prognostic factors in our cohort. Peak levels of D-dimer, ferritin, and CRP levels were also evaluated as markers of prognosis. We divided our cohort into an initial phase (first 25 admissions, over the first 3 weeks) and a later phase (beyond 3 weeks) and studied the mortality in each quartile to understand the change of trends over time.

Statistical methods

The results were expressed as numbers with percentages, mean ± standard deviation or median with range as appropriate. The comparison between survivors and non-survivors was done by Student *t* test, Mann–Whitney *U* test, Chi-square test, or Fischer's exact test as justified. The effect of various putative prognostic factors was evaluated by binary logistic regression. A P value of <0.05 was taken as significant. Statistical analysis was performed with SPSS Statistics for Windows, Version 20 (Armonk, NY, IBM Corp.).

Results

A total of 913 patients were admitted to our COVID-19 hospital between May 13, 2020, and July 2, 2020. Subsequently, from July 3, 2020, a total of 242 patients with CKD and posttransplant patients were admitted. A total of 593 patients were COVID-19 positive by RT-PCR test. We identified 76 patients with known CKD fulfilling the inclusion criteria. After exclusions, 58 patients were included in the final analysis.

The demographic and clinical profiles are presented in Table 1. There were more males in our cohort, with a median dialysis vintage of 18 months. Twenty-two patients had no urine output at baseline. Fourteen patients were recorded to have a decrease in urine output after COVID-19 infection, five became anuric, whereas nine developed oliguria. Eighteen patients had no change in urine output. Data were missing in four patients. Five (8.6%) patients were asymptomatic, detected by screening for surgical or vascular access procedures. Fever and upper respiratory symptoms were the commonest presenting features. Data pertaining to other minor symptoms such as anosmia, loss of taste, conjunctivitis, and rash were not available in a lot of patients. This deficit probably reflects the sheer overwhelming number of patients, severity of cases at presentation, and lack of properly trained manpower. Half (50%) the patients had respiratory distress at presentation. One third of the patients had severe disease at presentation. Most (84.5%) patients had bilateral lung infiltrates on the X-ray of the chest. The laboratory parameters of the patients at presentation are described in Table 2.

Twelve (20.7%) patients never needed oxygen during their hospital course. The modalities of oxygen supplementation in the remaining patients are shown

Table 1: Epidemiology of patients included in the study

Patient Characteristics	Values[a]
No. of patients	58
Age	48.7±16.9
Age >60 years	16
Males	32 (55.1%)
Cause of CKD/Comorbidities	
Hypertension	38 (65.5)
Diabetes	11 (19)
ADPKD	3 (5.1)
Glomerular disease	8 (13.8)
Obstructive uropathy	5 (8.6)
Cardiovascular disease	9 (15.5)
CKD of unknown etiology	10 (17.2)
Data not captured	9 (15.5)
Dialysis Vintage (months) Median DIalysis Vintage	18 (10-24)
Access	
AVF/Graft	37 (63.8)
Tunneled catheters	5 (8.7)
Temporary access	20 (34.5)
Hospital stay (days)	8.25±6.01
Duration of symptoms prior to admission (days)	3.5 (2-6)
History of exposure to patient with COVID-19	48 (82.6)
Presenting features	
Fever	40 (69)
Sore throat/URT symptoms/Cough	21 (36.2)
Respiratory distress	29 (50)
Diarrea	8 (13.8)
Altered sensorium	5 (8.6)
Pain abdomen	2 (3.4)
Asymptomatic	5 (8.6)
Hypotension at presentation	8 (13.8)
Hypoxemia at presentation	26 (44.8)
SpO_2 on room air (%)	91.6±6.9
Radiological features	
Normal	7 (12.1)
Predominantly unilateral lung infiltrates	2 (3.4)
Bilateral lung infiltrates	49 (84.5)
Disease severity	
Asymptomatic	5 (8.6)
Mild	23 (39.7)
Moderate	7 (12.1)
Severe	19 (32.7)
Missing	4 (6.9)

ADPKD=Autosomal Dominant Polycystic Kidney Disease, AVF=arterovenous fistula, CKD=chronic kidney disease, COVID-19=coronavirus disease 2019, SpO_2=oxygen concentration, URT=upper respiratory tract, [a]Values represent mean±standard deviation, number (percentage), median (interquartile range)

in Table 3. Most patients received oxygen via prongs, masks, or non-rebreathing masks. High-flow nasal canula, noninvasive or mechanical ventilation was required in six (10%) cases. Outlines of management provided are presented in Table 3.

There were 22 deaths (37.9%) in the dialysis subpopulation compared with 149 deaths among 593 total hospitalized patients (25.1%, $P = 0.041$ for intergroup difference). There was a significant difference in the death rates between the patients admitted in the first 3 weeks (14 deaths out of 25 admissions) and those admitted later (eight deaths out of 33 admissions, $P = 0.017$). The probability of in-hospital deaths correlated with the disease severity at presentation (mortality 33% for mild and 58.3% for severe disease, $P = 0.03$). CRP levels above 175 mg/L were also significantly associated with mortality ($P = 0.04$). No other demographic, clinical, or laboratory parameters affected the probability of in-hospital mortality [Table 4]. We excluded the asymptomatic and mild cases and evaluated the effect of all the potential prognostic markers; none of the parameters were predictive of mortality in these subgroups. In the 16 patients with severe disease, where interleukin (IL)-6 levels were available, there was a significant difference between survivors and non-survivors ($P = 0.03$) [Table 4].

Discussion

Our study presents a single-center, public sector experience of management of CKD-5D patients hospitalized with COVID-19. As of writing of this article, no other detailed study from India has been published in this subgroup of patients. CKD-5D patients faced unique health issues during the pandemic. Such patients are burdened with high comorbidity loads such as age, diabetes, hypertension, obesity or malnutrition, cardiac comorbidities, and immunosuppressed state.[8] The necessity to travel for life-saving dialysis made lockdown restrictions impractical for HD patients.

Clinical profile

The first report of hemodialysis patients with COVID-19 came from Wuhan. In this study, most cases had mild to moderate disease and 21% were asymptomatic, and symptomatic patients were also less likely to have classic features such as fever, cough, or respiratory symptoms compared with the general population.[9-11] Another Chinese study reported that the disease was milder in HD patients, possibly due to their impaired cellular immunity.[4] Two Spanish cohorts also reported the initial presentation to be milder in the HD cohort.[12,13] These are in agreement with our findings. Twenty-eight (48.3%) had minimal or no symptoms and one third of patients had severe disease at presentation in our study. A pervious observational study from India reported relatively more asymptomatic cases (35.1%) and a similar number of moderate and severe disease presentations compared to our cohort. However, the details of the treatment or laboratory features have not been provided in this report.[14] A major observation of their

Table 2: Laboratory parameters of the entire cohort

Parameter	*n*	Value[a]
Hemoglobin (g/dL)	57	9.3±2.3
Total leucocyte counts (×1,000/mm^3)	57	7.8±3.9
Absolute neutrophil count (×1,000/mm^3)	57	6.7±3.75
Absolute lymphocyte count, ALC (×1,000/mm^3)	57	1.28±0.81
Lymphopenia (ALC <1,000/mm^3)	57	19 (32.7%)
Neutrophil-lymphocyte ratio	57	5.54±3.4
Nadir of ALC	57	1.0 (0.69-1.40)
Platelets (×1,000/mm^3)	57	188.6±88
Low platelet counts (<150 ×10^3/mm^3)	57	23 (39.6%)
Creatinine (mg/dL)	57	9.62±4.09
Sodium (mmol/L)	52	134.4±4.9
Potassium (mmol/L)	52	4.85±1.08
Bilirubin (mg/dL)	48	0.54±0.3
ALT[b] (U/mL)	50	16 (11-26.3)
AST[b] (U/mL)	50	33 (23-48.5)
Serum albumin (mg/dL)	48	3.1±0.6
APTT (Seconds)	45	26.1±3.7
INR[c]	45	1.00±0.15
Serum ferritin (ng/mL)	51	998 (593.9-1998)
D-dimer (ng/mL)	47	2370 (1250-5250)
C-reactive protein (mg/L)	52	88.8 (34.5-142.3)
LDH (U/L)	46	362.5 (290.8-448.5)
IL-6 (pg/mL)	18	111 (39.3-185.4)
Procalcitonin (ng/mL)	29	3.26 (0.73-9.70)
Procalcitonin >0.5	29	25 (43.1%)

ALT=alanine transaminase; AST=aspartate aminotransferase; [a]Values represent mean±standard deviation, number (percentage), median (interquartile range); [b]One patient had concomitant ischemic hepatitis with ALT and AST >3,000. [c]International Normalized Ratio

Table 3: Summary of therapeutic interventions

Therapeutic Interventions	Number (percentage) of patients[a]
Oxygen support modalities	
No oxygen	12 (20.7)
Prongs/mask	32 (55.2)
Nonrebreathing mask	27 (46.6)
High-flow nasal canula	2 (3.4%)
Noninvasive ventilation	2 (3.4%)
Invasive ventilation	2 (3.4%)
Therapy	
Methylprednisolone	42 (72.4)
Heparin	38 (65.5)
Hydroxychloroquine	48 (82.6)
Favipiravir	12 (20.7)
Remdesivir	4 (6.8)
Tocilizumab	3 (5.2)
Convalescent plasma	2 (3.4)

[a]Numbers are with overlap due to treatment step-up or step-down

cohort was that many patients missed their dialysis as they were turned away by dialysis centers.

Most COVID-19 patients (82%–85%) develop bilateral radiological abnormalities.[4,10] Seven (12.1%) patients had normal X-rays at admission in our study. Normal chest X-rays have been reported in COVID-19 patients from the hemodialysis as well as the general population.[4,15]

Treatment

There was initial enthusiasm as well as safety concerns (especially in hemodialysis) around the combination of hydroxychloroquine and azithromycin.[16,17] Corticosteroids were successfully used in the management of COVID-19 patients with severe disease.[18,19] The RECOVERY trial and, more recently, the METCOVID (Methylprednisolone in the Treatment of Patients With Signs of Severe Acute Respiratory Syndrome in COVID-19) study contrasting results with corticosteroids.[20,21] Anticoagulation was also shown to have clinical benefit in COVID-19 patients with severe disease.[22,23] Other therapeutic modalities including antivirals (remdesivir and favipiravir), tocilizumab, and convalescent plasma were also found beneficial in small cohorts.[24-27] In our study, the number of patients on each therapy was small, and it was not designed to compare the efficacy of treatment protocols.

Table 4: Comparison of potential prognostic markers among survivors and nonsurvivors

Parameter	*n*	Survivors (*n*=36)	Nonsurvivors (*n*=22)	*P*
Age (years)	58	45.8±15.5	53.4±18.3	0.596
Age above 60 years		8/36	8/22	0.364
Saturation on room air (%)	54	93.94±4.9	88.8±7.6	0.044
Disease severity (Mild/Moderate/Severe)	53	21/4/7	7/3/12	0.033
Hemoglobin (g/dL)	57	9.32±2.3	9.09±2.4	0.564
Platelets[a]	57	198.5±97.2	171.4±68.1	0.277
Low platelets[b]	57	15 (42.8%)	8 (40%)	0.836
Total leucocyte counts[a]	57	6.99±3.3	9.15±4.6	0.188
ANC[a]	57	5.56±3.2	7.14±4.4	0.288
ALC[a]	57	1.21±0.48	1.39±1.18	0.052
Lymphopenia[c]	57	12/36	7/22	0.948
Nadir ALC[a]	57	1.17±0.88	1.29±1.22	0.868
Neutrophil-lymphocyte ratio	57	4.94±3.18	6.52±3.6	0.203
Albumin (g/dL)	52	3.05±0.6	3.2±0.45	0.228
D-Dimer (ng/ml)	47	2240 (1060-5450)	3090 (1643-4908)	0.698
Peak D-dimer	47	2740 (1300-5980)	3415 (1665-8957)	0.653
CRP (mg/dl)	52	88.8 (31.25-141.3)	131.6 (45.3-176.0)	0.296
Peak CRP	52	98.9 (71.5-165.1)	131.6 (48.4-178.6)	0.513
CRP >175 mg/L	52	2/32	5/13	0.041
Ferritin (ng/mL)	51	1000 (538.5-2017)	989.7 (625.5-1448.5)	0.071
Peak ferritin	51	1223 (728-2034)	1083 (625-1908.7)	0.629
Lactate dehydrogenase (U/L)	46	358 (296-434)	393 (276.5-665)	0.187
IL-6 (pg/mL)	18	86.0 (20.1-143.7)	170.6 (130.9-886.2)	0.031
Procalcitonin	29	3.04 (0.79-9.24)	5.7 (0.62-25.6)	0.456
Hospital stay (days)	58	9.5 (4.25-12.5)	5.5 (1.75-11.5)	0.187

ANC=Absolute neutrophil counts, ALC=Absolute lymphocyte counts, CRP=C-reactive protein, IL-6=Interleukin 6, [a](×1,000/mm^3), [b]Low platelets were defined as platelet counts <150,000/mm^3, [c]Lympmphopenia was defined as ALC <1,000/mm^3

We monitored the corrected QT interval (QT_c) in all patients and found the combination of HCQ and azithromycin safe in our cohort. We followed patients with blood counts, CRP, procalcitonin, X-ray chest, and blood culture while they were on steroids or tocilizumab. No attributable worsening was found. The safety of remdesivir is not established in advanced renal failure. We used remdesivir in our patients without any dose modification. We observed no elevation in hepatic transaminases or infusion reactions with remdesivir (n = 4) in our cohort.

Outcomes

As per the World Health Organization data, mortality from COVID-19 is 2.9%.[1] Severe disease has been associated with higher mortality (around 40%).[28] Smaller cohorts from China reported moderately high (16.2%) deaths in hemodialysis patients, all in non-ICU patients. They emphasized the importance of comorbidities in the mortality associated with COVID-19 in HD patients.[29] A subsequent study of hemodialysis patients from Spain observed 30.5% mortality in the whole cohort. The patients who had severe disease had higher death rates (61.1%). These trends are reflected in our cohort almost exactly. The Indian cohort had an identical death rate (37.8%) compared with our study.[14]

Predictors of prognosis

The previous studies have reported age, dialysis vintage, comorbidities, high serum levels of blood urea nitrogen, CRP, LDH, ferritin, high leucocyte counts, and lymphopenia to predict death in COVID-19 patients on dialysis.[30,31] However, inconsistency in published evidence does exist. Other studies in hemodialysis patients have found none of the laboratory parameters at admission predict in-hospital mortality.[12,32] A French cohort reported LDH over two times the upper normal and CRP more than 175 mg/dL predict mortality.[33] In comparison, Goicoechea *et al*.[12] reported mean CRP levels as low as 18.7 mg/dL in non-survivors.

We found higher mortality in the initial 3 weeks of functioning as a COVID-19 hospital. The initial high mortality rates may be attributed to delay in diagnosis, limited availability of testing and drugs, fear and misinformation, and poor logistic support. Although resource limitation in health care staffing, testing, and medical management was universal during the pandemic, it was more common in the developing world.

Limitations of our study include a retrospective design and a small sample size. Inclusion was hospital based and does not include data from asymptomatic patients on dialysis because they were not routinely screened with RT-PCR or COVID-19 antigen testing. Patients with normal chest X-rays may have shown abnormal findings in a computed tomography (CT) thorax. However, a CT scan was not done routinely and hence not reported here. Treatment protocols with COVID-19 patients were continuously evolving at the time of the study.

Conclusion

The COVID-19 pandemic poses serious problems for the hemodialysis population. Mortality rates in this subpopulation were significantly higher than the average in-hospital death rates. Although in unselected cohorts several clinical and laboratory markers are known to be associated with mortality, only clinical severity and a few biomarkers significantly correlated with mortality in our cohort. Further studies and analysis of registry data may help clarify certain limitations of the study.

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Conflicts of interest

There are no conflicts of interest.

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