Kidney & Blood Pressure Research

Kidney Blood Press Res
DOI: 10.1159/000511082
Received: June 12, 2020
Accepted: August 23, 2020
Published online: September 8, 2020

Case Report

COVID-19 in Grade 4–5 Chronic Kidney Disease Patients

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Keywords
SARS-CoV-2 · COVID-19 · Chronic kidney disease · Pneumonia

Abstract
Introduction: Chronic kidney disease (CKD) increases the risk of mortality during coronavirus disease 2019 (COVID-19) episodes, and some reports have underlined the high incidence and severity of this infection in dialysis patients. Information on COVID-19 in nondialysis CKD patients is not available yet. ***Case Reports:*** Here we present 7 patients with grade 4–5 CKD who developed symptomatic COVID-19; they comprise 2.6% of our 267 advanced CKD patients. The estimated GFR was between 12 and 20 mL/min during the month prior to COVID-19. The 3 major symptoms were fever, cough, and dyspnea, and 5 patients showed bilateral pneumonia. Hydroxychloroquine, azithromycin, ceftriaxone, and steroids were the most frequently prescribed drugs. Two patients needed noninvasive mechanical ventilation. All patients showed minimal to moderate kidney function deterioration during admission, with an eGFR decline below 5 mL/min in 6 cases. No patient required acute dialysis. Six patients were discharged alive and remained dialysis free athe t the time of reporting, and one 76-year-old patient died. ***Conclusions:*** COVID-19 affects grade 4–5 CKD patients, but prognosis may be acceptable if prompt supportive measures are applied. These findings should be confirmed in larger cohorts, and further observations will be needed to understand the full spectrum of clinical features and the optimal approach to COVID-19 in patients with advanced CKD.

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic has affected over 233,000 people in Spain since early March 2020 [1]. The reported fatality rate in the general population with COVID-19 admitted to a large tertiary Spanish hospital was 20.7%, with 34% in the subgroup aged 70–79 years [2]. Chronic kidney disease (CKD) patients have several conditions that make them a target population for the virus, i.e., an older age, comorbidities, and a frail immunological system. There is scarce information regarding the impact of COVID-19 on renal patients. In descriptive studies in Spain that have included more than 20,000 people, CKD in COVID-19 patients has been found to be directly related to mortality [3]. Patients on hemodialysis attending treatment centers have a high risk of acquiring the infection [4, 5] and our group early designed a protocol to limit the spread of the infection in dialysis facilities [6].

Distinctively, outpatient advanced grade 4–5 CKD recipients may have a high risk of acquiring the infection since they have more contact with hospital facilities. Information regarding the impact of COVID-19 in an advanced CKD program is not available yet.

Here we present the incidence of COVID-19 in our prevalently grade 4–5 CKD patients, controlled at our outpatient clinic, as well as the characteristics of the first 7 symptomatic COVID-19 patients and their outcomes until death or a minimum of 1 month after the start of symptoms.

Case Reports

All patients from our cohort with advanced grade 4–5 CKD (eGFR <30 mL/min) studied at our institution between March 11 and April 20, 2020, for suspected COVID-19 infection were included. Clinical data were prospectively obtained through review of medical records. Each patient was followed until death or at least for 1 month after dialysis. Confirmed COVID-19 corresponds to a patient with a positive reverse transcription-polymerase chain reaction (RT-PCR) SARS-CoV2 assay of a specimen collected on a nasopharyngeal swab or bronchoalveolar lavage. Suspected but nonconfirmed COVID-19 correspond to a patient with a negative RT-PCR.

As of April 20, a total of 10 patients had been admitted with suspected COVID-19; 7 of those cases were confirmed. This led to a prevalence of 2.6% among our 267 ACKD patients oriented to future dialysis.

Demographic factors, comorbidities, baseline treatments, clinical characteristics, laboratory and chest X-ray findings, specific treatments, and outcomes in the 7 COVID-19 confirmed cases are shown in Table 1. The estimated GFR was between 12 and 20 mL/min during the month prior to infection; 2 patients were grade 5 CKD and 5 were grade 4 CKD. The 3 major symptoms observed in COVID-19-confirmed patients were fever, cough, and dyspnea. Other common symptoms included asthenia, myalgia, diarrhea, and headache. Five patients showed bilateral pneumonia on chest X-ray and 1 had unilateral pneumonia (Fig. 1). Two patients (No. 5 and 7) did not present respiratory symptoms but showed a gastrointestinal pattern, with nausea and diarrhea as the presenting features. All of the patients were admitted to the hospital ward, except for patient No. 5; this patient did not have respiratory syndrome or pneumonia and was monitored at home.

Hydroxychloroquine, azithromycin, ceftriaxone, and glucocortocoids were the most frequently prescribed drugs (Table 1). The glucocorticoids were given in different dosages as follows: case 1, three i.v. boluses of 200 methylprednisolone; cases 3 and 7, dexamethasone at 8 mg every 8 h for 4 days, 4 mg every 8 h for 4 days, and 4 mg every 24 h for 4 additional

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Table 1. Demographics and baseline clinical characteristics

Patient No.:	1	2	3	4	5	6	7
Age, years	54	47	62	76	75	79	83
Sex	Female	Female	Male	Female	Female	Male	Female
Known COVID-19 contact	Yes	Yes	No	Yes	No	No	No
Flu vaccination	Yes	No	No	Yes	Yes	Yes	No
Comorbidities and baseline kidney function							
Charlson index	4	4	7	4	10	10	13
Do-not-resuscitate order	No	No	No	No	No	No	Yes
Diabetes mellitus	No	No	Yes	No	Yes	Yes	Yes
Arterial hypertension	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Smoker	No	No	No	No	No	No	Past
Dyslipidemia	Yes	Yes	Yes	No	Yes	Yes	Yes
Obesity	Yes	Yes	No	No	Yes	Yes	No
Heart disease	No	No	No	Yes	No	Yes	Yes
Lung disease	No	No	No	No	No	Yes	No
Previous cancer	No	No	No	No	Yes	Yes	Yes
ACEI/ARB treatment	Yes	No	Yes	Yes	No	Yes	Yes
Estimated GFR in the previous month, mL/min	12	20	18	16	14	18	18
SCr, mg/dl	3.98	2.56	3.37	2.87	3.18	3.32	2.51
PCOR, mg/g	534	2,200	930	2,089	745	1,539	640
Symptoms and signs							
Fever	Yes	Yes	Yes	Yes	No	Yes	No
Cough	Yes	Yes	Yes	No	No	Yes	No
Dyspnea	No	Yes	Yes	Yes	No	Yes	No
Fatigue	Yes	Yes	Yes	No	No	Yes	Yes
Myalgia	Yes	Yes	Yes	No	No	Yes	No
Headache	No	Yes	Yes	No	No	No	No
Ageusia/anosmia	No	No	No	Yes	No	No	No
Gastrointestinal symptoms	No	No	No	No	Yes	No	Yes
Time from symptoms to hospital admission and PCR, days	3	9	3	5	5	7	4
Bilateral pneumonia	Yes	Yes	Yes	Yes	No	No	Yes
Respiratory insufficiency	Yes	No	Yes	Yes	No	Yes	No
Laboratory tests at admission							
Hemoglobin, g/dL	10.9	11.7	9.9	10.7	9.6	11.3	12.9
Leucocytes, $n \times 10^3/\mu L$	5.14	5.41	7.99	14.6	4.09	6.8	5.6
Lymphocytes, $n \times 10^3/\mu L$	3.8	3.62	0.49	0.46	0.64	0.47	1

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Table 1 (continued)

Patient No.:	1	2	3	4	5	6	7
Neutrophils, $n \times 10^3/\mu L$	1.2	1.4	7.39	13.68	2.78	5.65	4
Platelets, $n \times 10^3/\mu L$	165	277	204	200	161	235	131
D-dimer, µg/L	2,110	670	1040	650	2620	590	ND
Fibrinogen, mg/dL	ND	>500	>500	>500	>500	>500	>500
GOT, UI/L at 37°C	30	127	66	37	17	17	21
LDH, UI/L at 37°C	269	406	97	259	196	175	349
Troponin T, ng/L	ND	ND	ND	ND	ND	98.7	38.5
CK, UI/L at 37°C	ND	71	558	ND	32	68	ND
Albumin, g/dL	4.2	3.1	3.3	3.4	3.9	3.4	3.1
IL-6, pg/mL	ND	11.4	3.2	98.6	ND	174	ND
C-reactive protein, mg/dL	11.2	5.2	4.3	0.7	0.3	15.5	2.2
Ferritin, ng/mL	2,800	990	944	1450	1,152	477	3,662
25-OH vitamin D_3, ng/mL	10	13	16	9	5	16	6
PTH, pg/mL	198	61	170	145	213	252	152
COVID-19 treatment							
Hydroxychloroquine	No	Yes	Yes	Yes	No	Yes	Yes
Azithromycin	No	Yes	Yes	Yes	No	Yes	Yes
Ceftriaxone	No	No	Yes	Yes	No	Yes	No
Corticoids	Yes	No	Yes	Yes	No	No	Yes
Lopinovir/ritonavir	Yes	No	No	No	No	No	No
Tocilizumab	Yes	No	No	Yes	No	No	No
Enoxaparin	No	Yes	Yes	Yes	No	Yes	Yes
Vitamin D	No	Yes	Yes	No	No	Yes	No
Other specific treatment	Igs	No	No	No	No	No	No
Evolution and outcome							
Hospital admission/ICU admission	Yes/no	Yes/no	Yes/no	Yes/no	No/no	Yes/no	Yes/no
Noninvasive mechanical ventilation	Yes	No	Yes	No	No	No	No
Peak SCr, mg/dL	4.94	2.96	6.78	3.55	3.80	3.34	2.60
Nadir estimated GFR, ml/min	11	17	8	12	11	17	15
Acute estimated GFR decrease during COVID-19 vs. the previous month, mL/min	–1	–3	–10	–4	–3	–1	–3
Need for dialysis	No	No	No	No	No	No	No
Time from symptoms to resolution, discharge, or death, days	11	18	10	9	27	21	9
Resolution and discharge	Yes	Yes	Yes	No (dead)	Yes	Yes	Yes

ND, not done; Igs, immunoglobulins because of associated Guillain-Barré syndrome.

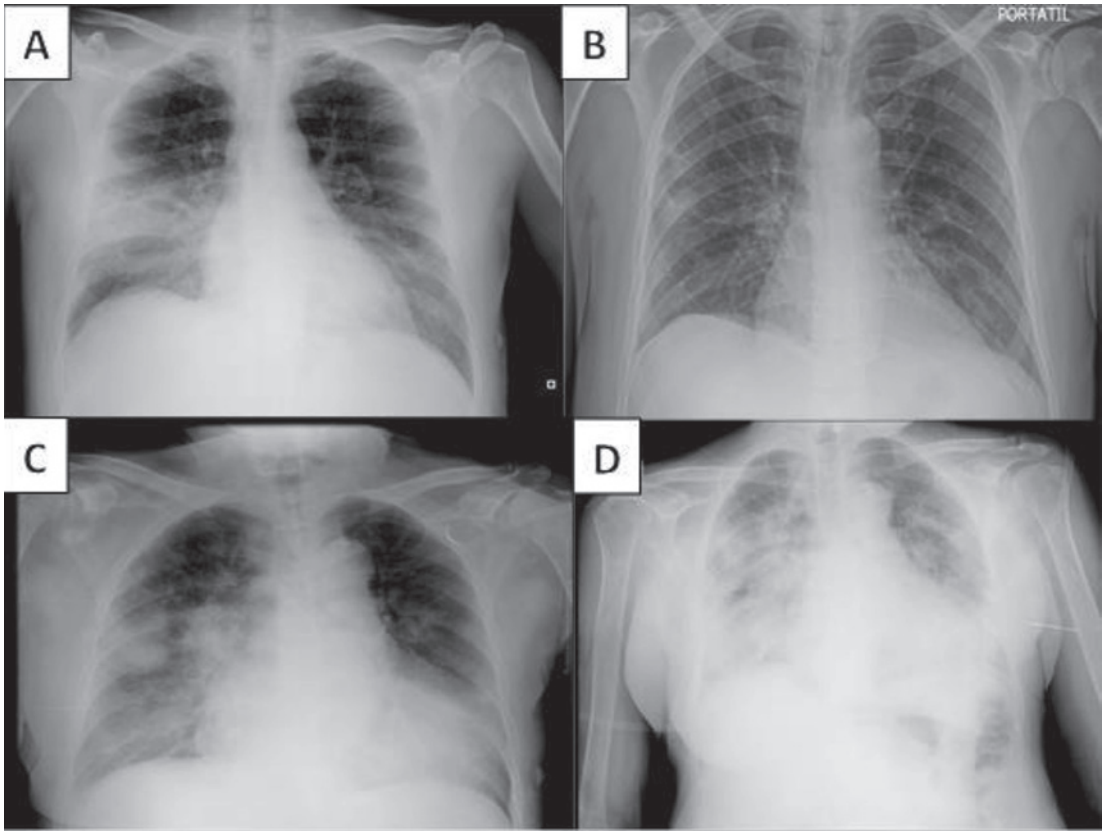

Fig. 1. Chest x-rays of two patients with advanced CKD and COVID-19. Patient No. 3 showed bilateral opacities at admission, predominantly in the right lung median lobe (**a**), which mostly disappeared at discharge (**b**). Patient No. 4 showed bilateral pneumonia at admission (**c**), which intensely worsened until the night before death (**d**).

days; and case 4, a single 60-mg i.v. dose of methylprednisolone on the day she died. Tocilizumab was given in a single i.v. 400-mg dose in cases 1 and 4. Prophylactic enoxaparin was prescribed in 5 cases and none of them presented thrombotic events. Two patients did not receive any specific treatment. Treatments with remdesivir or favipiravir were not available at that time. We did not detect any drug-related adverse event.

ICU admission was not indicated for any patient and 2 patients were managed with noninvasive mechanical ventilation. All of the patients showed minimal to moderate kidney function deterioration during admission, but the estimated GFR decline was lower than 5 mL/min in 6 cases and 10 mL/min in the remaining one, and none required acute dialysis. The lowest estimated GFR during the COVID-19 episode was 8 mL/min/m^2.

At the end of follow-up, 6 patients were discharged alive (5 of them from the hospital and another one from home hospitalization) and remained dialysis free. One patient died. She was a 73-year-old woman who presented to the emergency room on March 29, 2020, due to a 5-day history of dyspnea, low-grade fever, anosmia, ageusia, and dry cough. She was admitted with a diagnosis of COVID-19 (PCR+) bilateral pneumonia and decompensated heart failure. Her twin sister presented similar symptoms and was admitted to another hospital. Treatment with hydroxychloroquine, azithromycin, and ceftriaxone was started on admission day, when she showed respiratory failure with oxygen requirements of up to 50% FiO_2. She had a bad evolution, with desaturation and the need for noninvasive mechanical ventilation, and started

treatment with tocilizumab and dexamethasone. Despite an initial improvement (O_2 saturation: 98%), on the morning of April 2nd, the patient was found with an absence of vital signs. Her twin sister died the same night in another hospital.

Discussion

We present our 7 patients with grade 4–5 CKD who had COVID-19 during the 40-day period of the epidemic peak in our city. This represents a prevalence of 2.6% of the patients controlled in our advanced CKD clinic, i.e., a lower proportion than expected in a high-risk population in a strongly affected region [7]. Only 1 of those patients died, and the majority were cured and discharged safely. The symptoms upon admission were those currently described for this entity. Fever was the most common, followed by cough, dyspnea, and fatigue. Chest x-ray findings showed pneumonia in 6 cases, with bilateral lung involvement in 5 of them, in agreement with many other studies [2, 7, 8]. Interestingly, as previously noted in hemodialysis patients in a short series [9], 2 patients did not present respiratory symptoms but showed a gastrointestinal pattern, with nausea and diarrhea as the presenting features. These patients showed a favorable evolution. Acute kidney injury superimposed to CKD was frequent but mild in these patients; all patients showed minimal kidney function deterioration during admission, but the estimated GFR decline was lower than 5 ml/min in most cases and none required acute dialysis. As a result, some of these patients showed lymphopenia, and in fact the lowest lymphocyte count was noted in the patient who died. Other laboratory findings such as high levels of C-reactive protein, IL-6, D-dimer, and procalcitonin were seen in some patients but without a clear pattern associated to severity. No effective treatment is available for COVID-19, but most of our patients received combinations of hydroxychloroquine and azithromycin. It is not possible to establish any therapeutic advantage for any of those treatments.

CKD patients have a high risk of symptomatic infection, mainly due to an impaired immune response, chronic inflammation, increased oxidative stress, uremic toxin accumulation, and endothelial dysfunction [10]. Despite the facts that CKD increases the risk of mortality during COVID-19 episodes [2, 11, 12] and some reports have underlined the risk and severity of this infection in dialysis patients [4, 5], information on the incidence and outcome of COVID-19 in nondialysis CKD patients is not available yet.

In summary, we described 7 advanced CKD patients who developed COVID-19. In addition to fever, cough, dyspnea, and fatigue, diarrhea was common. These findings should be confirmed in larger cohorts, and further observations will be needed to understand the full spectrum of clinical features and the optimal diagnostic and treatment approach for COVID-19 in patients with advanced CKD. Our small series confirms that COVID-19 affects grade 4–5 ACKD patients, but the prognosis may be quite good if prompt supportive measures are applied.

Acknowledgement

We thank all of the medical and nursing staff at the Hospital del Mar for their dedicated care of our renal patients during the COVID-19 epidemic.

Statement of Ethics

This study was conducted ethically in accordance with the World Medical Association Declaration of Helsinki. The authors declare that they obtained consent from each patient reported in this article for publication of the information about him or her that appears within this case report.

Conflict of Interest Statement

The authors have no conflict of interests to declare.

Funding Sources

No funding was received for this work.

Author Contributions

All of the authors contributed to the management of these patients, made substantial contributions to the concept of this work, and approved the final version of this paper. S.C. and M.D.A contributed equally.

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