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BRIEF COMMUNICATION

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COVID-19 in elderly kidney transplant recipients

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The SARS-Cov-2 infection disease (COVID-19) pandemic has posed at risk the kidney transplant (KT) population, particularly the elderly recipients. From March 12 until April 4, 2020, we diagnosed COVID-19 in 16 of our 324 KT patients aged ≥65 years old (4.9%). Many of them had had contact with healthcare facilities in the month prior to infection. Median time of symptom onset to admission was 7 days. All presented with fever and all but one with pneumonia. Up to 33% showed renal graft dysfunction. At infection diagnosis, mTOR inhibitors or mycophenolate were withdrawn. Tacrolimus was withdrawn in 70%. The main treatment combination was hydroxychloroquine and azithromycin. A subset of patients was treated with anti-retroviral and tocilizumab. Short-term fatality rate was 50% at a median time since admission of 3 days. Those who died were more frequently obese, frail, and had underlying heart disease. Although a higher respiratory rate was observed at admission in nonsurvivors, symptoms at presentation were similar between both groups. Patients who died were more anemic, lymphopenic, and showed higher D-dimer, C-reactive protein, and IL-6 at their first tests. COVID-19 is frequent among the elderly KT population and associates a very early and high mortality rate.

KEYWORDS
clinical research/practice, infection and infectious agents – viral, kidney transplantation/nephrology, patient survival

1 | INTRODUCTION

The World Health Organization has declared the SARS-CoV-2 infection (COVID-19) outbreak as a Public Health Emergency of International Concern and characterized it as a pandemic.[1,2] Since early March, 2020, the Spanish cases curve started to rise, with more than 177 000 people infected in 6 weeks.[3] The reported fatality-rate in the general population with COVID-19 admitted to a large tertiary Spanish Hospital is 20.7%, 34% in the subgroup of age 70-79 years.[4]

Abbreviations: ACE, angiotensin converting enzyme; AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; COVID-19, SARS-COV-2 infection disease; IQR, interquartile range [IQR]; KT, kidney transplantation; SD, standard deviation.

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More than 60 000 patients are currently on dialysis or transplanted in Spain,[5] and they reunite several conditions for being a target population for the virus: age, comorbidities, and a frail immunological system. There is scarce information regarding the impact of COVID-19 in renal patients. Patients on hemodialysis attending treatment centers are at high risk of acquiring the infection. Our group early designed a protocol to limit the spread of the infection on dialysis facilities.[6] Worried about the potential of infection during transplantation, the Spanish transplant community advised on avoiding active kidney transplantation (KT) for the risk of infection but also for the competing use of facility resources needed by COVID-19 patients during the pandemic.[7] Distinctively, outpatient KT recipients are at a high risk of acquiring the infection. Therefore, we disseminated general protection rules (informing patients, avoiding live consultation) and worked on some consensus on the management of immunosuppression in case of infection.[7]

Some publications have reported short series and case reports of COVID-19 in KT recipients,[8-18] which describe the clinical course and illustrate the management of immunosuppression during the evolution of the disease. Information regarding the impact in a KT program is not available yet. It has been communicated that the fatality-rate of COVID-19 in the general population is higher in older patients with comorbidities, that is, hypertension and cardiovascular disease.[4,19] The KT population in Spain is older than in other countries and more comorbid, nevertheless with substantial survival benefit compared to remaining on dialysis.[20] There are no data exploring whether the same variables are important risk factors for mortality in KT recipients.

Here we present the incidence of COVID-19 in our prevalent elderly KT patients, the characteristics of the first 16 symptomatic COVID-19 elderly KT recipients from our program and their outcomes until death or a minimum of 2 weeks after symptoms started.

2 | METHODS

2.1 | Population and COVID-19 screening policy

At Hospital del Mar, we actively follow 803 KT recipients performed between 1979 and 2019. Of them, 324 (39.8%) are currently older than 65 years of age.

Different screening policies for the infection have accounted in Spain during this time. General population were screened for COVID-19 if they presented with moderate to severe symptoms. All KT recipients were advised to be evaluated if symptoms—even mild—were present.

Clinical data were prospectively obtained through review of medical records. The data reported here are those available through May 2, 2020. Each patient has been followed until death or at least 28 days of follow-up.

2.2 | Definitions

Confirmed COVID-19 corresponds to a patient with positive reverse-transcriptase–polymerase-chain-reaction assay of a specimen collected on a nasopharyngeal swab or bronchoalveolar lavage. Only laboratory-confirmed cases were included. This study includes only KT recipients with symptoms.

2.3 | Statistical analysis

Quantitative variables with a normal distribution are expressed as mean and standard deviation (SD) and the remaining as median and interquartile range (IQR). Categorical variables are summarized as counts and percentages. Cox univariate analyses were performed. A $P < .05$ was considered statistically significant. Statistical analysis was performed using SPSS V 21.0 (SPSS Inc).

3 | RESULTS

3.1 | Baseline demographic and clinical characteristics

From March 12 until April 4, we diagnosed COVID-19 in 16 of our 324 KT patients aged 65 years or over, resulting in an incidence of 4.9% in our elderly KT population. During the same period, we diagnosed only four COVID-19 cases among our 479 KT recipients younger than 65 years of age (0.8%). The baseline characteristics of the elderly patients are shown in Table 1. They were most frequently men, with a good functioning kidney graft and receiving conventional immunosuppression. Only two had been transplanted within the last 2 months, one still hemodialysis-dependent due to severe rejection. Seventy-five percent of them had had contact with a healthcare facility in the month prior to infection, either the transplant center, other hospital or were institutionalized. Forty-four percent of them were frail,[21] 50% diabetics and frequently had arterial hypertension and underlying heart disease.

3.2 | Clinical characteristics and laboratory findings at COVID-19 presentation

These data are summarized in Table 2. Symptoms started a median of 7 days before admission. Nine patients were admitted to the transplant center, six patients were admitted in other centers and one remained at home. Clinically, all patients presented with fever and all but one had pneumonia on the chest x-ray. The only one without documented pneumonia was managed at home throughout the whole process. Anemia was prevalent as well as lymphopenia, high C-reactive protein, ferritin, D-dimer, and IL6. SCr was higher at admission compared with baseline creatinine. At least 75% developed

TABLE 1 Baseline characteristics of the patients

	Alive (n = 8)	Dead (n = 8)	Total (n = 16)
Recipient age (y, mean ± SD)	72.6 ± 4.2	74.6 ± 5.3	73.6 ± 4.7
Sex female (n, %)	1 (12.5)	3 (37.5)	4 (25)
Caucasian race (n, %)	7 (87.5)	7 (87.5)	14 (87.5)
Deceased donor (n, %)	7 (87.5)	8 (100)	15 (93.5)
Primary kidney disease			
Unknown etiology (n, %)	1 (12.5)	2 (25)	3 (18.8)
Alport syndrome (n, %)	2 (25)	0 (0)	2 (12.5)
IgA nephropathy (n, %)	1 (12.5)	1 (12.5)	2 (12.5)
Interstitial nephropathy (n, %)	0 (0)	2 (12.5)	2 (12.5)
pANCA glomerulonephritis (n, %)	1 (12.5)	0 (0)	1 (6.3)
Vascular (n, %)	2 (25)	0 (0)	2 (12.5)
Diabetic nephropathy (n, %)	1 (12.5)	2 (12.5)	3 (18.8)
Polycystic kidney disease (n, %)	0 (0)	1 (12.5)	1 (6.3)
Frailty (fried score >0, n%)	2 (25)	5 (62.5)	7 (43.7)
Smoker (past or current, n, %)	5 (62.5)	3 (37.5)	8 (50%)
Weight (kg, mean ± SD)	73.4 ± 7.8	77.2 ± 11.9	75.3 (9.9)
Height (cm, mean ± SD)	168.4 ± 9.3	166 ± 10.7	167.6 (9.7)
Body mass index (mean ± SD)	26.1 ± 3.9	27.7 ± 2.9	26.9 (3.5)
Serum creatinine (last before COVID-19) (mg/dL, mean ± SD)	1.5 ± 0.4	2.7 ± 1.4[a]	2.04 (1.14)
Time after transplant (mo, median [interquartile range, IQR])	53 (24.5-132.5)	41 (7.5-87.5)	49 (11.5-116.5)
Contact with healthcare facilities in the prior month (n, %)	5 (62.5)	7 (87.5)	12 (75)
Immunosuppression			
T cell depletion induction (n, %)	1 (12.5)	2 (25)	3 (18.8)
Calcineurin inhibitor (n, %)	7 (87.5)	7 (87.5)	14 (87.5)
Prednisone (n, %)	6 (75)	7 (87.5)	13 (81.2)
Mycophenolate (n, %)	3 (37.5)	5 (55.6)	8 (50)
mTOR inhibitor (n, %)	2 (25)	3 (37.5)	5 (31.3)
Comorbidities[a]			
Lung disease (n, %)	2 (25)	1 (12.5)	3 (18.8)
Heart disease (n, %)	2 (25)	6 (75)	8 (50)
Arterial hypertension (n, %)	8 (100)	6 (75)	14 (87.5)
Type 2 diabetes mellitus (n, %)	3 (37.5)	5 (62.5)	8 (50)
Obesity (n, %)	2 (25)	5 (62.5)	7 (43.8)
Estimated GFR below 60 mL/min	8 (100)	8 (100)	16 (100)
Cancer (n, %)	3 (37.5)	2 (25)	5 (31.3)
ACE inhibitors or ARB treatment (n, %)	1 (12.5)	1 (12.5)	2 (12.5)

[a]The incidences of comorbidities in a general COVID-19 population hospitalized in Spain[5] are: lung disease 13.3%, heart disease 19.3%, arterial hypertension 41.3%, type 2 diabetes mellitus 17.1%, obesity 10.9%, eGFR < 60 7.8%, malignant disease 17.3%,

acute respiratory syndrome at some point with PaO2 to FiO2 below 300. Symptoms at presentation were similar between patients who died and patients who survived except for respiratory rate, which was higher at admission in those patients who ultimately died. There were some clear differences in analytics. Patients who eventually died were more anemic, lymphopenic, had higher creatinine, and showed higher D-dimer and CRP at their first tests; 30% of cases showed renal dysfunction, and three of them needed renal replacement therapy.

3.3 | Treatment of COVID-19

These data are summarized in Table 2. At the onset of infection, mTOR inhibitors or mycophenolate were withdrawn in all cases when the patient was on tacrolimus too, and tacrolimus was withdrawn at different stages of infection in 70% of those who received it. The main treatment combination was antibiotic (100%), mainly azithromycin (87.5%), plus hydroxychloroquine (81.2%). A

TABLE 2 Clinical and analytical features at admission during the COVID-19 episode

	Alive (n = 8)	Dead (n = 8)	Total (n = 16)
Time onset of symptoms to admission (days, median [IQR])	−7 (−6.5 to −14)	−5.5 (−4.5 to −8)	−7 (−5 to −10)
Time since transplant team knew to admission (days, median [IQR])	0 (−2.5 to +6.5)	−1.5 (−6 to +4)	−1 (−5 to +5)
Admission to transplant center (n, %)	6 (75)	3 (37.5)	9 (56.3)
Symptoms			
Fever (n, %)	8 (100)	8 (100)	16 (100)
Dyspnea (n, %)	5 (62.5)	7 (87.5)	12 (75)
Myalgia (n, %)	3 (37.5)	1 (12.5)	4 (25)
Diarrhea (n, %)	4 (50)	4 (50)	8 (50)
Blood test at admission			
Hemoglobin (gr/dL, mean ± SD)	12.3 ± 2.5	9.8 ± 2.2	11.2 (2.5)
White blood cells ($\times 10^{*3}$/μL, mean ± SD)	10.5 ± 4.2	8.1 ± 4.0	9.49 (4.2)
Lymphocytes ($\times 10^{*3}$/μL, mean ± SD)	1.5 ± 1	0.6 ± 0.7*	1.14 (0.99)
Platelets ($\times 10^{*3}$/μL, mean ± SD)	159.1 ± 45.7	151 ± 64.6	155 (51.0)
Serum creatinine (mg/dL, mean ± SD)	1.5 ± 0.4	3.1 ± 1.5*	2.1 (1.2)
Ferritin (ng/mL, median [IQR])	1426 (1032-4091)	1577 (1564-2083)	1557 (1170-3704)
D-dimer (mcg/L, median [IQR])	806 (561-2872)	2276 (1885-4486)	1870 (583-3874)
AST (UI/L, mean ± SD)	34.7 ± 24.4	43 ± 54.1	40.2 (37.6)
ALT (UI/L, mean ± SD)	27.1 ± 19.8	33.1 ± 24.1	29.2 (21.6)
LDH (UI/L, mean ± SD)	333.3 ± 248	413 ± 88.1	368 (222.4)
CPK (U/L, mean ± SD)	82.4 ± 61.7	49.3 ± 37.1	77.7 (70.4)
CRP (mg/L, mean ± SD)	111.8 ± 67.7	187.5 ± 88.9	144.3 (83.8)
Procalcitonin (ng/mL, mean ± SD)	1.03 ± 1	2.3 ± 2.1	1.8 (2.1)
IL-6 (ng/mL, mean ± SD) (pg/mL, mean ± SD)	54 (44-345)	236 (24-344)	2.9 (4.2)/ 290 (415)
PaO_2/FiO_2 (mm Hg, median [IQR]) (n = 12)	262 (254-312)	242 (148-276)	266 (173-320.7)
Acute respiratory distress syndrome moderate-severe (PaFi < 200) (n, %)	1/12 (14.3)	2/12 (40)	3/12 (25)
Acute respiratory distress syndrome moderate-severe (PaFi < 300) (n, %)	5/12 (71.4)	4/12 (80)	9/12 (75)
Respiratory rate (per minute, median [IQR])	21 (18-24.5)	36 (24-46)**	24 (18-35)
Heart rate (per minute, median [IQR])	76 (69-88)	80 (74-96)	78 (69-91)
Systolic blood pressure (mm Hg, median [IQR])	120 (115-143)	155 (112-164)	122 (112-159)
Diastolic blood pressure (mm Hg, median [IQR])	68.5 (63-72)	63 (60-80)	68 (60-74)
Bilateral infiltrates in chest x-ray (n, %)	7/8	7/7	14/15 (93.3)
Acute kidney injury (n, %)	0 (0)	5 (71.4)	5/15[a] (33.3)
With acute hemodialysis need	0 (0)	3 (37.5)	3 (18.7)
Noninvasive mechanical ventilation (n, %)	2 (25)	1 (14.3)	3 (18.8)
Endotracheal intubation (n, %)	0 (0)	2 (28.6)	2 (12.5)
Intensive care unit admission (n, %)	0 (0)	2 (28.6)	2 (12.5)
Immunosuppression management			
Calcineurin inhibitor withdrawal (n, %)	5/7	3/7	8/14 (71.4)
Mycophenolate mofetil withdrawal (n, %)	4/4	4/4	8/8 (100)
mTOR inhibitor withdrawal (n, %)	2/3	2/2	4/5 (80)
COVID-19 treatment			
Antibiotics (n, %)	7 (87.5)	7 (87.5)	14 (87.5)
Steroids (n, %)	3 (37.5)	3 (37.5)	6 (37.5)

(Continues)

TABLE 2 (Continued)

	Alive (n = 8)	Dead (n = 8)	Total (n = 16)
Hydroxychloroquine (n, %)	8 (100)	5 (62.5)	13 (81.2)
Ritonavir-lopinavir/darunavir (n, %)	2 (25)	3 (37.5)	5 (31.2)
Tocilizumab (n, %)	3 (37.5)	1 (12.5)	4 (25)

[a]1 patient 6 wk posttransplant with a nonfunctioning graft due to rejection.

*$P = .02$.

**$P = .03$ (dead vs alive).

subset of patients was treated with steroid boluses (37.5%), the anti-retrovirals ritonavir-lopinavir/darunavir (31.2%), and/or tocilizumab (25%). Numerically, patients who survived had received hydroxychloroquine (8/8 vs 5/8 of nonsurvivors) and tocilizumab (3/8 vs 1/8 respectively).

3.4 | Outcomes and related factors

Short-term 14-day fatality rate in this group has been 50%. In Tables 1 and 2 we compared KT recipients alive at follow-up with those who died within the same period. Those who died had worse renal function before infection. They were more frequently obese, frail and had underlying heart disease. Contrarily, they had similar rates of arterial hypertension, diabetes, cancer, or lung disease. We found no differences in the treatment they were receiving before infection in terms of immunosuppression or angiotensin blockage.

Interestingly, no survivor showed acute kidney injury (AKI), while five of the eight patients who ultimately died developed AKI ($P = .07$).

Three patients required noninvasive mechanical ventilation and two of them survived. Among the eight dead patients, at least six of them had ICU admission criteria. Two of them were intubated and admitted to the ICU, but finally died, other two patients did not accept transition to ICU and denied mechanical ventilation, and the remainder two patients were not finally considered as candidates to intubation. One of them was admitted in a nursing home and the other one was 79 years old. Cause of death was respiratory in all cases, and no malignant arrhythmia was recorded.

Median time from admission to death was 3 days and to discharge was 14 days (Table 3).

TABLE 3 Outcome of the 16 patients

Death (n, %)	8 (50)
Time after admission (days, median [IQR]))	3 (3-9.5)
Time after KT team knew (days, median [IQR]))	3.5 (–1 to +7.5)
Resolution (n, %)	8 (50)
Time after admission (days, median [IQR]))	14 (8.7-18.7)
Time follow-up [May 2nd-2020] (days, %)	21 (3-28)

4 | DISCUSSION

Up to 5% of our elderly cohort of KT recipients suffered from COVID-19 during the first month of Spanish COVID-19 pandemic. This is a much higher incidence than the 0.20% in the whole general population in Spain on the same date,[22] and 6-fold higher than our own incidence in younger KT recipients (0.8%). The proportion of patients of advanced age receiving a KT in Spain is higher than in other countries,[20,23] and the fact that the COVID-19 pandemic is impacting strongly in this country poses at special risk the elderly KT population.

In addition to this high incidence, mortality is very early and high in our elderly COVID-19 KT patients. Half of them died during the episode due to refractory respiratory failure at a median time of 3 days after admission. At least six of those eight patients who died had ICU admission criteria, but in two of them, their general physicians in charge did not consider intensive care and in another two cases the patients denied consent. Advanced age and the perception of KT as a co-morbid condition itself would have probably increased this mortality rate, especially when the transplant nephrologist was not the responsible physician. Another possible bias toward a high mortality is the selection of severe cases admitted. Although we are not aware of older patients that were not admitted at the hospital because a mild course, the inclusion of those cases in our series would likely decrease the mortality rate.

The first large report on COVID-19 outcomes in hospitalized patients in Europe is a Spanish report showing high mortality rates up to 20.7%.[4] Age was the main factor associated to mortality, with rates of 3.8% in patients aged 50-59 years, 11% in those aged 60-69 years and 34% in patients aged 70-79 years.[4] This report shows the percentages of patients suffering from associated comorbidities at baseline. Heart disease, hypertension, obesity, reduced GFR and cancer were much more frequent in our COVID-19 KT elderly patients than in the general COVID-19 Spanish population, It is likely that the increased mortality we observed is related to this increased baseline morbidity rather that the KT condition itself.

Searching in the recent literature, four more groups have reported COVID-19 in KT recipients aged over 65 years.[15-18] In the largest Italian series, Alberici et al reported that 5 out of their 20 COVID-19 KT recipients were older than 65.[15] Mortality was 40%, and an additional 40% remained inpatient at the time of reporting. The other reported Italian old KT patient with COVID-19 died during admission.[16] In the report from the London hospitals, two out of their seven patients were older than 65 years of age, and one of

them died. Finally, another small Spanish series of eight KT recipients with COVID-19 included six cases aged over 65 years.[18] Two of them died, three more were still inpatient with severe disease and only one had been discharged home at the time of reporting. Overall, mortality in these 14 elderly previously reported cases has been 43%, with an additional 36% severely ill still inpatient. These results are like our experience.

Interestingly, the elderly patients who died during the COVID-19 episode were not older than survivors but showed some characteristics that may advance an ominous prognosis.[24-26] The obese, frail, with underlying heart disease and graft dysfunction showed the worst outcomes. Regarding disease presentation, clinical data are not different between survivors and those patients who ultimately died except for a higher respiratory rate in non-survivors, suggesting a more severe pulmonary involvement. In addition, fatal evolution is associated with more severe analytical alterations such as anemia, lymphopenia, increased D-dimer, and CRP. Median days from onset or identification of symptoms till admission were 7, and median time since admission to death was short, only 3 days. This underline the need for very early identification of mild symptoms of the disease and prompt admission and action in elderly COVID-19 KT recipients. The admission should be tried in the transplant center, as our series shows a trend to better survival in this subgroup of patients.

All our patients underwent profound immunosuppression minimization, all of them withdrew mycophenolate or mTOR inhibitors, and most of them also tacrolimus. There is hot debate on the potential role of tacrolimus or cyclosporine in the therapeutic management of COVID-19. Some studies have suggested that either cyclosporine or tacrolimus may prevent replication of HCoV-NL63 which depends on active immunophilin pathways.[27,28] Whether or not tacrolimus intensification or even switching to cyclosporine may be of benefit in the hyperinflammation status generated by COVID-19 remains unknown and pending prospective studies.

Another potential risk in our elderly KT population could have been the administration of drugs that prolong QT, hydroxychloroquine, and azithromycin.[29] Although arrhythmia cannot be completely ruled out, no such cardiac events were recorded in our population.

In our elderly KT population, apart from comorbidities like arterial hypertension or heart disease in increasing mortality, immunosenescence may play a role. In these patients, naïve T cell population decreases while memory T cells comprise an important portion of T cell population.[29] Consequently, the ability of immune system of elderly to never-exposed pathogens is much more limited than in young individuals, who show a very important proportion of naïve T cells. The central role of inflammatory cytokines in inducing the quick and frequently prompt clinical deterioration in association with worsening chest radiology and speedy oxygen requirements has suggested the use of tocilizumab despite lack of previous experiences in KT recipients under infection.[30] Our sample size precludes to establish strong conclusions on any attempted treatment. We tried tocilizumab in four patients and three of them survived. Again, this approach needs to be sustained in larger and prospective trials.

This study has limitations: the small sample size and the short median follow-up. Our comparisons are univariable and would need a much larger cohort to accurately determine the co-morbidities associated with poor outcome. However, ours is the first series focused on the elderly KT recipient and clinical and analytical work-up is extensive despite the early frequent mortality.

Our frontline experience shows that COVID-19 is frequent among the elderly KT population and associates a very early and high mortality rate. Consequently, preventive measures are of paramount importance in this population, and adaptive treatment trials are urgently needed.

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DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

AUTHOR CONTRIBUTIONS

MC, MJP-S, D.R-P, and JP designed the study, analyzed the data, and drafted and revised the paper; all authors revised the paper, made substantial contributions, and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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