CASE REPORT

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SARS-CoV-2 infection in kidney transplant recipients: Early report of five cases

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Abstract

From December 2019 to March 2020, China was the epicenter of the SARS-CoV-2 infection pandemic, but from that moment on, Europe surpassed China in the number of new cases and deaths related to this novel viral respiratory infection. The emergence of this world pandemic is particularly important for solid organ transplant recipients, who might have an increased risk of mortality, not only due to their chronic immunosuppression status, but also to the cardiovascular risk that correlates with several years of chronic kidney disease. To the extent that there is still a lack of knowledge about the clinical characteristics, evolution, and prognosis of SARS-CoV-2 infection in kidney transplant recipients, we will report the first 5 cases diagnosed and followed in our transplant unit, as well as share the therapeutic strategies adopted.

KEYWORDS
COVID-19 infection, kidney transplantation

1 | INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a positive-sense single-stranded RNA virus that belongs to the family *Coronaviridae*.[1] From December 2019 to March 2020, China was the epicenter of the SARS-CoV-2 infection pandemic, but from that moment on, Europe surpassed China in the number of new cases and deaths related to this novel viral respiratory infection. Since then the disease was officially named coronavirus disease 2019 (COVID-19).[2]

Transplant recipients are at high risk for severe disease for a variety of reasons. For one hand, advanced age and other comorbidities as diabetes, hypertension, chronic kidney disease, obesity, heart disease, and chronic lung disease were identified as risk factors for development of severe disease.[3] For another hand, these populations seem to have a higher risk for severe bacterial and viral infections due to reduced T-cell immunity, suggesting that could be more susceptible to COVID-19 infection. Another issue to consider is that, due to chronic immunosuppression, they could have inflammatory responses that appear to constitute an important cause of organ injury.[4]

The best therapeutic strategy for solid organ transplant (SOT) recipients remains uncertain and it has been based largely on supportive care and clinical experience shared by other international centers.

TABLE 1 Baseline characteristics of kidney transplant recipients with SARS-CoV-2 infection

Patient	Age/Gender	CKD etiology	Other comorbidities	Type of TR	Date of TR	IS therapy in use	Basal renal function (pCr (mg/dL)/eGFR CKD-EPI (mL/min/1.73 m²))
1	35/F	Diabetic nephropathy	DM, hypertension	TRP	12/2017	TAC + AZA +Pred	0.8/95.9
2	37/M	Reflux nephropathy	Hypertension, obesity, gout	TR, living donor, preemptive	3/2014	TAC + MMF +Pred	1.77/48
3	56/M	Diabetic nephropathy	DM, hypertension, diabetic retinopathy and neuropathy, hepatic steatosis	TR, deceased donor	2/2019	TAC + MMF +Pred	1.2/67.2
4	63/M	Unknown	Hypertension, obesity, ex-smoker, anti-phospholipid syndrome and obstructive sleep apnea syndrome	TR, deceased donor	8/2019	TAC + MMF +Pred	2.5/26.3
5	63/F	Unknown	Hypertension, NODAT, obesity, non-stratified heart disease, atrial fibrillation, CVD and sequelae of past tuberculosis with atelectasis in RLL	TR, deceased donor	5/1995	Cyclosporine + AZA +Pred	2.7/18

Abbreviations: AZA, azathioprine; CKD, chronic kidney disease; CVD, cerebrovascular disease; DM, diabetes mellitus; F, female; NODAT, new-onset diabetes after transplantation; TR, transplant; TRP, renal and pancreas transplant; KT, kidney transplant; TAC, tacrolimus; M, male; MMF, mycophenolate mofetil; Pred, prednisolone; RLL, right lower lobe.

To the extent that there is still a lack of knowledge about the clinical characteristics, evolution, and prognosis of SARS-CoV-2 infection in kidney transplant recipients, we will report the first 5 cases diagnosed and followed in our transplant unit, as well as share the therapeutic strategies adopted.

2 | METHODS

2.1 | Study design

We performed a retrospective, single-center study of adult kidney transplant (KT) recipients observed with SARS-CoV-2 infection in our tertiary care center. Epidemiological, demographic, clinical, management, and outcome data were analyzed.

Our center serves a geographical area with 350 000 inhabitants and our transplant unit performs an average of 110 kidney and kidney-pancreas transplants per year and it currently has 1850 transplant recipients in active follow-up. The first proven case of SARS-CoV-2 infection in Portugal was diagnosed at our center on March 1, 2020.

The case definition was made in the presence of both suggestive symptoms and laboratory confirmation of SARS-CoV-2 RNA in nasopharyngeal and oropharyngeal swab samples collected at the time of presentation. Hence, we recruited all KT recipients with COVID-19 throughout March 2020 (n = 5).

2.2 | Microbial sample collection and analysis

Nasopharyngeal and oropharyngeal swab samples were collected upon validation of suspected cases. The laboratory diagnosis of SARS-CoV-2 infection was carried out through nucleic acid amplification tests (NAAT) that detect unique sequences of the virus, using real-time reverse transcription-polymerase chain reaction (RT-PCR). At this point, we used Liferiver Novel Coronavirus (SARS-CoV-2) real-time multiplex RT-PCR kit (Liferiver/Shanghai ZJ Bio-Tech Co.), which is a CE-IVD marked test for the simultaneous qualitative detection of 3 SARS-CoV-2 target viral genes (gene E, gene N, and gene ORF1ab). Laboratory procedures were strictly performed according to the manufacturers' instructions, and appropriate biosafety practices were applied. To the best of our knowledge, there are no analytical performance issues, such as inappropriate false-positive or false-negative rates, directly associated with the laboratory use of this commercial kit.

2.3 | Therapeutic and clinical management

In our center, all patients with confirmed SARS-CoV-2 infection underwent blood tests and imaging studies. The clinical protocol for hospitalized patients included initial evaluation of D-Dimer, ferritin, C-reactive protein (CRP), procalcitonin, high-sensitivity troponin. In

TABLE 2 Symptoms and laboratory findings of kidney transplant recipients with SARS-CoV-2 infection on hospital admission

Patient	Symptoms	Data of first symptoms	Date of diagnosis	Respiratory insufficiency (PaO2/FiO2 < 300)	White blood cell count (N: 4000-11 000 × 10⁶/L)/Lymphocyte (N:20%-45%)	LDH (N:135.214 U/L)	AKI (pCr peak)	CRP (N: <5 mg/L)	CT
1	Fever, myalgia, asthenia	16/03/20	28/03/20	No	4830/34	244	No	8	No
2	Fever, rhinorrhea, asthenia, myalgia, diarrhea	14/03/20	28/02/20	Yes	3290/51	469	Yes (2.3)	124	Bilateral interstitial infiltrate
3	Fever, dry cough	14/03/20	21/03/20	No	6070/61.5	383	No	6	Multifocal ground-glass opacities
4	Fever, cough with mucous expectoration, diarrhea, anosmia	23/03/20	31/3/20	Yes	5540/27.6	273	Yes (3.0)	114	Multifocal ground-glass opacities
5	Fever, dyspnea, asthenia, odynophagia, nausea, abdominal pain	22/03/20	22/03/20	Yes	8120/9.6	370	Yes (4.5)	31	Bilateral interstitial infiltrate

Abbreviations: AKI, acute kidney injury; AKIN, acute kidney injury injury network classification; FiO2, fraction of inspired oxygen; TAC, tacrolimus; TC, thoracic computed tomography; MMF, mycophenolate mofetil; PaO2, partial pressure of arterial oxygen; Pred, prednisolone.

KT patients admitted, blood cultures and chest X-ray or computed tomography (CT) was also performed.

According to clinical severity, the patients were admitted to hospital or home hospitalization.

While in home hospitalization patients stayed in isolation according to World Health Organization (WHO)[5] and were called daily by clinicians to monitor the clinical evolution and the need of reassessment at the emergency department.

Concerning treatment, upon diagnosis, the antimetabolite was immediately suspended with the reduction or suspension of the calcineurin inhibitor (CNI) discussed on a case-by-case basis according to the severity of the clinical condition. In all cases, the steroid dose was increased slightly (usually from 5 to 10 mg/d). Regarding to antiviral treatment, all patients with documented pneumonia or respiratory failure started hydroxychloroquine 400 mg twice daily on day one, followed by 200 mg twice daily until day 5-10. In all these patients, an electrocardiogram were performed before starting treatments to access Qtc interval.

The study was approved by the Health Ethics Committee of our hospital. Requirement to obtain informed written consent from everyone was waived as the study was limited to the review of existing medical records. To ensure confidentiality, each case was anonymized by the assignment of a random identification number.

2.4 | Follow-up

After 7 to 14 days of symptoms resolution, a patient was considered cured, when two negative SARS-CoV-2 RNA test samples were obtained 24-48 hours apart.

The clinical outcome was evaluated until April 30th or until death.

3 | RESULTS

In our hospital center, during March 2020, 2178 NAAT were performed to screen for SARS-CoV-2 infection in adult patients (range 18-101 years-old). Of these, 26% were positive (n = 559) and 74% were negative (n = 1619).

Of the positive tests, five were in KT patients, four from deceased and one from living donor. One of them had a simultaneous renal and pancreas transplant. The baseline characteristics of each patient are shown in Table 1. Three patients were males, and the median age was 56 (range 35-63) years old. Regarding the etiology of chronic kidney disease (CKD), two had diabetic nephropathy, one was due to reflux nephropathy, and in the last two it was unknown. The median time from transplantation was 28 (range 7-303) months. The median baseline serum creatine (pCr) and estimated glomerular filtration rate (eGFR) by CKD-EPI were 1.77 (range 0.8-2.5) mg/dL and 48 (range: 18-95.5) mL/min/1.73 m², respectively. All the patients had hypertension but none of them were on angiotensin-converting enzyme inhibitors or angiotensin II receptor blocker.

TABLE 3 Complications and treatment of kidney transplant recipients with SARS-CoV-2 infection

Patient	ICN level (ng/mL)	IS alteration	Treatment	Admission decision	Fever for how many days	RI for how many days	IV	RRT	Worse pCr	Graft function at discharge (pCr (mg/dL)/eGFR CKD-EPI (mL/min/1.73 m²))
1	7.3	MMF suspension	None	Home hospitalization	3	NA	No	No	NA	NA
2	10.8	MMF suspension, reduction of TAC in 50%, prednisolone 10 mg/d	Hydroxychloroquine	Hospital admission	5	5	No	No	1.39	2.2/36.9
3	12.1	MMF suspension, reduction of TAC in 25%, prednisolone 10 mg/d	None	Hospital admission	2	NA	No	No	2.31	1.42/54.8
4	12.7	MMF suspension, reduction of TAC in 25%, pred 10 mg/d	Hydroxychloroquine	Hospital admission	4	4	No	No	2.99	1.98/34.9
5	266.8	AZA and ciclosporin suspension, pred 20 mg/d	Hydroxychloroquine, broad spectrum antibiotics, systemic steroids	Hospital admission	10	10	Yes	No	4.5	4.5/9.7

Abbreviations: AZA, azathioprine; IS, imunossupression; MMF, mycophenolate mofetil; NA, not applicable; pCr, plasmatic concentration of creatinine; Pred, prednisolone; TAC, tacrolimus; RRT, renal replacement therapy; IV, invasive ventilation.

Symptoms and laboratory findings are presented in Table 2. The median duration from first symptoms to hospital admission was 8 (range 4-14) days. Four patients had a previous history of contact with at least one other patient with confirmed infection. Fever was present in all patients at admission. The three other most common symptoms were asthenia (3/5), myalgia (2/5), and diarrhea (2/5).

Three patients presented with respiratory insufficiency (RI), defined as PaO2/FiO2 < 300. On admission, one patient had leukopenia and another had lymphopenia, all had increased lactate dehydrogenase (LDH) and two had moderately increased C-reactive protein (CRP). Three patients had acute renal injury (AKI) at admission with different degrees of severity but none of the patients came to need renal replacement therapy. The complications and treatment of these patients were detailed in Table 3.

After laboratory diagnosis of SARS-CoV-2 infection, mycophenolate mofetil (MMF) was suspended in all patients and prednisolone was increased for 10 mg per day. The presence of RI or pneumonia on thoracic CT were criteria for the reduction of tacrolimus (TAC) or cyclosporine dose in 25%-50% and initiate hydroxychloroquine adjusted to renal function.

Among these who were diagnosed, only one was immediately discharged with home hospitalization due to the absence of RI after several days from the beginning of the disease. All others were admitted to hospital care.

The median time to feverish defervescence was 4 (range 2-10) days and the median time to respiratory improvement was 5 (range 4-10) days. Four patients evolved with clinical improvement and were discharged after a median time 5 (range 4-6) days.

One patient had an unfavorable clinical course. Patient 5 worsened clinically at day nine of symptoms, developing acute pulmonary edema due to hypervolemia and atrial fibrillation with rapid ventricular response requiring invasive ventilation with admission in the intensive care unit (ICU). The patient evolved with development of acute respiratory distress syndrome (ARDS) and hypertensive pneumothorax. Despite all efforts, the patient maintained feverish peaks and ascending profile of inflammatory parameters due to the presence of nosocomial infection with bacteraemia to *Serracia spp.* Unfortunately, this patient died 10 days after the onset of symptoms. No anti-retroviral or anti-IL-6 receptor mAb tocilizumab was used. Clinical evolution, outcomes, and follow-up were resumed in Table 4.

The median follow-up time since diagnosis was 30 days (range 10-37). At last evaluation, the median pCr and eGFR by CKD-EPI were 2.09 (range 1.42-4.5) mg/dL and 35.9 (range 9.7-54.8) mL/min/1.73 m², respectively.

After hospital discharged, patients maintained home care hospitalization with daily telephone contact by a doctor to assess symptoms and fever.

4 | DISCUSSION

So far, the ongoing pandemic of COVID-19 has become a one-time per century health challenge worldwide.[2]

The clinical presentation of SARS-CoV-2 infection can vary widely in severity, ranging from asymptomatic or mild symptoms to ARDS and death.[6] At the onset of disease, the most common symptoms are fever, nonproductive cough, dyspnea, myalgia, and fatigue, but some patients can experience gastrointestinal symptoms.[7] In SOTs, presentation with febrile illness accompanied by gastrointestinal symptoms may be quite common, described in 15% in one series.[8] In our experience, all patients presented with fever combined with either respiratory symptoms, myalgia, or gastrointestinal symptoms.

In the few case reports in kidney transplant recipients, the symptoms were quite variable. Gandolfini et al[9] reported that the clinical presentation and the course of disease did not vary significantly between kidney transplant and non-kidney transplant patients, while Guillen et al[10] pointed to more atypical clinical presentations, which proved to be a challenge in the differential diagnosis process. In our experience, patients presented with both typical and atypical symptoms, with fever being detected in all cases.

Decreased lymphocyte count, prolonged prothrombin time, and elevated dehydrogenase were the blood test abnormalities most frequently found.[7] Laboratory findings in our patients are detailed in Table 2. In Wang et al report, the decrease in absolute lymphocyte count was seen more frequently in patients who progressed rapidly to ARDS and sepsis.[7] Curiously, in our case series, the single patient with lymphopenia was also the only one who worsened clinically with the development of ARDS and subsequent death. However, she already had chronic renal graft dysfunction with proteinuria and presented with the most severe AKI. Other laboratory tests were elevated as triglycerides, ferritin, partial thromboplastin time, D-dimer, and pro-calcitonin levels. Platelets, liver enzymes, markers of myocardial necrosis, and rhabdomyolysis remained normal. IL-6 levels were not available.

In all cases of KT recipients with COVID-19 that described poor outcomes the immunosuppression had been withdrawn.[9-11] Considering the cytokine storm and previous publications that show that immunosuppression might be a protective factor in sepsis providing a survival advantage,[12,13] the concept of removing all the immunosuppression should be subject of discussion considering that could contribute to poor prognosis. Another factor to take in consideration is the number of years under immunosuppression. In Bhoori et al report, the deaths occurred in long-term patients rather than recently transplanted, fully immunosuppressed patients.[14]

Additionally, the many years of evolution and the several comorbidities associated with chronic kidney disease seem to be associated with an increased risk of severe disease and poor outcomes[3,6,7] of SARS-CoV-2 infection. Chen et al justify that with a weaker immune function associated with the underlying chronic diseases, such as diabetes, hypertension and cardio and vascular disease.[6] Their susceptibility seems to be related with reduced lymphocytes.[6]

Our series reports five patients with different ages and with different comorbidities. The outcomes were also variable; however, the only case that evolved unfavorably occurred in the patient with more comorbidities and with more time of chronic disease and immunosuppression. The occurrence of these cases in our unit led to the development of a protocol in order to standardize the adjustment in immunosuppression according to the severity of the infection.

So far, there is still no agreement on any best strategy to adopt in transplant recipients. Some drugs have been put forward and used off-label.[15-18] Lopinavir-ritonavir showed no benefit when compared to supportive treatment[15] and hydroxychloroquine seems to had an antiviral effect at both pre- and post-infection stages.[18] Furthermore, Gautret et al showed that the addition of azithromycin to hydroxychloroquine reduces the nasopharyngeal shedding of SARS-CoV-2.[16] In our center, the introduction of hydroxychloroquine was based on the presence of respiratory dysfunction although the lack of clinical trials in these population due the time of outbreak. Due to small sample of patients, no significant conclusion can be drawn from their use, but no adverse reactions were reported.

The optimal management of immunosuppression also remains uncertain. Most SOT recipients are subject to immunosuppressive drugs that increase the risk of opportunistic infections, including viral infections.[19-21] European transplant centers have been consistent in the early reduction of IS with the immediate suspension of the antimetabolite; in the discontinuation or major reduction of CNI; and in the increase of the steroid doses.[8-10,22] Carbajo-Lozoya reported that TAC inhibits the replication of SARS-CoV with a reduction of virus titers[23] suggesting that its maintenance in low doses could be beneficial. Even when CNI were not suspended, their levels should be monitored closely. All patients suspended MMF but CNI were maintained in 4/5 cases based on clinical severity and patient's immune risk (no dose adjustment in mild disease; 50% dose reduction in moderate disease; and suspension in severe disease). The impact of this approach is not clear.

TABLE 4 Clinical evolution, outcome, and follow-up of kidney transplant recipients with SARS-CoV-2 infection

Patient	Evolution	Outcome	Time in follow up (d)	SARS-CoV-2 repetition
1	Clinical improvement	Home hospitalization	30	NA
2	Clinical improvement	Discharge with home hospitalization	30	Stay positive (2 tests)
3	Clinical improvement	Discharged with home hospitalization	37	Stay positive (3 tests)
4	Clinical improvement	Discharged with home hospitalization	27	Cured (2 negative tests)
5	Clinical worsening	Deceased	10	NA

Overall, the best therapeutic approach and adjustment of IS in these patients are challenging. Our strategy was based on experience with other viral infections, namely cytomegalovirus, in which the first measure consists of reducing and/or withdrawing the antiproliferative drug. Our rationale was founded on the concept that poor virologic control could lead to a more severe disease and more prolonged viral shedding. Hence, the withdrawal of antiproliferative could improve the immune responses in these cases. Moreover, several international guidelines recently published have supported this approach.[4,24]

Most of the patients (3/5) experienced worsening of renal function in context of infection. At the time of discharge, there was a discrete worsening of eGFR, however, given the short follow-up time, we cannot draw conclusions regarding to the impact on the graft function and the potential recovery that still underway.

Given the small sample of patients, it is difficult to inquire about the behavior of COVID-19 in SOT recipients and whether it differs from the natural course of disease. Despite different grades of disease severity, all the infected patients presented with fever. A greater number of comorbidities, a longer time of immunosuppression and an older age seem to be correlated with more severity and worse prognosis.

AUTHORS CONTRIBUTION

Filipa Silva MD involved in research design, acquisition of the data, data analysis, and paper writing. Ana Cipriano MD involved in acquisition of the data, data analysis, and paper writing. Hugo Cruz MD involved in acquisition of the data, data analysis, and paper writing. Joana Tavares MD involved in acquisition of the data and data analysis. Joana Fragoso MD involved in acquisition of the data and data analysis. Jorge Malheiro MD, PhD involved in research design, acquisition of the data, data analysis and paper writing. Manuela Almeida MD involved in acquisition of the data, data analysis and paper writing. LaSalete Martins MD, PhD involved in acquisition of the data and data analysis. Miguel Abreu MD involved in acquisition of the data and data analysis. Sofia Pedroso MD involved in acquisition of the data and data analysis. Leonídio Dias MD involved in acquisition of the data and data analysis. António Castro-Henriques MD involved in research design and data analysis.

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