LETTER TO THE EDITORS

COVID-19 among kidney-transplant recipients requiring hospitalization: preliminary data and outcomes from a single-center in Brazil

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To the Editors,

Data on COVID-19 among solid organ transplant recipients (SOTR) are scarce, and the outcomes may differ from the general population. Recently, de Barros Machado et al. reviewed the literature on the first 40 cases with a pooled case-fatality rate of 20% [1]. We present a retrospective description of 51 kidney transplant recipients (KTR) with confirmed moderate-to-severe COVID-19 pneumonia both through positive real-time reverse transcription–polymerase chain reaction (rRT-PCR) for SARS-CoV-2 in a respiratory specimen (n = 48 patients); or positive serology IgM and/or IgG (n = 3 patients). The patients were hospitalized in a tertiary university public hospital in São Paulo metropolitan city and followed up to July 7, 2020. It is the largest Latin America hospital and its main build comprising approximately 900 beds was transformed to attend COVID-19-infected patients in response to the current outbreak.

Moderate-to-severe disease was defined by oxygen saturation (SpO_2) less than 93% in room air, respiratory rate >22 breaths per minute, axillary temperature ≥ 39°C, and/or abnormal pulmonary auscultation. Patients whose SpO_2 did not improve in spite of O_2 supply (SpO_2 < 93% with 6 l/min) or those presenting arterial hypotension, signs of peripheral hypoperfusion, decreased consciousness, or oliguria were transferred to intensive care unit (ICU). The evaluated outcome was ICU admission and the variables were compared between patients with ICU admission and those without ICU admission using chi-square, Fisher exact test, and Mann–Whitney tests, when appropriate. The threshold for significance was set at P-value < 0.05 and tests were two-tailed. All statistical analyses were performed with STATA software package (version 16.0).

Baseline characteristics, management, and outcome of the patients are presented in Table 1. The median age was 51.9 years, 55.6% were female, and comorbidities were frequent. Median time from transplantation to the onset of symptoms was 74 months. Cough, dyspnea, and fever were the most common presenting symptoms, but diarrhea was common. Laboratory evaluation at admission revealed wide variation levels. Twenty-three (45.0%) patients were admitted to ICU up to 48 h from the hospital admission. As per the institutional guideline on COVID-19 management, the majority patients (74.1%) received an association of ceftriaxone plus azithromycin for 5 days and anticoagulation prophylaxis during hospitalization). Full dose heparin was used only in cases of thromboembolic events. Antimetabolite (azathioprine and mycophenolic acid) and mTOR inhibitors were withdrawn and calcineurin inhibitors (CNI) were given at a reduced dosage for the majority patients; in those severe cases only glucocorticoid (hydrocortisone 300 mg per day or equivalent) was given. Three patients who developed acute respiratory distress syndrome received methylprednisolone (0.5 to 1.0 mg per day for 3–5 days). No patient used dexamethasone. The CNI was reintroduced during the hospital stay for those patients who recovery of COVID-19. Antimetabolite and mTOR inhibitor drug reintroduction were performed only after hospital discharge. None patient developed graft rejection and patients discharged from hospital regained graft function.

doi:10.1111/tri.13745

Table 1. Baseline characteristics, management, and outcome of hospitalized kidney-transplant recipients with confirmed COVID-19 pneumonia according to ICU admission

Variables	All patients *N* = 51	Admitted to ICU *N* = 23	Nonadmitted to ICU *N* = 28	RR (CI 95%)	*P*-value
Baseline characteristics					
Age in years (median, min-max)	51.9 (17–78)	52.4 (36–78)	51.9 (17–78)	-	0.25
Gender (Female)	26 (51.0%)	13 (56.5%)	13 (46.4%)	1.20 (0.73–1.98)	0.47
Race (White)	33 (64.7%)	12 (52.2%)	21 (75.0%)	0.61 (0.32–1.15)	0.09
Associated comorbidities					
Hypertension	45 (88.2%)	21 (91.3%)	24 (85.7%)	1.25 (0.67–2.34)	0.68
Heart diseases	13 (25.5%)	8 (34.8%)	5 (17.9%)	1.57 (0.76–3.28)	0.17
Diabetes Mellitus	25 (49.0%)	14 (60.9%)	11 (39.3%)	1.49 (0.88–2.51)	0.13
Obesity*	20 (39.2%)	12 (52.2%)	8 (28.6%)	1.61 (0.89–2.93)	0.09
Cancer	5 (9.8%)	3 (13.0%)	2 (7.4%)	1.39 (0.46–4.19)	0.65
Systemic lupus erythematosus	2 (3.9%)	1 (4.3%)	1 (3.6%)	1.10 (0.27–4.51)	>0.99
Previous tuberculosis diagnosis	2 (3.9%)	1 (4.3%)	1 (3.6%)	1.10 (0.27–4.51)	>0.99
Deceased donor	35 (68.6%)	15 (71.4%)	20 (71.4%)	1.00 (0.59–1.71)	>0.99
Time from transplant (months), median (range)	74 (0–321)	96 (0–272)	66 (0–321)	-	0.85
COVID-19 within the first 3 months post-transplant	7 (13.7%)	3 (13.0%)	4 (14.3%)	0.96 (0.48–1.91)	>0.99
Baseline immunosuppression regime					
Tacrolimus	44 (86.3%)	22 (95.7%)	22 (78.6%)	1.71 (1.12–2.62)	0.11
Mycophenolate	38 (74.5%)	19 (82.6%)	19 (67.9%)	1.39 (0.86–2.42)	0.34
Azathioprine	8 (15.7%)	2 (8.7%)	6 (21.4%)	0.68 (0.42–1.12)	0.27
Everolimus	4 (7.8%)	2 (8.7%)	2 (3.9%)	1.11 (0.40–3.05)	>0.99
Cyclosporin	7 (13.7%)	2 (8.7%)	5 (17.9%)	0.73 (0.42–1.27)	0.44
Use of ACEI	6 (11.8%)	3 (13.0%)	3 (10.7%)	1.11 (0.48–2.58)	>0.99
Use of ARB	8 (15.7%)	3 (13.0%)	5 (17.9%)	0.86 (0.47–1.57)	0.72
Use of statin	16 (31.4%)	6 (26.1%)	10 (35.7%)	0.82 (0.50–1.35)	0.46
Suspected nosocomial acquisition†	8 (15.7%)	4 (17.4%)	4 (14.3%)	1.12 (0.53–2.35)	>0.99
Days from symptoms onset to hospital admission, median (range)	7 (0–29)	6 (0–20)	7 (0–29)	-	0.38
Initial clinical presentation					
Cough	39 (76.5%)	18 (78.3%)	21 (75.0%)	1.08 (0.62–1.90)	0.79
Dyspnea	35 (68.6%)	22 (95.7%)	13 (46.4%)	2.52 (1.61–3.96)	<0.001
Fever	33 (64.7%)	16 (69.6%)	17 (60.7%)	1.19 (0.72–1.95)	0.51
Myalgia	17 (33.3%)	7 (30.4%)	10 (35.7%)	0.90 (0.54–1.50)	0.69
Diarrhea	25 (49.0%)	11 (47.8%)	14 (50.0%)	0.96 (0.59–1.58)	0.88
Anosmia	5 (9.8%)	1 (4.3%)	4 (14.3%)	0.65 (0.39–1.10)	0.36
Dysgeusia	5 (9.8%)	2 (8.7%)	3 (10.7%)	0.91 (0.37–3.49)	>0.99

Table 1. Continued.

Variables	All patients *N* = 51	Admitted to ICU *N* = 23	Nonadmitted to ICU *N* = 28	RR (CI 95%)	*P*-value
Radiological findings at ED admission					
Bilateral patchy consolidation affecting more than 50% of the lung parenchyma‡	17 (33.3%)	15 (65.2%)	2 (7.1%)	6.50 (1.75–24.21)	<0.001
Vital signals at ED admission (median, min-max)					
Heart rate (beats per min)	86 (56–162)	87 (56–162)	85 (60–120)	-	0.47
Respiratory rate (breaths/min)	22 (14–35)	25 (16–35)	20 (14–32)	-	0.01
O_2 saturation (%)	94 (88–99)	93 (80–99)	95 (88–98)	-	0.02
Maximum Temperature (°Celsius)	36.5 (34.5–38.8)	36.5 (34.5–37.6)	36.5 (35.7–38.8)	-	0.51
Mean arterial pressure (mmHg)	93.3 (57.3–123.0)	91.6 (57.3–123.0)	96.6 (66.6–122.6)	-	0.28
$SatO_2/FiO_2$ ratio	438 (80–466)	237 (80–457)	448 (261–467)	-	<0.001
AKI stage I at ED admission§	30 (58.8%)	16 (69.6%)	14 (50.0%)	1.43 (0.88–2.33)	0.16
Respiratory failure at ED admission¶	20 (39.2%)	19 (37.3%)	1 (2.0%)	17.42 (2.57–118.24)	<0.001
Laboratory findings at ED admission					
Serum lactate (mmol/L)	11.5 (1.5–30)	13 (6–30)	11.5 (1.5–17)	-	0.10
Lactate dehydrogenase (U/L)	356 (157–1280)	464 (209–1280)	297 (157–445)	-	<0.001
C-reactive protein (mg/L)	87 (5–500)	95 (5–500)	77 (6–253)	-	0.21
Lymphocytes count (per mm^3)	540 (120–1680)	486 (120–1680)	630 (240–1420)	-	0.19
Neutrophils count (per mm^3)	3810 (1100–19380)	4150 (1100–19380)	3505 (1200–8000)	-	0.27
Platelets count (per $mm^3 \times 10^3$)	185 (17–393)	185 (17–360)	187 (96–393)	-	0.71
D-dimer (ng/mL)	1041 (190–85506)	1173 (372–85506)	994 (190–29408)	-	0.51
ALT (U/L)	26 (6–81)	37 (9–81)	19 (6–45)	-	0.002
AST (U/L)	30 (10–135)	48 (10–135)	25 (11–51)	-	<0.001
eGFR (MDRD) (ml/minute)**	24.4 (5.0–100)	22.3 (9.4–100)	29.4 (5.0–79.6)	-	0.38
Management of COVID-19					
Initial antimicrobial therapy					
Macrolide	30 (58.8%)	13 (56.5%)	17 (60.7%)	0.92 (0.55–1.55)	0.76
Narrow-spectrum for GNB	35 (68.6%)	16 (69.6%)	19 (67.9%)	1.04 (0.61–1.76)	0.90
Broad-spectrum for GNB	6 (11.8%)	3 (13.0%)	3 (10.7%)	1.11 (0.48–2.58)	>0.99
Glycopeptide	2 (3.9%)	1 (4.3%)	1 (3.6%)	1.10 (0.27–4.51)	>0.99
No antimicrobial	9 (17.7)	3 (13.0%)	6 (21.4%)	0.70 (0.26–1.86)	0.34
Anticoagulation prophylaxis with enoxaparin or unfractionated heparin**	48 (94.1%)	22 (95.7%)	26 (92.9%)	1.23 (0.53–2.86)	>0.99
Immunosuppression modification					
Unchanged	0	0	0		
Withdrawn antimetabolite and mTOR inhibitors drugs and maintain steroid and CNI at reduced dose	32 (62.7%)	6 (26.1%)	26 (92.9%)	7.72 (2.06–28.94)	<0.001

Table 1. Continued.

Variables	All patients $N = 51$	Admitted to ICU $N = 23$	Nonadmitted to ICU $N = 28$	RR (CI 95%)	*P*-value
Withdrawn antimetabolic and CNI and maintain steroid (hydrocortisone)	19 (37.3%)	17 (73.9%)	2 (7.1%)		
Outcomes of kidney transplant recipients with COVID-19					
Renal replacement therapy during hospital stay	13 (25.5%)	12 (52.2%)	1 (3.6%)	9.24 (1.39–61.39)	<0.001
Proven bacterial coinfection during hospital stay	17 (33.3%)	12 (23.5%)	5 (9.8%)	2.30 (1.06–4.98)	0.01
CMV positive viremia during hospital stay at weekly surveillance protocol with indication of antiviral treatment	8 (15.7%)	6 (11.8%)	2 (3.9%)	2.42 (0.71–8.23)	0.12
Thromboembolic event**	7 (13.7%)	7 (30.4%)	0	-	0.002
Length of hospital stay, days (median, min-max	15 (2–45)	20 (5–45)	8 (2–28)	-	<0.001
Mechanical ventilation uses during hospital stay	17 (33.3%)	17 (73.9%)	0	5.57 (2.74–11.71)	<0.001
Death	13 (25.5%)	13 (56.5%)	0	-	<0.001

ICU, intensive care unit; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blockers; ED, emergency department; AKI, acute kidney injury; CMV, cytomegalovirus; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate (ml/min/1.73 m^2).

*Defined as body index mass of 30 or higher.

†Suspected for patients developing COVID-19 symptoms after at least 5 days from the hospital admission.

‡Thoracic CT scan at the hospital admission was available for 37 patients.

§Acute kidney failure (AKI) stage I according to KDIGO definition and classification.

¶Defined as $PaO_2 < 60$ mmHg, $SpO_2 < 91\%$ or $PaO_2/FiO_2 < 300$ in room air.

**Calculated by the Simplified Modification of Diet in Renal Disease (MDRD) equation.

††Unfractionated heparin was indicated for patients with eGFR < 30/ml/min/1.73 m^2.

‡‡Thromboembolic events: myocardial infarction ($n = 1$); deep venous thrombosis ($n = 6$).

Bacterial coinfection was proven in 17 cases, mostly urinary tract infection; one case had a concomitant miliary tuberculosis diagnosis (both COVID-19 and tuberculosis confirmed by positive specific PCR). There was no confirmed respiratory virus coinfection. CMV positive viremia was identified in 5 (18.5%) patients – three cases were classified as probable disease and two cases were considered asymptomatic viremia above treatment threshold. All cases were treated appropriately with intravenous ganciclovir for at least two weeks.

The overall mortality rate was 25.5%. No patients died in the non-ICU group. At hospital admission, patients admitted to ICU up to 48 hours from hospital admission had more frequently dyspnea (P-value < 0.001), larger pulmonary involvement area (P-value < 0.001), higher rate of respiratory failure (P-value < 0.001), and higher LDH (P-value = 0.002) and alanine (P = value = 0.002) and aspartate (P-value < 0.001) aminotransferases levels compared with those with a non-ICU admission. No significant differences were found for the other baseline characteristics.

Brazil is currently the second country in the world in absolute number of COVID-19 totally about 1.5 millions of reported cases at the end of June 2020 and is the second country in the world in absolute number of kidney and liver transplant procedures; moreover, São Paulo state is the epicenter of COVID-19 Brazilian pandemic [2] and is responsible for about one third of kidney transplant performed in the country [3]. Therefore, we have faced a constant challenge to assist transplant recipients in a COVID-19 referral hospital during a pandemic period.

Cough, dyspnea, and fever were the major presentation in this series of patients, similar to the general population with COVID-19 [4,5]. However, gastrointestinal manifestations have been more frequent compared with the lower incidence in the general population (3.8%) [4]; in accordance with our results, previous studies have shown that gastrointestinal symptoms ranged from 15% to about 30% among transplant recipients [6–9]. Possible explanations for the higher incidence of gastrointestinal symptoms in the transplant patients might be disease severity, increased viral replication, concomitant use of drugs that cause diarrhea, such as mycophenolic acid, or CMV coinfection.

We showed a significant graft dysfunction during the hospitalization period in this population. AKI incidence have ranged from 30% to 60% in KTR [6,10,11], a higher incidence compared with the general population (ranging from 0.5% to 22%) [4,5,12]. Both inflammation caused by the cytokine storm syndrome related to COVID-19 and direct kidney infection by SARS-CoV-2 in tubules expressing ACE might explain the high incidence of renal abnormalities in these patients [13]. Virus RNA has been identified in urine and in a localized pattern in tubular epithelium cells [14].

No patient from our cohort received antiviral or other experimental therapy. Data regarding immunosuppression management for transplant recipients with COVID-19 disease have been limited to case and series reports. Given the reported fatality rates, it seems unlikely that common transplant immunosuppression would attenuate the COVID-19 hyperinflammatory response and ultimately lead to more favorable outcomes. Although tacrolimus strongly inhibited other coronaviruses in vitro [15], its effect against SARS-CoV-2 is unknown [16]. Additionally, mycophenolate-treated animals had worse outcomes in a MERS-CoV experimental study [17], thus supporting the common practice of mycophenolate withdrawal for COVID-19.

In this case series, the fatality rate of 25.5% among KTR with moderate-or-severe COVID-19 pneumonia was quite similar to the fatality rates reported among hospitalized patients with COVID-19 pneumonia in the general population, ranging from 11% to 28% [5,12]. It is no surprise that fatality rates among hospitalized patients are greater than the reported overall rate of 6.9% in the general population [18]. Fatality rates vary greatly because they depend on diagnostic capacity to identify oligo and asymptomatic patients with SARS-CoV-2, the healthcare system capacity to attend severe patients, the incidence of the risk factors for mortality and probably other factors that remain unknown.

Our study has some intrinsic limitations, as the small number of patients, and the observational retrospective design. In addition, as a reference COVID-19 center, our hospital has been designed to receive more severe cases of the disease requiring hospitalization. Therefore, the case-fatality rate found in this study can be biased and overestimated.

In conclusion, we showed our initial experience with KTR with moderate-to-severe COVID-19 pneumonia admitted to hospital and treated with supportive therapy and no experimental drugs. Clinical and laboratory markers to identify transplant patients with higher risk of severe disease remain undefined.

Conflicts of interest

The authors of this manuscript have no conflicts of interest to disclose as described by the *Transplant International*.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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