



## COVID-19 Infection in Kidney Transplant Recipients: A Single-Center Case Series of 22 Cases From Belgium

Arnaud Devresse, Leila Belkhir, Bernard Vo, Benoit Ghaye, Anaïs Scohy, Benoit Kabamba, Eric Goffin, Julien De Greef, Michel Mourad, Martine De Meyer, Jean-Cyr Yombi, and Nada Kanaan

**Rationale & Objective:** The world is facing a global pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Although kidney transplant recipients are at increased risk for viral infections, the impact of their chronic immunosuppressed status on the risk for acquiring coronavirus disease 2019 (COVID-19) and disease severity is unknown.

**Study Design:** All cases of COVID-19 infection in our cohort of kidney transplant recipients were prospectively monitored. Clinical features, management, and outcomes were recorded. A standard strategy of immunosuppression minimization was applied: discontinue the antimetabolite drug and reduce trough levels of calcineurin or mammalian target of rapamycin inhibitors. Unless contraindicated, hydroxychloroquine was administered only to hospitalized patients.

**Setting & Participants:** 22 COVID-19 infections were diagnosed in our cohort of 1,200 kidney transplant recipients.

**Results:** Most common initial symptoms included fever, cough, or dyspnea. 18 (82%) patients

required hospitalization. Of those patients, 3 had everolimus-based immunosuppression. Computed tomography of the chest at admission (performed in 15 patients) showed mild (n = 3), moderate (n = 8), extensive (n = 1), severe (n = 2), and critical (n = 1) involvement. Immunosuppression reduction was initiated in all patients. Hydroxychloroquine was administered to 15 patients. 11 patients required supplemental oxygen; 2 of them were admitted to an intensive care unit (ICU) with mechanical ventilation. After a median of 10 days, 13 kidney transplant recipients were discharged, 2 were hospitalized in non-ICU units, 1 was in the ICU, and 2 patients had died.

**Limitations:** Small sample size and short follow-up.

**Conclusions:** The clinical presentation of COVID-19 infection was similar to that reported in the general population. A standard strategy of immunosuppression minimization and treatment was applied, with 11% mortality among kidney transplant recipients hospitalized with COVID-19 infection.

Complete author and article information provided before references.

Correspondence to N. Kanaan ([nada.kanaan@uclouvain.be](mailto:nada.kanaan@uclouvain.be))

*Kidney Med.* 2(4):459-466. Published online June 15, 2020.

doi: 10.1016/j.xkme.2020.06.001

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Since the first case was diagnosed in Wuhan, China, in December 2019, the world has faced a rapidly growing outbreak of a newly discovered contagious infectious disease: coronavirus disease 2019 (COVID-19). COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and primarily manifests as an acute respiratory illness with interstitial and alveolar pneumonia, but can affect multiple organs, such as heart, kidney, digestive tract, blood, and central nervous system.<sup>1</sup> As of April 18, 2020, a total of 2,338,335 cases of COVID-19 infection have been confirmed in more than 185 countries and territories and at least 161,030 deaths have been reported to date.<sup>2</sup>

In Belgium, the first case of COVID-19 infection in the general population was diagnosed on February 4, 2020. To date, more than 42,000 cases have been reported, including more than 12,000 hospitalizations.<sup>3</sup>

Specific questions arise for transplant recipients who are facing COVID-19 infection. As with other infections, could the risk for acquiring COVID-19 be increased due to the chronic state of immunosuppression? Will the infection be more severe than in patients with normal immunity? Moreover, how should immunosuppressive therapy be handled in that context?

Case reports of COVID-19 infection in kidney transplant recipients<sup>4-13</sup> and limited case series<sup>14-16</sup> with a small number of patients have been published to date. In this study, we report 22 COVID-19 disease cases among our cohort that currently includes 1,200 kidney transplant recipients followed up in our academic institution in Belgium.

## METHODS

### Patient Selection

Before the outbreak onset, about 1,200 kidney transplant recipients who underwent transplantation and were followed up in our hospital in collaboration with peripheral centers were recorded in our database as alive with a functioning graft. Since the first case of COVID-19 infection was diagnosed in Belgium, we have been prospectively monitoring all cases of proven COVID-19 infection in our cohort of kidney transplant recipients followed up in our academic center. Colleagues from peripheral centers with whom we share routine follow-up and managerial decisions of patients were invited by mail to report on all their patients with COVID-19 infection. To date, 22 kidney transplant recipients have been diagnosed with COVID-19 infection (n = 14 in our transplantation center and n = 8 in

**PLAIN-LANGUAGE SUMMARY**

Specific questions arise for kidney transplant recipients who are facing coronavirus disease 2019 (COVID-19) infection. As with other infections, the risk for acquiring COVID-19 might be increased due to the chronic state of immunosuppression. Also, the disease could present with increased severity with eventually poor outcome. Moreover, handling immunosuppression in that context can be challenging. We report our experience with 22 kidney transplant recipients followed up at our academic center in Belgium, in whom we applied a standard strategy of immunosuppression minimization and treatment. Clinical symptoms were similar to those reported in the general population. Among kidney transplant recipients hospitalized with COVID-19 infection, 11% died. Our study expands the knowledge base of COVID-19 infection in kidney transplant recipients.

peripheral centers). Clinical features, management, and outcomes were recorded.

The study was approved by the local ethics committee (Comité d’Ethique Hospitalo-Facultaire Saint-Luc- Brussels-Belgium; approval number: B 403). The need for informed consent was waived due to deidentified information.

**Impact of COVID-19 on Daily Transplantation Activities**

Since the onset of the COVID-19 outbreak in Belgium, daily transplantation activities have been severely affected in the whole country. Kidney transplantation is considered only in patients with “high-urgency” status (ie, imminent lack of access for dialysis or psychiatric contraindication to dialysis) or in hypersensitized patients on the waiting list for more than 5 years. In our center, no kidney transplantations have been performed since March 1, 2020. The activity of the outpatient clinic has also been dramatically reduced. Patients were advised very early to stay at home, avoid public transportation and unnecessary contact, and report every symptom before coming to the outpatient clinic. The vast majority of consultations are made by telephone and patients are asked to come in our center only if they underwent transplantation less than 6 months ago or if they have an unstable clinical situation (increase in serum creatinine level, new-onset proteinuria,...), or newly developed symptoms. In case of COVID-19 infection suspicion, patients were sent to a dedicated COVID unit at the emergency department.

**Diagnosis**

All kidney transplant recipients presenting symptoms compatible with COVID-19 infection were tested and fully evaluated by a physician (clinical evaluation, chest x-ray, and/or pulmonary computed tomography [CT] and nasopharyngeal swab for reverse-transcriptase polymerase

chain reaction [PCR] laboratory test). The laboratory diagnosis of SARS-CoV-2 infection was confirmed by using the Coronavirus COVID-19 genesig Real-Time PCR assay (Primerdesign Ltd) on a nasopharyngeal swab, targeting the RNA-dependent RNA polymerase (RdRp) gene. The amplification was performed on the LightCycler 480 instrument (Roche Diagnostics) according to the manufacturer’s recommendations. A cycle threshold value less than 40 was defined as a positive test.

**Assessment of Pulmonary Involvement Using CT**

In patients in whom CT of the chest was performed at admission, the type of lesion and degree of pulmonary parenchyma involvement were reported using the French Society of Radiology classification.<sup>17</sup>

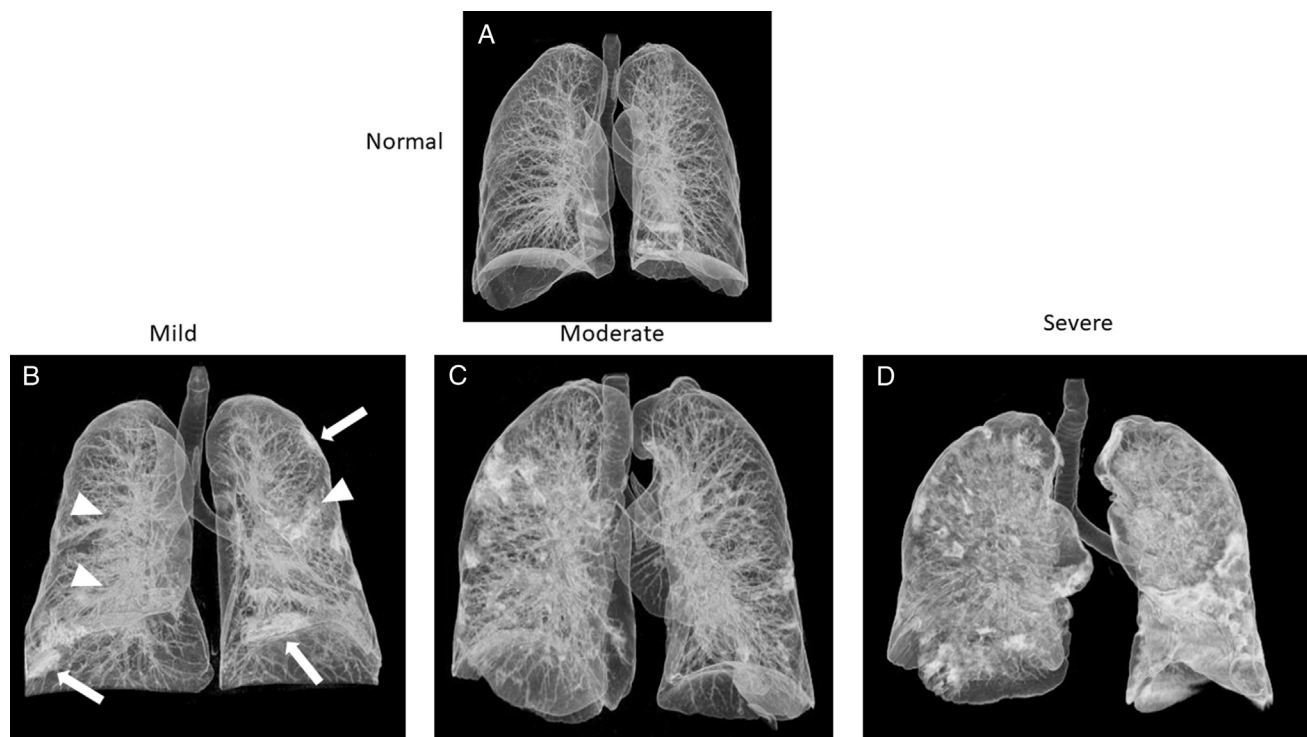
Pulmonary involvement is classified as mild (<10%), moderate (10%-25%), extensive (25%-50%), severe (50%-75%), or critical (>75%). Figure 1 illustrates 3 CT patterns: mild, moderate and severe patterns, respectively.

**Treatment and Management of Immunosuppression**

Kidney transplant recipients receive standard immunosuppression in our center, based on a combination of tacrolimus, mycophenolate, and steroids. Daily mycophenolate and steroid doses are 1 g and 4 mg, respectively. Tacrolimus trough levels are 10 to 13 ng/mL during the first month, 7 to 10 ng/mL for the next 2 months, and then 5 to 7 ng/mL. Everolimus is used in case of history of cancer or calcineurin inhibitor nephrotoxicity with a trough level of 5 to 7 ng/mL. Cyclosporine therapy is continued in patients who underwent transplantation before the use of tacrolimus or because of tacrolimus intolerance with trough levels of 50 to 70 ng/mL. Azathioprine is used at a daily dose of 1 mg/kg in case of mycophenolate intolerance or pregnancy desire.

For COVID-19–infected kidney transplant recipients, we have designed a standard strategy of immunosuppression minimization and treatment, which was sent to our colleagues from peripheral centers at the onset of the outbreak. In all cases, treatment with the antimetabolite drug (mycophenolate or azathioprine) is stopped; the daily dose of tacrolimus, cyclosporine, or everolimus is reduced to reach trough levels at 3 to 5 ng/mL, 30 to 40 ng/mL, and 3 to 5 ng/mL, respectively. The routine steroid dose is unchanged (4 mg/d of methylprednisolone). In case of life-threatening situations (eg, critical admission in the intensive care unit [ICU]), tacrolimus, cyclosporine, or everolimus treatment is stopped. Adjunctive treatment with corticosteroids has been provided to some patients after careful case-by-case evaluation, considering the extent of respiratory involvement and hyperinflammatory status.

In all kidney transplant recipients requiring hospitalization, following interim Belgian recommendations,<sup>18</sup> hydroxychloroquine can be administered in patients with no cardiac contraindication at the discretion of the



**Figure 1.** Images are presented in 3-dimensional volume-rendering technique mode to allow an optimal comparison between patients on a single frontal view. (A) Healthy patient. Only the lung contours and walls of bronchi and pulmonary vessels can be depicted. The normal lung parenchyma containing air appears in black. (B) Patient with mild coronavirus disease 2019 (COVID-19) involvement. Ground glass opacities (GGOs) appear in grey (arrowheads) mostly in the central part of the lungs, while consolidations appear in white in the peripheral and basal parts of both lungs (long arrows). (C) Patient with moderate COVID-19 involvement. The GGO is more extensive than in B, while consolidations are prominent in the right upper area. (D) Patient with severe COVID-19 involvement. Both lungs are involved with extensive central and peripheral GGOs. Consolidations are preferentially seen in the peripheral parts of both lungs.

physician depending on the patient clinical situation for 5 days (400 mg twice daily day 1 and then 200 mg twice daily up to day 5; for estimated glomerular filtration rates  $< 30$  mL/min/1.73 m<sup>2</sup>, 400 mg twice daily day 1 and then 200 mg/d up to day 5). Hydroxychloroquine treatment is initiated only if the corrected QT interval on the electrocardiogram is  $> 500$  milliseconds.

## RESULTS

### Baseline Characteristics

From March 14, 2020, to April 15, 2020, a total of 22 COVID-19 infections were diagnosed in our cohort. Four patients were mildly ill and were sent back home after their first clinical evaluation. In all 4 patients, the antimetabolite treatment was stopped. They were called by telephone at least twice a week by a transplant physician. Symptoms rapidly improved in all 4 patients.

Eighteen patients required hospitalization. Their baseline characteristics are summarized in Table 1. Except for 2 patients, all had comorbid conditions, including treated hypertension, treated diabetes, history of cardiovascular event, obesity, dementia/intellectual disability, and active metastatic malignancy.

### Clinical, Laboratory, and Radiologic Presentation at Diagnosis

The clinical, laboratory, and radiologic presentation of the 18 hospitalized patients is summarized in Table 1. Interestingly, patient 18 (Table 2), currently in the ICU, showed the highest C-reactive protein (CRP) level. Fifteen underwent CT of the chest at admission. Pulmonary lesions were classified as mild ( $n = 3$ ), moderate ( $n = 8$ ), extensive ( $n = 1$ ), severe ( $n = 2$ ), and critical ( $n = 1$ ), respectively.

### Management of Hospitalized Patients

The management and outcomes of hospitalized patients are described in Table 2. With the exception of 1 patient (patient 7, discussed later), our local protocol of immunosuppression minimization was applied: the antimetabolite treatment was stopped and the tacrolimus/cyclosporine/everolimus dose was reduced to reach trough level targets, as per protocol. Fifteen of the 18 (83%) hospitalized patients were treated with hydroxychloroquine and 2 (11%) had an increase in steroid doses (Table 2). We did not observe cardiac side effects during hydroxychloroquine treatment. However, we observed an

**Table 1.** Characteristics of the 18 Hospitalized COVID-19–Infected Kidney Transplant Recipients

Characteristics	Population (n = 18)
Age, y	57 (41-73)
Women	10 (56%)
Race	
White	11 (61%)
North African	4 (22%)
Asian	1 (6%)
Black	2 (11%)
Delay from KT, mo	89 (1-402)
ACE inhibitor/ARB use	10 (56%)
Comorbid conditions	
Hypertension	14 (78%)
Diabetes	4 (22%)
Cardiovascular	4 (22%)
Obesity	4 (22%)
Active malignancy	1 (6%)
Dementia/intellectual disability	2 (11%)
Immunosuppression	
Induction <sup>a</sup>	6 (33%)
Tac/MPA/St	7 (39%)
Tac/Aza/St	1 (6%)
Tac/St	2 (11%)
EVL/MPA/St	3 (16%)
Csa/MPA/St	2 (11%)
Csa/Aza/St	2 (11%)
Csa/St	1 (6%)
Clinical presentation	
Fever	14 (78%)
Cough	12 (67%)
Dyspnea	7 (39%)
Digestive symptoms	5 (28%)
Neurologic symptoms	3 (16%)
Radiological presentation on CT <sup>b</sup>	
Mild	3/15 (20%)
Moderate	8/15 (53%)
Extensive	1/15 (7%)
Severe	2/15 (13%)
Critical	1/15 (7%)
Laboratory parameters at admission	
Baseline eGFR, mL/min/1.73 m <sup>2</sup>	45 (15-95)
C-Reactive protein, mg/L <sup>c</sup>	56 (1.5-314)
Lymphocyte count, /μL <sup>d</sup>	730 (50-1440)

Note: Values for categorical variables are given as number (percent); values for continuous variables are given as median (range).

Abbreviations: ACE, angiotensin-converting-enzyme; ARB, angiotensin II receptor blocker; Aza, azathioprine; COVID-19, coronavirus disease 2019; Csa, cyclosporine; CT, computed tomography; eGFR, estimated glomerular filtration rate; EVL, everolimus; KT, kidney transplantation; MPA, mycophenolate; Tac, tacrolimus; St, steroids.

<sup>a</sup>Antithymocyte globulin (n = 4) or basiliximab (n = 2).

<sup>b</sup>Available for 15 patients.

<sup>c</sup>Normal value < 5.0 mg/L.

<sup>d</sup>Normal value of 800 to 5,000/μL.

increase in tacrolimus trough levels in 5 patients after the initiation of hydroxychloroquine treatment. One patient (patient 2) also received 5 days of intravenous cefuroxime because of suspected additional pulmonary infection.

Eleven (61%) patients received supplemental oxygen during hospitalization. Only 2 patients were transferred to the ICU and received invasive ventilation (patients 2 and 18). Both were receiving everolimus because of a history of cancer. Patient 2 was a man in his 60s with a history of osteosarcoma of the thigh and was known for advanced dementia with Lewy bodies. He was admitted for dyspnea and worsening confusion. Chest x-ray findings were compatible with COVID-19 infection that was confirmed by reverse-transcriptase PCR in a nasopharyngeal swab. Oxygen saturation level was normal at admission, but his neurologic status deteriorated within hours, associated with severe hypercapnia. He was admitted to the ICU and rapidly intubated. Nevertheless, the clinical situation improved promptly and invasive ventilation was stopped after 48 hours. He was sent back home 10 days after admission.

Patient 18 was a man in his 40s with a history of Hodgkin cervical lymphoma at age 15 years. He was admitted for fever, dyspnea, dry cough, and diarrhea. Clinical workup showed mild hypoxemia requiring oxygen at 2 L/min using a nasal cannula. CT of the chest showed bilateral pneumonia classified as moderate. Mycophenolate treatment was stopped and hydroxychloroquine treatment was started. However, oxygen needs increased progressively. Five days after admission, the patient showed signs of severe respiratory distress with hypoxemia. He was admitted to the ICU and rapidly intubated. Everolimus treatment was stopped and steroid dosages were increased at 16 mg/d of methylprednisolone for 2 days and then at 1 mg/kg (80 mg) per day because he did not improve. At the time of writing of this report, his condition remains critical, requiring invasive ventilation with a high level of oxygen (fraction of inspired oxygen of 100%).

Five cases of acute kidney injury (defined as plasma creatinine increase > 50% from baseline or plasma creatinine increase  $\geq$  0.3 mg/dL)<sup>19</sup> were observed during hospitalization (28%). However, acute kidney injury rapidly resolved with intravenous hydration, and no patient required dialysis. Overall, kidney function remained stable in the hospitalized patients (Table 2). Baseline estimated glomerular filtration rate (calculated using the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation) before COVID-19 infection was 45 (range, 15-95) mL/min/1.73 m<sup>2</sup> versus 38 (range, 15-101) mL/min/1.73 m<sup>2</sup> at last follow-up. One patient (patient 9) presented with an acute pyelonephritis associated with bacteremia during hospitalization, but rapidly responded to antibiotic treatment.

## Outcomes

After a median follow-up of 18 (range, 5-30) days, 13 (72%) of the 18 hospitalized patients recovered and were sent home (no readmissions to date) after a median of 10 (range, 2-26) days. Three (17%) patients are still currently hospitalized in our institution, and 2 (11%) have died. Both patients (patients 7 and 8) who died from COVID-19 infection also presented with very severe comorbid

**Table 2.** Clinical Features of the 18 Hospitalized COVID-19–Infected Kidney Transplant Recipients

Patient	Length of Stay, d	Age, y	Sex	Delay From KT, mo	IS	Symptoms	CT	IS Management	Other Treatment	O <sub>2</sub>	AKI	ICU	Outcome
1	13	50s	M	191	Tac-MPA-St	Fever+C+Dig	Severe	Stop MPA ↘ Tac	HC	NC	No	No	Home
2	10	60s	M	102	EVL-MPA-St	D+C+N	ND	Stop MPA ↘ EVL	HC <sup>a</sup>	NC + IV	No	Yes, 2 d	Home
3	16	60s	F	1	Tac-MPA-St	Fever+D+C	Moderate	Stop MPA ↘ Tac	HC	No	No	No	Home
4	16	60s	F	250	Tac-St	N+Dig	Moderate	↘ Tac	HC	No	No	No	Home
5	17	50s	M	2	Tac-MPA-St	Fever+C	Moderate	Stop MPA ↘ Tac	HC + ↗ steroids <sup>b</sup>	NC	Yes	No	Home
6	17	60s	M	357	Csa-St	Fever+C	Mild	None	HC	NC	No	No	Home
7	2	60s	F	260	Csa-MPA-St	Fever+D+C+N	ND	None	No	No	No	No	Death <sup>c</sup>
8	20	50s	F	101	Tac-Aza-St	C	Moderate	Stop Aza ↘ Tac	HC	NC	Yes	No	Death <sup>c</sup>
9	26	60s	F	36	Tac-MPA-St	Fever+C	Moderate	Stop MPA ↘ Tac	HC <sup>d</sup>	NC	Yes	No	Home
10	3	50s	F	402	CsA-Aza-St	Fever+Dig	Mild	Stop Aza	No	NC	No	No	Home
11	6	40s	F	268	Csa-MPA-St	Fever+C+D	Moderate	Stop Aza ↘ Csa	HC	No	No	No	Home
12	Ongoing	40s	F	376	Csa-Aza-St	Fever+C+Dig	ND	Stop Aza ↘ Csa	No	No	No	No	Non-ICU COVID unit
13	7	40s	F	3	EVL-MPA-St	Fever	Extensive	Stop MPA ↘ EVL	HC	No	No	No	Home
14	7	50s	M	74	Tac-MPA-St	Fever+C+D	Mild	Stop MMF ↘ Tac	HC	NC	No	No	Home
15	8	50s	M	48	Tac-St	Asthenia	Severe	None <sup>e</sup>	HC	NC	Yes	No	Home
16	10	70s	M	10	Tac-MPA-St	Fever	Moderate	Stop MPA ↘ Tac	HC	No	No	No	Home
17	Ongoing	60s	F	5	Tac-MPA-St	Fever+D	Critical	Stop MPA ↘ Tac	HC	NC	No	No	Non-ICU COVID unit
18	Ongoing	40s	M	77	EVL-MPA-St	Fever+C+D+Dig	Moderate	Stop MPA Stop EVL	HC + ↗ steroids <sup>f</sup>	NC +IV	Yes	Yes, ongoing	ICU, critical

Abbreviations: AKI, acute kidney injury; Aza, azathioprine; C, cough; COVID-19, coronavirus disease 2019; Csa, cyclosporine; CT, computed tomography; D, dyspnea; Dig, digestive symptoms; EVL, everolimus; F, female; HC, hydroxychloroquine; ICU, intensive care unit; IS, immunosuppression; IV, invasive ventilation; KT, kidney transplantation; M, male; MMF, mycophenolate mofetil; MPA, mycophenolate; N, neurologic symptoms; NC, nasal cannula; ND, not done; Tac, tacrolimus; St, steroids.

<sup>a</sup>This patient received 5 days of intravenous cefuroxime for suspected concomitant bacterial infection.

<sup>b</sup>Three-day course of methylprednisolone, 32 mg/d.

<sup>c</sup>No ICU because of severe comorbid conditions, death in palliative unit.

<sup>d</sup>This patient received antibiotics for concomitant acute pyelonephritis.

<sup>e</sup>Tac already reduced for BK virus viremia.

<sup>f</sup>Methylprednisolone, 16 mg/d, for 2 days and then 1 mg/kg (ongoing).

conditions: the first had metastatic uterine carcinoma and was terminally ill, and the second had severe active scleroderma associated with very impaired general health status, which had been deteriorating during the past months. Both patients were considered terminally ill and died in palliative care units. The rate of death of hospitalized COVID-19–infected kidney transplant recipients in our cohort is 11.1% (2/18).

The severity of pulmonary parenchyma involvement on CT performed at admission did not seem to influence outcome. For example, both patients who showed the most severe involvements on CT (patients 15 and 17) had rapidly favorable clinical evolutions (the first patient was dismissed from the hospital after 8 days and the second patient, though still hospitalized, no longer requires supplemental oxygen). Conversely, patient 18, who is currently intubated in the ICU, needing very high levels of oxygen, had moderate pulmonary involvement on CT at admission.

## DISCUSSION

Because of their chronic immunosuppressed status, kidney transplant recipients are at increased risk for many viral infections (cytomegalovirus, herpes zoster, norovirus infections...).<sup>20,21</sup> Thus, higher rates of infection with COVID-19 and/or increased severity of the disease in our transplant population was feared. However, in past epidemics with Middle East respiratory syndrome (MERS) and SARS-CoV-1, this increased risk was not observed.<sup>22</sup>

As in the general population,<sup>1</sup> the most common symptoms in our cohort of kidney transplant recipients with COVID-19 infection were fever, dry cough, and dyspnea. As reported,<sup>5,23,24</sup> we also observed some atypical presentations with predominant digestive symptoms and acute confusion. Interestingly, the severity of pulmonary involvement on CT of the chest at admission was not associated with worse clinical outcome. Some patients with images of severe pulmonary involvement recovered well, whereas the only patient currently in the ICU had moderate involvement at admission with subsequent dramatic evolution. This suggests that CT of the chest at admission is useful for diagnosis but does not provide prognostic information. However, other factors may affect the severity of the pulmonary involvement on the first CT of the chest, such as the interval between the onset of symptoms and the CT and the presence of underlying chronic pulmonary diseases. Little is known about early markers that may predict the clinical evolution. Tan et al<sup>25</sup> recently showed that CRP level increased early in severe COVID-19 infection, before CT findings, suggesting that the initial evolution of CRP levels might provide more prognostic information than early CT. In line with this hypothesis, patient 18 (Table 1) showed a rapid increase in CRP level from 90 mg/L on the day of admission to 304 mg/L on the day of transfer to the ICU (6 days after).

The current management of COVID-19 disease in kidney transplant recipients still remains ill-defined despite guidelines provided by many scientific societies.<sup>26–28</sup> All these guidelines suggest drastically reducing immunosuppression, especially in clinical situations requiring admittance to the ICU. Of course, no randomized controlled trials have been conducted to assess how immunosuppression should be reduced and how to resume it after remission.

One important question is the optimal management of kidney transplant recipients who are receiving a mammalian target of rapamycin inhibitor (mTORi)-based regimen. Though mTORis are known to reduce the risk for developing cytomegalovirus or BK virus infections after kidney transplantation,<sup>29</sup> their impact on SARS-CoV-2 is currently unknown. mTORis are believed to lead to a proinflammatory status by increasing the production of some cytokines, including interleukin 12 (IL-12), IL-6, IL-1, and IL-23), and tumor necrosis factor  $\alpha$ . Thus, the mTORi capacity to boost the deleterious inflammatory response involved in COVID-19 infection is an important yet unresolved question. In this context, some guidelines<sup>26,27</sup> have advocated withdrawing mTORis in all COVID-19–infected kidney transplant recipients requiring hospitalization. In our cohort, 3 (16.6%) of the 18 hospitalized kidney transplant recipients had mTORi-based immunosuppression. mTORi treatment was reduced, but maintained, in 2 patients (patients 2 and 13) who finally recovered. By contrast, mTORi treatment was stopped the day patient 18 was admitted to the ICU. He is to date the only patient who has developed such a severe pulmonary illness. Factors associated with worse respiratory outcomes still need to be identified. In patient 18, besides mTORi, comorbid conditions and history of cancer might have put him at risk for untoward evolution. Genetic background such as HLA antigen polymorphisms or angiotensin-converting enzyme polymorphism could also be implicated in the individual response to infection; their precise identification will probably shed some light on how to better handle infection in high-risk populations.<sup>30,31</sup>

Eighty-three percent of our hospitalized kidney transplant recipients received hydroxychloroquine. Early reports suggest a role for hydroxychloroquine in reducing the viral load.<sup>32</sup> However, the impact of hydroxychloroquine on the clinical outcome of COVID-19–infected patients is largely unknown and highly debated. Even if hydroxychloroquine was safely used in our cohort, we cannot draw any conclusion regarding its efficacy because of the absence of a control group. The currently recruiting DISCOVERY and SOLIDARITY trials (NCT04315948 and NCT04321616, respectively) will provide some answers regarding treatment efficacy in the general population. The results of these trials will then need to be extrapolated to the kidney transplant recipient population.

None of our patient received the antivirals currently in the pipeline<sup>33</sup> or promising specific anti-inflammatory drugs such as the anti-IL-6 tocilizumab<sup>34</sup> because of

their unavailability outside of a clinical trial. Interesting data regarding the use of tocilizumab were reported by Alberici et al<sup>15</sup> in 6 kidney transplant recipients with severe pneumonia: 3 patients experienced reduction in oxygen requirements and 2 showed improvement in radiologic findings. Two patients eventually died and 1 was discharged from the hospital 9 days after tocilizumab administration.<sup>15</sup>

In our cohort, the kidney function outcome was satisfactory. Although 28% of hospitalized patients experienced acute kidney injury, none required hemodialysis. Moreover, kidney function rapidly stabilized after appropriate hydration. To date, we have not observed any acute rejection episodes, but the current follow-up of our patients is short. Because there is a correlation between immunosuppression reduction and increased risk for acute rejection,<sup>35</sup> appropriate monitoring of kidney function should be continued and reintroduction of immunosuppressive drugs should be tailored after infection recovery.

At the time of writing this report, 2 kidney transplant recipients from our cohort died of COVID-19 infection. However, as mentioned, both patients had very severe comorbid conditions and were terminally ill. Italian and Spanish teams have reported higher mortality rates of 27.8% and 25% in the former and latter studies, respectively.<sup>14,15</sup> Closer to our findings, a British team reported a 14% mortality rate in their series that included 7 kidney transplant recipients.<sup>16</sup>

Larger data from US centers have been recently published. Pereira et al<sup>36</sup> recently reported a 2-center experience of 90 solid-organ transplant recipients with COVID-19 infection, including 46 kidney transplant recipients. Among the kidney transplant recipients, 12 had severe disease defined as a need for mechanical ventilation, ICU admission, or death. The general management was similar to ours with immunosuppression reduction (88%) and the use of hydroxychloroquine (91%). Sixteen patients from the entire cohort (24%) had died by the end of follow-up. Although this report provides a broad picture of COVID-19 infection in solid-organ transplant recipients, it does not focus on kidney transplant recipients, making it difficult to compare with our population.

Akalin et al<sup>37</sup> also published a US case-series including 36 kidney transplant recipients with 28 (78%) requiring hospitalization. Management was not uniform as in our series because immunosuppression reduction and hydroxychloroquine treatment were used in 86%, and patients also received azithromycin (46%), the CCR5 inhibitor leronlimab (21%), and tocilizumab (7%). Interestingly, although kidney transplant recipients from this cohort seem similar to ours regarding comorbid conditions, the outcome appears more severe, with 11 (39%) kidney transplant recipients requiring mechanical ventilation and 6 (21%) requiring kidney replacement therapy. The mortality rate was also higher at the end of follow-up (28% vs 11% in our patients). A possible explanation might be the ethnic origin of the patients in that cohort

because 39% and 42% were black and Hispanic, respectively, which differs from our population. These differences in disease severity and outcomes between centers and countries will need to be closely analyzed in larger cohorts with longer follow-up.

In conclusion, we report our experience of 22 kidney transplant recipients with COVID-19 infection, of whom 18 required hospitalization. Clinical symptoms were similar to those reported in the general population. A standard strategy of immunosuppression minimization and treatment was applied, with a mortality rate for kidney transplant recipients hospitalized for COVID-19 infection of 11%. Further studies with a higher number of patients and longer follow-up are required to better assess the optimal management and outcomes of kidney transplant recipients with COVID-19 infection.

## ARTICLE INFORMATION

**Authors' Full Names and Academic Degrees:** Arnaud Devresse, MD, Leila Belkhir, MD, PhD, Bernard Vo, MD, Benoit Ghaye, MD, PhD, Anaïs Scohy, PharmD, MSc, Benoit Kabamba, MD, PhD, Eric Goffin, MD, Julien De Greef, MD, Michel Mourad, MD, PhD, Martine De Meyer, MD, Jean-Cyr Yombi, MD, and Nada Kanaan, MD, MSc.

**Authors' Affiliations:** Division of Nephrology (AD, BV, EG, NK), Internal Medicine and Infectious Disease (LB, JDG), Radiology (BG), Microbiology (AS, BK, J-CY), and Abdominal Surgery and Transplantation (MM, MDM), Cliniques Universitaires Saint-Luc, Université Catholique de Louvain, Brussels, Belgium.

**Address for Correspondence:** Nada Kanaan, MD, MSc, Cliniques Universitaires Saint-Luc, Avenue Hippocrate, 10, 1200 Brussels, Belgium. E-mail: [nada.kanaan@uclouvain.be](mailto:nada.kanaan@uclouvain.be)

**Authors' Contributions:** Research idea, study design, data analysis: AD, NK; data acquisition: AD, BV; providing and interpreting CT scans images: BG; performed PCR analysis: AS, BK; patient care: AD, BV, NK, EG, MM, MDM, JCY, JDG, LB. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

**Support:** None.

**Financial Disclosure:** The authors declare that they have no relevant financial interests.

**Peer Review:** Received April 27, 2020. Evaluated by 2 external peer reviewers, with direct editorial input from an Associate Editor and the Editor-in-Chief. Accepted in revised form June 3, 2020.

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