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## CASE REPORT

# Earliest cases of coronavirus disease 2019 (COVID-19) identified in solid organ transplant recipients in the United States

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With the rapidly expanding pandemic of SARS-CoV-2, there is concern that solid organ transplant recipients will be particularly vulnerable to infection and may experience a more severe clinical course. We report four cases of COVID-19 in solid organ transplant recipients including recipients of kidney, liver, lung, and heart transplants. We describe each patient's medical history including transplantation history, their clinical presentation and workup, and their course from diagnosis to either hospital discharge or to improvement in symptoms. These reports demonstrate a range of symptoms, clinical severity, and disease course in solid organ transplant recipients with COVID-19, including two hospitalized patients and two patients managed entirely in the outpatient setting.

## KEYWORDS

clinical research/practice, infection and infectious agents – viral, infectious disease, lung disease: infectious, organ transplantation in general, outpatient care

## 1 | INTRODUCTION

Health systems around the world are facing a pandemic of SARS-CoV-2, the causative agent of coronavirus disease 2019 (COVID-19).<sup>1</sup> COVID-19 is suspected to have a higher case fatality rate compared to other respiratory viruses, and older patients or patients with medical comorbidities appear to be at higher risk.<sup>2</sup> There are concerns that solid organ transplant (SOT) recipients may have a more severe clinical course due to their immunosuppression and high rate of comorbid conditions. Available reports of SARS-CoV-2 in SOT recipients from China, Italy, and France highlight atypical presentations and variable outcomes, despite immunosuppression.<sup>3-12</sup> In one case, there was delayed clinical worsening after 1 week of illness, followed by improvement.<sup>13</sup> More severe illness and death are also described.<sup>14-17</sup>

We report what we believe to be the earliest laboratory-confirmed cases of COVID-19 in SOT recipients in the United States (Table 1). The patients in this series were identified consecutively at our center based on the results of SARS-CoV-2 RT-PCR testing performed by the University of Washington Virology Laboratory.<sup>18</sup>

## 2 | CASE PRESENTATIONS

### 2.1 | Case 1: kidney transplant, hospitalized and recovered

The patient is a 54-year-old man who underwent deceased donor renal transplantation due to end-stage renal disease of unknown

**Abbreviations:** CLAD, chronic lung allograft dysfunction; COVID-19, coronavirus disease 2019; CXR, chest X-ray; ESRD, end-stage renal disease; HFpEF, heart failure with preserved ejection fraction; RSV, respiratory syncytial virus; RT-PCR, real-time polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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**TABLE 1** Summary of 4 cases of COVID-19 in solid organ transplant recipients

	Case 1	Case 2	Case 3	Case 4
Patient age	54	67	53	74
Transplanted organ	Kidney	Liver	Lung	Heart
Time posttransplant	20 y	19 y	20 y	23 y
Pertinent medical history	Chronic allograft dysfunction Hypertension Diabetes on insulin	Cirrhosis of allograft	CLAD ESRD on peritoneal dialysis HFpEF	Ulcerative colitis Cerebrovascular accident Obstructive sleep apnea Basal cell carcinoma of skin
Immunosuppressive medications	Tacrolimus (target level 5-10 ng/mL) Mycophenolate mofetil	Cyclosporine (target level 100-150 ng/mL)	Cyclosporine (target level 100-150 ng/mL) Azathioprine Prednisone	Tacrolimus (target level 4-6 ng/mL) Mesalamine
Fever	Documented	Subjective	None reported	Subjective
Symptoms	Fatigue Dry cough and dyspnea Nausea and vomiting Diarrhea	Fatigue Increased confusion Dry cough Diarrhea	Fatigue Dry cough and dyspnea	Sore throat Dry cough
White blood cell count (thousands/microL)	6.23	1.93	3.94	Not performed
Absolute lymphocyte count (thousands/microL)	Admission: 1.98 Nadir: 0.87	0.9	0.16	Not performed
Creatinine (mg/dL)	Baseline: 1.9 Admission: 3.43 Peak: 5.19 Discharge: 3.59 Follow-up: 2.85	Baseline: 1.3 Admission/Peak: 1.7 Discharge: 1.3	Peritoneal dialysis patient	Not performed
Urinalysis	Specific gravity 1.011 g/mL Protein 4+ Occult Blood 1+ RBCs 3-5 per hpf	Not performed	Not performed	Not performed
Aspartate aminotransferase and alanine aminotransferase	48 (mild elevation) and 34 (normal)	39 and 12 (normal)	20 and 17 (normal)	Not performed
Cardiac troponin (ng/mL)	<0.03	<0.04	Not performed	Not performed
SARS-CoV-2 test results	Illness day 4: Positive Illness day 16: Positive Illness day 22: Negative Illness day 39: Negative	Illness day 5: Positive	Illness day 5: Inconclusive (RT-PCR at University internal laboratory) Illness day 5: Positive (RT-PCR at State Public Health Laboratory)	Illness day 2: Positive
Additional respiratory virus test results	Influenza A/B: Negative Extended respiratory viral panel: Negative <sup>a</sup>	Influenza A/B: Negative Extended respiratory viral panel: Negative <sup>a</sup>	Influenza A/B: Negative Extended respiratory viral panel: Negative <sup>a</sup>	Influenza A/B: Negative Extended respiratory viral panel: Negative <sup>a</sup>
Chest X-ray findings	Illness day 1: No new abnormalities Illness day 3: Subtle lobar opacity Illness day 8: Multifocal infiltrates	No new abnormalities	No new abnormalities	Not performed
Outcome	Hospitalized 13 d Discharged home Symptoms resolved	Hospitalized 6 d Discharged home Symptoms resolved	Supportive care at home Symptoms resolved	Supportive care at home Symptoms resolved

(Continues)

**TABLE 1** (Continued)

	Case 1	Case 2	Case 3	Case 4
Days of follow-up from initial test	43	41	34	32

Abbreviations: CKD, chronic kidney disease; CLAD, chronic lung allograft dysfunction; CXR, chest X-ray; ESRD, end-stage renal disease; HFpEF, heart failure with preserved ejection fraction; hpf, high powered field; PCR, polymerase chain reaction; RSV, respiratory syncytial virus; RT-PCR, real-time polymerase chain reaction.

<sup>a</sup>Extended respiratory viral panel is performed at University of Washington Virology Laboratory. The panel tests for bocavirus, human metapneumovirus, parainfluenza virus 1, parainfluenza virus 2, parainfluenza virus 3, parainfluenza virus 4, respiratory syncytial virus, influenza A, influenza B, commonly circulating non-SARS-CoV-2 coronaviruses, rhinovirus, and adenovirus, using RT-PCR.

etiology 20 years earlier, complicated by transplant glomerulopathy with chronic kidney disease stage III and baseline serum creatinine 1.9 mg/dL. The patient's maintenance immunosuppressive medications were tacrolimus and mycophenolate mofetil. He additionally has a history of insulin-dependent diabetes mellitus and hypertension, and was taking the angiotensin receptor blocker losartan, 50 mg twice daily. He had recent health-care contacts and was living in an area with local SARS-CoV-2 transmission, but had no known direct contact with a case.

The patient's initial symptoms were insidious in onset and included fever to a maximum of 40°C, chills, malaise, nausea, vomiting, diarrhea, dry cough, and dyspnea. One day after symptoms began the patient was seen in a walk-in clinic where influenza testing and chest X-ray were negative. The patient's symptoms persisted and after 3 days without resolution of fevers he presented to a tertiary care center emergency department.

On admission, he was febrile to 38.9°C, with normal heart rate and blood pressure. Oxygen saturation was 93% on ambient air. Exam was notable for mild tachypnea and increased work of breathing with clear lungs on auscultation. Laboratory studies revealed initially a normal white blood cell count and differential, and acute-on-chronic kidney injury. A chest X-ray demonstrated a subtle consolidation in the left mid-lung. Nasopharyngeal swab real-time polymerase chain reaction (RT-PCR) testing detected SARS-CoV-2 RNA. Testing for other respiratory viruses was negative. Cultures of blood and urine were negative.

Mycophenolate mofetil was held on admission to improve immune function, and tacrolimus dose was reduced based on worsened renal function. The patient's tacrolimus level decreased to 2.8 ng/mL prior to re-starting the medication. Prednisone 10 mg daily was added to the patient's immunosuppression regimen on hospital day 8 to provide additional immunosuppression in the setting of the decreasing tacrolimus level. The patient's losartan was held on admission due to acute kidney injury that was attributed to volume depletion from vomiting, diarrhea, and decreased oral intake. Empiric ceftriaxone and azithromycin for community acquired pneumonia were administered, although concomitant bacterial infection or superinfection ultimately were not suspected.

The severity of the patient's symptoms peaked on hospital day 5 and illness day 8. The patient's oxygen saturation decreased to 88% on 2 L/min nasal cannula. He required a maximum supplemental

oxygen support of 4 L/min via nasal cannula. A repeat chest X-ray showed interval development of bilateral patchy consolidations. The patient was started on chloroquine 500 mg twice daily based on a hypothesized antiviral effect. This was changed on hospital day 8 to hydroxychloroquine, given as 400 mg twice on the first day followed by 200 mg twice daily for 4 days, based on a report of increased in-vitro efficacy published by Yao et al.<sup>19</sup> By hospital day 12, the patient had normal oxygenation on ambient air. He was discharged home on hospital day 13 and instructed to practice self-quarantine until 72 hours after resolution of all symptoms and clearance by his transplant physician. Tacrolimus and prednisone were continued. Mycophenolate mofetil and losartan were not re-started at discharge. Repeat qualitative nasopharyngeal RT-PCR for SARS-CoV-2 was positive on the day of discharge, 16 days after symptom onset, but was subsequently negative on days 22 and 39 after symptom onset.

## 2.2 | Case 2: liver transplant, hospitalized and recovered

A 67-year-old man underwent deceased donor liver transplantation for cirrhosis due to hepatitis C infection 19 years previously, complicated by Child Pugh class B cirrhosis of the transplanted liver due to hepatitis C with hepatic encephalopathy, ascites, pancytopenia, and coagulopathy at baseline. The patient's maintenance immunosuppressive medication was cyclosporine monotherapy. The patient sustained a pelvic fracture due to a ground-level fall and was living in a subacute care facility affected by an outbreak of COVID-19. The patient's wife also tested positive for SARS-CoV-2.

On presentation to the emergency department, the patient reported several days of dry cough, subjective fever, fatigue, increased confusion, and increased frequency of loose bowel movements from a baseline of 2 bowel movements per day with lactulose up to 5 bowel movements per day. He was afebrile and oxygen saturation was 92% on ambient air. Exam was notable for occasional wheezing. Laboratory studies revealed leukopenia, lymphopenia, and mild acute kidney injury. A chest X-ray was normal. Nasopharyngeal RT-PCR testing for SARS-CoV-2 RNA was positive. Testing for other respiratory viruses was negative.

The patient was initially admitted to the intensive care unit due to hypotension, which resolved with hydration in less than 24 hours.

The acute kidney injury resolved with hydration. His maximal supplemental oxygen requirement was 2 L/min via nasal cannula. The patient's cyclosporine was continued without adjustment. His respiratory symptoms remained mild, and he was discharged home after 6 days. He was contacted 12 days after admission and reported feeling at his baseline.

### 2.3 | Case 3: lung transplant, outpatient

The patient is a 53-year-old woman who underwent bilateral lung transplantation 20 years earlier for chronic obstructive pulmonary disease, and had chronic lung allograft dysfunction not requiring supplemental oxygen. Her history also included multifactorial pancytopenia, heart failure with preserved ejection fraction, transarterial aortic valve replacement 1 year earlier due to aortic dissection, and end-stage renal disease due to calcineurin inhibitor toxicity, on peritoneal dialysis. The patient's immunosuppressive medications are cyclosporine, azathioprine, and prednisone. The patient had contact with a family member visiting from another state who had respiratory symptoms. The patient's relative was unable to undergo COVID-19 testing, but was instructed to self-isolate out of suspicion for infection.

The patient presented to the lung transplant clinic for a routine visit. She reported mild increased dyspnea for 4-5 days, a mild nonproductive cough, and fatigue. She had no fevers, chills, or gastrointestinal symptoms. She was afebrile in the clinic with a normal heart rate and blood pressure. Oxygen saturation was 98% on ambient air. Exam was notable for baseline low body mass index 15 kg/m<sup>2</sup>, and mild worsening of baseline global weakness. The pulmonary examination was unremarkable. Laboratory studies revealed leukopenia and slightly worsened lymphopenia (absolute lymphocyte count 0.16 thousands/ $\mu$ L from 0.3 to 0.5 thousands/ $\mu$ L at baseline). A chest X-ray was unchanged from previous imaging. RT-PCR performed at our University's virology laboratory detected one SARS-CoV-2 RNA target in a nasopharyngeal swab sample, and confirmatory testing of the same sample performed at the Washington State Public Health Laboratory was positive. Testing for other respiratory viruses was negative.

The patient returned home following her clinic visit. She was notified of the test result and instructed to self-isolate. Her immunosuppressive medications were not changed. Five days after being seen in the clinic, she reported an increase in cough and dyspnea. These symptoms improved the next day with increased volume removal by peritoneal dialysis. She did not develop fevers. Nine days after being seen in the clinic, the patient reported that her cough and dyspnea had improved. She was otherwise at her baseline health.

### 2.4 | Case 4: heart transplant recipient, outpatient

A 74-year-old man underwent heart transplantation 23 years previously, with a medical history also significant for ulcerative colitis,

cutaneous basal cell carcinomas, previous cerebrovascular accident for which the patient was taking warfarin, and obstructive sleep apnea for which the patient uses nocturnal bilevel noninvasive mechanical ventilation. The patient takes tacrolimus for maintenance immunosuppression and mesalamine for ulcerative colitis. In the weeks prior to disease onset, the patient visited a local grocery store and coffee shop sporadically but was otherwise relatively isolated and living alone.

The patient first noticed a high fever with a maximum temperature of 40°C measured at home. At a clinic visit the following day, he reported no cough, shortness of breath, sore throat, rhinorrhea, nausea, or diarrhea. At the time of evaluation he was afebrile. Oxygen saturation at rest was 95% on ambient air. Exam revealed faint rales at the R lung base. A chest X-ray revealed a stable elevation of the left hemidiaphragm but no new abnormality. RT-PCR testing for SARS-CoV-2 was positive from a nasopharyngeal swab. Testing for other respiratory viruses was negative.

The patient returned home following his clinic visit. He was notified of the test result and instructed to self-isolate. Two days after being seen in the clinic, he reported continued intermittent fevers as high as 38.7°C associated with chills, a new mild dry cough and new mild sore throat but no shortness of breath. Seven days after being seen in the clinic, his fevers had resolved. Eleven days after presentation, all symptoms were resolved.

## 3 | DISCUSSION

These cases demonstrate a range of severity of clinical presentations and course of COVID-19 in SOT recipients, including two patients requiring hospitalization and two managed as outpatients. None of these patients died of the infection, despite risk factors for severe disease including older age, immunosuppression, and other comorbidities. In one case, there was clinical worsening associated with progression of imaging findings around 1 week after symptom onset, which is also described in the experience from China.<sup>20</sup> Only one patient, with the most severe symptoms, received experimental therapy, which was well tolerated. All patients have been followed for at least 1 month with resolution of all symptoms. One patient with a kidney transplant has persistence of elevated serum creatinine above pre-illness baseline.

Although immunosuppression is associated with increased severity for many viral infections, the pathogenesis of COVID-19 may involve exaggerated or dysregulated host inflammatory response.<sup>21</sup> This may be dampened by immunosuppression, potentially modulating clinical presentation and/or course of COVID-19. The practice of routinely reducing immunosuppression in the context of viral illness may need to be re-examined in this context. We note that all of these patients are remote from transplant and were receiving relatively low-dose maintenance immunosuppression. Thus we are unable to extrapolate to SOT recipients in the early posttransplant period or otherwise receiving intensified immunosuppression. Previous data on the clinical severity of COVID-19 in nontransplant patients were from settings where testing was largely restricted to the seriously ill.<sup>22-24</sup> A broader

range testing protocol at our center, including immunosuppressed patients with mild symptoms, may have led to identification of more mild cases. Given the data in this report, we encourage SOT programs and others caring for these patients to be alert for possible cases of COVID-19, and to consider testing in a broad range of clinical presentations. Still, the favorable outcomes in our series suggest that it may be appropriate for some patients diagnosed with COVID-19 with mild symptoms, despite perceived increased risk related to transplant status, to continue supportive care at home with close monitoring.

We acknowledge the small number of patients and short duration of follow-up in this group. We report these early cases of COVID-19 in SOT recipients in the United States to contribute to a broader effort to characterize the clinical presentation and clinical course of SARS-CoV-2 in SOT recipients. Challenges include triage and testing of immunosuppressed patients, protection of other patients in clinical environments, management of maintenance immunosuppression for infected patients, treatment with novel agents in the context of organ dysfunction, infection control with atypical symptoms or prolonged viral shedding, and planning future transplants in health systems under strain.

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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*.

## DATA AVAILABILITY STATEMENT

Due to the nature of this research, participants of this study did not agree for their data to be shared publicly, so supporting data are not available.

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