COVID-19 and Solid Organ Transplantation: A Review Article

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Abstract. The coronavirus pandemic has significantly impacted solid organ transplantation (SOT). Early in the outbreak period, transplant societies recommended suspending living kidney transplant programs in communities with widespread transmission to avoid exposing recipients to increased risk of immunosuppression, while recommendations were made to reserve deceased-donor kidney transplantation for likely life-saving indications. SOT recipients may be at high risk from COVID-19 disease due to chronic immunosuppressive treatment and other medical comorbidities. Mortality rates reported between 13 to over 30% in SOT recipients. In addition to high rates of complications and mortality attributable to COVID-19 infections, the pandemic has also led to additional complexities in transplantation including new questions regarding screening of donors and recipients, decision making to accept a patient for kidney transplant or wait after pandemic. The clinical implications of COVID-19 infection may also differ depending on the type of the transplanted organ and recipient comorbidities which further impacts decisions on continuing transplantation during the pandemic. Transplant activity during a pandemic should be tailored with careful selection of both donors and recipients. Furthermore, while tremendous strides have been made in treatment strategies and vaccinations, the impact of these in transplant recipients may be attenuated in the setting of their immunosuppression. In this review, we aim to summarize several aspects of COVID-19 in transplantation, including the immune response to SARS-CoV-2, SARS-CoV-2 diagnostics, clinical outcomes in SOT recipients, and end-stage kidney disease patients, transplant activity during the pandemic, and treatment options for COVID-19 disease.

(*Transplantation* 2021;105: 37–55).

INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was first identified in December 2019 and subsequently designated as causing coronavirus disease 2019 (COVID-19).[1,2] Since that time, the COVID-19 pandemic has dramatically impacted the global economy, healthcare systems, and our regular way of life. Solid organ transplantation (SOT) has been significantly impacted during the pandemic, resulting in a substantial decrease in transplant activity and an increase in mortality due to infection in transplant recipients. In this review, we aim to summarize the immune response to SARS-CoV-2, diagnostics, clinical outcomes in SOT recipients, transplant activity during the pandemic and treatment options.

Received 9 October 2020. Revision received 14 October 2020.

Accepted 15 October 2020.

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The authors declare no funding or conflicts of interest.

Y.A., J.S., P.L.C., and R.B. participated in the writing of the article and in the performance of the research. E.A. participated in research design, in the writing of the article, and in the performance of the research.

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ISSN: 0041-1337/21/1051-37

DOI: 10.1097/TP.0000000000003523

CORONAVIRUSES AND IMMUNE RESPONSE TO SARS-CoV-2

Coronaviruses are known to cause disease in humans and animals. Among these, 4 human coronaviruses (229E, NL63, OC43, and HKU1) typically infect only the upper respiratory tract and cause relatively minor symptoms. However, severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1), middle east respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2 can replicate in the lower respiratory tract and cause pneumonia.[2,3] The spike (S) protein, compromised of a S1 and S2 subunit, is expressed on the surface of viral particles, giving the characteristic "crown" appearance of coronaviruses. SARS-CoV-2 infects cells expressing angiotensin-converting enzyme 2 and TMPRSS2 surface receptors. Innate immune cells secrete proinflammatory cytokines that inhibit viral replication, stimulate the adaptive immune response, and recruit other immune cells to the site of infection.[3,4] Neutralizing antibodies can block viral infection, and alveolar macrophages and neutrophils phagocytose infected and apoptotic cells. Activated dendritic cells present pathogen-derived antigens

<zdoi;10.1097/TP.0000000000003523>

to naïve helper T cells to initiate the adaptive immune response, which eliminate the infected cells before the virus spreads. Both T- and B-cell responses against SARS-CoV-2 are detected in the blood around 1 week after the onset of COVID-19 symptoms.[5-7] CD8+ T cells are important for directly killing virus-infected cells, whereas CD4+ T cells are crucial to prime both CD8+ T cells and B cells and are responsible for cytokine production to recruit other immune cells. Natural killer (NK) cells kill virally infected cells via degranulation, receptor-mediated apoptosis, and antibody-dependent cell-mediated cytotoxicity. Finally, the complement system plays a role in immune cell recruitment, activation, and destruction of pathogens. These initial immune responses lead to clearance of the virus with minimal lung damage and results in recovery.

Some patients' symptoms gradually worsen within a week after developing symptoms, suggesting that severe COVID-19 pathogenesis could be mediated by a dysregulated immune response.[4] Transcriptional and serum profiling of COVID-19 patients consistently revealed a unique and inappropriate inflammatory response.[4] Type I interferons are essential in antiviral immunity. There is an impaired interferon type 1 response and exacerbated NF-κB-driven inflammatory response with increased IL-6 and TNF-alpha production in patients with COVID-19 infection.[8] Higher circulating IL-6, IL-1Ra, CCL2, CCL8, CXCL2, CXCL8, CXCL9, and CXCL16 were observed in SARS-CoV-2+ patients in comparison to patients with non-COVID-19-related respiratory issues.[9] Significant elevation of CXCL9 and CXCL16 (chemoattractants of T or NK cells), CCL8 and CCL2 (which recruit monocytes and macrophages), and CXCL8 (a neutrophil chemoattractant) suggest that the presence of these cells may be a primary driver of the signature pathology observed in COVID-19 patients.[10] Uncontrolled inflammation with cytokine storm inflicts multiorgan damage leading to heart, liver, and kidney failure. IL-6 has been documented to be a driving cytokine in pathogenesis, and increased serum IL-6 levels are associated with mortality.[11-13]

Recent studies have suggested that genetic susceptibilities may contribute to severe clinical manifestations seen in COVID-19 patients, particularly in younger patients without other medical comorbidities. Inborn errors of Toll-like receptor-3 and IRF-7 dependent type 1 interferon immunity[14,15] and neutralizing autoantibodies to interferon[16] have been reported. A genome-wide association study involving 1980 patients with COVID-19 and severe disease identified a 3p21.31 gene cluster as a genetic susceptibility locus in patients with COVID-19 with respiratory failure.[17]

Lymphocytopenia and decreased CD3, CD4, CD8 counts are common in patients with COVID-19 and correlate with disease severity.[8,18,19] There are multiple possible mechanisms for this, including pulmonary recruitment of lymphocytes from the blood, direct virus killing of lymphocytes, T-cell apoptosis, and exhaustion.[20] Severe COVID-19 patients have depleted peripheral NK cell counts and increased neutrophil-to-lymphocyte ratio compared with mild cases and healthy controls.[21,22] Cellular immunity to coronavirus could be more sustained, and T helper cell responses are critical in the generation of neutralizing antibodies.[7,23] SARS-CoV-2 S-reactive CD4+ T cells were detected in 83% of patients with COVID-19 but also in 35% of an unexposed healthy population.[7] In another study, circulating SARS-CoV-2-specific CD8+ and CD4+ T cells were identified in ~70% and 100% of COVID-19 convalescent patients, respectively[5] but also in ~40%–60% of unexposed individuals, suggesting cross-reactive T-cell recognition between other commonly circulating coronaviruses and SARS-CoV-2. The role of preexisting SARS-CoV-2 cross-reactive T cells for clinical outcomes remains to be determined in larger cohorts. Based on epidemiological data, adults contract coronavirus infections on an average of every 2–3 years. Protective antibodies may wane overtime, but cellular immunity could remain.[24] In contrast to some studies, Thieme et al reported that virus clearance and COVID-19 survival are not associated with either SARS-CoV-2 T-cell kinetics or magnitude of T-cell responses and disprove the hypothesis of insufficient SARS-CoV-2-reactive immunity in critical COVID-19.[25] Conversely, it indicates that activation of differentiated memory effector T cells could cause hyperreactivity and immunopathogenesis in critical patients.

DIAGNOSIS OF SARS-CoV-2

Reverse-transcription polymerase chain reaction (RT-PCR) assay of upper respiratory secretions, typically collected via nasopharyngeal swab, is the current diagnostic test of choice for COVID-19.[26] However, RT-PCR of SARS-CoV-2 has been associated with high rates of false negative results.[27] Serologic assays of SARS-CoV-2 IgG and IgM antibodies could help to diagnose patients who have a negative RT-PCR despite COVID-like symptoms as well as identify those with past asymptomatic infection.[28] Screening for antibody testing in the general population has shown that COVID-19 infections are 6–24 times more prevalent than initially thought.[29] However, antibody responses to coronavirus are variable and could be short lived. In a study of asymptomatic cases with positive RT-PCR, 81% were SARS-CoV-2 IgG + at 4 weeks postinfection, while only 60% remained positive at 8 weeks.[30] Similar positivity rates have been reported among kidney transplant recipients. At Montefiore Medical Center, 912 kidney transplant recipients were screened for SARS-CoV-2 IgG antibodies during routine clinic visits, of which 152 (16.6%) tested positive.[31] Fifty-five of the 152 patients had previously tested positive by RT-PCR, while the remaining 97 did not recall significant symptoms and had not been previously tested by RT-PCR. The prevalence of SARS-CoV-2 infection was 23.4% in the 975 kidney transplant recipients tested by either RT-PCR (n = 132) or SARS-CoV-2 IgG (n = 97). Eighty percent of the RT-PCR positive kidney transplant recipients tested positive for SARS-CoV-2 IgG antibodies during routine follow-up (median of 44 d postinfection; IQR, 31–58).[31] Another study reported that 16 of 18 kidney transplant recipients mounted an antibody response.[32] Seroprevalence of SARS-CoV-2 in patients receiving hemodialysis has been reported as high as 36.2%,[33] but it was 8.0%[34] in 28 503 randomly selected adult patients receiving dialysis in July 2020 in 1300 dialysis facilities across United States.

In addition to RT-PCR and serologic assays, viral antigen testing can also be performed for SARS-CoV-2 diagnosis. These tests, which detect the presence of viral proteins rather than genetic material, are frequently used in the community setting as they are easy to perform, inexpensive, and have a short turnaround time compared with RT-PCR

testing. However, these are limited by lower sensitivity, and, therefore, negative results should be interpreted cautiously, especially in patients with COVID-like symptoms.

CLINICAL FEATURES AND OUTCOMES IN GENERAL POPULATION

Clinical features of COVID-19 include respiratory symptoms of cough and dyspnea and at least 2 of the following per CDC guidelines: fever, chills, muscle pain, headache, sore throat, and new loss of taste or smell. Diarrhea is also reported, especially in transplant recipients.[18,35] Approximately 80%–85% of COVID-19 patients are asymptomatic or experience mild symptoms that do not require hospitalization. Among hospitalized patients, approximately half develop moderate to severe disease requiring oxygen, and 20%–25% develop critical disease, characterized by respiratory failure, systemic shock, or multiorgan failure.[36] The median incubation period for infection is approximately 4–6 days (range 2–14), with 98% of symptomatic patients developing symptoms within 12 days.[3,37,38] Initial reports from Wuhan[39,40] and New York[13,41,42] reported high mortality rates of 20%–39% among hospitalized patients, which could be in part due to lack of social distancing and inappropriate personal protective equipment use leading to high viral exposure at the beginning of the pandemic.[43] The overall mortality rate among patients with COVID-19 has been difficult to determine due to lack of widespread available testing. Initial reports by Johns Hopkins Coronavirus Resource Center (https://coronavirus.jhu.edu/map.html) documented mortality as high as 8%–15% in patients with positive RT-PCR; however, during that time testing was limited and available only to sicker patients. As testing has become more readily available, mortality has decreased to 3% in the United States and would likely decrease further if antibody testing was more widely used. In Iceland, 44% of individuals infected with SARS-CoV-2 were not diagnosed by PCR but by antibody testing only and 91% of PCR positive patients developed antibodies.[44]

Autopsy findings from the lungs of COVID-19 patients showed distinctive vascular features, consisting of severe endothelial injury. Histologic analysis of pulmonary vessels showed widespread thrombosis with microangiopathy.[45] Microthrombi of the lower limbs, brain, heart, liver, and kidneys were also described.[46] COVID-19–associated macrophage activation, hyperferritinemia, cytokine storm, and release of pathogen-associated molecular patterns and damage-associated molecular proteins can result in release of tissue factor and activation of coagulation factors that create a predisposition to hypercoagulability. A multisystem inflammatory syndrome and its temporal association with COVID-19 has been reported in 186 previously healthy children and adolescents.[47]

COVID-19 IN SOLID ORGAN TRANSPLANT RECIPIENTS

A summary of articles reporting clinical features and outcomes in kidney transplant recipients with COVID-19 are reported in Table 1. We limited our review to include those reporting data on at least 10 patients. The first report came from Wuhan, China, and documented only 1 death in 10 patients.[48]The initial report from the United States was from Montefiore Medical Center in New York, which found a 28% mortality in 36 kidney transplant recipients at a median follow-up of 21 days.[18] Of these patients, 78% required hospital admission. Ninety-six percent of hospitalized patients had chest x-ray findings consistent with viral pneumonia, 39% required mechanical ventilation, and 21% required renal replacement therapy. Additional reports from other transplant centers in New York had variable mortality (13%–30%) and hospitalization rates (32%–100%).[49-53] Most European studies came from Italy, Spain, and France, which were the epicenter early in the pandemic. These studies reported outcomes like New York centers, with mortality ranging from 19% to 50%.[54-62] While most studies were single center experiences, some studies reported clinical outcomes of national and international registries. TANGO international consortium reported outcomes of 144 hospitalized kidney transplant recipients at 12 centers in the United States, Italy, and Spain.[11] During a median follow-up period of 52 days (IQR, 16–66 d), acute kidney injury (AKI) occurred in 52% of cases, respiratory failure requiring intubation in 29%, and mortality was 32%. A nationwide registry from France described 279 kidney transplant recipients[56] of which 87% required hospitalization and 36% of hospitalized patients required ICU care. Thirty-day mortality was 23%. A registry of the Spanish Society of Nephrology reported 94% hospitalization, 9% intensive care unit (ICU) stay, and 19% mortality in 286 kidney transplant recipients.

Some studies reported clinical outcomes of solid organ transplant recipients together, including kidney, liver, heart, and lung, and these results are summarized in Table 2. The University of Washington Registry has the largest series of patients, including 318 kidney or kidney-pancreas, 73 liver, 57 heart, and 30 lung transplant recipients.[63] Overall mortality was 18.7% and 20.5% in hospitalized patients. Seventy-eight percent of reported cases required hospitalization, 31% mechanical ventilation, and 44% developed AKI. Five additional studies from US centers involving mostly kidney transplant recipients reported a 67%–87% hospitalization rate, 30%–35% requiring mechanical ventilation, and overall mortality rate of 5%–18% with 7%–24% mortality in hospitalized patients.[64-68] A study of 53 SOT recipients from Sweden reported lower mortality (9.4% overall and 14% in-hospital) and lower rates of mechanical ventilation (22%).[69]Miarons et al compared 46 SOT recipients with 166 controls in a matched retrospective cohort study in Spain.[70] Mortality was higher in SOT recipients (37% versus 23%), but it was not statistically significant. While the mortality was 20% in 85 SOT recipients in Iran,[71] the lowest mortality was reported in Saudi Arabia[72] (3%).

AKI is a frequent complication of COVID-19 and is seen in 30%–89% of hospitalized kidney transplant recipients (Table 1). AKI is likely due to multiple factors, including reduced renal perfusion, multiorgan failure, and cytokine storm. While it may be transient, Lubetzky et al reported a graft loss of 11% post COVID-19 associated AKI,[51] Caillard et al from France reported 4% and our experience at Montefiore Medical Center was 6.3%.[56] Immunohistochemistry studies of postmortem analysis showed viral particles in the kidney.[74] Viral infection induces CD68+ macrophage infiltration and enhances complement C5b-9 deposition on tubules. It has been suggested that the virus may trigger direct cytopathic changes in the kidney as well.[74,75]

TABLE 1.

Clinical outcomes of kidney transplant recipients with COVID-19

Article/country	Patient number	Patient's characteristics and comorbidities	Clinical outcomes	Predictors of mortality
Cravedi et al United States, Spain, Italy TANGO Registry[11]	144 patients	Sex: 94/144 (65%) Median age: 62 IQR (52–69) Race: 56/144 (40%) Hispanic, 43/144 (31%) Caucasian, 35/144 (25%) African American hypertension 137/144 (95%) Diabetes mellitus 75/144 (52%) Obesity 71/144 (49%) Heart disease 41/144 (29%) Lung disease 27/144 (19%)	Mortality 46/144 (32%) Hospitalized 144/144 (100%) Intubation 42/144 (29%) AKI 74/144 (52%)	Older age Respiratory rate ≥20/min Elevated IL-6 levels Low eGFR
Lubetzky et al United States Single center[51]	54 patients	Sex: Male 38/54 (70%) Median age: 57 IQR (29–83) Race: Caucasian 17/54 (31%), Hispanic 17/54 (31%), Black 13/54 (24%), Asian 6/54 (11%), Middle Eastern 1/54 (2%) Hypertension 50/54 (90%) Diabetes mellitus 16/54 (30%) Heart disease 19/54 (35%) Lung disease 8/54 (15%)	Mortality 7/54 (13%) Hospitalized 39/54 (72%) ICU stay 11/54 (20%) AKI 21/54 (39%) Graft loss 6/54 (11%) Discharged 30/39 (77%)	N/A
Mehta et al United States Single Center[53]	44 patients	Sex: Male 22/34 (65%) Median age: 59 IQR (52.5–63.8) Race: Black 15/34 (44%), Hispanic 8/34 (24%), White 7/34 (21%), Asian 2/34 (7%)	Mortality 6/44 (14%) Hospitalized 34/44 (77%) ICU stay 13/34 (39%) AKI 18/34 (53%) Discharged 27/34 (79%)	N/A
Husain et al United States Single Center[50]	41 patients	Sex: Male 30/41 (73%) Median age: 49 IQR (41–63) Hypertension 23/41 (56%) Diabetes mellitus: 37/41 (90%) Obesity: 12/41 (29%)	Hospitalized 13/41 (32%)	N/A
Akalin et al United States Single Center[18]	36 patients	Sex: Male 26 of 36 (72%) Median age: 60 range (32–77) Race: Black 15/36 (39%), Hispanic 14/36 (42%) Hypertension 34/36 (94%) Diabetes mellitus 25/36 (69%) Heart disease 6/36 (17%)	Mortality 10/36 (28%) Hospitalized 28/36 (78%) Intubation 11/28 (39%) RRT 6/28 (21%) Discharged 10/28 (36%)	N/A
Hartzell et al United States Multicenter[32]	18 patients	Sex: Male 30/54 (56%) Mean age: 55.2 SD (±14) Race: Black 7/18 (39%), White 3/18 (17%), Others 8/18 (44%) Ethnicity: Hispanic 7/18 (39%) Hypertension 17/18 (94%) Obesity 6/18 (33%) Heart disease 3/18 17%) Lung disease 3/18 (17%) Cancer 4/18 (22%)	Mortality 7/18 (39%) Hospitalized 18/18 (100%) ICU stay 11/18 (61%) AKI 16/18 (89%) Discharged 11/18 (61%)	N/A
Mohan et al United States Single Center[49]	15 patients	Sex: Male 10/15 (66%) Median age: 51 IQR (28–72)	Mortality 2/15 (13%) Hospitalized 15/15 (100%) Intubation 4/15 (27%) AKI 6/15 (40%) RRT 2/15 (13%) Discharged 8/15 (53%)	N/A
Nair et al United States Single Center[52]	10 patients	Sex: Male 6/10 (60%) Median age: 57 IQR (47–67) Race: Caucasian 6/10 (60%), Black 4/10 (40%) Hypertension 10/10 (100%) Diabetes mellitus 8/10 (80%) Heart disease 2/10 (20%)	Mortality 3/10 (30%) Hospitalized 10/10 (100%) ICU stay 5/10 (50%) AKI 3/10 (30%) Discharged 7/10 (70%)	N/A

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TABLE 1. (Continued)

Clinical outcomes of kidney transplant recipients with COVID-19

Article/country	Patient number	Patient's characteristics and comorbidities	Clinical outcomes	Predictors of mortality
Sanchez-Alvarez et al Spain Registry of Spanish Society of nephrology[61]	286 patients	Sex: Male 189/286 (66%) Mean age: 60 SD (±13)	Mortality 53/286 (19%) Hospitalized 268/286 (94%) ICU stay 25/286 (9%)	Older age Pneumonia on imaging
Fava et al Spain Multicenter[60]	104 patients	Sex: Male 60/104 (56%) Mean age: 59.7 SD (±12.48) Race: Caucasian 90/104 (87%), Hispanic 9/104 (9%), African American 4/104 (4%) Hypertension 90/104 (87%) Diabetes mellitus 32/104 (31%) Obesity 28/104 (27%) Heart disease 31/104 (30%) Lung disease 16/104 (15%)	Mortality 28/104 (27%) Hospitalized 104/104 (100%) ICU stay 24/104 (23%) AKI 47/100 (47%)	Older age ARDS on admission Elevated LDH on admission
Crespo et al Spain Multicenter[57]	16 patients	Sex: Male 12/16 (75%) Mean age: 73.6 SD (±4.7) Race: Caucasian 14/16 (88%) Hypertension 14/16 (88%) Diabetes mellitus 8/16 (50%) Obesity 7/16 (44%) Heart disease 8/16 (50%) Lung disease 3/16 (19%) Cancer 5/16 (31%)	Mortality 8/16 (50%) Hospitalized 15/16 (94%) ICU stay 2/16 (13%) AKI 5/15 (33%)	Higher respiratory rate on admission Anemia on admission Lymphopenia on admission Higher serum creatinine, D-Dimer and C-Reactive protein on admission
Bossini et al Italy Multicenter[55]	53 patients	Sex: Male 42/53 (79%) Median age: 60 IQR (50–67) Hypertension 42/53 (79%) Diabetes mellitus 11/53 (21%) Heart disease 10/53 (19%)	Mortality 15/45 (33%) Hospitalized 45/53 (85%) ICU stay 10/45 (22%) AKI 15/45 (33%) RRT 3/15 (20%) Discharged 27/45 (60%)	Age >60 Dyspnea on admission
Alberici et al Italy Single Center[54]	20 patients	Sex: Male 16/20 (80%) Median age: 59 IQR (51–64) Hypertension 17/20 (85%) Diabetes mellitus 3/20 (15%) Heart disease3/20 (15%)	Mortality 5/20 (25%) Hospitalized 20/20 (100%) ICU stay 4/20 (20%) AKI 6/20 (30%) RRT 1/6 (17%) Discharged 3/20 (15%)	N/A
Caillard et al France French Registry[56]	279 patients	Sex: Male 182/279 (65%) Median age: 61.6 IQR (50.8–69) Hypertension 201/252 (90%) Diabetes mellitus 92/223 (41%) Heart disease 81/224 (36%) Lung disease 33/223 (15%) Cancer 35/226 (16%)	Mortality at 30 d (23%) Hospitalized 243/279 (87%) ICU stay 88/243 (36%) AKI 106/243 (44%) RRT 27/243 (11%) Graft loss 9/243 (4%)	Age >60 Cardiovascular disease Dyspnea on admission
Elias et al France Multicenter[59]	66 patients	Sex: Male 37/66 (56%) Mean age: 56.4 SD (±12.5) Race: Non-white 24/66 (36%) Hypertension 58/66 (88%) Diabetes mellitus 31/66 (47%) Obesity 20/66 (30%) Heart disease 1/66 (2%) Lung disease 13/66 (20%)	Mortality 16/66 (24%) Hospitalized 60/66 (91%) ICU stay 15/66 (22%) AKI 28/66 (42%) RRT 7/28 (25%)	N/A
Benotmane et al France Single Center[62]	49 patients	Sex: Male 37/49 (76%) Median age 62.2 IQR (52.3–67.8) Hypertension 41/49 (84%) Diabetes mellitus 23/49 (47%) Obesity 22/49 (45%) Heart disease 18/49 (37%) Lung disease 9/49 (18%)	Mortality 9/49 (19.5%) Hospitalized 41/49 (84%) ICU stay 14/41 (34%) AKI 31/41 (76%)	C-reactive protein >100 mg/L Interleukin-6 >65 ng/L D-dimer >960 ng/ml High-sensitivity Troponin I >30 ng/L

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TABLE 1. (Continued)

Clinical outcomes of kidney transplant recipients with COVID-19

Article/country	Patient number	Patient's characteristics and comorbidities	Clinical outcomes	Predictors of mortality
Mohamed et al United Kingdom Multicenter (*Transplantation* in press)	28 patients	Sex: Male 16/28 (57%) Median age: 57 IQR (25–72) Hypertension 23/28 (85%) Diabetes mellitus 10/28 (37%) Overweight 21/28 (75%) Heart disease 5/28 (18%) Lung disease 4/28 (14%)	Mortality 9/28 (32%) Hospitalized 25/28 (89%) ICU stay 5/25 (20%) AKI 14/25 (56%)	Older age (trend toward increased mortality) C-reactive protein >86 mg/L
Demir et al Turkey Multicenter[58]	40 patients	Sex: Male 20/40 (50%) Mean age: 44.9 SD (±14.8) Hypertension 26/40 (65%) Heart disease 3/40 (7.5%) Lung disease 3/40 (7.5%)	Mortality 5/40 (12.5%) Hospitalized 39/40 (98%) ICU stay 7/40 (18%) AKI 14/40 (35%0	Anti-rejection therapy on admission Cyclosporine use was associated with lower risk of death
Zhu et al China Single Center[48]	10 patients	Sex: Male 8/10 (80%) Age range: 24–65 Hypertension 5/10 (50%) Heart disease 3/10 (30%) Lung disease 1/10 (10%)	Mortality 1/10 (10%) Hospitalized 10/10 (100%) AKI 5/10 (50%) Discharged 8/10 (80%)	N/A

AKI, acute kidney injury; ICU, intensive care unit; IQR, interquartile range; LDH, lactic dehydrogenase; RRT, renal replacement therapy.

Kidney transplant recipients are expected to be at an increased risk of complications from COVID-19 not only due to their chronic immunosuppression but also due to their other comorbidities. In the studies discussed above, hypertension was observed in 50%–100% of patients, diabetes mellitus in 15%–90%, cardiovascular disease in 8%–50%, chronic lung disease in 8%–20%, and obesity in 29%–69%. Williamson et al reviewed 10 926 COVID-19-related deaths and identified organ transplant as a risk factor for mortality with a hazard ratio of 6.00.[76] However, Chaundry et al compared 47 SOT recipients (38 kidneys and 9 nonkidney organs) with 100 hospitalized nontransplant controls and did not find an association between transplant status and mortality.[64] Similarly, in a multicenter cohort study of over 4000 adults admitted to ICUs with COVID-19, Molnar et al found that death within 28 days of ICU admission was similar in SOT and non-SOT patients using propensity matched scoring (40% and 43%, respectively).[73] It is not clear if chronic immunosuppressive treatment of transplant recipients could decrease the severity of cytokine storm and clinical picture.

Factors associated with higher mortality included older age,[11,13,40,41,55,56,60,61,63-67,77-79] diabetes mellitus,[67,78] obesity,[63,79] frailty,[40,64] chronic heart,[13,56,63,66,77,79] kidney,[11,57,67,79] and lung disease[13,63,67] and longer dialysis vintage.[80] Dyspnea, a common symptom of COVID-19, has also been reported as a risk factor for mortality in multiple studies.[55-57] In terms of laboratory values, lymphopenia and higher levels of C-reactive protein, ferritin, procalcitonin, IL-6, D-dimer, and lactate dehydrogenase have been reported to be predictors of mortality.[11,13,39,40,57,62-67,77] African-American and Hispanic patients, also have a higher prevalence of COVID-19, are more frequently hospitalized and have higher mortality.[81] Mortality is also higher among patients with lower income and those who live in more densely populated areas.[81] Higher mortality has also been observed in males.[79] Female patients mount a significantly more robust T-cell activation than male patients during SARS-CoV-2 infection.[82] A blood-group–specific analysis showed a higher risk in blood group A and a protective effect in blood group O as compared with other blood groups.[17] The impact of immunosuppression on COVID-19 is also unclear.[83,84] In a report of 40 patients from Turkey with COVID-19, immunosuppression regimen on admission was associated with high mortality, though interestingly, patients who were on cyclosporine tend to have a survival benefit in this series.[58]

COVID-19 IN NONRENAL SOLID ORGAN TRANSPLANT RECIPIENTS

Publications related to clinical outcomes in liver, heart, and lung transplant recipients are summarized in Table 3. Webb et al reported the largest series of 151 liver transplant recipients from 18 countries.[85] Eighty-two percent required hospitalization, 28% ICU admission, and mortality was 19%. Interestingly, mortality was lower than nontransplant controls (19% versus 27%; $P = 0.046$). AKI was common and 32% of patients required dialysis. Patients had other comorbidities, including hypertension (42%), diabetes mellitus (43%), obesity (29%), and cardiovascular disease (15%), and mortality has associated these comorbidities along with older age and higher baseline serum creatinine levels. The other 3 studies from the United States, Spain, and Europe reported similar mortality rates of 12%–18% with older age, male sex, lymphopenia, increased D-dimer, and elevated ferritin levels identified as predictors of mortality.[86-88] These reports suggested lower mortality in liver transplant recipients compared with kidney transplant recipients.

Four studies with small numbers of heart transplant recipients (between 13 and 28) reported overall mortality rate of 15%–33% and 25%–41% in hospitalized patients.[89-92] Among heart transplant recipients with COVID-19 other medical comorbidities were common,

TABLE 2.

Clinical outcomes of solid organ transplant recipients with COVID-19 (results reported as combined in kidney, liver, heart, and lung transplant recipients)

Author/ country	Transplanted organ	Patient number	Cohort studied/ transplant to COVID diagnosis (y/mo)	Comorbid conditions/ patient characteristics	Reported clinical events (hospitalized patients)	Predictors of adverse outcome
Kates et al United States and Spain[63]	Multiple SOT (kidney, liver, heart, and lung)	482	318 kidney or kidney-pancreas/73 liver/57 heart/30 lung The median interval from transplantation was 5 y.	Hypertension 77% Diabetes mellitus 51% CKD 37% Obesity 35% Chronic lung disease 10% CHF 8% 61% male Median age: 58 Caucasians 47.5% African American 41.1%	Mortality rate: 18.7%. In-hospital mortality rate: 20.5%. 78% Hospitalized AKI: 44%. Mechanical ventilation 31%. ICU admission: 39%. New thromboembolic events: 3%.	Age (>65). Congestive heart failure (CHF), chronic lung disease and obesity. Presence of pneumonia at baseline (abnormal chest imaging) Lymphopenia (<0.5 thousand/mL)
Molnar et al United States[73]	Multiple SOT (Kidney, liver, heart, and lung).	98	67 kidney/13 liver/13 heart/4 lung/1 pancreas.	Hypertension 84% Diabetes mellitus 65% CKD 56% CAD 27% CHF 20% Active malignancy 7% COPD 6% 73% male. Median age: 58 African American 44% Caucasians 30%	Mortality rate: 40% 100% Hospitalized. ARDS: 74%. AKI requiring dialysis: 37% New infection 24% ICU Admission: 100%. Mechanical ventilation 56%.	Similar 28-d mortality in SOT patients to non-SOT patients. SOT patients had a non-significant trend toward a higher risk of AKI.
Pereira et al United States[65]	Multiple SOT (kidney, liver, heart, and lung).	90	46 kidney/17 lung/13 liver/9 heart/5 dual organs. The median interval from transplantation was 6.6 y.	Hypertension 64% CKD 63% Diabetes mellitus 46% Chronic lung disease 19%. Obesity 6% ESRD 6% Cancer 3% 59% male. Median age: 57. Caucasians 63% Hispanics 42%	Mortality rate: 18%. In-hospital mortality rate: 24%. 76% hospitalized. Mechanical ventilation 35%. ICU admission: 34%.	Older age. Hypertension. Dyspnea on presentation. Elevated procalcitonin level.
Roberts et al United States[66]	Multiple SOT (kidney, liver, heart, and lung).	52	29 kidney/6 lung/9 liver/6 heart/2 dual organs. The median interval from transplantation was 43.5 mo.	Hypertension 83% CKD 75% Smoker 44% Diabetes mellitus 35% ischemic heart disease 23% CHF 19% Chronic lung disease 17%. Cancer 2% 65% male Median age: 58 Caucasians 48% Hispanics 33%	Mortality rate: 16% In-hospital mortality rate: 21% 77% hospitalized. Mechanical ventilation 35%. ICU admission: 35%.	Older age. Ischemic heart disease. Elevated WBC and ANC. Greater elevation of liver function tests, LDH, CRP, procalcitonin, and creatinine kinase. The requirement for supplemental oxygen.
Chaudhry et al United States[64]	Multiple SOT (kidney, liver, heart, and lung).	47	38 kidney/4 lung/5 heart/1 liver /1 pancreas. The median interval from transplantation: N/A.	Hypertension 94% Diabetes mellitus 66% CKD 89% CHF 23% CAD 12.8% Active malignancy 8.5% 68% male. Median age: 61 African American 83%	Mortality rate: 17% In-hospital mortality rate: 23% 74% hospitalized. ARDS:35.5%. AKI: 46.8%. AKI requiring dialysis: 20% ICU admission: 37%. Mechanical ventilation 34%.	Age >60 y. Higher qSOFA, NEWS, HFH COVID-19 severity score. Ferritin >500 ng/mL. ICU Admission.

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TABLE 2. (Continued)

Clinical outcomes of solid organ transplant recipients with COVID-19 (results reported as combined in kidney, liver, heart, and lung transplant recipients)

Author/ country	Transplanted organ	Patient number	Cohort studied/ transplant to COVID diagnosis (y/mo)	Comorbid conditions/ patient characteristics	Reported clinical events (hospitalized patients)	Predictors of adverse outcome
Sharma et al United States[67]	Multiple SOT (kidney, liver, heart, and lung).	41	16 kidney/3 lung/9 heart/8 liver/5 dual organs. The median interval from transplantation was 9 y.	Hypertension 77% Diabetes mellitus 51% CKD 37% Obesity 35% Chronic lung disease 10%. CHF 8% 80% male. Median age: 60 African American 66% Caucasians 32%	Mortality rate: 14.6%. In-hospital mortality rate: 17%. 87% Hospitalized. Mechanical ventilation 30.5%. Dialysis: 30.5%. Severe COVID-19 disease: 50%.	Older age Heart disease, dementia, diabetes mellitus and COPD. Decreased absolute lymphocyte count. Elevated BUN and potassium.
Yi et al United States[68]	Multiple SOT (kidney, liver, heart, and lung).	21	12 kidney/3 liver/2 heart/4 multiorgan	90% had at least 1 comorbidity such as hypertension, DM, obesity, chronic lung Disease, and cardiovascular disease	Mortality rate 5% 67% hospitalized ICU admission: 50%. AKI 56%	N/A
Felldin et al Sweden[69]	Multiple SOT (kidney, liver, heart, and lung).	53	31 kidney/5 lung/5 heart/8 liver /4 dual organs. The median interval from transplantation was 6.9 y.	Hypertension 53% Diabetes mellitus 28% CKD 26% Cardiovascular disease 21% 80% male. Median age: 56	Mortality rate: 9.4% In-hospital mortality rate: 14% 70% hospitalized. ICU admission: 22%. Dialysis: 32%. Severe COVID-19 disease: 32% Mechanical ventilation 19%.	Higher median WBC. Higher median creatinine on admission. Raised CRP and serum ferritin.
Miarons et al Spain[70]	Multiple SOT (Kidney, liver, and lung).	46	30 kidney/13 lung/3 liver	Hypertension 67%, Diabetes mellitus 44%, CKD 78%, Cardiovascular disease 22%, chronic lung disease 36%, median age 62.7	Mortality 37%, 100% hospitalized, ICU admission 22%, ARDS 20%	N/A
Ali et al Saudi Arabia[72]	Multiple SOT (kidney, liver and lung).	67	44 kidney/15 liver/8 lung	Hypertension 34%, Diabetes mellitus 43%, ischemic heart disease 15%, mean age 52	Mortality 3%, 70% hospitalized, ICU admission 15%, AKI 19%	Higher D-dimer and LDH
Malekhosseini et al Iran[71]	Multiple SOT (kidney, liver, and pancreas).	85	66 liver/16 kidney/2 kidney/pancreas, and 1 liver/kidney	Hypertension 19%, diabetes mellitus 26%, cardiac 2.4%	Mortality 20%, 66% hospitalized, 34% ICU admission,	Leukopenia, low albumin levels, shorter duration between transplantation and COVID-19

AKI, acute kidney injury; ANC, absolute neutrophil count; ARDS, acute respiratory distress syndrome; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ICU, intensive care unit; LDH, lactate dehydrogenase; SOT, solid organ transplant; WBC, white blood cell.

including diabetes mellitus (15%–69%), hypertension (58%–85%), chronic kidney disease (28%–85%), and cardiac allograft vasculopathy (19%–57%). Rivinius et al[89] reported 28% of COVID-19 + heart transplants had reduced right ventricular function and increased pulmonary pressures, while Latif et al[90] found evidence of myocardial injury in 77% of heart transplant patients.

Three studies reported outcomes in lung transplant recipients.[93-95] Most of these patients had other medical comorbidities as summarized in Table 3. The largest series from Aversa et al included 32 patients and showed an overall mortality rate of 34% with rates of 40% in hospitalized patients and 100% in intubated patients.[93] Thirty-four percent of lung transplant recipients required ICU admission, 31% had shock, 63% developed AKI, and 47% had coinfections.

COVID-19 IN END-STAGE RENAL DISEASE PATIENTS

When determining the safety of performing kidney transplantation during the COVID-19 pandemic, the risk of this procedure must be weighed against the risk of COVID-19 in patients with end-stage kidney disease (ESKD) and those waiting for transplantation. We reviewed 9 publications related to ESKD and COVID-19 (Table 4). Early reports from European centers found a mortality rate of 20%–31% among patients on chronic dialysis who were

TABLE 3.

Clinical outcomes of liver, heart, and lung transplant recipients with COVID-19

Author/country	Transplanted organ	Patient number	Cohort studied/ transplant to COVID diagnosis (y/mo)	Comorbid conditions/patient characteristics	Reported clinical events (hospitalized patients)	Predictors of adverse outcome
Webb et al Multicenter (18 countries)[85]	Liver	151	The median interval from transplantation: N/A	Diabetes mellitus 43% Hypertension 42% Obesity 29% cardiovascular disease 15% Active malignancy 5% COPD 3% 68% males, Age: 60 Caucasians 74% African American 11%	Mortality rate: 19% In-hospital mortality rate: 14% 82% hospitalized. ICU admission: 28%. Dialysis: 32%.	Older age. Presence of comorbidities. Higher baseline creatinine. Active malignancy.
Colmenero et al Spain[87]	Liver	111	The median interval from transplantation was 105 mo.	Diabetes 57% Hypertension 29% Cardiomyopathy11% Bronchopulmonary disease 71.2% males, Age: 65.34 ± 10.96	Mortality rate: 18% In-hospital mortality rate: 21% 86.5% Hospitalized. Respiratory insufficiency: 39.6%. Respiratory support: 19.8%. ICU admission: 10.8%. Severe COVID-19 disease: 31.5%	Older age Male gender, Increased comorbidities Raised D-dimer and serum ferritin decreased absolute lymphocyte count. PaFiO2 and dyspnea at admission
Becchetti et al Europe [5 Countries][86]	Liver	57	The median interval from transplantation was 72 mo.	Hypertension 56% Cardiovascular disease 37%. Diabetes mellitus 37% 70% male, Median age: 65 Caucasians 93%	All Mortality rate: 12% In-hospital Mortality rate: 17% 72% Hospitalized. ARDS: 19%. ICU Admission: 10%.	Older age Male gender, Diagnosis of cancer Decreased absolute lymphocyte and platelet count.
Lee et al United States[88]	Liver	38	The median interval from transplantation was 4.7 y.	Hypertension 71% CKD 71% Cardiovascular disease 42%. Diabetes mellitus 50% 70% male, Median age: 65 Caucasians 39% Hispanics 37%	Mortality rate: 18% In-hospital mortality rate: 29% 71% Hospitalized. Respiratory support: 75%. ICU admission: 33%. Severe COVID-19 disease: 45%	Older age Male gender, One or more comorbidities. AKI. raised D-dimer, CRP and serum ferritin decreased absolute lymphocyte count.
Rivinius et al Germany[89]	Heart	21	The median interval from transplantation was 95 mo.	Hypertension 71% Dyslipidemia 71% diabetes mellitus 33% ESRD 28% COPD/asthma 19% Cardiac allograft vasculopathy 19% 81% male, Age: 58.6 ± 12.3 y	Mortality rate: 33%. In-hospital mortality rate: 36%. 90% Hospitalized. Reduced RV function: 28% Elevated pulmonary artery pressure: 28% Moderate-to-severe tricuspid regurgitation: 19%. ECG abnormalities: 19% New thromboembolic events: 19% Severe COVID-19 Disease: 38%	RV dysfunction. Elevated pulmonary artery pressures. Tricuspid valve regurgitation. Thromboembolic events. Severe COVID-19 Disease. Older age Raised LDH, Troponin-T and NT-proBNP. Elevated D-dimer and decreased absolute lymphocyte count.

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TABLE 3. (Continued)

Clinical outcomes of liver, heart, and lung transplant recipients with COVID-19

Author/country	Transplanted organ	Patient number	Cohort studied/ transplant to COVID diagnosis (y/mo)	Comorbid conditions/patient characteristics	Reported clinical events (hospitalized patients)	Predictors of adverse outcome
Latif et al United States[90]	Heart	28	The median interval from transplantation was 8.6 y.	Hypertension 71% diabetes mellitus 61% cardiac allograft vasculopathy 57% CKD 36% Obesity 25% Active malignancy 18%. 79% male, Median age: 64.	Mortality rate: 25%. In-hospital mortality rate: 32%. 79% Hospitalized. evidence of myocardial injury: 77% Severe COVID-19 disease: 25%	N/A
Ketcham et al United States[91]	Heart	13	The median interval from transplantation was 9.6 y.	Hypertension 85% CKD 85% Diabetes mellitus 69% Cardiac allograft vasculopathy 46% Heart failure 38% 100% male. Median age: 61. 100% African American	Mortality rate: 15%. In-hospital mortality rate: 25% 61.5% Hospitalized. AKI: 84%. Dialysis:38%. Severe COVID-19 disease: 46%	N/A
Iacovoni et al Italy[92]	Heart	26	The median interval from transplantation was 6 y.	Hypertension 58% CKD 50% Diabetes mellitus 15% COPD/asthma 4% 77% male. Median age: 63.	Mortality rate: 27%. In-hospital mortality rate: 41%. 65% Hospitalized. Severe COVID-19 Disease: 31%. New thromboembolic events: 7%	Age (>65). Higher incidence of CKD and diabetes. Higher respiratory rate and lower oxygen saturation at the first clinical evaluation. Raised procalcitonin. Elevated CRP.
Aversa et al United States[93]	Lung	32	The median interval from transplantation was 5.6 y.	Hypertension 56% CKD 66% Cardiovascular disease 19%. Diabetes mellitus 44%. Obesity 25% Active malignancy 3%. 50% male, Median age: 65 Caucasians 80% Hispanics 20%	Mortality rate: 34% In-hospital mortality rate: 40%. 84% Hospitalized. mortality on mechanical ventilation:100%. Severe COVID-19 disease: 41% AKI: 63%. Shock: 31%. ARDS:25% Coinfections: 47%. ICU Admission: 34%.	Hypotension at admission. AKI. Leukocytosis. Raised D-dimer, IL-6 serum ferritin and CRP. Decreased absolute lymphocyte count. Multiple comorbidities[γ].
Verleden et al Belgium[94]	Lung	10	The median interval from transplantation was 26 mo.	Hypertension 50% CKD 50% Diabetes mellitus 30%. Obesity 20% 30% male, Median age: 60.5	Mortality rate: 10%. In-hospital mortality rate: 11%. 90% Hospitalized. Severe COVID-19 disease: 50%	Male gender, One or more comorbidities. Raised CRP and decreased absolute lymphocyte count.
Myers et al United States[95]	Lung	8	The interval from transplantation was 10±10 y.	Hypertension 37% Dyslipidemia 37% CKD 37% Atrial Fibrillation 37% Diabetes mellitus 35%. 87% male, Median age: 59.6	Mortality rate: 25%. 100% Hospitalized. Severe COVID-19 disease: 62% ICU admission: 37%. AKI: 37%. Shock: 25%. Other complications: liver failure and pancreatitis.	Coinfection. Recent transplantation.

AKI, acute kidney injury; ANC, absolute neutrophil count; ARDS, acute respiratory distress syndrome; CHF, congestive heart failure; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; ICU, intensive care unit; LDH, lactate dehydrogenase; SOT, solid organ transplant; WBC, white blood cell.

TABLE 4.

Clinical outcomes in end stage kidney disease patients with COVID-19

Article/country	Patient number	Patient's characteristics and comorbidities	Clinical outcomes	Predictors of mortality
Ng et al United States Multicenter[101]	419 patients (408 hemodialysis, 11 peritoneal dialysis)	Sex: Male 260/419 (62%) Median age: 66 IQR (55–75) Race: Black 152/419 (36%), White 93/419 (22%), Hispanic 87/419 (21%) Hypertension 382/419 (91%) Diabetes mellitus 248/419 (59%) Coronary artery disease 121/419 (29%) Heart failure 102/419 (24%) Lung disease 34/419 (8%) Cancer 36/419 (9%)	Mortality 133/419 (32%) Hospitalized 419/419 (100%)	Increased age Mechanical ventilation Vasoactive medication use Lymphopenia Elevated BUN Elevated ferritin
Fisher et al United States Single Center[99]	114 patients (all on hemodialysis)	Sex: Male 70/114 (61%) Median age: 64.5 IQR (55–73) Race: Black 56/114 (49%), Hispanic 45/114 (40%), White 7/114 (6%), Asian 6/114 (5%) Hypertension 102/114 (90%) Diabetes mellitus 76/114 (67%) Heart disease 63/114 (55%) Lung disease 40/114 (35%) Cancer 14/114 (12%)	Mortality 32/114 (28%) Hospitalized 114/114 (100%) ICU stay 15/114 (13%) Discharged 73/114 (64%)	Elevated respiratory rate on admission Lower oxygen saturation on admission Initial elevated procalcitonin, ferritin, lactic dehydrogenase and lower lymphocytes count
Valeri et al United States Single Center[100]	59 patients (57 hemodialysis, 2 peritoneal dialysis)	Sex: Male 33/59 (56%) Median age: 63 IQR (56–78) Race: Black 15/59 (25%), White 11/59 (19%), Other 33(56%) Ethnicity: 44/59 (75%) Hypertension 58/59 (98%) Diabetes mellitus 41/59 (69%) Heart disease 27/59 (46%) Lung disease 10/59 (17%)	Mortality 18/59 (31%) Hospitalized 59/59 (100%) ICU stay 8/59 (14%) Discharged 41/59 (69%)	Initial higher WBC, lactate dehydrogenase and C-reactive protein
Sanchez-Alvarez et al Spain Registry of Spanish Society of Nephrology[61]	582 patients (547 hemodialysis, 35 peritoneal dialysis)	Sex: 381/582 (66%) Mean age: 71 SD (±15)	Mortality 145/582 (25%) Hospitalized 471/582 (81%) ICU stay 35/582 (6%)	Age Pneumonia on imaging Hydroxychloroquine has been associated with better survival
Goicoechea et al Spain Single Center[80]	36 patients (24 hemodialysis, 12 hemodiafiltration)	Sex: Male 23/36 (64%) Mean age: 71 SD (±12) Hypertension 35/36 (97%) Diabetes mellitus 23/36 (64%) Heart disease 19 (53%) Lung disease 7/36 (19%)	Mortality 11/36 (31%) Hospitalized 36/36 (100%) Discharged 7/36 (19%)	Longer dialysis vintage Increased LDH levels
Corbett et al United Kingdom Imperial College healthcare NHS Trust[96]	300 patients (290 in-center hemodialysis, 8 peritoneal dialysis, 2 home hemodialysis)	Sex: Male 180/300 (60%) Median age: 67 IQR (57–77) Race: Asian 137/300 (46%), White 84/300 (28%), Black 75/300 (25%) Diabetes mellitus 155/300 (52%)	Mortality 61/300 (20%)	Older age Inactive on kidney transplant waitlist
Keller et al France Multicenter[98]	123 patients (all hemodialysis)	Sex: Male 70/122 (57%) Median age: 77 IQR (68–83) Hypertension 120/123 (98%) Diabetes mellitus 63/119 (53%) Obesity 40/112(36%) Ischemic heart disease 54/123 (46%) Lung disease 40/119 (34%) Cancer 24/123 (20%)	Mortality 29/123 (24%) Hospitalized 87/123 (71%) ICU stay 7/87 (8%) Complete recovery 30 /123 (24%)	Body temperature C-Reactive Protein at admission

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TABLE 4. (Continued)

Clinical outcomes in end stage kidney disease patients with COVID-19

Article/country	Patient number	Patient's characteristics and comorbidities	Clinical outcomes	Predictors of mortality
Tortonese et al France Single Center[97]	44 patients (mix of hemodialysis and peritoneal dialysis)	Sex: Male 29/44 (66%) Median age: 61 IQR (51.5–72.5) Hypertension 43/44 (98%) Diabetes mellitus 22/44 (50%) Obesity 15/44 (34%) Heart disease 17/44 (39%) Lung disease 12/44 (27%) Cancer 8/44 (18%)	Mortality 12/44 (27%) Hospitalized 41/44 (93%) ICU stay 15/44 (34%) Discharged 26/44 (59%)	Cough at presentation, thrombocytopenia ≤120, lactic dehydrogenase ≥2x normal limit, C-Reactive protein ≥175 mg/L
Alberici et al Italy Brescia Renal COVID Task Force[77]	94 patients (69 hemodialysis, 23 hemodiafiltration, 2 acetate-free biofiltration)	Sex: Male 62/94 (66%) Median age: 73 IQR (60–77) Hypertension 87/94 (93%) Diabetes mellitus 40/94 (43%) Heart disease 33/94 (35%) Lung disease 10/94 (11%) Cancer 11/94 (12%)	Mortality 24/94 (26%) Hospitalized 57/94 (61%) Discharged 11/57 (19%)	Fever at diagnosis Cough at diagnosis Elevated serum C-Reactive protein at diagnosis ≥50 mg/L

ICU, intensive care unit; IQR, interquartile range; LDH, lactic dehydrogenase.

hospitalized for COVID-19.[61,77,80,96-98] The mortality rate in 114 ESKD patients admitted to our center was 28%[99] and 31% at another New York center.[100]Another study investigated 10482 patients with COVID-19 admitted to 13 New York hospitals from March 1, 2020, to April 27, 2020, 419 of which had ESKD.[101] Patients with ESKD had a higher rate of in-hospital death (31.7% versus 25.4%; odds ratio, 1.38; 95% confidence interval, 1.12-1.70) and independent risk factors for in-hospital mortality were increased age, mechanical ventilation, lymphopenia, and higher blood urea nitrogen and serum ferritin levels. Risk factors for mortality from other studies are further summarized in Table 4.

Ravanan et al examined the incidence of SARS-CoV-2 infection and subsequent mortality in patients on the active waiting list for a deceased donor SOT and recipients with a functioning SOT.[102] This study reported that 197 (3.8%) of the 5184 waitlisted patients and 597 (1.3%) of the 46789 SOT recipients tested positive for SARS-CoV-2.

Mortality for those testing positive for SARS-CoV-2 was 10.2% (20/197) for waitlisted patients and 25.8% (154/597) for SOT recipients. Mohamed et al reported 15% mortality in 32 waitlisted patients and 32% in 28 kidney transplant recipients, but the difference was not statistically significant (*Transplantation* in press). Massie et al conducted a simulation study of immediate-kidney transplant versus delay until-after-pandemic for different patient phenotypes under a variety of potential COVID-19 scenarios.[103] A calculator was created (http://www.transplantmodels.com/covid_sim), and machine learning approaches were used. In most scenarios of COVID-19 dynamics and patient characteristics, immediate kidney transplant provided survival benefit; and only began showing evidence of harm in scenarios where Case Fatality Rates were substantially higher for kidney transplant recipients (eg, ≥50% fatality) than for waitlist registrants.

TRANSPLANT ACTIVITY DURING COVID-19 PANDEMICS

Like other areas of medicine, the clinical practice of transplantation has been dramatically affected by the COVID-19 pandemic.[1,37,104] COVID-19 has had broad-reaching effects on transplant activity, both for donation and for transplantation,[18,105-107] as well as transplant-related research activities.[108] Although, kidney transplantation reduces the morbidity and long-term mortality and is cost-saving compared with dialysis, it is rarely an immediate life-saving procedure. Early in the outbreak period, transplant societies recommended suspending living kidney transplant programs in communities with widespread transmission to avoid exposing recipients to increased risk of immunosuppression during the pandemic as well as limiting the risk to living donors.[106,107,109,110] Deceased-donor kidney transplantation has been suggested to be reserved for likely life-saving indications such as for patients lacking options for dialysis access or a panel reactive antibody titer >98% with a perfectly matched kidney without donor-specific antibody. Due to life-saving nature of heart, liver, and lung transplantation, those activities continued in sicker patients with an expected survival of <6 months. In the United States, there was a 51.1% drop in transplant activity, which was largely driven by reductions in kidney transplantation.[105,111] A similar trend was observed in France, with a greater (90.6%) reduction in clinical transplant activity.[105] A significant decreases in total waitlist additions and increases in waitlist deaths were noted in most US transplant domains.[112] In the Netherlands, transplant volumes decreased by 67% in the first month after the pandemic began.[113] Italy observed a 25% reduction in transplant activity during the first 4 weeks of the COVID outbreak, with similar decreases observed in most major organ groups.[114] In the Italian experience, authors concluded there was urgent need to closely monitor ICU availability for transplant patients during the developing COVID-19 response to preserve transplant activity, particularly for Europe and the United States, where deceased donation is more common. In Belgium, transplant activity was dramatically reduced, and some typically busy hospitals completely ceased transplant procedures.[115] In the United Kingdom, the number of deceased donors decreased by 66%, and the number of deceased donor

transplants decreased by 68%.[116] Liver transplant activity was decreased 25% in the United States and over 80% in the United Kingdom and India between February and May 2020.[117] A stepwise approach to practice during pandemic was suggested by University of California at San Francisco Transplant Center.[118]

PRECAUTIONS TO TAKE IN ACCEPTING ORGANS DURING PANDEMIC

The initial reduction in transplant surgery rates in the United States and Europe resulting from the COVID-19 pandemic was partly driven by lack of clarity around which donors and recipients were SARS-CoV-2+ as well as a poor understanding of how COVID infections would affect transplanted patients.[119,120] As widespread testing for transplant donors and recipients became available, transplant rates began to increase.[121,122] A recent report by The Transplant Society ethics committee stated that reinvigoration of transplant activity will be "contingent on availability of COVID-19 testing for donors, recipients, and healthcare practitioners."[122] It is now accepted that, before organ acceptance, both donor and recipient should be SARS-CoV-2 RT-PCR (–), typically in the 48 hours before recovery or transplantation.[123] In the early phases of the COVID-19 pandemic, and as COVID-19 testing became more accessible, chest CT scans were frequently ordered before organ recovery for organ donors, and in some cases, transplant candidates as well. Chest CT scans are thought an important complement to RT-PCR testing and may show signs of COVID-19 related disease for asymptomatic patients, 8 days before eventual positive RT-PCR test.[124]

Further pretransplant considerations for organ acceptance during COVID-19 include proximity of donors to COVID-19(+) patients. For example, organ donation from a patient in an ICU with other COVID-19(+) patients or in a hospital considered to a "hot spot" should be considered cautiously, and the clinical history of the donor should be taken into consideration. Indeed, New York City reported a 90% reduction in donation volumes during the month of April 2020. Close proximity of COVID-19(+) patients to organ donors prompted many declined organs despite negative PCR testing, particularly in areas hardest hit by COVID-19.[120] Further, because many surgeons recover their own organs for transplantation, the workflow around travel for organ recovery has been limited by both hospital policies disallowing outside provider access and physician disinterest in travel, further suppressing organ transplant rates.[122]

Recipient selection has also forced providers accepting organs to reconsider the robustness of their recipients before transplantation. For example, elderly patients who are more likely to require an inpatient rehabilitation stay after transplantation may be considered too risky given the proclivity for COVID-19 to disproportionately affect nursing home residents, particularly early in the pandemic.[125] Additional patient selection criteria includes highly sensitized patients. Indeed, T-cell depletion has been discouraged due to potent and long-lasting immunosuppression after induction, which theoretically decreases recipients' viral clearance and diminishes the ability to mount an antibody response if infected with COVID-19 posttransplant. However, dose reductions in immunosuppression may increase the risk of transplant rejection.[126] Thus, organ acceptance is particularly challenging for patients who must receive T-cell depletion due to increased sensitization.

Another question is how long patients on the waiting list should wait after recovery from COVID-19 to be active for transplantation. Although there are no reported studies, we suggest waiting at least 4–6 weeks after recovery from COVID-19, and patients' should undergo pulmonary function testing as well as SARS-CoV-IgG and RT-PCR.

ETHICAL QUESTIONS FACING TRANSPLANTATION DURING THE PANDEMIC

A number of important, yet minimally addressed, ethical issues have challenged transplantation during the COVID-19 pandemic.[122] For example, is it ethical to skip someone on the list because they live with people who are high risk for spreading COVID-19? Is it ethical to skip patients with long-waiting times, but who are at higher risk for death on the waiting list because when the pandemic ends, they are may still be likely to attract good organ offers?[122] Is it ethical for hospitals to suppress transplant volumes to maintain ICU beds in anticipation of additional future COVID-19 resource burden? Indeed, these questions are weighty and perhaps overwhelming at times. Addressing these circumstances, Stock et al recently commented in *Transplantation* that during COVID-19, "programmatic decisions about transplantation will weigh more heavily on distributive justice, beneficence, and nonmaleficence than respect for autonomy."[122]

TREATMENT

Since the start of the pandemic, there has been a worldwide effort to discover effective treatment options for COVID-19. A wide variety of therapeutics from antivirals to immunomodulators to convalescent plasma have been studied and while not specific for SOT recipients, these patients have not been excluded in most trials. While supportive care remains a mainstay of treatment, we now have more evidence to provide treatment guidance for patients with COVID-19. Recently, the Infectious Diseases Society of America released guidelines regarding management of COVID-19, including 7 treatment recommendations and narrative summaries of other treatments currently undergoing evaluation.[127]

Management of Immunosuppression

Reduction or withdrawal of calcineurin inhibitors, mycophenolate mofetil, mycophenolic acid, azathioprine, or mTOR-inhibitors (mammalian target of rapamycin) was considered in most published articles. However, complete withdrawal of immunosuppression or significant reduction of immunosuppression could hypothetically exacerbate inflammation in the absence of antiinflammatory agents. In contrast, continuation of immunosuppressive treatment could decrease the ability to mount an antibody response to COVID-19, especially given the documented lymphopenia and low T-cell counts in kidney transplant recipients. It is not clear at what point during progression of clinical deterioration that immunosuppression should be minimized or stopped.

Antivirals

Remdesivir

Based on data suggesting efficacy against SARS-CoV-1 and MERS-CoV[128] as well as in vitro activity against SARS-CoV-2,[129] clinical trials of remdesivir, an inhibitor of viral RNA polymerase, began early in the pandemic. In a multicenter, randomized, placebo-controlled trial (ACT-1) of 1063 patients, patients receiving a 10-day course of remdesivir had a shorter time to recovery compared with placebo (11 versus 15 d, ratio for recovery 1.32, 95% CI: 1.12-1.55), with the most significant improvement seen in nonintubated patients receiving supplemental oxygen.[130] However, despite the improved rate of recovery, no mortality benefit was seen. Given the large number of anticipated infections and high demand for remdesivir, an additional small randomized study attempted to evaluate the optimal duration of therapy by comparing a 5-day versus 10-day course of antiviral therapy.[131] This study of 397 nonintubated patients found no difference in clinical status at day 14 after adjusting for baseline severity, suggesting that shorter courses may be adequate. In both ACT-1 as well as the study by Goldman et al, remdesevir was well tolerated and based on these studies, the US Food and Drug Administration (FDA) issued an emergency use authorization for the treatment of confirmed or suspected COVID-19 in both adults and children in May 2020. Studies evaluating remdesivir as part of combination therapy are ongoing (https://clinicaltrials.gov/ct2/show/NCT04401579 and https://clinicaltrials.gov/ct2/show/NCT04492475).

Lopinavir/Ritonavir

While there was interest in protease inhibitors, notably lopinavir/ritonavir, based on data suggesting efficacy against other coronaviruses, this practice was abandoned early in the pandemic after results published by Cao et al found no benefit with this treatment in patients with severe COVID-19 infection.[132]

Antimalarials

The antimalarial agents, chloroquine and hydroxychloroquine (HCQ), which are also used as disease modifying agents in several autoimmune conditions, quickly become the mainstay of treatment during the early days of the pandemic. These agents have antiviral activity against SARS-CoV-2 in vitro, and the immunomodulatory activities were hypothesized to limit the host inflammatory response elicited by SARS-CoV-2 infection.[133] These factors led to the FDA authorizing emergency use of HCQ in March 2020. However, since that time, a number of randomized, controlled trials in several clinical settings have failed to show any benefit.[134-139] Early observational data suggested the addition of azithromycin to HCQ may be beneficial.[136] However, a study of over 500 patients randomized to HCQ versus HCQ + azithromycin versus standard of care found that HCQ with or without azithromycin was not associated with improved clinical outcomes but did have higher adverse events.[135] Based on the large number of controlled trials failing to show any benefit to HCQ, the FDA revoked its emergency use authorization in June 2020.

Corticosteroids

Given the robust inflammatory response that is thought to be a significant driver of morbidity and mortality in COVID-19, corticosteroid use has been of interest since the beginning of the pandemic. Initial data from cohort and case-controlled studies suggested minimal benefit or even worse outcomes in those receiving steroids, and subsequently cautious use was recommended.[140] However, recent data have emerged from several large RCTs suggesting benefits with corticosteroid therapy.[141-144] Initial benefits were suggested by the RECOVERY Collaborative group in a large, open-label trial comparing a number of treatments for COVID-19, including dexamethasone. This large study, which compared 2104 patients who received dexamethasone to over 4000 patients receiving usual care, found a significant mortality benefit at 28 days (22.9% in dexamethasone group versus 25.7% in usual care group, $P < 0.001$).[141] However, based on subgroup analysis, dexamethasone was only beneficial in those receiving mechanical ventilation and supplemental oxygen but not among those without hypoxia. Following the publication of this data, 3 additional trials evaluating corticosteroid therapy in COVID-19 stopped enrollment early.[142-144] While none of these trials showed a mortality benefit, there were trends toward clinical improvement despite likely being underpowered. To further evaluate this data, a metaanalysis of pooled data from 7 randomized controlled trials (including those above) was subsequently performed. This study found that patients with severe COVID-19, that is, requiring either mechanical ventilation or high levels of supplemental oxygen, who received steroid therapy had a lower mortality rate at 28 days compared with standard care alone.[142]

In addition to oxygenation, certain biochemical markers may be useful in determining who may benefit from corticosteroids. In an observational study by Keller et al, steroid use was not associated with an overall benefit on mortality; however, there was a significantly reduced risk of mortality in patients with baseline C-reactive protein >20 mg/dL (OR, 0.23; 95% CI, 0.08-0.70).[145] Furthermore, there was an increase in risk of mortality seen in patients with a CRP <10 mg/dL (OR, 2.64; 95% CI, 1.39-5.03). These findings along with those published by the RECOVERY Collaborative group suggest that while steroids may be beneficial in patients with severe COVID-19, more judicious use is warranted in mild disease.

Biologic Agents

Similarly to corticosteroids, the use of biologics has been high touted based on the inflammatory response associated with COVID-19 infection, especially given early data suggesting that elevated inflammatory cytokines are associated with more severe disease.[146,147] While a number of biologics have been evaluated, IL-6 inhibitors have been the most widely studied. Early observational cohort studies of tocilizumab, a monoclonal antibody that blocks the IL-6 receptor, found that patients receiving tocilizumab had reduced mortality compared with standard of care.[148,149]

However, preliminary data from a randomized, double-blind, placebo-controlled phase III clinical trial found that tocilizumab failed to meet its primary endpoint of improved clinical status in patients hospitalized with severe COVID-19 and found no difference in overall mortality at 28 days (19.7% in tocilizumab group versus 19.4% in placebo; $P = 0.9410$), although full results from this trial have yet to be published (https://www.roche.com/investors/updates/inv-update-2020-07-29.htm). Tocilizumab use in 29 SOT

recipients did not show in mortality rate compared with controls.[150] Another IL-6 receptor antagonist, sarilumab, also stopped its phase III, placebo-controlled clinical trial after preliminary data failed to show clinical improvement in COVID-19 patients requiring mechanical ventilation (https://www.sanofi.com/en/media-room/press-releases/2020/2020-07-02-22-30-00). Full results from this trial have also not yet been reported.

Based on observations that the hyperinflammatory state in COVID-19 is similar to secondary haemophagocytic lymphohistiocytosis (sHLH),[151] anakinra, an IL-1receptor antagonistic that is used for sHLH, was also evaluated for COVID-19 in an observational, cohort study.[152] While patients treated with anakinra had lower rates of death and mechanical ventilation in this study, these results should be interpreted cautiously and larger, randomized trials are needed to further evaluate its efficacy.

Antibody Therapy

Convalescent Plasma

Passive antibody therapy through the use of convalescent plasma is another potential therapy for COVID-19, which may be effective through viral neutralization.[153] Based on its use in other viral illnesses and pandemics, the Mayo clinic and FDA established a large Expanded Access Program, which has been used to treat >35 000 hospitalized patients with COVID-19. Early data from this program found that convalescent plasma is well tolerated with a low rate of serious adverse events attributable to plasma (<1%) and an overall mortality rate of 8.6%.[154] More recent data found that patients receiving plasma had a significant mortality benefit at 30 days when treated earlier in their disease course.[155]Further, a mortality benefit was also found in patients receiving plasma containing higher antibody levels compared with lower antibody levels. Based on this data, the FDA issued an emergency use authorization for convalescent plasma for treatment of COVID-19 in August 2020.

Despite these early reports and FDA authorization, data from randomized trials is lacking. A randomized trial from China revealed a trend toward clinical improvement with plasma therapy (51.9% versus 43.1%) but failed to meet statistical significance ($P = 0.26$), possibly due to underpowering after the study closed early as a result of declining COVID cases in China.[156]

Based on difficulty with enrollment, pooled analyses of patient data available from RCTs, matched control studies, and case series were performed on 804 patients with COVID-19. Aggregate data from controlled studies showed improved mortality rate in patient receiving plasma compared with those receiving standard care (13% versus 25%; $P < 0.001$) (https://www.medrxiv.org/content/10.1101/2020.07.29.20162917v1). However, despite these early signals, a recently completed randomized trial of 464 patients with moderate COVID-19 did not find any mortality benefit or decrease in disease progression in patients treated with convalescent plasma (https://www.medrxiv.org/content/10.1101/2020.09.03.20187252v2). Currently, the benefit of plasma remains unclear, although several randomized trials are ongoing and can hopefully provide more definitive data.

Other Antibody Therapy

Based on data supporting efficacy of convalescent plasma in other infections, efforts have also been made to generate effective neutralizing antibodies of the SARS-CoV-2 spike protein to create a "therapeutic antibody cocktail."[157] Clinical data on the use of this therapy is limited, but trials are underway, including the RECOVERY trial.

Vaccines

Similarly to effective treatments focused efforts on vaccine development started quickly after the discovery of SARS-CoV-2 and have evolved at an impressive rate. According to the World Health Organization, there are over 169 vaccines under development with 26 already in the human phase of trials. Several vaccine candidates have reported good safety and immunogenicity outcomes in phase 1/2 and phase 2 studies.[158-162] Large scale, phase 3 trials are currently underway worldwide. While live-attenuated vaccinations are contraindicated in transplant recipients, most of the phase III trials currently underway utilize mRNA or nonreplicating viral vector as a mechanism of action, which do not pose a known risk to immunosuppressed patients. However, the safety and efficacy of these vaccinations in transplant recipients will need further study.

CONCLUSION

The COVID-19 pandemic has dramatically impacted all aspects of medicine, and SOT is no exception. The effects of this virus on SOT have created challenges in clinical management and unfortunately, have led to significant morbidity and mortality. On a broader scale, the pandemic has impacted policy decisions on a hospital as well as a national level with respect to the practice of transplantation. Despite these challenges, tremendous progress has been made over the past several months regarding the care of patients with COVID-19 as advances have been made in therapeutics and vaccine studies are being performed at an unprecedented rate. As the understanding of COVID-19 pathogenesis and management continues to evolve, advances in the care of SOT recipients will allow for transplantation to be performed safely and optimally in the COVID era.

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