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Effects of Coronavirus Disease 2019 on Solid Organ Transplantation
Hassan Aziz, Nassim Lashkari, Young Chul Yoon, Jim Kim, Linda S. Sher, Yuri Genyk, and Yong K. Kwon

ABSTRACT

Background. As the novel coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has emerged as a viral pandemic, data on the clinical characteristics and outcomes of patients with SARS-CoV-2 infection undergoing solid organ transplant are emerging. The objective of this systematic review was to assess currently published literature relating to the management, clinical course, and outcome of SARS-CoV-2 infection in liver, kidney, and heart solid organ transplant recipients.

Methods. We conducted a systematic review to assess currently published literature relating to the management, clinical course, and outcome of SARS-CoV-2 infection in liver, kidney, and heart solid organ transplant recipients. Articles published through June 2020 were searched in the MEDLINE, ClinicalTrials.gov, and PubMed databases. We identified 49 eligible studies comprising a total of 403 solid organ transplant recipients.

Results. Older age, male sex, and preexisting comorbidities, including hypertension and/or diabetes, were the most common prevailing characteristics among the solid organ transplant recipients. Clinical presentation ranged from mild to severe disease, including multiorgan failure and death. We found an overall mortality rate of 21%.

Conclusion. Our analysis suggests no increase in overall mortality or worse outcome in solid organ transplant recipients receiving immunosuppressive therapy compared with mortality in the general surgical population with SARS-CoV-2. Our findings suggest that transplant surgery and its immunosuppressive effects should not be a deterrent to proper surgical care for patients in the SARS-CoV-2 era.
Table 1. Summary of Clinical Outcomes of Severe Acute Respiratory Syndrome Coronavirus 2-positive Solid Organ Transplant Recipients, by Study

| SOT       | Author [reference] | Location       | No. of Cases (n) | Age and Sex | Comorbidities                                                                 | Immunosuppressive Regimen | Time From Transplant | Presentation (Symptoms) | Treatment | Clinical Course | Outcomes                  |
|-----------|--------------------|----------------|------------------|-------------|-------------------------------------------------------------------------------|---------------------------|----------------------|------------------------|-----------|----------------|---------------------------|
| Multiple  | Tschopp et al [18] | Switzerland    | 21               | Median 56 years, 71% male | HTN (87%), DM (45%), Obesity (24%), TAC (86%) | TAC (96%); Prednisone (93%); MMF (77%); CSA (70%); Azathioprine (70%); mTOR (5%) | Median 47 months | Fever (76%), dry cough (51%), nausea (23%), diarrrhea (23%) | Immunosuppressant modified in 14 pts (87%); HCQ, azithromycin, lopinavir/ritonavir | 20 pts (95%) hospitalized, 5 pts (25%) ICU admission | 16 pts (80%) discharged, 3 pts (15%) remain hospitalized, 2 pts (10%) died |
| SOT types |                    |                |                  |             |                                                                               |                           |                      |                        |           |                  |                           |
| Multiple  | Fernández-Ruiz et al [11] | Spain       | 18               | Median 71 years, 59% male | HTN (92%), DM (50%), Cerebro (20%), TAC (56%); EVE (22%); CSA (71%) | Prednisone (87%); MMF/MPA (81%); Azathioprine (81%); Lopinavir/ritonavir (81%); HCQ monotherapy (28%); Interferon-β (17%) | Median 9.3 years | Fever (83%), gastrointestinal symptoms (28%), respiratory failure (28%) | Lopinavir/ritonavir + HCQ (50%); 4 pts (22%) developed progressive respiratory failure | 2 pts (11%) required ICU and invasive mechanical ventilation, 5 pts (28%) hospitalized, 8 pts (44%) discharged | 5 pts (28%) died, 2 pts (11%) required ICU and invasive mechanical ventilation |
| Multiple  | Pereira et al [8]  | United States | 90               | Median 57 years, 59% male | HTN (84%), DM (46%), Chronic lung disease (19%), Diabetes (6%), Obesity (6%) | Calcineurin inhibitor modified (84%); MMF (72%); Steroid (6%); MMF (72%); EVE (22%) | Median 6.04 years | Fever (70%), cough (45%), dysorexia (45%), fatigue (28%), myalgia (24%), diarrhea (21%) | Immunosuppressant held or reduced in majority of hospitalized pts (91%); Asthmophen (86%); Remdesivir (17%); Tocilizumab (31%); Botul steroid (24%) | 22 (24%) patients were discharged, 10 pts (28%) died, 37 pts (54%) discharged | 15 pts (38%) died, 37 pts (54%) discharged |
| Multiple  | Pietri et al [10]  | Italy         | 13               | Median 55 years, 59% male | HTN (54%), DM (37%) | TAC (54%); CSA (38%); MMF (38%); Steroid (46%); Belatacept (8%) | Median 5.3 years | Respiratory symptoms | Immunosuppressant medication HCQ (67%); HCQ + lopinavir/ritonavir (23%); Remdesivir (9%); High-dose steroids (23%); Tocilizumab (9%); Immunosuppressive medications decreased in 8 of 9 pts (20% enrolled in RCT 3 (30%) with either HCQ, azithromycin, lopinavir/ritonavir, 7 (70%) abx | 62% had reduction or change in condition; 69% developed respiratory failure | 1 pt died |
| Multiple  | Fung et al [20]    | United States | 10               | Median 56.5 years, 60% male | HTN, DM, cardiovascular disease | Triple immunosuppression (70%); CNI + MMF (61%); 19, DM (95%); 10, diabete (22%); 5 | Median 6.1 years | Fever (80%), cough (80%), dysorexia (65%), myalgia (60%), fatigue (50%) | Immunosuppressant medication HCQ (65%); HCQ + lopinavir/ritonavir (23%); Remdesivir (9%); High-dose steroids (23%); Tocilizumab (9%); Immunosuppressive medications decreased in 8 of 9 pts (20% enrolled in RCT 3 (30%) with either HCQ, azithromycin, lopinavir/ritonavir, 7 (70%) abx | 70% hospitalized 30% required ICU admission; all developed ARDS and shock | 5 pts (50%) discharged, 2 pts (20%) remain hospitalized |
| Multiple  | Hsu et al [22]     | Los Angeles, CA| 1                 | Median 59 years, 78% male | HTN (93%), DM (43%), CNI + MMF (14%); CM, MIF - steroid (39%); Steroid (4%); EVE (4%); 1 | <1 year (4%); >1 year (98%) Complete | Fever (81%) 19, cough (71%); diarrrhea (16%); | 57% remained on immunosuppressive medications 13; All hospitalized pts received abx HCQ (73%); 3 | 83% required hospitalization 19; 13 monitored at home without additional treatment | 5 (22%) died, 14 (65%) recovered and discharged, 4 (17%) with clinical improvement |
| Multiple  | Hoek et al [21]    | Netherlands   | 23               | Mean 59 years, 78% male | HTN (93%); 19, DM (43%); 10, diabete (22%); 5 | CNI + MMF (14%); CM, MIF - steroid (39%); Steroid (4%); EVE (4%); 1 | Fever (81%) 19, cough (71%); diarrrhea (16%); | 57% remained on immunosuppressive medications 13; All hospitalized pts received abx HCQ (73%); 3 | 83% required hospitalization 19; 13 monitored at home without additional treatment | 5 (22%) died, 14 (65%) recovered and discharged, 4 (17%) with clinical improvement |
| Multiple  | Hsu et al [22]     | Los Angeles, CA | 1                | 38 years, male | DM, HTN, obesity, chronic foot ulcer, TAC, MMF, prednisone | Fever, headache, sore throat, dry cough, dysorexia, fatigue, myalgia | Fever, headache, sore throat, dry cough, dysorexia, fatigue, myalgia | HCQ Enrolled in clinical trial | Toc; prednisone, continued for entirety of illness course, MMF held starting SD 2; Presented to ED on SD 2; Home quarantine SD 3; worsening symptoms and hospitalization SD 4; discharge SD 5; readmission SD 6; worsening hypoxia and transfer to ICU SD 9; transferred out of ICU, discharged SD 15 | Alive, discharged |
| SOT          | Author [reference] | Location | No. of Cases (n) | Age and Sex | Comorbidities | Immunosuppressive Regimen | Time From Transplant | Initial Presentation (Symptoms) | Treatment | Clinical Course | Outcomes |
|-------------|-------------------|----------|------------------|-------------|---------------|--------------------------|---------------------|--------------------------------|------------|-----------------|----------|
| Kidney      | Yi et al [23]     | Houston, TX | 21               | Mean 54.8 years, 62% male/13% female | 30% with other HTN, DM, obesity, chronic lung disease, CVD | Triple immunosuppression | Median of 5.58 years | 95% with fever, cough, SOB | Immunosuppressive medications adjusted daily based on organ type | 33% treated as outpatients | 1 pt (5%) died (heart-lung) |
|             |                   |          |                  |             |               |                          |                     |                                |            |                 |          |
| Heart       | Holzhauser et al [25] | United States | 2               | Pt 1: 59 years/female, 62% male/38% female | Kidney (57%) | Tac, MMF | Pt 1: H1N2, DM, CKD | Pt 2: Fever, cough, fatigue, anorexia | Path: Csf, leukocytosis, respiratory failure, meningitis, pneumonia | Path: | Died Pt 2: Alive, discharged |
|             | Li et al [26]     | China    | 2                | Pt 1: 51 years/male, Pt 2: 43 years/male | Hyperlipidemia, IGT | Tac, MMF | Pt 1: H1N2 | Pt 2: Tac, MPA | Path: Csf, leukocytosis, respiratory failure, meningitis, pneumonia | Path: | Died Pt 2: Alive, discharged |
|             | Russell et al [30] | United States | 1               | 3 years/female | EBV | Tac | 25 months | Productive cough, rhinorrhea, nasal congestion | Path: Csf, leukocytosis, respiratory failure, meningitis, pneumonia | Path: | Alive, discharged |
|             | Latif et al [27]  | United States | 28              | Median age 64 years, 79% male | H1N2 (31%), DM (31%), CAV (37%), Obesity (25%) | Tac, MMF | Pt 1: H1N2, DM, CKD | Pt 2: Fever | Path: Csf, leukocytosis, respiratory failure, meningitis, pneumonia | Path: | Died 7 pts (25%) managed outpatient, 11 pts (35%) discharged |
|             | Alberici et al [31] | Italy     | 20              | Not reported | Not reported | Not reported | Not reported | Not reported | Path: Csf, leukocytosis, respiratory failure, meningitis, pneumonia | Path: | Died 5 pts (25%) discharged, 3 pts (15%) discharged |
|             | Banerjee et al [32] | England   | 7               | Median age 54 years, 65-68 | PT: 1: 48/50, MP: 5: 65/54, Ph: 7: 45/54 | Tac, MMF | Pt 1: H1N2, DM, CKD | Pt 2: Tac, MPA | Path: Csf, leukocytosis, respiratory failure, meningitis, pneumonia | Path: | Died 12 days after hospitalization |

Table 1: (continued)
| Author et al.    | Location | Age/Gender | Dose | Symptoms | Course |
|-----------------|----------|------------|------|----------|--------|
| Arpali et al.   | Turkey   | 1          | 28   | female   | Tac and prednisone 6 months |
| Guillén et al.  | Spain    | 1          | 50   | male     | Tac, EVE, prednisone 4 years |
| Zhu et al.      | China    | 1          | 52   | male     | Tac, MMF, prednisone 12 years |
| Mars et al.     | France   | 1          | 58   | male     | Belatacept, MMF, prednisone 3 years |
| Gandolfi et al. | Italy    | 2          |       |          | Pt 1: COPD, heart disease, HTN, obeity Pt 2: HTN |
| Akalin et al.   | United States | 36     | Median of 60 years 72% males | Tac (97%) Prednisone (94%) MMF (86%) |
| Chen et al.     | China    | 1          | 49   | male     | HTN |
| Fontana et al.  | Italy    | 1          | 61   | male     | CKD, malignancy, coagulopathy, Parkinson disease |

Fever, malaise, sore throat, rhinorrhea continued on Tac and prednisone; oseltamivir given at second ED visit. Initially presented to ED, treated with amoxicillin, no SARS-CoV-2 testing done; presented following day to ED with high fever, sepsis, tested positive for SARS-CoV-2, admitted to hospital; 6 days after discharge required ventilatory support. Presented to ED with productive cough, diagnosed with CAP, tested positive for SARS-CoV-2, admitted to hospital; 6 days later, discharged to home. Presently at home, reports no symptoms. Alive, discharged to home. Alive, at home, reports no symptoms. Alive, discharged from hospital. Alive, resolution of fever and respiratory symptoms 5 days after discharge. Alive, discharged to home. Alive, died 5 days after admission. Alive, remained on noninvasive ventilation and discharged from hospital. Alive, remained on noninvasive ventilation and discharged from hospital. Alive, died 3 days after admission. Alive, died 3 days after admission. Alive, discharged to home. Alive, died 5 days after admission. Alive, died. Alive, died. Alive, died 5 days after admission. Alive, died 5 days after admission.
| SOT | Author [reference] | Location | No. of Cases (n) | Age and Sex | Comorbidities | Immunosuppressive Regimen | Time From Transplant | Initial Presentation (Symptoms) | Treatment | Clinical Course | Outcomes |
|-----|------------------|----------|-----------------|-------------|--------------|--------------------------|---------------------|-------------------------------|-----------|----------------|----------|
| 2   | Zhang et al [38] | China    | 5               | Mean 45 years 80%; male 4 | HTN (40%); 2 DM (40%); 2 Malignancy (20%); 1 | MMF, CM, and steroid (80%); 4 | Range of 2 months to 4 years | Fewer (100%), cough (100%), myalgia/ fatigue (80%), 3 Spurium (90%); 3 Oseltamivir or artibol (100%) | Azithromycin (70%), lopinavir/ritonavir (70%), abs (100%); IFV given if pt hypoxic | Immunosuppressant modified after symptom onset None required intubation or ICU admission | 2 (40%) discharged 3 (60%) remain hospitalized |
| 2   | Abirshami et al [39] | Iran    | 12              | Mean 47.66 years 75%; male 10 | HTN (17%); All on triple therapy (steroid, CNI/sirolimus, MMF/Aza) | HCQ, lopinavir/ritonavir, abx | Not reported | Fewer (75%), cough (80%), dyspepsia (42%) | Azithromycin (100%); HCQ, methylprednisolone (100%) | Immunosuppressant modified for all 100% pts hospitalized; 10 (83%) admitted to ICU; 90% in ICU were intubated | 8 (87%) died 4 (33%) discharged |
| 2   | Columbia University Kidney Transplant Program [10] | United States | 15              | Median 51 years 80%; male 10 | HTN, CAD, COPD, abx (80%); 10 | Tac (20%); 13 MMF/MPA (80%); 12 Prednisone (80%); 10 Belatacept (70%); 2 Leflunomide (70%); 1 | Median 49 months | Fewer (87%), cough (85%), dyspepsia (30%); 9 Myalgia (20%); 3 | Azithromycin (87%); HCQ (70%); Remicade (7%); | 93% had immunosuppressant regimen changed 14 4 (27%) required intubation 8 (46%) developed ARDS | 2 (15%) died 6 (40%) remain hospitalized |
| 2   | Nair et al [41] | United States | 10             | Median 57 years 80%; male 6 | HTN (100%), majority also with DM | Tac (70%); 9 MMF/MPA (80%); 7 Steroid (70%); 7 | Median 7.7 years | Fewer, cough, myalgia, fatigue, diarrhea | Hospitalized patients had antimalarial agent stopped | 90% hospitalized 5 (50%) admitted to ICU 5 (50%) developed acute kidney injury; Mild symptoms in 20% Severe symptoms in 50% Critical symptoms in 30% 30% required noninvasive mechanical ventilation | 3 (30%) died 7 (72%) discharged |
| 2   | Zhu et al [32] | China    | 10              | Age between 24 and 65 years 80%; male 6 | HTN, CAD, COPD, abx (80%); 10 | Tac (90%); 14 MMF (70%); Steroid (70%); 10 Methylprednisolone (10%) | 6 mo to 12 years | Fewer (90%), cough (80%), shortness of breath (90%), fatigue (90%), diaphoresis (30%) | Methylprednisolone (80%); IVIG (70%); Azithromycin (70%); Methylprednisolone (10%) | None underwent intubation Developed mild ARF and severe metabolic acidosis; did not require supplemental oxygen; improved over course of hospitalization | 80% recovered 1 (10%) remained hospitalized 1 (10%) died |
| 2   | Machado et al [42] | Brazil   | 1               | 69 years/male 80% | HCQ, DM, HTN | Tac, MMF, prednisone | 6 years | Fewer, fatigue, confusion, diarrhea, decreased urine output | MMF held; Tac decreased, prednisone increased on hospitalization HCQ, ribavirine, ceftriaxone, azithromycin | None underwent intubation Developed mild ARF and severe metabolic acidosis; did not require supplemental oxygen; improved over course of hospitalization | Alive, discharged |
| 2   | Kim et al [43] | Korea    | 2               | Pt 1: 37 years/male; Pt 2: 56 years/male | Not reported | Pt 1: Tac, MMF, prednisone; Pt 2: Tac, MMF, prednisone | Pt 1: 4 years Pt 2: 8 years | Fewer (90%), cough (90%), shortness of breath (90%), fatigue (90%), diaphoresis (30%) | Azithromycin (80%); HCQ; IFV | Immunosuppressant medication modified in 80%; Methylprednisolone (80%); IVIG (70%); Azathioprine (100%) | Pt 1: Recovered Pt 2: Recovered |
| 2   | Seminari et al [44] | Italy    | 1               | 50 years/male 49 years/male | HTN, DM | Tac, MMF | 4 years | Fewer, cough, respiratory symptoms Caffeine? | Immunosuppressant medications continued Lopinavir/ritonavir, ribavirin, interferon-2b, methylprednisolone | Immunosuppressant medications continued Lopinavir/ritonavir | Alive, discharged Recovered |
| 2   | Wang et al [45] | China    | 1               | 49 years/male 49 years/female | HTN, DM | Tac, MMF | 2 years | Fewer, cough, chest tightness, myalgia | Caffeine? | Improvement in clinical course Required supplemental oxygen; respiratory status improved over course of admission | Alive, discharged Recovered |
| 2   | Bilal et al [44] | United States | 1                | 44 years/M | Not reported | Tac, MMF, prednisone | 7 years | Dyspnea | Methylprednisolone | Developed ARF requiring dialysis; Intubated for respiratory failure | Alive, discharged |
| 2   | Cheng et al [46] | China    | 2               | Pt 1: 48 years/male; Pt 2: 65 years/male | Not reported | Pt 1: Tac, MMF, prednisone; Pt 2: Tac, MMF, prednisone | Pt 1: 11 years Pt 2: 9 years | Fewer, cough, chest tightness, myalgia | Lopinavir/ritonavir, ribavirin, methylprednisolone | Immunosuppressant medications held; methylprednisolone | 2 (10%) died 8 (46%) developed ARDS | 2 (15%) died 6 (40%) remain hospitalized |
| Study                  | Country | Age/sex   | Diagnosis/Indicators               | Survival/Outcome                                                                 |
|------------------------|---------|-----------|-------------------------------------|--------------------------------------------------------------------------------|
| Crespo et al [10]      | Spain   | Median 73.5 years, 75% male 12 | HTN (86%), 14, DM (55%), heart disease (50%), obesity (44%), T, malignancy (31%), lung disease (19%), 3 HFN | 15 pts (94%) hospitalised, 8 pts (60%) required ICU admission, 8 pts (53%) died |
| Ning et al [11]        | China   | 29 years/male | MMF, CSA, methylprednisolone 2 years Fever/chills, fatigue | Developed oliguria and hyponatremia; clinical course improved over course of admission, Required NC, remained hemodynamically stable |
| Bush et al [12]        | United States | 13 years/male | Sirolimus, MMF 6 years Rheumato, cough, fever | Alive, discharged to home |
| Kumar et al [13]       | United States | 50 years/male | Tac, MMF 14 months Fever/chills, nasal congestion, cough | Not reported |
| Liver SOT              | Italy   | 61 years/male | Basiliximab, prednisolone, and Tac Pl 1: Not reported | Not admitted, enrolled in COVID-19 monitoring program, Health improved to baseline |
| Maggi et al [14]       | Italy   | 85 years/male | HTN, hypothyroidism, DM (100%) Tac, MMF 10 years Respiratory symptoms similar to CAP | 100% died between 3 and 12 days after the onset of pneumonia, Authors report 3 recently (within last 2 years) transplanted patients with positive test result for SARS-CoV-2 (on full immunosuppression); all experienced uneventful course of disease (no further details about this cohort provided) |
| D'Antiga et al [15]   | Italy   | 37 years/male | Tac, glucocorticoid PI developed SARS-CoV-2 infection during hospitalization for transplant | Presented with fever following hepatic arterial chemoembolization, continued to have persistent fever 2 days following embolization; RT-PCR confirmed infection; fever subsided on day 35 of hospitalization, Alive, discharged to home |
| Qin et al [16]         | China   | 6 months/female | Not reported | None developed clinical pulmonary disease |
| Lagana et al [17]      | United States | 6 months/female | Not reported | Alive, discharged to home |
| Huang et al [18]       | China   | 59 years/male | Tac, MMF 3 years Fever, cough, chills, fatigue, diarrhea, jaundice, anorexia, splenomegaly Respiratory failure on day 4 of hospitalization, placed on NC; hypoxemia worsened requiring intubation; on day 12, bilirubin ox positive for Candida, pleural fluid positive for Pseudomonas; ECCHO on day 15 due to worsened respiratory status; condition deteriorated to multigorgan failure | Alive, discharged on day 45 of admission |
| SOT | Author [reference] | Location | No. of Cases (n) | Age and Sex | Comorbidities | Immunosuppressive Regimen | Time From Transplant | Initial Presentation (Symptoms) | Treatment | Clinical Course | Outcomes |
|-----|-------------------|----------|----------------|-------------|--------------|--------------------------|-------------------|-------------------------------|-----------|--------------|----------|
| Bin et al [58] | China | 1 | 50 years/male | Not reported | Tac | 3 years | Fever | Immunosuppression was increased to full dose on discharge | Pt became progressively dyspnic requiring NC on day 5 of hospitalization; symptoms resolved on day 21; discharged after 4 weeks of hospitalization | Alive, at home |
| Lee et al [59] | United States | 38 | Median 60 years | For hospitalized pts (n = 24) | Tac (96%) CSA (4%) MPA (54%) Steroid (42%) 10 obesity (42%),10 | Not reported | Gastrointestinal symptoms (42%) | Hospitalized patients 7 (29%) died 63% hospitalized 8 (33%) required mechanical ventilation | Died (unrelated to SARS-CoV-2) | 7 (29%) died 3 (13%) remained hospitalized 14 (54%) discharged |
| Patrono et al [60] | Italy | 10 | Pt 1: 69 years/male | ESRD, DM, HTN, HF, PVD | Tac, prednisone | 5 days | Fever, diarrhea, dyspnea | Patients were administered HCQ, 3 high-dose steroids, and 2 antimalarials | Alive | Pt 1: Alive Pt 2: Alive Pt 3: Alive Pt 4: Alive Pt 5: Alive Pt 6: Alive Pt 7: Alive Pt 8: Died (unrelated to SARS-CoV-2) Pt 9: Died Pt 10: Alive |
| Hammami et al [61] | United States | 1 | 63 years/male | ESRD, DM, HTN, HF, PVD | Tac | 10 years | Fever, dry cough, fatigue, headache | HCQ, ceftriaxone, azithromycin, ceftriaxone, vancomycin, tocilizumab | Alive | Pt 1: Alive Pt 2: Alive Pt 3: Alive Pt 4: Alive Pt 5: Alive |
| Modi et al [62] | United States | 1 | 32 years/male | HIV | Tac, MMF, prednisone | 7 years | Fatigue, fever, headache, dry cough | MMF held, Tac reduced, prednisone continued | Discharged home | Admitted with mild symptoms which gradually improved over course of hospitalization |
| Morand et al [63] | France | 1 | 4 years/female | EBV | Tac | 5 months | Rheitis, fever, cough | Tac dose reduced Antipyretics | Improvement in clinical symptoms during hospitalization | Recovered |

Abbreviations: Abx, antibiotics; AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; AzA, azathioprine; CAD, coronary artery disease; CAP, community-acquired pneumonia; CAV, cardiac allograft vasculopathy; CNI, calcineurin inhibitor; CMV, cytomegalovirus; CPAP, continuous positive airway pressure; CSA, cyclosporine; Cx, culture; CVV, cytomegalovirus; CVD, cardiovascular disease; Dx, diagnosis; d/c, discontinued; DDi, drug–drug interaction; DM, diabetes mellitus; EBV, Epstein-Barr virus; ED, emergency department; ESRD, end-stage renal disease; EVE, everolimus; HCQ, hydroxychloroquine; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HTN, hypertension; IGT, impaired glucose tolerance; IL-6, interleukin 6 receptor antagonist; IVIG, intravenous immunoglobulin; MMF, mycophenolate mofetil; MPA, mycophenolate acid; mTOR, mammalian target of rapamycin; NC, nasal cannula; Pt(s), patient(s); POD, postoperative day; PVD, peripheral vascular disease; RCT, randomized controlled trial; rh-GCSF, recombinant human granulocyte colony-stimulating factor; SD, symptom day; SMZ-TMP; sulfamethoxazole-trimethoprim; Tac, tacrolimus; TCDA, T-cell-depleting agents; Tx, treatment.
concomitant medical conditions [7,8]. The surgical management and outcomes of SARS-CoV-2 in SOT recipients remain unclear [9], because published reports on SARS-CoV-2 positive SOT recipients and their outcomes are limited and largely unknown [9-11]. Case reports from Asia, Europe, and the United States suggest a wide range in severity of clinical symptoms from mild and nonspecific to severe respiratory distress and pneumonia [11-13]. Furthermore, reports of atypical presentations with an absence of respiratory symptoms may confound the diagnosis [12-14].

Although the American Society of Transplant Surgeons has recommended best practice guidelines for transplantation in the SARS-CoV-2 era, regional and institutional variation in transplant practice persists [15,16]. In addition, limitation and regional variance in testing pose a significant difficulty in the early identification of suspected SARS-CoV-2 cases in SOT recipients. A recent survey of 111 transplant centers in the United States found a marked reduction in transplant activity despite the tier 3b designation, a wide variation in SARS-CoV-2 testing practices, and substantial differences in the use of off-label and investigational therapies for treatment [17].

There is an urgent need to better understand the effects of SARS-CoV-2 on SOT recipients. We reviewed published literature in this rapidly evolving field to examine the current management practice; the clinical course of the disease; and the outcomes of SARS-CoV-2 infection in liver, kidney, and heart SOT recipients.

MATERIALS AND METHODS

We conducted a review of SARS-CoV-2 infection in SOT recipients according to the recommended Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.

Study Search

Articles published through June 6, 2020, were searched in the MEDLINE, ClinicalTrials.gov, and PubMed databases. A combination of the following Medical Subject Heading terms was used to identify articles discussing SARS-CoV-2 infection in solid organ transplant recipients: “coronavirus,” “SarsCov,” “SarsCov2,” “SARS-CoV-2,” “Severe Acute Respiratory Syndrome,” “COVID,” “COVID-19,” “kidney,” “heart,” “liver,” “solid organ transplant,” “transplant,” “transplantation,” “outcome,” and “immunosuppressant.”

Inclusion and Exclusion Criteria

Only case reports, case series, and prospective and retrospective cohort studies published between 2019 and 2020 were included for final analysis and discussion. No restriction was placed on the publication status of the article. All non-English, investigational, animal, in vitro, and cadaveric studies were excluded. In addition, book chapters, conference abstracts, review articles, management guidelines, and any article that did not include discussion of clinical course, treatment, or outcomes of SARS-CoV-2 infection in SOT recipients were also excluded.

Data Collection and Analysis

Articles were screened independently by the authors. Any disagreements were reconciled through discussion between reviewers. Data extracted from each article included study type, year and month of publication, study country, number of patient cases, SOT type (heart, kidney, liver, or multiple), patient demographics, presence of comorbidities, immunosuppressant medications, time from transplant to initial presentation, initial presenting symptoms, treatment, clinical course, and outcomes (Table 1). Reporting of all of the above variables was not a requirement for article inclusion, and any unavailable variables were documented as “not reported.” Data were reported using the median and interquartile range (IQR) for non-normally distributed continuous variables and absolute counts and percentages for categorical variables.

RESULTS

Study Selection

A total of 1455 citations were identified in the initial search. After removing 211 duplicates, a total of 1244 studies were screened by title and abstract (Fig 1). Studies were excluded if they did not mention SOT, SARS-CoV-2 infection, or associated clinical course and outcomes or did not fulfill the inclusion criteria. After excluding 1164 studies, we completed a full-text assessment of the remaining 80 studies. Forty-nine studies were included in our final analysis after the exclusion of 31 studies after a full-text screen. Exclusion of these 31 studies at the full-text review included the following reasons: discussed management and recommendations (n = 10), review
Overall mortality was reported as 21% (Table 3). The median time from transplant was 48 months (IQR, 12-108). The median age was 54 years (IQR, 45-64), and the majority were men (n = 252; 58.2%). Seventeen individuals (3.9%) received more than one SOT. A majority were men (n = 264; 61.0%). The most common SOT type, including those reporting lung, pancreas, and multiple SOT, whereas death for kidney, heart, and liver SOT recipients was determined solely from studies discussing each individual organ separately. Additional immunosuppressant regimens included unspecified calcineurin inhibitors (CNIs) (12%), mTOR inhibitors (4.6%), and belatacept (2%). Fever was the most common presenting symptom (71.3%), followed by cough (39.3%) and dyspnea (26%). Ninety-three individuals (62%) were hospitalized, and 10.7% developed acute kidney injury. Mechanical ventilation, supplemental oxygen, and transfer to an intensive care unit (ICU) for a higher level of care were required in 20%, 11.3%, and 19.3% of the individuals, respectively. Nearly half (46.7%) of those reported had their maintenance immunosuppressant reduced when the infection was suspected or confirmed. The most commonly used treatments were hydroxychloroquine (HCQ) (65.3%), antibiotics (43.3%), steroids (20.7%), and lopinavir/ritonavir (15.3%). Thirty-three patients were reported as alive (22%), discharged to home (n = 45; 30%), or remaining hospitalized (non-ICU, n = 27 [18%]; ICU, n = 3 [2%]), and 26% of individuals died (n = 39).

Liver. Fifty-three liver SOT recipients were identified from 12 studies reporting liver SOT, and males comprised 28.3% of the population (n = 15). Hypertension, chronic kidney disease, and diabetes were the most common comorbidities (39.6%, 32.1%, and 30.2%, respectively). Tacrolimus (79.2%), MMF/mycophenolic acid (MPA) and 26% of individuals died (n = 39).

Table 2. Characteristics of Total Solid Organ Transplant Recipients With Severe Acute Respiratory Syndrome Coronavirus 2 Infection

| Location          | No.  | %     |
|-------------------|------|-------|
| United States     | 249  | 57.51%|
| Italy             | 55   | 12.7% |
| China             | 26   | 6%    |

| Organ transplanted | No.  | %     |
|--------------------|------|-------|
| Kidney             | 252  | 58.2% |
| Liver              | 89   | 20.6% |
| Heart              | 51   | 11.8% |
| Other organ*       | 42   | 9.6%  |

| Sex                | No.  | %     |
|--------------------|------|-------|
| Male               | 264  | 61.0% |

| Comorbidity        | No.  | %     |
|--------------------|------|-------|
| HTN                | 249  | 57.5% |
| DM                 | 159  | 36.7% |
| Obesity            | 44   | 10.2% |
| CKD                | 77   | 17.8% |

| Immunosuppressive  | No.  | %     |
|--------------------|------|-------|
| Tac                | 160  | 37.0% |
| CNI                | 122  | 28.2% |
| Prednisone or other steroid | 217 | 50.1% |
| MMF/MPA            | 214  | 49.4% |
| Other immunosuppressive* | 125 | 28.8% |

| Abbreviations: CKD, chronic kidney disease; CNI, calcineurin inhibitor; DM, diabetes mellitus; HTN, hypertension; MMF, mycophenolate mofetil; MPA, mycophenolic acid; Tac, tacrolimus. *Includes lung, pancreas, and multiple solid organ transplant.

Table 3. Presentation, Clinical Course, and Outcome of Total Solid Organ Transplant Recipients

| No. | %     |
|-----|-------|
| Initial presentation |
| Fever | 291 | 67.2% |
| Cough | 220 | 50.8% |
| Gastrointestinal symptoms | 120 | 27.7% |
| Dyspnea | 169 | 39.0% |
| Asymptomatic | 3 | 0.7% |

| Treatment |
| Immunosuppressant modified | 235 | 54.3% |
| Antibiotics | 178 | 41.1% |
| HCQ | 242 | 55.9% |
| Methylprednisolone or other steroid | 78 | 18.0% |

| Clinical course |
| Hospitalized | 283 | 65.4% |
| Outpatient | 50 | 11.5% |
| Respiratory failure | 18 | 4.2% |
| Transfer to ICU | 78 | 18.0% |

| Outcome* |
| Death (all studies) | 91 | 21.0% |
| Kidney | 39 | 26.0% |
| Heart | 8 | 24.2% |
| Liver | 14 | 26.4% |

Abbreviations: HCQ, hydroxychloroquine; ICU, intensive care unit. *Death for all studies includes studies for multiple solid organ transplant (SOT) type, including those reporting lung, pancreas, and multiple SOT, whereas death for kidney, heart, and liver SOT recipients was determined solely from studies discussing each individual organ separately.

Study Characteristics

Of the 49 studies included, 22 were case reports, 8 were case series, and 19 were cohort studies. Four studies discussed heart SOT, 25 discussed kidney SOT, 12 discussed liver SOT, and 8 included multiple SOTs. A total of 433 SOTs were reported among all studies (Table 2). The most common SOT was the kidney with 252 (58.2%), followed by liver with 89 (20.6%), heart with 51 (11.8%), lung with 24 (5.5%), and pancreas with 1 (0.2%). Seventeen individuals (3.9%) received more than one SOT. A majority were men (n = 264; 61%). The median age was 54 years (IQR, 45-64), and the median time from transplant was 48 months (IQR, 12-108). Overall mortality was reported as 21% (Table 3).

Characteristics, Clinical Course, and Outcomes by SOT Type

Kidney. Among the 25 studies reporting solely kidney SOT, 150 recipients with SARS-CoV-2 infection were identified. Ninety-five (63.3%) were male. The most common comorbidities were hypertension (55.3%) and diabetes mellitus (26.7%). Tacrolimus (52%), mycophenolate mofetil (MMF) (56%), and prednisone/steroid (64.7%) were the most commonly used maintenance immunosuppressants.
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(39.6%), and steroids (35.8%) were the most commonly used maintenance immunotherapies. Fever and gastrointestinal symptoms were the 2 most common initial presenting symptoms, followed by cough (28.3%, 28.3%, and 18.9%, respectively). Thirty-four individuals (64.2%) were hospitalized, and 45.3% subsequently had their maintenance immunosuppressant medication reduced. HCO and antibiotics were used in 39.6% and 39.6%, respectively, for treatment of SARS-CoV-2 infection. In addition, 47.2% of individuals required supplemental oxygen during hospitalization, and 14 (26.4%) individuals died after the onset of illness.

**Heart.** Thirty-three individuals who underwent heart SOT were reported in 4 studies; 25 (75.8%) were male. The most common comorbidities were hypertension (69.7%), diabetes (57.6%), and cardiac allograft vasculopathy (48.5%). The most commonly used maintenance immunotherapies were CNI (81.8%) and MMF/MPA (69.7%). Fever (81.8%), cough (94.8%), dyspnea (75.8%), and gastrointestinal symptoms (48.5%) were the most common initial presenting symptoms. Twenty-seven (81.8%) patients were hospitalized, and intubation/mechanical ventilation was required in 24.2% of those individuals. Twenty-four (72.7%) patients received HCO, and high-dose steroids were administered to 15 patients (45.5%). Maintenance immunotherapy was modified in 75.8% of the cases. Fifteen (45.5%) were reported as discharged, and 24.2% of the individuals died during their illness.

**DISCUSSION**

As the number of SARS-CoV-2 infections continues to grow worldwide, clinical data in SOT recipients are emerging, and our study showed overall mortality of 21% with no substantial variations among the different types of SOT (Table 3). The mortality rate is in concordance with published data in terms of outcomes reported in patients undergoing acute care surgery and cancer surgery: Lei et al, Liang et al, and the COVIDSurg Collaborative group reported mortality in the general surgical population of 20.5%, 39%, and 23.8%, respectively [4,64,65].

Older age, male sex, and preexisting conditions such as hypertension and diabetes were the most common characteristics among the SOT recipients. As predicted, we saw a broad spectrum of clinical courses ranging from having only a few mild symptoms to multiorgan failure leading to death. Despite the concerns of atypical disease presentation in immunocompromised patients, the most common presenting symptoms were similar to general population symptoms [7,66,67]; however, there were some variations in the incidence of the initial presenting symptoms among the different SOT types (Table 1).

Modification of immunosuppressant therapy at confirmation or suspicion of SARS-CoV-2 infection was reported in 54.3% of the patients, reflecting individualized adjustment based on the severity of the disease, type of transplanted organ, interval time since transplant, and risk of rejection [8]. On a similar note, the American Association for the Study of Liver Diseases recently published management guidelines for liver transplant recipients in the COVID era [68]: continuing the routine immunosuppressive regimen in nonsymptomatic recipients and reducing the immunosuppression regimen, including prednisone, azathioprine, or MMF and CNI in symptomatic patients with COVID-19. Our study suggests that the current practice of reducing immunosuppression upon the diagnosis of SARS-CoV-2 infection appears to be an appropriate measure without causing significant short-term adverse effects on graft function while maintaining patient survival comparable to that of the general population.

The median time from transplant to infection was 48 months in our study; the majority of the studies focused on patients who had received SOTs many years ago. Although it is a small number, we identified 4 cases in which the SOT recipient contracted SARS-CoV-2 infection during the transplant perioperative period, and we found no significant difference in their initial presentation, clinical course, and outcome when compared with a cohort of patients who received a transplant more than 1 year ago.

Although our study provides a general overview of SOT recipients’ clinical course and outcomes with SARS-CoV-2 infection, we recognize several limitations of the study. First, the inclusion of early case reports may be biased toward those with increased severity of disease and worse outcome, leading to publication bias with overinterpretation. Second, the inclusion of a mixed transplant population and a wide heterogeneity in study inclusion criteria may not be a true representation of the study samples and therefore precluded the ability to derive causality. Furthermore, data were based on absolute counts and therefore can be used only for descriptive purposes. Last, a certain degree of reporting bias inevitably played a role because SOT recipients are trained to be more vigilant with their health conditions and have a low threshold for seeking medical attention. This reporting bias could have led to more disease diagnosis in our study group than in the general population.

In conclusion, SARS-CoV-2 infection in SOT recipients in general appears to have similar presentation, clinical course, and outcome as in the general non-SOT surgical population. We found that the patient demographics, preexisting risk factors, and outcomes were similar within each SOT type, and we saw no substantial differences in mortality rate among the different SOT types. Although our data show that the overall short-term survival is about the same, long-term patient survival and graft function data are needed to fully understand the impact of COVID in SOT patients.

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