COVID-19 in solid organ transplant recipients: a single-center experience

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SUMMARY

Solid organ transplant (SOT) recipients may be at risk for severe COVID-19. Data on the clinical course of COVID-19 in immunosuppressed patients are limited, and the effective treatment strategy for these patients is unknown. We describe our institutional experience with COVID-19 in SOT. Demographic, clinical, and treatment data were extracted from the electronic patient files. A total of 23 SOT transplant recipients suffering from COVID-19 were identified (n = 3 heart; n = 15 kidney; n = 1 kidney-after-heart; n = 3 lung, and n = 1 liver transplant recipient). The presenting symptoms were similar to nonimmunocompromised patients. Eighty-three percent (19/23) of the patients required hospitalization, but only two of these were transferred to the intensive care unit. Five patients died from COVID-19; all had high Clinical Frailty Scores. In four of these patients, mechanical ventilation was deemed futile. In 57% of patients, the immunosuppressive therapy was not changed and only three patients were treated with chloroquine. Most patients recovered without experimental antiviral therapy. Modification of the immunosuppressive regimen alone could be a therapeutic option for SOT recipients suffering from moderate to severe COVID-19. Pre-existent frailty is associated with death from COVID-19.

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Introduction

The first case of coronavirus disease 2019 (COVID-19) was diagnosed in December 2019 in Wuhan, China [1–3]. Since then, this novel infectious disease, which is caused by the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), has grown into a pandemic with over 4 million infected individuals worldwide (https://who.sprinklr.com/; accessed May 14th, 2020) [1–3]. Various compounds with presumed antiviral activity are now being tested in clinical trials, but at present there is no demonstrated effective therapy other than supportive care [4–10].

Solid organ transplant (SOT) recipients are perceived to be at increased risk for severe COVID-19 because of their chronic immunosuppressed state. However, there are indications that severe COVID-19 results from a hyper-inflammatory state and that immunosuppressive
therapy may even be beneficial in selected cases as it may mitigate lung inflammation [11]. Data on SOT recipients suffering from COVID-19 are scarce, and only a few cases have been reported in the English literature [12–19]. Most of these patients had symptoms that were comparable to those of the general population affected by COVID-19. Several interventions were followed in these SOT recipients with COVID-19, including reduction and withdrawal of immunosuppression, high-dose glucocorticoids, and treatment with experimental antiviral agents including chloroquine, lopinavir/ritonavir, remdesivir, and umifenovir [12–19].

Here, we report 23 SOT recipients with COVID-19 from a single institution and describe the clinical outcomes and the treatments that were instituted.

Materials and methods

All SOT recipients who were diagnosed with COVID-19 in our center or in one of the local referring hospitals since the first case was diagnosed in the Netherlands (February 27, 2020; source https://www.rivm.nl/corona virus-covid-19/actueel) were included. At the Erasmus MC, approximately 200 kidney, 70 liver, 35 lung, and 15 heart transplants are performed on an annual basis. Patients were identified from the transplant database of the departments of Pulmonary Medicine (n = 175 lung transplant recipients), Cardiology (n = 306 heart transplant recipients), Hepatology (n = 950 liver transplant recipients), and Nephrology (n = 2150 kidney transplant recipients) or after consultation by local medical specialists. We included all cases until April 30th, 2020.

A diagnosis of COVID-19 was made whenever a patient had typical symptoms (either a temperature >38°C, cough, rhinitis, dyspnea, or a combination of these), and PCR testing of a throat and nasal swab was positive for SARS-CoV-2. Only patients with reported complaints were tested; no pre-emptive testing was performed.

Of all patients, demographic data, clinical and laboratory parameters, radiological findings, treatment data (use of antiviral drugs, use of experimental antiviral therapy, and modification of immunosuppression) were collected from the electronic patient files.

Disease severity was scored from mild to critical for all patients [20,21]. Health status of patients was scored by using the Canadian Study of Health and Aging (CSHA) Clinical Frailty Scale (CFS) [22]. The medical ethical review board of our hospital approved collection of clinical data in COVID-19 patients. Furthermore, all SOT recipients in our institution provided written informed consent for collection of clinical data as part of an ongoing quality improvement program.

Results

A total of 23 SOT recipients were identified: 15 kidney (10 living donor; five deceased donor), four heart, three lung, one kidney-after-heart (living donor kidney), and one liver transplant recipient (Table 1). The first case was diagnosed with COVID-19 on March 12, 2020, 15 days after the first case was diagnosed in the Netherlands. Fourteen recipients were Caucasian, six were of African ethnicity, two were Latin American, and one was of Asian descent. Eighteen patients (78%) were male, and patients had a mean age of 59 years (range 21–81). Most patients presented with typical symptoms, including fever (81%), cough (71%), and dyspnea (59%; Table 2). Three renal transplant patients had symptoms consistent with concomitant urinary tract infection, and three patients had diarrhea. Only one patient was in his first postoperative year after transplantation. All 23 patients had a baseline immunosuppressive regimen consisting of a calcineurin inhibitor, combined with either mycophenolate mofetil (MMF; n = 14), MMF plus prednisolone (n = 6), prednisolone alone (n = 1), or everolimus (ERL; n = 1).

Three patients only had mild disease and were monitored at home without additional treatment. For one frail patient, it was decided to provide best supportive care at home. The majority of patients (19 out of 23) was hospitalized, and all of these received broad-spectrum antibiotic therapy to treat possible bacterial pneumonia or suspected urinary tract infection. The median length of stay in the hospital was 10 days (range 3–21). Laboratory results on admission are shown in Table 2. All hospitalized patients had chest radiographs consistent with viral pneumonia. In 13 of the 23 patients, no change in immunosuppressive treatment was made. In the other 10 SOT recipients, MMF or ERL was reduced or withdrawn (Table 2). Three heart transplant recipients received a 5-day course of chloroquine. The other 17 patients did not receive any antiviral therapy (Table 2).

At present, 14 (61%) of the total of 23 SOT recipients have recovered and have been discharged from hospital, and another 4 (17%) patients are recovering with documented clinical improvement. Two patients (9%) were admitted to the intensive care unit (ICU) and were in need of mechanical ventilation. One of these two died from respiratory failure. The other
Table 1. Characteristics of the 23 SOT recipients with COVID-19.

| Patient | Sex | Age | Type of transplant | Transplant date | Type of transplantation | Primary disease | Immunosuppression |
|---------|-----|-----|-------------------|-----------------|------------------------|----------------|-------------------|
| 1       | M   | 56  | Kidney            | 27-05-2010      | LRD, ABOi              | PKD            | Tac, MMF          |
| 2       | F   | 58  | Kidney            | 21-08-2012      | LURD                   | PKD            | Tac, MMF          |
| 3       | M   | 81  | Kidney            | 07-11-2014      | LURD                   | ATN during sepsis | Tac, MMF, pred |
| 4       | M   | 65  | Kidney            | 28-09-2017      | LURD, ABOi             | ATN            | Tac, MMF          |
| 5       | M   | 62  | Kidney            | 07-12-2018      | DCD                    | MGP            | Tac, MMF, pred   |
| 6       | F   | 21  | Kidney            | 18-10-2016      | LRD                    | Reflux nephropathy | Tac, MMF         |
| 7       | M   | 59  | Kidney            | 09-09-2013      | DCD                    | Diabetic nephropathy | Tac, MMF       |
| 8       | M   | 53  | Kidney            | 18-04-2018      | LURD                   | PKD            | Tac, MMF          |
| 9       | M   | 59  | Kidney            | 17-01-2019      | LRD                    | MGP            | Tac, MMF          |
| 10      | M   | 67  | Kidney            | 18-02-2015      | DCD                    | Hypertensive nephropathy | Tac, MMF     |
| 11      | M   | 73  | Kidney            | 04-10-2011      | LRD                    | Obstructive nephropathy | Tac, MMF    |
| 12      | M   | 49  | Kidney            | 08-09-2007      | DBD                    | IgA nephropathy   | Tac, MMF         |
| 13      | F   | 60  | Kidney            | 16-03-2018      | DCD                    | Hypertensive nephropathy | Tac, MMF   |
| 14      | F   | 75  | Kidney-after-heart | 31-03-1999     | Orthotopic HTx, LRD KTx| Ischemic CMP; CNI nephrotoxicity | CsA, pred |
| 15      | M   | 65  | Heart             | 16-01-2010      | Orthotopic HTx         | Ischemic CMP     | Tac, ERL         |
| 16      | M   | 51  | Heart             | 05-03-2010      | Orthotopic HTx         | Ischemic CMP     | Tac, MMF, pred   |
| 17      | M   | 50  | Heart             | 30-03-2014      | Orthotopic HTx         | Dilated CMP due to TTN mutation | Tac, MMF |
| 18      | M   | 70  | Lung              | 18-11-2018      | Unilateral Left LuTx   | IPF             | Tac, MMF, pred   |
| 19      | M   | 63  | Lung              | 15-11-2019      | Bilateral LuTx         | Sarcoidosis      | Tac, MMF, pred   |
| 20      | M   | 47  | Liver             | 22-12-2000      | Orthotopic LTx         | Cryptogenic liver cirrhosis | Tac         |
| 21      | F   | 51  | Kidney            | 16-01-2014      | LRD, ABOi              | Hypertensive nephropathy | Tac, MMF |
| 22      | M   | 79  | Kidney            | 16-07-2013      | LRD                    | Diabetic nephropathy | Tac, MMF       |
| 23      | M   | 52  | Lung              | 13-11-2005      | Bilateral LuTx         | Cystic Fibrosis  | Tac, MMF, pred   |

ABOi, blood group ABO incompatible; ATN, acute tubular necrosis; CMP, cardiomyopathy; CsA, cyclosporine A; DBD, deceased after brain death; DCD, deceased after circulatory death; ERL, everolimus; HTx, heart transplantation; IgAN, immunoglobulin A nephropathy; IPF, idiopathic pulmonary fibrosis; IS, immunosuppression; LRD, living-related donor; LTx, liver transplantation; LURD, living-unrelated donor; LuFx, lung transplantation; MGP, membranous glomerulopathy; MMF, mycophenolate mofetil; PKD, polycystic kidney disease; pred, prednisolone; Tac, tacrolimus.
Table 2. Clinical features and outcomes in the solid organ transplant recipients.

| Variable | Value |
|----------|-------|
| Clinical presentation—no/total no (%) | |
| Fever | 17/21 (81%) |
| Cough | 15/21 (71%) |
| Dyspnea/tachypnea | 13/22 (59%) |
| Clinical suspicion of ARI | 18/23 (78%) |
| Other | 17/23 (74%) |
| Comorbid disease—no/total no (%) | |
| BMI 25–30 kg/m² | 10/23 (43%) |
| BMI >30 kg/m² | 5/23 (22%) |
| Hypertension | 19/23 (83%) |
| ARB therapy | 5/23 (22%) |
| ACE-i therapy | 2/23 (9%) |
| Diabetes mellitus | 10/23 (43%) |
| Hospitalization—no/total no (%) | 19/23 (83%) |
| Length of hospital stay—median days (range) | 10 (3–21) |
| SpO₂ at presentation—median % (range) | 94.9 (92–100) |
| Disease severity score—no | |
| Mild | 3 |
| Moderate | 14 |
| Severe | 4 |
| Critical | 2 |
| Treatment—no/total no (%) | |
| Azithromycine | 11/23 (48%) |
| Antibiotics, other | 19/23 (83%) |
| Immunosuppression dose reduction | 10/23 (43%) |
| Hydroxychloroquine | 3/23 (13%) |
| None | 4/23 (17%) |
| No change IS | 13/23 (57%) |
| Laboratory | |
| CRP—mg/l | Median (range) 70.73 (6.3–236) |
| CRP >50 mg/l—no/total no (%) | 8/16 (50%) |
| Procalcitonin—ng/ml | Median (range) 0.33 (0.04–0.76) |
| PCT >0.2—no/total no (%) | 3/10 (30%) |
| Ferritin—µg/l | Median (range) 485 (77–1588) |
| Ferritin >900—no/total no (%) | 2/9 (22%) |
| Leukocyte count × 10⁹/l | Median (range) 5.4 (1.9–12.8) |
| Leukocyte >10—no/total no (%) | 2/15 (13%) |
| Lymphocyte count (×10⁹/l) | Median (range) 0.75 (0.13–1.18) |
| D dimer (mg/l) | Median (range) 0.60 (0.19–1.25) |
| D dimer >0.5—no/total no (%) | 4/8 (50%) |
| Serum creatinine (µmol/l) | 196 (87–401) |
| Outcome | |
| ICU admission and intubation—no/total no (%) | 2/23 (8.7%) |
| Oxygen therapy—no/total no (%) | 14/22 (64%) |
| Need for RRT—no/total no (%) | 1/23 (4.3%) |
| Deceased—no/total no (%) | 5/23 (21.7%) |
| Deceased—Rockwood clinical frailty score—mean | 5.80 |
| Recovered—no/total no (%) | 14/23 (61%) |
| Recovered—Rockwood clinical frailty score—mean | 1.92 |
| Recovering—no/total no (%) | 4/23 (17%) |
| Recovering—Rockwood clinical frailty score—mean | 2 |

ARI, acute respiratory infection; CRP, C-reactive protein; ICU, intensive care unit; IS, immunosuppression; PCT, procalcitonin; RRT, renal replacement therapy; SpO₂, peripheral oxygen saturation.
patient was recently transferred from the ICU to the general ward and is recovering. Five patients (22%) died from COVID-19. The first was a 75-year-old kidney-after-heart transplant recipient who was 21 years after orthotopic heart transplantation. She suffered from severe transplant coronary artery vasculopathy, and her life expectancy was estimated as being less than one year before she was infected with SARS-CoV-2. Because of her extensive comorbidity, transfer to the ICU and mechanical ventilation was deemed futile and best supportive care was provided. The second patient was a lung transplant recipient who presented with respiratory failure and died while on mechanical ventilation. The other three patients were frail kidney transplant recipients (aged 65, 67, and 73 years of age) who were and 2, 5, and 10 years after transplantation, respectively, and presented with severe respiratory failure. All three had hypertension, one suffered from obesity (BMI of 35.4 kg/m²), and two had type 2 diabetes mellitus. Because of their poor physical status, a decision was made not to transfer these three kidney transplant recipients to the ICU but to provide best supportive care.

Mortality was highly correlated with CFS. Patients who died from COVID-19 had a mean CFS of 5.8 compared to 1.92 for survivors. Moreover, among the 10 patients who were treated with a reduction of their immunosuppression because of moderate to severe COVID-19, survivors (n = 7) had a mean CFS of 2.3 compared to 6.0 for nonsurvivors (n = 3). The length of hospital stay in this group was higher (14.7; range 14–39 days) compared to the group that did not receive a reduction of immunosuppression (8.2; range 3–16 days). Also, mortality was higher in the group that received a reduction of immunosuppression (30% vs. 15.4%).

**Discussion**

Here, 23 SOT recipients from a single center who were diagnosed with COVID-19 are reported. The majority of these patients (83%) required hospitalization but unlike previously reported cases [2,12–19], most of our patients suffered from moderately severe disease which only required supportive treatment with oxygen. In addition, in 10 patients, a decision was made to stop or reduce the dose of the anti-proliferative agents. Of note is that in this cohort there was only one patient with COVID-19 who was in his first transplant year. We can only speculate on the role of (high-dose) immunosuppression in this group on the development of severe COVID-19. The CFS correlated with poor outcome and was higher in nonsurvivors compared with survivors. A correlation between outcome and CFS was reported previously for ICU patients [23].

Apart from three heart transplant recipients, none of the other SOT recipients was treated with drugs with presumed antiviral activity. Most of the hospitalized patients were treated with azithromycin, which may have contributed to the relatively mild COVID-19 course in the majority of patients. It has been suggested that macrolide antibiotics have an immunomodulatory effect on neutrophil, macrophage, and lymphocytic activity, leading to a reduced inflammatory response and increased production of anti-inflammatory mediators [24–26]. While MMF has reported in vitro antiviral properties, clinical studies do not suggest a benefit in coronavirus infection and even possible harm [27]. Therefore, in more severe disease, we stopped MMF. In the group of patients in whom the immunosuppression was reduced, the length of hospital stay and mortality were higher, which probably related to the higher disease severity at presentation. Tacrolimus has antiviral properties against coronaviruses in vitro, but no human studies have been performed to date [28,29]. Therefore, the tacrolimus dose was not changed, except in one patient in whom the trough concentration was above target. Potentially, immunosuppressive medication may mitigate the viral replication or the immune response, modifying disease outcome.

In the Netherlands, there have been 43 211 confirmed cases of COVID-19 of which 11 430 patients needed hospitalization (source [https://www.rivm.nl/coronavirus-covid-19/actueel; accessed May 14th, 2020]). Of these, 2831 were admitted to the ICU, representing 6.55% of all confirmed cases of COVID-19 in the general Dutch population [source [https://www.stichting-nice.nl/; accessed May 14th, 2020]. The number of SOT recipients followed at our center approximates 3575, and the number of confirmed COVID-19 transplant cases therefore equals 0.64%. We believe that the low number of affected transplant recipients reflects the strict social distancing measures and above average hand hygiene application that most patients have taken. Possibly, strict governmental regulations on social distancing have added to this effect. Furthermore, only two patients (or 9%) were transferred to the ICU which does not appear to be in excess of the general population. Transplant activity during the COVID-19 pandemic was negatively affected at our center due to decreased organ donation numbers and prioritization of healthcare services for severe COVID-19 patients [30].
transplantation activity was temporarily put on hold for kidney transplantation, and deceased donor activity was limited to medically urgent and highly immunized patients only. The liver, heart, and lung transplantation programs continued where possible but experienced a marked decline in transplantations.

Five (or 22%) of our patients died from COVID-19. In the Netherlands, there have been 5562 confirmed deaths from COVID-19 but this is likely an underestimation (source https://www.rivm.nl/coronavirus-covid-19/actueel; accessed May 14th, 2020). The mortality rate in the present series appears to be higher than the 12.9% death rate in the general Dutch population.

To the best of our knowledge, this is one of the first series of patients with COVID-19 after various types of SOT. We believe our observations are of interest as they demonstrate that immunosuppressed patients suffering from COVID-19 and who have a frail phenotype are at risk for poor outcome. Also, in patients with low CFS, adaptation of their immunosuppressive regimen only and without the administration of potentially toxic and as yet unproven antiviral therapy is a therapeutic option.

Authorship
RH, OM, and DH: participated in research design, data collection, data analysis, and writing of the paper. MB, MH, LS, JK, KC, JW, MH, and HM: contributed to research design, data analysis, and review of the paper.

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Conflicts of interest
The authors declare no conflicts of interest.

REFERENCES

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497.
2. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020; 382: 727.
3. Ahn C, Amer H, Anglilceau D, et al. Global transplantation COVID report March 2020. Transplantation 2020; https://doi.org/10.1097/TP000000000002358 [Epub ahead of print].
4. Dong L, Hu S, Gao J. Discovering drugs to treat coronavirus disease 2019 (COVID-19). Drug Discover Ther 2020; 14: 58.
5. Liu C, Zhou Q, Li Y, et al. Research and development on therapeutic agents and vaccines for COVID-19 and related human coronavirus disease. ACS Cent Sci 2020; 6: 315.
6. Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. N Engl J Med 2020; 382: 1787.
7. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res 2020; 30: 269.
8. Murthy S, Gomersall CD, Fowler RA. Care for critically ill patients with COVID-19. JAMA 2020; 323: 1499.
9. Poston JT, Patel BK, Davis AM. Management of critically ill adults with COVID-19. JAMA 2020; 323: 1839. https://doi.org/10.1001/jama.2020.4914. [Epub ahead of print].
10. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020; 395: 1569.
11. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. The Lancet 2020; 395: 1033.
12. Zhu L, Xu X, Ma K, et al. Successful recovery of COVID-19 pneumonia in a renal transplant recipient with long-term immunosuppression. Am J Transplant 2020: 1. https://doi.org/10.1111/ajt.15869. [Epub ahead of print].
13. Guillen E, Pinoeiro GJ, Revuelta I, et al. Case report of COVID-19 in a kidney transplant recipient: does immunosuppression alter the clinical presentation? Am J Transplant 2020: 1. https://doi.org/10.1111/ajt.15874. [Epub ahead of print].
14. Huang J, Lin H, Wu Y, et al. COVID-19 in posttransplantation patients: report of two cases. Am J Transplant 2020: 1. https://doi.org/10.1111/ajt.15896. [Epub ahead of print].
15. Li F, Cai J, Dong N. First cases of COVID-19 in heart transplantation from China. J Heart Lung Transplant 2020; 39: 496.
16. Qin J, Wang H, Qin X, et al. Perioperative presentation of COVID-19 disease in a liver transplant recipient. Hepatology 2020. https://doi.org/10.1002/hep.31257. [Epub ahead of print].
17. Bin L, Yangzhong W, Yuanzaun Z, et al. Successful treatment of severe COVID-19 pneumonia in a liver transplant recipient. J Am Transplant Soc 2020; 1. https://doi.org/10.1111/ajts.15901. [Epub ahead of print].
18. Aigner C, Dittmer U, Kamler M, et al. COVID-19 in a lung transplant recipient. J Heart Lung Transplant 2020; 39: 610.
19. Akalin E, Azzi Y, Bartash R, et al. Covid-19 and kidney transplantation. N Engl J Med 2020. https://doi.org/10.1056/NEJMoa2011117. [Epub ahead of print].
20. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020; 323: 1239.
21. Gandhi RT, Lynch JB, Del Rio C. Mild or moderate Covid-19. N Engl J Med 2020. https://doi.org/10.1056/NEJMcp2009249.
22. Rockwood K, Song X, MacKnight C, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005; 173: 489.
23. Brummel NE, Bell SP, Girard TD, et al. Frailty and subsequent disability and mortality among patients with critical illness. Am J Respir Crit Care Med 2017; 196: 64.
24. Sunazuka T, Yoshida K, Oohori M, et al. Effect of 14-membered macrolide compounds on monocyte to macrophage differentiation. J Antibiot (Tokyo) 2003; 56: 721.
25. Murphy BS, Sundaresan V, Cory TJ, et al. Azithromycin alters macrophage phenotype. J Antimicrob Chemother 2008; 61: 554.
26. Meyer M, Huaux F, Gavilanes X, et al. Azithromycin reduces exaggerated cytokine production by M1 alveolar macrophages in cystic fibrosis. Am J Respir Cell Mol Biol 2009; 41: 590.
27. Mo Y, Fisher D. A review of treatment modalities for middle east respiratory syndrome. J Antimicrob Chemother 2016; 71: 3340.
28. Carbajo-Lozoya J, Müller MA, Kallies S, et al. Replication of human coronaviruses SARS-CoV, HCoV-NL63 and HCoV-229E is inhibited by the drug FK506. Virus Res 2012; 165: 112.
29. Carbajo-Lozoya J, Ma-Lauer Y, Malesevic M, et al. Human coronavirus NL63 replication is cyclophilin A-dependent and inhibited by non-immunosuppressive cyclosporine A-derivatives including Alisporivir. Virus Res 2014; 184: 44.
30. de Vries APJ, Alwayn IPJ, Hoek RAS, et al. Immediate impact of COVID-19 on transplant activity in the Netherlands. Transpl Immunol 2020; 61: 101304. https://doi.org/10.1016/j.trim.2020.101304. [Epub ahead of print].