

## ORIGINAL ARTICLE

# 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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## Key words

COVID-19, organ transplantation, SARS-CoV-2, solid organ transplantation

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## Introduction

The first case of corona virus 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; LuTx, 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/m <sup>2</sup>	10/23 (43%)
BMI >30 kg/m <sup>2</sup>	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)
SpO <sub>2</sub> at presentation—median % (range)	94.9 (92–100)
Disease severity score—no	
Mild	3
Moderate	14
Severe	4
Critical	2
Treatment—no/total no (%)	
Azitromycine	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)
CRP >50 mg/l—no/total no (%)	70.73 (6.3–236)
Procalcitonin—ng/ml	Median (range)
PCT >0.2—no/total no (%)	0.33 (0.04–0.76)
Ferritin—μg/l	Median (range)
Ferritin >900—no/total no (%)	485 (77–1588)
Leukocyte count × 10 <sup>9</sup> /l	Median (range)
Leukocyte >10—no/total no (%)	2/9 (22%)
Lymphocyte count (×10 <sup>9</sup> /l)	Median (range)
D dimer (mg/l)	Median (range)
D dimer >0.5—no/total no (%)	5.4 (1.9–12.8)
Serum creatinine (μmol/l)	2/15 (13%)
Serum creatinine (μmol/l)	Median (range)
Serum creatinine (μmol/l)	0.75 (0.13–1.18)
Serum creatinine (μmol/l)	Median (range)
Serum creatinine (μmol/l)	0.60 (0.19–1.25)
Serum creatinine (μmol/l)	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; SpO<sub>2</sub>, 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 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/m<sup>2</sup>), 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]. Living donor

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.

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