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COVID-19 in Recent Lung Transplant Recipients: Clinical Outcomes and Management Strategies

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ABSTRACT

Background. COVID-19 causes a wide range of symptoms, with particularly high risk of severe respiratory failure and death in patients with predisposing risk factors such as advanced age or obesity. Recipients of solid organ transplants, and in particular lung transplantation, are more susceptible to viral infection owing to immune suppressive medication. As little is known about the SARS-CoV-2 infection in these patients, this study was undertaken to describe outcomes and potential management strategies in early COVID-19 infection early after lung transplantation.

Methods. We describe the incidence and outcome of COVID-19 in a cohort of recent lung transplant recipients in Munich. Six of 186 patients who underwent lung transplantation in the period between March 2019 and March 2021 developed COVID-19 within the first year after transplantation. We documented the clinical course and laboratory changes for all patients showing differences in the severity of the infection with COVID-19 and their outcomes.

Results. Three of 6 SARS-CoV-2 infections were hospital-acquired and the patients were still in inpatient treatment after lung transplantation. All patients suffered from symptoms. One patient did not receive antiviral therapy. Remdesivir was prescribed in 4 patients and the remaining patient received remdesivir, bamlanivimab and convalescent plasma.

Conclusions. COVID-19 does not appear to cause milder disease in lung transplant recipients compared with the general population. Immunosuppression is potentially responsible for the delayed formation of antibodies and their premature loss. Several comorbidities and a general poor preoperative condition showed an extended hospital stay.

A novel pneumonia was first reported in Wuhan (China) in December 2019. In January 2020 the origin was identified as new severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [1−5]. The COVID-19 pandemic followed thereafter [6]. Until December 2021 the world health organization (WHO) confirmed almost 260 million cases of COVID-19 worldwide, including 2.5 million deaths [7].

SARS-CoV-2 is transmitted via inhalation, direct contact, or contaminated surfaces. The course of disease varies and ranges from asymptomatic to death within a short time. The exponential spreading, especially via asymptomatic carriers and the incubation period of 2 to 14 days are the biggest challenges to stop the pandemic [8−11].

Several strategies and therapies were developed to combat the spreading and to treat patients affected. For quite a while no

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specific medicine or vaccine was available, therefore the treatment was based on different experimental approaches [10,12-17].

The majority of COVID-19 cases are either asymptomatic or result in a mild disease. People who were hospitalized owing to a severe course of disease often had comorbidities and risk factors connected with poor prognosis [18−21]. A special, smaller group suffering from a severe course are those patients having received a solid organ transplantation (SOT). It was hypothesized the first time that this group is more susceptible to the virus owing to their immunosuppressive drug treatment, as this impairs the immune response and therefore increases risk for an infection. Furthermore, delayed or missing formation of antibodies in these patients might have an impact on the course of the disease. A weakened immune response will impact therapy success or cause a prolonged recovery. Moreover, the dependency of high-dose immunosuppression therapy promotes the occurrence of bacterial and fungal infection [22−24]. Initial observations indicated that independent of any SOT in a patient's prehistory, severe course results are significantly driven by a hyper-inflammatory state. Hence, an immunosuppressive therapy is still considered beneficial [25,26].

The group of immunosuppressed patients infected with SARS-CoV-2 is small. Considering just the lung transplant recipients' (LTRs) experience of manifestation, management, and treatment, the group gets even smaller and there is still no evidence-based recommendation [27−29]. With almost 100 lung transplants (LTs) per year, the Munich lung transplantation group is one of the most experienced centers in Europe. Since the beginning of the pandemic, the number of LTs has only decreased slightly. This study deals with LTRs infected with SARS-CoV-2 within the first year (early phase) after transplantation. Knowledge about such a specific patient collective is rare [30,31]. These patients need a particularly high dose of immunosuppressive medications to reduce early organ rejection and to prevent superinfections at the same time.

The aim of this study was to identify possible risk factors of a poor outcome in early COVID-19 after LT. Furthermore, we aimed at identifying indicators influencing the clinical outcome.

MATERIAL AND METHODS

Setting and Statistical Analysis

This is a retrospective, monocentric study of all adult LTRs with confirmed SARS-CoV-2 infections in the early phase after LT at the Ludwig-Maximilians-University of Munich. During the period from March 2019 and March 2021 186 patients underwent LT. The first LTR with confirmed SARS-CoV-2 infection in the early phase was diagnosed on November 2, 2020. Until March 2021, we diagnosed COVID-19 in 6 patients. Three of these SARS-CoV-2 infections were hospital-acquired and the patients were still in inpatient treatment after LT. The remaining 3 patients had already been discharged after transplantation and presented themselves to the emergency room with typical COVID-19 symptoms as well as worsening general condition. An admission to the hospital was necessary.

The diagnosis was verified by high-resolution computer-tomography (HR-CT) and positive real-time reverse-transcriptase polymerase chain reaction (rRT-PCR) after a nasopharyngeal and oropharyngeal swab. Results of the rRT-PCR are presented in cycle threshold values (ct-values).

In order to describe qualitative values, absolute frequencies and percentages are used. The description of qualitative variables is presented as the median and range.

Data Collection

A database was established with study data collected anonymously. Parameters included demographics, baseline clinical characteristics, radiological and pathologic findings, immunologic status, type, date and underlying diagnosis of the LT, parameter for possible organ rejection, microbiological results, comorbidities, type of current or recent immunosuppressive therapies, and the treatment of COVID-19. Data used within this study cover the period August, 2019 (pre-transplantation) up to and including March 10, 2021.

ETHICS STATEMENT

The Clinical Research Ethics Committee of the Ludwig-Maximilians-University Munich approved the study (21-0312).

RESULTS

Baseline Demographics and Clinical Characteristics

A total of 6 early LTRs diagnosed with COVID-19 were identified. An overview of demographics and clinical characteristics pre infection is shown in Table 1. Median age at LT was 59 years (range, 37-69), 4 patients were male, and all of them had an interstitial lung disease before the transplantation was performed. Half of the patients (3 of 6) had idiopathic pulmonary fibrosis.

Perioperative Transplant Details

The median lung allocation score was 39.6. One patient had been treated with awake veno-venous extracorporeal membrane oxygenation as bridge to transplantation. All 6 patients received a double lung transplantation. The operation time ranged between 4:15 hours and 7:36 hours. Mechanical ventilation could be stopped within the first 48 hours for 4 patients, and 2 required a tracheotomy. Two patients developed a postoperative hemothorax, and a re-operation was necessary. Donor-specific HLA antibodies could be detected in 3 patients after LT and were treaded by IvIg infusion. After LT a bronchoscopy and transbronchial biopsies were performed. Two patients had a mild cellular rejection (A1,B0; nomenclature in the diagnosis of lung rejection; ISHLT [32]), and intravenous pulse prednisolone was prescribed. One of these patients received this therapy right before SARS-CoV-2 infection.

Before COVID-19 onset, a triple immunosuppressive therapy with tacrolimus (trough level 12-15 ng/mL), mycophenolate mofetil, and prednisolone was prescribed for all. The median forced vital capacity in the early phase after lung transplantation was 2605 mL and a 2050 mL forced expiratory volume in the first second was achieved.

Table 1. Number of Demographics and clinical characteristics pre SARS-CoV-2 infection

	Total (n = 6)	ICU (n = 2)	General ward (n = 4)	Survivors (n = 5)	Nonsurvivors (n = 1)
Age, years at LT, median (range)	59 (37-69)	59	62 (37-69)	59 (37-69)	59
Age, years at COVID-19, median (range)	60 (38-69)	60 (59-60)	62 (38-69)	60 (38-69)	
Gender m/f	4/2	1/1	3/1	3/2	1/0
BMI kg/m^2, median (range)	26.93 (22.55-28.73)	26.93 (26.17-27.68)	27.11 (22.55-28.73)	26.17 (22.55-28.73)	27.68
Blood type 0	2 (33)	2 (100)	0 (0)	1 (20)	1 (100)
Blood type A	3 (50)	0 (0)	3 (75)	3 (60)	0 (0)
Blood type B	1 (17)	0 (0)	1 (25)	1 (20)	0 (0)
Prior smoker, n (%)	3 (50)	2 (100)	1 (25)	2 (40)	1 (100)
Pack years, median (range)	2.5 (0-100)	60 (20-100)	0 (0-5)	0 (0-20)	100
Indication for LT, n (%)					
IPF, n (%)	3 (50)	2 (100)	1 (25)	2 (40)	1 (100)
IPAF, n (%)	1 (17)	0 (0)	1 (25)	1 (20)	0 (0)
Hypersensitivity pneumonitis, n (%)	1 (17)	0 (0)	1 (25)	1 (20)	0 (0)
Sarcoidosis, n (%)	1 (17)	0 (0)	1 (25)	1 (20)	0 (0)
Comorbid conditions pre-LT, n (%)					
Heart failure, n (%)	3 (50)	1 (50)	2 (50)	2 (40)	1 (100)
Peripheral vascular disease, n (%)	1 (17)	0 (0)	1 (25)	1 (20)	0 (0)
Arterial hypertension, n (%)	2 (33)	0 (0)	2 (50)	2 (40)	0 (0)
Coronary heart disease, n(%)	1 (17)	0 (0)	1 (25)	1 (20)	0 (0)
Atrial fibrillation, n (%)	1 (17)	0 (0)	1 (25)	1 (20)	0 (0)
Pulmonary hypertension, n (%)	3 (50)	1 (50)	2 (50)	2 (40)	1 (100)
Transplant details					
LAS, median (range)	39.6 (36.9-86.9)	41.3 (37.8-44.8)	39.6 (36.9-86.9)	37.8 (36.9-86.9)	44.83
CMV donor status +/-	5/1	2/0	3/1	4/1	1/0
CMV recipient status +/-	5/1	2/0	3/1	4/1	1/0
Preoperative ECMO, n (%)	1 (16.7)	0 (0)	1 (25)	1 (20)	0 (0)
Double lung, n (%)	6 (100)	2 (100)	4 (100)	5 (100)	1 (100)
Intraoperative ECMO, n (%)	4 (66.7)	2 (100)	2 (50)	3 (60)	1 (100)
Intraoperative blood loss in ml (range)	3250 (2000-6300)	4900 (3500-6300)	2500 (2000-6000)	3000 (2000-6300)	3500
Operation time, hh:mm (range)	05:59 (04:15-07:36)	06:12 (04:49-7:36)	05:59 (4:15-6:41)	06:35 (4:15-07:36)	04:49
Immunosuppression after LTx					
Tacrolimus, n (%)	6 (100)	2 (100)	4 (100)	5 (100)	1 (100)
Mycophenolate mofetile, n (%)	6 (100)	2 (100)	4 (100)	5 (100)	1 (100)
Prednisolon, n (%)	6 (100)	2 (100)	4 (100)	5 (100)	1 (100)
Complications post LT, n (%)					
Mechanical ventilation >48h, n (%)	4 (67)	1 (50)	3 (75)	4 (80)	0 (0)
Re-intubation, n (%)	2 (33)	0 (0)	2 (50)	2 (40)	0 (0)
Tracheotomy, n (%)	2 (33)	1 (50)	1 (25)	2 (40)	0 (0)
Reperfusion edema, n (%)	2 (33)	1 (50)	1 (25)	1 (20)	1 (100)
Pneumonia, n (%)	1 (17)	1 (50)	0 (0)	1 (20)	0 (0)
Pulmonary artery embolism, n (%)	2 (33)	1 (50)	1 (25)	2 (40)	0 (0)
Arrhythmia, n (%)	1 (17)	0 (0)	1 (25)	1 (20)	0 (0)
Delir >72h, n (%)	1 (17)	0 (0)	1 (25)	1 (20)	0 (0)
Re-operation, n (%)	2 (33)	1 (50)	1 (25)	2 (40)	0 (0)
Wound infection, n (%)	1 (17)	1 (50)	0 (0)	0 (0)	1 (100)
Gastrointestinal complication, n (%)	3 (50)	1 (50)	2 (50)	3 (60)	0 (0)
Critical Illness Polyneuropathy, n (%)	2 (33)	1 (50)	1 (25)	2 (40)	0 (0)
Donor specific HLA antibodies, n (%)	3 (50)	1 (50)	2 (50)	3 (60)	0 (0)
Mild cellular rejetion, n (%)	2 (33)	1 (50)	1 (25)	1 (20)	1 (100)

(*continued*)

Table 1 (*Continued*)

	Total (n = 6)	ICU (n = 2)	General ward (n = 4)	Survivors (n = 5)	Nonsurvivors (n = 1)
Lung function early phase post LT					
FVC, ml, median (range)	2605 (1540-3630)	2425 (1840-3010)	2200 (1540-3630)	2020 (1540-3630)	3010
FEV1, ml, median (range)	2050 (1320-3130)	1840 (1510-2170)	1930 (1320-3130)	1720 (1320-3130)	2017
FEV1/FVC, %, median (range)	85.7 (82-88)	77.1 (72-82)	86.2 (86-88)	86 (82-88)	72.1

Abbreviations: LT, lung transplantation; COVID-19, coronavirus disease 2019; BMI, body mass index; ASA, American Socitety of Anesthesiologists Classification; IPF, ideopathic pulmonary fibrosis; IPAF, interstitial pneumonia with autoimmune features; LAS, lung allocation score; CMV, cytomegalovirus; EMCO, extracorporeal membrane oxygenation; FVC, forced vital capacity; FEV1, forced expiratory volume in the first second.

Clinical Characteristics, Laboratory, and Radiological Findings at COVID-19 Diagnosis

Clinical, laboratory, and radiological characteristics during SARS-CoV-2 infection are summarized in Table 2. The median interval between transplantation and COVID-19 diagnosis was 99 days (range, 18-345). All patients suffered from fatigue, half of them had fever. Eighty-three percent of the patients had dyspnea and cough and 4 patients developed diarrhea during the infection. Headache, expectoration, nausea, and vomiting were reported in 33% of each.

Five patients developed a leukopenia (median 1.5 × 10E3/μl; reference range 4.0-10.4 × 10E3/μl). Elevation of inflammatory biomarkers such as ferritin (median 733 ng/mL; reference range 15-150 ng/mL), d-dimer (median 0.6 μg/mL; reference range <0.5 μg/mL), interleukin 6 (median 144 pg/mL; reference range <5.9 pg/mL), lactate dehydrogenase (median 673 U/L; reference range <249 U/L), and C-reactive protein (median 10.8mg/dL; reference range <0.5 mg/dL) was noted in all patients. Beside the inflammatory biomarkers an elevation in serum creatinine (median 2.2 md/dL; reference

Table 2. Clinical, radiological and laboratory characteristics of patients at COVID-19 diagnosis

	Total (n = 6)	ICU (n = 2)	General ward (n = 4)	Survivors (n = 5)	Nonsurvivors (n = 1)
Positive rRT-PCR since transplant, days, median (range)	99 (18-345)	184 (22-345)	99 (18-221)	103 (18-345)	22
Positive rRT-PCR to discharge/death, days, median (range)	50 (25-122)	86 (49-122)	43 (25-85)	49 (25-85)	122
Symptoms					
Fatigue, n (%)	6 (100)	2 (100)	4 (100)	5 (100)	1 (100)
Fever, n (%)	3 (50)	1 (50)	2 (50)	3 (60)	1 (100)
Dyspnea, n (%)	5 (83)	2 (100)	3 (75)	4 (80)	1 (100)
Cough, n (%)	5 (83)	2 (100)	3 (75)	4 (80)	1 (100)
Asthenia, n (%)	3 (50)	2 (100)	1 (25)	2 (40)	1 (100)
Diarrhoea, n (%)	4 (67)	2 (100)	2 (50)	3 (60)	1 (100)
Myalgia, n (%)	1 (17)	1 (50)	0 (0)	0 (0)	1 (100)
Nausea/Vomiting, n (%)	2 (33)	1 (50)	1 (25)	2 (40)	0 (0)
Expectoration, n (%)	2 (33)	1 (50)	1 (25)	1 (20)	1 (100)
Headache, n (%)	2 (33)	1 (50)	1 (25)	1 (20)	1 (100)
Abdominal pain, n (%)	1 (17)	0 (0)	1 (25)	1 (20)	0 (0)
Temp <38.4°C, n (%)	3 (50)	1 (50)	2 (50)	3 (60)	0 (0)
Temp 38.4-39.4°C, n (%)	3 (50)	1 (50)	2 (50)	2 (40)	1 (100)
Laboratory findings					
Lowest leukocyte count x 10E3/ul, median (range)	1.5 (0.2-4.5)	1.3 (0.6-2.0)	1.6 (0.2-4.5)	2.0 (0.2-4.5)	0.6
Highest ferritin, ng/ml, median (range)	733 (519-2249)	2249	710 (519-1694)	710 (519-1694)	2249
Highest D-dimer, µg/ml, median (range)	0.6 (0.3-2.9)	1.6 (0.3-2.9)	0.6 (0.5-1.0)	0.5 (0.3-1.0)	02/Sep
Highest Interleukin-6, pg/ml, median (range)	144 (52-4795)	2408 (21-4795)	114 (52-840)	88 (21-840)	4795
Highest LDH, U/l, median (range)	673 (404-1220)	1014 (807-1220)	499 (404-889)	538 (404-889)	1220

(*continued*)

Table 2 (*Continued*)

	Total (n = 6)	ICU (n = 2)	General ward (n = 4)	Survivors (n = 5)	Nonsurvivors (n = 1)
Highest C-reactive protein, mg/dl, median (range)	10.8 (2.6-29.1)	28.9 (28.6-29.1)	7.6 (2.6-13.7)	7.8 (2.6-29.1)	28.6
Highest serum creatinine, mg/dl, median (range)	2.2 (1.0-4.4)	3.1 (1.8-4.4)	2.2 (1.0-4.1)	1.9 (1.0-4.1)	4.4
Tracrolimus level, ng/ml, median (range)	12.5 (11.5-15.4)	14.3 (12.5-16.0)	12.2 (11.5-13.3)	12.5 (11.5-16.0)	15.4
Anti-SARS-CoV-2-antibody, n = 5 (%)	5 (100)	1 (100)	4 (100)	4 (100)	1 (100)
Antibody loss during hospital stay, n = 5 (%)	3 (60)	1 (100)	2 (40)	2(50)	1 (100)
Complications					
Atelectasis, n (%)	1 (17)	1 (50)	0 (0)	1 (20)	0 (0)
Renal failure, n (%)	5 (83)	2 (100)	3 (75)	4 (80)	1 (100)
Heart failure, n (%)	1 (17)	1 (50)	0 (0)	0 (0)	1 (100)
Bacterial Bronchitis, n (%)	1 (17)	1 (50)	0 (0)	0 (0)	1 (100)
Bacterial Pneumonia, n (%)	2 (33)	2 (100)	0 (0)	1 (20)	1 (100)
Circulatory shock, n (%)	1 (17)	1 (50)	0 (0)	0 (0)	1 (100)
Liver failure, n (%)	2 (33)	1 (50)	1 (25)	1 (20)	1(100)
Acute pancreatitis, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Pleural effusion, n (%)	3 (50)	2 (100)	1 (25)	2 (40)	1(100)
CMV reactivation, n (%)	2 (33)	1 (50)	1 (25)	2 (40)	0 (0)
Chest CT					
Ground glass opacities, n (%)	6 (100)	2 (100)	4 (100)	5 (100)	1 (100)
Consolidation, n (%)	4 (67)	2 (100)	2 (50)	3 (60)	1 (100)
Interstitial abnormalities, n (%)	4 (67)	2 (100)	2 (50)	3 (60)	1 (100)
Pleural effusion, n (%)	3 (50)	1 (50)	2 (50)	2 (40)	1 (100)
Treatment					
Anticoagulation, n (%)	6 (100)	2 (100)	4 (100)	5 (100)	1 (100)
Antibiotic therapy, n (%)	4 (67)	2 (100)	2 (50)	3 (60)	1 (100)
Change from Prednisolon 15mg to Dexamethason 8mg, n (%)	4 (67)	2 (100)	1 (25)	1 (20)	1 (100)
Pulse steroid (>125mg/d), n (%)	2 (33)	1 (50)	1 (25)	1 (20)	1 (100)
Switch Tacrolimus by Cyclosporin, n (%)	2 (33)	1 (50)	1 (25)	1 (20)	1 (100)
IvIg, n (%)	2 (33)	1 (50)	1 (25)	1 (20)	1 (100)
Remdesivir, n (%)	5 (83)	2 (100)	3 (75)	4 (80)	1 (100)
Bamlanivimab, n (%)	1 (17)	1 (50)	0 (0)	0 (0)	1 (100)
Convalescent Plasma, n (%)	1 (17)	1 (50)	0 (0)	0 (0)	1 (100)
Max respiratory support					
O2 therapy, n (%)	4 (67)	0 (0)	4 (100)	4 (80)	0 (0)
Maximum regular nasal cannula in l	2.0		2.0	2.0	
Mechanical, n(%)	2 (33)	2 (100)	0 (0)	1 (20)	1 (100)

Abbreviations: COVID-19, coronavirus disease 2019; rRT-PCR, real-time reverse-transcriptase-polymerase chain reaction; LDH, lactate dehydrogenase; CMV, cytomegalovirus; CT, computertomography; IvIg, intravenous immunglobulin; O2, oxygen;

range 0.7-1.2 mg/dL) was noted. The tacrolimus trough level was within the limits (median 12.5 ng/mL). The interim presence of anti-SARS-CoV-2 antibodies could be detected in 5 patients, and one patient was not tested. Three patients who expressed anti-SARS-CoV-2-antibodies showed an antibody loss during their inpatient stay. rRT-PCR ct-values and anti-SARS-CoV-2-antibodies are shown in Fig 1 for each patient.

The most frequently associated complication was renal failure (83%), followed by pleural effusion (n = 3; 50%). Thirty-three percent developed bacterial pneumonia and hepatopathy/liver failure each. Two patients developed cytomegalovirus reactivation during the infection, without cytomegalovirus organ disease.

Besides the positive rRT-PCR the diagnosis was confirmed by HR-CT scan. The course of a mild (patient A; treated in the general ward) and a severe (patient B, admitted to the intensive care unit [ICU]) infection is pictured in Fig. 2 and 3. During the infectious period ground glass opacities were described in at least one HR-CT scan in all patients. Four patients had additional consolidations and interstitial abnormalities, and 3 had pleural effusion.

Treatment and Outcome of COVID-19 in LTR

In the absence of consensus guidelines, treatment was based on individual decisions and dependent on clinical, laboratory, and radiological findings. The description of the antiviral and immunomodulatory therapies is shown in Table 2.

Regarding medical treatment all patients received thromboprophylaxis. Antibiotic therapy was given in 67% (n = 4). The basic immunosuppression was not stopped, apart from mycophenolate mofetil in a case of pronounced leukopenia.

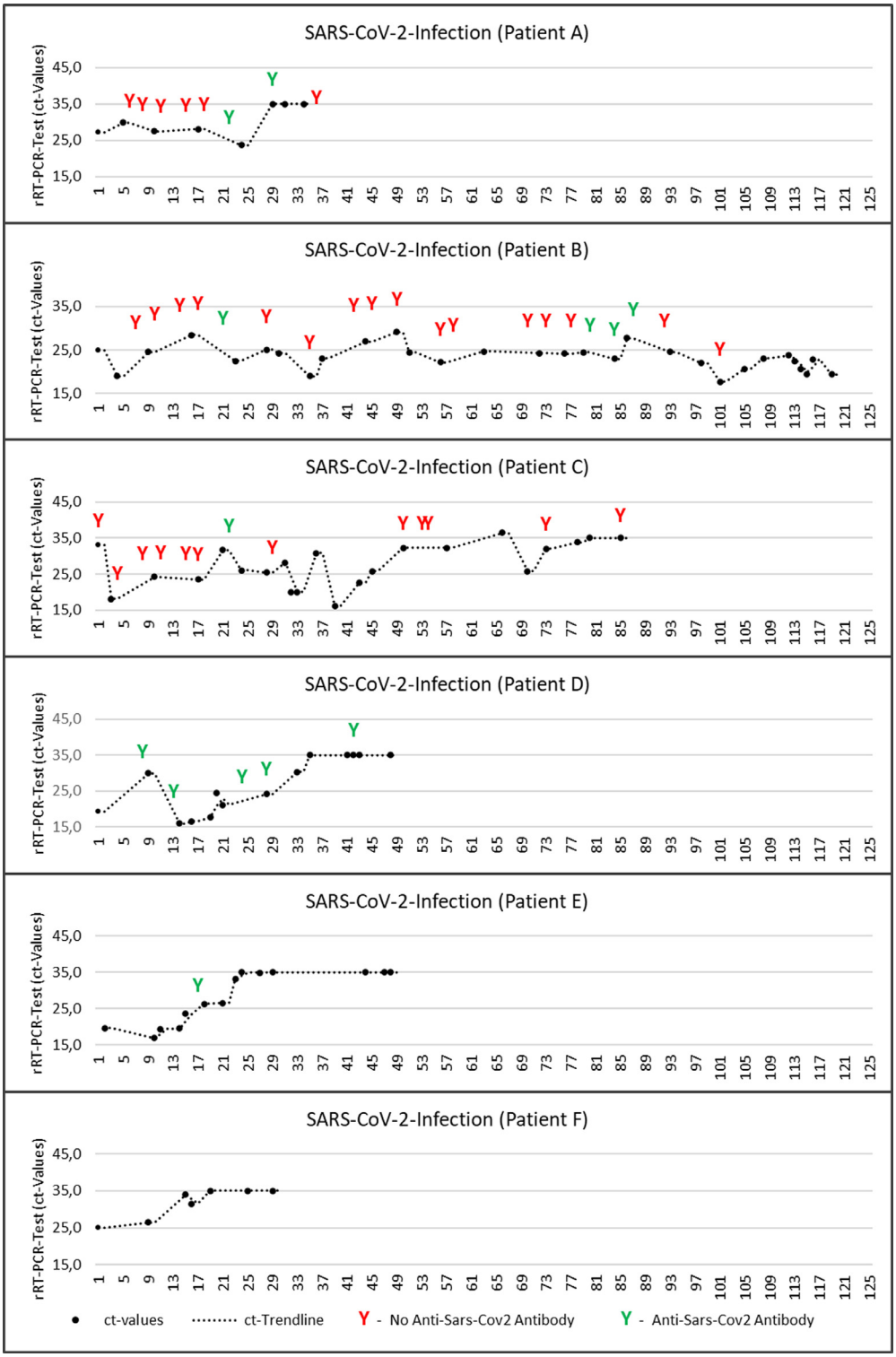

Fig 1. rRT-PCR ct-values and anti-SARS-CoV-2-antibodies in detail for each patient (Patients A-F). ct-Values are shown as black dots, connected by a trend line. No anti-SARS-CoV-2-antibodies represented by a red Y and anti-SARS-CoV-2-antibodies as a green Y. X-axis represents days; day 1 started after the first positive rRT-PCR. Y-axis shows the ct-values. ct-values ≥35 represents noninfectious patients. rRT-PCR, real-time reverse-transcriptase-polymerase chain reaction.

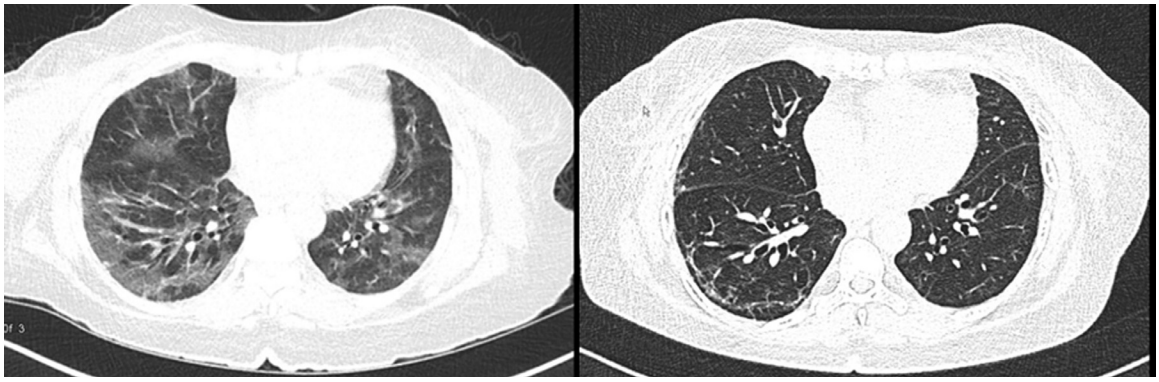

Fig 2. Patient A. Axial high-resolution CT scan of a mild SARS-CoV-2 infection. Left: Images 10 days after diagnosis; bilaterally moderate patchy ground glass opacities in the bases. Right: 73 days after the first negative rRT-PCR test. Almost complete recovery of the lung parenchyma. rRT-PCR, real-time reverse-transcriptase-polymerase chain reaction. CT, computed tomography.

Prednisolone was stopped in favor of high-dose dexamethasone in 4 patients (67%) for a period of time during the acute infection. Intravenous pulse prednisolone was prescribed in 2 patients, as well as IvIg infusion. Additionally, in 2 cases tacrolimus was stopped and cyclosporine was given.

In terms of the specific SARS-CoV-2 treatment, one patient did not received antiviral therapy (patient A; Fig. 2 and 4). Remdesivir was prescribed in 4 patients and the remaining patient (patient B; Fig. 3 and 5) received remdesivir, bamlanivimab, and convalescent plasma.

All patients required respiratory support. Two patients had to be admitted to the ICU where invasive mechanical ventilation was applied. Incidental findings showed a bacterial pneumonia in these 2 patients. Both patients requiring ICU care had blood type 0. Four patients were treated on the general ward. Survival was 83% (n = 5) and median time to discharge was 49 days after initial diagnosis. Owing to multiorgan failure and Acute Respiratory Distress Syndrome, patient B died 122 days after the first positive rRT-PCR.

In order to emphasize the variation in severity of the SARS-CoV-2 infection in initially comparable patients, patient A and B of our series were examined more closely (Fig. 4 and 5). These figures represent an individual course of a mild and a severe (admission to ICU) infection from LT to discharge/death. The diagrams are based on a timeline including rRT-PCR ct-values, the presence of anti-SARS-CoV-2-antibodies, medical treatment above the curve, and symptoms, as well as other special events under the curve.

Patient A, a 66-year-old woman, underwent a double LT owing to interstitial lung disease based on hypersensitivity pneumonitis on October 15, 2020. The intraoperative course was without any complications. Invasive mechanical ventilation could be stopped on the second postoperative day, and she was transferred to the normal ward on day 7. Eighteen days after LT the first positive rRT-PCR was recorded (ct-value 27.2). The symptoms that occurred during the infection were mild. Six days after the positive test the patient developed diarrhea, followed by fatigue and dyspnea. Several laboratory abnormalities were observed. Inflammation markers elevated moderately (C-reactive protein 9.9 mg/dL, interleukin 6 51.6 pg/mL). Ferritin increased up to 1694 ng/mL, and the maximum value of serum creatinine was recorded on November 26 (2.4 mg/dL). An HR-CT scan on November 12 showed bilaterally moderate patchy ground glass opacities in the bases (Fig 2). Twenty-two days after the first positive rRT-PCR, anti-SARS-CoV-2 antibodies were detected on 2 different days. Fifteen days later, the antibodies were no longer detectable. During the infection period she did not need any specific antiviral therapy or change of prednisolone dosage. On December 2 and 5, the patient was tested negative and discharged.

Patient B was a 59-year-old man with idiopathic pulmonary fibrosis who received a double LT on October 12. Immediately before the transplantation a high-flow therapy was necessary owing to a pulmonary exacerbation. Invasive mechanical ventilation could be stopped on the first postoperative day, and 3 days after the LT he was transferred to the normal ward. Routine postoperative transbronchial biopsies were performed on October 28, and showed mild cellular rejection without lymphocytic bronchiolitis (A1, B0 ISHLT). High-dose cortisone therapy was initiated. On November 3 (1 day after patient A, 23 days after LT) he tested positive for SARS-CoV-2 (ct-value 24.9)—Fig 3 shows the course in detail. His further stay in hospital was marked by many setbacks and resulted in the death of the patient. Ct-values undulated. At the beginning of the infection, symptoms were mild and increased over the course. Twenty-one days after the first positive test result, anti-SARS-CoV-2antibodies were detected once. On January 4 the patient suffered from dyspnea and cough. An antiviral therapy with remdesivir was started, followed by application of convalescent plasma. Only within the period January 21 to 28 anti-SARS-CoV-2 antibodies were detected. Monoclonal antibodies (bamlanivimab) were given twice on January 28 and 29. Despite specific antiviral therapy, the patient's physical condition deteriorated. The HR-CT scans showed a progression of the disease (Fig 3) and the patient was moved to the ICU on February 4. Mechanical ventilation, bacterial superinfection,and multiorgan failure followed. The patient died on March 3, 122 days after he was tested positive.

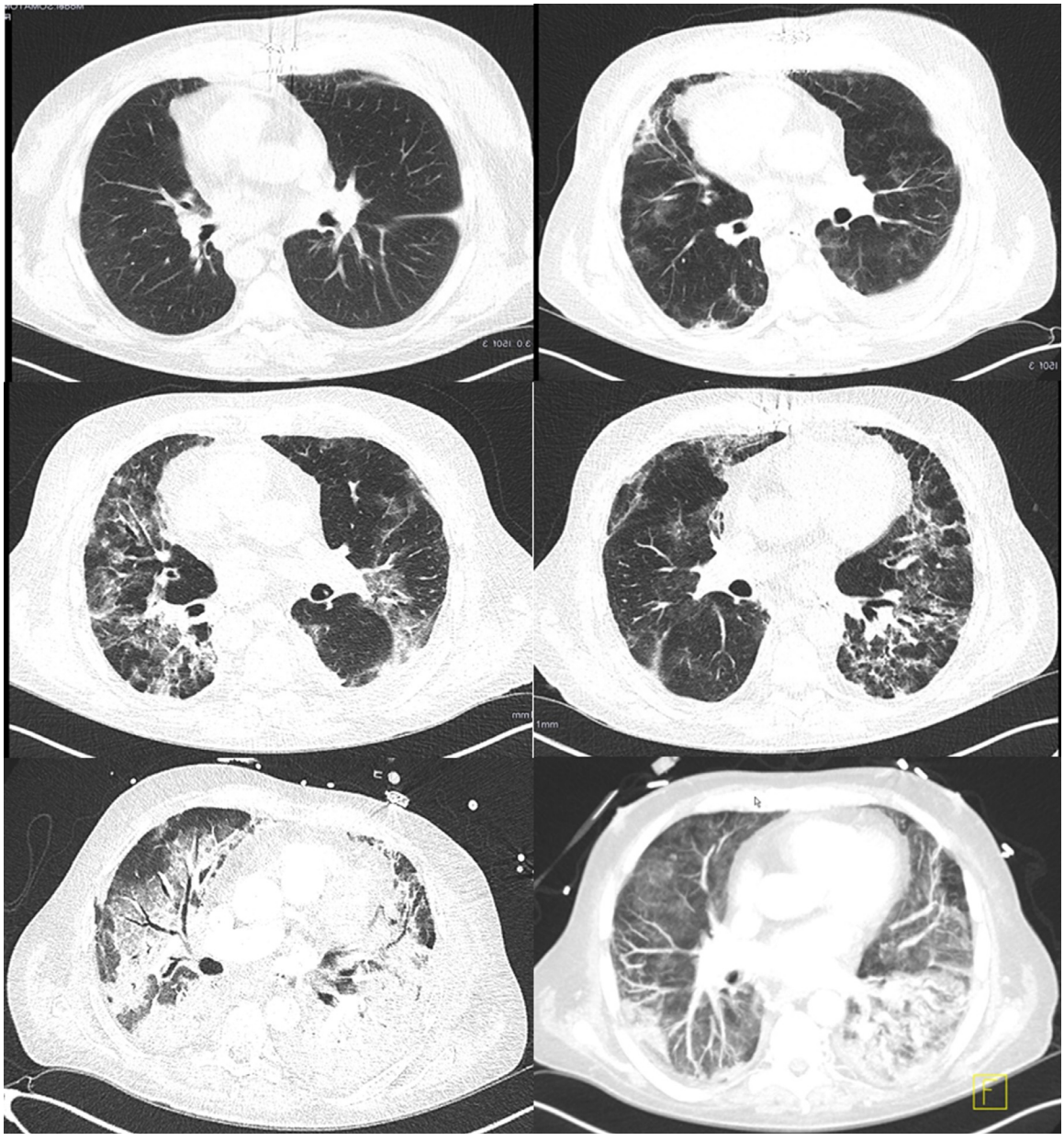

Fig 3. Patient B. Axial high-resolution CT scan of a severe SARS-CoV-2 infection. Course from top left to bottom right. Seven days after diagnosis and on day 37, 69, 90, 102, and 111 (11 days before death). Initial CT scan almost inconspicuous (top left); ground glass opacities, consolidation, and bacterial superinfection are shown in the following images. CT, computed tomography.

DISCUSSION

We describe the clinical presentation and course of COVID-19 in a cohort of patients in the acute phase (1 year) after lung transplantation. COVID-19 in LTRs, especially in recipients during the early post-transplant period, has not been well documented and has likely been quite rare [30,31]. COVID-19 is challenging to treat and effective therapies for severe disease are lacking. COVID-19 infections in LTRs, in particular during the early phase in which many postoperative physical, medical, and immunologic changes take place is even more complex. Changes in treatment have to be carefully weighed and in the case of recurrent symptoms or laboratory findings, a SARS-CoV-2-independent cause must not be overlooked.

In our study each patient had at least one cardiovascular risk factor, which is associated with significantly increased risk for mortality in COVID-19. Moreover, 5 of them were male

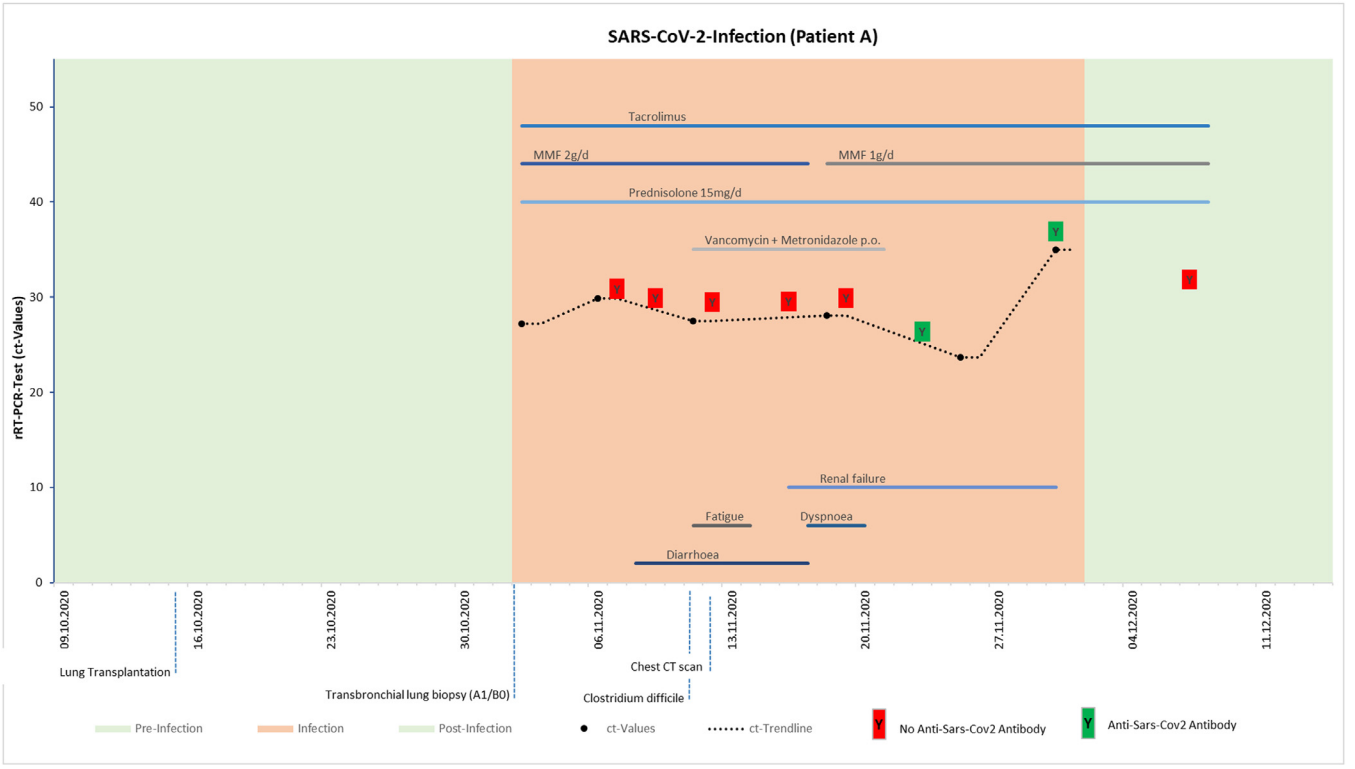

Fig 4. Individual course of a mild infection (patient A) from lung transplantation to discharge. The diagram is based on a timeline including rRT-PCR ct-values represented in black dots, which are connected by a trendline. The presence of anti-SARS-CoV-2-antibodies is shown as green Y's, and no anti-SARS-CoV-2-antibodies are marked by red Y's. Medical treatment is shown above the curve and symptoms as well as other special events under the curve and on the x-axis. The green background color describes the pre- or post-infection period and red the infection. rRT-PCR, real-time reverse-transcriptase-polymerase chain reaction.

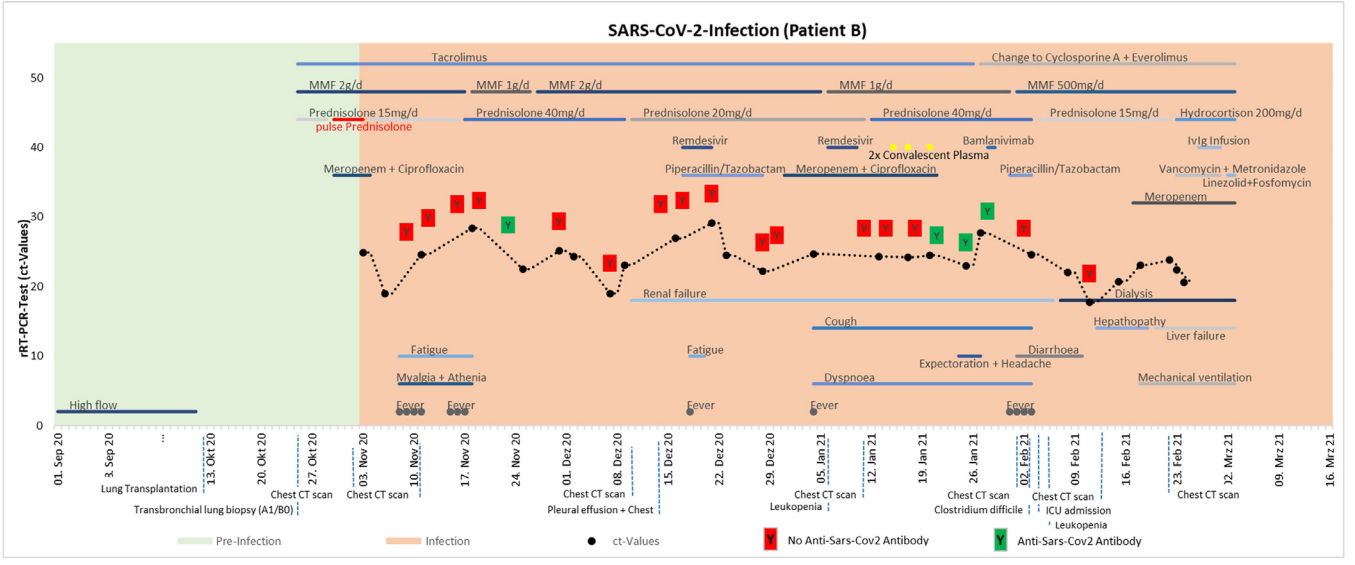

Fig 5. Individual course of a severe infection (patient B) from lung transplantation to death. The diagram is based on a timeline including rRT-PCR ct-values represented in black dots, which are connected by a trendline. The presence of anti-SARS-CoV-2-antibodies is shown as green Y's, and no anti-SARS-CoV-2-antibodies are marked by red Y's. Medical treatment is shown above the curve and symptoms as well as other special events under the curve and on the x-axis. The green background color describes the pre-infection period and red the infection. rRT-PCR, real-time reverse-transcriptase-polymerase chain reaction.

[20,21,33-35]. The woman infected by SARS-CoV-2 had a mild course, and the female patient who initially shared her room did not become infected. Patients with several comorbidities and a general poor preoperative condition showed an extended hospital stay in our study, including one death. Many of the risk factors for a severe course of COVID-19 (defined as admission to ICU) as described in literature were present in our early-phase LTRs infected with SARS-CoV-2. In addition, 2 LTRs admitted to the ICU had clinical and radiological evidence of a bacterial superinfection. Bacterial pneumonia in LTRs with COVID-19 seemed clearly associated with admission to the ICU and invasive mechanical ventilation.

Compared with other series without SOT, our patients had a similar incidence of common COVID-19 symptoms [18,36,37]. Fewer patients had fever (50%) and more patients developed diarrhea (83%), which was associated with clostridium difficile in half of the cases. Within our patient collective, the frequency of symptoms correlated with the severity and duration of the course of infection. Radiological findings match those described in literature and correlate with the severity of the course as well as the additional occurrence of superinfections [38].

The duration of the course in our patients was prolonged compared with the general population [37]. Five patients were tested regularly for anti-SARS-CoV-2-antibodies and expressed them at least once during the infection. The detection of antibodies in the patient who died was also recorded after convalescent plasma was given. With 3 of these 5 patients (including the patient who died), an antibody loss was detected during the inpatient stay. Fig 1 shows the rRT-PCR ct-values and antibodies in detail for each patient. Patients A, B, and C were already in hospital treatment, when infection was proven. Owing to the fact that the onset of symptoms of patients A, B, and C was delayed and that their antibody formation took significantly longer, we can assume that the other 3 patients who presented themselves to the emergency room with typical symptoms had already been infected by the coronavirus for a longer period of time and were asymptomatic. That would also explain the faster detection of antibodies and shorter infectiousness compared with patients A, B, and C (Fig 1). It is likely that the course was not shorter, we missed the onset of the disease owing to the missing of symptoms and lack of routinely performed tests, because the patients had already been discharged after LT and were already at home.

The difficulty to express anti-SARS-CoV-2-antibodies or their loss in SOT is described in a few cases [27,39]. Owing to our laboratory observations and the fact that the patient who received convalescent plasma also had a loss of antibodies within a short time, it is our opinion that immunosuppression is potentially responsible for the delayed formation of antibodies and their premature loss.

There are currently no specific treatment options for this disease, therefore various therapeutic approaches have been used based on expert opinions. In the asymptomatic period of the infection, we made no changes in medication. Our LTRs received an increased dose, bolus, or switched to a more potent corticosteroid, as the general condition deteriorated and the respiratory component increased. Calcineurin inhibitor therapy was continued. In patients with pronounced leukopenia, mycophenolate mofetil was reduced or suspended. The first 3 cases received remdesivir at the time of medical deterioration. In the remaining patients it was added prophylactically, assuming it would shorten the time to recovery [40]. This approach seemed to show success in the acute post-transplant period. Other systemic treatments were not broadly used. One patient who developed very severe disease received monoclonal antibodies (bamlanivimab) and convalescent plasma for several times, however, he did not recover. He had initially presented with very mild symptoms, and his general condition and respiratory state deteriorated rapidly after a long period of mild symptoms. Convalescent plasma and monoclonal antibodies have been described to alter the course of disease. However, they may aggravate lung injury in patients with multiple organ failure and should be infused early in the course of the disease [41−43]. However, it is unclear whether the administration of the convalescent plasma and monoclonal antibodies had a positive impact or if it even contributed to clinical deterioration in our patient.

Owing to the different courses of the infection in our series, it is difficult to make a statement about the role of immunosuppressive drugs. In our experience, it is justifiable to continue calcineurin inhibitor and metabolic therapy during the infection in the early phase after LT, not least to avert early rejection of the organ.

In our series, acute phase lung transplant patients showed a worse prognosis compared with the general population and were clinically similar to other SOTs [27,29,36,44,45].

The following limitations of our study need to be addressed. The study design was retrospective and the size of the cohort does not allow for significant statistical analysis. In addition, we could not ensure that we had included the entire acute post-transplant patient collective infected by SARS-CoV-2. There might be asymptomatic patients who did not present themselves to the emergency room or who were diagnosed coincidentally. Moreover, follow-up in the post-COVID period varied between patients and did not include scheduled HR-CT scans and pulmonary function testing.

CONCLUSION

Contrary to some initial assumptions that immunosuppression might protect from severe disease, COVID-19 does not appear to cause milder disease in LTRs compared with the general population. Patients with several comorbidities and a general poor preoperative condition showed an extended hospital stay. In our series bacterial superinfection in COVID-19 patients is associated with high rates of admission to the ICU and invasive mechanical ventilation. Immunosuppression is potentially responsible for the delayed formation of antibodies and their premature loss, which seems to be typical for LTR in the early phase after transplantation. It is still unclear whether the administration of the convalescent plasma and monoclonal antibodies had a positive impact or if it even contributed to clinical worsening, especially in patients with a prolonged course. Further severe individual courses need to be examined more closely in order to improve on future prognosis. The diversity of the

courses of COVID-19 in general in conjunction with the general complexity of postoperative management in the early phase after LT require more interdisciplinary collaboration to predict future course scenarios based on actual courses and to determine the best treatment options.

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