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COVID-19 in lung transplant recipients

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JM designed the study, coordinated the study, collected the data, analyzed and interpreted the results, and wrote the manuscript.

PE designed the study, coordinated the study, analyzed the results and critically reviewed the manuscript.

AR and SM designed the study, collected the data and critically reviewed the manuscript.

HM designed the study, interpreted the results and wrote the manuscript.

MPD reviewed the chest CT-scans and critically reviewed the manuscript.

SH, AN, JLP, AS, SCR, NC, XD, ALB, AT, LB, BRP, MRG, JFM, CP, VB, JJ collected the data and critically reviewed the manuscript.

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Abbreviations:

COVID-19: coronavirus disease 2019

ICU: intensive care unit

LT: lung transplant

mTOR: mammalian target of rapamycin

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

SOT: solid organ transplantation

Abstract

Background

A concern about the susceptibility of immunocompromised patients to the worldwide pandemic of coronavirus disease 2019 (COVID-19) has been raised. We aimed at describing COVID-19 infections in the French cohort of lung transplant (LT) patients.

Methods

Multicenter nationwide cohort study of all LT recipients with COVID-19 diagnosed from March 1 to May 19, 2020. Recipient main characteristics and their management were retrieved. Hospitalization characteristics, occurrence of complications and survival were analyzed.

Results

Thirty-five LT patients with a COVID-19 infection were included. Median age was 50.4 [40.6-62.9] years, 16 (45.7%) were female, and 80% were double-LT recipients. Infection was community-acquired in 25 (71.4%). Thirty-one (88.6%) required hospitalization, including 13 (41.9%) in the intensive care unit. The main symptoms of COVID-19 were fever, cough, and diarrhea, present in 71.4%, 54.3%, and 31.4% of cases, respectively. Extension of pneumonia on chest CT was moderate to severe in 51.4% of cases. Among the 13 critically ill patients, seven (53.9%) received invasive mechanical ventilation. Thrombotic events occurred in four patients. Overall survival rate was 85.7% after a median follow-up of 50 days [41.0-56.5]. Four of five non-survivors had had bronchial complications or intensification of immunosuppression in the previous weeks. On univariate analysis, overweight was significantly associated with risk of death (odds ratio 16.0 [95% confidence interval 1.5-170.6], $p=0.02$).

Conclusion

For the 35 LT recipients with COVID-19, the presentation was severe, requiring hospitalization in most cases, with a survival rate of 85.7%.

Introduction

In the time of the worldwide coronavirus disease 2019 (COVID-19) pandemic, comorbidities significantly affect prognosis.¹⁻³ Among comorbidities, immunosuppression has scarcely been reported. Nevertheless, a concern was internationally raised for solid organ transplantation (SOT) recipients,⁴ and reports emerged from various areas.⁵⁻¹⁷ From these reports, a few observations can be drawn: the clinical presentation, severity and outcomes are heterogenous, as in the general population;^{1,2,18} co-infections or co-isolations of other pathogens might appear at the onset of symptoms;¹⁹ and clear management of the immunosuppressive maintenance regimen and antiviral treatments during the episode must be set up.^{17,20,21}

Besides immunosuppression, lung transplantation (LT) recipients are particularly scrutinized because the main injury of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is respiratory, patients sometimes have impaired respiratory function,²² and clinical presentation may be altered by local factors. The first case reports of COVID-19 pneumonia in LT recipients described an uneventful evolution: some patients were hospitalized with low-flow oxygen^{8,17}, and others remained at home.⁹ Moreover, published series of SOT recipients with COVID-19 described a small number of LT recipients.^{9,13,15,16} Nevertheless, no comprehensive study has described COVID-19 manifestations in LT recipients.

We aimed to identify LT patients presenting COVID-19 in all French LT centers and describe their clinical presentation, characteristics, and outcome (including intensive care unit [ICU] admission), with associated risk factors.

Patients and methods

Setting and study subjects

We conducted a retrospective, multicenter cohort study in the 11 French lung transplant centers. All adult LT recipients with a biologically confirmed or highly suspected SARS-CoV-2 infection who were followed in one of these centers from March 1 to May 19, 2020 were enrolled. The study was approved by the Institutional Review Board of the Société de Pneumologie de Langue Française (CEPRO 2020-015). According to French law, the patients (or their proxies) were informed of the study, its purpose and objectives and did not object to the collection of their data.

Data collection

Study data were collected anonymously and managed by physicians and research teams by use of an electronic data capture tool²³ (see Supplemental Digital Content). Demographic data collected included sex and age. Type of LT (single or double lung, combined organs), date of LT, and the underlying diagnosis were recorded. Type and stage of chronic lung allograft dysfunction before the episode were defined.²² Comorbid conditions and type of current or recent immunosuppressive therapies were recorded. Data were collected on clinical, biological and CT findings at COVID-19 diagnosis, type of sample positive for SARS-CoV-2, community- or hospital-acquired type of episode, and the co-isolation of a pathogen or the occurrence of a superinfection. Patients were followed after the episode until May 19, 2020, when the data collection system was frozen.

Outcome

The primary endpoint was death at follow-up. Secondary endpoints were ICU admission, need for invasive mechanical ventilation, time elapsed from 1) LT to COVID-19 diagnosis, 2) the first symptoms to COVID-19 diagnosis, 3) the first symptoms to hospital admission,

4) the first symptoms to ICU admission, and 5) the first symptoms to mechanical ventilation onset and COVID-19 complications.

Definitions

Diagnosis of SARS-CoV-2 infection was ascertained by a positive SARS-CoV-2 result on real-time RT-PCR assay¹ of a respiratory sample or highly suspected in an LT recipient presenting the association of clinical presentation of COVID-19, typical chest CT-scan pattern²⁴, and no alternative diagnosis during the study period.

Chronic kidney disease was defined by estimated glomerular filtration rate < 60 mL/min/1.73m².²⁵ Fever was defined as corporeal temperature > 37.8°C. A hospital-acquired COVID-19 episode was defined for patients who had been admitted 5 days or more before the first symptom(s), and healthcare-associated COVID-19 was defined for patients who lived in a nursing home or extended-care facility or who received chronic dialysis. Other episodes were considered community-acquired. A typical chest CT-scan pattern was defined according to Salehi et al.,²⁴ and chest CT-scans were centrally reviewed and scored by a skilled radiologist (MPD). Extension of pneumonia was considered minimal with the pulmonary injury representing < 10% of the pulmonary field, moderate with 10% to 25%, extensive with 25% to 50%, severe with 50% to 75%, and critical with > 75%.

The need for ICU admission and occurrence of thrombo-embolic disease, acute respiratory distress syndrome,²⁶ and acute kidney injury²⁷ were considered COVID-19 complications, and data on overdose of calcineurin inhibitors was collected.

Statistical analysis

Continuous variables are described with median and interquartile range [IQR] unless otherwise indicated. Categorical variables are described with number (%). For analysis of

factors associated with mortality or ICU admission, univariate analyses assessed associations between outcomes and demographic characteristics, comorbidities, and treatments with a logistic regression model. Variables with $P < .20$ in univariate analysis were tested in multivariate models. Mann-Whitney test was used for analysis of continuous variables and chi-square or Fisher exact test as appropriate for categorical variables. All tests were two-tailed, and $p < .05$ was considered statistically significant. Statistical analysis was performed with R v4.0.1.

Results

Diagnosis of infection

We report the cases of 35 patients from the 11 French LT centers who experienced COVID-19 during the study period. Diagnosis was ascertained by a positive RT-PCR test for SARS-CoV-2 in 30 (85.7%) patients and was highly suspected in five (14.3%).

Demographics and comorbid conditions

Main demographic characteristics are reported in Table 1. Median age was 50.4 [IQR 40.6-62.9] years, and 16 (45.7%) patients were female. In total, 28 (80%) patients had double LT, seven single LT (20%; five right, two left), and none cardio-pulmonary transplantation. Time from LT was 38.2 [6.6-78.3] months. Two patients had received another solid organ transplant (one kidney, one liver).

Chronic lung allograft dysfunction had been diagnosed in six (17.1%) patients; six had bronchial complications (17.1%), four of whom required interventional endoscopic procedure within 3 months before COVID-19 onset. All but one patient (97.1%) received calcineurin inhibitor therapy before COVID-19 onset. Most (n=33) received daily oral corticosteroids at a median dose of 8.75 [5.0-11.25] mg/day prednisone or equivalent and 15 (42.9%) were on azithromycin before the episode.

Seven patients (20%) had undergone an intensification of their immunosuppression regimen in the last 6 months (median time from intensification to COVID-19 onset 89.0 [5.0-140.0] days). This intensification always included high-dose corticosteroid pulses, associated with another therapy for five (induction therapy in three; plasmapheresis in two, and one who also received rituximab infusion).

Characteristics of COVID-19

SARS-CoV-2 infection was most often community-acquired (25 [71.4%] patients); hospital-acquired in seven (20%), including one who was already in the ICU at the time of diagnosis; and healthcare-associated in three (8.6%).

The manifestations of COVID-19 are summarized in Table 2. Median time from the first symptoms to diagnosis was 4.0 [1.0-7.0] days. Fever was the first and most frequent sign, occurring in 25 (71.4%) patients, followed by cough (n=19; 54.3%). Diarrhea occurred in 11 (31.4%) patients and acute renal failure in four (11.4%). A chest CT-scan was performed at a median of four [1-7] days after first symptoms in 25 (71.4%) patients: one had no abnormalities (despite a positive RT-PCR result in a respiratory sample). The main findings were ground-glass opacities in 24 (92.3%) patients. Extension of pneumonia was considered minimal in six (23.1%), moderate in nine (36%), and extensive or severe in nine (34.6%). None had pulmonary extension > 75%.

The main biological features at first hospital admission are in Table 2. Seven (20%) patients had a respiratory bacterial co-isolation at diagnosis, documented on the initial respiratory sample (*Pseudomonas aeruginosa*, n=5, *Streptococcus pneumoniae*, n=1, and *Corynebacterium sp.*, n=2). Two had a viral co-isolation: cytomegalovirus reactivation in one and rhinovirus/enterovirus sampled in the respiratory tract in one. Finally, *Aspergillus sp.* was isolated from a single respiratory sample from one patient.

Treatment settings (Figure 1)

Four (11.4%), 25 (71.4%), and six (17.1%) patients were exclusively cared for as outpatients, primarily hospitalized in the general ward, and primarily cared for in the ICU, respectively. Among the 25 patients primarily hospitalized in the general ward, seven (28.0%) were secondarily cared for in the ICU. Overall, 13 (37.1%) patients were admitted

to the ICU, including one who was already in the ICU at the time of diagnosis. For the 12 patients who were not in the ICU at diagnosis, ICU admission occurred after a median of 13.0 [5.5-14.8] days from the onset of symptoms and 1.0 [0-4.0] days from hospital admission for the eight with COVID-19 acquired outside the hospital.

Immunosuppression management

For 13 (37.1%) patients, the antimetabolite therapy was discontinued, with an increase in corticosteroids in seven, combined with withdrawal of the mammalian target of rapamycin (mTOR) inhibitor in one and withdrawal of calcineurin inhibitor in one. Two (5.7%) others had a withdrawal of the mTOR inhibitor without any antimetabolite therapy change: one had increased corticosteroids dosage and three only increased corticosteroids dosage. The 11 (31.4%) patients with an increase in corticosteroids dosage received a median dose of 100 [40-125] mg/day of prednisone or equivalent.

Management of specific infection

Eleven (31.4%) patients received at least one specific treatment intended to treat the SARS-CoV-2 infection: hydroxychloroquine for nine (25.7%), remdesivir for two; and lopinavir-ritonavir association for two. Of note, two patients received two different treatments (remdesivir followed by chloroquine or lopinavir-ritonavir followed by remdesivir). All 15 (42.9%) patients who received azithromycin before COVID-19 continued it, and two additional patients received azithromycin associated with hydroxychloroquine (*i.e.*, 17 [48.6%] patients overall received azithromycin).

Outcomes and complications

Survival was 85.7% (n=30) after a median follow-up of 50 [41.0-56.5] days. Five patients died (14.3%, 95% CI [5.4-31.0]), due to multi-organ failure and acute respiratory distress

syndrome in four, and one was not admitted to the ICU because of limitation of therapeutic effort.

Among the 25 patients primarily hospitalized in the general hospital ward, 22 (88.0%) received low-flow oxygen therapy. Among the 13 patients (37.1%, 95% CI [21.9-55.1]) in the ICU, five received non-invasive respiratory support (i.e., nasal high-flow oxygen therapy only, because no patient received continuous positive pressure or non-invasive ventilation), seven (53.8%) received invasive mechanical ventilation, four had prone positioning, and one had veno-venous extracorporeal membrane oxygenation. Four received catecholamine infusion and five (38.5%) renal replacement therapy.

Three of the seven patients with invasive ventilation died. At the end of follow-up, six patients remained hospitalized, including four in the ICU.

During follow-up, a thrombotic event occurred in four patients (three with pulmonary embolism and one arterial embolic manifestation of the lower limb due to an intracardiac thrombus). Twelve (34.3%) patients had at least one pulmonary superinfection (11 bacterial and one fungal). Two had bacteremia during follow-up (detailed in Table 3).

Risk factors for death and ICU admission

The five non-survivors had undergone LT at a median of 9.6 [7.2-16.3] months before the COVID-19 diagnosis, including three during the previous 12 months. For two, the post-operative period was complicated by bronchial issues, requiring bronchial intervention in the previous 3 months; one patient with LT 87 months before had had bronchiolitis obliterans syndrome grade 1; and one patient who had double LT 52 days before received intravenous corticosteroid pulses and plasmapheresis at 9 and 7 days, respectively, before diagnosis.

Univariate exploratory analysis is summarized in Figures 2 and 3 (and Supplemental Digital Content Table 2). Odds of death were increased with only overweight status (*i.e.* body mass index ≥ 25 and < 30 kg/m²) (OR 16.0 [1.5-170.6], $p=0.02$). No other characteristics were significantly associated with ICU admission or death. Intensification of immunosuppression therapy in the last 6 months was associated but not significantly with ICU admission (OR 6.25 [1.00-39.1], $p=0.08$). On multivariate analysis, no other risk factor was significantly associated with death or ICU admission.

Discussion

We report here the first national series of LT patients with SARS-CoV-2 infection in the 11 French LT centers. For the 35 LT recipients who had proven or highly suspected COVID-19 during the study period, the presentation was severe for most, with hospitalization in 31 (88.6%). COVID-19 was responsible for death in five (14.3%) patients, after a median follow-up of 50.0 [41.0-56.5] days.

As described in non-immunocompromised hosts,^{1,2} COVID-19 clinical presentation was consistent with a viral pulmonary infection, with fever (in 25; 71.4%), cough (in 19, 54.3%), and sputum production (in 12; 34.3%). Other symptoms of viral infection such as headache (in 12; 34.3%) or diarrhea (in 11; 31.4%) were also present, as in larger series with unbiased recruitment.^{1,2}

CT-scan findings were consistent with those described in non-immunocompromised individuals.²⁴ In single-LT patients, the challenge of the CT-scan interpretation involves detecting ground-glass opacities on the native lung. Our series included seven single-lung transplanted patients, one showing bilateral involvement. The native lung might be difficult to analyze, because ground-glass opacities might occur in the native lung as a manifestation of interstitial lung disease, for example. Or, conversely, when the parenchyma is destructed by emphysema, the pattern of viral infection might be missing. In our series, despite these limitations, bilateral involvement was indeed detected.

Although four (11.4%) patients received treatment on an outpatient basis, in LT hosts, COVID-19 might have a dreadful course: the crude hospital mortality reached 14.2%, because five patients died during their hospital stay after a median follow-up of 15 [7.0-15.0] days and six patients remained hospitalized at the end of follow-up.

Significant risk factors for death in COVID-19 are scarce. An increased risk for markedly severe COVID-19 was previously described in ICU populations^{28,29}, and the increased risk of death with overweight was evidenced in previously published studies³⁰. The median body mass index of our LT patients was not high (21.5 kg/m²), and only 10 were overweight, all with BMI < 30 kg/m². Nevertheless, odds of death were increased with overweight status. Recent intensification of immunosuppression was not found associated with poor prognosis of COVID-19 course.

Our results agree with those from the largest series of SOT recipients with COVID-19.¹⁰ Akalin et al. reported a single-center cohort of 36 kidney transplant recipients: eight (22.2%) had received treatment as outpatients, and 11 (39%) received mechanical ventilation. Mortality reached 28% at a median follow-up of 21 days. The mortality rate of our cohort seems lower. To date, COVID-19 infection in LT recipients has been sparsely described: a first report of an LT recipient was recently published.⁸ the evolution was uneventful because the patient required supplemental nasal oxygen therapy at 1 to 2 L/min. Another series of four SOT recipients⁹ described one LT recipient with COVID-19, who despite having comorbid conditions (e.g., chronic lung allograft dysfunction and chronic renal failure), showed resolution with simple home supportive care. Hoek et al.¹³ reported a single-center series of 23 SOT recipients, three with LT. Data on prognosis for these patients are unfortunately unavailable. Finally, Yi et al.¹⁶ reported a single-center series of 21 SOT recipients with COVID-19, including two with LT. Only 14 (66.7%) of these required inpatient management; seven were admitted in the ICU. The median follow-up reached 18 [13-30] days, and, at follow-up, only one patient had died, and four were still in the ICU.

Management of SOT patients with COVID-19 remains based on expert opinion. A consensus approach was derived from the guidelines of 22 transplant societies.³¹ A medium-strength recommendation to decrease immunosuppression was proposed, as advocated by 9 of the societies. The guidelines from the French Transplant Society³² were not included in the previous consensus approach,³¹ but they advocated different strategies according to the severity of the condition. In all cases, a modification of the antimetabolite therapy (a decrease if outpatient care is possible or an interruption with need for hospitalization) is suggested, as is withdrawal of the mTOR inhibitor with acute respiratory failure. No definite attitude stems from recent case reports, toward neither immunosuppressive treatment withdrawal nor antiviral treatments.⁵⁻¹⁶

In our series, no definite strategy was adopted: antimetabolite withdrawal was the most frequent immunosuppression therapy modification (in 13 of 29 patients, 44.8% of the patients under antimetabolites before COVID-19). Antimetabolite withdrawal was not restricted to only patients with severe disease because six hospital-ward patients had a withdrawal of antimetabolite therapy. The second most frequent modification was an increase in corticosteroids regimen, in 11 (31.4%) patients. These findings agree with the reported strategies in other SOT recipients.^{5-14,16}

Collateral damage of COVID-19 pandemics has been reported all over the world and has been described early in its course.³³ It includes reduced available ICU beds resulting from the need for admission of critically ill COVID-19 patients, the transformation of operating theatres into intensive care beds, the decrease in donation organs, and the risk of nosocomial transmission of SARS-CoV-2 to a newly transplanted recipient. In our series, four patients acquired COVID-19 in the 3 months following LT: three had a nosocomial COVID-19, not donor-derived, and the fourth had a healthcare-associated infection.

Limitations

Although retrospective, this report is likely complete because all French LT centers participated, and missed cases are unlikely. Actually, LT patients are used to getting in touch with their LT center in case of any intercurrent event and therefore informed their LT center of their infection. Nevertheless, our study was not designed to measure the incidence of COVID-19 in the French cohort of LT recipients. Moreover, some asymptomatic cases might have occurred, and we might have underestimated the burden of COVID-19 in LT recipients. We acknowledge that the cohort described here is of limited size but therefore assume that all data on French symptomatic COVID-19 infections in LT patients have been collected. The absence of a control group (e.g., non-immunocompromised hosts, or non-lung SOT recipients) prevents us from comparing the outcomes of COVID-19. Still, our study aimed at describing the course of COVID-19 in LT recipients.

Finally, our study lacked long-term follow-up of outcomes, including graft outcome. These outcomes remain to be explored.

Conclusions

This first comprehensive multicenter series of 35 LT recipients with COVID-19 shows a diverse prognosis. The presentation was severe, requiring hospitalization in most cases. Overall mortality was 14.3%. Death rate in the ICU was 30.7%. Overweight was significantly associated with odds of death. Long-term outcomes remain to be investigated.

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Tables

Table 1. Demographics and comorbid conditions

	Total n=35	ICU n=13	Hospital ward n=18	Outpatients n=4	Survivors n=30	Non-survivors n=5
Age - years	50.4 [40.6-62.9]	59.7 [47.9-63.2]	45.5 [40.3-61.0]	40.9 [33.4-52.3]	48.1 [40.5-63.0]	58.1 [50.4-60.5]
Gender – M/F	19/16	8/5	7/11	4/0	16/14	3/2
BMI – kg/m ²	21.5 [20.3-22.6]	23.8 [20.4-27.4]	21.0 [20.2-24.8]	21.0 [20.4-21.4]	21.0 [20.2-24.0]	25.9 [25.6-27.4]
<25	25 (71.4)	7 (53.8)	14 (77.8)	4 (100)	24 (80)	1 (20)
≥ 25 to <30	10 (28.6)	6 (46.2)	4 (22.2)	0	6 (20)	4 (80)
≥ 30	0	0	0	0	0	0
Type of LT, n (%)						
Single lung	7 (20)	2 (16.7)	4 (22.2)	1 (25)	6 (20)	1 (20)
Double lung	28 (80)	11 (84.6)	14 (77.8)	3 (75)	24 (80)	4 (80)
Heart-lung	0	0	0	0	0	0
Indication for LT						
Obstructive pulmonary disease	12 (34.3)	3 (23.1)	7 (38.9)	2 (50)	11 (36.7)	1 (20)
Interstitial lung disease	9 (25.7)	7 (53.8)	2 (11.1)	2 (50)	5 (16.6)	4 (80)
Cystic fibrosis	11 (31.4)	2 (15.7)	7 (38.9)	0	11 (36.7)	0
Pulmonary arterial hypertension	1 (2.9)	0	1 (5.6)	0	1 (3.3)	0
Graft-vs-host pulmonary disease	1 (2.9)	0	1 (5.6)	0	1 (3.3)	0
Lymphangioleiomyomatosis	1 (2.9)	1 (7.7)	0	0	1 (3.3)	0
Age at LT – years	48.1 [35.0-59.8]	55.4 [45.8-62.4]	40.8 [35.0-59.4]	32.7 [30.4-40.4]	44.3 [35.0-59.7]	56.8 [49.6-59.9]
Comorbid conditions						
Recipient of another solid organ, n (%)	3 (8.6)	1 (7.7)	2 (11.1)	0	3 (10)	0
Liver	1 (2.9)	0	1 (5.6)		1 (3.3)	
Pancreas	1 (2.9)	0	1 (5.6)		1 (3.3)	
Kidney	1 (2.9)	1 (7.7)	0		1 (3.3)	
CLAD, n (%)	7 (20)	3 (23.1)	3	1 (25)	6 (20)	1 (20)
CLAD stage, n (%)						
Stage 1	4 (11.4)	2 (14.4)	2 (11.1)	0	3 (10)	1 (20)
Stage 2	2 (5.7)	1 (7.7)	0	1 (25)	2 (6.7)	
Stage 3	1 (2.9)	0	1 (5.6)	0	1 (3.3)	
Bronchial complications, n (%)	6 (17.1)	3 (23.1)	3 (16.7)	3 (75)	4 (13.3)	2 (40)
Stable bronchial stenosis	2 (5.7)	0	2 (11.1)	2 (50)	2 (6.7)	
Bronchial interventions in the last 3 months	4 (11.4)	3 (23.1)	1 (5.6)	1 (25)	2 (6.7)	2 (40)
Chronic arterial hypertension, n (%)	15 (42.9)	6 (46.2)	6	3 (75)	13 (43.3)	2 (40)
Incl. requiring treatment with renin-aldosterone blockers	10 (28.6)	5 (38.5)	4	1 (25)	9 (30)	2 (40)
Chronic renal failure, n (%)	14 (40)	4 (30.8)	8 (47.1)	2 (50)	15 (50)	1 (20)
Incl. requiring renal replacement therapy	1 (2.9)	0	1 (5.6)	0	1 (3.3)	0
Median eGFR (mL/min/1.73m ²)	63.0 [43.0-90.0]	76.5 [53.8-90.0]	65.0 [39.0-77.0]	47.5 [30.5-67.5]	62.0 [42.0-83.3]	90.0 [63.0-90.0]

Ongoing treatment before COVID-19 episode, n (%)						
Calcineurin inhibitor	35 (100)	13 (100)	18 (100)	4 (100)	30 (100)	5 (100)
Antimetabolite	29 (82.9)	10 (76.9)	15 (83.3)	4 (100)	25 (83.3)	4 (80)
Oral corticosteroids (median dose)	33 (94.3)	13 (100)	17 (94.4)	3 (75)	28 (93.3)	5 (100)
mTOR inhibitor	8.8 [5.0-11.3]	10.0 [9.4-19.4]	7.5 [5.0-10.0]	7.5 [7.3-8.8]	7.5 [5.0-12.5]	10 [7.5-10.0]
Azithromycin	7 (20)	3 (23.1)	3 (16.7)	1 (25)	6 (20)	1 (20)
Inhaled corticosteroids	15 (42.9)	4 (30.8)	9 (50)	2 (50)	14 (46.7)	1 (20)
Inhaled β 2-receptor agonist	4 (11.4)	3 (23.1)	0	1 (25)	2 (6.7)	2 (40)
Insulin	7 (20)	4 (30.8)	1 (5.6)	2 (50)	5 (16.7)	2 (40)
Intensification of immunosuppression therapy during the last 6 months, n (%)	10 (28.6)	4 (30.8)	5 (27.8)	1 (25)	8 (26.7)	2 (40)
Induction therapy	7 (20)	5 (38.5)	2 (11.1)	0	6 (20)	1 (20)
Intravenous corticosteroid pulses	3 (8.6)	1 (7.7)	2 (11.1)		3 (10)	0
Rituximab infusion	7 (20)	5 (38.5)	2 (11.1)		6 (20)	1 (20)
Plasmapheresis	1 (2.9)	1 (7.7)	0		1 (3.3)	0
Bortezomib	2 (5.7)	2 (15.4)	0		1 (3.3)	0
Bortezomib	0	0	0		0	0
Time from the last intensification therapy, days	89.0 [5.0-140.0]	7.0 [3.0-89.0]	162.5 [154.2-170.8]	115.0 [78.3-154.3]	111.5 [24.5-143.0]	7
Time from LT, months	38.2 [6.6-78.3]	9.6 [4.5-98.9]	44.6 [16.5-66.8]	59.6 [24.7-114.9]	43.0 [7.0-86.3]	9.6 [7.2-16.3]

Data are median [interquartile range] unless otherwise indicated.

ICU: intensive care unit; BMI: body mass index; CLAD: chronic lung allograft dysfunction; eGFR: estimated glomerular filtration rate by Chronic Kidney Disease Epidemiology Collaboration; LT: lung transplant; mTOR: mammalian target of rapamycin

Table 2. Clinical, radiologic and laboratory findings of 35 lung transplant patients at COVID-19 diagnosis

	total n=35	ICU n=13	Hospital ward n=18	Outpatients n=4	Survivors n=30	Non-survivors n=5
Time from LT (months)	38.2 [6.6-78.3]	9.6 [4.5-98.9]	44.6 [16.5-66.8]	59.6 [24.7-114.9]	43.0 [7.0-86.3]	9.6 [7.2-16.3]
Settings of COVID-19 acquisition, n (%)						
Community-acquired	25 (71.4)	6 (46.2)	15 (83.3)	4 (100)	23 (76.7)	2 (40)
Hospital-acquired	7 (20)	5 (38.5)	2 (11.1)	0	5 (16.7)	2 (40)
Healthcare-associated	3 (8.6)	2 (15.4)	1 (5.6)	0	2 (6.7)	1 (20)
Signs and symptoms						
Fever	25 (71.4)	10 (76.9)	13 (72.2)	2 (50)	21 (70)	4 (75)
Cough	19 (54.3)	6 (46.2)	11 (61.1)	2 (50)	17 (56.7)	2 (40)
Dyspnea	15 (42.9)	9 (69.2)	4 (22.2)	2 (50)	11 (36.7)	4 (75)
Expectoration	12 (34.3)	4 (30.8)	8 (44.4)	0	10 (33.3)	2 (40)
Diarrhea	11 (31.4)	2 (15.4)	8 (44.4)	1 (25)	10 (33.3)	1 (20)
Headache	12 (34.3)	2 (15.4)	9 (50)	1 (25)	12 (40)	0
Myalgia	13 (37.1)	3 (23.1)	8 (44.4)	2 (50)	13 (43.3)	0
Acute renal failure	4 (11.4)	2 (15.4)	2 (11.1)	0	3 (10)	1 (20)
Asthenia	16 (45.7)	7 (53.8)	8 (44.4)	1 (25)	15 (50)	1 (20)
Chest CT-scan findings						
No abnormalities, n (%)	1 (3.8)	0	1 (7.1)		1 (4.8)	0
Extension of abnormalities, n (%)						
Minimal or < 10%	6 (23.1)	0	6 (42.8)	0	5 (23.8)	1 (20)
Moderate or 10% to 25%	9 (36.0)	4 (40.0)	5 (35.7)	0	7 (23.3)	2 (40)
Extensive or 25% to 50%	7 (26.9)	4 (40.0)	2 (14.3)	1	5 (23.8)	2 (40)
Severe or 50% to 75%	2 (7.7)	2 (20.0)	0	0	2 (9.5)	0
Critical or > 75	0	0	0	0	0	0
Radiological pattern, n (%)						
Ground-glass opacities	24 (92.3)	10 (100)	13 (86.7)	1 (100)	19 (90.5)	5 (100)
Incl. with crazy paving	7 (26.9)	4 (40.0)	3 (20.0)	1 (100)	6 (28.6)	1 (20)
Consolidations	12 (46.2)	6 (60.0)	5 (33.3)	1 (100)	9 (42.9)	3 (60)
Single sided abnormalities, n (%)	3 (11.5)	0	3 (20.0)	0	2 (9.5)	1 (20)
Bilateral abnormalities, n (%)	22 (84.6)	10 (100)	11 (73.3)	1 (100)	18 (85.7)	4 (80)
Laboratory findings at diagnosis						
PaO₂/FiO₂	278.6 [162.8-357.7]	187.5 [100.0-319.0]	357.7 [275.4-429.5]	-	319.0 [186.2-375.0]	179.9 [118.1-187.5]
White cell count, per mm³	6085 [4720-9425]	5840 [4100-9400]	6200 [5180-9800]	5650 [5425-5875]	6100 [4655-9450]	4580 [3910-7030]
< 4000, n (%)	5 (17.9)	3 (23.1)	2 (15.4)		4 (17.4)	1 (20)
≥4000 to ≤10000, n (%)	19 (67.9)	8 (61.5)	9 (50)	2 (100)	16 (69.7)	3 (60)
>10 000, n (%)	4 (14.3)	2 (15.4)	3 (69.2)		3 (13.0)	1 (20)
Lymphocyte count, per mm³	790 [585-1200]	670 [515-925]	1100 [780-1750]	1185 [877-1495]	985 [713-1635]	560 [500-600]
< 800, n/total, n (%)	14 (51.9)	8 (66.7)	5 (38.5)	1 (50)	9 (40.9)	5 (100)
> 800, n/total, n (%)	13 (44.8)	4 (33.3)	8 (61.5)	1 (50)	13 (59.1)	
Creatinine, μmol/L	104.0 [84.0-154.0]	92.0 [81.0-141.0]	122.0 [88.4-170.2]	185.0 [144.5-225.5]	112.5 [84.8-154.3]	96.0 [81.0-141.0]
>133, n/total, n (%)	12 (41.4)	5 (38.5)	6 (42.9)	1 (50)	10 (41.7)	2 (40)
C-reactive protein, mg/L	67.0 [25.0-126.0]	88 [38-126]	49 [24.3-131.3]	4.4 [3.5-5.2]	49.0 [21.8-99.0]	147 [67-177]
Procalcitonin, ng/ml	0.22 [0.12-0.41]	0.15 [0.07-0.23]	1.53 [0.27-6.09]	NA	0.23 [0.13-0.34]	0.22 [0.15-1.50]
< 0.1, n/total, n (%)	3 (27.3)	3 (42.9)	0		2 (25.0)	1 (33.3)
≥0.1 to < 0.25, n/total n (%)	4 (36.4)	3 (42.9)	1 (25.0)		3 (37.5)	1 (33.3)
≥0.25 to < 0.5, n/total n (%)	1 (9.1)	0	1 (25.0)		1 (12.5)	0

≥0.5 ng/mL, n /total n (%)	3 (27.3)	1 (14.3)	2 (50.0)		2 (25.0)	1 (33.3)
Creatine kinase	40 [32.0-86.8]	60.0 [31.0-93.0]	37.5 [32.8-70.5]	39.0	39.5 [32.0-55.0]	115.0 [57.0-206.2]
Serum ferritin, µg/L	1156 [570-2200]	1156 [573-1658]	1292 [382-2325]	NA	1163 [571-2065]	841.0 [704.5-2052.5]
Incl. >300 µg/L, n (%)	13 (100)	9 (100)	4 (100)		10 (100)	3 (100)
D-dimer, ng/mL	991.5 [495.5 – 1592.0]	743 [633-1824]	1240 [215-1357]	NA	991.5 [578.5-1441.8]	1294 [852-1736]
≤ 500, n (%)	3 (25.0)	1 (14.3)	2 (40.0)		2 (22.2)	1 (50)
>500 to ≤1000, n (%)	3 (25.0)	3 (42.9)	0		3 (33.3)	0
>1000, n (%)	5 (41.7)	2 (28.6)	3 (60.0)		4 (44.4)	1 (50)

Data are median [interquartile range] unless otherwise indicated.

A chest CT-scan was performed for 25 (71.4%) patients (10 finally admitted in the ICU), after a median time of 4 [1-7] days from diagnosis; PaO₂/FiO₂ ratio was available for the 17 patients who underwent blood-gas analysis, 6 ward patients, 13 survivors and 4 non-survivors; white blood cell count for 28 patients, 13 ICU patients, 13 ward patients and 2 outpatients, 23 survivors and 5 non-survivors; lymphocyte count for 27 patients, 12 ICU patients, 13 ward patients, 2 outpatients, 22 survivors and 5 non-survivors; creatinine level for 29 patients, 13 ICU patients, 14 ward patients, 2 outpatients, 24 survivors and 5 non-survivors; C-reactive protein level for 29 patients, 13 ICU patients, 14 ward patients, 2 outpatients, 24 survivors and 5 non-survivors; procalcitonin level for 11 patients, 7 ICU patients, 4 ward patients, no outpatient, 8 survivors, 3 non-survivors; ferritin level for 13 patients, 9 ICU patients, 4 ward patients, no outpatient, 10 survivors, 3 non-survivors; D-dimer level for 12 patients, 7 ICU patients, 5 ward patients, no outpatient, 10 survivors and 2 non-survivors; creatine kinase level for 14 patients, 9 ICU patients, 4 ward patients, 1 outpatient 10 survivors, and 4 non-survivors.

NA, not available

Table 3. Treatments and outcomes

	total n=35	ICU n=13	Hospital ward n=18	Outpatients n=4	Survivors n=30	Non-survivors n=5
Withdrawal of calcineurin inhibitor	1 (2.9)	0	1 (5.5)	0	1 (3.3)	0
Withdrawal of antimetabolite	13 (37.1)	7 (53.8)	6 (33.3)	0	11 (36.7)	2 (40)
Tapering of oral corticosteroids	0	0	0	0		0
Withdrawal of mTOR inhibitor	3 (8.6)	1 (7.7)	2 (11.1)	0	2 (6.7)	1 (20)
Anti-inflammatory management						
Continuation or initiation of azithromycin	17 (48.6)	4 (30.7)	10 (55.6)	3 (75)	16 (53.3)	1 (20)
High-dose corticosteroid	12 (31.4)	7 (53.8)	4 (22.2)	0	8 (26.7)	3 (75)
Dose (prednisone equivalent, mg)	100 [50-125]	120 [90-125]	50 [35.0-76.3]		70.0 [35.0-106.3]	125 [122.5-125]
Anti-interleukin 6 treatment, n (%)						0
Tocilizumab	1 (2.9)	1 (7.7)	0	0	1 (3.3)	
Sarilumab	1 (2.9)	1 (7.7)	0	0	1 (3.3)	
Anti-interleukin 1 treatment – anakinra n (%)	2 (5.7)	2 (15.4)	0		1 (3.3)	1 (20)
Specific infection management						
Lopinavir-ritonavir	2 (5.7)	2 (15.4)	0	0	2 (6.7)	0
Hydroxychloroquine	9 (25.7)	3 (23.1)	5 (27.8)	1 (25)	8 (26.7)	1 (20)
Remdesivir	2 (5.7)	2 (15.4)	0	0	2 (6.7)	0
Organ failure management						
Low-flow oxygen, n (%)	22 (69.9)	9 (69.2)	13 (72.2)	0	18 (60)	4 (75)
High-flow nasal cannula, n (%)	5 (14.3)	5 (38.5)	0	0	3 (10)	2 (40)
Non-invasive mechanical ventilation, n (%)	0	0	0	0	0	0
Invasive mechanical ventilation, n (%)	7 (20)	7 (53.8)	-	-	4	3 (60)
Length, days	10.5 [9.0-13.5]	10.5 [9.0-13.5]			9 [9.0-22.0]	12 [8.5-13.0]
Incl. prone positioning	4 (11.4)	4 (30.8)			1 (3.3)	3 (60)
ECMO, n (%)	1 (2.9)	1 (7.7)	-	-	1 (3.3)	0
Length, days	6	6			6	
Renal replacement therapy	5 (14.3)	4 (33.3)	1 (5.5)		3 (10)	2 (40)
Length, days	3 [2.5-21]	6.5 [2.3-26.5]	3		10 [3.0-32.0]	2.5 [2.0-3.0]
Catecholamine infusion	4 (11.4)	4 (30.8)			1 (3.3)	3 (60)
Length, days	8.5 [5.3-11.8]	8.5 [5.3-11.8]			3	11.0 [8.5-12.5]
Bacterial superinfection, n (%)	11 (31.4)	5 (41.7)	6 (33.3)	0	9 (30)	2 (40)
Pneumonia	11 (31.4)	5 (41.7)	6 (33.3)	0	9	2 (40)
Bacteremia	2 (5.7)	2 (15.4)	0			
Fungal superinfection, n (%)	1 (2.9)	0	1 (5.6)	0		0
Complications						
Calcineurin inhibitor overdose, n (%)	9 (25.7)	7 (53.8)	2 (11.1)	0	7 (23.3)	2 (40)
ARDS, n (%)	9 (25.7)	9 (69.2)	-	-	5 (16.7)	4
Worst PaO ₂ /FiO ₂	68.0 [50.0-142]	68.0 [50.0-142]			142.0 [50.0-148.0]	62.0 [51.5-92.0]
Pulmonary embolism, n (%)	3 (8.6)	3 (23.1)	0	0	2 (6.7)	1 (20)
Time from onset of illness to pulmonary embolism						
Other embolic manifestation*	1 (2.9)	0	0	1 (25)	1 (3.3)	0
Renal failure, n (%)	4 (11.4)	2 (15.4)	2 (11.1)	0	4 (13.3)	
Outcomes						

Death, n (%)	5 (14.3)	4 (30.8)	1 (5.6)	0	-	-
Length of ICU stay, days	11.5 [5.5-20.3]	11.5 [5.5-20.3]	-	-	12.5 [5.5-37.8]	9.0 [4.5-12.8]
Length of follow-up, days	50 [41.0-56.5]	49.0 [24.0-57]	49.5 [42.3-55.8]	54 [46.5-55.0]	52.5 [46.5-57.0]	-

Data are median [interquartile range] unless otherwise indicated.

Bacterial pulmonary superinfection were due to: *Pseudomonas aeruginosa* (n=6), *Streptococcus pneumoniae* (n=1), Methicillin-susceptible *Staphylococcus aureus* (n=2), *Haemophilus influenzae* (n=1), *Enterobacter sp* (n=1), *Corynebacterium sp.* (n=1), *Stenotrophomonas maltophilia* (n=1); Bacteremia was caused by *Enterococcus sp* (n=1), and *Pseudomonas aeruginosa* (n=1); Fungal superinfection was due to *Aspergillus fumigatus*; worst PaO₂/FiO₂ was obtained for 7 patients who underwent invasive mechanical ventilation, 4 survivors, and 3 non-survivors.

*one patient had arterial embolic manifestation with lower-limb ischemia.

ICU: intensive care unit; ARDS: acute respiratory distress syndrome; ECMO: Extracorporeal membrane oxygenation; mTOR, mammalian target of rapamycin

Figure legends

Figure 1. Flowchart of the cohort. Among the 35 lung transplant recipients with COVID-19, four were cared for as outpatients. Twenty-five were treated in the respiratory ward, including seven who were secondarily admitted in the intensive care unit; six were initially treated in the intensive care unit, including one who acquired COVID-19 in the ICU. In total, 30 were alive after a median follow up of 50 [41.0-56.5] days.

Figure 2. Forest plot of death outcome. Plots represent point estimate of odds ratio for each risk factor and lines their 95% confidence interval.

Figure 3. Forest plot of intensive care unit (ICU) admission outcome. Plots represent point estimate of odds ratio for each risk factor and lines their 95% confidence interval