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# COVID-19 in pediatric lung transplant recipients: Clinical course and outcome

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**KEYWORDS:**
COVID-19;
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**BACKGROUND:** COVID-19 causes high morbidity and mortality in adult lung transplant (LTX) recipients. Data on COVID-19 in children after LTX is limited. We report the clinical presentation and outcome of SARS-CoV-2 infection in 19 pediatric LTX recipients.

**METHODS:** Between March 2020 and June 2022, SARS-CoV-2 testing was performed on all pediatric LTX patients with COVID-19 symptoms or contact with a SARS-CoV-2 infected person. Positive patients were prospectively evaluated for symptoms, treatment and outcome. Vaccination status and immune response were recorded.

**RESULTS:** Nineteen out of 51 pediatric LTX recipients had a SARS-CoV-2 infection. Mean age was 12.3 years (IQR 9-17), 68% were female, 84% had preexisting comorbidities. Mean time between LTX and SARS-CoV-2 infection was 4.8 years (IQR 2-6). No patients experienced severe COVID-19: 11% were asymptomatic, and 89% had mild symptoms, primarily rhinitis (74%), fever (47%), and cough (37%). One SARS-CoV-2 positive patient was hospitalized due to combined fungal and bacterial infection. Mean duration of symptoms was 10.5 days (IQR 3-16), whereas mean period of positivity by antigen test was 21 days (IQR 9-27, $p = 0.013$). Preventive antiviral therapy was initiated in 3 patients. After a mean follow-up of 2.5 months (IQR 1.1-2.4), no patient reported persistent complaints related to COVID-19. Lung function tests remained stable.

**CONCLUSIONS:** Unlike adult LTX recipients, children and adolescents are at low risk for severe COVID-19, even with risk factors beyond immunosuppression. Our findings cast doubt on the necessity of excessive isolation for these patients and should reassure clinicians and caregivers of LTX patients.

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Since the discovery of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in December 2019 in Wuhan, China, the virus has caused a pandemic of Coronavirus Disease 19 (COVID-19). In contrast to its devastating

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effects on elderly populations and adults with preexisting conditions such as diabetes mellitus, obesity, and cardiovascular comorbidities,[1,2] data suggest that children overwhelmingly experience asymptomatic or mild disease.[3,4] However, children with various underlying illnesses, including chronic lung disease, are reportedly at higher risk of developing severe COVID-19.[5] Currently, little is known about the risks of SARS-CoV-2 infection in children with solid organ transplants. Some studies on children with liver or kidney transplants suggest that severe courses of infection are rare.[6-8] However, to the best of our knowledge, no study has yet examined the clinical course of SARS-CoV-2 infection in children after lung transplantation. This is especially interesting since adult solid organ recipients, especially lung transplant recipients who contract SARS-CoV-2 frequently experience severe disease, with intensive care admission in more than 50% of cases and a mortality rate as high as 10% to 49%.[9-14]

## Material and methods

### Study cohort

We conducted a single-center study from March 2020 to June 2022 at Hannover Medical School Children's Hospital in Germany, one of the largest LTX centers in Europe. All pediatric post-LTX patients in regular follow-up care ($n = 51$) were eligible for this study. All patients are routinely instructed to immediately report all symptoms of infection, deterioration of daily pulmonary function, reduction in general wellbeing or contact with a SARS-CoV-2 infected person to the pediatric LTX care team. All patients reporting any of these complaints were tested by rapid antigen test. If rapid antigen testing revealed a positive result, PCR testing was conducted to confirm the infection. Additionally, schoolchildren regularly performed rapid antigen tests up to 3 times per week and all patients were tested during their regularly scheduled visits in our outpatient clinic, which occur every 3 months.

During this period, the administration of SARS-CoV-2-specific drugs or modification of immunosuppressive therapy during COVID-19 was not yet standardized. These decisions were based on individual assessment by the medical team or consultant on call after a careful risk-benefit analysis.

### Data collection

Electronic charts were reviewed to collect data on demographics, date of transplantation, SARS-CoV-2 vaccination status, immunoglobulin levels, SARS-CoV-2 specific antibodies pre-and postvaccination, comorbidities, chronic lung allograft dysfunction (CLAD), immunosuppressive regimen, clinical signs and symptoms of SARS-CoV-2 infection, transient or persistent decline in lung function testing, COVID-19 treatments, clinical course and outcome. Time of follow-up was variable, depending on the timing of infection. Data from the last available visit prior to SARS-CoV-2 infection were used for baseline parameters. Depending on the individual clinical course, data were recorded during clinical presentation in our outpatient clinic, hospitalization if indicated or by regularly conducted telemedicine visits during the acute infection. Follow-up visits after infection occurred in the context of routine presentation to our outpatient clinic or by telephone visit.

SARS-CoV-2 infection was defined as a positive result on nasopharyngeal swab by rapid antigen test confirmed by polymerase chain reaction (PCR) in any medical laboratory available to outpatients. In 1 adolescent, repetitive antigen tests were positive and the family refused PCR testing. Period of positivity was determined as the time period between the first positive testing result (by rapid antigen test or PCR) to first negative testing result by rapid antigen test. One adolescent hospitalized due to a superinfection received serial PCR tests in the context of inpatient treatment, and did not undergo antigen testing. This patient was therefore excluded from the calculation of the period of positivity.

SARS-CoV-2 specific IgG antibodies were determined by CE marked ELISAs for nucleocapsid protein (NCP) and the Spike domain (Euroimmun, Lübeck Germany) pre- and postinfection in a single laboratory at our medical center. Positive antibody response was defined according to manufacturer instructions and to a calibrator provided with the assay (extinction ratio sample/calibrator $\geq 1.1$). All pediatric LTX patients in our center perform daily lung function testing using standardized portable pulmonary function test devices, starting at age 4. Three children under the age of 4 did not perform daily lung function testing. Reported results were used for lung function evaluation before, during and after SARS-CoV-2 infection. CLAD was defined according to the current recommendations of the International Society of Heart and Lung Transplantation.[15] Disease severity of SARS-CoV-2 infection was classified according to criteria of German Society for Pediatric Infections which are in line with the National Health Institution recommendations.[16,17]

### Statistical analysis

Statistical analysis was performed by Excel or GraphPad Prism V9 (San Diego, CA). Descriptive data were calculated as mean with interquartile range (IQR), categorical data as frequencies and percentages. Differences between groups were analyzed by *t*-test unless data were not normally distributed. Here, Mann-Whitney-U test was used. A $p$-value $<0.05$ was considered statistically significant.

### Ethical approval

Written informed consent was provided by all patients or their legal guardians regarding anonymized use of personal clinical data for research purposes. Study approval by the institutional ethical review board was waived given its retrospective observational design.

## Results

### Study group

During the study period, 19 out of 51 (37.3%) pediatric LTX recipients tested positive for SARS-CoV-2 infection and were included in our analysis (Figure 1). A total of 13 (68%) patients were female, mean age was 12.3 years (IQR 9.1-17.0) and 3 children were younger than 5 years of age. A total of 16 (84%) patients had at least 1 cardiovascular comorbidity and 6 (32%) were diagnosed with diabetes mellitus prior to infection. Most of COVID-19 in our cohort occurred in the later phases of the pandemic. No patient contracted the disease in 2020 and 2 of the 19 cases

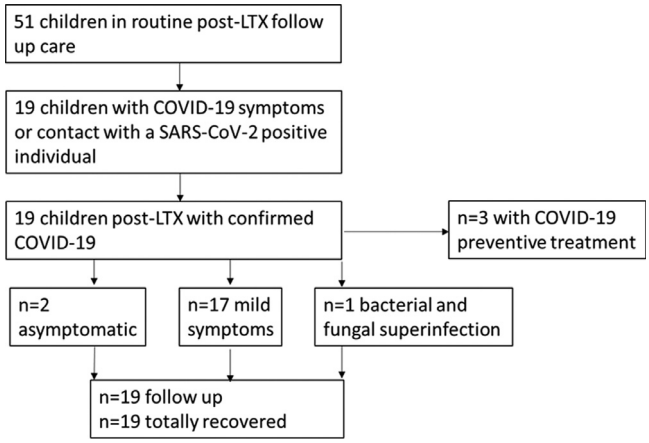


**Figure 1** Study group.
Abbreviations: LTX, lung transplantation.

occurred in 2021 (1 in February and 1 in December). The remaining 17 cases (89.5%) occurred in 2022. During the study period we did not observe any cases of patients with COVID-19 typical symptoms and suggestive radiological or blood signs who were tested negative for the virus.

Detailed characteristics of the study group including comorbidities and immunosuppressive regimens are given in Table 1.

**Table 1** Patients Characteristics at Time of SARS-CoV-2 Infection

| Demographic data | |
|---|---|
| Female | 13 (68) |
| Mean age at SARS-CoV2 infection, years (IQR) | 12.3 (9.1-17.0) |
| Mean time after LTX until SARS-CoV-2 infection, years. (IQR) | 4.8 (2.4-6.3) |
| **Diagnosis leading to LTX** | |
| PHT | 10 (52) |
| child | 3 (16) |
| CF | 6 (32) |
| Comorbidities | 16 (84) |
| CRI | 9 (47) |
| CLAD | 0 |
| AH | 14 (74) |
| DM | 6 (32) |
| **Immunosuppression before infection** | |
| Tac/MMF/Pred | 17 (89) |
| Tac/Eve/MMF/Pred | 1 (5) |
| Tac/Eve/Predni | 1 (5) |
| High-dose Steroids within 6 month | 1 (5) |
| Rituximab > 12 month before SARS-CoV2 infection | 9 (47) |
| Rituximab < 12 month prior SARS-CoV2 infection | 1 (5) |
| Hypogammaglobulinemia requiring Immunoglobuline substitution | 3 (16) |

Abbreviations Table 1
AH, arterial hypertension; CF, cystic fibrosis; chILD, children's interstitial lung disease; CLAD, chronic lung allograft dysfunction; class., classification; CRI, chronic renal insufficiency; Eve, everolimus; DM, diabetes mellitus; FU, follow up; IQR, interquartile range; LTX, lung transplantation; MMF, mycofenolat-mofetil; Pred, prednisolon; Tac, tacrolimus.

## Clinical course of SARS-CoV-2 infection

Data on symptoms, clinical course and treatment were available in all patients. Two children (11%) remained asymptomatic. All other patients experienced mild symptoms. Rhinitis (74%), fever (47%), cough (37%), and cephalgia (32%) were the most common complaints (Table 2A). Mean duration of symptoms was 10.5 days (IQR 3-16). Mean period of positivity by rapid antigen test was 21.0 days (IQR 9-27, $p = 0.013$).

Transient FEV1 decline during infection was noted in 4 patients (maximum decrease: -18%) with complete recovery at the latest 3 days after symptoms began. No patient reported dyspnea.

COVID19-specific antiviral treatment was given to 3 patients. One 3-year-old (Patient 14, Table 3) received Sotrovimab due to her age. The patient was too young to be vaccinated against SARS-CoV-2 at the time. An adolescent (Patient 16, Table 3) received Remdesivir on 3 consecutive days due to severe immunosuppression with recent high-dose steroid treatment and 6 rituximab courses (375 mg/m2) following relapse of post-transplant lymphoproliferative disease 4 months prior to SARS-CoV-2 infection. A 16-year-old girl (Patient 1, Table 3) with arterial hypertension, diabetes mellitus and terminal renal failure necessitating daily peritoneal dialysis 1.6 years after transplantation was treated with Sotrovimab directly after her positive test result, 1 day after onset of mild symptoms. The symptoms persisted for 3 days. Transient FEV1 decline of -18% was recorded during this period. After further 6 days without any complaints, she developed severe invasive aspergillosis and bacterial pneumonia. The patient remained hospitalized and under intensive antibiotic treatment for 56 days; the period of SARS-CoV-2 positivity was 43 days. Lung function returned to baseline 44 days after symptoms of invasive aspergillosis and bacterial superinfection began. The patient recovered fully and was asymptomatic with a normalized lung function at a follow-up visit 101 days after the first positive PCR test.

Except for patient 1, we did not prescribe mucolytics, anticoagulants, antibiotics or other antiviral treatment due to the satisfactory clinical conditions of our patients (Table S1). In cases of fever, some families gave paracetamol or metamizole to their children.

Mean time of follow up was 2.5 months (IQR 1.1-2.4). All patients were asymptomatic at the end of the observation period (Table 2B). We did not observe any graft related complications, new appearance of other organ dysfunctions, or post/long-COVID complications.

## SARS-CoV-2 specific antibody response

SARS-CoV-2 specific postvaccination antibodies were available for 13 of the 14 patients who received at least 1

**Table 2** COVID-19 Related Symptoms (A) and Patient Outcome (B)

(A)

| Symptoms | n (%) |
|---|---|
| Rhinitis | 14 (74) |
| Fever | 9 (47) |
| Cough | 7 (37) |
| Cephalgia | 6 (32) |
| GI symptoms | 4 (21) |
| Decrease FEV1 ≥ 10% from baseline | 4 (25) |
| Anosmia | 2 (11) |
| Fatique | 2 (11) |
| Myalgia | 1 (5) |
| Hypoxemia | 0 |
| Dyspnea | 0 |
| Tachypnea | 0 |

(B)

| | |
|---|---|
| Mean time of symptoms, days (IQR) | 10.5 (3-16) |
| Mean time of SARS-CoV-2 positivity, days (IQR) | 21.0 (9-27) |
| Mean time of FU after SARS-CoV2 infection, month (IQR) | 2.5 (1.1-2.4) |
| Hospitalization[a] | 3 |
| Graft related complications | 0 |
| Other organ dysfunction | 0 |
| Death | 0 |

Data on symptoms were available in all patients ($n = 19$). Daily lung function testing was performed in all patients over the age of 5 years ($n = 16$).

[a]$n = 2$ for Sotrovimab application; $n = 1$ for bacterial and fungal superinfection.Abbreviations: FU, follow up; IQR, inter quartile range.

dose of vaccine. However, of these 13, only 1 patient produced measurable amounts of anti-Spike-IgG in response to vaccination.

In 14 children (74%) who experienced SARS-CoV-2 infection, specific antibody response was determined after a mean time of 79 days (IQR 34-72) after the first day of COVID-19 symptoms. Six of previously vaccinated children developed a positive anti-Spike-IgG-antibody response after infection. None of these children developed detectable levels of anti-NCP-IgG-antibodies. Four of 5 unvaccinated children developed anti-Spike-IgG-antibodies. One child (Patient 14, Table 3) without SARS-CoV-2 vaccination and 1 adolescent (Patient 1, Table 3) with previous vaccination received Sotrovimab which may have resulted in detectable levels of anti-Spike-IgG in these children. Only 2 children (both previously unvaccinated) developed anti-NCP-IgG-antibodies (Table 3).

## Discussion

To the best of our knowledge, this is the first report on the clinical course and outcomes of pediatric lung transplant recipients with confirmed SARS-CoV-2 infection. In contrast to previous studies on adult lung transplant recipients, which show a high rate of hospitalization and death,[9-14] we did not observe any severe disease or deaths related to SARS-CoV-2 infection. Furthermore, no long-term effects or graft related complications occurred within the observation period, although preexisting comorbidities and immunosuppressive regimens in our cohort are comparable to previously described adult lung transplant populations.[4,5] This observation supports previous findings that age is 1 of the main risk factors for severe COVID-19.[1,2] There are

**Table 3** Vaccination Status and Antibody Detection

| Patient ID | Amount of SARS-CoV2 vaccinations | Anti-Spike IgG titer prior infection | Anti-NCP IgG detection post infection | Anti-Spike IgG detection post infection |
|---|---|---|---|---|
| **1**[a] | 4 | - | - | + |
| **2** | 3 | - | n.a. | n.a. |
| **3** | 2 | - | n.a. | n.a. |
| **4** | 0 | n.a. | + | + |
| **5** | 0 | n.a. | - | - |
| **6** | 3 | n.a. | - | + |
| **7** | 3 | + | - | + |
| **8** | 3 | - | n.a. | n.a. |
| **9** | 3 | - | - | - |
| **10** | 3 | - | - | - |
| **11** | 1 | - | - | + |
| **12** | 0 | n.a. | + | + |
| **13** | 0 | n.a. | - | + |
| **14**[a] | 0 | n.a. | - | + |
| **15** | 3 | - | - | + |
| **16** | 4 | - | - | + |
| **17** | 2 | - | n.a. | n.a. |
| **18** | 4 | - | - | - |
| **19** | 3 | - | n.a. | n.a. |

Abbreviations: n.a., not analyzed; -, negative antibody response; +, positive antibody response.

[a]Patient 1 and 14 received Sotrovimab, which may have resulted in detectable levels of anti-Spike IgG in these children.

several explanations for the less severe courses observed in our study cohort. First, the young age of our patients likely impacted their clinical outcome, reflecting overall less severe COVID-19 in children compared to adults.[3,4] This is in line with previous studies, showing that children with kidney or liver transplants had less severe disease compared to adults with solid organ transplants.[6,7] Second, no child with preexisting CLAD contracted a SARS-CoV-2 infection. CLAD patients are known to carry elevated risk of mortality (50%) from COVID-19 in adult lung transplant recipients.[9] Third, the majority of SARS-CoV-2 infections in our cohort occurred in 2022, when the Omicron variant (B.1.1.529) was prevalent in Germany.[18] Previous studies included mainly adults infected by the British (B.1.1.7) or Delta variant (B.1.617.2), which may cause more severe disease. Fourth, our cohort comprised a high rate of vaccinated children (74%). Of note, only 1 patient had a positive anti-spike-antibody titer after vaccination and before infection, which is in line with previous reports showing extremely low response rates following vaccination in lung transplant recipients due to their intensive immunosuppressive regimens compared to other solid organ recipients.[19] It is possible that SARS-CoV-2-specific T-cells may have played a role in protecting our cohort from severe disease. Unfortunately, this question cannot be definitively answered as data on SARS-CoV-2 specific T-cells in these patients are not available.

Although none of our patients had severe COVID-19, 1 patient developed invasive pulmonary aspergillosis in association with a confirmed SARS-CoV-2 infection. This complication has been previously described in the context of COVID-19.[20,21] It is important to consider invasive aspergillosis as a diagnosis in immunocompromised patients with COVID-19 and secondary clinical deterioration.

Our study has several limitations. First, it is a single center study with a small number of patients. However, lung transplantation in children is extremely rare and few centers routinely provide pediatric lung transplantation care. To our knowledge, this is the first report in this rare patient population. Secondly, we did not perform chest-X-ray imaging, computer tomography or blood tests during SARS-CoV-2 infection except in the patient with aspergillosis and bacterial superinfection, because all other patients did not experience severe disease courses and therefore further diagnostic work-up was not indicated.

In conclusion, our data demonstrate that in contrast to adult LTX recipients, children and adolescents are at considerably lower risk for severe COVID-19 even with preexisting risk factors beyond immunosuppression. Only 1 adolescent developed severe disease due to superinfection. This finding casts doubt on the value of preventive antiviral treatment in this population, in the context of significant side effects related to treatment. Further studies are needed to evaluate the benefit of COVID-19 specific treatment to prevent severe disease in this patient subset. Importantly, many families of pediatric LTX recipients have been hesitant to reengage in social interaction with peers, regular school attendance and other higher-risk activities due to their childrens' immunosuppressed state and failure to produce measurable antibody titers post-vaccination. Data suggest that social isolation, particularly absence from in-person schooling, may negatively impact psycho-social health, normal development and academic success.[22-27] The results of our study suggest that the risk of severe COVID-19 in children and adolescents post-LTX without CLAD is low, and this should be considered when creating recommendations for these patients and in conversations with parents and caregivers.

## Disclosure statement

The authors have no competing interests to declare. The authors would like to thank all the patients and families for their contribution. This manuscript contains no individual person's data in any form.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.healun.2022.11.006.

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