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ORIGINAL ARTICLE

COVID-19 infection in patients with history of pediatric heart transplant in Germany, Austria, and Switzerland

Sarah Ulrich[1] | Christian Balmer[2] | Kolja Becker[3] | Josefin Bruhs[4] | Friederike Danne[5] | Volker Debus[6] | Leonie Dewein[7] | Stefano Di-Bernardo[8] | Ulrike Doll[9] | Thilo Fleck[10] | Theodor Tirilomis[11] | Martin Glöckler[12] | Maria Grafmann[13] | Sabine Greil[14] | Urte Grosser[15] | Patrick Saur[16] | Susanne Skrzypek[17] | Michael Steinmetz[18] | On behalf of the Working group thoracic organ transplantation DGPK

[1]Department for Pediatric Cardiology and Intensive Care Medicine, Ludwig-Maximilians-University Munich, Munchen, Germany

[2]Department of Pediatric Cardiology, University Children's Hospital Zürich, Zurich, Switzerland

[3]Department of Congenital Heart Disease and Pediatric Cardiology, University Hospital Schleswig-Holstein, Kiel, Germany

[4]Center of Congenital Heart Disease/Pediatric Cardiology, HDZ-NRW, Ruhr-University, Bad Oeynhausen, Germany

[5]Department of Pediatric Cardiology, Deutsches Herzzentrum Berlin, Berlin, Germany

[6]Department of Pediatric Cardiology, University Hospital Münster, Münster, Germany

[7]Department of Pediatrics, University Hospital Ulm, Ulm, Germany

[8]Department of Pediatric Cardiology, University Hospital Lausanne, Lausanne, Switzerland

[9]Department of Pediatric Cardiology, University Hospital Erlangen, Erlangen, Germany

[10]Department of Congenital Heart Disease and Pediatric Cardiology, University Heart Center Freiburg – Bad Krozingen, Medical Center – University of Freiburg, Faculty of Medicine, University of Freiburg, Freiburg, Germany

[11]Department of Pediatric Cardiac Surgery, Georg-August-University-Goettingen, Gottingen, Germany

[12]Center for Congenital Heart Disease, University Hospital for Cardiology, Bern, Switzerland

[13]Department of Pediatric Cardiology, UKE Hamburg, Hamburg, Germany

[14]Department of Pediatric Cardiology, University Hospital Wien, Wien, Austria

[15]Department of Pediatric Cardiology, University Hospital Hannover, Hannover, Germany

[16]Department of Pediatric Cardiology, University Hospital Heidelberg, Heidelberg, Germany

[17]Department of Pediatric Cardiology, University Hospital Giessen, Giessen, Germany

[18]Department of Pediatric Cardiology and Intensive Care Medicine University Medical Center, Georg-August-University-Goettingen, Germany and German Center for Cardiovasvular Research (DZHK), Gottingen, Germany

Correspondence
Sarah Ulrich, Department of Pediatric Cardiology and Intensive Care Medicine, Ludwig-Maximilians-University Munich, Marchioninistr. 15, 81377 Munich, Germany.
Email: Sarah.Ulrich@med.uni-muenchen.de

Abstract

COVID-19 is a heterogenous infection—asymptomatic to fatal. While the course of pediatric COVID-19 infections is usually mild or even asymptomatic, individuals after adult heart transplantation are at high risk of a severe infection. We conducted a retrospective, multicenter survey of 16 pediatric heart transplant centers in Germany,

Austria and Switzerland to evaluate the risk of a severe COVID-19 infection after pediatric heart transplantation between 02/2020 and 06/2021. Twenty-six subjects (11 male) with a median age of 9.77 years at time of transplantation and a median of 4.65 years after transplantation suffered from COVID-19 infection. The median age at time of COVID-10 infection was 17.20 years. Fourteen subjects had an asymptomatic COVID-19 infection. The most frequent symptoms were myalgia/fatigue ($n = 6$), cough ($n = 5$), rhinitis ($n = 5$), and loss of taste ($n = 5$). Only one subject showed dyspnea. Eleven individuals needed therapy in an outpatient setting, four subjects were hospitalized. One person needed oxygen supply, none of the subjects needed non-invasive or invasive mechanical ventilation. No specific signs for graft dysfunction were found by non-invasive testing. In pediatric heart transplant subjects, COVID-19 infection was mostly asymptomatic or mild. There were no SARS-CoV-2 associated myocardial dysfunction in heart transplant individuals.

KEYWORDS
asymptomatic course, COVID-19 infection, pediatric heart transplantation, SARS-CoV-2 associated myocardial dysfunction

1 | INTRODUCTION

In the last two years we learned that the individual course of a COVID-19 patient can be anywhere between asymptomatic and critically ill.[1–3] In adult patients several comorbidities as cardiovascular diseases, arterial hypertension, diabetes, obesity, chronic obstructive pulmonary disease, malignancies and immunosuppression were identified as risk factors for critical infection with COVID-19.[3–6] The Meta-analysis of Li et al. showed that diabetes, malignancy, and immunosuppression were the strongest risk factors for a severe COVID-19 infection. Older age, male gender, arterial hypertension and diabetes were additional risk factors for higher mortality.[4]

To which extent patients after transplantation are at higher risk of a critical infection with COVID-19 is somewhat unclear. Both Yi et al. and Sharma et al. reported on mild courses of COVID-19 infection in adult patients after solid organ transplantation.[7,8] However, Kates et al. and Coll et al. revealed a mortality of 20.5% and 27%, respectively, of adult patients after solid organ transplantation.[9,10] A nationwide Italian study reported about a 30.6% mortality of COVID-19 patients after solid organ transplantation and therefore twice as much the mortality rate of non-transplanted patients after COVID-19 infection.[11] Adult patients after heart transplantation (HTx) showed a high mortality rate after COVID-19 infection, 16% among symptomatic patients and 24% among hospitalized patients.[12] A German study showed a mortality rate of 87.5% in adult heart transplant patients that had to be mechanically ventilated because of a severe COVID 19-infection.[13]

Compared to adult patients pediatric patients more often showed mild or even asymptomatic courses of COVID-19 infection.[14,15] According to Forrest et al. about 66% of the patients with COVID-19 infection <18 years were asymptomatic.[16] Risk factors of a severe COVID-19 infection in children are diabetes and cardiac and circulatory congenital anomalies as well as prematurity in children younger than 2 years of age.[17] Also, comorbidities as malignancies are possible risk factors.[18] If pediatric patients after heart transplantation are comparable with adult patients after heart transplantation or with healthy pediatric patients regarding the severity of a COVID-19 infection is uncertain. On the one hand, Bock et al. reported about mild COVID-19 infections in patients after pediatric heart transplantation with only 5% admission from home and no mortality.[19] On the other hand, a study of the pediatric heart transplant society showed a hospitalization rate of 21%. Nevertheless, mortality rate was very low in this cohort, too, with only one death in 206 patients.[20] Therefore the Working Group Thoracic Organ Transplantation Of The German Society Of Pediatric Cardiology initiated a multicenter study, to evaluate the course of COVID-19 infection after pediatric heart transplantation in Germany, Austria and Switzerland.

2 | METHODS

2.1 | Study design

Retrospective, multicenter survey including all pediatric heart transplant centers in Germany, Austria, and Switzerland to evaluate the clinical course of COVID-19 infection in pediatric heart transplant patients (age < 18 years at time of transplantation). Therefore, 15 centers with almost 600 patients in total after pediatric heart transplantation that are in regular follow up were included. The study followed the ethical standards of the Declaration of Helsinki and was approved by the institutional review board of the Ludwig Maximilians University of Munich.

2.2 | Inclusion criteria

All patients with a COVID-19 infection between 02/2020 and 06/2021 and history of pediatric heart transplantation (<18 years at time of transplantation) with regular follow up in one of the transplantation centers in Germany, Austria or Switzerland were included in the study. The diagnosis of COVID-19 infection was counted in the case of a positive PCR in nasopharyngeal swabs or SARS-CoV-2 antibody detection in the blood without history of vaccination.

2.3 | COVID-19 testing

In the pediatric heart transplant centers the regular testing of COVID-19 infection was different. Some centers performed antibody testing as well as PCR during each visit. Most of the centers performed PCR only with symptoms of COVID-19 infection. For inclusion to the study the positive testing of COVID-19 infection could also be performed by another hospital or out-patient office.

2.4 | Data acquisition

Demographic data of the patients and data regarding the COVID-19 infection as clinical symptoms, laboratory values, treatment and outcome data were collected from the medical records.

2.5 | Risk factors and definitions

The following frequent comorbidities of pediatric transplant patients were regarded as possible risk factors for a severe COVID-19 infection: arterial hypertension, hyperlipidemia, obesity, renal insufficiency, diabetes, malignancy, and pulmonary diseases.

Hyperlipidemia, arterial hypertension and diabetes mellitus were defined es preexisting diagnosis with or without medical treatment. Renal insufficiency was evaluated according to the KDIGO guidelines 2012.[21]

3 | RESULTS

3.1 | Patient characteristics

During the study period 26 patients (42% male) after pediatric heart transplantation were diagnosed with COVID-19 infection across all pediatric heart transplant centers in Germany, Austria and Switzerland (Table 1). The mean age at the time of COVID-19 infection was 16.71 ± 7.39 years. Seventeen patients (65%) were under the age of 18 years at the time of the COVID-19 infection. The mean age at the time of transplantation was 8.94 ± 5.29 years. The reasons for heart transplantation were dilated cardiomyopathy in 19 patients (73%), restrictive cardiomyopathy in three patients (12%) and congenital heart disease in four patients (15%). The immunosuppressive therapy consisted of a calcineurin inhibitor (tacrolimus $n = 20$; cyclosporine A $n = 5$) and mycophenolate mofetil ($n = 15$) or everolimus ($n = 9$) or azathioprine ($n = 1$). Only one patient received a calcineurin inhibitor free therapy with mycophenolate mofetil and everolimus. Only four patients (15%) were treated with steroids as a maintenance therapy. For more details of the immunosuppressive therapy see Table 2. Additional medications included anticoagulation in seven patients (27%), statins in 15 patients (58%) and antihypertensive medication in 18 patients (69%). The most common comorbidity was hypertension in 18 patients (69%). Only one patient showed a renal insufficiency (G3 according to KDIGO[21]) and none of the patients had a restricted cardiac function or a pulmonary disease (Table 1).

The COVID-19 infection occurred in average 7.63 ± 7.94 years after HTx. Two patients had a COVID-19 infection about half a year after HTx. One patient had a COVID-19 infection one month prior to transplantation, and a reinfection with a slightly positive PCR a few weeks after transplantation. Eleven patients suffered from a COVID-19 infection 1–5 years after HTx, seven patients were >5 years and ≤10 years after HTx and five patients were >10 years after HTx (Figure 1).

3.2 | COVID-19 infection—Symptoms

About half of the patients ($n = 14$) showed an asymptomatic COVID-19 infection. The remaining 12 subjects showed two to five different symptoms. The most common complaints in symptomatic patients with a COVID-19 infection were myalgia/fatigue in six patients (23%) and cough, rhinitis and loss of taste in five patients (19%) each. Fever, pain, and anosmia were document in four patients (15%) each. Only one patient (4%) showed dyspnea. Diarrhea was only documented in one patient (4%). None of the patient showed a reduced cardiac function. Only one patient showed a worsening of a tricuspid valve regurgitation. None of the patient presented with thrombotic event (Table 1).

3.3 | COVID-19 infection—Treatment

Of the 26 patients eleven did not need any treatment. Eleven patients were under out-patient therapy consisting of clinical check-ups and/or check-ups of a pediatric cardiologist as well as symptomatic therapy because of cold symptoms. Only one patient received low molecular weight heparin. Of these eleven patients five were asymptomatic. Four patients were hospitalized during COVID-19 infection, however two were completely asymptomatic. One of these patients was admitted on ICU, however not because of the COVID-19 infection. This patient suffered from a COVID-19 infection about one month before HTx. Shortly after HTx PCR-Testing was slightly positive again. The patient was still treated on the intensive care unit because of the short period after transplantation. However, he had no symptoms of COVID-19 infection after HTx even under rather high immunosuppression with cyclosporine A (target level 175–225 mg/L) and steroids (3 mg/kg/d). One of the hospitalized patients needed oxygen supply for three days. The other two hospitalized patients were treated in the hospital for

TABLE 1 Patient characteristics.

Variable	Value
Age at COVID-19 infection	17.20 (6.07) years
Age at HTx	9.77 (7.62) years
Indication for heart transplantation	Dilated cardiomyopathy ($n = 19$; 73%) Restrictive cardiomyopathy ($n = 3$; 12%) Congenital heart disease ($n = 4$; 15%)
Comedication	Anticoagulation ($n = 7$; 27%) Statin ($n = 15$; 58%) Antihypertensive medication ($n = 18$; 69%) (monotherapy $n = 12$; two medications $n = 3$; three medications $n = 3$)
Comorbidities	Hypertension ($n = 18$; 69%) Hyperlipidemia ($n = 3$; 12%) Renal insufficiency ($n = 1$; 4%) Diabetes ($n = 1$; 4%) Malignancy ($n = 2$; 8%) Pulmonary disease ($n = 0$) Obesity ($n = 5$; 19%)
Graft function	CAV according to ISHLT ($n = 2$; 8%)* History of rejection ($n = 13$; 50%) Restricted cardiac function ($n = 0$)
COVID-19 infection	Symptomatic ($n = 14$; 54%) Asymptomatic ($n = 12$; 46%)
Symptoms of COVID-19 infection	Cough ($n = 5$; 19%) Rhinitis ($n = 5$; 19%) Fever ($n = 4$; 15%) Dyspnea ($n = 1$; 4%) Myalgia/fatigue ($n = 6$; 23%) Diarrhea ($n = 1$; 4%) Pain ($n = 4$; 15%) Anosmia ($n = 4$; 15%) Loss of taste ($n = 5$; 19%)

Note: Data is shown as median (IQR)
Abbreviations: CAV, cardiac allograft vasculopathy; HTx, heart transplantation.
*Both patients showed CAV 1 according to ISHLT.

safety's sake, as they were diagnosed with a COVID-19 infection quite at the beginning of the pandemia.

None of the patients needed antibiotic or antifungal therapy. The immunosuppression was neither reduced, nor was the immunosuppressive regimen changed in any of the patients. None of the patients needed non-invasive or invasive mechanical ventilation. New-onset dialysis or extracorporeal life support was not necessary in any of the patients.

4 | DISCUSSION

COVID-19 was perceived as a potentially great threat for patients receiving immunosuppression after organ transplantation.[22] Especially children undergoing heart transplantation require lifelong high level immunosuppression.[23] Thus parents, patients and treating transplant physicians alike were cautious as to whether the current COVID-19 pandemic would affect children after HTx with severe course of COVID-19 infection or an increased death or rejection rate.

Our data collected in Germany, Austria and Switzerland presents a comprehensive overview of Covid infections during the first three waves of the COVID-19 pandemic. Due to differences in COVID-regulation in the three countries, COVID-19 incidence per 100.000 inhabitants was higher for each wave in Switzerland and Austria compared to Germany. The COVID-19 peak incidence per 100.000 inhabitants was as follows: in the first wave (March 2020): Germany 42.9, Switzerland 86.7, Austria 60.6; in the second wave (November/December 2020): Germany 211.7, Switzerland 663.9, Austria 580.0; in the third wave (April/May 2021): Germany 174.6, Switzerland 205.5, Austria 257.6. Covid variants during that time were mainly alpha and delta. (Johns-Hopkins-University, https://github.com/CSSEGISandData/COVID-19).

In relation to the treated heart transplanted children the percentage of COVID-19 positive pediatric HTx patients was higher in Switzerland (10%) and Austria (10%) compared to Germany (3%). According to the John-Hopkins-University the percentage of COVID-19 positive persons between 2020 and Juni 2021 was 4.4% in Germany, 7.2% in Austria and 8,1% in Switzerland.

TABLE 2 Outcome related to immunosuppressive therapy ($n = 26$).

Immunsuppression					
Cyclosporine A					
+ MMF[a]	3	3	–	2	–
+ steroids	1	–	1	1*	–
+ everolimus	1	1	–	–	1
Tacrolimus					
+ MMF	9	3	6	–	6
+ MMF + steroids	2	1	1	–	1
+ everolimus	6	2	4	–	2
+ everolimus + MMF	1	1	0	1	–
+ everolimus + steroids	1	–	1	–	–
+ azathioprine	1	1	–	–	–
Everolimus					
+ MMF	1	–	1	–	1

Note: Of the 26 patients 14 were asymptomatic and 12 symptomatic. Additionally four of the 26 patients were hospitalized and 11 were under out-patient therapy.

[a]Mycophenolate mofetil

*ICU stay prior to infection due to HTx.

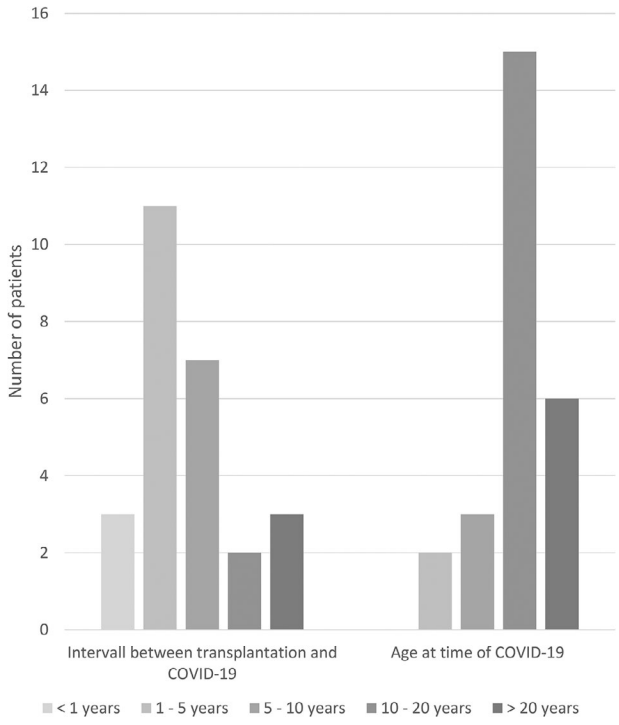

FIGURE 1 Distribution of COVID-19 infection regarding interval to transplantation and age at time of COVID-19 infection.

Patients after pediatric HTx that contracted COVID-19 were fortunately not affected by a severe or prolonged course of the disease. Almost 50% had incidental SARSCoV2 positive PCR testing or new SARS-CoV 2 antibody detection without any symptoms. Those with symptoms exhibited only mild symptoms of general viral infection, although nine patients were >18 years at time of the infection and 20 patients had at least one risk factor like arterial hypertension, obesity, renal insufficiency, diabetes or malignancy.[4,5]

The nine patients with COVID-19 infection with >18 years of age were between 19.20 and 38.01 years at time of the infection. The interval between HTx and COVID-19 infection ranged between 2.1 and 30.02 years. Only three patients were asymptomatic. One patient was hospitalized. Two patients had no risk factors, five patients had arterial hypertension, one patient had hyperlipidemia and one patient was diagnosed with obesity. Additionally, one patient suffered from renal insufficiency and one from malignancy. The very mild course of COVID-19 infection in these adult patients differs from the literature. After solid organ transplantation 78% patients were hospitalized and 20.5% of them died within 28 days after diagnosis. However, risk factors of a severe infection were age >65 years, congestive heart failure and chronic lung disease as well as obesity.[9] Only one of our patients was obese and no one suffered from one of the other risk factors. According to Hadi et al. the comorbidities influenced the mortality after heart transplantation the most, so that these missing risk factors could explain the mild course in our adult patients.[24]

Since we have learned by now from very close scrutiny of the clinical course and immunologic basis of COVID-19 that one part of the harm is done by the virus itself and a greater part is done by the immunologic response especially in older patients,[25–27] this last insight might help to explain the mild course in children after HTX.[26]

On one hand, children have been shown to have a rather mild course of COVID-19 in general.[28] Possibly, this is partly due to enhanced innate immune response.[29,30] The pediatric immune system is adjusted to deal with an abundance of viruses and is rather effective in clearing

those. One might speculate that, an early elimination of SARSCoV2 virus helps to limit the damage caused directly by viral action.

On the other hand, children receiving immunosuppressant medication may ameliorate the effect of an overshoot of the immune response triggered by SARS-CoV2. This immunoresponse comprised in elder patients of pneumonia, pleuritis, endothelitis, systemic and pulmonary embolism, peri-myocarditis, enteritis may be halted or decreased by the immune modulating agents that HTx patients have to take for the survival of their graft.

That systemic steroids are now part of the mainstay of Covid 19 treatment in children and adults[31] and that immunosuppressant and modulating therapy in the form of steroids and intravenous human immune globuline is included in the treatment of Pediatric Inflammatory Multiorgan Syndrom (PIMS)[29,32] backs this notion.

Last but not least, a rather protective behavior of parents and children after HTX with regard to school or leisure activities may be part of the effect as well. General distancing, hygiene and mask recommendations were observed very diligently by patients after organ transplantation. Thus, it could be argued, that exposition to high viral loads was prevented in general in HTx children by minimizing contacts at school, sports or with friends. Overall, families of children after HTx are usually rather aware of hygiene rules and recommendations and thus did not have to adjust too much to increased recommendations due to COVID-19.

Off note, the activation of the immune system by SARS CoV2 did not result in an increase in transplant rejections.

In the general population six mechanism are held responsible for the myocardial dysfunction after COVID-19 infection including hyperinflammation, respiratory failure, down regulation of ACE2 expression, hypercoagulability, diffuse endothelial injury and inflammation.[33] Higher age seems to be a risk factor for myocardial injury.[34] The missing myocardial dysfunction in our study cohort could be caused by the young age of the patients and the mild causes without signs of hyperinflammation or hypercoagulation.

4.1 | Limitations of the study

Because of the retrospective structure of the study and the inclusion of 16 pediatric heart transplant centers the standard to examine for COVID-19 infection differed. Additionally, only a few centers performed regular SARS-COV2 testing in asymptomatic patients, therefore the number of asymptomatic COVID-19 infections could be underestimated. Additionally, in the last 4 months of the study testing at home was possible, which could confound the data.

The study only includes COVID-19 infections until 6/21. Thereafter the number of COVID-19 infection increased due to the different COVID variants and the reduction in COVID-regulations.

5 | CONCLUSION

In summary, children after HTX had rather mild COVID-19 disease. No critical or severe course was observed even under high immune suppression right after HTX during the first three COVID-19 waves in Switzerland, Austria and Germany. SARSCoV2 infections of mainly alpha and delta variants did not result in increased morbidity in our cohort of patients after pediatric HTx.

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design and the data collection. Data analyses were performed by Sarah Ulrich. The first draft of the manuscript was written by Sarah Ulrich, Theodor Tirilomis and Michael Steinmetz. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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CONFLICTS OF INTEREST STATEMENT

The authors have no relevant financial or non-financial interests to disclose.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

ORCID

Sarah Ulrich https://orcid.org/0000-0001-6513-1739

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