Received: 27 July 2021 | Revised: 8 April 2022 | Accepted: 24 May 2022

DOI: 10.1111/petr.14335

ORIGINAL ARTICLE

WILEY

Incidence and outcome of SARS-CoV-2 infection in a pediatric kidney transplant recipient cohort from a single center in Northern Italy

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Abstract

Background: Concern about SARS-CoV-2 infection has increased over the possible effects on immunocompromised patients. Among them, recipients of solid organ transplantation deserve special attention. Data from the adult population suggest they may be at high risk for developing severe COVID-19, but little data are available for pediatric solid organ transplantation recipients.

Methods: From March 2020 to April 2021, KT recipients aged <21 years, routinely managed at our center, who underwent RT-PCR testing with nasopharyngeal swabs to detect SARS-CoV-2 infection, were studied. Tests were performed according to clinical and/or epidemiological criteria.

Results: One hundred one transplanted patients were managed at our center during the observation period. Among this population, 57 patients were tested for SARS-CoV-2 infection with a RT-PCR test and were subsequently enrolled. A total of 111 swabs were performed. Twelve out of the 57 patients tested (21.1%) had a positive RT-PCR test result. Among the positive patients, eight were symptomatic (66.7%). Median duration of symptoms and RT-PCR positivity was two days (IQR 1–2.25) and 17 days (IQR 11–27.25), respectively. No patients required specific treatment or IS therapy reduction; no one was admitted to hospital.

Conclusions: Our data show that pediatric renal transplant recipients are at low risk of clinically relevant COVID-19, as is the healthy age-related population. On the contrary, our results differed substantially from those seen in adult SOT recipient populations that have a high incidence and an even earlier and higher mortality rate.

KEYWORDS
adolescents, children, pediatric kidney transplant, pediatric transplantation, SARS-CoV-2 infection, solid organ transplant

Abbreviations: ACE2, angiotensin-converting enzyme 2; COVID-19, coronavirus disease 2019; CsA, cyclosporine; IQR, interquartile range; IS, immunosuppressive; KT, kidney transplant; PKT, pediatric kidney transplant; RT-PCR, real-time polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SOT, solid organ transplant; Tac, tacrolimus.

1 | INTRODUCTION

Since the first recorded case at the end of December 2019 in Wuhan, China, SARS-CoV-2 has spread rapidly and caused a global pandemic. Worldwide, Coronavirus disease 2019 (COVID-19) remains a great challenge for health systems due to its high hospitalization and mortality rates.

Italy is currently one of the most affected countries with more than 3 million cases and a case fatality rate of 3%.[1] In particular, our region, Lombardy, has become the Italian epicenter of the SARS-CoV-2 epidemic with more than 800 000 reported cases and 32 000 deaths.[2]

Patients with advanced age and medical comorbidities, including hypertension, cardiovascular and lung disease, diabetes mellitus, obesity, and malignancies, are known to be at increased risk of severe COVID-19.[3] Children and adolescents, instead, appear to be less vulnerable to the infection, to have milder symptoms and a less severe disease course compared with adults.[4,5]

As the outbreak grew to pandemic status, concern about the possible effects of the infection on immunocompromised patients rose. However, unlike common viral agents (such as adenovirus, rhinovirus, norovirus, influenza, and respiratory syncytial virus), SARS-CoV-2 does not seem to cause a more severe disease in immunosuppressed patients, compared with the general population. This may be explained through the potential protective effect of a weaker immune response against the pathogen, resulting in a milder disease course.[6]

Among immunosuppressed patients, SOT recipients deserve special attention. Indeed, data from the adult population suggest that they may be at high risk for the development of severe COVID-19. A multicenter study involving more than 100 adult KT recipients showed a case fatality rate of 32%[7] and a nationwide population-based study conducted in Italy showed a cumulative incidence of SARS-CoV-2 infection three times higher than that estimated for the Italian population and a case fatality rate of 29.1% in KT patients.[8]

However, to date, few data are available for pediatric SOT recipients.

To better understand the SARS-CoV-2 infection prevalence and clinical presentation in the PKT population, we report our data on COVID-19 in PKT recipients in a Northern Italy transplant Center. The aim of the study was to investigate the incidence of SARS-CoV-2 infection and the clinical course of the COVID-19 in PKT recipients.

2 | PATIENTS AND METHODS

2.1 | Study design

We performed a single-center retrospective, observational study involving all PKT recipients aged under 21 years routinely managed by our Pediatric Nephrology, Dialysis and Transplantation Unit. The observation period ranged between March 1, 2020, and April 30, 2021.

2.2 | Patients

We included all patients who underwent at least one RT-PCR test with nasopharyngeal swab to detect SARS-CoV-2 infection. Tests were performed according to the criteria listed below:

1. symptoms suggestive of SARS-CoV-2 infection (fever, cough, sore throat, dyspnea, myalgia, diarrhea, vomiting, anosmia or dysgeusia);
2. contact tracing;
3. screening at hospitalization for any other indication (e.g., diagnostic procedure);
4. positive serological Rapid Test.

During the entire observation period, PKT patients underwent at least one clinical evaluation every 60 days and were contacted monthly by email or telephone in order to investigate the presence of symptoms likely related to COVID-19 or SARS-CoV-2-positive contacts. According to national COVID-19 protocols for immunosuppressed patients, in the case of swab positivity, the test was repeated after 10 days. In patients with persistent RT-PCR swab positivity, the test was performed weekly until negative. All the symptomatic patients who were tested, but were SARS-CoV-2 negative, were thoroughly evaluated for viral and bacterial infection, in order to determine an alternative diagnosis.

2.3 | Methods and laboratory tests

Nasopharyngeal swab RT-PCR tests were processed at our hospital or at an accredited national laboratory facility.

Epidemiological, demographic, clinical, and outcome data were extracted from electronic medical records using a specifically designed data collection form.

The local Institutional Review Board approved the study. Written informed consent was obtained from a parent or guardian or the participants themselves.

2.4 | Analysis

Data for continuous variables are presented as median and inter quartile range (IQR). Categorical data are presented as count and percentage. Statistical significance was analyzed by Mann–Whitney test for continuous variables. A p value $<.05$ was considered statistically significant. Analyses were performed using Stat-View software 5.0.1 (SAS Institute Inc.).

3 | RESULTS

A total of 101 patients (66 males), aged 2.2–20.9 years (15.7 years IQR 12.5–18.7), were managed at our center during the observation

period of the study. From March 1, 2020, to April 30, 2021, 57 (35 males) patients underwent at least one nasopharyngeal RT-PCR test to detect SARS-CoV-2 infection according to epidemiological or clinical criteria and were thus enrolled in the study (Figure 1). All patients who were tested by RT-PCR consent to participate in the study.

Demographics and clinical characteristics of the cohort are detailed in Table 1. Comorbidities, known as risk factors for severe COVID19, were present in 43 patients (75.4%). All patients were on maintenance IS therapy, including corticosteroids, calcineurin inhibitors (cyclosporine or tacrolimus), and anti-proliferative agents (mycophenolate or azathioprine). One patient had also been treated with plasma exchange for a recurrence of focal and segmental glomerulosclerosis during the observational period. Median time from KT was 16.8 months (IQR 0–45.6); 19 patients were enrolled at KT.

A total of 111 swab tests were performed; the repeat tests performed (as per protocol) due to positivity were not taken into account in the total swab count. The indications that prompted testing were presence of symptoms suggestive of SARS-CoV-2 infection for 39 swabs (35.1%), contact tracing for 28 (25.2%), screening at hospitalization for 41 (37.0%), and positive serological Rapid Test for three (2.7%). Overall, 12 (10.8%) tests were positive. The indications are summarized in Figure 1.

Twelve out of the 28 tests performed due to contact tracing (43%) were indicated because of exposure to a SARS-CoV-2-positive household member and 16 (57%) because of exposure in a school or other setting. The former resulted positive in eight out of the 12 (66.7%) cases and the latter in one out of 16 (6.3%).

Out of the 57 patients who underwent RT-PCR testing 12 (six males) were positive (21.1%); but if we consider the entire PKT population, the percentage of positivity decreases to 11.9%. Among the positive patients, median age at evaluation was 15.0 years (IQR 10.7–18.6). Pre-existing comorbidities were present in seven patients (58.3%). We did not observe any temporal clusters of infection.

Looking at the overall tested population, patients with a positive result had clinical and demographic characteristics similar to those with negative results. In particular, median age of the patients who tested negative was 15.0 years (IQR 10.8–18.1) and 64.4% were male. Interestingly, there were no differences between the median time from KT in the two groups of patients (22.8 months vs. 16.8 months; p:0.7). Among the patients who tested positive, four remained asymptomatic and eight developed mild symptoms, as follows: fever in seven patients; upper respiratory tract symptoms in two patients; diarrhea in one patient; headache in one patient; and osteo-muscular pain in three patients. No patients had anosmia, dysgeusia, or kidney dysfunction. Median duration of symptoms and RT-PCR positivity was two days (IQR 1–2.25) and 17 days (IQR 11–27.25), respectively.

All patients were managed as outpatients and treated with antipyretics (acetaminophen) when appropriate. None required specific COVID-19 treatment (e.g., antiviral or monoclonal antibodies). Immunosuppressors were neither withdrawn nor reduced. No

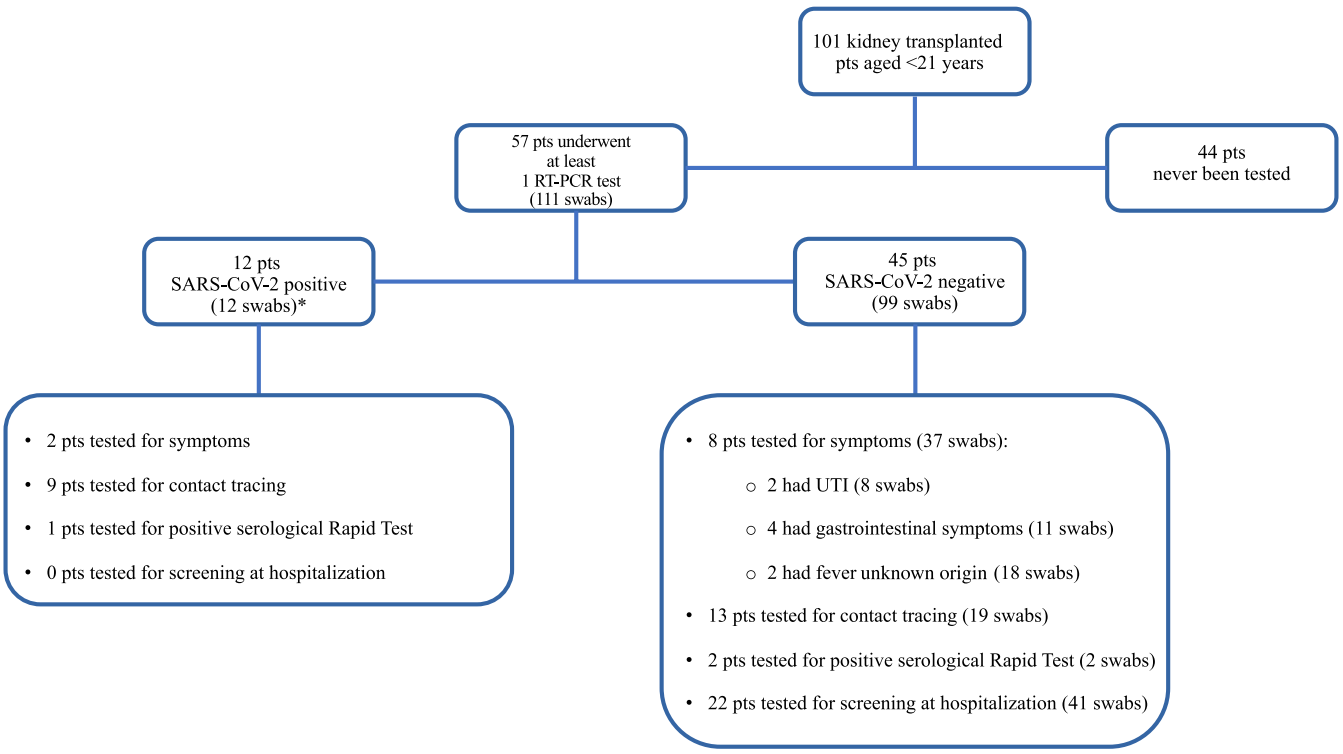

FIGURE 1 Flow diagram for patient enrollment. *Positive tests repeated per protocol were not taken into account in the total swab count

TABLE 1 Demographics and clinical characteristics of the patients

Patients characteristics	*N* = 57
Age, *years* (median, IQR)	15.0 (10.8–18.1)
Gender, *n male* (%)	35 (61.4)
Race, *n* (%)	
Caucasian	49 (86.0)
Asian	3 (5.2)
Hispanic	3 (5.2)
Black	2 (3.6)
Underlying etiology of ESKD, *n* (%)	
CAKUT	24 (42.1)
Glomerular disease	16 (28.1)
Cystic kidney disease	9 (15.8)
Tubulointerstitial kidney disease	4 (7.0)
HUS	4 (7.0)
Time from KT, *months* (median, IQR)	16.8 (0–45.6)
BMI categorization *n* (%)	
Normal weight (BMI 18.5–24.9 Kg/m^2)	49 (86.0)
Overweight (BMI 25–29.9 Kg/m^2)	8 (14.0)
Obese (≥30 Kg/m^2)	0 (0)
Comorbidities *n* (%)	
Overweight/obesity	8 (14)
Arterial hypertension	34 (59.6)
Diabetes mellitus	3 (5.3)
Prematurity (< 34 weeks of gestational age)	2 (3.5)
Congenital heart disease	2 (3.5)
Other SOT	2 (3.5)
Other (Prune Belly Syndrome, congenital diaphragmatic hernia)	2 (3.5)
IS therapy:	
Tac + MMF/AZA + Pdn *n* (%)	52 (91.2)
Tac + Pdn *n* (%)	1 (1.8)
CsA + MMF/AZA + Pdn *n* (%)	2 (3.5)
CsA/Tac + MMF *n* (%)	2 (3.5)

Abbreviations: AZA, azathioprine; CsA, cycosplorine; MMF, mycophenolate mofetil; Pdn, prednisone; Tac, tacrolimus.

patients experienced reinfection. The clinical data of the patients during SARS-CoV-2 infection are summarized in Table 2.

4 | DISCUSSION

It is well known that the incidence of SARS-CoV-2 infection in the pediatric population is low, and that it generally has benign clinical outcome. The possible reasons for this being that children have fewer comorbidities, do not smoke, have a lower ACE2 expression, and present a different inflammatory response, with higher numbers of B and T regulatory cells involved in immune tolerance, leading to a "less inflammatory" immune response. In addition, according to cross-protection to other coronaviruses in children, in vitro memory T cells that are specific to other pathogens, probably can play an important role in protective immunity arising from heterologous infectious agents.[9] Interestingly, Yuan et al. have recently published data from a retrospective study performed at two COVID-19 designated hospitals in China, showing that, in pediatric patients, the immune response was not excessive, with no "cytokine storm". In contrast, in adult patients, an altered immune response was observed, characterized by evidently abnormal T-cell inhibition and excessive cytokine production.[10]

Immunocompromised patients, including SOT recipients, are, in general, at higher risk of severe viral and bacterial infections, since IS medication has effects on humoral and cell-mediated immunity, and neutrophil function. To date, the COVID-19 clinical course in this population remains unclear and seems to be different in the adult compared with the pediatric population. The latter, in fact, seems to have low risk of SARS-CoV-2 infection and a favorable evolution in the case of disease, similarly to immunocompetent children and adolescents. A study involving approximately 200 pediatric liver transplant recipients showed that none had developed clinical pulmonary disease, despite three having tested positive for SARS-CoV-2.[11] Similarly, data from a multicenter study in the United States recently published by Varnell et al. showed that among the 281 patients tested for SARS-CoV2 by PCR in a population of more than 2700 pediatric KT recipients, 8.5% tested positive, and 63% of whom were symptomatic. No episodes of respiratory failure, graft loss, or death associated with COVID-19 were recorded.[12] Singer et al. reported on five patients out of a cohort of 22 who were positive at SARS-CoV-2-Antibody or RT-PCR testing, but only two of the five were mildly symptomatic, suggesting that PKT patients may be at higher risk for SARS-CoV-2 infection, but their clinical course appears benign.[13] More recently, Alshami et al. published analogues data on a population of 72 KT children, positive results for SARS-CoV-2 IgG antibodies being found in 11.1% patients that were asymptomatic or with a history of mild symptoms.[14]

In our study, the annual incidence of SARS-CoV-2 infection varied between 19.5%, if we consider the tested patients only, and 11.0% in the overall KT pediatric population. The first figure is likely an overestimation of the real incidence in our population; this is because we only tested patients at risk of COVID-19 (symptomatic, contact tracing, etc.), therefore selecting a cohort at higher risk. On the contrary, the second value could conceal unreported cases that were not tested because they were asymptomatic. Both percentages are significantly higher than the annual incidence in the general Italian pediatric population, which is 3.6%.[15] Differences in data may be a consequence of the design of the study and the method of enrolment. Our study was observational, and according to the inclusion criteria, all the patients who were symptomatic or had been in contact with a SARS-CoV-2 positive subject were tested. Indeed, no patients who were potentially positive for these

TABLE 2 Clinical and demographic characteristics of COVID-19-positive patients and infection course

Patients	Gender	Age (*years*)	Pre-exiting comorbidity	Time from KT (*months*)	IS therapy	Tac/CsA level (ug/L)[a]	Indication for RT-PCR test	Symptoms	Duration of symptoms (*days*)	Duration of RT-PCR positivity (*days*)	Number of swabs performed	ΔsCr (*mg/dl*)
1	F	19.2	None	50.4	Tac + MMF + Pdn	4.5	Contact tracing	Fever, osteo-muscular pain, diarrhea	2	10	2	+0.11
2	M	20.9	AI; DM	Enrolled at KT	Tac + MMF + Pdn	7.6	Contact tracing	Fever, osteo-muscular pain	2	14	3	+0.56
3	M	12.9	OS	79.2	CsA + MMF + Pdn	520	Symptoms	Diarrhea, headache, rhinitis	5	30	5	−0.2
4	F	10.8	AI; DM	0.3	Tac + MMF + Pdn	8.8	Contact tracing	None	–	11	2	−0.27
5	F	14.4	AI	Enrolled at KT	Tac + MMF + Pdn	13.3	Contact tracing	None	–	2	2	−0.54
6	M	5	None	6	Tac + MMF + Pdn	7	Contact tracing	Fever	1	31	4	+0.01
7	M	9.8	None	16.8	Tac + MMF + Pdn	5	Contact tracing	None	–	11	2	+0.07
8	M	14.7	AI	4.8	Tac + MMF + Pdn	7.6	Contact tracing	Fever	1	22	3	−0.09
9	F	13.5	None	0.3	Tac + MMF + Pdn	6.7	Positivity at serological Rapid Test	None	–	16	3	+0.17
10	F	12.1	AI	33.6	Tac + MMF + Pdn	7	Contact tracing	Fever	2	28	4	+0.05
11	F	17.2	None	56.4	Tac + Az + Pdn	5.7	Symptoms	Fever, cough, sore throat	2	27	4	+0.09
12	M	20.8	AI; O	117.6	Tac + MMF + Pdn	7	Contact tracing	Fever, osteo-muscular pain	3	18	3	+0.04

Abbreviations: AI, arterial hypertension; CHD, congenital heart disease; DM, diabetes mellitus; O, overweight/obesity; OS, other SOT; P, prematurity.

[a]Tac level is meant as trough level, CsA level is meant as 2-h post-dose level.

reasons were missed at diagnosis. In contrast, in the general population, testing was not universal, and presumably, many symptomatic individuals were not tested and not all their contacts were traced.

Differently from data obtained in the adult population by Trapani et al[8] and Cravedi et al.[7], in our cohort, SARS-CoV-2 infection was not associated with poor clinical or graft outcomes. Even in the patients from our pediatric cohort, who have comorbidities reported as independent risk factors for more severe COVID-19 (e.g., hypertension, obesity, and diabetes),[16] the course of the disease was mild. Thus, we might claim that pediatric age itself in SOT recipients is protective and associated with a benign course, independently from coexisting risk factors such as immunosuppression and comorbidities.

The first data available indicated that the viral load persisted for up to 8 days after the onset of symptoms in mild cases and peaked on day 11 in more severe cases.[17] However, the clearance of SARS-CoV-2 from nasopharyngeal samples remains unclear. Carmo et al. reported that it took most of the immunocompetent patients over 20 days to receive their first negative test.[18] In comparison with this finding, our results might suggest that immunosuppression does not prolong viral clearance since the median duration of RT-PCR positivity was 17 days in our population.

Time from KT, and thus IS therapy "load" (3 intravenous boluses of methylprednisolone with an average dose of 9 mg/kg and then in the first 3 months an average daily dose of 0.625 mg/kg of prednisone, calcineurin inhibitors at maximum level with tacrolimus trough 8–10 μg/L or cyclosporine 2-h post-dose level between 1000–1200 μg/L and anti-proliferative agents), does not seem to influence the risk of infection.

According to the existing COVID-19 pediatric literature, we found that a history of exposure to an individual with SARS-CoV-2 infection represents a major risk factor for developing the infection. Apparently, contact within the family seems to be a more common mode of transmission than contact at school.

Lastly, to date, there are no general recommendations for the management of IS therapy during COVID-19. In our study cohort, since the severity and the duration of the disease were mild and short, we did not modify the IS regimens. However, it is well known that IS can affect immune response, mainly to viral agents. Several studies in the KT population support the negative association between mycophenolate mofetil and seroconversion following different vaccinations.[19,20] Conversely, tacrolimus seems to have a protective role against the potential cytokine storm caused by COVID-19, through the reduced synthesis of IL-2 necessary for the activation of lymphocytes. Furthermore, in vitro studies have shown that tacrolimus and mycophenolate mofetil have a potential inhibitory effect on SARS-CoV-2 viral replication in vitro,[21,22] so the best management of IS therapy is still unclear.

The main limitation of our study is its monocentric design. However, our cohort size, considering the rarity of KT in the pediatric population, the long follow-up period (13 months), and the highly specific test method utilized make our findings consistent.

5 | CONCLUSION

Our data show pediatric immunosuppressed KT recipients are at low risk for clinically relevant COVID-19. The clinical course of the disease is typically mild, and kidney function is not negatively affected. There is no need for preemptive hospitalization in this category of patients, considered at risk of severe viral infections. Admission to hospital should be of course considered based on the clinical manifestations. Moreover, these results are in favor of keeping the PKT program active, as a life-saving procedure, despite the COVID-19 pandemic.

AUTHOR CONTRIBUTIONS

MC, MB, and ST wrote the manuscript and designed the topic. ST and GM designed the topic and revised the manuscript. AV and MV revised the manuscript. All authors read and approved the final manuscript and agree to be accountable for the content of the work.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

DATA AVAILABILITY STATEMENT

Data are available on request from the authors.

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How to cite this article: Cazzaniga M, Testa S, Brambilla M, Vergori A, Viganoni M, Montini G. Incidence and outcome of SARS-CoV-2 infection in a pediatric kidney transplant recipient cohort from a single center in Northern Italy. *Pediatric Transplantation*. 2022;00:e14335. doi: 10.1111/petr.14335