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A single-center report of COVID-19 disease course and management in liver transplanted pediatric patients

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Abstract

Background: In 2019, SARS-CoV-2 causing COVID-19 emerged. Severe COVID-19 symptoms may evolve by virtue of hyperactivation of the immune system. Equally, immunocompromised patients may be at increased risk to develop COVID-19. However, treatment guidelines for children following liver transplantation are elusive.

Methods: As a liver transplantation center, we diagnosed and followed up 10 children (male/female: 8/2) with a median age of 8.5 years (IQR: 5.2–11.0), with COVID-19 post-liver transplant between March 2019 and December 2020. COVID-19 diagnosis was based on PCR test and or florid X-ray findings compatible with COVID-19 in the absence of other cause. We retrospectively collected clinical and laboratory data from electronic patient records following written consent from patients/parents.

Results: Nine patients were diagnosed as definitive (PCR positive) with one patient being diagnosed as probable COVID-19. Seven patients recovered without any support whereas three were admitted for non-invasive oxygenation. Lymphopenia and/or high levels of serum IL-6 were detected in four patients. Six patients mounted anti-SARS-CoV-2 antibodies at median 30 days (IQR: 26.5–119.0) following COVID-19 diagnosis. Antibiotic therapy, favipiravir, anakinra, and IVIG were used as treatment in 4,1,1 and 2 patients, respectively. Furthermore, we kept the tacrolimus with or without everolimus but stopped MMF in 2 patients. Importantly, liver allograft function was retained in all patients.

Conclusions: We found that being immunocompromised did not affect disease severity nor survival. Stopping MMF yet continuing with tacrolimus was an apt treatment modality in these patients.

KEYWORDS
antibody, children, IL-6, immunosuppression, lymphopenia, SARS-CoV-2, solid organ, tacrolimus

Abbreviations: ALT, Alanine transaminase; AST, Aspartate transaminase; COVID-19, Severe respiratory syndrome; CRP, C-reactive protein; EBV, Epstein-Barr virus; GGT, Gamma-glutamyl transferase; IQR, Interquartile range; IST, Immunosuppressive treatment; IVIG, intravenous immunoglobulin; LDH, Lactate dehydrogenase; LT, Liver transplantation; MMF, Mycophenolate mofetil; mTOR, mammalian target of rapamycin; PCR, Polymerase chain reaction; PTLD, Post-transplant lymphoproliferative disease; SARS-CoV-2, The novel β-Coronavirus.

1 | INTRODUCTION

In 2019, SARS-CoV-2 causing COVID-19 emerged first in China and spread throughout the world in 2020, which the World Health Organization declared as a pandemic.[1,2] A plethora of studies have already shown that patients with severe COVID-19 symptoms suffer from an uncontrolled hyperactivation of the immune system.[1,3–5] Several studies reported deranged liver enzyme levels ranging from 14% to 74% COVID-19 patients.[6–8] Yet it is to be clarified whether immunosuppressed pediatric patients underwent LT fair well pertaining to their general status as well as the allograft liver. Hitherto, pediatric case reports of LT or kidney transplantation and COVID-19 are documented though current data are insufficient to guide appropriate treatment strategies.[1,9–11] Here, we report the demographics, clinical, and laboratory parameters of ten pediatric LT patients diagnosed with COVID-19, by PCR, who were followed at our pediatric gastroenterology and hepatology department between March 2019 and December 2020.

2 | METHODS AND SUBJECTS

We performed a retrospective review of the medical charts of 10 pediatric liver transplant recipients who were diagnosed with COVID-19. Demographic, clinical, laboratory, and outcome data of the patients were collected from medical records and charts following informed written consent from patients and or parents conform the stipulations made by the 1975 Helsinki Declaration and Koç university ethical approval (2019.255.IRB2.077).

2.1 | Immunosuppression

Standard IST protocol was used (tacrolimus) in all cases unless otherwise specified. Steroids were uniformly weaned off within 9 months post-transplant according to patients' status. If required, MMF or mTOR was added. Decisions to adjust tacrolimus dose and to introduce other immunosuppressive medications were made on a case-by-case basis, as determined by graft function, primary disease, and ongoing complications such as allergy, EBV viremia, and development of PTLD. Trimethoprim sulfamethoxazole and acyclovir/ganciclovir were administered to all patients as post-transplant prophylaxis.

2.2 | Diagnosis of COVID

Throat and nose swab sample were taken to perform a PCR assay in the clinical routine laboratory by using commercial kits (EZ1 Mini Kit for RNA extraction and QIAprep&amp Viral RNA kit for PCR, both from Qiagen) to screen for the COVID-19 virus.[12] SARS-CoV-2 spike protein-specific IgG antibody testing was done with commercially available SARS-Cov-2 IgG Quant Reagent Kit.[13] Patient with fever, respiratory symptoms with radiologic evidence typical for COVID-19 was accepted as possible COVID-19 infection in absence of other causative agents. Furthermore, we have classified COVID-19 patients according to the severity of the disease as asymptomatic, mild, moderate, and severe, based on the clinical characteristic, laboratory results, and chest radiography findings. Asymptomatic: cases with a positive PCR test without any clinical and radiological findings. Mild: cases with upper respiratory tract infection symptoms, such as fever, fatigue, myalgia, cough, sore throat, nasal flow with normal respiratory system examination. Moderate: cases with pneumonia with complaints of fever and cough but without the symptoms of dyspnea and hypoxemia or cases with findings of COVID-19 on chest computed tomography scan without any symptoms. Severe: Cases with fever and cough in the early period who develop dyspnea and central cyanosis within a week (arterial oxygen saturation of <92%). Critical: cases who develop acute respiratory distress or respiratory failure rapidly, and who tend to develop shock, encephalopathy, myocardial affection, coagulation dysfunction, and acute kidney injury.[14]

2.3 | Statistics

Demographic and clinical characteristics of the patients were summarized using frequency and percentage for categorical variables, and median (interquartile range) for continuous variables, in case of non-normality. All analyses were performed using SPSS 26 statistical software. Alpha was set as 0.05 for statistical significance.

3 | RESULTS

3.1 | Characteristics of the cohort

During the COVID-19 pandemic between March 2019 and December 2020, 10 patients (M/F: 8/2) had undergone COVID-19 PCR test to evaluate various symptoms such as fever, sore throat, headache, vomiting, diarrhea, abdominal pain, feeding refusal, fatigue, and contact with COVID-19 positive persons. 9 of these patients were found positive and one patient (case 6) who had multifocal pulmonary infiltrates consistent with COVID-19 but remained PCR negative was accepted as probable COVID-19. The median age of patients at the diagnosis and was 8.5 (IQR: 5.2–11.0). Median interval between transplantation and time of COVID-19 infection was 40 months (IQR: 16.5–111.5). All patients had undergone ABO compatible living donor LT. Tacrolimus was the predominant immunosuppressant, either alone (n = 7) or in combination with MMF (n = 2) or everolimus (n = 3). The symptomatic patient ratio was 70% being moderate or severe in 40% of the patients. Asymptomatic patients (n = 3) were tested for COVID-19 because of a high-risk contact. The patients' characteristics are summarized in (Tables 1 and 2).

TABLE 1 Characteristics of Patients with COVID-19

Parameters		
Age (years)		8.5 (5.2–11.0)
Gender (male/female)		8/2
post-transplant time to infection (months)		40 (16.5–111.5)
Time frame	**Pre–COVID-19 Median (IQR)**	**Post–COVID-19 Median (IQR)**
immunosuppressive treatment	TAC = 7/ TAC+EVE = 3	TAC = 7/ TAC+EVE = 3
White blood cell count/mm^3	6.5 (4.1–10.0)	5.0 (3.6–8.2)
hemoglobin (g/dl)	13.2 (11.3–28.0)	12.2 (10.7–16.9)
Platelets count/mm^3	172.0 (105.5–369.5)	152.5 (91.7–377.0)
Lymphocyte count/mm^3	3.0 (1.7–3.6)	2.3 (1.4–3.9)
AST (IU/L)	52.0 (43.0–70.0)	47.5 (30.7–62.7)
ALT (IU/L)	48.5 (32.5–63.7)	36.0 (24.7–63.2)
GGT (IU/L)	50.5 (20.5–89.7)	35.0 (17.5–77.5)
LDH (IU/L)	288.5 (241.0–316.5)	254.5 (201.3–400.3)

3.2 | Laboratory parameters

Regarding laboratory parameters, prior to COVID-19, the median lymphocyte count was $3 \times 10^3/mm^3$ (IQR: 1.7–3.6) but was $2.3 \times 10^3/mm^3$ (IQR: 1.4–3.9) following the infection whereas D dimer-max was 815.0 ng/ml (IQR: 475.0–2048.0) (Table 2). The median CRP-max levels were 35.5 (IQR: 2.2–72.7) during the infection. The chest X-ray showed abnormalities in 30% of patients (Table 2). Liver tests were normal in 7 patients at diagnosis whereas three (cases 2, 9, and 10) patients had elevated liver tests of whom two patients (cases 9 and 10) had already raised GGT prior to the infection due to biliary problem. Moreover, serum IL-6 was observed in 4 patients. Interestingly, the median values for total white blood cell count, number of platelets, and hemoglobin fell following infection whereas lymphocyte counts did not alter. Similarly, the median ALT, AST, GGT, and LDH levels appeared to be lower after COVID-19. However, no alteration was statistically significant (Tables 1 and 2).

3.3 | Treatment and outcome of COVID-19

Immunosuppressive regimens were adjusted in 2 of 10 children namely the cessation of MMF. The tacrolimus blood level was kept between 3 and 5 ng/dl. Three out of ten patients received steroids 1 mg/kg/day, favipiravir, and enoxaparin (patient 2, 3, 7). Respiratory insufficiency occurred in 2 patients (patient 2 and 7) and they required non-invasive respiratory support for 2 and 5 days, respectively. Patients 6 who developed severe pulmonary involvement received a single dose of anakinra with azithromycin, meropenem-teicoplanin combination. Patients 6 and 7 also received IVIG (Table 2).

After a median of 14 days (IQR: 14–15), a PCR negative result for COVID-19 was confirmed in 9 patients. COVID-19 PCR became negative at one month only in patient (case 1). Additionally, the presence of SARS-CoV-2-specific IgG antibody was investigated in 9 patients after a median of 30 (IQR: 26.5–119.0) days and positivity was found in six patients.

The median follow-up after the diagnosis of COVID-19 was 46 (IQR: 32.0–68.0) days. Importantly none of the patients developed graft loss nor liver graft dysfunction. All patients are alive and doing well.

4 | DISCUSSION

To the best of our knowledge, this is the first case series of 10 pediatric LT patients contracting SARS-CoV-2. In this report, we presented the characteristics and outcomes of liver transplanted children with COVID-19. The main features of this case series are favorable outcomes and majority of children did not require hospitalization and successfully followed up as outpatients with close tele-interview.

The current understanding is that children with native liver tend to experience a milder COVID-19 disease course, as opposed to adults, even when co-morbidities are present.[15,16] Albeit, immunosuppression is associated with increased risk of infections, morbidity, and mortality. The main culprits are opportunistic bacteria but also fungal infection early on the LT whereas CMV and EBV virus infection/reactivation occurs later in the post-transplant period.[9,17,18] For example, EBV was reported to be correlated with a more severe course of COVID-19. The authors noted that EBV-positive COVID-19 patients had a 3.64-fold higher risk of presenting with fever, higher CRP levels, than EBV-negative patients.[10] Moreover, a recent study demonstrated that immunocompromised children contracting the (non-SARS-CoV-2) common coronavirus, between the years 2012 and 2016, had an increased likelihood (odds ratio 2.5) of developing severe lower respiratory tract disease compared with non-immunocompromised ones.[19] To date, only seven pediatric LT patients, with confirmed COVID-19, are documented as case reports.[9,10,20–23] Out of the seven, one 3 years

TABLE 2 Characteristics of patients with COVID-19

Parameters	During- COVID-19 Median (IQR)
CRP-max	35.5 (2.2–72.7)
IL-6-max (pg/ml)	226.5 (209.8–918.3)
Fibrinogen-max (mg/dl)	312.0 (275.0–504.5)
D dimer-max (ng/ml)	815.0 (475.0–2048.0)
Ferritin-max (mg/dl)	54.2 (19.6–193.0)
Chest X-ray	Pneumonia = 3/10
Disease severity	Asymptomatic = 3/Mild = 3/ Moderate = 3 Severe = 1
Treatment for COVID-19	Azitromycine/Cefoxime, Favipiravir/Enoxaparin, IVIG/Anakinra/Azitromycin, Teicoplanin/Meropenem, IVIG/Teicoplanin/ Meropenem, Azitromycin
Hospitalization	Yes = 3/10
Duration of follow-up (day)	46 (32.0–68.0)
Outcome	All alive
SARS-CoV-2-specific IgG time (days)	3.5 (0.5–7.3) 30.0 (26.5–119.0)

old pediatric LT patient succumbed from multi-organ failure following diagnosis of COVID-19.[9] However, it is debatable as to whether this particular patient died of COVID-19 or rather passed away owing to over treatment of the infection and simultaneously cessation of all immunosuppressive drugs leading to graft failure. Indeed, the patient was treated with (i) a cocktail of antibiotics/antifungal (vancomycin, meropenem, azithromycin, voriconazole, and co-trimoxazole), (ii) antiviral drugs such as (oseltamivir, lopinavir, and hydroxychloroquine). Additionally, tacrolimus and prednisolone were stopped. By virtue, the patient developed acute kidney failure and liver failure with coagulopathy and heart failure and died. The remaining patients continued to receive immunosuppressive drugs at either same or reduced doses.

Given the lack of solid scientific evidence, the therapeutic approach against COVID-19 varied. In our cohort, the first step of treatment was to cease IST drugs other than tacrolimus and mTOR. Furthermore, we did not change the IST dosage if the tacrolimus level was below 6 ng/ml. None of the patients showed progressive worsening under this approach. Two patients were subjected to COVID-19-specific treatment. The one patient who we depicted as probable COVID-19 patient was treated with anakinra and demonstrated dramatical improvement after a single dose. The other patient (case 3) an adolescent with malnutrition and listed for second LT due to chronic rejection on triple IST regimen received favipiravir with clexane for 1 week.

The discrepancy of COVID-19 course/severity between pediatric and adult immunocompromised patients becomes more apparent. Studies from a single center demonstrated that 3 immunocompromised (following solid organ transplantation) adult patients contracting COVID-19 eventually all succumbed to their infection whereas their pediatric counterparts either had no or minor symptoms.[21] Furthermore, they found that both immunocompetent and immunocompromised pediatric patients were equally capable of mounting a SARS-CoV-2 virus-specific antibody response. Actually, the relationship between immunosuppression and COVID-19 outcomes is frequently referred to as a double-edged sword.[24] Too much immunosuppression could result in increased viral load and delayed recovery whereas a competent immune system could be responsible for the most severe forms of the disease. Interestingly, in a recent paper describing outcomes in COVID-19 patients with LT, baseline immunosuppression containing mycophenolate was an independent predictor of severe COVID-19 at doses higher than 1000 mg/day. This deleterious effect was not observed with tacrolimus or mTOR and complete immunosuppression withdrawal showed no benefit.[25] Even more, the use of calcineurin inhibitors such as tacrolimus (main IST in LT) has shown the intriguing capacity to inhibit the replication of human coronaviruses.[4,26–29] Mechanistically, this could be explained by the fact that coronaviruses use the calcineurin pathway for their replication. Another dimension to COVID-19 immunity is the presence of IL-6. It is a driving cytokine in COVID-19 pathogenesis and increased serum IL-6 levels are associated with mortality.[30] IL-6 was undetectable in the majority (n = 6) of our cohort which potentially could be linked with the inhibitory effect of tacrolimus on IL-6 production/secretion.[31] Overall, the antiviral and anti-inflammatory effects of tacrolimus used in all our patients may explain in part our cohort's mild symptoms and rapid recovery.

Regarding the severe COVID-19 in liver transplantation, data depend mostly on adult studies reporting similar mortality rates of 12%–18% with older age, male sex, lymphopenia, predictors of mortality. These reports suggested lower mortality in liver transplant recipients compared with kidney transplant recipients as well as healthy population.[32–35] These factors are less prevalent in the pediatric population. Furthermore, we did not observe any mortality. In our case series, only three out of 10 patients had a chest X-ray compatible with COVID-19 though no infection was noted during the post–COVID-19 period.[20] The patients also remained negative for EVB and CMV throughout.

In addition, we observed that in all eight patients (eight households) the parents or the siblings were the cause of infection as at least one family member was PCR positive for SARS-CoV-2. They recovered spontaneously. The parent and sibling of probable COVID-19 patient were negative for COVID-19 PCR.

Furthermore, five patients were diagnosed over 3 years after LT. Despite the interval from LT until SARS-CoV-2 infection was reported not to have an impact on the risk of developing severe COVID-19, the number of patients diagnosed with COVID-19 within the first year after LT was limited in previous reports. In our case series, five patients developed COVID-19 infection within first year of LT.

Some limitations of the present study should be highlighted. First, we adopted this research in a retrospective manner, limiting its implications as not all laboratory tests were performed in all

patients. Furthermore, as SARS-CoV-2 virus is continuously mutating resulting in more (and likely less) infectious and harmful variants, our conclusions may not be applied in other counties in the future. A real-time follow-up of SARS-CoV-2 virus mutation and its consequences is mandatory for customised policymaking.

In summary, based on the data available from individual cases and our case series we conclude that the most appropriate treatment manner in SARS-CoV-2 infected LT pediatric patients is to maintain the IS treatment regimen without MMF as it is highly associated with lymphopenia. The main source of infection was the parents/siblings demonstrating that LT patients/relatives require tight follow-up preferably by phone with the nurse transplant coordinator at each center to report any health issue but more importantly to raise awareness pertaining to the risks the first-degree relatives constitute for the patients. Importantly, transplanted children are able to develop antibodies against COVID-19. However, one ought to focus on antibody kinetics such as the presence, the amount and type of neutralizing antibodies to understand the long-term effects of COVID-19 infection in pediatric liver transplant recipients.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

CA, MY, and HA envisaged and designed the project. MY, HA, CA, and ET wrote the manuscript. MY, OM, ET, and CA analyzed the data. CA, HA, and ET recruited patients. ET and OM collected all data and all authors critically read the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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