Acute Liver Injury Among Pediatric Liver Transplantation Recipients With Coronavirus Disease 2019: An International Collaborative Study

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ABSTRACT

Coronavirus disease 2019 (COVID-19) is an ongoing pandemic. The occurrence of acute liver injury (ALI) has been reported in liver transplant (LT) recipients; however, the findings on children remain controversial. This is the first extensive, worldwide report on the impact of COVID-19 on pediatric LT recipients. Our online survey reported 110 pediatric LT recipients with severe acute respiratory syndrome coronavirus 2 infection. Of these, 37 were symptomatic and 20 out of them (54%) had complicated COVID-19, which included ALI and acute liver graft rejection. No mortality was reported. Pediatric LT recipients who had undergone transplantation less than 6 months before contracting COVID-19 had a greater number of hospital admissions and a higher ALI frequency ($P = 0.013$ and $P = 0.033$, respectively) than those who had undergone transplantation more than 6 months prior. Our study found that COVID-19 cases among pediatric LT recipients demonstrated a high complication rate. We propose that these patients must be followed up strictly.

Key Words: Coronavirus disease 2019, immunosuppression, pediatric liver transplantation, severe acute respiratory syndrome coronavirus 2, viral hepatitis

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What is Known

- Acute liver injury has been described in adult and children with coronavirus disease (COVID-19) patients.
- The impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in a large series of pediatric liver transplant recipients is yet to be determined.

What is New

- This survey found that pediatric liver transplant recipients who were diagnosed with COVID-19 had no mortality due to SARS-CoV-2 infection, in contrast to the high mortality described in adult liver transplant patient cohorts.
- Pediatric liver transplant recipients had a high rate of acute liver injury throughout the COVID-19 course.
- Children with liver transplants who presented with SARS-CoV-2 infection less than 6 months after receiving the transplant had worse COVID-19-related outcomes.

Coronavirus disease 2019 (COVID-19) is an ongoing pandemic, and its impact on the immunocompromised population is still unknown. Adults with solid organ transplants are thought to have higher morbidity and mortality due to COVID-19 than the general population (1,2); however, data are very limited in the pediatric population. The occurrence of acute liver injury (ALI) (3) and multisystem inflammatory disease in children (4) have been reported in COVID-19; however, its effect on pediatric liver transplant (LT) recipients remains undefined. Initial data determined that pediatric LT recipients would mainly be asymptomatic or have mild respiratory COVID-19 symptoms (5); however, a recent single-center cohort study of patients of all

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ages reported four pediatric COVID-19 patients who died while infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (2). To the best of our knowledge, to date, this is the most extensive cohort study that describes the impact of SARS-CoV-2 infection on pediatric LT recipients worldwide.

METHODS

Supported by the Latin-American Society of Pediatric Gastroenterology, Hepatology and Nutrition (LASPGHAN), we created an online survey to assess the impact of SARS-CoV-2 infection on pediatric LT recipients. The survey included 25 questions regarding center- and patient-specific information that was used to characterize each symptomatic COVID-19 patient. The questions focused on laboratory abnormalities (transaminase, bilirubin, and gamma-glutamyl transpeptidase levels; international normalized ratio [INR]; and acute liver graft rejection [GR]), multiple organ failure, and patient management (Supplemental data, Supplemental Digital Content, *http://links.lww.com/MPG/C398*).

We defined SARS-CoV-2 infection as any SARS-CoV-2 positive test through real-time polymerase chain reaction testing of a respiratory sample. The indications for testing asymptomatic patients for SARS-CoV-2 included exposure to infected patients and mandatory testing before travel, hospital admission, or procedures, among others. The English and Spanish versions of the questionnaire were distributed online using SurveyMonkey (SurveyMonkey, San Mateo, CA, USA) between June 26, 2020 and July 24, 2020. It was distributed by e-mail to 1409 pediatric gastroenterologists worldwide. Furthermore, it was uploaded to the LASPGHAN website. The survey was anonymous, and each physician provided informed consent to participate. This study was approved by our institutional scientific ethics committee.

According to the World Health Organization guidelines, we classified the reported COVID-19 respiratory symptoms as mild-moderate, severe, and critical (6). ALI was defined by elevated transaminases or cholestasis that was considered above the upper limit of normal according to each center's laboratory. Liver dysfunction was defined as an INR >2 or >1.5 with liver encephalopathy. To analyze the case severity, we defined ''uncomplicated COVID-19'' as mild/moderate respiratory illness and ''complicated COVID-19'' by the presence of at least one of the following characteristics: severe/critical respiratory illness, ALI, or multiorgan failure (with or without gastrointestinal [GI] symptoms).

Statistical Analysis

Continuous data were described using the mean and standard deviation, median, and interquartile ranges for variables without normal distributions. Normal distributions were evaluated using the Kolmogorov-Smirnov test. Nominal data were described as percentages. Categorical variables were tested using Fisher exact test. Statistical analysis was performed using SPSS software version 22.0 (SPSS Inc, Chicago, IL, USA). Statistical significance was set at $P < 0.05$.

RESULTS

A total of 263 responses (19% response rate) were collected from 134 different centers, including 52 pediatric LT programs, in 32 countries in North and Latin America, Europe, Asia, and Oceania. Of the 7019 pediatric LT recipients that were followed up, the responses included 110 reported cases of SARS-CoV-2 infection. There were 73 (66%) asymptomatic and 37 (34%) symptomatic COVID-19 patients, respectively. The geographical distributions are shown in Table 1.

Of the 37 symptomatic COVID-19 cases, 3 (8%) were ages <1 year old, 13 (35%) were between 1 and 9 years old, and 14 (38%) were between 10 and 19 years old. There was no clinical information provided for seven of the cases. A total of 26 of 37 patients (70%) reported respiratory symptoms: 21 and 5 (57% and 13%) had mild-moderate and severe symptoms, respectively. Seven patients (19%) reported GI symptoms.

Moreover, of the 37 symptomatic COVID-19 cases, 13 (35%) received outpatient care, 16 (43%) were admitted to the hospital, 10 (27%) were cared for in a basic hospital unit and 6 (16%) were admitted to an intensive care unit (ICU). Details of the treatment location were not available for eight patients (22%). We identified 10 uncomplicated COVID-19 cases (27%), of which eight and two (22% and 5%, respectively) had isolated mild-moderate respiratory symptoms and isolated GI symptoms. Contrastingly, 20 of 37 cases (54%) had complicated COVID-19, including 17 (46%), 2 (5.4%), and 2 (5.4%) cases of ALI, acute

TABLE 1. Geographical distribution of SARS CoV-2 infection cases

Continent	Country	Centers	Centers with LT programs	Patients followed up	Asymptomatic SARS CoV-2 infection cases	Symptomatic SARS CoV-2 infection cases	Total SARS CoV-2 infection cases
North America	Canada	9	1	1409	2	1	3
	United States	53	20	3796	51	24	75
Latin America	Brazil	3	3	181	3	2	5
	Argentina	3	1	307	2	1	3
	Chile	14	3	187	1	2	3
	Colombia	4	2	105	1	0	1
	Peru	1	1	35	3	0	3
	Panama	1	0	20	1	0	1
Europe	United Kingdom	3	2	261	7	2	9
	France	1	1	500	0	2	2
	Switzerland	1	0	7	0	1	1
Asia	India	2	2	50	0	1	1
	Indonesia	1	1	45	0	1	1
	Saudi Arabia	4	2	116	2	0	2
Total		**100**	**39**	**7019**	**73**	**37**	**110**

SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

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TABLE 2. The clinical course of pediatric liver transplant patients with symptomatic coronavirus disease 2019

Clinical characteristics	Cases N (%)
Symptomatic COVID-19 cases among PLT recipients	37 (100)
Complicated COVID-19 cases	20 (54)
Severe respiratory symptoms (dyspnea, oxygen requirement)	5 (13)
Acute liver injury (cholestasis and/or elevated transaminases)	17 (46)
Liver dysfunction (INR > 2.0 or INR > 1.5 plus liver encephalopathy)	2 (5.4)
Acute liver graft rejection	2 (5.4)
Admission to the hospital	16 (43)
Admission to the ICU	6 (16)

COVID-19 = coronavirus disease 2019; ICU = intensive care unit, INR = international normalized ratio; PLT = pediatric liver transplantation.

GR during COVID-19 course, and severe respiratory illness, respectively (Table 2).

Specific therapy for SARS-CoV-2 infection was indicated in two patients. Both patients had received their transplants within 6 months of contracting the SARS-CoV-2 infection and developed moderate respiratory symptoms that required ICU admission and oxygen therapy. For one patient, hydroxychloroquine was administered and mycophenolate mofetil (MMF) was discontinued. This patient developed allograft rejection that required further escalation of their immunosuppression. The second patient presented with cholestasis and elevated transaminase levels while infected with SARS-CoV-2. The patient was treated with dexamethasone and no changes to their immunosuppressive therapy were made. Both patients recovered well with no long-lasting graft damage.

Immunosuppressive protocols were available for 21.6% of the patients and were modified in five of the patients who were infected with SARS-CoV-2. Four had complicated COVID-19 with liver involvement. Of these four patients, three had their MMF discontinued and one had their dose of tacrolimus reduced. The remaining patient presented with mild COVID-19-related respiratory symptoms and their MMF course was discontinued. There was no information available regarding the clinical course of seven of the patients (19%).

Patients who were diagnosed with COVID-19 and who had received their LTs <6 months prior had a greater number of hospital admissions (6/6 vs 9/22, $P = 0.013$), more complicated disease courses (6/6 vs 12/22, $P = 0.49$), and higher prevalence of ALI (6/6 vs 11/22, $P = 0.033$) and acute GR (2/6 vs 0/22, $P = 0.40$) when compared to those who had received their LTs >6 months before infection.

DISCUSSION

This survey found that pediatric LT recipients who were diagnosed with COVID-19 had no mortality due to SARS-CoV-2 infection; however they had a high rate of ALI throughout the COVID-19 disease. The course of SARS-CoV-2 infection in pediatric LT recipients varies. A prior study that included 44 pediatric LT recipients reported that children with LT experienced a milder disease course (7). Contrastingly, a single-center cohort study reported 66 COVID-19 cases among LT recipients of all ages; four of whom were children and all of whom died (2). This study included 110 pediatric LT recipients who were infected with SARS-CoV-2. We reported a broad spectrum of clinical presentations from asymptomatic to complicated disease, including severe respiratory illness, ALI, and acute GR (one of the cases reported previously (8)). Fortunately, our case series had no mortality, in contrast to adult LT recipients, in whom a recent study reported a 14% mortality in the context of COVID-19 (9).

Our study found a higher rate of severe respiratory illness in pediatric LT recipients than in the general pediatric population (13.5% vs 2%, respectively). Moreover, we identified a higher ICU admission rate than that in a systematic review of 62 studies and 7480 patients (16.2% vs 2%) (10). COVID-19 related ALI has a variable frequency among the general population, with a frequency of 53% in adults and a lower frequency reported in children (5–22%) (11,12). Similar to the observations described by Cantor et al (4), our study had a high ALI rate (46%). We found a higher GR rate than the Spanish cohort, which had three liver GR cases among 111 adult LT recipients (5.4% vs 2.7%, respectively) (11).

Pediatric LT recipients who had undergone transplantation <6 months before contracting COVID-19 had significantly more hospital admissions, more complicated COVID-19 courses, and a higher ALI rate than those who had undergone transplantation >6 months prior. This results could be explained by increased angiotensin-converting enzyme 2 (ACE-2) expression due to liver regeneration in the early postoperative phase following liver transplantation (5); however, this theory is yet to be confirmed. The postulated mechanism of SARS-COV-2 entry into cells is through the host ACE-2 receptors (13). Chun-Yan et al (14) found that the protein expressions of ACE-2 were significantly elevated in the post transplanted livers at 48 hours in rats, compared with only trace expression in normal livers. An alternative to explain the worse outcome found, in pediatric LT recipients who had undergone transplantation <6 months before contracting COVID-19, is the level of immunosuppression in this particular group. In the first 6 months post-LT, most protocols include the use of potent immunosuppressive therapy that may result in an environment that is more prone to the hypoxia and inflammatory damage caused by SARS-CoV-2 infection (3).

This is the first large international collaborative study that reports more than one hundred SARS-CoV2 pediatric LT recipients cases. This study has limitations of a self-report survey and missing relevant data, including gender, ethnicity, primary indications for transplantation and comorbidities.

In conclusion, our study found that one-third of pediatric LT recipients infected with SARS-CoV-2 experienced symptomatic COVID-19. These patients exhibited a high rate of complications, ALI, and acute liver GR, and more frequent ICU admissions. Our study also described worse outcomes in pediatric LT recipients who were infected early after undergoing LT. Therefore, COVID-19 cases among pediatric LT recipients must be followed up strictly to anticipate possible clinical deterioration.

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