


BRIEF COMMUNICATION

Treatment adherence and behavior of pediatric liver transplant recipients during the COVID-19 pandemic

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Abstract

Background: The COVID-19 pandemic has affected medical care worldwide. Thus, we aimed to assess the impact of the COVID-19 pandemic on pediatric LT recipients.

Methods: A cross-sectional study based on a structured internet or telephone survey was conducted among pediatric LT recipients. Survey results were compared with results of a survey conducted among pediatric patients with IBD.

Results: Seventy-six pediatric LT patients participated in the study. Of them, 58 (76.3%) reported fear of severe COVID-19 infection due to LT or LT-associated medications. Half of the patients reported needing emotional support. Most patients (51, 67.1%) reported strictly following official guidance, while more stringent protective measures were taken by 64 (84.2%) patients. None of the patients discontinued their medications due to COVID-19. Compared to pediatric patients with IBD, a higher proportion of pediatric LT recipients reported fears of contracting severe COVID-19 infection due to their illness or medications (45, 59.2% vs. 110, 45.1%).

Conclusion: Among pediatric LT recipients a higher proportion reported fear of severe COVID-19 infection, implemented additional protective measures and expressed a need for emotional support, compared to patients with IBD. Medical teams should provide adequate information and offer a support system for this vulnerable population.

KEYWORDS

coronavirus disease, healthcare, liver transplantation, tele-health

1 | INTRODUCTION

The novel COVID-19 has spread rapidly, striking more than 150 million of people worldwide. The disease is caused by SARS-CoV-2, which outbreak was initiated in China in December 2019. The WHO announced the disease as a global pandemic 3 months later.¹

Starting March 2020, the Israeli authorities implemented wide-scale social distancing measures which included school shutdown, discontinuation of nonessential work and commerce, traffic limitations and travel restrictions. Escalation in traffic limitation was implemented by complete national curfew during national holidays.² Gradual restrictions easing, including reopening

Abbreviations: COVID-19, coronavirus disease 2019; IBD, inflammatory bowel diseases; IQR, interquartile ranges; LT, liver transplant; MMF, mycophenolate mofetil; MOH, Israeli Ministry of Health; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; WHO, World Health Organization.

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of nurseries and schools, was applied 2 months later, starting mid-May 2020.

Medical care provision changed during the COVID-19 pandemic, to include more telemedicine-based practice and less frequent outpatient visits, as guided by the Center for Disease Control and Prevention.³ These changes have affected all individuals with chronic diseases, including pediatric LT recipients. LT recipients are treated with chronic immunosuppressive therapy, turning them more vulnerable to infectious diseases. However, data are sparse regarding the effect of COVID-19 on these patients, including effects on daily life and routine. Moreover, data are conflicting as to whether LT recipients are at increased risk for severe COVID-19 infection.⁴⁻⁶ The management of solid organ transplant recipients, infected with COVID-19, was diverse given no guidelines at that time, especially in pediatrics, and was changing along with the pandemic. The majority of adult patients were hospitalized and with some reduction in their immunosuppressive treatment.⁷

In a consensus statement, the American Association for the Study of Liver Diseases advised that treating physicians should not make anticipatory adjustments to immunosuppressive therapy to LT recipients during the COVID-19 period.⁸ At the end of the lockdown in Israel, the national pediatric association published a statement permitting school and nursery attendance by the general population, including immunocompromised individuals, such as solid organ transplant recipients.

Despite the official recommendation of medical authorities to attend educational institutions, some LT recipients and their families considered avoiding nurseries and schools due to fear of infection and limited data regarding the possibility of more severe infection.

In our study, we assessed the impact of the COVID-19 pandemic on healthcare provision, fear of COVID-19 infection, adherence to medical treatment, and compliance with officially recommended protective measures, in LT recipient children and adolescents early in the pandemic. The study was conducted after the first COVID-19 outbreak in Israel, prior to the second outbreak, at a time when there was no lockdown. Additionally, we compared this cohort to pediatric patients sharing similar characteristics of chronic disease with immunosuppressive therapy, namely IBD. As official recommendations for both groups were the same; we aimed to understand whether there are differences between the groups on how they perceive themselves in the pandemic.

2 | METHODS

A cross-sectional study based on a structured internet or telephone survey was conducted of all pediatric LT recipients, aged 0–18 years, treated in the Institute of Gastroenterology, Nutrition and Liver Diseases in Schneider Children's Medical Center of Israel. Surveys were distributed early in the pandemic, after the first major COVID-19 outbreak in Israel and after the lockdown was released, between July 1, 2020, and September 10, 2020.

TABLE 1 Characteristics of the cohort

Sex, female (n, %)	40 (50.2%)
Age, years (median, IQR)	10 (5.8–14)
Time after transplantation, years (median, IQR)	5.5 (3.5–8.5)
Treatment (n, %)	
Tacrolimus	60 (79%)
Tacrolimus + steroids + MMF	4 (5.3%)
Tacrolimus + steroids + sirolimus	1 (1.3%)
Sirolimus	4 (5.3%)
Tacrolimus + steroids + MMF	5 (6.6%)
No treatment	2 (2.6%)

Data were collected of demographic characteristics, diagnoses, and current therapies. The survey questionnaire was designed specifically for this study and included 11 questions assessing behavior and treatment adherence of the patients: six questions with a 5-point Likert scale score, four yes/no questions, and one open-ended question regarding the impact of the COVID-19 pandemic. The survey was completed by one of the parents of each patient along with the patient itself, unless the patient could not cooperate (i.e., young age) in which case the parent replied solely. The survey results were descriptively compared with the recently published results of the same survey conducted among 244 pediatric patients with IBD.⁹ Participants in both groups were not vaccinated during study conduction as the vaccines were not available in Israel at that time.

Continuous variables are presented as means \pm standard deviations for normally distributed variables and as medians with IQRs for abnormally distributed variables. Qualitative variables were expressed as numbers and proportions.

The study protocol was approved by the local institutional review board. Patients aged 18 years old and the parents of all the other patients gave informed consent to participate in the survey.

3 | RESULTS

Of 152 pediatric LT recipients who met study inclusion criteria, 76 patients or their parents participated in the study. The majority of surveys (53, 69.7%) were completed over the internet and 23 (30.3%) over the phone. The characteristics of the cohort are depicted in Table 1.

The median age of the study population was 11 (IQR 5.9–14) years; four were aged 18 years. Forty (52.6%) were females. The median time after transplantation was 5.5 (IQR = 3.5–8.5) years. The survey questions and responses are presented in Table 2.

Most respondents (44, 57.9%) did not feel any difference in health service provision during the COVID-19 pandemic, while 6 (7.9%) noted a deterioration and 26 (34.2%) noted improvement. The majority of respondents (39, 51.3%) reported no change in their gastroenterologist/hepatologist's availability, whereas 32 (42.1%)

TABLE 2 Summary of the responses to the survey

	Significant worsening	Worsening	No change	Improvement	Significant improvement
	1	2	3	4	5
Was there a change in healthcare provision due to the COVID-19 pandemic?	1 (1.3%)	5 (6.6%)	44 (57.9%)	11 (14.5%)	15 (19.7%)
Was there a change in the availability of your gastroenterologist/hepatologist due to the COVID-19 pandemic?	1 (1.3%)	4 (5.3%)	39 (51.3%)	13 (17.1%)	19 (25%)
	To a very great extent	To a great extent	To a medium extent	To a minor extent	Not at all
	1	2	3	4	5
Are you afraid of a severe COVID-19 infection due to your illness or your medications?	34 (44.7%)	11 (14.5%)	13 (17.1%)	6 (7.9%)	12 (15.8%)
Do you feel a need for emotional support due to the COVID-19 pandemic?	7 (9.2%)	5 (6.6%)	15 (19.7%)	11(14.5%)	38 (50%)
Do you abide by the MOH restrictions and guidance?	51 (67.1%)	19 (25%)	2 (2.6%)	0 (0%)	4 (5.3%)
	Not at all	Not enough	Sufficiently	Updated	Very updated
	1	2	3	4	5
Do you feel informed about the effect of COVID-19 on patients with LT?	12 (15.8%)	9 (11.8%)	16 (21.1%)	22 (29%)	17 (22.4%)
	Yes	No			
Have you taken protective measures, in addition to the measures recommended by the MOH?	64 (84.2%)	12 (15.8%)			
Did you stop or change your treatment because of the COVID-19 pandemic?	0 (0%)	76 (100%)			
Did you consider stopping or changing your treatment due to the COVID-19 pandemic?	2 (2.6%)	74 (97.4%)			
Have you refrained from going to the pharmacy to purchase your medications during the COVID-19 pandemic?	9 (11.8%)	67 (88.2%)			

reported greater availability during the COVID-19 pandemic. Five (6.6%) respondents reported that their gastroenterologist was less available to them.

Fear of severe COVID-19 infection due to LT or LT-associated medications was reported by most patients (45, 59.2%); 34 (44.7%) expressed deep concern about developing a severe COVID-19 infection. Thirty-eight (50%) patients expressed a need for emotional support; of these, 12 (15.8% of the total) stated a great need.

Fifty-one (67.1%) patients reported strict adherence to the guidelines of the MOH, while five (6.6%) did not adhere to the MOH guidance at all. The vast majority of patients (64, 84.2%) reported taking additional protective measures. The most common measure, adopted by 36/76 (47.4%) patients, was avoidance of school or nursery despite approval of attendance by the MOH. Moreover, in eight (10.5%) families, siblings of the patients also avoided school. Voluntary lockdown was implemented by 27 (35.5%) patients. Other protective measures included avoidance of social contacts, parents not attending work, and frequent disinfection measures.

The majority of respondents (55, 72.4%) felt they were adequately informed regarding the potential effects of COVID-19 on patients with LT.

Two (2.6%) patients considered discontinuation or change in treatment; however, none of the patients changed or discontinued their medications due to COVID-19. Nine (11.8%) patients avoided pharmacy visits. No statistically significant difference was found between surveys answered over the phone compared with survey answered via the internet.

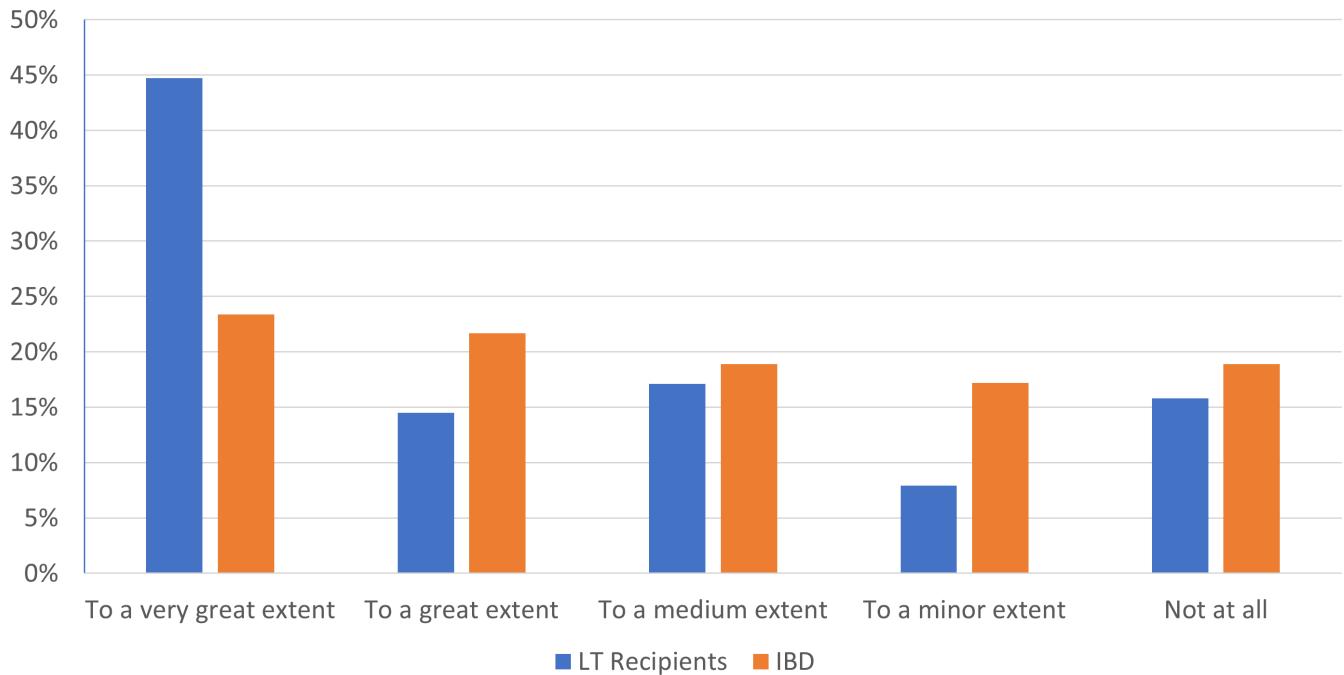
Compared to pediatric patients with IBD, the LT recipients were younger (by a median of 11 years (IQR: 5.8–14) vs. 15.3 (IQR: 12.5–17.3)). Higher proportions of pediatric LT recipients or their parents reported fears of contracting severe COVID-19 infection due to their illness or medications (45, 59.2% vs. 110, 45.1%) and declared taking extra protective measures (64, 84.2% vs. 120, 49.2%). A higher proportion of pediatric LT recipients than pediatric patients with IBD perceived improvements in healthcare provision (26, 34.2% vs. 32, 13.1%) and in availability of their treating

gastroenterologist (32, 42.1% vs. 40, 16.4%) during the COVID-19 pandemic. A higher proportion of pediatric LT recipients or their parents expressed feeling sufficiently informed regarding the effect of COVID-19 on their disease (55, 72.4% vs. 110, 45.1%; Figure 1).

4 | DISCUSSION

This study investigated perceptions of medical care and behavior of 76 pediatric LT recipients. Comparing this population to individuals with chronic gastrointestinal disease treated with

Are you afraid of a severe COVID-19 infection due to your illness or your IBD medications?



Do you feel informed about the effect of COVID-19 on patients with IBD / LT?

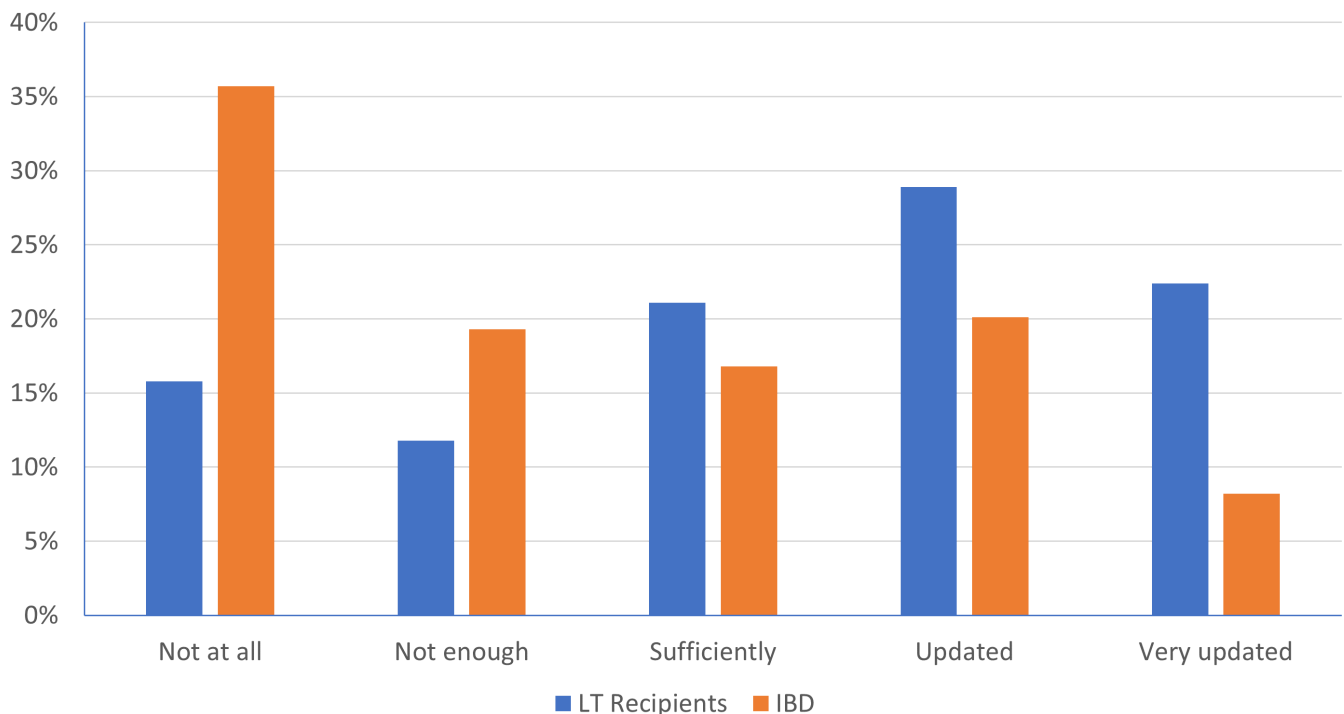


FIGURE 1 Comparison of survey results of LT recipients to patients with IBD

immunosuppressive therapy (pediatric IBD patients) highlighted the distinct features of pediatric LT recipients.

The majority of pediatric LT recipients expressed fears of developing severe SARS-CoV-2 infection, due to their illness or to their immunosuppressive therapy. Interestingly, this proportion was higher than for patients with IBD. This finding may result from disseminated information that patients with IBD were not more susceptible to severe COVID-19 unless treated with high-dose corticosteroids.¹⁰ In contrast, at the beginning of the pandemic, data were not consistent regarding risks of COVID-19 among pediatric LT recipients. The comparison to the descriptive findings among patients with IBD should be done with caution, due to age difference between the cohorts. The pediatric LT cohort was younger than the IBD cohort. As the survey was answered by one of the parents, it might reflect greater parental anxiety regarding younger children, or the families' perception that the LT recipients were "sicker" or at greater risk.

A higher proportion of pediatric LT recipients felt well informed compared with IBD patients. Nonetheless, more than 25% of the LT recipients or their parents felt not sufficiently informed regarding the effect of COVID-19 on their disease. This substantial proportion should prompt LT centers to invest particular effort to provide this population with reliable and periodically updated information. In a survey of pediatric LT recipients in India, 85% of the respondents gained their information from television and over 40% from social media.¹¹ Such information might be inaccurate and misleading, with a potentially hazardous effect on pediatric LT health. Thus, provision of information by treating physicians is crucial.

The proportion of families who adopted additional protective measures was considerably higher among the pediatric LT recipients than the pediatric IBD patients: 84% versus 50%. Similarly, 88% of parents of pediatric LT recipients in India stated a desire to keep their children strictly at home and to avoid visitors.¹¹ In our cohort, voluntary lockdown was implemented by more than 35% of the patients. Additional protective measures, including extreme social distancing, had a great impact on the daily life of the patients' families. For example, more than 10% of siblings of the LT recipients avoided school. Other concerning measures included avoidance of social contacts and parents not attending work. The harm of extreme measures, which are not advised by the national public health authorities, implemented by patients and their families should be addressed by treating physicians, especially in light of the minimal increased risk of COVID-19 infection in this population.¹²

Despite the high rate of protective measures and their major impact on daily life, only 50% of the respondents expressed feeling a need for emotional support. The COVID-19 pandemic is characterized by uncertainty, which is reflected by various coping measures by patients and their families. This report is in line with other publications describing heightened anxiety regarding health and well-being among children with chronic health conditions during the pandemic.^{13,14} To minimize hazardous effects of unnecessary protective measures, a pro-active approach including provision of guidance and mental support might be beneficial.

Interestingly, despite lockdown and fewer in-person clinic visits, most of the pediatric LT patients felt that their healthcare provision improved, and that the availability of their gastroenterologist/hepatologist did not change substantially. This finding apparently reflects effectiveness of the telemedicine provided. Notably, in various disciplines a shift toward telemedicine was a major impact of the COVID-19 pandemic on the management and follow-up of patients with chronic diseases.^{15,16} Telemedicine technology was found efficient among adult patients with advanced liver disease, without compromising clinical care.¹⁷ In light of the pandemic, our institute implemented a strategy that combined telemedicine with in-person outpatient visits. This strategy enabled close follow-up and frequent communication with LT recipients during the pandemic. The effectiveness of this strategy was demonstrated by most patients expressing that they were well informed regarding the effect of the pandemic on their health, and that healthcare provision did not change substantially. Despite the limitations of telemedicine, such as the inability to perform physical examination,¹⁸ we believe that this practice has a role in the follow-up of pediatric LT recipients. The optimal combination of in-person visits with virtual appointments is yet to be determined.

Only a minority of patients reported that they considered changing or discontinuing their medications, while none of the patients actually stopped treatment. Cessation of treatment might have significant implications on disease control and potential complications, including rejection and graft loss. Patient-caregiver-provider communication was described as being crucial to identifying treatment adherence, especially in chronic patients.¹⁹ High treatment adherence reflects well-established patient-doctor communication, and is in line with the high proportion of patients that reported being well informed.

The main implication of our study is universal—as it prompts clinicians to address families and patients fears and concerns, which might reflect their wellbeing and treatment adherence.

Our study has several limitations including the lack of a control group of patients without immunosuppressive treatment who attended our pediatric gastrointestinal clinic during the pandemic and self-reporting of treatment adherence. Other limitations include the unvalidated questionnaire due to lack of validated tools for assessing during COVID-19 pandemic, age differences between the LT and the IBD groups and comparison of the LT group and a selection bias of patients who were interested to participate and answer the survey over the phone or via the internet. Additionally, only one parent was interviewed, thus precluding a full perspective for each patient. Despite the limitations, our study highlights the need to provide comprehensive and updated guidelines for patients, along with establishing programs to relate to patients and family stress and anxiety during those times.

As our study was conducted early in the pandemic, further studies are needed and ongoing to assess the effect of COVID-19 pandemic in the long term, on the behavior and treatment adherence of pediatric LT patients, along with studies determining the effect of dedicated programs to provide comprehensive support.

In conclusion, we found several distinct effects of the COVID-19 pandemic on pediatric LT recipients. These included high proportions who expressed fear of contracting severe COVID-19 infection, adopted more stringent protective measures than those recommended and reported high treatment adherence. We believe that further pro-active patient education and provision of emotional support can address these findings.

CONFLICT OF INTEREST

None declared.

AUTHORS' CONTRIBUTIONS

OW and LD conceptualized and designed the study; MR, IO, YM, RG, AA, and RS participated in designing the study. LD, MS, RG, and RN participated in acquisition of data and analysis and interpretation of data. OW and LD drafted the manuscript. All the authors critically revised the manuscript and approved the final version.

DATA AVAILABILITY STATEMENT

The data are available on request from the authors.

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How to cite this article: Dorfman L, Nassar R, Rozenfeld Bar-Lev M, et al. Treatment adherence and behavior of pediatric liver transplant recipients during the COVID-19 pandemic. *Pediatr Transplant*. 2022;26:e14250. doi:10.1111/petr.14250