



REVIEW

Paediatric Liver Transplantation During COVID-19 Pandemic: Lessons Learned and Unanswered Questions

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Abstract

COVID-19 pandemic has imposed many challenges on paediatric liver transplantation (PLT) services and has necessitated several adaptations in different stages of the process to ensure transplant centres can still deliver the proposed services in addition to protecting patients and staff against infection. This review article digs through the current literature to clarify the challenges imposed by SARS-CoV2 on PLT centres globally. It provides an overview of current practice as well as suggestions from experts in the field to overcome multiple obstacles. In paediatrics, the reaction to SARS-CoV2 may be less severe than that seen in the adult population, but this can change in view of newly discovered virus strains. Response of transplant centres to the current pandemic was variable depending on the anticipated risk and available resources. Telemedicine has helped PLT programmes to continue their activities while protecting patients, as well as staff against the risk of SARS-CoV2 virus. Further studies are needed to guide immunosuppression management in post-transplant infected candidates; answering this critical question will help PLT centres solve this dilemma.

Keywords SARS-CoV2 virus · Paediatric liver transplantation · Immunosuppression · Organ donation · Telemedicine

Abbreviations

COVID-19	Coronavirus disease 2019
PLT	Paediatric liver transplantation
ICU	Intensive care unit
ACE2	Angiotensin-converting enzyme 2
UK	United Kingdom
CDC	Centres for disease control and prevention
PUI	Patient under investigation
CT	Computed tomography
CXR	Chest X-ray
LRTI	Lower respiratory tract infection symptoms

RT-PCR	Transcriptase polymerase chain reaction assay
SARS-CoV	Severe acute respiratory syndrome-coronavirus-2
NP	Nasopharyngeal
NPS	Nasal-pharyngeal swab

Introduction

The recently discovered coronavirus disease 2019 (COVID-19) is seen as an unpredicted public health crisis for the general population and especially for those with a background of chronic underlying health conditions [1]. The current pandemic has imposed many challenges on paediatric liver transplantation (PLT) services and has necessitated a number of adaptations in different stages of the process to ensure transplant centres can still deliver the proposed services in addition to protecting patients and staff against infection. The leading drive for this review is to demonstrate changes that were introduced to PLT activities during the pandemic, to raise the unanswered questions in this field and to summarize data available so far.

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Paediatric Response to SARS-CoV2 Virus

The immune reaction of children to SARS-CoV2 virus has been a field of active research; as compared with adults, children seem to have a less severe form of the disease, with comparably fewer children requiring active medical care or admission to intensive care unit (ICU) [2].

Theories Behind Children Tolerance to SARS-CoV2 Infection

The secret behind children's resistance to some infectious diseases remains unrevealed [3]. This may be explained by the fact that children have less outdoors activity, more active innate immunity, healthier lungs as they have not been in contact with as many deleterious materials as adults, and more importantly, fewer underlying chronic health issues. A more developed immune system in adults may also explain the deleterious immune response that is usually seen in acute respiratory distress syndrome [4].

Another theory that can explain the relative resistance to SARS-CoV2 virus in children is the age-related difference in maturation and functioning of viral receptors. The SARS virus, COVID-19, and human coronavirus-NL63 (HCoV-NL63) all use the angiotensin-converting enzyme (ACE2) as human cell receptor [5, 6]. Earlier reports showed that HCoV-NL63 infection is more prevalent in adults than in children [7, 8]. ACE2 receptors in paediatric lung tissue may also ameliorate severe acute lung injury that can be evoked by acid aspiration, sepsis, SARS, and lethal avian influenza A H5N1 virus infection [9]. Such observations should not be taken as a fixed fact especially in view of the newly discovered COVID-19 strains that may behave differently.

PLT Centres Activity During COVID-19 Pandemic

At the beginning of the pandemic, data regarding the burden and threat of SARS-CoV2 virus in PLT recipients as well as detailed protocols to be used in this special category of patients were scarce [10, 11]. To navigate through this pandemic, several modifications have been introduced in paediatric transplant centres in line with international recommendations [12, 13]. This kept the door open for candidates on the transplant waiting list who cannot afford to wait; this was also consistent with Centres for Medicare &

Medicaid Services (CMS) 'Adult Elective Surgery and Procedures Recommendations,' which considered transplants as 'tier 3b' (high acuity surgery/unhealthy patients) with the consecutive action directive to not delay surgery.

Adaptation of European Paediatric Transplant Centres to the First Wave of the Pandemic

A multicentre comparative analysis was conducted among the members of the European Reference Network on Paediatric Transplantation (ERN TransplantChild) to measure the consequences of the COVID-19 pandemic on paediatric transplant activity [14]; 10 out of 18 centres (55%) continued usual activity during the month of March 2020, while seven (39%) reduced their activity to critical cases only and one completely suspended its PLT programme. Reduction of activity or programme suspension was justified by concerns about transmission of SARS-CoV2 virus as well as the limited resources especially due to the pressure on intensive care beds which were occupied by COVID-19 patients. In terms of living donor programmes, 3 programmes (2 renal and 1 liver) suspended their living donor activities and in the rest of the centres, the living donors were reserved for critical candidates.

How Did UK PLT Centres Navigate Through the First Wave of the Pandemic?

The PLT centre in Leeds Teaching Hospitals in the United Kingdom (UK) continued living donor programme activity for sick patients during COVID-19 pandemic. Seven PLTs from living donors were operated since April 2020 until the present day. All these PLTs were planned for very sick patients during the pandemic. As these patients do not have the luxury to wait for a deceased donor to be available, it was felt that it is in their benefit to proceed while following all protective precautions. These safety measures included donor testing and counselling regarding increased risk of mortality if they unfortunately caught COVID-19 during their admission. The Leeds altruistic programme was suspended during the pandemic as it was difficult to justify on ethical grounds. Protecting healthy living donors against potential detrimental effect of SARS-CoV2 virus by postponing elective PLTs for stable candidates is the safe practice in such challenging times. There is no clear definition of critical or sick patients for centres who decided to continue LDLT during the pandemic, but in general, LDLT was justified for candidates with mortality risk while on the waiting list that exceeds the risk of SARS-CoV-2 infection. This involves candidates who suffer from tense ascites and may require repetitive paracentesis by high volumes particularly with known spontaneous bacterial peritonitis, those who experienced severe acute kidney damage, recent or persistent life-endangering

portal hypertensive bleeding, and candidates with background of liver tumour who should be transplanted within a narrow window following chemotherapy completion.

In the UK, there has been a collaboration between the three PLT centres during such unpredictable times, which included the three centre’s agreement on prioritizing the sickest children on the waiting list and allowing them to receive the next suitable graft irrespective of organ allocation. This has helped to reduce mortality and waiting time despite difficulties imposed by declined donor numbers.

Changes Imposed on Post-Transplant Follow-up and Role of Telemedicine

Follow-up appointments for PLT recipients were also affected, outpatient visits were completely suspended in some centres, while some centres limited the face-to-face visits to urgent patients, and other centres relied completely on telemedicine [14].

There is no doubt that telephone and video clinics have helped PLT centres to deliver their services within accepted standards and at the same time limited the exposure of both patients and staff to SARS-CoV2 virus. As most of the follow-up appointments for stable cases do not necessarily need face-to-face contact, outpatient appointments should be offered only to urgent cases after a screening call to exclude COVID-19 symptoms or contact with confirmed/suspected cases. This hybrid model looks like an appropriate way to face the challenges imposed by the pandemic on post-transplant follow-up process.

In view of the multiple waves of COVID-19 that the world is facing currently, paediatric transplant centres should identify solutions for critical and extraordinary situations, such as prioritizing candidates on transplant waiting list if resources become limited and deciding on the best post-transplant follow-up strategies that would potentially limit patient exposure and protect staff.

Changes to Cadaveric Organ Donation Process in the Pandemic

Organ donation rates showed obvious decline during COVID-19 pandemic [15]. The reason for this is both complex and multi-factorial: firstly, diminished intensive care

resources for donor selection and management; secondly, limited capability of testing and uncertainty around donor COVID-19 status; thirdly, lockdown rules resulting in less trauma victims; fourthly, more family refusals for unknown reasons; and finally, the expectation that donation/transplantation programmes have been paused [16].

Laboratory and Imaging Evaluation for Potential Donors in the Pandemic

The American Society of Transplant Surgeons (ASTS) COVID-19 Strike Force Guidance, published online in March 2020, discourages the use of organs from donors infected with COVID-19 [17]. As a result, testing of potential donors for COVID-19 became routine practice. Due to the insufficient sensitivity of the nasopharyngeal swab test [18], chest imaging using CT was incorporated for potential donors to improve sensitivity [19]. This was recommended based on the observation that over half of asymptomatic patients demonstrate findings on CT consistent with COVID-19 and the sensitivity of CT chest changes rises as the COVID-19 progresses [20–22].

Criteria of Potential Donor Acceptance in the COVID-19 Era

The team at Baylor College of Medicine, Houston, Texas, developed a protocol to help transplant surgeons to decide on donor selection for solid organ transplantation during COVID-19 era [23] (Tables 1, 2, and 3).

Changes to Patients on Waiting List During COVID-19 Pandemic

Risks Implicated on PLT Candidates During COVID-19 Pandemic

The COVID-19 pandemic had a particularly negative impact on PLT candidates as the challenges that the transplant process must face at different stages are multiple: first, the risk of liver disease progression on the waiting list, which may lead to patient being considered ‘too sick

Table 1 Donor exposure assessment

Category 1	The donor has not travelled to CDC high-risk area (levels 2–3) in the past 21 days and has had no contact with either PUI or confirmed case
Category 2	The donor has been in an area deemed as a CDC high-risk area (levels 2–3) in the preceding 21 days, and exposures are unknown
Category 3	The donor had direct unprotected contact with a PUI for COVID-19 in the last 21 days
Category 4	The donor had direct unprotected contact with a confirmed case of COVID-19 in the last 28 days

Legend: CDC, centres for disease control and prevention; PUI, patient under investigation
 This table has been reported by Galvan et al. [23]

Table 2 Donor clinical risk

Category 0	Asymptomatic, negative RT–PCR for SARS–CoV–2, as well as CXR and CT chest without signs of COVID–19
Category 1	Symptomatic (LRTI, fever, anosmia) with negative RT–PCR for SARSCoV–2, and CXR and CT chest without signs of COVID–19
Category 2	Symptomatic (LRTI, fever, anosmia) with negative RT–PCR for SARSCoV–2 and CXR or CT chest concerning for COVID–19
Category 3	Symptomatic (LRTI, fever, anosmia) with positive RT–PCR for SARSCoV–2 and CXR or CT chest concerning for COVID–19

Legend: COVID-19, coronavirus disease 2019; CT, computed tomography; CXR, chest X-ray; LRTI, lower respiratory tract infection symptoms; RT-PCR, reverse transcriptase polymerase chain reaction assay; SARS-CoV, severe acute respiratory syndrome-coronavirus-2

This table has been reported by Galvan et al. [23]

for transplant' or even patient mortality [10, 24, 25]; second, persistent pressure on healthcare resources (substantial redeployment of healthcare personnel especially ICU specialists to manage COVID-19 patients); third, decline in organ donation rates that exacerbated the already existing graft shortage [26, 27]; and fourth, the risk of SARS-CoV2 virus infection early or late after transplantation and even while on the waiting list [16]. All of these factors have a significant impact on the likelihood of transplantation proceeding [10].

Patients with advanced liver disease are categorized by the Centres for Disease Control and Prevention as a group potentially at risk for severe SARS-CoV2 virus infection [28], which is why declining a matching graft for a candidate on the waiting list while applying all protective precautions does not sound appropriate.

COVID-19 Infection While on the PLT Waiting List

The situation is different for candidates who unfortunately tested positive for COVID-19; even in urgent candidates, most programmes have advised against transplanting a COVID-19-infected patient. Based on ASTS guidance [17], it is concluded that patients with active or recent SARS-CoV2 virus infection will possibly encounter adverse outcomes if transplanted. At least 2, possibly 3, weeks after a positive COVID-19 test, several negative COVID-19 tests

are proposed by most transplant programmes to consider such patients for transplantation [15].

Measures Upon Admission for Potential Transplant During COVID-19 Pandemic

The European Association of the Study of the Liver (EASL) and the European Society of Clinical Microbiology and Infectious Disease (ESCMID) advised that all candidates who would potentially receive a LT should be tested for and be informed about the nosocomial COVID-19 risk [25].

Measures Before Potential Recipient Admission on Transplant Day

When a matching graft is being offered for outpatient candidates, any possible recipient should be screened for exposure history and clinical symptoms by the transplant coordinator over the telephone before hospital admission. If the candidate gives a history of recent travel, had exposure to a suspected COVID-19 positive patient in the last 21 days, or had contact with a confirmed case in the last 28 days and/or has the presence of lower respiratory tract symptoms (cough, shortness

Table 3 COVID-19 risk categorization for liver donors

Risk category	Exposure category	Clinical category	Decision
Low	0–3	0	Accept
Moderate	0–3	1–2	Consider (if negative SARS–CoV–2 RT–PCR, CT chest without signs of COVID–19 and based on risk/benefit)
High	0–3	3	Reject

Legend: COVID-19, coronavirus disease 2019; CT, computed tomography; CXR, chest X-ray; NP, nasopharyngeal; RT-PCR, reverse transcriptase polymerase chain reaction assay; SARS-CoV-2, severe acute respiratory syndrome-coronavirus-2

This table has been reported by Galvan et al. [23]

of breath, chest pain), then the transplant should be cancelled [23].

Measures After Potential Recipient Admission on Transplant Day

On admission to the hospital, the transplant candidate should wear a face mask. Clinical examination, nasopharyngeal swab, and non-contrast CT chest imaging should be undertaken to rule out SARS-CoV2 virus infection. Inpatient candidates should have a negative nasopharyngeal swab within the previous 48 h, a non-contrast CT chest imaging will be obtained for all transplant candidates within 7 days of anticipated transplant date, if feasible.

Upon availability of suitable graft and with ensuring all proposed precautions, the medical director of transplantation should check availability of health care resources with the chief medical officer before the procedure. In case of ICU bed unavailability, the graft should be redirected to other suitable candidates within accepted limits of cold ischemia time. As less children required ICU admission from COVID-19 perspective, pressure on ICU beds was less pronounced in paediatric centres compared to adult ones.

Challenges in PLT Recipients Management During COVID-19 Era

Clinical Picture of COVID-19 Infected PLT Recipients

The number of reported liver transplant recipients who had documented SARS-CoV2 virus infection remains few. The reported clinical signs and symptoms are not divergent from those of the general population. However, it has been noted that transplant recipients may present with low-grade fever or no fever at all [29] presumably due to their immunosuppression. In addition to respiratory failure which is known to be the primary mechanism of injury in COVID-19, liver parenchymal damage (reflected by a raised serum alanine aminotransferase and aspartate aminotransferase) is common, ranging from 14 to 53% of COVID-19 patients, and seems to correlate with disease severity [30].

Experience of Transplant Centres in the Management of COVID-19 Infected Recipients

The first mortality in liver transplant recipient due to SARS-CoV2 virus was reported in China. Following that, case reports and series describing morbidity and mortality of liver transplant candidates after documented COVID infection were published [31–34].

In a study conducted on PLT recipients in Lombardy, Northern Italy [35], 5 (4%) out of 138 PLT recipients had had a close contact with a documented COVID-19 cases (3 of them were parents). Luckily, none of the PLT recipients developed symptoms related to COVID-19, nor required oxygen supplementation or hospital admission for COVID-19-related condition. Three of these patients had undergone nasal-pharyngeal swab (NPS) and fortunately, the results came back negative. This raises questions about whether children are protected in some way from SARS-CoV2 virus infection and that PLT recipients are not at higher risk of more severe clinical complications of infection.

In the same survey, another 13 (9%) PLT recipients had contact with suspected COVID-19 cases who were household members in 5 candidates. Eight patients (61%) reported symptoms related to COVID-19, which were fever and cough in 7 (54%), malaise in 2 (15%), and anosmia, dysgeusia, and loss of appetite in one patient. Diagnostic NPS or chest radiography for suspected pneumonia was not requested for any of these PLT recipients as none required medical attention. None of the PLT recipients in this survey developed respiratory failure and pneumonia and required oxygen administration or hospitalization. Interestingly, none of PLT recipients reduced or stopped their immunosuppression treatment. Thirty-nine (85%) candidates recovered completely when the survey was conducted; the others were at home in good general condition. These results must be taken with caution as COVID-19 testing was not offered for candidates with suspicious symptoms due to limited availability; this can explain why infection rate in the studied group of patients 7 folds above the estimated number of infections in the age-matched general population is so the recorded mild respiratory syndromes could be related to other pathogens than SARS-CoV2. There have been reports for patients aged between 5 and 10 months who received PLT in COVID-19 era and subsequently developed a rapid and aggressive respiratory deterioration which necessitated mechanical ventilation and extracorporeal life support, and who eventually died, and thus question such a smooth course in PLT recipients [36].

Despite labelling LT recipients as high-risk group due to immunosuppression, the situation may be milder in the paediatric population. This is based on reports concerned with liver transplant recipients which concluded that conditions which are not commonly seen in children such as body mass index above 25, previous cardiovascular event, arterial hypertension, hyperlipidaemia, and diabetes are negative predictive factors for this cohort [31, 37, 38].

Immunosuppression Management for Transplant Recipients During the Pandemic

There is an on-going discussion about whether liver transplant recipients should be kept on low immunosuppression during the pandemic [15]. The answer is probably no, as there is no evidence to suggest that these patients are at particular risk due to their immune suppression. The decision in this area should be based on solid evidence as unnecessary reduction of immunosuppression will potentially expose recipients to graft rejection.

Management of immunosuppression in PLT recipients who are COVID confirmed/suspected is a dilemma especially with scarce studies in this field. Immunosuppression was considered in some reports as neutral or even protective when it comes to SARS-CoV2 virus or complications which are heavily precipitated by a proinflammatory state [35]. This observation was augmented by results in children receiving anticancer chemotherapy and in those taking immunosuppressant treatment for inflammatory bowel disease [39, 40] as well as by the finding that mortality in liver transplant recipients was reported in patients who are on minimal immunosuppressive regimens [34, 38]. It is difficult to reach solid conclusions from these results because all the studies were case reports and case series within a very short observational time.

The Beijing working party for liver transplantation advised that liver transplant recipients who tested positive for COVID-19 should be managed with steroids for a brief period to control the gravity of pneumonia. The same working party also advised that immunosuppression should not be paused for patients with mild SARS-CoV2 virus infection or those who remain infection free, and calcineurin inhibitor doses should be decreased in moderate to severe cases [29]. This is in contrast to the EASL-ESCMID recommendation that immunosuppression should be titrated depending on the antiviral treatment protocols as there is a high probability that the drugs from different treatment protocols can potentially interact [25]. Further studying of the relationship between immunosuppression in PLT recipients and gravity of SARS-CoV2 virus is needed to guide decisions in this sensitive group of patients.

Conclusions

The unforeseen COVID-19 pandemic has imposed a lot of new regulations on PLT services to ensure both patient and staff safety. Transplant activity during the COVID-19 era has varied considerably between different centres reflecting divergent local risks as well as variability of available resources. In the absence of definitive treatment and insufficient vaccination coverage, following strict protective

procedures during different stages of transplant process appears to be the only safe way to achieve successful procedure. Telemedicine has offered a successful alternative to regular face-to-face post-transplant follow-up appointments in stable candidates. Transplant centres should invest in this field to be ready for the unknown course of the pandemic especially in view of newly discovered COVID-19 strains. Contradicting recommendations regarding post-transplant immunosuppression management in COVID-19 confirmed cases is stressful for transplant teams, and further studies are needed to answer this critical question and to help transplant centres navigate management strategies for this special category of patients through the course of the pandemic.

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