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Challenges in liver transplantation in the context of a major pandemic

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Abstract

Coronavirus disease-2019 (COVID-19) has led to a temporary suspension of liver transplant activity across the world and the remodelling of care for patients on the waiting list and transplant recipients with the increasing use of remote consultations. Emerging evidence show that patients ¹⁰ with more advanced liver disease are at increased risk of severe COVID-19 and death, whereas transplant recipients have similar risk with the general population which is mainly driven by age and metabolic comorbidities. Tacrolimus immunosuppression might have a protective role in the post-transplant population. Vaccines that became rapidly available seem to be safe in liver patients, but the antibody response in transplant patients is likely suboptimal. Most transplant centres were gradually able to resume activity soon after the onset of the pandemic and after modifying their pathways to optimize safety for patients and workforce. Preliminary evidence regarding utilizing grafts from positive donors and/or transplanting recently recovered or infected recipients under certain circumstances are encouraging and may allow offering life-saving transplant to patients at the greatest need. This review summarises the currently available data on liver transplantation in the context of a major pandemic and discusses areas of uncertainty and future challenges. Lessons learnt from the COVID-19 pandemic might provide invaluable guidance for future pandemics.

INTRODUCTION

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Introduction

The rapid spread of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and the severe disease precipitated by the virus (COVID-19) has had a profound impact on healthcare systems worldwide. The challenges posed on liver transplantation (LT) programmes were unprecedented, and can be summarised in the following: 1. pre-transplant aspects (management of patients on the LT waiting list, impact of COVID-19 on patients with advanced liver disease), 2. peri-transplant aspects (temporary suspension of LT programmes, testing of donors/recipients, LT after recovery from COVID-19, utilization of grafts from positive donors), and 3. post-transplant aspects (COVID-19 in LT recipients, management of immunosuppression, safety of vaccination against SARS-CoV-2). The aim of this review is to provide an outline of the unforeseen challenges that the COVID-19 pandemic posed on LT programmes worldwide.

Management of patients on the waiting list

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The declaration of COVID-19 pandemic by the World Health Organization in March 2020 precipitated significant changes in the delivery of healthcare in an effort to minimize patient and staff exposure to SARS-CoV-2. The traditional face-to-face consultations, which have been the basis of patient-doctor communication, ceased suddenly, and gave place to new virtual models of communication [1]. Patients were encouraged to have blood tests or other essential investigations performed locally (usually with their general practitioner) to avoid travelling. Telephone- and/or video-assisted consultations rapidly became the norm during the pandemic. Sending prescriptions and medications *via* post was another measure utilized to reduce risk of transmission/acquisition.

Patients with chronic liver disease (CLD) and in particular those with decompensated cirrhosis -including those on the waiting list for LT- were classified as high-risk for severe COVID-19, and were, therefore, instructed to strictly self-isolate for prolonged

periods of time. Their assessment and management were performed remotely to a significant extent, while maintaining very limited face-to-face consultations for highly selected patients that were considered at risk for CLD complications [2]. Procedures such as ultrasonography for hepatocellular carcinoma (HCC) surveillance or endoscopy for variceal surveillance, were deferred unless the patient was considered at high risk of HCC or variceal bleeding, respectively, and following individual risk-benefit assessment. The international hepatology associations (European Association for the Study of the Liver (EASL), American Association for the Study of Liver Diseases (AASLD), Asian Pacific Association for the Study of the Liver (APASL)) released promptly guidance for the management of patients with CLD, patients on the waiting lists and LT recipients [3-5]. The guidance included strict preventive measures (i.e. vaccinations against *Streptococcus pneumoniae* and influenza, prophylaxis against spontaneous bacterial peritonitis) to avoid hospital attendance and/or admission. The common denominator was avoidance of commuting and face-to-face contact unless it was considered essential. The caveats of no direct patient contact, in particular for patients on the waiting list, were acknowledged by clinicians, but it was felt that the risks of severe COVID-19 and death outweighed the risks associated with remote or virtual assessments [6]. An Austrian study that included patients with CLD admitted to hospital just before and after the outbreak of the pandemic, demonstrated the impact of the restrictions on patient satisfaction with regards to the quality of liver care [7]. The same study showed that CLD patients that were hospitalised during the pandemic were sicker indicating a higher threshold for hospital attendance and admission, and that liver-related mortality was higher.

Evaluation and selection of candidates for liver transplantation

The same restrictions applied to the evaluation and selection process of LT candidates. Many LT centres developed local policies for selecting patients and for prioritizing those who were already on the waiting list. Patients that were prioritised included those with acute liver failure, higher model for end-stage liver disease (MELD) score and

those at risk for decompensation or HCC progression [4]. The evaluation process had to be remodelled taking into consideration travelling restrictions, distancing measures and minimisation of exposure to SARS-CoV-2. An important element of LT assessments, i.e. patients and family education, social work and dietitian consultations, had to be performed either *via* video or telephone consultations. In several LT centres, the group education sessions were replaced by internet-based sessions with multiple participants. The impact of COVID-19 on the waiting list for solid organ transplantation (SOT) was investigated in a study that used the Scientific Registry of Transplant Recipients (SRTR) data [8]. In March 2020 coinciding with the onset of the pandemic and in winter 2020/2021 coinciding with the second surge, there was a rapid decline in the length of the waiting list for all SOT and a decline in the number of removals. The former can be interpreted by the decline in listings, and the latter by a decline in removal due to transplant. With regards to removals due to death, waiting list mortality remained constant for liver, but increased for kidney. The results of this study reflect the reduction in the activity (decreased transplant assessments/Listings, decreased transplant activity) in many transplant centres not only in the US, but also worldwide.

Transplantation activity

The COVID-19 pandemic had a profound impact on SOT that was primarily driven by safety concerns regarding transmission (in particular in the first phase when access to SARS-CoV-2 testing was very limited) and by limited resources (mainly intensive care beds). A web-based survey between 7th September 2020 and 31st December 2020 organised by three international societies (EASL, ESOT-ELITA, ILTS) compared transplant activity in the first six months of 2020 *vs* 2019 [9]. Most transplant centres ceased activity for up to a month with the exception of patients with acute liver failure, high MELD score or acute-on-chronic liver failure, in which cases the decisions were taken on a case-by-case basis. Out of 128 centres that responded to the survey, 30-50% performed transplants on patients with previous COVID-19. The majority reported lower transplant activity, fewer candidates being listed and higher waitlist mortality in

2020 compared to 2019. These differences were more profound in 'hit' countries (COVID-19 case fatality >3.4%) than in 'non-hit' countries [9].

The analysis of the Global Observatory for Organ Donation and Transplantation data for 2019 and 2020 showed a global decrease in LT by 11.3% [10]. Almost all geographic regions were affected, but developed countries were able to subsequently recover transplant activity, whereas developing countries lagged. In the United States, 32,594 transplants were expected in 2020, and only 30,566 occurred (observed/expected (O/E) 0.94, confidence interval (CI) 0.88–0.99) [11]. 58,152 waitlist registrations were expected and 50,241 occurred (O/E 0.86, CI 0.80–0.94). The observed/expected ratio for LT was 0.96 (0.89–1.04). There was a similar reduction in organ donation. The months with the lowest activity were April, May and December 2020. In Europe, there was a similar reduction in LT activity with areas with the highest incidence of COVID-19 showing the greatest reduction in activity.

The reduction in LT activity ranged from 25% (US and France) to 80% (United Kingdom and India) [12]. Some countries/areas managed to maintain their LT activity (South Korea, some centers in Italy even in medium or high-incidence areas) by means of a rapid response to the pandemic and re-modelling of their pathways [12]. In the US, significant variabilities in LT activity were observed within regions of similar COVID-19 incidence [13]. This was presumably attributed to differences in resources, SARS-CoV-2 transmission among members of staff and leadership philosophy. The wider availability of SARS-CoV-2 testing might have been associated with the restoration of LT activity later in 2020.

COVID-19 in transplant candidates

Abnormal liver function tests are common in patients with COVID-19, and can be attributed to direct viral cytopathic effect, immune-mediated liver injury, hypoxia or drug-induced liver injury. Liver involvement in COVID-19 has been associated with higher mortality [14]. In patients with pre-existing chronic liver disease, COVID-19 can lead to exacerbation of the underlying disease, which in patients with cirrhosis can

result in acute decompensation ^[15]. Studies consistently show increased risk of mortality in patients with cirrhosis and COVID-19 ^[16]. A study that included 305 SARS-CoV-2 positive patients with cirrhosis and compared them with ¹² SARS-CoV-2 positive patients without cirrhosis, and SARS-CoV-2 negative patients with and without cirrhosis, demonstrated 3.5-fold increased mortality among patients with cirrhosis, and 1.7-fold increased mortality among SARS-CoV-2 positive patients ^[17]. Predictors of mortality in SARS-CoV-2 positive patients with cirrhosis were advanced age, decompensation, and higher MELD score.

The risk of death with COVID-19 is higher in patients with cirrhosis compared to patients with CLD without cirrhosis, and the risk increases with more advanced stages of liver disease. One of the largest international studies (29 countries) included 386 SARS-CoV-2 positive patients with cirrhosis, 359 SARS-CoV-2 positive patients with CLD without cirrhosis and 620 SARS-CoV-2 positive patients without CLD ^[18]. Mortality in patients with cirrhosis was significantly higher compared to those with CLD without cirrhosis (32% vs. 8%, $p < 0.001$). Mortality in Child-Pugh A cirrhosis was 19%, B 35% and C 51%. The main cause of death among patients with cirrhosis was respiratory failure in 71%. Acute decompensation occurred in 46%. Age and severity of liver disease were predictors of mortality.

In view of this data. International societies recommend testing for SARS-CoV-2 in every patient presenting with acute decompensation, and early admission for all patients with cirrhosis developing COVID-19.

Screening of donors and recipients

International societies (AASLD, EASL and APASL) released guidance recommending screening of donors and recipients for ⁹ SARS-CoV-2 with reverse transcription-polymerase chain reaction (RT-PCR) of upper respiratory tract secretions ^[3-5]. A negative RT-PCR is required within 48 h from graft retrieval or LT ^[19]. In view of the high rates of false negative RT-PCR results, AASLD and APASL also recommend

screening donors for recent exposure, fever or symptoms suggestive of COVID-19 and utilizing imaging of the chest (chest radiograph or computed tomography). CT of the chest is being increasingly used in the evaluation of COVID-19 patients, and has the ability to demonstrate lung changes even before RT-PCR becomes positive [19]. Screening of the recipient is similar and includes molecular testing, history of recent exposure, symptoms/signs and findings on imaging studies.

COVID-19 in transplant recipients

It was initially hypothesized that LT recipients with SARS-CoV-2 infection might be at increased risk of death due to age, immunosuppression and metabolic comorbidities. Cohort studies published after the outbreak of the pandemic showed a case-fatality rate of 12-25% which was not increased compared to the general population [20-28]. Tacrolimus immunosuppression was not found to be associated with the risk of death in the context of SARS-CoV-2 infection, on the contrary, it seemed to be protective in some studies [27]. Age and comorbidities were the main predictors of outcome in most studies, similar to the general population [26].

An analysis of the ELITA-ELTR COVID-19 registry between 1st March and June 27th 2020 included 243 adult LT recipients with COVID-19 across Europe [27]. 84% required hospital admission and 19% admission to the ICU. Overall mortality was 20%, and 25% among those who required hospital admission. ²Respiratory failure was the main cause of death. Age >70 years, diabetes mellitus and chronic kidney disease were independently associated with the risk of death. Tacrolimus was associated with lower probability of death.

A Spanish cohort study (SETH cohort) reported the outcomes of 111 LT recipients diagnosed with COVID-19. The incidence of SARS-CoV-2 infection in this cohort was almost double compared to the general population. 86.5% required hospital admission and 10.8% admission to the ICU [20]. Overall mortality rate was 18% and was ²lower than in the matched general population. Mycophenolate-containing immunosuppression

was associated with increased risk of death, but not tacrolimus or everolimus. Immunosuppression withdrawal had no effect on outcome.

Similar results were reported by an international cohort study (18 countries) with 151 LT recipients with COVID-19 against 627 non-transplant COVID-19 patients [25]. Similar to previous reports, 82% of LT recipients required hospital admission. LT recipients were more likely to require ICU admission (28% vs. 8%). Mortality rate was lower among LT recipients (19% vs. 27%, $P = 0.046$). When the groups were matched for age, sex and comorbidities, LT was not associated with increased risk of death. Risk factors for death among LT recipients were age, creatinine and non-liver cancer.

One study reported on the incidence of acute liver injury (defined by ALT 2-5x ULN) in LT recipients when compared to non-transplant CLD patients with COVID-19 [22]. The incidence was lower in LT recipients (47.5% vs. 34.6%, $P = 0.037$), but the presence of liver injury in the context of COVID-19 significantly increased the risk of mortality and ICU admission.

A systematic review of 1076 published cases provided more robust evidence on the outcomes of SARS-CoV-2 infection in LT recipients [29]. The majority of patients were male (67%). With regards to established risk factors for COVID-19, 39% had diabetes mellitus type 2, 44% had arterial hypertension, and 16% were obese. Overall, 65% required hospital admission, and 23% of the hospitalized patients required ICU admission. Death was reported in 135 cases. Infection was more common in middle-aged men with metabolic comorbidities. The mortality rate and case-fatality rate were not higher than in the general population. This finding does not confirm the initial concerns regarding COVID-19 course and outcomes in this presumably vulnerable population.

In summary, although incidence of SARS-CoV-2 infection might be higher in LT recipients, the risk of death or ICU admission does not seem to be higher than in the general population. Age, metabolic comorbidities and cancer, which are established risk factors for severe COVID-19 and mortality, also increase the probability of worse outcomes in LT recipients similarly to the general population.

Management of immunosuppression in LT recipients

The initial concerns regarding risk of severe COVID-19 and death in the context of immunosuppression in LT recipients were not confirmed by subsequent published evidence. Despite concerns, complete withdrawal of immunosuppression was rarely adopted and only in extremely severe cases. The ELITA-ELTR COVID-19 registry study demonstrated that tacrolimus ⁶ was associated with lower risk of mortality (hazard ratio (HR) 0.55, 95%CI 0.31–0.99) raising the possibility of a protective effect against SARS-CoV-2 [27]. This effect of calcineurin inhibitors might be mediated by inhibition of CoV growth *via* the cyclophilin pathway, and modulation of T-cell activation [30, 31]. This potential protective effect was also demonstrated in the SETH cohort and the smaller COVID-LT study [20, 29].

Data regarding the effect of mycophenolate mofetil (MMF) indicate a potential negative impact on the course of COVID-19. In the SETH cohort, patients receiving MMF had a more severe course of the disease, and this was more evident for doses higher than 1000 mg/day [20]. MMF was an independent predictor of mortality. This observation could be interpreted by the cytostatic effect that MMF exerts on activated lymphocytes, which alongside the cytotoxic effect of SARS-CoV-2 on the same target, might result in worse outcomes [32, 33]. On the other hand, ¹ complete withdrawal of MMF at diagnosis ameliorated the risk of severe COVID-19.

Complete withdrawal of immunosuppression does not seem to be associated with improved prognosis, hence is not encouraged [34]. However, immunosuppression might be associated with prolonged viral shedding following SARS-CoV-2 infection [35]. The currently available data indicate that comorbidities, which are not uncommon among LT recipients, rather than immunosuppression per se, increase the risk of severe COVID-19 and death. Although data are not extensive, CNI immunosuppression might reduce the risk of severe disease and fatal outcomes presumably by suppressing the augmented immune response precipitated by SARS-CoV-2. MMF at high doses might be associated with disease severity. It should be taken into consideration that reduction

in immunosuppression is associated with risk acute cellular rejection and graft loss. In this context, most international societies recommend against modifications of CNI immunosuppression. MMF reduction or temporary withdrawal is justified in the context of moderate-severe disease. Tacrolimus has numerous drug-to-drug interactions, and vigilance is required with drugs used in the context of COVID-19, such as tocilizumab and ritonavir-boosted nirmatrelvir [36].

Immunity and vaccination in LT recipients

The rapid spread of SARS-CoV-2 has led to the exceptionally fast development of vaccines with proven short-term safety and efficacy. In LT recipients, immunosuppressive therapy might be associated with impaired immune response to vaccination and lower immunogenicity than in immunocompetent individuals. Live attenuated vaccines are usually avoided after LT unless the benefit of vaccination outweighs the associated risks. Vaccines are also avoided in the first 3-6 mo after LT, which corresponds to the period of maximal immunosuppression, because of concerns regarding attenuated immune responses to vaccination [37]. Another theoretical concern is that immune responses to vaccines might trigger immune-mediated rejection, although this has not been confirmed in a meta-analysis [38]. EASL recommends that vaccination should be completed prior to LT whenever possible. Vaccines against SARS-CoV-2 are either mRNA or nonreplicating viral vector vaccines, which are safe in the context of immunosuppression.

With regards to COVID-19 vaccines, clinical trials have not included transplant patients receiving immunosuppressive therapy. Long-term safety and duration of protection in this population remains unclear. The ORCHESTRA SOT recipients cohort assessed antibody response after the first and second dose of mRNA vaccine [39]. The analysis included 1062 SOT patients (liver, 17.4%) and 5045 health care workers (HCWs). The antibody response was significantly lower in SOT recipients (52.3% vs. 99.4%), and the antibody levels were significantly lower in the same group. Predictors of better response were interval ≥ 3 years, liver transplant and azathioprine. A study of 35 LT

recipients demonstrated partial antibody response to inactivated vaccines [40]. Interleukin-2 receptor induction therapy and a shorter time post LT were associated with lower antibody response. These findings raise the possibility that booster vaccines might be required in LT recipients.

EASL recommends vaccination against SARS-CoV-2 after the first 3-6 mo following LT, because vaccination in the context of high immunosuppression might not be effective [37]. In this setting, vaccination of household members is highly recommended. In the first phases of the pandemic, priority for vaccination was given to healthcare professionals caring for transplant patients in an effort to protect this vulnerable population.

Transplant from SARS-CoV-2 positive donors

The initial response of transplant societies to the challenges posed by COVID-19 pandemic was to recommend testing for SARS-CoV-2 RNA in donors/recipients before transplant, and to recommend against LT in cases of positivity. In the course of the pandemic some centers started performing life-saving LT for high-risk patients utilizing grafts from SARS-CoV-2 positive donors to recipients with active or resolved infection [41]. A multicenter Italian study included 10 LTs from donors with active COVID-19 [41]. Two recipients were SARS-CoV-2 RNA positive at the time of LT. None of the remaining 8 recipients developed SARS-CoV-2 RNA positivity. Eight recipients had IgG antibodies against SARS-CoV-2. SARS-CoV-2 RNA was not detected in donor liver tissue at the time of LT. This study introduced the concept that using grafts from SARS-CoV-2 positive donors might be a safe practice, particularly in patients who are the highest need for LT.

The safety of this practice was confirmed in smaller case series. A series from the US with 5 SOTs (2 Livers, 1 simultaneous liver-kidney, 1 kidney and 1 simultaneous kidney-pancreas) from SARS-CoV-2 positive donors to negative recipients showed no risk of transmission to recipients [42]. SARS-CoV-2 RNA was not detected in allograft biopsies.

A systematic review of all SOT from past or active SARS-CoV-2 infected donors until December 2021, included 69 recipients that received 48 kidneys, 18 Livers and 3 hearts from 57 donors, and 6 additional lung transplants [43]. 10/57 (17.5%) donors had active COVID-19 and 18/57 had detectable SARS-CoV-2 RNA. Viral transmission was not documented among non-lung SOT recipients. However, viral transmission occurred in three lung recipients, who developed COVID-19 symptoms, one of which subsequently died. Strategies to mitigate the risk of donor/graft-recipient transmission potentially include SARS-CoV-2-directed monoclonal antibody therapy and/or pre-emptive remdesivir administration, although the efficacy of this approach needs to be confirmed [44].

Decision-making regarding SOT from SARS-CoV-2 positive donors should take into consideration the risk of transmission/acquisition and the sequelae of developing COVID-19, as well as the risk of disease progression and death associated with the underlying disease [45]. Patients with cirrhosis, and in particular those with decompensated disease, who develop COVID-19 are at high risk of death. On the other hand, patients on the waiting list are at risk of death unless they are offered life-saving LT, and the suspension of LT activity has led to increased mortality on the waiting list. Utilizing non-lung grafts from carefully selected infected donors might benefit patients who are at the highest risk of death without immediate transplant. Although this practice seems to be safe based on limited currently available data, patients and their families should be informed and actively involved in shared decision-making.

Transplant of SARS-CoV-2 positive recipients

LT following recovery from COVID-19 has been a challenge as the appropriate time interval is not well defined as yet. Several cases of recipients with previous or active SARS-CoV-2 infection have been reported [46, 47]. The decision to proceed to LT was made on a case-by-case basis taking into consideration the risk of death without immediate LT. The largest case series included 14 patients who received LT following symptomatic SARS-CoV-2 infection, 4 of which had detectable RNA at the time of LT

[48]. One recipient who was negative at the time of LT became positive 9 days post-LT. None of the patients developed SARS-CoV-2-related complications. In another case series, 4 patients received LT 2 wk after SARS-CoV-2 positivity and 2 patients 4 wk after a positive test [49]. One recipient died secondary to sepsis. Despite the encouraging results, there have been two reports of portal vein thrombosis and hepatic artery thrombosis in SARS-CoV-2 positive recipients of LT [50, 51].

SARS-CoV-2 RNA negativity has been proposed as a prerequisite for proceeding safely with LT, and a time interval of 2-4 wk between resolution of symptoms and LT has been also proposed [13]. However, prolonged SARS-CoV-2 RNA shedding can have an impact on decisions to proceed and delay life-saving LT. Therefore, the absence of severe COVID-19 symptoms, in particular respiratory complications, might be a more important parameter in decision-making than RNA negativity per se. More evidence is required to form more specific guidance in that direction.

CONCLUSION

Since March 2020, the transplant community has been faced with unprecedented challenges derived from very limited resources and risk of transmission among patients and healthcare workers. The immediate response was suspension of activities that required face-to-face contact, conversion to technology-assisted remote consultations and suspension of transplant activity for most LT centers. Published evidence demonstrated that patients with CLD, especially those with more advanced stages of the disease, were at higher risk for severe COVID-19 and death. In person consultations and LT was reserved for selected patients when the risk associated with the underlying liver disease outweighed the risk associated with SARS-CoV-2 transmission/acquisition. In the course of the pandemic, SARS-CoV-2 testing, antiviral treatments and vaccines became available and changed outcomes and practices. Many LT centers resumed transplant activity, though at different paces. Increasing evidence did not show that LT recipients are at increased risk of severe COVID-19 or death, and immunosuppression not only does not increase the risk, but might be protective against

the immune-mediated sequelae of the virus. Our understanding of utilizing grafts from SARS-CoV-2 positive donors or transplanting SARS-CoV-2 positive recipients has increased dramatically and allowed a life-saving procedure to be performed for patients who might otherwise have died due to their liver disease. Preliminary data confirm the short-term safety of vaccines, but also showed a partial antibody response in LT recipients. There is no doubt that we need more data to be able to form evidence-based guidance in areas such as:

Optimal and appropriate use of novel telemedicine technologies

Balancing the risk from the underlying CLD and the rapidly spreading virus

Continuing transplant activity without compromising safety for patients and workforce

Utilizing grafts from infected donors to address shortage of grafts

Transplanting actively or recently infected recipients who might otherwise die

Managing immunosuppression in patients who acquire the infection

Safety of antiviral therapies in patients with CLD and transplant recipients

Schedule for vaccination and the need for booster doses

Long-term safety of vaccines.

The COVID-19 pandemic has provided lessons with regards to rapid remodelling of care in the context of a pandemic with a view to reducing the risk for vulnerable patient groups such as transplant candidates and recipients.

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