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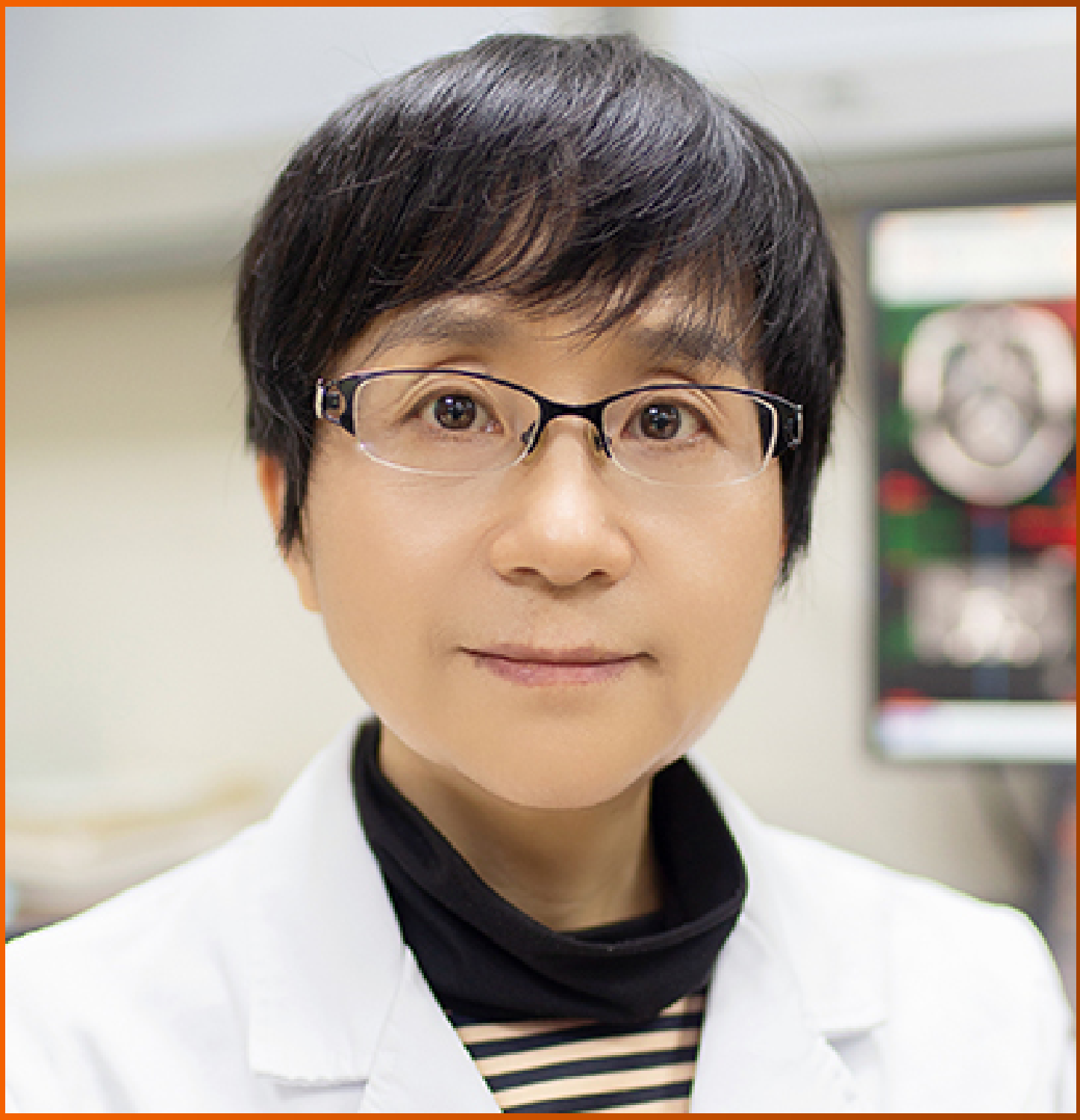

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MINIREVIEWS

Impact of the COVID-19 pandemic on liver donation and transplantation: A review of the literature

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Abstract

The coronavirus disease 2019 (COVID-19) pandemic has upended healthcare systems worldwide and led to an inevitable decrease in liver transplantation (LT) activity. During the first pandemic wave, administrators and clinicians were obliged to make the difficult decision of whether to suspend or continue a life-saving procedure based on the scarce available evidence regarding the risk of transmission and mortality in immunosuppressed patients. Those centers where the activity continued or was heavily restricted were obliged to screen donors and recipients, design COVID-safe clinical pathways, and promote telehealth to prevent nosocomial transmission. Despite the ever-growing literature on COVID-19, the amount of high-quality literature on LT remains limited. This review will provide an updated view of the impact of the pandemic on LT programs worldwide. Donor and recipient screening, strategies for waitlist prioritization, and posttransplant risk of infection and mortality are discussed. Moreover, a particular focus is given to the possibility of donor-to-recipient transmission and immunosuppression management in COVID-positive recipients.

Key Words: Severe acute respiratory syndrome coronavirus type 2; Liver cirrhosis; Donor and recipient screening; Donor-to-recipient transmission; Immunosuppression; Resource allocation in transplantation

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Core Tip: The coronavirus disease 2019 (COVID-19) pandemic has reduced liver transplantation (LT) activity worldwide at different rates in different regions. Testing for COVID-19 has been included in routine donor and recipient evaluations. LT recipients are likely at increased risk of infection, but COVID-related mortality appears to be comparable with the general population if corrected for concurrent risk factors. Immunosuppression could exert a protective effect against the most severe forms of COVID-19, and its complete withdrawal or reduction may not be useful. Transplant centers and administrators should allocate resources considering the actual burden of the infection, waitlist priority, risk of posttransplant infection, and mortality.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) has upended healthcare systems worldwide. During the first pandemic wave, overwhelming hospitals rapidly reallocated their resources and increased their capacity to attend to an exponential increase in the number of critically ill patients, leading to the limitation of oncological and elective surgery[1]. Organ donation and transplantation have also suffered an inevitable decrease[2,3]. The second pandemic wave in most European countries has posed similar issues regarding resource allocation, although most patients are asymptomatic or present with less severe symptomatology[4].

In the field of liver transplantation (LT), administrators and clinicians were forced to make difficult decisions regarding whether to suspend or continue a life-saving procedure during the pandemic. Therefore, the main ethical question was whether it was riskier to accept a patient for LT or to wait until the peak of the infection had decreased. The pandemic has also led to additional complexities regarding donor and recipient testing, obliged to design COVID-safe clinical pathways, and promoted telehealth to prevent nosocomial transmission.

An ever-growing number of papers on COVID-19 have been published since its initial outbreak, making it difficult to keep up with the most recent evidence on this topic. However, the amount of high-quality literature on LT remains limited, and particular care should be taken in drawing any conclusions[5]. Indeed, preliminary data during the first pandemic wave were often obtained in difficult conditions, and the race to publication has led, in some cases, to corrections and retractations[6,7]. Aware of these limitations, in this review, we aim to analyze the impact of the pandemic on LT programs worldwide, mainly focusing on donor and recipient screening, waitlist prioritization, and immunosuppression management in COVID-positive recipients.

TRENDS IN ORGAN DONATION AND TRANSPLANT ACTIVITY DURING THE PANDEMIC

The first pandemic wave between February and March 2020 led to a reduction in organ donation compared to the same period in 2019, varying between 0–30% in different countries (Table 1). For example, early data from Italy – one of the first Western countries dealing with the COVID-19 outbreak – reported a 25% decrease in procured organs during the first month of the outbreak, which paralleled the progressive rise of patients admitted to the intensive care unit (ICU)[8]. Particularly regarding LT, the United Network for Organ Sharing (UNOS) data revealed a more than 25% decrease between February and April 2020, with an inactivation rate of waitlisted patients between 5%-10%[3]. This trend is consistent with the 29% decrease registered in the Eurotransplant network in approximately the same period, which inevitably led to increased death and dropout from the waitlist[9]. Moreover, in most

Table 1 Reduction in LT activity around the world during the pandemic

Ref.	Country	Reduction in organ donations	Reduction in LT activity	Period
Putzer *et al*[9], 2020	Europe[1]	N/A	-29%	mid-March – mid-June, 2020 *vs* 2015 – 2019
Agopian *et al*[18], 2020	United States	N/A	-24%	February – March, 2020 *vs* 2019
Turco *et al*[19], 2020	France	-28%	-22%	January 1 – May 31, 2020 *vs* 2019
Domínguez-Gil *et al*[4], 2020	Spain	N/A	-75.8% LT/wk	March 13 – April 23 *vs* weekly mean 2019
Angelico *et al*[8], 2020	Italy	-30% (North)-9% (South)	-17%	February 24 – March 22, 2020 *vs* 2015-2019
Lee *et al*[20], 2020	South Korea	No difference	No difference	January – March, 2020 *vs* 2000-2019

[1]Eurotransplant data. N/A: Not applicable; LT: Liver transplantation.

countries, LT activity slowly recovered in the following months from this abrupt reduction due to a second pandemic wave[4,9].

Three different scenarios have been observed during the pandemic among centers in both Europe and the United States:

Complete shutdown of activity

This was a last-resort measure in situations where no ICU or healthcare personnel were available[10]. It was estimated that 6% of centers in Europe temporarily halted LT activity due to the lack of donors and logistical problems correlated to the first pandemic wave[2].

The limitation of transplant activity favors a "sickest-first" approach

LT activity continued even in some highly stressed hospitals without being stopped a priori, but evaluating each organ offer based on the resources available at the moment[11]. Two-thirds of centers in Europe have adopted the policy of selecting only urgent recipients[2]. However, this sickest-first approach poses the risk of prolonged hospital stays for such patients, thus conversely increasing the ICU length of stay[12]. For this reason, some centers have temporarily suspended treating aging patients with comorbidities and surgical complexities to minimize the chance of complications[10,13,14]. Likewise, different centers have reduced the use of marginal grafts and those from donation after circulatory death for both fear of poor transplant outcomes and heavier commitment on ICU personnel[3,15,16].

Continuation of routine transplant activity

Other centers in areas where COVID-19 prevalence was low – or the infection reached its peak slowly – have continued their activity at a routine or even increased rate compared to 2019, being able in some cases to shunt COVID-19 affected patients elsewhere[17-20].

Significant heterogeneity has been noted in the three aforementioned levels of activity across centers within the same country or even the same region. These differences were unrelated to the local prevalence of COVID-19 but more likely reflected a different perception of risk and prioritization of hospital resources[18,19,21]. In this context, a phased approach has been proposed to decrease transplant activity based on risk tolerance, hospital capacity, and degree of virus activity in different areas[10]. Nevertheless, it is essential to note that the decision of whether to continue LT activity was made in an emergent situation and based on the very limited evidence available at the moment on the risk of transmission and mortality in LT recipients[5]. These aspects will be analyzed in the following sections.

LIVING DONOR LIVER TRANSPLANTATION ACTIVITY DURING THE PANDEMIC

Living donor LT (LDLT) poses additional issues during the pandemic due to the risk of nosocomial transmission to donors as they recover from major surgery. Given the mainly elective nature of the procedure, most programs have considered postponing LDLT an ethically appropriate action during the pandemic peak[2,3]. In April 2020,

LDLT activity nearly stopped in Spain[4]. According to UNOS data, LDLT has been performed seldomly, comprising only 32 cases throughout April 2020[3]. However, some centers have continued this practice even in high COVID-19 prevalence regions by creating COVID minimal-exposure pathways and reported favorable outcomes[3,22,23]. Surprisingly, data from South Korea showed that LDLT – the main type of transplantation performed in this county – did not significantly decrease even during the peak of the epidemic, thanks to a strict screening and tracing policy based on the experience of the previous Middle Eastern Respiratory Syndrome Coronavirus (MERS-CoV) infection[20].

TRANSPLANT-RELATED TRANSMISSION AND UTILIZATION OF COVID-POSITIVE DONORS

Most scientific societies worldwide have strongly recommended nucleic acid testing for SARS-CoV-2 to be part of the routine evaluation of both donors and recipients (Table 2). Significant variability in the false-negative rate has been reported in testing for SARS-CoV-2 by nasopharyngeal swabs (NFSs)[3,24]. For this reason, the results should be interpreted alongside clinical history and chest computed tomography when available. Molecular testing on NFS is the recommended screening method for living donors in centers where LDLT has not been halted[24]. Conversely, bronchoalveolar lavage (BAL) should be preferred for deceased donor screening, as it has a very low false-negative rate[25]. However, it should be considered that BAL may not be logistically feasible and has the greatest sensitivity later in the course of the infection, whereas NPS has the greatest sensitivity during the early period[3,10]. Donor and recipient testing can significantly extend the timing and complicate the logistics of transplantation. In this context, many local medical centers are now beginning to obtain consistent access to rapid reverse transcription-polymerase chain reaction (RT-PCR) diagnostics[3,15]. Moreover, machine perfusion has been used to extend preservation times of the liver graft while awaiting SARS-CoV-2 test results to be available[26]. As no molecular test is perfectly sensitive or specific, an additional epidemiological and clinical screening (which includes travel to a high-risk area, contact with a confirmed case, or onset of symptoms) of each case has been suggested[24]. The organs of donors who are positive for the epidemiological and clinical screening are considered high risk and should not be used for transplantation.

There is no consensus on time and testing requirements before recovering organs from donors who had previously documented COVID-19 infection. Waiting periods after the resolution of symptoms vary between 14-28 d, and most groups specifically recommend repeating a single or two negative tests before proceeding to donation[10,27]. The use of liver grafts from donors testing positive for COVID-19 is widely considered unacceptable[4,10,24]. However, their use is hotly debated for super-urgent patients. Some authors have suggested that for selected patients with imminently life-threatening organ failure, transplants from deceased donors with asymptomatic or mild SARS-CoV-2 infection may offer a favorable risk-benefit balance[14,28,29]. The two main arguments in favor of this position were as follows:

There is little evidence that SARS-CoV-2 can directly infect the liver in initial reports

SARS-CoV-2 was initially thought to be less likely to infect the liver due to lower expression in the hepatocytes of angiotensin-converting enzyme 2 (ACE-2), the cell surface receptor for SARS-CoV-2. This was considered consistent with the limited initial autopsy studies, which failed to demonstrate SARS-CoV-2 in the liver[28,29].

There was no transmission after blood transfusions or transplantation in initial reports

To date, there have been no reports of recognized transmissions of SARS-CoV-2 following blood transfusion, even in immunosuppressed patients[28,30]. Moreover, Hong *et al* reported the case of a patient who underwent LDLT without knowing that the donor was infected with COVID-19 at the time of the procedure. Donor-derived transmission to the recipient was not identified, and retrospective RT-PCR for SARS-CoV-2 from the liver biopsy confirmed no evidence of viral infection in the liver[22].

Conversely, other authors advise against the use of livers from COVID-19-positive donors in any case[31]. In this context, the main arguments are as follows:

Table 2 Recommendations of international societies

	AASLD[58]	EASL[51]	APASL[32]
Donor screening	RT-PCR for SARS-CoV-2. Screen for exposure and clinical symptoms/fever compatible with COVID-19. Additionally, consider chest X-ray	RT-PCR for SARS-CoV-2	SARS-COV-2 RNA on NPS or BAL. Exclude any evidence of COVID-19 infection on chest CT scan
Recipient testing	Screen for exposure and clinical symptoms/fever compatible with COVID-19. RT-PCR for SARS-CoV-2	Evaluation of clinical history, chest radiology, and SARS-CoV-2 testing. Screening before admission	Assess recipients for COVID-19 infection, particularly in the presence of symptoms or contact with a known COVID-19 case
Liver allocation policy	High MELD scores. HCC based on their risk of drop-out and disease progression	Acute liver failure. ACLF. High MELD score. HCC at the upper limits of the Milan criteria	Acute liver failure. High MELD. High risk of HCC progression
Living donation	Consider suspending, except for pediatric patients with acute liver failure	Should be considered on a case-by-case basis	Not specified (avoid if evidence of COVID-19 infection)
Immunosuppression in COVID-19 positive recipients	Standard immunosuppression protocol. Reduction of immunosuppression may be considered in the setting of lymphopenia, fever, or worsening pulmonary status	Standard immunosuppression protocol. Reduction should only be considered under special circumstances	Standard immunosuppression protocol. Reduction of immunosuppression may be considered in patients diagnosed with moderate COVID-19 infection

AASLD: American Association for the Study of Liver Diseases; ACLF: Acute on chronic liver failure; APASL: Asian-Pacific Association for the Study of the Liver; BAL: Bronchoalveolar lavage; CT: Computerized tomography; EASL: European Association for the Study of the Liver; HCC: Hepatocellular carcinoma; MELD: Model for end stage liver disease; NAT: Nucleic acid test; RT-PCR: Reverse transcription-polymerase chain reaction; SARS-CoV-2: Severe acute respiratory syndrome coronavirus type 2; COVID-19: Coronavirus disease 2019.

More recent evidence indicates that SARS-CoV-2 can directly infect the liver

The expression of ACE-2 in cholangiocytes was found to be comparable to that in alveolar type 2 cells[32]. Wang *et al* recently demonstrated that SARS-CoV-2 can directly infect hepatocytes, most likely through alternative extra-ACE-2 receptors, causing conspicuous cytopathy[33]. Moreover, Lagana *et al*[34] reported a case of likely COVID-related hepatitis in a pediatric recipient whose living donor subsequently tested positive for COVID-19, although no RT-PCR for SARS-CoV-2 was performed on liver biopsy.

There is an unclear understanding of the risk associated with transmission

The impossibility of clearly defining the risk of transmission prevents the recipient from providing adequate informed consent. This is further accentuated by the absence of effective prophylaxis[31].

Exposure of healthcare workers during organ procurement is a concern

Staff members contracting the disease or in quarantine can result in the shutdown of a program for weeks. Organ recovery teams moving across centers and regions are exposed to the risk of transmission, and they must take appropriate respiratory and contact precautions throughout the procedure, even if the donor tested negative[15,20]. To reduce the exposure of recovery teams, many transplant centers have started relying on local teams and information sharing between centers *via* secure digital platforms[3].

Theoretically, the possibility exists to transplant these organs in patients who recovered from COVID-19 infection or received the vaccine, thus having developed a protective antibody titer[35]. Nevertheless, cases of reinfection with different SARS-CoV-2 clades have been documented, and this practice still entails healthcare workers' exposure[36].

RISK OF INFECTION AND COVID-ASSOCIATED MORTALITY AMONG LT RECIPIENTS

Qin *et al*[37] first reported the case of an LT recipient who experienced COVID-19 infection in the perioperative period and was discharged without sequelae after 56 days. Two reports from the same high-prevalence Italian region reported extremely low infection rates of 1.25% and 1.5% among 640 adult and 200 pediatric LT recipients, respectively[38,39]. The apparently lower risk of COVID-19 infection among LT recipients

compared to the general population could be explained partly by the higher degree of surveillance[38]. A survey from Germany has shown that during the pandemic, LT recipients used personnel protective equipment and practiced social distancing significantly more frequently than waitlist candidates[40]. Moreover, many transplant centers preferred suspending family visits during the posttransplant course and providing postdischarge follow-up care *via* telehealth[41]. However, the incidence of infection among LT recipients might also be underestimated due to the milder disease expression in these patients[38]. Therefore, short-term LT recipients seem to present fewer atypical symptoms, frequently of the gastrointestinal type, most likely because higher immunosuppression attenuates typical COVID-19 presentation[42,43]. In fact, a nationwide experience in Spain revealed that LT patients had almost double the incidence rates of COVID-19 compared with the age- and gender-matched general population[44].

Rabiee *et al*[45] recently reported a liver injury rate of 34.6% among COVID-19-positive LT recipients, which was higher than that of the general population but lower than that of nontransplant patients with chronic liver disease. Likewise, mortality among LT recipients testing positive for COVID-19 varies between 0%-23% in most studies (Table 3) and seems higher than that in the general population but lower than that in cirrhotic patients, where it was estimated to be between 34%-40%[15,41,46]. Male sex, advanced age, and metabolic comorbidities, which are known to increase COVID-19 severity, are more frequent among LT recipients than among the general population and could account for this difference[2,47]. However, risk factors that may increase mortality among LT recipients are not completely clear. Preliminary data from Italy and the European Liver Transplant Registry (ELTR) suggested that mortality could be higher among recipients with a longer time since transplantation, which was not confirmed by the analysis of the COVID-hep and SECURE-Cirrhosis registries[42,48,49]. It seems, however, that biological age and comorbidities rather than time from transplantation are most strongly correlated with death[42]. Different studies have confirmed the association between age and mortality among LT recipients with COVID-19[42,50]. Bhoori *et al*[49] first reported increased mortality among LTs who tested positive for COVID-19 with metabolic-related comorbidities, such as hypertension, chronic kidney disease, and diabetes. While the analysis of the COVID-hep and SECURE-Cirrhosis registries confirmed this finding, Becchetti *et al*[43] found no correlation between comorbidities and mortality in their series.

IMMUNOSUPPRESSION MANAGEMENT DURING THE PANDEMIC

Clinicians should be aware of the high reported rates of fear and anxiety regarding COVID-19 in LT recipients and the consequent risk of scarce compliance with immunosuppressive medication[40,51]. The immunocompromised status seemed not to affect mortality during previous coronavirus-related infections, such as SARS-CoV in 2003 and MERS-CoV in 2015[39]. Moreover, the pathogenesis of severe COVID-19 was found to be mainly explained by the immune-mediated inflammatory reaction rather than direct cellular damage[52]. Thus, immunosuppression could theoretically have a protective role in LT patients[49,53].

There is limited guidance related to immunosuppression management during the pandemic. Societies advise against the reduction of maintenance immunosuppressive therapy to prevent SARS-CoV-2 infection. Some authors have initially suggested a reduction in the use of lymphocyte depletion therapy for induction immunosuppression during the pandemic to reduce the risk of nosocomial infection[5,51].

The management of immunosuppression in LT recipients testing positive for COVID-19 is currently under debate. In the aforementioned report by Qin *et al*[37], tacrolimus and steroids were gradually titrated and then increased due to the suspicion of acute rejection. The retrospective analysis of different series during the first pandemic wave showed that immunosuppression was modified in nearly half of the cases, most frequently among patients with moderate and severe COVID-19, but rarely discontinued. Frequently reported changes were mycophenolate withdrawal, steroid dosing increase, and calcineurin inhibitor reduction[2,54,55]. However, the target trough levels of the immunosuppressants were rarely reported in these studies[56].

An analysis of data from the COVID-Hep and SECURE-Cirrhosis registries has shown that the immunosuppressive regimen used had no impact on the outcome of COVID-19[42]. Moreover, Becchetti *et al*[43] reported no impact on the disease course whether immunosuppression was decreased or left unchanged. Therefore, most transplant societies have recommended the continuation of immunosuppression at

Table 3 Mortality, hospitalization, intensive care unit admission, and risk factors among liver transplantation recipients

Ref.	Registry	*n*	Mortality (%)	Hospital admission (%)	ICU admission (%)[1]	Major correlations with mortality
Polak *et al*[2], 2020	ELTR	272	15	N/A	14	sexage
Rabiee *et al*[45], 2020	COLD	112	22.3	72.3	26.8	N/A
Colmenero *et al*[44], 2020	SETH	111	18	86.5	10.8	Charlson comorbidity index; Male sex; Dyspnea at diagnosis; Immunosuppression with mycophenolate
Bhoori *et al*[49], 2020	–	111 (long term); 40 (short term)	30	N/A	N/A	N/A
Belli *et al*[48], 2020	ELTR/ELITA	103	16	66	15	N/A
Becchetti *et al*[43], 2020	–	57	12	72	7	N/A
Webb *et al*[42], 2020	COVID-hep and SECURE-cirrhosis	39	23	N/A	N/A	N/A
Patrono *et al*[41], 2020	–	10	10	N/A	N/A	N/A

[1]Calculated as proportion of the total cohort. N/A: Not applicable; COLD: Consortium of investigators to study COVID-19 in chronic liver disease; ELITA: European Liver and Intestine Transplantation Association; ELTR: European Liver Transplant Registry; SETH: Spanish Society of Liver Transplantation; COVID: Coronavirus disease.

stable doses for asymptomatic or mildly symptomatic patients[45,55].

A Spanish nationwide prospective study recently showed that mycophenolate was an independent predictor of severe COVID-19, particularly at doses higher than 1000 mg/d, and complete withdrawal of mycophenolate at COVID-19 diagnosis ameliorated the risk of severe COVID-19[44]. This datum was, however, not confirmed in another study[42].

Belli *et al*[50] showed that the use of tacrolimus was independently associated with reduced mortality among LT recipients testing positive for SARS-CoV-2. The biological explanation of this effect is still unknown but may be due to the inhibition of viral replication and interaction with the inflammatory cascade triggered by the infection. Based on this background, a Spanish randomized clinical trial has been started to test the effect of tacrolimus plus steroids in the management of COVID-19 occurring in immunocompetent patients (ClinicalTrials.gov Identifier: NCT04341038).

RISK ASSESSMENT AND DECISION-MAKING

In light of the aforementioned data on transmission and mortality among LT patients, some authors have attempted a quantitative approach to the question of whether to continue transplant activity during the pandemic. Chew *et al*[16] proposed a score to guide the regulation of LT activity despite the competing needs of the pandemic through the 3 aforementioned scenarios based on 4 main ethical instances: waiting list mortality, donor and graft safety, recipient outcome, and healthcare resources available. Likewise, in the field of kidney transplantation, a machine learning algorithm has recently been developed to quantify the benefit-to-harm ratio of immediate transplant *vs* delay until after the pandemic[57]. COVID-19, like other pandemics, tends to come in several waves over a protracted period until hopefully subsiding through vaccination and herd immunity. These quantitative tools are potentially helpful in decision-making during pandemic peaks but still need to be fully validated. During the interpeak phases, every effort should be made to restore LT activity to regular rates and indications to prevent accumulated death and dropout from the waitlist over the long term.

CONCLUSION

The COVID-19 pandemic has heavily affected health care systems worldwide and, despite some exceptions, has generally led to a reduction in LT activity, with different rates in different countries. Donor and recipient molecular screening for SARS-CoV-2 has become a routine practice in LT to prevent infection in the peritransplant period, although the possibility of using positive donors in super-urgent patients is currently debated. LT recipients seem to have an increased risk of being infected with SARS-CoV-2 but a milder and frequently atypical presentation. Mortality, in particular, seems comparable with the general population if corrected for concurrent risk factors. Immunosuppression could exert a protective effect against the most severe forms of COVID-19, and complete withdrawal or significant reduction in immunosuppression may not be useful, thus increasing the risk of acute rejection. The decision of whether to continue or suspend LT activity during the pandemic should be based on the actual strain on the healthcare system, waitlist priority, risk of posttransplant infection, and mortality.

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