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

De Carlis R *et al*. COVID-19 and liver transplantation

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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.

**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 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:

***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 ofthe 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 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.

**REFERENCES**

1 **Turaga KK**, Girotra S. Are We Harming Cancer Patients by Delaying Their Cancer Surgery During the COVID-19 Pandemic? *Ann Surg* 2020 epub ahead of print [PMID: 32487802 DOI: 10.1097/SLA.0000000000003967]

2 **Polak WG**, Fondevila C, Karam V, Adam R, Baumann U, Germani G, Nadalin S, Taimr P, Toso C, Troisi RI, Zieniewicz K, Belli LS, Duvoux C. Impact of COVID-19 on liver transplantation in Europe: alert from an early survey of European Liver and Intestine Transplantation Association and European Liver Transplant Registry. *Transpl Int* 2020; **33**: 1244-1252 [PMID: 32609908 DOI: 10.1111/tri.13680]

3 **Merola J**, Schilsky ML, Mulligan DC. The Impact of COVID-19 on Organ Donation, Procurement and Liver Transplantation in the United States. *Hepatol Commun* 2020; **5**: 5-11 [PMID: 33043228 DOI: 10.1002/hep4.1620]

4 **Domínguez-Gil B**, Fernández-Ruiz M, Hernández D, Crespo M, Colmenero J, Coll E, Rubio JJ. Organ Donation and Transplantation During the COVID-19 Pandemic: A Summary of the Spanish Experience. *Transplantation* 2021; **105**: 29-36 [PMID: 33165237 DOI: 10.1097/TP.0000000000003528]

5 **Weiss MJ**, Lalani J, Patriquin-Stoner C, Dieudé M, Hartell D, Hornby L, Shemie SD, Wilson L, Mah A. Summary of International Recommendations for Donation and Transplantation Programs During the Coronavirus Disease Pandemic. *Transplantation* 2021; **105**: 14-17 [PMID: 33141806 DOI: 10.1097/TP.0000000000003520]

6 **Soltani P**, Patini R. Retracted COVID-19 articles: a side-effect of the hot race to publication. *Scientometrics* 2020; 1-4 [PMID: 32836531 DOI: 10.1007/s11192-020-03661-9]

7 **Polak WG**, Fondevila C, Karam V, Adam R, Belli LS, Duvoux C; for European Liver, Intestine Transplant Association (ELITA), the COVID-19 ELITA Study Group. Reply to Rodriguez-Peralvarez et al. *Transpl Int* 2020 epub ahead of print [PMID: 33037657 DOI: 10.1111/tri.13765]

8 **Angelico R**, Trapani S, Manzia TM, Lombardini L, Tisone G, Cardillo M. The COVID-19 outbreak in Italy: Initial implications for organ transplantation programs. *Am J Transplant* 2020; **20**: 1780-1784 [PMID: 32243677 DOI: 10.1111/ajt.15904]

9 **Putzer G**, Martini J, Gasteiger L, Mathis S, Breitkopf R, Hell T, van Enckevort A, Oberhuber R, Öfner D, Schneeberger S. Liver Transplantation Activity in the Eurotransplant Area Is Recovering Slowly During the COVID-19 Crisis. *Transplant Direct* 2020; **6**: e611 [PMID: 33134487 DOI: 10.1097/TXD.0000000000001064]

10 **Kumar D**, Manuel O, Natori Y, Egawa H, Grossi P, Han SH, Fernández-Ruiz M, Humar A. COVID-19: A global transplant perspective on successfully navigating a pandemic. *Am J Transplant* 2020; **20**: 1773-1779 [PMID: 32202064 DOI: 10.1111/ajt.15876]

11 **Lauterio A**, De Carlis R, Belli L, Fumagalli R, De Carlis L. How to guarantee liver transplantation in the north of Italy during the COVID-19 pandemic: A sound transplant protection strategy. *Transpl Int* 2020; **33**: 969-970 [PMID: 32348586 DOI: 10.1111/tri.13633]

12 **Stratigopoulou P**, Paul A, Hoyer DP, Kykalos S, Saner FH, Sotiropoulos GC. High MELD score and extended operating time predict prolonged initial ICU stay after liver transplantation and influence the outcome. *PLoS One* 2017; **12**: e0174173 [PMID: 28319169 DOI: 10.1371/journal.pone.0174173]

13 **Boyarsky BJ**, Po-Yu Chiang T, Werbel WA, Durand CM, Avery RK, Getsin SN, Jackson KR, Kernodle AB, Van Pilsum Rasmussen SE, Massie AB, Segev DL, Garonzik-Wang JM. Early impact of COVID-19 on transplant center practices and policies in the United States. *Am J Transplant* 2020; **20**: 1809-1818 [PMID: 32282982 DOI: 10.1111/ajt.15915]

14 **Mazzola A**, Kerbaul F, Atif M, Monsel A, Malaquin G, Pourcher V, Scatton O, Conti F. The impact of Coronavirus 19 disease on liver transplantation in France: The sickest first approach? *Clin Res Hepatol Gastroenterol* 2020; **44**: e81-e83 [PMID: 32646848 DOI: 10.1016/j.clinre.2020.06.007]

15 **Niriella MA**, Siriwardana RC, Perera MTPR, Narasimhan G, Chan SC, Dassanayake AS. Challenges for Liver Transplantation During Recovery From the COVID-19 Pandemic: Insights and Recommendations. *Transplant Proc* 2020; **52**: 2601-2606 [PMID: 32586665 DOI: 10.1016/j.transproceed.2020.05.032]

16 **Chew CA**, Iyer SG, Kow AWC, Madhavan K, Wong AST, Halazun KJ, Battula N, Scalera I, Angelico R, Farid S, Buchholz BM, Rotellar F, Chan AC, Kim JM, Wang CC, Pitchaimuthu M, Reddy MS, Soin AS, Derosas C, Imventarza O, Isaac J, Muiesan P, Mirza DF, Bonney GK. An international multicenter study of protocols for liver transplantation during a pandemic: A case for quadripartite equipoise. *J Hepatol* 2020; **73**: 873-881 [PMID: 32454041 DOI: 10.1016/j.jhep.2020.05.023]

17 **Saracco M**, Martini S, Tandoi F, Dell'Olio D, Ottobrelli A, Scarmozzino A, Amoroso A, Fonio P, Balagna R, Romagnoli R. Carrying on with liver transplantation during the COVID-19 emergency: Report from piedmont region. *Clin Res Hepatol Gastroenterol* 2020; 101512 [PMID: 32859555 DOI: 10.1016/j.clinre.2020.07.017]

18 **Agopian V**, Verna E, Goldberg D. Changes in Liver Transplant Center Practice in Response to Coronavirus Disease 2019: Unmasking Dramatic Center-Level Variability. *Liver Transpl* 2020; **26**: 1052-1055 [PMID: 32369251 DOI: 10.1002/lt.25789]

19 **Turco C**, Lim C, Soubrane O, Malaquin G, Kerbaul F, Bastien O, Conti F, Scatton O. Impact of the first Covid-19 outbreak on liver transplantation activity in France: A snapshot. *Clin Res Hepatol Gastroenterol* 2020; 101560 [PMID: 33176991 DOI: 10.1016/j.clinre.2020.10.005]

20 **Lee JM**. Effect of COVID-19 on liver transplantation in Korea. *Transpl Infect Dis* 2020; **22**: e13384 [PMID: 32574408 DOI: 10.1111/tid.13384]

21 **Loupy A**, Aubert O, Reese PP, Bastien O, Bayer F, Jacquelinet C. Organ procurement and transplantation during the COVID-19 pandemic. *Lancet* 2020; **395**: e95-e96 [PMID: 32407668 DOI: 10.1016/S0140-6736(20)31040-0]

22 **Hong HL**, Kim SH, Choi DL, Kwon HH. A case of coronavirus disease 2019-infected liver transplant donor. *Am J Transplant* 2020; **20**: 2938-2941 [PMID: 32400013 DOI: 10.1111/ajt.15997]

23 **Dhampalwar S**, Saigal S, Choudhary N, Saraf N, Bhangui P, Rastogi A, Thiagrajan S, Soin AS. Outcomes of Coronavirus Disease 2019 in Living Donor Liver Transplant Recipients. *Liver Transpl* 2020; **26**: 1665-1666 [PMID: 33021025 DOI: 10.1002/lt.25909]

24 **Di Maira T**, Berenguer M. COVID-19 and liver transplantation. *Nat Rev Gastroenterol Hepatol* 2020; **17**: 526-528 [PMID: 32651555 DOI: 10.1038/s41575-020-0347-z]

25 **Wang W**, Xu Y, Gao R, Lu R, Han K, Wu G, Tan W. Detection of SARS-CoV-2 in Different Types of Clinical Specimens. *JAMA* 2020; **323**: 1843-1844 [PMID: 32159775 DOI: 10.1001/jama.2020.3786]

26 **Bogensperger C**, Cardini B, Oberhuber R, Weissenbacher A, Gasteiger S, Berchtold V, Otarashvili G, Öfner D, Schneeberger S. Dealing With Liver Transplantation during Coronavirus Disease 2019 Pandemic: Normothermic Machine Perfusion Enables for Donor, Organ, and Recipient Assessment: A Case Report. *Transplant Proc* 2020; **52**: 2707-2710 [PMID: 32800515 DOI: 10.1016/j.transproceed.2020.07.011]

27 **Nasralla D**, Coussios CC, Mergental H, Akhtar MZ, Butler AJ, Ceresa CDL, Chiocchia V, Dutton SJ, García-Valdecasas JC, Heaton N, Imber C, Jassem W, Jochmans I, Karani J, Knight SR, Kocabayoglu P, Malagò M, Mirza D, Morris PJ, Pallan A, Paul A, Pavel M, Perera MTPR, Pirenne J, Ravikumar R, Russell L, Upponi S, Watson CJE, Weissenbacher A, Ploeg RJ, Friend PJ; Consortium for Organ Preservation in Europe. A randomized trial of normothermic preservation in liver transplantation. *Nature* 2018; **557**: 50-56 [PMID: 29670285 DOI: 10.1038/s41586-018-0047-9]

28 **Kates OS**, Fisher CE, Rakita RM, Reyes JD, Limaye AP. Emerging evidence to support not always "just saying no" to SARS-CoV-2 positive donors. *Am J Transplant* 2020; **20**: 3261-3262 [PMID: 32502313 DOI: 10.1111/ajt.16119]

29 **Kates OS**, Fisher CE, Rakita RM, Reyes JD, Limaye AP. Use of SARS-CoV-2-infected deceased organ donors: Should we always "just say no?" *Am J Transplant* 2020; **20**: 1787-1794 [PMID: 32400087 DOI: 10.1111/ajt.16000]

30 **Cho HJ**, Koo JW, Roh SK, Kim YK, Suh JS, Moon JH, Sohn SK, Baek DW. COVID-19 transmission and blood transfusion: A case report. *J Infect Public Health* 2020; **13**: 1678-1679 [PMID: 32405329 DOI: 10.1016/j.jiph.2020.05.001]

31 **Shah MB**, Lynch RJ, El-Haddad H, Doby B, Brockmeier D, Goldberg DS. Utilization of deceased donors during a pandemic: argument against using SARS-CoV-2-positive donors. *Am J Transplant* 2020; **20**: 1795-1799 [PMID: 32368850 DOI: 10.1111/ajt.15969]

32 **APASL Covid-19 Task Force.**, Lau G, Sharma M. Clinical practice guidance for hepatology and liver transplant providers during the COVID-19 pandemic: APASL expert panel consensus recommendations. *Hepatol Int* 2020; **14**: 415-428 [PMID: 32447721 DOI: 10.1007/s12072-020-10054-w]

33 **Wang Y**, Liu S, Liu H, Li W, Lin F, Jiang L, Li X, Xu P, Zhang L, Zhao L, Cao Y, Kang J, Yang J, Li L, Liu X, Li Y, Nie R, Mu J, Lu F, Zhao S, Lu J, Zhao J. SARS-CoV-2 infection of the liver directly contributes to hepatic impairment in patients with COVID-19. *J Hepatol* 2020; **73**: 807-816 [PMID: 32437830 DOI: 10.1016/j.jhep.2020.05.002]

34 **Lagana SM**, De Michele S, Lee MJ, Emond JC, Griesemer AD, Tulin-Silver SA, Verna EC, Martinez M, Lefkowitch JH. COVID-19 Associated Hepatitis Complicating Recent Living Donor Liver Transplantation. *Arch Pathol Lab Med* 2020 epub ahead of print [PMID: 32302212 DOI: 10.5858/arpa.2020-0186-SA]

35 **Italian Ministry of Health - National Transplant Center.** Dispositions on the utilization of organs from COVID-positive deceased donors. [cited Dec 31, 2020]. [Internet]. Available from: http://www.trapianti.salute.gov.it/imgs/C\_17\_cntAvvisi\_299\_0\_file.pdf

36 **Selhorst P**, Van Ierssel S, Michiels J, Mariën J, Bartholomeeusen K, Dirinck E, Vandamme S, Jansens H, Ariën KK. Symptomatic SARS-CoV-2 reinfection of a health care worker in a Belgian nosocomial outbreak despite primary neutralizing antibody response. *Clin Infect Dis* 2020; ciaa1850 [PMID: 33315049 DOI: https://doi.org/10.1093/cid/ciaa1850]

37 **Qin J**, Wang H, Qin X, Zhang P, Zhu L, Cai J, Yuan Y, Li H. Perioperative Presentation of COVID-19 Disease in a Liver Transplant Recipient. *Hepatology* 2020; **72**: 1491-1493 [PMID: 32220017 DOI: 10.1002/hep.31257]

38 **Donato MF**, Invernizzi F, Lampertico P, Rossi G. Health Status of Patients Who Underwent Liver Transplantation During the Coronavirus Outbreak at a Large Center in Milan, Italy. *Clin Gastroenterol Hepatol* 2020; **18**: 2131-2133.e1 [PMID: 32334081 DOI: 10.1016/j.cgh.2020.04.041]

39 **D'Antiga L**. Coronaviruses and Immunosuppressed Patients: The Facts During the Third Epidemic. *Liver Transpl* 2020; **26**: 832-834 [PMID: 32196933 DOI: 10.1002/lt.25756]

40 **Reuken PA**, Rauchfuss F, Albers S, Settmacher U, Trautwein C, Bruns T, Stallmach A. Between fear and courage: Attitudes, beliefs, and behavior of liver transplantation recipients and waiting list candidates during the COVID-19 pandemic. *Am J Transplant* 2020; **20**: 3042-3050 [PMID: 32515125 DOI: 10.1111/ajt.16118]

41 **Patrono D**, Lupo F, Canta F, Mazza E, Mirabella S, Corcione S, Tandoi F, De Rosa FG, Romagnoli R. Outcome of COVID-19 in liver transplant recipients: A preliminary report from Northwestern Italy. *Transpl Infect Dis* 2020; **22**: e13353 [PMID: 32500942 DOI: 10.1111/tid.13353]

42 **Webb GJ**, Marjot T, Cook JA, Aloman C, Armstrong MJ, Brenner EJ, Catana MA, Cargill T, Dhanasekaran R, García-Juárez I, Hagström H, Kennedy JM, Marshall A, Masson S, Mercer CJ, Perumalswami PV, Ruiz I, Thaker S, Ufere NN, Barnes E, Barritt AS 4th, Moon AM. Outcomes following SARS-CoV-2 infection in liver transplant recipients: an international registry study. *Lancet Gastroenterol Hepatol* 2020; **5**: 1008-1016 [PMID: 32866433 DOI: 10.1016/S2468-1253(20)30271-5]

43 **Becchetti C**, Zambelli MF, Pasulo L, Donato MF, Invernizzi F, Detry O, Dahlqvist G, Ciccarelli O, Morelli MC, Fraga M, Svegliati-Baroni G, van Vlierberghe H, Coenraad MJ, Romero MC, de Gottardi A, Toniutto P, Del Prete L, Abbati C, Samuel D, Pirenne J, Nevens F, Dufour JF; COVID-LT group. COVID-19 in an international European liver transplant recipient cohort. *Gut* 2020; **69**: 1832-1840 [PMID: 32571972 DOI: 10.1136/gutjnl-2020-321923]

44 **Colmenero J**, Rodríguez-Perálvarez M, Salcedo M, Arias-Milla A, Muñoz-Serrano A, Graus J, Nuño J, Gastaca M, Bustamante-Schneider J, Cachero A, Lladó L, Caballero A, Fernández-Yunquera A, Loinaz C, Fernández I, Fondevila C, Navasa M, Iñarrairaegui M, Castells L, Pascual S, Ramírez P, Vinaixa C, González-Dieguez ML, González-Grande R, Hierro L, Nogueras F, Otero A, Álamo JM, Blanco-Fernández G, Fábrega E, García-Pajares F, Montero JL, Tomé S, De la Rosa G, Pons JA. Epidemiological pattern, incidence, and outcomes of COVID-19 in liver transplant patients. *J Hepatol* 2021; **74**: 148-155 [PMID: 32750442 DOI: 10.1016/j.jhep.2020.07.040]

45 **Rabiee A**, Sadowski B, Adeniji N, Perumalswami PV, Nguyen V, Moghe A, Latt NL, Kumar S, Aloman C, Catana AM, Bloom PP, Chavin KD, Carr RM, Dunn W, Chen VL, Aby ES, Debes JD, Dhanasekaran R; COLD Consortium. Liver Injury in Liver Transplant Recipients With Coronavirus Disease 2019 (COVID-19): U.S. Multicenter Experience. *Hepatology* 2020 epub ahead of print [PMID: 32964510 DOI: 10.1002/hep.31574]

46 **Iavarone M**, D'Ambrosio R, Soria A, Triolo M, Pugliese N, Del Poggio P, Perricone G, Massironi S, Spinetti A, Buscarini E, Viganò M, Carriero C, Fagiuoli S, Aghemo A, Belli LS, Lucà M, Pedaci M, Rimondi A, Rumi MG, Invernizzi P, Bonfanti P, Lampertico P. High rates of 30-day mortality in patients with cirrhosis and COVID-19. *J Hepatol* 2020; **73**: 1063-1071 [PMID: 32526252 DOI: 10.1016/j.jhep.2020.06.001]

47 **Rinaldi M**, Bartoletti M, Bussini L, Pancaldi L, Pascale R, Comai G, Morelli M, Ravaioli M, Cescon M, Cristini F, Viale P, Giannella M. COVID-19 in solid organ transplant recipients: No difference in survival compared to general population. *Transpl Infect Dis* 2020; e13421 [PMID: 32779808 DOI: 10.1111/tid.13421]

48 **Belli LS**, Duvoux C, Karam V, Adam R, Cuervas-Mons V, Pasulo L, Loinaz C, Invernizzi F, Patrono D, Bhoori S, Ciccarelli O, Morelli MC, Castells L, Lopez-Lopez V, Conti S, Fondevila C, Polak W. COVID-19 in liver transplant recipients: preliminary data from the ELITA/ELTR registry. *Lancet Gastroenterol Hepatol* 2020; **5**: 724-725 [PMID: 32505228 DOI: 10.1016/S2468-1253(20)30183-7]

49 **Bhoori S**, Rossi RE, Citterio D, Mazzaferro V. COVID-19 in long-term liver transplant patients: preliminary experience from an Italian transplant centre in Lombardy. *Lancet Gastroenterol Hepatol* 2020; **5**: 532-533 [PMID: 32278366 DOI: 10.1016/S2468-1253(20)30116-3]

50 **Belli LS**, Fondevila C, Cortesi PA, Conti S, Karam V, Adam R, Coilly A, Ericzon BG, Loinaz C, Cuervas-Mons V, Zambelli M, Llado L, Diaz F, Invernizzi F, Patrono D, Faitot F, Bhooori S, Pirenne J, Perricone G, Magini G, Castells L, Detry O, Cruchaga PM, Colmenero J, Berrevoet F, Rodriguez G, Ysebaert D, Radenne S, Metselaar H, Morelli C, De Carlis L, Polak WG, Duvoux C; ELITA-ELTR COVID-19 Registry. Protective role of tacrolimus, deleterious role of age and comorbidities in liver transplant recipients with Covid-19: results from the ELITA/ELTR multi-center European study. *Gastroenterology* 2020 epub ahead of print [PMID: 33307029 DOI: 10.1053/j.gastro.2020.11.045]

51 **Boettler T**, Marjot T, Newsome PN, Mondelli MU, Maticic M, Cordero E, Jalan R, Moreau R, Cornberg M, Berg T. Impact of COVID-19 on the care of patients with liver disease: EASL-ESCMID position paper after 6 months of the pandemic. *JHEP Rep* 2020; **2**: 100169 [PMID: 32835190 DOI: 10.1016/j.jhepr.2020.100169]

52 **Ciceri F**, Beretta L, Scandroglio AM, Colombo S, Landoni G, Ruggeri A, Peccatori J, D'Angelo A, De Cobelli F, Rovere-Querini P, Tresoldi M, Dagna L, Zangrillo A. Microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome (MicroCLOTS): an atypical acute respiratory distress syndrome working hypothesis. *Crit Care Resusc* 2020; **22**: 95-97 [PMID: 32294809]

53 **Buscemi V**, De Carlis R, Lauterio A, Merli M, Puoti M, De Carlis L. Does interval time between liver transplant and COVID-19 infection make the difference? *Dig Liver Dis* 2021; **53**: 169-170 [PMID: 32921600 DOI: 10.1016/j.dld.2020.08.027]

54 **Merli M**, Pasulo L, Perricone G, Travi G, Rossotti R, Colombo VG, De Carlis R, Chiappetta S, Moioli MC, Minetti E, Frigerio M, De Carlis LG, Belli L, Fagiuoli S, Puoti M. Impact of immunosuppressive therapy on the severity of COVID-19 in solid organ transplant recipients. *J Infect* 2020 epub ahead of print [PMID: 33127455 DOI: 10.1016/j.jinf.2020.10.024]

55 **Rodriguez-Peralvarez M**, Salcedo M, Colmenero J, Pons JA. Modulating immunosuppression in liver transplant patients with COVID-19. *Gut* 2020 epub ahead of print [PMID: 32816964 DOI: 10.1136/gutjnl-2020-322620]

56 **Reiberger T**, Mandorfer M. Letter to the Editor: Perioperative Presentation of COVID-19 in a Liver Transplant Recipient. *Hepatology* 2021; **73**: 868-869 [PMID: 32654313 DOI: 10.1002/hep.31458]

57 **Massie AB**, Boyarsky BJ, Werbel WA, Bae S, Chow EKH, Avery RK, Durand CM, Desai N, Brennan D, Garonzik-Wang JM, Segev DL. Identifying scenarios of benefit or harm from kidney transplantation during the COVID-19 pandemic: A stochastic simulation and machine learning study. *Am J Transplant* 2020; **20**: 2997-3007 [PMID: 32515544 DOI: 10.1111/ajt.16117]

58 **Fix OK**, Hameed B, Fontana RJ, Kwok RM, McGuire BM, Mulligan DC, Pratt DS, Russo MW, Schilsky ML, Verna EC, Loomba R, Cohen DE, Bezerra JA, Reddy KR, Chung RT. Clinical Best Practice Advice for Hepatology and Liver Transplant Providers During the COVID-19 Pandemic: AASLD Expert Panel Consensus Statement. *Hepatology* 2020; **72**: 287-304 [PMID: 32298473 DOI: 10.1002/hep.31281]

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**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 | Europe1 | 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 |

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

**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 failureACLFHigh MELD scoreHCC 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.

**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 | * sex
* age
 |
| 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 |

1Calculated 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.