

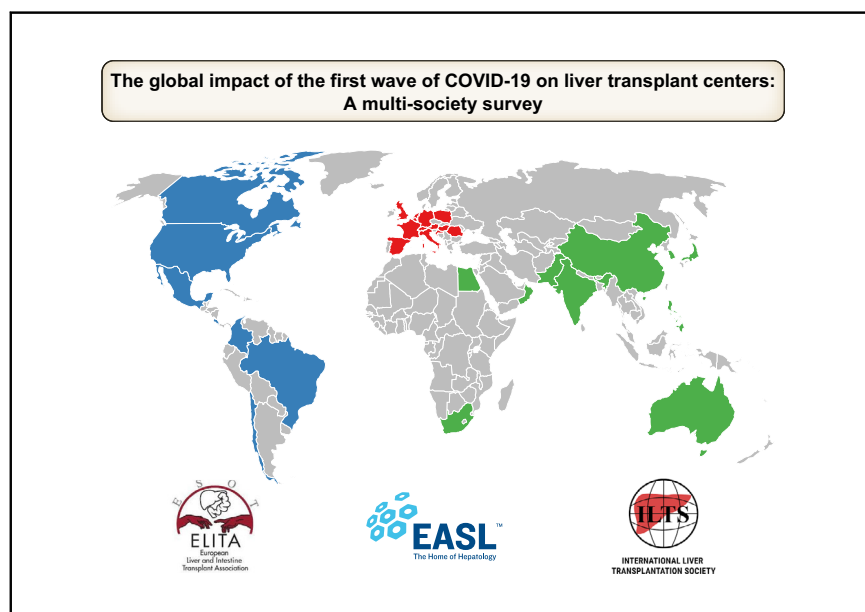


Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

# Global impact of the first wave of COVID-19 on liver transplant centers: A multi-society survey (EASL-ESOT/ELITA-ILTS)

## Graphical abstract



## Highlights

- An international multi-society taskforce evaluated the real impact of the first wave of SARS-CoV-2 on liver transplantation.
- The pandemic detrimentally impacted transplant operations in heavily hit countries.
- Transplant centers' resilience led to efficient accommodations in clinical practice.
- These observations may guide how we handle future emergencies of this magnitude.

## Authors

Francesco Paolo Russo, Manhal Izzy, Ashwin Rammohan, ..., Thomas Berg, Marina Carmen Berenguer, Wojciech Grzegorz Polak

## Correspondence

[francescopaolo.russo@unipd.it](mailto:francescopaolo.russo@unipd.it)  
(F.P. Russo).

## Lay summary

The health emergency caused by the coronavirus pandemic has dramatically changed clinical practice during the pandemic. The first wave of the pandemic impacted liver transplantation differently across the world, with particularly detrimental effects on the countries badly hit by the virus. The resilience of the entire transplant network has enabled continued organ donation and transplantation, ultimately improving the lives of patients with end-stage liver disease.



# Global impact of the first wave of COVID-19 on liver transplant centers: A multi-society survey (EASL-ESOT/ELITA-ILTS)

Francesco Paolo Russo<sup>1,\*†</sup>, Manhal Izzy<sup>2,†</sup>, Ashwin Rammohan<sup>3,†</sup>, Varvara A. Kirchner<sup>4,†</sup>,  
Tommaso Di Maira<sup>5,6,7,†</sup>, Luca Saverio Belli<sup>8,†</sup>, Thomas Berg<sup>9,†</sup>, Marina Carmen Berenguer<sup>5,6,7,†</sup>,  
Wojciech Grzegorz Polak<sup>10,†</sup>

<sup>1</sup>Department of Surgery, Oncology and Gastroenterology, University Hospital Padua, Padua Italy; <sup>2</sup>Department of Medicine, Division of Gastroenterology, Hepatology, and Nutrition, Vanderbilt University Medical Center, USA; <sup>3</sup>The Institute of Liver Disease & Transplantation, Dr. Rela Institute & Medical Centre, Bharath Institute of Higher Education and Research, Chennai, Tamil Nadu, India; <sup>4</sup>Department of Surgery, University of Minnesota School of Medicine, Minneapolis, Minnesota, USA; <sup>5</sup>Liver Transplantation and Hepatology Unit, Hospital Universitari I Politècnic La Fe, Valencia, Spain; <sup>6</sup>CIBERehd, Instituto de Salud Carlos III, Madrid, Spain; <sup>7</sup>ISS La Fe, Valencia, Spain; <sup>8</sup>Department of Hepatology and Gastroenterology, Niguarda Hospital, Milan, Italy; <sup>9</sup>Division of Hepatology, Department of Medicine II, Leipzig University, Medical Center, 04103 Leipzig, Germany; <sup>10</sup>Department of Surgery, Division of HPB and Transplant Surgery, Erasmus MC Transplant Institute, University Medical Centre, Rotterdam, the Netherlands

**Background and Aims:** The global impact of SARS-CoV-2 on liver transplantation (LT) practices across the world is unknown. The goal of this survey was to assess the impact of the pandemic on global LT practices.

**Method:** A prospective web-based survey (available online from 7<sup>th</sup> September 2020 to 31<sup>st</sup> December 2020) was proposed to the active members of the EASL-ESOT/ELITA-ILTS in the Americas (including North, Central, and South America) (R1), Europe (R2), and the rest of the world (R3). The survey comprised 4 parts concerning transplant processes, therapy, living donors, and organ procurement.

**Results:** Of the 470 transplant centers reached, 128 answered each part of the survey, 29 centers (23%), 64 centers (50%), and 35 centers (27%) from R1, R2, and R3, respectively. When we compared the practices during the first 6 months of the pandemic in 2020 with those a year earlier in 2019, statistically significant differences were found in the number of patients added to the waiting list (WL), WL mortality, and the number of LTs performed. At the regional level, we found that in R2 the number of LTs was significantly higher in 2019 ( $p < 0.01$ ), while R3 had more patients listed, higher WL mortality, and more LTs performed before the pandemic. Countries severely affected by the pandemic (“hit” countries) had a lower number of WL patients ( $p = 0.009$ ) and LTs ( $p = 0.002$ ) during the pandemic. Interestingly, WL mortality was still higher in the “non-hit” countries in 2020 compared to 2019 ( $p = 0.022$ ).

**Conclusion:** The first wave of the pandemic differentially impacted LT practices across the world, especially with detrimental effects on the “hit” countries. Modifications to the policies of recipient and donor selection, organ retrieval, and

postoperative recipient management were adopted at a regional or national level.

**Lay summary:** The health emergency caused by the coronavirus pandemic has dramatically changed clinical practice during the pandemic. The first wave of the pandemic impacted liver transplantation differently across the world, with particularly detrimental effects on the countries badly hit by the virus. The resilience of the entire transplant network has enabled continued organ donation and transplantation, ultimately improving the lives of patients with end-stage liver disease.

© 2021 European Association for the Study of the Liver. Published by Elsevier B.V. All rights reserved.

## Introduction

In late 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in China as a serious threat to public health.<sup>1</sup> Since then, SARS-CoV-2 has become a devastating pandemic that has overwhelmed healthcare systems around the world, resulting in more than 168 million infections with a death toll exceeding 3.5 million as of May 2021.<sup>2</sup> Additionally, the collateral damage of the SARS-CoV-2 pandemic has been extensive, disrupting the clinical management of patients with acute and chronic diseases globally.<sup>3–5</sup>

The early days of the pandemic had demonstrated that SARS-CoV-2 affected liver transplantation (LT) at the organizational level, as well as the individual patient and provider level.<sup>6</sup> The operation of the LT program, including evaluation and selection of potential candidates, waiting list management, donor evaluation, transplantation, and subsequent recipient and living donor follow-up, requires substantial resources and infrastructure that were compromised, especially early in the pandemic, as demonstrated by regional studies.<sup>7</sup> In countries with primarily deceased donations, the situation was further complicated as individual LT programs depend on the donor networks to continue LT.<sup>8</sup> Patients with cirrhosis<sup>9</sup> and recipients of LTs<sup>10</sup> are thought to be at a higher risk of morbidity and mortality from SARS-CoV-2. Liver donor to recipient transmission has also been reported.<sup>11</sup> Frontline healthcare workers have been at a higher

Keywords: Sars-Cov-2; pandemic; COVID; Liver Transplantation; survey.

Received 14 June 2021; received in revised form 30 August 2021; accepted 27 September 2021; available online 13 October 2021

\* Corresponding author. Address: Gastroenterology and Multivisceral Transplant Unit, Department of Surgery, Oncology and Gastroenterology, Azienda Ospedale-Università Padova, Via Giustiniani 2, Padova, Italy; Tel.: +39.0498217024.

E-mail address: francescopaolo.russo@unipd.it (F.P. Russo).

† All authors contributed equally

<https://doi.org/10.1016/j.jhep.2021.09.041>



ELSEVIER

risk of SARS-CoV-2 infection,<sup>12</sup> causing a large proportion of the workforce to be temporarily out of service. These factors have led LT centers worldwide to adopt various strategies to mitigate the risk to their patients and care providers. These strategies involved every aspect of the LT process, including managing infected or exposed patients on the waiting list, pausing or limiting transplant and donor operations, implementing new policies regarding retrieval of the donated organs, adjusting post-transplant immunosuppression, and adopting virtual technology for patient follow-up, among other policies.<sup>13</sup> Currently, there is insufficient data on the changes in these practices and/or risk mitigation approaches and policies. Therefore, a task force was formed in mid-2020 by the European Association for the Study of Liver disease (EASL), International Liver Transplantation Society (ILTS), and the European Liver and Intestine Transplant Association (ELITA) of the European Society of Organ Transplantation (ESOT) to investigate the global impact of the first wave of the SARS-CoV-2 pandemic on LT centers and their patient care practices using a multidisciplinary online survey. Herein, we report the results of the survey and their implications, which may help the LT centers to operate better if they continue to encounter the sequelae of the current pandemic and optimize these programs for future pandemics.

## Materials and methods

A prospective cross-sectional web-based survey (available online from 7<sup>th</sup> September 2020 to 31<sup>st</sup> December 2020) was designed by a group of investigators dedicated to the care of patients in need of LTs from 3 international societies: EASL, ESOT-ELITA, and ILTS. The survey was created using Google Forms (Google LLC, Mountain View, CA, USA) and consisted of single-choice items and open-answer questions.

The study protocol conformed to the ethical guidelines and was approved by the institutional review board of Vanderbilt University Medical Center, USA. The survey was available on the websites of all 3 societies, and all members of the societies were invited by email to respond, ensuring not to duplicate the emails or the personnel at each center. The survey was also promoted via social media platforms (Twitter and Facebook accounts of the participating societies). Participants were given a choice to disclose their transplant center names and contact information; 97% of participants disclosed this information. Non-respondents were contacted at least twice. The survey was divided into 4 independent parts. Section 1 assessed the influence of the pandemic on LT programs across the globe, evaluating different topics such as listing, transplant volumes, mortality, and others, compared to the same period in the previous year. Section 2 evaluated the impact of special precautions, modifications, and demands required for the continuation of services during the first wave of the pandemic. Section 3 dealt with different aspects of living donations during the pandemic. Finally, Section 4 highlighted the effects of the pandemic on deceased liver donations, especially regarding strategies to recover organs (Supplementary Section 1).

Data was collected and categorized into 3 regions: the Americas (including North, Central, and South America) (R1), Europe (R2), and the rest of the world (R3).

## Statistical analysis

Data was expressed as a median and interquartile range, while categorical variables were expressed as percentages. Continuous

variables were compared by unpaired Student's *t* test, Mann-Whitney *U* test. The equality of matches pairs of observations was assessed using the Wilcoxon matched-pairs signed-rank test. Distribution was assessed by normality plots and the Shapiro-Wilk test. Categorical variables were compared by determining  $\chi^2$  values by performing Fisher's exact test. Trends in the number of patients listed for LT, waiting list mortality, and the number of LTs performed between similar periods before and after the pandemic were expressed as a ratio (e.g., variable between 1st January and 1st July in 2019/variable between 1st January and 1st July in 2020) and changes were assessed by multivariable linear regression after adjusting for COVID-19 case-fatality rate, living donor activity and country. Analysis of subgroups was performed to assess outcomes according to the continents "hit" vs. "non-hit" countries, and volume of living donor activity. Continents were classified as Africa (Egypt, South Africa); the Americas (Brazil, Canada, Chile, Colombia, Costa Rica, Mexico, the United States of America); Asia (China, India, Japan, Jordan, Oman, Pakistan, the Republic of the Philippines, Singapore, South Korea); and Europe (Austria, Belgium, Croatia, France, Germany, Hungary, Italy, Netherlands, Poland, Portugal, Romania, Russia, Spain, Switzerland, Turkey, the United Kingdom). In order to define "hit" and "non-hit" countries a multivariate adaptive regression splines was modeled, considering 3 gradients per spline, in order to define the best cut-off explaining a change in the trend of the number of patients listed for LT, mortality on the waiting list, and the number of LTs performed pre- and post-pandemic, according to the case-fatality rate of COVID-19 across the countries, see Supplementary Section 2 Fig. S1 (data obtained from the World Health Organization, <https://covid19.who.int>). The best cut-off was chosen, and Bayesian credibility intervals were assessed. Centers in which more than 30% of LTs were living donor liver transplants (LDLTs) were considered as having a high volume of LDLT activity. *Post hoc* Bayesian credibility intervals and correction for multiple comparisons were performed by the Bonferroni test. Missing data were treated by list-wise deletion. All statistical analyses were performed with STATA 15/IC.1 (StataCorp. 2017; Stata Statistical Software: Release 15; College Station, TX: Stata-Corp LLC).

## Results

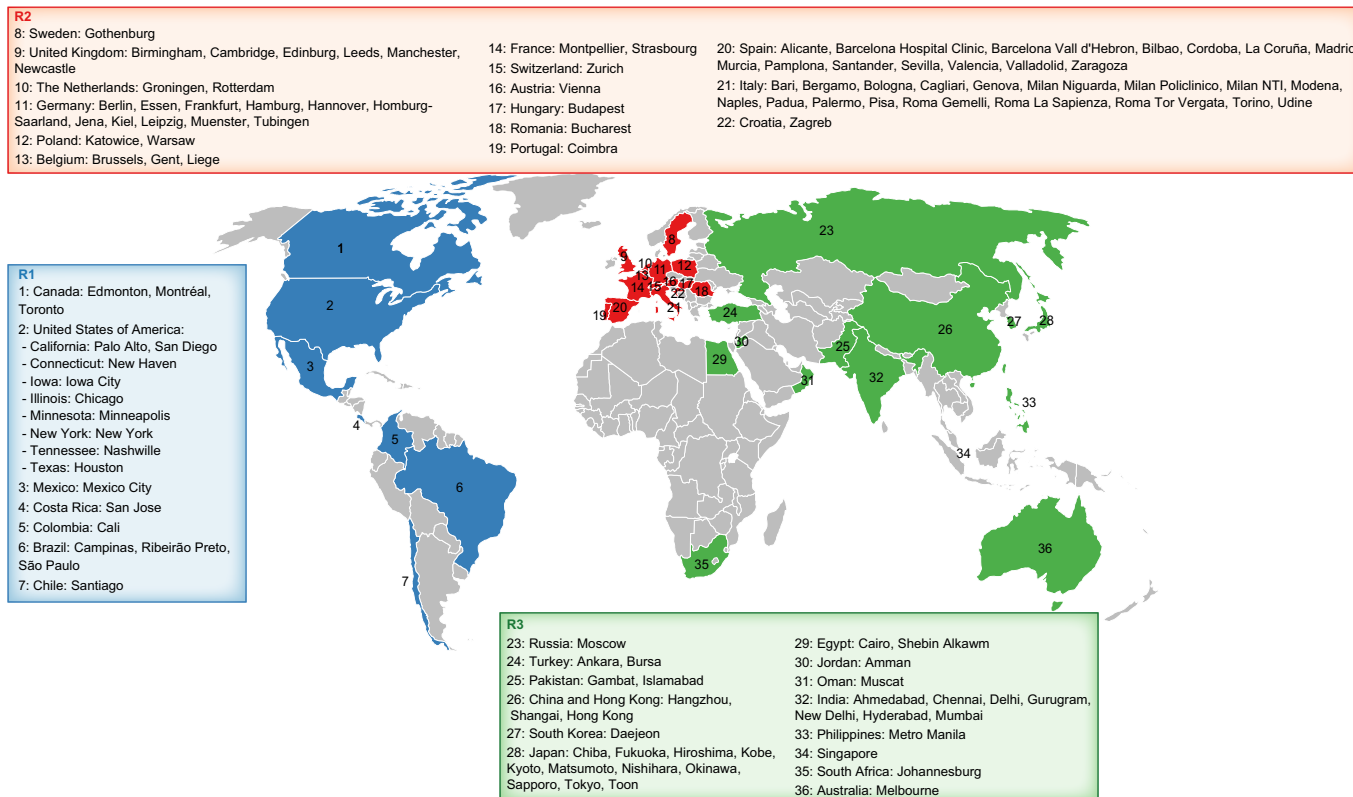
### Transplant processes

A total of 470 LT centers were reached across the world. Among these, 128 centers responded by filling in all parts of the survey. This included 29 centers (23%), 64 centers (50%), and 35 centers (27%) from R1, R2, and R3, respectively (Fig. 1 and Supplementary Section 3 Table S1).

Most hospitals (62.1–71.4%) across the globe had specific areas dedicated to COVID-19, and very few remained COVID-19-free hospitals. Most transplant centers withheld donor deceased LT services for up to a month (R1 = 45.5%, R2 = 50%, and R3 = 28.6%). Nevertheless, acute liver failure (ALF) remained an exemption to this hold (R1 = 52.6%, R2 = 54.8%, and R3 = 31.2%), and patients were managed in most centers on a case-by-case basis.

Globally, 30–50% of the centers performed transplants on recipients with a previous diagnosis of COVID-19 (R1: 52.4%, R2: 28.8, and R3: 29.4%). About 30% of the centers reported that fear of COVID-19 was the cause of the denial of the transplant proposal.

Comparing the overall transplant practices across the globe during the first 6 months of the pandemic with the corresponding



**Fig. 1. The global distribution of centers that responded to our survey.** (This figure appears in color on the web.)

period from 2019 revealed significant differences in the number of wait-listed candidates (32.5% vs. 60.7% of centers had more wait-listed candidates in 2020 vs. 2019,  $p = 0.004$ , respectively), waiting list mortality (52.3% vs. 26.1% of centers had higher waiting list mortality in 2020 vs. 2019,  $p = 0.006$ ) and number of LTs performed (36.4% vs. 59.5% of centers performed more LTs in 2020 vs. 2019,  $p = 0.001$ ) (Table 1). A further sub-analysis to assess the impact of the geographical heterogeneity of the pandemic on regional LT services across countries and continents showed that Asia had fewer wait-listed patients in 2020 than at a similar period in the previous year (33.3% vs. 63.3% of centers had more wait-listed candidates in 2020 vs. 2019,  $p = 0.040$ ) (Table 2). Europe also showed a non-significant trend with fewer wait-listed patients in 2020 (59.4% and 31.3% of centers in 2019 and 2020, respectively) (Table 2). In 2020, waiting list mortality was higher in Asia ( $p = 0.041$ ), while showing a non-significant trend in Europe (Table 2). Correspondingly, a higher number of LTs were performed in 2019 than in 2020 in Asia and Europe ( $p = 0.011$  for both continents), while these trends were not

**Table 1. Percentage of centers with a higher number of candidates listed, higher waiting list mortality, and higher number of LTs performed between 2019 and 2020.**

	Global		
	2019	2020	<i>p</i> value
Centers with more candidates listed	60.7%	32.5%	<b>0.004</b>
Centers with higher waiting list mortality	26.1%	52.3%	<b>0.006</b>
Centers performing more LTs	59.5%	36.4%	<b>0.001</b>

The sum of percentages does not reach 100% because of the centers with the same level of activity in 2019 and 2020: e.g., 60.7% of centers had a higher number of listed patients in 2019; 32.5% had a higher number of listed patients in 2020 and 6.8% had the same number of listed patients. Values in bold indicate statistical significance.

observed in the Americas (Table 2). However, corrections for *post hoc* comparisons showed no significant difference across the continents (corrected significance of  $p \leq 0.006$ ). With low respondents from Africa and Australia, these continents were excluded from the analyses (Table 2, Supplementary Section 2 Fig. S2).

Out of the 33 countries, Egypt had a greater number of patients listed in 2019 than in 2020 ( $\beta$  3.386, 95% CI 0.963; 5.808,  $p = 0.007$ ). India and Mexico had a similar trend ( $\beta$  2.011, 95% CI -0.871; 4.109,  $p = 0.060$  and  $\beta$  2.163, 95% CI -0.259; 4.585,  $p = 0.079$ , respectively). The ratio of LTs performed in 2019 compared to 2020 was significantly higher in India, Oman, and the Philippines ( $\beta$  2.470, 95% CI 0.1208; 4.820,  $p = 0.040$ ;  $\beta$  8.121, 95% CI 4.940; 11.303  $p < 0.001$  and 3.288, 95% CI; 0.106; 6.469,  $p = 0.043$ , respectively) compared the other countries. These results were confirmed by Bayesian inference (Supplementary Section 3 Table S2).

**“Hit” vs. “non-hit” countries**

A COVID-19 case-fatality rate of 3.4% was considered the best cut-off for “hit” vs. “non-hit” countries, with a 95% of probability of falling between 0.028 and 0.051 bounds based on the main outcomes of LT activity.

“Hit” countries had a lower number of wait-listed patients ( $p = 0.009$ ) and LTs ( $p = 0.002$ ) (Table 3) during the pandemic compared to a similar period in 2019. Moreover, the “non-hit” countries had a similar number of wait-listed patients ( $p = 0.097$ ) and LT numbers ( $p = 0.109$ ) (Table 3) during the pandemic compared to 2019. Interestingly, waiting list mortality was higher in the “non-hit” countries than in the “hit” countries in 2020. However, only wait-listed patients and the number of LTs performed in “hit countries” were significantly diminished in the

**Table 2. Percentage of centers with a higher number of candidates listed, higher waiting list mortality, and higher number of LTs performed between 2019 and 2020 based on geographic area (R1: Americas, R2: Europe, R3: rest of the world).**

	R1			R2			R3		
	2019	2020	p value	2019	2020	p value	2019	2020	p value
Centers with more candidates listed	60.0%	35.0%	0.490	59.4%	31.3%	0.072	63.3%	33.3%	<b>0.040</b>
Centers with higher waiting list mortality	23.5%	47.1%	0.301	27.4%	51.6%	0.100	20.7%	58.6%	<b>0.041</b>
Centers performing more LTs	52.4%	42.9%	0.958	59.4%	35.9%	<b>0.011</b>	63.6%	33.3%	<b>0.011</b>
<b>Corrected p value was ≤0.006</b>									

The sum of percentages does not reach 100% because of the centers with the same level of activity in 2019 and 2020. Values in bold indicate statistical significance.

pandemic era after *post hoc* comparison correction (corrected *p* ≤0.013) (Supplementary Section 2 Fig. S3).

**Living donor liver transplantation**

Another subgroup analysis of LDLT centers categorized as low volume (≤30% LDLT activity) and high volume (>30% LDLT activity) showed that the influence of the pandemic was more obvious in high volume LDLT centers. There were significantly fewer wait-listed patients (*p* = 0.005) and fewer LTs performed in high volume LDLT centers (*p* = 0.013) (Table 4) after the pandemic compared to in 2019 (Table 4). The “low volume” LDLT centers were predominantly from the Americas and Europe and had a similar number of wait-listed patients, but a lower number of LTs performed in 2020 compared to 2019 (*p* = 0.006). However, waiting list mortality in both high and low volume LDLT centers was similar across the 2 periods (Table 4). Moreover, waiting list mortality was not associated with the COVID-19 case-fatality rate once adjusted for country and LDLT activity. Data were confirmed after *post hoc* comparison correction (corrected *p* ≤0.013) (Supplementary Section 2 Fig. S4).

**Organ donation**

Most transplant teams (R1 = 83.3%, R2 = 42.6%, and R3 = 44.1%) made specific policy changes to their organ recovery protocols for safety during the pandemic. Only 12–17% of the centers transplanted organs from previously SARS-CoV-2-infected donors, mostly when the disease-to-donation interval was over a month. Four LDLT donors from R1 and R3 were diagnosed with COVID-19 in the postoperative period. Three of them had an

uneventful course and were discharged; no data were available on the 4<sup>th</sup> donor.

**Recipient outcomes**

Between 18.2% and 36.4% of the recipients tested positive for SARS-CoV-2 after LT with a mortality rate of R1 = 25%, R2 = 20%, and R3 = 8.3% across the 3 regions. Only 23% of the centers retested donors/recipients for COVID-19 at discharge.

**Immunosuppression and anticoagulation**

Only 8–14% of the centers routinely reduced calcineurin inhibitor doses in LT recipients following COVID-19 infection. Most centers managed immunosuppression on a case-by-case basis (52.8–75%). The regular use of anticoagulants in recipients differed significantly across the 3 regions (R1 = 45.8%, R2 = 38.2%, and R3 = 64.3%; *p* = 0.03).

**Telemedicine**

Nearly all transplant centers depended heavily on virtual technology during the pandemic, and very few centers did not use telemedicine (R1 = 0%, R2 = 12.3%, and R3 = 14.3%).

**Discussion**

SARS-CoV-2, an invisible microorganism, has put the whole world under pressure, with devastating health, human and economic costs.<sup>14</sup> Yet, it is crucial to recognize that the frequency of pandemics have increased over the past 20 years and it is unlikely that SARS-CoV-2 will be the last global health crisis that we witness, as discussed by Drs. Morens and Fauci in their recent

**Table 3. Percentage of centers with a higher number of candidates listed, higher waiting list mortality, and higher number of LTs performed between 2019 and 2020 in hit vs. non-hit countries.**

	Non-hit countries			Hit countries		
	2019	2020	p value	2019	2020	p value
Centers with more candidates listed	56.5%	34.8%	0.097	66.7%	29.2%	<b>0.009</b>
Centers with higher waiting list mortality	25.4%	54.0%	<b>0.022</b>	27.1%	50.0%	0.124
Centers performing more LTs	52.1%	43.8%	0.109	47.9%	25.0%	<b>0.002</b>
<b>Corrected p value was ≤0.013</b>						

The sum of percentages does not reach 100% because of the centers with the same level of activity in 2019 and 2020. Values in bold indicate statistical significance.

**Table 4. Percentage of centers with a higher number of candidates listed, higher waiting list mortality, and higher number of LTs performed between 2019 and 2020 in areas of low LDLT activity vs. high LDLT activity.**

	Low LDLT activity			High LDLT activity		
	2019	2020	p value	2019	2020	p value
Centers with more candidates listed	57.7%	33.8%	0.100	70.3%	27.0%	<b>0.005</b>
Centers with higher waiting list mortality	29.0%	47.8%	0.123	25.7%	57.1%	0.089
Centers performing more LTs	59.7%	34.7%	<b>0.006</b>	62.5%	35.0%	<b>0.013</b>
<b>Corrected p value was ≤0.013</b>						

The sum of percentages does not reach 100% because of the centers with the same level of activity in 2019 and 2020. Values in bold indicate statistical significance.

publication “Emerging Pandemic Diseases: How We Got to COVID-19”.<sup>15</sup> Therefore, the lessons learned from the current pandemic including the impact on the individual areas of medical practice could be critical knowledge for the future in the instance of a new health crisis.

Although it has been recognized that the SARS-CoV-2 pandemic had a profound impact on the healthcare system, data about the global impact of the virus on LT practices across the world are limited.

This survey showed an early cessation of activity in LT centers, generally for 4 weeks. However, an exception was made for patients referred to the centers in severe conditions (ALF, high model for end-stage liver disease [MELD], and acute-on-chronic liver failure). Before the first wave, little was known regarding the impact of an immunosuppressed state on COVID-19 and vice-versa, and most recommendations were extrapolated from previous SARS/MERS epidemics. Scientific evidence remained scarce, and strategies were based only on expert opinion. This is also reflected in results of our survey, wherein there remained a heterogeneity in the answers with regards to transplantation of infected patients, their ‘cooling off’ period, and the urgency of operation. In those more uncertain times, based on available evidence, various transplant societies across the world came up with their recommendations.<sup>16–20</sup> Interestingly, a study based on consensus-based guidance derived from individual information from 22 transplant societies highlighted a high degree of consensus.<sup>21</sup> Fourteen of 19 societies recommended either a temporary suspension or reduction of elective transplantation to a minimum. It was recommended that the decision to perform LT should be made on a case-by-case basis, giving priority to those who were unstable or had an MELD of over 25 or 30. Furthermore, a relaxation of rules was based on the availability of intensive care unit beds and staff required for the transplantation procedure. More recently, strong evidence-based data, e.g. from the ELITA/ELTR cohort, corroborate previously suggested recommendations with regards to the urgency and safety of transplanting patients with high MELD scores.<sup>22</sup> Furthermore, reducing transplantation activities allowed for the establishment of necessary COVID-19 wards, freeing the intensive care units for the management of COVID-19-affected critically ill patients, and allowing the mobilization of health personnel (both medical and non-medical) to COVID-19-affected areas.

Interestingly in some cases, patients on the waiting list for a transplantation withdrew their consent for transplantation because of fear of being infected, probably due to more hypochondriasis. It is likely that transplant patients, particularly those who are more vulnerable and have impaired self-awareness, may need more information about their illness, about the possible changes and fears associated with the spread of an infectious disease, their medication and treatment strategies for stress reduction, and about how to protect themselves from being infected with SARS-CoV-2.<sup>23</sup> Based on the fears and information deficits reported by patients in a German survey,<sup>24</sup> transplant centers are advised to intensify communication strategies and consider implementing telehealth in order to provide optimum medical care for LT recipients and patients on the waiting list. As underlined by Holmes *et al.*,<sup>25</sup> feeling distressed or anxious is understandable for many going through such unprecedented times. Clearly, for those who are vulnerable, it is important to be vigilant to mitigate risks to mental health. We also need to consider longer term preventive approaches more broadly, so

that we are more responsive to the chronic outcomes of the current pandemic as well as being better prepared for future public health crises.

As expected, the regions most affected by the pandemic were the ones that had fewer patients added to the LT waiting list and fewer LTs performed in the first 6 months of 2020 compared to 2019. However, the survey showed an interesting result, a higher waiting list mortality in non-hit countries compared to hit countries. This could have been due to the severe lockdown in these regions during the pandemic. This hypothesis fits with another interesting result in our survey, *i.e.*, the areas with high living transplant activity had more patients added to the waiting list and more LTs performed in 2019 compared to 2020. Although cessation of transplant activity, especially in the setting of living donation, is prudent during a pandemic, special attention should be paid to sick patients on the waiting list. If increased waiting list mortality in non-hit countries during the pandemic was the result of severe lockdowns or the fear of seeking medical care, then a reassessment of how we manage patients with chronic liver disease during a pandemic would be warranted.<sup>25–27</sup>

In the survey, only a percentage of the transplant centers decided to consider previous positive candidates for transplantation. In a recent international series,<sup>22</sup> patients with prior COVID-19 had favorable outcomes, with early survival of 96% (25/26) after receiving a LT. Median ICU and total hospital stay were 3 (IQR 3–6) and 11 (IQR 8–19) days, which concur with what is observed in more recent series.<sup>28</sup> The ideal timing for readmission of patients to the transplant waiting list is not yet clear; however, in clinical practice, most guidelines suggest to consider patients after at least 2 weeks from the negative swab.<sup>29,30</sup> However, a negative RT-PCR rhinopharyngeal swab and an additional negative swab at the time of LT should be enough to readmit the patient to the waiting list, because to date, zero cases of SARS-CoV-2 recurrence have been observed after LT. With the paucity of data, it is not known if patients recently affected by COVID-19 can be safely transplanted.

Immunosuppression in these patients may result in adverse outcomes, and the optimal disease-free interval is currently unknown.<sup>31–35</sup> For the reduction of immunosuppression to prevent SARS-CoV-2 infection, most centers evaluated recipients on a case-by-case basis. The EASL guidelines confirmed these findings, suggesting that reduction should only be considered under special circumstances (e.g., medication-induced lymphopenia or bacterial/fungal superinfection in case of severe COVID-19).<sup>36</sup> The results from the ELITA-ELTR multicenter study demonstrated that the use of tacrolimus was associated with better survival in 243 symptomatic LT recipients.<sup>37</sup> Recent data from Spanish transplant centers showed that the baseline immunosuppression using mycophenolate was an independent predictor of severe COVID-19 and it was dose-dependent.<sup>38</sup>

We also found a discrepancy in the prophylactic use of subcutaneous anticoagulants to prevent thromboembolism. In most of the European centers and a few centers from other regions, heparin or heparin-like drugs were routinely administered in transplant patients.

Another issue raised by the survey was whether donors/recipients were tested for SARS-CoV-2 at discharge. Most transplant centers did not check for infection because, as suggested by the survey, transplant patients were hospitalized in COVID-19-free areas, where both patients and health personnel were subjected to serial swabs. Most of the transplant centers adopted the

policy of repeating the swab at the time of discharge only if the patient was symptomatic or for specific reasons.

Our survey has some limitations. Given the rapid development of the pandemic that placed an extraordinary burden on healthcare providers, the overall response rate for our survey was only 27%, ranging between 23-50%; however, the authors felt that the timely report on specific practices by transplant centers in different world regions during the first wave of the pandemic was a valuable addition to the transplant literature. Particularly, as the world lives through recurrent waves of the pandemic, the information from our report may alert transplant centers to the processes of waiting list activation, management, and transplant decisions. First of all, the impact of the first wave of SARS-CoV-2 infection was different across the world, so it is difficult to compare the consequences at a global level. Another limitation of the survey is that unfortunately we do not have the absolute number of patients belonging to the centers that responded, but the percentages of responses of colleagues who report their experience. Even with a large number of responses, we cannot exclude a global underestimation of the impact of COVID-19 in the transplant setting. Finally, while analyzing the data at a global scale, we cannot exclude missing some peculiarities of the impact of the infection at a local scale. Specifically, center-based COVID-19-related epidemiologic data were not available at the time of the study. Therefore, the analyses were done based on the available country- or state-based data."

Nevertheless, our study has strengths, including real-time data collection by the international multi-society collaborative survey. Importantly, the global nature of this study offered a unique opportunity to demonstrate intercontinental and inter-regional differences in LT-related outcomes and practices. Furthermore, these observations may serve as lessons to guide how LT programs handle future waves of this pandemic, other pandemics, or other hurdles of this magnitude.

In conclusion, this international survey suggests that the first wave of the pandemic impacted LT across the world differently, with particularly detrimental effects on the hit countries. However, the survey has shown the resilience of the entire transplantation network to support liver donation and transplantation during testing times.

### Abbreviations

ALF, acute liver failure; LDLT, living donor liver transplantation; LT, liver transplant(ation); MELD, model for end-stage liver disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

### Financial support

This manuscript received no financial support.

### Conflict of interest

The authors of this manuscript have no conflicts of interest to disclose.

Please refer to the accompanying ICMJE disclosure forms for further details.

### Authors' contributions

All authors made substantial contributions to the conception and design, the acquisition, analysis, and interpretation of the data, FPR, MI, AS, VAK, TDM drafted the article and made critical revisions for important intellectual content. TDM performed statistical analysis. All authors approved the version to be published, and agreed to be

accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved.

### Data availability statement

The data that support the findings of this manuscript are available from the corresponding author.

### Acknowledgements

We sincerely and deeply acknowledge all respondents for their precious participation in this time-sensitive survey (all the centers are listed in the [Supplementary Section 3, table 1](#)).

We would like to acknowledge Luca Segantini from the European Society for Organ Transplantation for the preparation of the survey, Rossana Mirabella, Joel Walicki and Ben Hainsworth from The European Association for the Study of the Liver and Jwana Ribeiro da Silva from the International Liver Transplant Society for their continuous technical support throughout the survey period.

### Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhep.2021.09.041>.

### References

*Author names in bold designate shared co-first authorship*

- [1] **Zhu N, Zhang D, Wang W, Li X, Yang B**, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med* 2020;382(8):727–733.
- [2] Organization WH. WHO coronavirus (COVID-19) dashboard. 2021.
- [3] **Sud A, Jones ME, Broggio J**, Loveday C, Torr B, Garrett A, et al. Collateral damage: the impact on outcomes from cancer surgery of the COVID-19 pandemic. *Ann Oncol* 2020;31:1065–1074.
- [4] **Chu K, Reddy CL, Makasa E, AfroSurg C**. The collateral damage of the COVID-19 pandemic on surgical health care in sub-Saharan Africa. *J Glob Health* 2020;10:020347.
- [5] **Moroni F, Gramegna M, Ajello S, Beneduce A, Baldetti L, Vilca LM**, et al. Collateral damage: medical care avoidance behavior among patients with myocardial infarction during the COVID-19 pandemic. *JACC Case Rep* 2020;2:1620–1624.
- [6] **Kumar D, Manuel O, Natori Y, Egawa H, Grossi P, Han SH**, et al. COVID-19: a global transplant perspective on successfully navigating a pandemic. *Am J Transpl* 2020;20:1773–1779.
- [7] **De Carlis R, Vella I, Incarboni N, Centonze L, Buscemi V, Lauterio A**, et al. Impact of the COVID-19 pandemic on liver donation and transplantation: a review of the literature. *World J Gastroenterol* 2021;27(10):928–938.
- [8] **Trotter JF**. Liver transplantation around the world. *Curr Opin Organ Transpl* 2017;22:123–127.
- [9] **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(1):5–11.
- [10] **Iavarone M, D'Ambrosio R, Soria A, Triolo M, Pugliese N, Del Poggio P**, et al. High rates of 30-day mortality in patients with cirrhosis and COVID-19. *J Hepatol* 2020;73:1063–1071.
- [11] **Belli LS, Duvoux C, Karam V, Adam R, Cuervas-Mons V, Pasulo L**, et al. COVID-19 in liver transplant recipients: preliminary data from the ELITA/ELTR registry. *Lancet Gastroenterol Hepatol* 2020;5:724–725.
- [12] **Heinz N, Griesemer A, Kinney J, Vittorio J, Lagana SM, Goldner D**, et al. A case of an infant with SARS-CoV-2 hepatitis early after liver transplantation. *Pediatr Transpl* 2020;24:e13778.
- [13] **Nguyen LH, Drew DA, Graham MS**, Joshi AD, Guo CG, Ma W, et al. Risk of COVID-19 among frontline healthcare workers and the general community: a prospective cohort study. *Lancet Public Health* 2020;5:e475–e483.
- [14] **Russo FP**. COVID-19 in Padua, Italy: not just an economic and health issue. *Nat Med* 2020;26(6):806.
- [15] **Morens DM, Fauci AS**. Emerging pandemic diseases: how we Got to COVID-19. *Cell* 2020;182(5):1077–1092.



- [16] **Tschopp J, L'Huillier AG**, Mombelli M, Mueller NJ, Khanna N, Garzoni C, et al. (STCS) STCS. First experience of SARS-CoV-2 infections in solid organ transplant recipients in the Swiss Transplant Cohort Study. *Am J Transpl* 2020;20(10):2876–2882.
- [17] Surgery C. Guidance from the international society of heart and lung transplantation regarding the SARS CoV-2 pandemic. 2020. p. 2–16 [Internet] [cited 2020 Jun 5] Available from: [https://ishlt.org/ishlt/media/documents/SARS-CoV-2\\_Guidance-for-Cardiothoracic-Transplant-and-VAD-centers.pdf](https://ishlt.org/ishlt/media/documents/SARS-CoV-2_Guidance-for-Cardiothoracic-Transplant-and-VAD-centers.pdf).
- [18] Transplantation CSO. [https://profe.du.blood.ca/sites/msi/files/20200327\\_covid-19\\_conse\\_nsus\\_guidance\\_final.pdf](https://profe.du.blood.ca/sites/msi/files/20200327_covid-19_conse_nsus_guidance_final.pdf). Accessed July 31, 2021;
- [19] Service BNH. <https://www.odt.nhs.uk/deceased-donation/covid-19-advice-for-clinicians/>. Accessed July 31, 2021.
- [20] Liu H, He X, Wang Y, Zhou S, Zhang D, Zhu J, et al. Management of COVID-19 in patients after liver transplantation: Beijing working party for liver transplantation 2020 Jul; 2020 Jul;14(4):432–436.
- [21] **Ritschl PV, Nevermann N**, Wiering L, Wu HH, Moroder P, Brandl A, et al. Solid organ transplantation programs facing lack of empiric evidence in the COVID-19 pandemic: a By-proxy Society Recommendation Consensus approach. *Am J Transpl* 2020;20(7):1826–1836.
- [22] **Belli LS, Duvoux C, Cortesi PA**, Facchetti R, Iacob S, Perricone G, et al. COVID-19 in liver transplant candidates: pretransplant and post-transplant outcomes - an ELITA/ELTR multicentre cohort study. 2021 Jul 19. [gutjnl-2021-324879](https://doi.org/10.1093/gutjnl/2021-324879).
- [23] O'Connor RC, Hotopf M, Worthman CM, Perry VH, Tracey I, Wessely S, et al. Multidisciplinary research priorities for the COVID-19 pandemic - authors' reply. *Lancet Psychiatry* 2020 Jul;7(7):e44–e45.
- [24] **Reuken PA, Rauchfuss F**, Albers S, Settmacher U, Trautwein C, Bruns T, et al. Between fear and courage: attitudes, beliefs, and behavior of liver transplantation recipients and waiting list candidates during the COVID-19 pandemic. *Am J Transpl* 2020;20(11):3042–3050.
- [25] **Holmes EA, O'Connor RC**, Perry VH, Tracey I, Wessely S, Arseneault L, et al. Multidisciplinary research priorities for the COVID-19 pandemic: a call for action for mental health science. *Lancet Psychiatry* 2020;7(6):547–560.
- [26] Saqib MAN, Siddiqui S, Qasim M, et al. Effect of COVID-19 lockdown on patients with chronic diseases. *Diabetes Metab Syndr* 2020;14(6):1621–1623.
- [27] Tapper EB, Asrani SK. The COVID-19 pandemic will have a long-lasting impact on the quality of cirrhosis care. *J Hepatol* 2020 Aug;73(2):441–445.
- [28] Rana A, Witte ED, Halazun KJ, Sood GK, Mindikoglu AL, Sussman NL, et al. Liver transplant length of stay (LOS) index: a novel predictive score for hospital length of stay following liver transplantation. *Clin Transpl* 2017;31(12). [https://www.aasld.org/sites/default/files/2021-03/AASLD-COVID19\\_Expert\\_PanelConsensusStatement-March92021.pdf](https://www.aasld.org/sites/default/files/2021-03/AASLD-COVID19_Expert_PanelConsensusStatement-March92021.pdf).
- [29] [https://www.aasld.org/sites/default/files/2021-03/AASLD-COVID19\\_Expert\\_PanelConsensusStatement-March92021.pdf](https://www.aasld.org/sites/default/files/2021-03/AASLD-COVID19_Expert_PanelConsensusStatement-March92021.pdf).
- [30] <https://www.ecdc.europa.eu/en>.
- [31] Di Maira T, Berenguer M. COVID-19 and liver transplantation. *Nat Rev Gastroenterol Hepatol* 2020 Sep;17(9):526–528.
- [32] Dhand A, Bodin R, Wolf DC, Schluger A, Nabors C, Nog R, et al. Successful liver transplantation in a patient recovered from COVID-19. *Transpl Infect Dis* 2021;23:e13492.
- [33] **Martini S, Patrono D**, Pittaluga F, Brunetto MR, Lupo F, Amoroso A, et al. Urgent liver transplantation soon after recovery from COVID-19 in a patient with decompensated liver cirrhosis. *Hepatol Commun* 2020;5(1):144–145.
- [34] Raut V, Sonavane A, Shah K, Raj CA, Thorat A, Sawant A, et al. Successful liver transplantation immediately after recovery from COVID-19 in a highly endemic area. *Transpl Int* 2021;34:376–377.
- [35] Gambato M, Germani G, Perini B, Gringeri E, Feltracco P, Plebani M, et al. A challenging liver transplantation for decompensated alcoholic liver disease after recovery from SARS-CoV-2 infection. *Transpl Int* 2021;34:756–757.
- [36] **Boettler T, Marjot T**, Newsome PN, Mondelli MU, Maticic M, Cordero E, et al. Impact of COVID-19 on the care of patients with liver disease: EASL-ESCMID position paper after six months of the pandemic. *JHEP Rep* 2020;2:100169.
- [37] Belli LS, Fondevila C, Cortesi PA, Conti S, Karam V, Adam R, et al. 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* 2021 Mar;160(4):1151–1163.e3.
- [38] **Colmenero J, Rodríguez-Perálvarez M**, Salcedo M, Arias-Milla A, Muñoz-Serrano A, Graus J, et al. Epidemiological pattern, incidence, and outcomes of COVID-19 in liver transplant patients. *J Hepatol* 2021 Jan;74(1):148–155.