PERSONAL VIEWPOINT

Strategies for liver transplantation during the SARS-CoV-2 outbreak: Preliminary experience from a single center in France

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Liver transplantation (LT) during the ongoing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic is challenging given the urgent need to reallocate resources to other areas of patient care. Available guidelines recommend reorganizing transplant care, but data on clinical experience in the context of SARS-CoV-2 pandemic are scarce. Thus, we report strategies and preliminary results in LT during the peak of the SARS-CoV-2 pandemic from a single center in France. Our strategy to reorganize the transplant program included 4 main steps: optimization of available resources, especially intensive care unit capacity; multidisciplinary risk stratification of LT candidates on the waiting list; implementation of a systematic SARS-CoV-2 screening strategy prior to transplantation; and definition of optimal recipient-donor matching. After implementation of these 4 steps, we performed 10 successful LTs during the peak of the pandemic with a short median intensive care unit stay (2.5 days), benchmark posttransplant morbidity, and no occurrence of SARS-CoV-2 infection during follow-up. From this preliminary experience we conclude that efforts in resource planning, optimal recipient selection, and organ allocation strategy are key to maintain a safe LT activity. Transplant centers should be ready to readapt their practices as the pandemic evolves.

KEYWORDS

cancer/malignancy/neoplasia, clinical decision-making, clinical research/practice, diagnostic techniques and imaging, infection and infectious agents – viral, liver transplantation/ hepatology, organ procurement and allocation, risk assessment/risk stratification

Abbreviations: ACLF, acute-on-chronic liver failure; ALF, acute liver failure; BAR, balance of risk; DBD, donation after brain death; DRI, donor risk index; ELD, end-stage liver disease; HCC, hepatocellular carcinoma; ICU, intensive care unit; IQR, interquartile range; LT, liver transplantation; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-Cov-2, severe acute respiratory syndrome coronavirus 2.

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1 | INTRODUCTION

Data on outcomes after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in liver transplantation (LT) recipients are scarce and the potential impact on LT activity remains uncertain. While reports on SARS-CoV-2 in long-term solid organ recipients including LT report a case-fatality rate as high as 27.8%, others suggest that LT recipients may be protected by immunosuppression-related mitigation of cytokine release.^{1,2} Besides unanswered questions on SARS-CoV-2 infections in transplant recipients, LT is particularly challenging during this pandemic, given the urgent need to reallocate healthcare resources, such as ventilators, intensive care unit (ICU) beds, and staff to treat SARS-CoV-2-infected patients.³ However, decreased LT activity has to be balanced against the potential negative impact for patients with end-stage liver disease or hepatocellular carcinoma.^{4,5} To face these challenges, guidelines suggest a phased reduction in LT activity based on available resources, ranging from performing only super-urgent transplantation to maintaining an active deceased donation-based program.^{6,7}

During the peak of the pandemic in France, a total of 7130 patients with SARS-CoV-2 infection required ICU treatment with a baseline availability of 5432 beds.⁸ In this context, we present the experience and preliminary outcomes from a LT program in one of the most exposed regions in France.⁸

2 | METHODS

This is a retrospective analysis of all consecutive adult patients undergoing LT at Croix Rousse University Hospital in Lyon, France during the first month after the beginning of the national SARS-CoV-2 Lock Down on March 16, 2019.

In accordance with the French National Organ Donor Agency's (Agence Nationale de Biomédecine) and the French Transplantation Society's recommendations to reduce LT activity, we reorganized our LT program based on available resources.^{7,9} This strategy included 4 major steps: (1) resource planning, (2) multidisciplinary risk stratification of LT candidates on the waiting list, (3) implementation of a systematic pre-LT SARS-CoV-2 screening strategy, and (4) definition of optimal recipient-donor matching to achieve benchmark outcomes.

2.1 | Resource planning

Our university hospital is one of the tertiary reference centers for SARS-CoV-2 infections, which forced us to substantially reorganize our LT program. Three separate surgical units were set up: 1 for all elective surgery in SARS-CoV-2-negative patients, 1 for SARS-CoV-2-positive patients, and a third SARS-CoV-2-negative unit for LT recipients. Of note, the transplant unit had only single rooms to avoid patient contact and post-LT visits by relatives were temporarily

suspended. Specific intrahospital SARS-CoV-2-free pathways especially for ultrasound and computed tomography (CT) scans were established.

The ICU capacity was a key consideration. Since this is the referral tertiary center for SARS-CoV-2 disease, the overall number of ICU beds in the center was increased by 67% during the early phase of the outbreak. The majority of the ICU beds were dedicated to SARS-CoV-2-infected patients and 17% of the ICU beds were dedicated to patients without SARS-CoV-2 infection including surgical patients and LT recipients. The ICU capacity available for LT including available beds, ventilators, and renal replacement therapy (RRT) were continuously reassessed during weekly multidisciplinary meetings.

Another important point was the implementation of strategies to mitigate in-hospital transmission of SARS-CoV-2 from healthcare personnel to LT recipients. Surgical face masks and scrubs were mandatory for all staff members upon entering the hospital compound and were worn during all clinical activity such as surgical rounds. All staff members were systematically screened with reverse transcriptase polymerase chain reaction (RT-PCR) if they presented symptoms compatible with SARS-CoV-2 and were put in quarantine until the RT-PCR results were available. Staff members with positive RT-PCR were quarantined for 2 weeks.

2.2 | Recipient risk stratification

Every week, a multidisciplinary team reviewed every LT candidate on the waiting list. We selected LT candidates with a MELD score >25 including acute liver failure (ALF) and/or with end-stage liver disease (ELD) with poor prognosis including refractory ascites, hepatopulmonary syndrome, or hepatocellular carcinoma (HCC). Except for ALF, we excluded LT candidates with expected high post-LT morbidity, long ICU stay, and continuous RRT requirements (eg retransplantations and multiorgan transplantations). Additionally, access to LT for patients admitted to the ICU with acute-on-chronic liver failure (ACLF) was discussed using risk stratification by the chronic liver failure consortium (CLIF-C) ACLF classification.¹⁰

2.3 | Recipient and donor SARS-CoV-2 screening

A systematic SARS-CoV-2 screening strategy was implemented for all recipients including (1) a questionnaire on prehospitalization symptoms and a clinical examination at hospital admission, (2) a nasopharyngeal swab for SARS-CoV-2 by RT-PCR IP2/4, and (3) a chest CT scan prior to LT. Chest CT images were interpreted according to the guidelines from the European Society of Radiology and the European Society of Thoracic Imaging. Of note, RT-PCR and chest CT scan were granted specific priority: results for RT-PCR were available within 4-6 hours after testing and LT recipients were prioritized for chest CT scan slots. LT was only performed if all 3 screening tests were negative. Following national recommendations, all donors were screened by both nasopharyngeal swab and chest CT scan and donation only proceeded if all screening tests were negative.⁷

Post-LT SARS-CoV-2 screening was based on symptoms and no routine screening by chest CT scan or RT-PCR was implemented.

2.4 | Recipient-donor matching

The donation after brain death (DBD) program was maintained, while the donation after circulatory death and living donor program were stopped to preserve resources. To optimize available ICU resources, the organ allocation policy was based on ideal donor-recipient matching with low expected post-LT morbidity according to published LT outcome benchmarks, donor risk index (DRI), D-MELD, and balance of risk (BAR) score.¹¹⁻¹⁴ The DRI is a quantitative score including 7 donor characteristics predictive of post-LT graft failure.¹² Estimated post-LT 1-year graft survival decreases with an increasing DRI score. The D-MELD is the product of donor age and preoperative Model for End-Stage Liver Disease (MELD) score of the recipient.¹³ A score beyond the cutoff of 1600 score points is predictive of a longer post-LT length of hospital stay and poorer recipient survival.¹³ The BAR score combines 6 independent donor and recipient

characteristics associated with post-LT survival.¹⁴ The score balances 1 risk factor by optimal matching of the others, for example, high MELD with short cold ischemia and low donor age.

Standard post-LT immunosuppressive treatment included induction with basiliximab (20 mg after graft reperfusion and on post-LT day 4), corticosteroids during 7 days (perioperative bolus and withdrawal on post-LT day 7), mycophenolate mofetil and tacrolimus introduction on post-LT day 3. Target tacrolimus serum levels were 8-10 ng/mL during the first month post-LT.

3 | RESULTS

Our transplant center was situated in a high SARS-CoV-2 incidence zone, with 10-20 SARS-CoV-2-infected patients hospitalized per 100 000 inhabitants (Figure 1). Compared to the monthly average over the past 5 years, LT activity during the 30-day study period decreased by 29% in France (77 LT vs 108 LT), while LT activity increased by 42% at our center (10 LT vs 7 LT).⁸

In total, 39% (13 out of 33) of LT candidates on the waiting list were temporarily put on hold. These patients were either planned for a multiorgan transplant, had HCC controlled by bridging therapy,

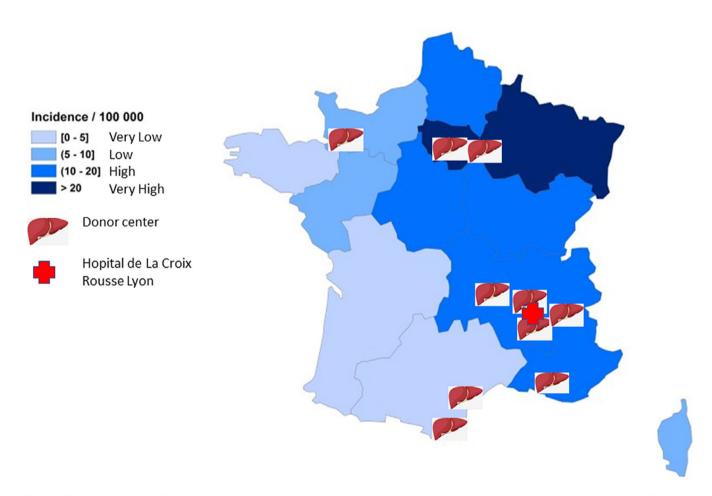


FIGURE 1 Geographical distribution of severe acute respiratory syndrome coronavirus 2 incidence based on number of hospitalizations per 100 000 inhabitants in France during the study period.⁸ The 10 donor centers included in the study as well as our transplant center are indicated on the map. (Figure adapted from reference 8) [Color figure can be viewed at wileyonlinelibrary.com]

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or had severe cardiovascular or respiratory comorbidities. The median MELD on the waiting list was 14 (interquartile range [IQR] 10-20) and the median CLIF-C acute-on-chronic liver failure (ACLF) score was 7 (IQR 6-8).

A total of 10 successful DBD LT in adult recipients were performed during the study period. Recipients had a median age of 51 years (IQR 38-60 years) with a median MELD score of 19 (IQR 12-28). The majority had compensated ELD (70%) and were admitted from home. Three recipients were inpatients with a MELD score >25 points: 1 had ACLF grade 1 and 2 had ACLF grade 2. Overall, HCC was present in 40% of the recipients. All recipients were screened by RT-PCR prior to LT and 7 underwent additional chest CT scan. No selected recipient was diagnosed with SARS-CoV-2 infection during the pre-LT screening and all recipients underwent LT.

Overall, 7/10 (70%) liver donors were from centers in a region with a high or a very high SARS-CoV-2 incidence (>10 SARS-CoV-2infected patients hospitalized per 100 000 inhabitants) (Figure 1). Liver donors had a median age of 33 years (IQR 25-59 years) with short cold ischemia times (median 7 hours, IQR 6-9 hours) resulting in a low median DRI of 1.37 (IQR 1.1-1.8). After recipient-donor matching, the median BAR score was 8 (IQR 2-11) (Table 1).

Median post-LT follow-up was 39 (IQR 35-45) days. Perioperative transfusion rates and posttransplant morbidity were within published benchmarks (Table 2) with a short median ICU stay of 2.5 (IQR 2-6) days. The median total hospital stay was 14 (IQR 13-21) days. The standard immunosuppressive protocol was followed for all patients. One liver graft recipient underwent liver biopsy for abnormal liver tests on post-LT day 30 and was diagnosed with an acute rejection classified BANFF 6, which was successfully treated by corticosteroids bolus.

During the 39 days of median post-LT follow-up, no case of SARS-CoV-2 was diagnosed in the 10 LT recipients.

4 | DISCUSSION

We report a single-center experience with LT during the peak of the SARS-CoV-2 outbreak in France. A careful assessment of available resources allowed the center to maintain an active LT program and to perform 10 successful DBD LT. The cornerstones of the implemented strategy were (1) flexible planning of ICU capacity including beds, equipment, and staff; (2) weekly multidisciplinary risk stratification of LT candidates; (3) systematic screening; and (4) optimal donor-recipient matching to reduce post-LT morbidity and ICU requirement. Results of this strategy show a low post-LT morbidity with short ICU stays. No SARS-CoV-2 infection during the post-LT follow-up was observed (Table 3).

The first question at the beginning of the SARS-CoV-2 pandemic was: Should LT activity be maintained? On the one hand, LT during the pandemic may have surpassed available capacities in ventilators, RRT, and ICU staff and thus jeopardized treatment options for SARS-CoV-2-infected patients.^{9,15} In addition, the risk of SARS-CoV-2-related morbidity and mortality in the context of immunosuppression is being actively debated within the transplant community with only few data from single cases available.^{1,2,16-19} On the other hand, from a patient perspective, suspending LT may have a negative impact on patients with ELD or HCC without any other curative treatment option.^{4,5}

After balancing these considerations, we opted to maintain a LT activity by following center-specific decisional steps based on available guidelines (Table 3).

A first step was the reorganization of the LT program and a continuous evaluation of available resources. Despite the significant increase in ICU beds required for SARS-CoV-2-infected patients, we were able to maintain a SARS-CoV-2-free ICU dedicated to LT and surgical oncology (17% of total ICU beds). In addition, to further prioritize LT activity, major elective interventions (eg, major hepatectomy, esophagectomy) in frail patients with potential long ICU stays were reduced according to the national guidelines.^{20,21} The LT ward was reorganized into single rooms and medical staff wore face masks and scrubs and were tested and quarantined if they showed SARS-CoV-2 symptoms. While logistically challenging, setting up these SARS-CoV-2-free pathways to mitigate in-hospital transmission should be the first priority to allow safe LT activity for both recipients and medical staff.²¹

The second step was a case-by-case evaluation and risk stratification of every LT candidate on the waiting list, resulting in a 39% reduction of actively listed candidates. As reported in other LT centers, candidates listed for multiorgan transplants or retransplantations were temporarily put on hold due to an expected higher morbidity and to transitory shortage in blood products and RRT equipment.^{11,22} In contrast, LT candidates with MELD > 25 or ELD with poor prognosis but expected benchmark outcomes and short ICU stay were kept active on the waiting list. Of note, the median overall hospital stay was longer than the expected benchmark because of the mitigation strategies in place in France and reduced rehabilitation capacities.

The third step was the implementation of a screening strategy to avoid peri-LT SARS-CoV-2 infection. In contrast to some centers that only test symptomatic recipients, we opted for systematic testing in all recipients prior to LT.^{9,23} For the first 3 recipients, we used RT-PCR and quickly added chest CT scan to the systematic screening protocol, based on data showing good sensitivity of chest CT scan for detecting symptomatic and asymptomatic SARS-CoV-2-infected patients.²⁴ Chest CT slots were available 24/24 hours and in collaboration with our virology laboratory we were able to have pre-LT results from RT-PCR within less than 6 hours. Since recipients selected for LT were admitted to the hospital at least 6 hours before the transfer to the operating room, no significant delay due to pending test results occurred. Additionally, potential liver graft donors were screened by RT-PCR and chest CT during their ICU stay, and a negative SARS-CoV-2 status was mandatory to initiate the organ donation process.⁷ There were thus no delays due to SARS-CoV-2 diagnostics once the donation was initiated.

Finally, the organ allocation strategy played a major role. Our results showed optimal donor-recipient matches (median BAR

	LT 1	LT 2	LT 3	LT 4	LT 5	LT 6	LT 7	LT 8	LT 9	LT 10
Donor and graft characteristics	CS									
Donor age (y)	26	33	56	66	31	46	66	20	12	33
Donor center	National	Local	Regional	National	National	National	Local	National	National	National
SARS-CoV-2 incidence in donor center	Low	High	High	Very high	Very low	High	High	High	Very high	Very low
Donor ICU stay (d)	e	1	2	2	т	9	4	ო	б	2
Type of grafts	Whole	Whole	Whole	Whole	Whole	Whole	Whole	Whole	Right lobe/ex-situ split	Whole
Cold ischemia (h)	6	10	8	7	9	Ø	7	5	10	6
DRI (points)	1.19	0.936	1.53	1.89	1.089	1.898	1.719	1.047	1.719	1.213
Recipient characteristics										
Recipient age (y)	17	43	46	61	57	64	59	33	59	39
ELD cause	Auto-immune hepatitis	PSC	NASH/ alcohol	Alcohol	NASH/ alcohol	NASH/ alcohol	Alcohol	Alcohol	HBV	HBV
HCC	No	No	No	No	No	No	Yes	No	Yes	Yes
Pre-LT status	Ward	Home	Home	Ward	ICU	Home	Home	Home	Home	Home
MELD (points)	32	10	18	38	27	18	21	19	7	12
CLIF-C ACLF (points)	10	6	7	11	6	7	7	7	6	9
ACLF grade	2	0	0	7	1	0	0	0	0	0
Pre-LT RT-PCR	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Pre-LT chest CT	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
SARS-CoV-2 positive	No	No	No	No	No	No	No	No	No	No
D-MELD (points)	832	330	1008	2508	837	828	1386	380	84	396
BAR score (points)	11	2	8	19	12	10	ø	5	2	Ļ

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TABLE 2 Posttransplant outcomes at hospital discharge compared to the

available benchmark

	LT n = 10	Benchmark value at hospital discharge ¹¹
Peri-LT course		
Operation duration (h)	7.6 (5.4-9.4) ^a	≤6 h
Intraoperative blood transfusions (units)	1 (0-4)	≤3 units
Renal replacement therapy, n (%)	2 (20) ^a	≤8%
ICU stay (d)	2.5 (2-6)	≤4 d
Hospital stay (d)	14 (13-21) ^a	≤18 d
Morbidity and mortality at hospital discharge	2	
Any complication, n (%)	7 (70)	≤80%
Clavien Dindo grade II, n (%)	6 (60)	≤69%
≥Clavien Dindo grade IIIa, n (%)	3 (30)	≤42%
Biliary complications, n (%)	0 (0)	≤12%
CCI score	20.9 (0-34.3)	≤29.6
Graft loss, n (%)	0 (0)	≤4%
Mortality, n (%)	0 (0)	≤2%

Note: Continuous variables are presented as median and interquartile range.

Abbreviations: CCI, complication comprehensive index; ICU, intensive care unit; LT, liver transplant.

^aValues are out of the benchmark range.

TABLE 3 Center-specific decisional steps to maintain a liver transplant activity based on international guidelines

	International guidelines ^{6,9,14,19,25}	Practical implementation in our center
Resource planning	Evaluation and adaptation to available resources	Dedicated SARS-CoV-2-negative transplant unit and in- hospital pathways
		Weekly multidisciplinary meetings to adapt liver transplant activity to available ICU and operating room capacity
Liver transplant waiting list	Reduction of active patients on the waiting list	39% of recipients are temporarily put on hold
Recipient risk stratification	Prioritize urgent transplant indications	Weekly multidisciplinary screening meetings
	(MELD > 25), ALF	ALF prioritized
		High MELD: CLIF-C ACLF Score assessment
		Low MELD: Recipients with HCC and expected benchmark outcomes
Recipient and donor screening	Implement pre-LT SARS-CoV-2 screening	Recipient
before LT		Questionnaire on prehospitalization symptoms and clinical examination
		Nasopharyngeal swap RT-PCR, results available within 4-6 h
		Chest CT scan prior to LT
		Donor
		Systematic donor screening by RT-PCR and chest CT scan
Recipient-donor matching	Reconsider organ allocation policies	Only DBD program maintained, DCD program suspended
		Optimization of donor-recipient matching to reduce post-LT morbidity and ICU stay (BAR, DRI)

Abbreviations: ACLF, acute-on-chronic liver failure; ALF, acute liver failure; BAR, balance of risk; DBD, donation after brain death; CLIF-C, chronic liver failure consortium; CT, computed tomography; DCD, donation after circulatory death; DRI, donor risk index; HCC, hepatocellular carcinoma; ICU, intensive care unit; LT, liver transplant; MELD, Model for End-Stage Liver Disease; RT-PCR, reverse transcriptase polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

score 8) with liver grafts procured from very young donors presenting a low DRI. This allowed balancing the high pre-LT risk in 2 recipients with a MELD > 25 by the use of optimal grafts. One explanation of the availability of such grafts may be the selection

policy of the donor centers, focusing efforts on these young donors. Furthermore, similar to the transfer of SARS-CoV-2-infected patients from hospitals with insufficient ICU capacity to less affected hospitals across France during the study period, we also observed reallocation of liver grafts from regions with a high number of hospitalized SARS-CoV-2 patients to our center (Figure 1).²⁵ For example, recipient No. 8 (Table 1) received a liver graft declined by a center from a region with a high SARS-CoV-2 incidence because the initial recipient was screened SARS-CoV-2 positive. We conclude that all transplant centers should be ready to accept or decline liver grafts according to their local SARS-CoV-2 dynamics in order to guarantee optimal utilization of available grafts. In this context, centers may anticipate a back-up recipient in case of SARS-CoV-2-positive screening in the initial recipient. Furthermore, as a consequence of reallocation of liver grafts, cold ischemia time may be extended as in the case of recipient No. 8, where total static cold storage duration was 10 hours. This may increase the risk of allograft dysfunction or primary nonfunction, and centers may consider using ex-vivo machine perfusion strategies to recondition grafts with extensive ischemic damage.²⁶

This retrospective single-center report has inherent limitations. Regarding the small patient sample and short follow-up, more data are required to confirm our results. Additionally, the present report reflects a specific experience from a single center and thus may not be transferable to other centers, regions, or countries. However, given the unprecedented situation, this preliminary clinical experience helps in the process of moving forward: Continuous evaluation of both resources and outcomes may allow further extension of LT activity over the next weeks and to quickly respond in the event of a second SARS-CoV-2 peak.

In conclusion, we report the successful preliminary experience of a French LT program during the peak of the SARS-CoV-2 pandemic. Efforts in resource planning, optimal recipient selection, and organ allocation are key to maintain a safe LT activity. Transplant centers should be ready to readapt their practices as the pandemic evolves.

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DISCLOSURE

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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