

Liver transplantation during the COVID-19 epidemic : recommendations from the Belgian Liver Intestine Transplant Committee (BeLIAC)

G. Dahlqvist¹, O. Ciccarelli¹, H. Van Vlierberghe², F. Berrevoet², T. Vanwollegem³, D. Ysebaert³, T. Gustot⁴, V. Lucidi⁴, J. Delwaide⁵, O. Detry⁵, M.H. Delbouille⁶, E. Sokal⁷, F. Nevens⁸, J. Pirenne⁸ on behalf of the BeLIAC

(1) UCL Liver Transplant Program; Cliniques Universitaires Saint-Luc, Brussels, Belgium ; (2) UZ Gent Liver Transplant Program, Universitair Ziekenhuis, Gent, Belgium ; (3) UZ Antwerpen Liver Transplant Program, Universitair Ziekenhuis, Antwerpen, Belgium ; (4) ULB Liver Transplant Program; Hopital Universitaire Erasme, Brussels, Belgium ; (5) ULg Liver Transplant Program, Hopital Universitaire du Sart Tilman, Liège, Belgium ; (6) BTS Section of the Transplant Coordinators, Hopital Universitaire du Sart Tilman, Liège, Belgium ; (7) Pediatric Liver Transplantation, Cliniques Universitaires Saint-Luc, Brussels, Belgium ; (8) KUL Liver Transplant Program, Universitair Ziekenhuis Gasthuisberg, Leuven, Belgium..

Abstract

Since January 2020, the Novel Coronavirus Disease 2019 (COVID-19) pandemic has dramatically impacted the world. In March 2020, the COVID-19 epidemic reached Belgium creating uncertainty towards all aspects of life. There has been an impressive capacity and solidarity of all healthcare professionals to acutely reconvert facilities to treat these patients. In the context of liver transplantation (LTx), concerns are raised about organ donation shortage and safety, the ethics of using limited healthcare resources for LTx, selection criteria for LTx during the epidemic and the risk of *de novo* COVID-19 infection on the waiting list and after LTx. BeLIAC makes several recommendations to try to mitigate the deleterious effect that this epidemic has/will have on donation and LTx, taking into account the available resources, and trying to maximize patients and healthcare professionals' safety. (*Acta gastroenterol. belg.*, 2020, 83, 340-343).

Key word : COVID-19 epidemic, liver transplantation, resources.

Background

Since January 2020, the Novel Coronavirus Disease 2019 (COVID-19) epidemic has dramatically impacted the world. In March 2020, the COVID-19 epidemic reached Belgium creating uncertainty towards all aspects of healthcare and questioning at the same time the challenge to both avoid viral dissemination and maintain standard of care for patients with other diseases. On the 28th of April 47859 cases were confirmed in Belgium leading to 7501 deaths (1).

The COVID epidemic has a particularly deleterious impact on liver transplantation (LTx) candidates. Nowadays, LTx still represents the only curative treatment for end stage liver diseases (2,3) and for hepatocellular carcinoma (HCC) and other rare cancers (4,5). The risk for these patients is multiple. First, there is a risk that the liver disease progresses during the waiting time on the list, impeding the possibility to be transplanted or even worse leading to their death (6-8). Second, this epidemic leads to a shortage of healthcare resources (substantial reallocation of intensive care units (ICU) and healthcare providers to COVID-patients) and, in addition, to an acute-on-chronic shortage of donors (9,10), altogether seriously reducing the possibility to get a transplant (6). Third, there is a risk of acquiring COVID-19 early or late after transplantation and even while on the waiting list.

In this epidemic context the aim of the Belgian Liver Intestine Transplant Committee (BeLIAC) was to provide a series of recommendations on the following aspects of LTx likely to be impacted by COVID-19: Donation, access to resources, selection criteria, pre-listing evaluation, COVID-19 screening of recipients, the place of living donor related liver transplantation, and information to patients. These recommendations are meant to provide additional guidance for the care of these patients. They will have to be adapted during the course of time, according to the evolution of the epidemic, its impact on resources, and the increase knowledge we will gain of the effect of COVID-19 in LTx candidates and recipients. We will not address the situations of the middle- and long-term post-transplantation follow-up (surveillance, invasive procedures) nor the surveillance of patients with HCC and advanced liver failure.

This publication is in line with the editorial policy of quality and scientific knowledge dissemination from our national societies (11,12).

Recommendations

Liver Donation

The reason for the reduction in organ donation is multifactorial: 1) less ICU resources for donor detection and management; 2) logistics and/or uncertainty about donor COVID-19 status; 3) less trauma victims (an indirect welcome effect of this crisis, but a small percentage of the donors); 4) a trend for more family refusals; and 5) the assumption in certain hospitals that donation/transplantation programs have been put on hold.

This unprecedented shortage of both healthcare resources and donors has caused an unprecedented reduction in LTx activity. The "pre-epidemic baseline"

Correspondence to : Jacques Pirenne, Abdominal Transplant Surgery and Coordination, University Hospitals Leuven, Herestraat 49, 3000 Leuven, Belgium.
E-mail : jacques.pirenne@uzleuven.be

Submission date : 03/05/2020

Acceptance date : 12/05/2020

mortality and drop-out rate (for progression of hepatocellular carcinoma (HCC) and/or a worsening medical condition) is about 15 % and will probably be impacted. We have to keep in mind that patients awaiting LTx are different from patients waiting for a kidney or for other solid organs since there is no middle- and long-term liver replacement therapy available.

Other countries, such as China, have proposed guidelines for organ procurement (13). Some of these recommendations are difficult to implement in the real-world practice with the spread of the epidemic (14).

In this context, the BeLIAC makes the following recommendations:

1. BeLIAC recommends each transplant and procurement center together with their cooperating donor hospitals to assess the possible measures to facilitate and optimize the donation process during the epidemic.

2. BeLIAC suggests to the Belgian Organ Procurement Committee (BEOPC) to follow the donation situation in Belgium and support donation activities wherever needed and however doable.

3. Although the risk of donor-derived COVID-19 is unknown yet, use of COVID-19 positive donors (diagnosis made on chest-CTs, nasopharyngeal swab) should be prohibited given the risks to patients and healthcare staff. In accordance with the Belgian transplantation society (BTS) and the national transplant council guidelines (15), BeLIAC recommends that all donors should be tested by COVID-19 PCR on nasopharyngeal swab, chest-CT, or COVID-19 PCR on bronchiolo-alveolar lavage if clinically indicated (chest-CT not interpretable, lung contusion/trauma, ...)

Priority access to non-COVID resources for LTx recipients

Transplantations are the only surgical procedures that are based on altruism, an important moral value in those difficult times. Organ donation has also an “instrumental” value essential to consider since it saves several lives.

In an ideal situation with no shortage of donors and where “one size (liver) fits all (recipients)”, LTx could be postponed for a few weeks in selected recipients with not yet decompensated liver failure or with relatively stable HCC.

However, even in the pre-epidemic reality, this ideal scenario does not exist, and as already mentioned, the shortage of donors causes a “baseline” mortality/drop-out of about 15% on the waiting list.

With the COVID-19 epidemic and the additional donor shortage that it causes, the situation is aggravated. By the end of April 2020, the reduction in LTx activity (minus 16 % compared to the same period in 2019) has led to an increase of 20 % in the number of patients registered on the waiting list (*communication from Luc Colenbier, Federal public service*). Even more than before, a suitable liver offer represents a unique life-saving chance

for the individual patient to whom this liver is allocated, and by the waiting line effect, this will impact the entire waiting list. *A contrario*, cancelling a LTx will *de facto* reflect in increased mortality (8).

4. BeLIAC recommends that LTx, by virtue of its life-saving nature, should be given priority access to non-COVID resources during this epidemic.

Selection of LTx recipients during the COVID epidemic

Belgium is part of Eurotransplant. Our country has one single national waiting list and livers procured in Belgium are shared nationally (with the exception of the hyper-urgent patients).

About two thirds of Belgian livers are allocated to particular patients based on the Model for End Stage Liver Disease (MELD). MELD allocation was introduced in 2007 to reduce mortality on the waiting list by distributing scarce liver grafts to the patients who would benefit the most (16). MELD is objective and transparent and takes into account elements of justice (greatest need) and of utility (greatest benefit). In short, MELD allocates a given liver to a given Belgian patient who at that given moment is the most urgent and most likely to benefit from this particular liver.

About one third of Belgian livers (mostly non-heart beating donors) are allocated to the procuring center. For these livers, the team in charge (hepatologist/transplant surgeon) at that center selects the medically/surgically most suitable listed patient who at that given moment is the most urgent and most likely to benefit from this transplant.

5. BeLIAC recommends not to deviate from the standard MELD allocation since it already makes an objective and transparent sorting of the most urgent patients.

6. One exception to that might be LTx in patients with high exceptional MELD for non-oncological reasons and preserved liver function (for example polycystic disease, rare metabolic diseases ...), taking into account patient symptomatology (pain, pruritis, psychological distress ...).

7. BeLIAC advocates an individualized decision making including a risk-benefit balance between the mortality on the waiting list without transplantation and the potential risk of peri- or postoperatively acquired (in-hospital or after discharge) COVID-19 infection and related death, and -at the time of writing- the lack of specific treatment against COVID-19 (14, 17).

8. In the course of the epidemic and depending upon the COVID-induced scarcity of resources, BeLIAC recommends to take more into account the balance between expected resource utilization and anticipated outcome in patient selection.

9. BeLIAC recommends that, in case of a liver offer, the team in charge (hepatologist/transplant surgeon) decides upon the suitability of that offer for a particular patient. If the offer is deemed suitable and before it is

actually accepted, intensivists and anesthesiologists are consulted to determine whether resources (ICU/OR/Healthcare staff for non-COVID patients) do allow the LTx to take place.

Pre-listing evaluation for LTx

Timely evaluation of patients with chronic liver diseases, HCC and other malignancies, and their registration on the waiting list -if deemed appropriate candidates- is essential to accelerate access to LTx and decrease mortality (18).

10. BeLIAC recommends not to postpone evaluation of LTx candidates, unless for quality-of-life reasons only and depending upon patient symptoms.

COVID-19 screening at time of LTx

LTx in a COVID-19 infected recipient has to be avoided, given the risks for these patients and for the healthcare staff (7,19).

11. In accordance with the Belgian transplantation society and the national transplant council guidelines (15), BeLIAC recommends to screen recipients, at the time of hospital admission by Covid-19 PCR on nasopharyngeal swab and by chest-CT and cancel transplantation in case one or both are compatible with Covid-19 infection.

Living Donor Related Liver Transplantation (LDRLT)

LDRLT is usually programmed electively, except for specific indications such as liver tumors when it must be coordinated with the chemotherapy schedule, or in case of immediate vital risk. Patients may be simultaneously registered on the deceased waiting list; in these cases, LDRLT can be programmed when the risk for additional waiting time and death exceeds the benefit of deceased LTx. In the context of the COVID epidemic, we need to take into account that LDRLT uses extra non-COVID resources for the living donor and that here is a risk for the living donor of in-hospital or postoperatively acquired COVID-19 infection (20).

12. Depending upon the stage of the epidemic and the resources available, BeLIAC suggests to postpone LDRLT in stable patients, but not to delay LDRLT if specialists in charge consider that this would lead to additional vital risk.

13. Prior to planning LDRLT, BeLIAC recommends consulting with all specialists involved given the extra amount of non-COVID resources required for the donor.

Information to patients

There is uncertainty as to the impact of COVID-19 on LTx patients. The risk of infection is present on the waiting list as well as after LTx.

There are only limited data linking the underlying liver disease and a more severe course of COVID-19 infection, but patients with advanced liver diseases should be considered at higher risk due to cirrhosis-associated liver dysfunction (8).

In addition, there is a serious concern that immunosuppression may favor spreading of the virus and aggravate the disease (7).

However, preliminary data from the European Liver Transplant Registry (ELTR) suggest that the incidence of COVID-19 might not be particularly high(er) in the LTx population. By May 8th 2020, ELTR reported 311 cases of COVID-19 in LTx recipients and 57 in wait listed candidates, among 125 European LTx centers. It has also been suggested that immunosuppression might not necessarily aggravate the disease, and might even be protective by downregulating the cytokine response (21). This information needs to be taken with extreme caution since data are incomplete at this stage and many patients may have self-quarantined.

In fact, severe cases of COVID-19 and mortality in wait listed patients and in *de novo* and already transplanted recipients has been reported. In-hospital acquisition of COVID-19 in LTx patients or candidates has also been reported. Finally, LTx recipients often present several co-morbidities likely to make them more susceptible to COVID-19 related morbidity and mortality (age, overweight, cardiovascular disease, diabetes, hypertension etc..). As already mentioned, all these potential risks have to be taken into account in the risk *versus* benefit assessment and the final decision whether to proceed with LTx or not.

14. BeLIAC recommends to inform wait listed patients of these possible risks of COVID-19 infection after LTx, and to give them the possibility to temporarily opt out from surgery on a case-by-case basis (particularly in those with quality-of-life indications).

Registries

Clearly, additional information is necessary to increase our knowledge on the effects of COVID-19 on LTx candidates and recipients, in order to take appropriate protective and curative measures, and to better inform patients (19). For this aim, various registries COVID-19 in LTx recipients have been developed.

- The ongoing ELTR registry:

Vincent Karam, ELTR manager, Paris, France
vincent.karam-ext@aphp.fr & Wojciech Polak, Surgery, Rotterdam, Netherlands w.polak@erasmusmc.nl

- A newly created Bern registry:

Jean-Francois Dufour, Hepatology, Bern, Switzerland
jean-francois.dufour@dbmr.unibe.ch & Frederik Nevens, Hepatology, Leuven, Belgium
frederik.nevens@uzleuven.be

- A newly created national registry (Belgian transplantation society) for all solid organ transplants:

Laurent Weekers, Nephrology, Liège, Belgium

l.weekers@chu.ulg.ac.be & Martin Wissing, Nephrology, Brussels, Belgium kwissing@uzbrussel.be

15. BeLIAC recommends Belgian LTx centers to participate to these registries.

Conclusion

The COVID-19 epidemic is a novel situation for all transplant specialists. This sanitary crisis is constantly evolving. All projections for the near future tell us that the COVID-19 is about to stay for at least a few months. Postponing the transplantation after the COVID-19 crisis is not feasible in the specific situation of LTx where no liver replacement therapies are available for patients with end-stage liver disease and where oncological aspects are at the forefront for patients suffering from HCC. Transplantation programs should receive prioritized access to non-COVID resources, while taking into account the benefit/risk balance of non-transplanting or developing *de novo* COVID-19 infection after LTx and maximizing patients and healthcare professionals' safety.

Conflict of interest

The authors declare no conflict of interest nor financial support for the present work.

References

1. SCIENSANO, 2020, Epidemiology monitoring of the COVID-19 epidemic in Belgium, viewed 28 April 2020, <<https://covid-19.sciensano.be>>.
2. FRANQUE S., LANTHIER N., VERBEKE L., REYNAERT H., VAN STEENKISTE C., VONGHIA L. *et al.* The Belgian Association for Study of the Liver Guidance Document on the Management of Adult and Paediatric Non-Alcoholic Fatty Liver Disease. *Acta Gastroentero. Belg.*, 2018, **81** : 55-81.
3. EASL Clinical Practice Guidelines : Liver transplantation. *J. Hepatol.*, 2016, **64** : 433-485.
4. SCHIELKE A., MEURISSE N., LAMPROYE A., HONORÉ P., DELWAIDE J., HUSTINX R. *et al.* Selection criteria for liver transplantation in patients with hepatocellular carcinoma. Eastern and western experiences, and perspectives for the future. *Acta Gastroentero. Belg.*, 2019, **82** : 314-318.
5. LAURENT S., VERHELST X., GEERTS A., GEBOES K., DE MAN M., TROISI R. *et al.* Update on liver transplantation for cholangiocarcinoma : a review of the recent literature. *Acta Gastroentero. Belg.*, 2019, **82** : 417-420.
6. ANGELICO R., TRAPANI S., MANZIA T. M., LOMBARDINI L., TISONE G., CARDILLO M. The COVID-19 outbreak in Italy: Initial implications for organ transplantation programs. *Am. J. Transplant.*, 2020.
7. FERNÁNDEZ-RUIZ M., ANDRÉS A., LOINAZ C., DELGADO J. F., LÓPEZ-MEDRANO F., SAN JUAN R. *et al.* COVID-19 in solid organ transplant recipients: a single-center case series from Spain. *Am. J. Transplant.*, 2020.
8. BOETTLER T., NEWSOME P. N., MONDELLI M. U., MATICIC M., CORDERO E., CORNBERG M. *et al.* Care of patients with liver disease during the COVID-19 pandemic : EASL-ESCMID position paper. *JHEP Rep.*, 2020, **2** : 100113-100113.
9. MORIS D., SHAW B. I., DIMITROKALLIS N., BARBAS A. S. Organ Donation During the Coronavirus Pandemic : An Evolving Saga in Uncharted Waters. *Transpl. Int.*, 2020.
10. MAGGI U., DE CARLIS L., YIU D., COLLEDAN M., REGALIA E., ROSSI G. *et al.* The impact of the COVID-19 outbreak on Liver Transplantation programmes in Northern Italy. *Am. J. Transplant.*, 2020.
11. LANTHIER N., MOREELS T. G. The future of Acta Gastro-Enterologica Belgica. *Acta Gastroentero. Belg.*, 2019, **82** : 3-4.
12. MOREELS T. G., LANTHIER N. The quest for quality. *Acta Gastroentero. Belg.*, 2018, **81** : 3-4.
13. PAN L., ZENG J., YANG H. Challenges and countermeasures for organ donation during the SARS-CoV-2 epidemic: the experience of Sichuan Provincial People's Hospital. *Intensive Care Med.*, 2020, 1-2.
14. BOYARSKY B. J., CHIANG T. P., WERBEL W. A., DURAND C. M., AVERY R. K., GETSIN S. N. *et al.* Early Impact of COVID-19 on Transplant Center Practices and Policies in the United States. *Am. J. Transplant.*, 2020.
15. Belgium transplantation society and the national transplant council guidelines, viewed April 28 2020, https://www.basl.be/wp-content/uploads/2020/04/BTS_NTC_position-statement-transplantation-COVID_final.pdf.
16. AHMAD J., DOWNEY K. K., AKOAO M., CACCIARELLI T. V. Impact of the MELD score on waiting time and disease severity in liver transplantation in United States veterans. *Liver Transpl.*, 2007, **13** : 1564-1569.
17. MOECKLI B., PELOSO A., OLDANI G., ORCI L. A., BANZ V., DUTKOWSKI P. *et al.* The Swiss approach to the COVID-19 outbreak. *Am. J. Transplant.*, 2020.
18. FIX O. K., HAMEED B., FONTANA R. J., KWOK R. M., MCGUIRE B. M., MULLIGAN D. C. *et al.* Clinical Best Practice Advice for Hepatology and Liver Transplant Providers During the COVID-19 Pandemic : AASLD Expert Panel Consensus Statement. *Hepatology*, 2020.
19. WEBB G. J., MOON A. M., BARNES E., BARRITT A. S., MARJOT T. Determining risk factors for mortality in liver transplant patients with COVID-19. *Lancet Gastroenterol. Hepatol.*, 2020 : S2468-1253(2420)30125-30124.
20. LAGANA S. M., DE MICHELE S., LEE M. J., EMOND J. C., GRIESEMER A. D., TULIN-SILVER S. A. *et al.* COVID-19 Associated Hepatitis Complicating Recent Living Donor Liver Transplantation. *Arch. Pathol. Lab. Med.*, 2020.
21. MEHTA P., MCAULEY D. F., BROWN M., SANCHEZ E., TATTERSALL R. S., MANSON J. J. COVID-19 : consider cytokine storm syndromes and immunosuppression. *The Lancet*, 2020, **395** : 1033-1034.