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Expanding Indications of Liver Transplantation in Spain: Consensus Statement and Recommendations by the Spanish Society of Liver Transplantation

Manuel Rodríguez-Perálvarez, MD, PhD,¹ Miguel Ángel Gómez-Bravo, MD, PhD,² Gloria Sánchez-Antolín, MD, PhD,³ Gloria De la Rosa, MD,⁴ Itxarone Bilbao, MD, PhD,⁵ and Jordi Colmenero, MD, PhD,⁶ on behalf of the Spanish Society of Liver Transplantation (SETH) Consensus Panel*

Background. The number of patients awaiting liver transplantation (LT) in Spain has halved from 2015 to 2019 due to the reduction of candidates with hepatitis C and the successful implementation of nonheart beating donation programs across the country. The Spanish Society for Liver Transplantation has committed to take advantage of this situation by developing consensus around potential areas to expand the current indications for LT. The consensus group was composed of 6 coordinators and 23 expert delegates, each one representing an LT institution in Spain. **Methods.** A modified Delphi approach was used to identify areas to expand indications for LT and to build consensus around paramount aspects, such as inclusion criteria and waitlist prioritization within each area. The scientific evidence and strength of recommendations were assessed by the “Grading of Recommendations Assessment, Development, and Evaluation” system. **Results.** The consensus process resulted in the identification of 7 potential areas to expand criteria in LT: recipient’s age, hepatocellular carcinoma, alcoholic hepatitis, acute-on-chronic liver failure, hilar and intrahepatic cholangiocarcinoma, and unresectable liver metastases of colorectal cancer. **Conclusions.** We present the main recommendations issued for each topic, together with their core supporting evidence. These recommendations may allow for expanding criteria for LT homogeneously in Spain and may provide a guidance to other countries/institutions facing a similar scenario.

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INTRODUCTION

Liver transplantation (LT) dramatically improves prognosis in patients with end-stage liver disease, but a strict selection of candidates is mandatory given the imbalance between available donors and potential recipients. Some patients who could obtain a less pronounced—although

significant—survival benefit are not considered eligible for LT in order to preserve the ethical principles of utility and justice. However, the changing landscape of LT is turning the classical donor/recipient paradigm. Spain holds the highest deceased donation rates worldwide, which

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¹ Department of Hepatology and Liver Transplantation, Hospital Universitario Reina Sofía, IMIBIC, CIBERehd, Córdoba, Spain.

² Department of Abdominal Surgery and Transplantation, Hospital Universitario Virgen del Rocío, Sevilla, Spain.

³ Department of Hepatology and Liver Transplantation, Hospital Universitario Río Hortega, Valladolid, Spain.

⁴ Organización Nacional de Trasplantes, Madrid, Spain.

⁵ Department of Liver Transplantation, Hospital Universitari Vall d’Hebron, Barcelona, Spain.

⁶ Department of Hepatology and Liver Transplantation, Hospital Clínic de Barcelona, IDIBAPS, CIBERehd, Barcelona, Spain.

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Correspondence: Jordi Colmenero, MD, PhD, Liver Transplant Unit, Hospital Clínic de Barcelona, Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Centro de Investigación Biomédica en Enfermedades Hepáticas y Digestivas (CIBERehd), University of Barcelona, Villarroel 170, 08036 Barcelona, Spain. (jcolme@clinic.cat).

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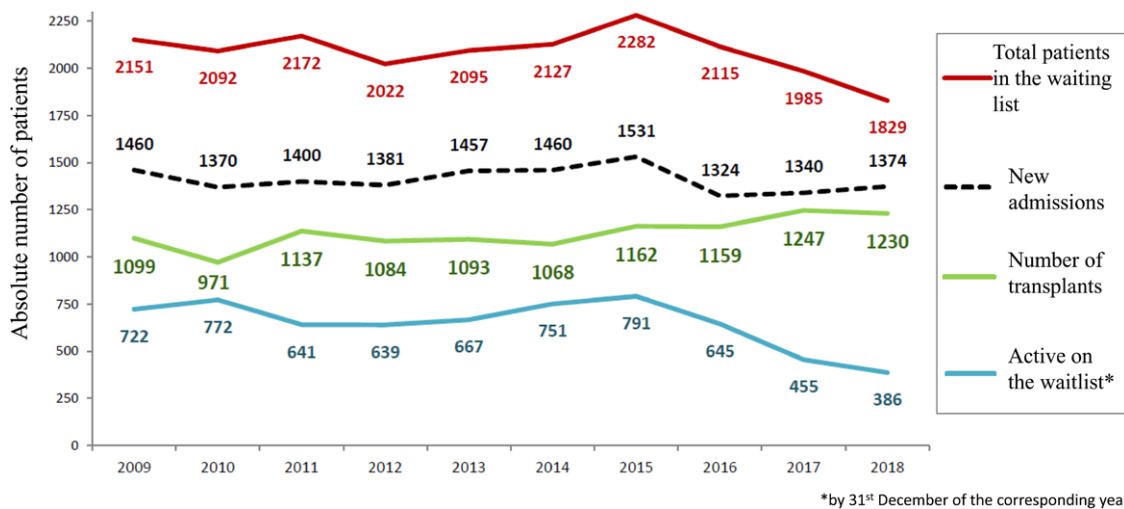


FIGURE 1. Trends in liver transplantation in Spain over the last decade. Data show the absolute number of patients per y. Adapted from the annual report of the Spanish liver transplant registry (full document available at www.ont.es).

continues to increase every year.¹ In addition, many programs of donation after circulatory death have been successfully implemented all over the country within the last decade.² These facts, together with the systematic prescription of direct antivirals against hepatitis C, have decreased the number of patients awaiting LT in Spain within the last decade (Figure 1).

The Spanish liver transplant network is composed by 24 transplant institutions distributed along 17 regions and coordinated by the National Transplant Organization (Organización Nacional de Trasplantes [ONT]). According to the annual report of the ONT,³ the number of patients included in the waiting list and the number of transplants performed were balanced until 2015, and thus the number of patients in the waiting list was relatively constant. From January 2015 to December 2018, due to the reasons outlined above, the number of transplants performed progressively raised by 13.1%, while the new inclusions dropped by 10.2%. As a result, the number of patients awaiting LT in Spain halved within the same period (from n=791 in December 2015 to n=386 in December 2018). Indeed, the yearly likelihood of transplantation was increased by 30%, and the median length of stay on the waiting list was shortened from 148 days in 2015 to 48 days in 2018. In December 2018, 58.3% of the Spanish transplant institutions had <10 patients included in their waiting lists. The probability of death within the waiting list or delisting due to clinical deterioration from 2015 to 2018 also declined from 12.3% to 8.5%, respectively, which were the lowest rates in this decade.

The Spanish Society of Liver Transplantation (SETH) has committed to take advantage of this scenario by delineating a consensus statement to homogeneously expand the current indications for LT in order to maximize organ utilization. In the present document, we summarize the main recommendations and the core supporting scientific evidence.

MATERIALS AND METHODS

The consensus group was composed of 6 topic coordinators and 23 expert delegates, each one representing an LT institution in Spain. A total of 7 potential areas to expand indications for LT were identified: recipient’s age, hepatocellular carcinoma, alcoholic hepatitis, acute-on-chronic

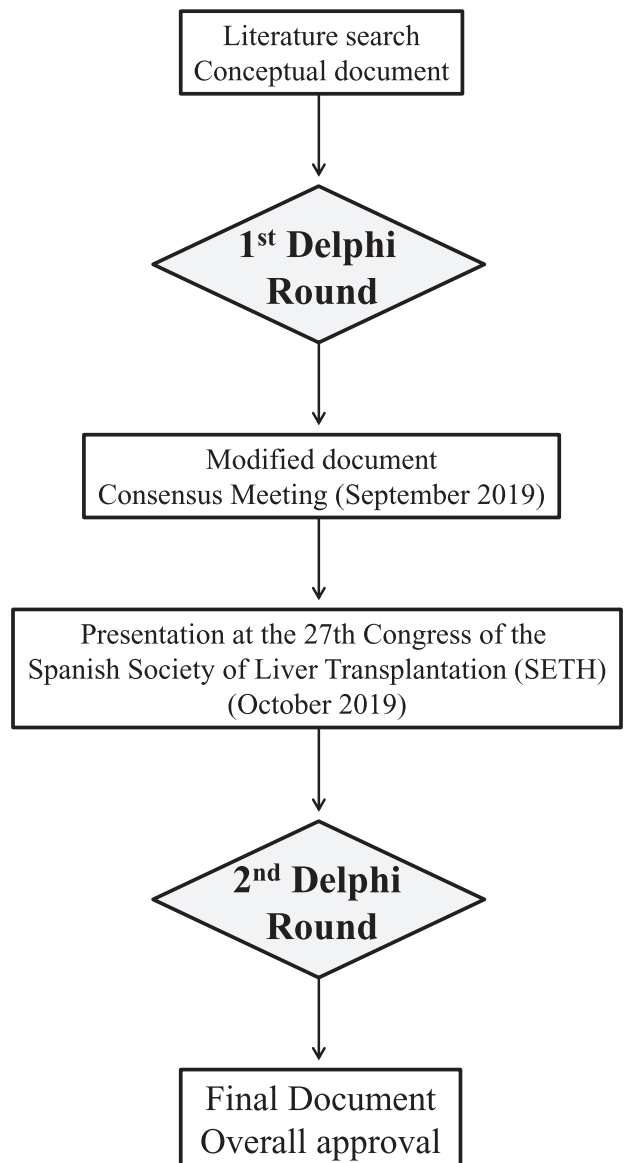


FIGURE 2. Flow chart illustrating the modified Delphi approach to obtain consensus regarding the expansion of criteria for liver transplantation in Spain.

TABLE 1.
Consensus recommendations for the expansion of liver transplant indications in Spain

	Recommendations	GRADE	Ref.
1. Recipient's age			
1.1	Recipient's age should not be a formal contraindication for LT, as this would pose an ethical concern.	1B	6-8
1.2	The following statements have been agreed unanimously by the consensus panel: Recipient's aged <70 y is the current standard of care in LT. Recipient's aged 70–75 y requires an exhaustive evaluation of comorbidities. LT should be strongly discouraged in recipients older than 75 y. There is no scientific evidence to support survival benefit of LT in these patients.	1C	9
1.3	Comorbidities and frailty should be evaluated by validated score systems such as the <i>Charlson comorbidity index</i> , the <i>UCLA frailty score</i> , and <i>liver frailty</i> , respectively.	2C	10-13
1.4	Pretransplant workup in older patients should emphasize on cardiovascular assessment and screening of cancer.	1B	6,7,14
1.5	Older donors could be allocated to older recipients.	2C	15-17
2. Hepatocellular carcinoma			
2.1	The presence of extrahepatic metastases or macrovascular invasion should preclude LT in patients with cirrhosis and hepatocellular carcinoma.	1A	18-22
2.2	Milan criteria are considered the standard of care to select candidates with hepatocellular carcinoma for LT.	1A	7,23
2.3	Patients within Milan criteria showing AFP >1000 ng/mL should undergo locoregional therapy to ensure a decline of AFP below 500 ng/mL to be included in the waiting list. If AFP remains >500 ng/mL, LT should be discouraged.	2C	24
2.4	A moderate expansion of Milan criteria is advised as long as the balance with other indications of LT is preserved.	1B	25,26
2.5	Among the expanded criteria for LT, the "Up-to-7" criteria are those with the strongest scientific background and may be preferred over other systems.	2B	27,28
2.6a	Patients beyond Milan but within "Up-to-7" criteria with serum AFP >400 ng/mL should undergo locoregional therapy with complete restaging 1 mo later, before being included in the waiting list (see recommendation 2.6b).	2B	29,30
2.6b	In patients beyond Milan but within "Up-to-7" without radiological response after locoregional therapy (partial or complete as defined by RECIST 1.1 criteria) and progressive increase of serum AFP despite locoregional therapy, LT should be contraindicated.	2C	31-33
2.7	The above-referred recommendations do not apply to downstaging strategies. Given the heterogeneity and complexity of the scientific evidence around this practice, a dedicated consensus document is warranted.	2C	N/A
3. Acute alcoholic hepatitis			
3.1	Patients with a first episode of severe acute alcoholic hepatitis (Maddrey score >32) who do not respond to corticosteroid therapy (Lille model score ≥ 0.45 at d +7) could be considered for LT unless otherwise contraindicated.	2A	34-37
3.2	In patients with previous episodes of acute alcoholic hepatitis (irrespective of their severity) or hepatic decompensations, the risk of heavy alcohol relapse after LT is unacceptably high. In the absence of high-quality interventional studies focused on this population, early LT should be contraindicated.	1C	N/A
3.3	Pretransplant workup should mirror other indications for LT, with a particular emphasis on exploring the psychosocial dimension and excluding latent infections and malignancy.	1A	37,38
3.4	The psychosocial evaluation should explore the most relevant predictors of heavy alcohol relapse after LT: psychiatric comorbidities, concomitant substance abuse, family support, prior failed rehabilitation attempts, and the number of drinks per d. The use of standardized tools to stratify patients according to the risk of alcohol relapse such as the <i>SALT score</i> is recommended.	1A	38,39
3.5	An addiction specialist should be incorporated within the transplant multidisciplinary team to get involved in the pretransplant workup and posttransplant long-term surveillance.	1C	37,40
4. ACLF			
4.1	LT should always be considered in patients with ACLF unless otherwise contraindicated	1C	41,42
4.2	Patients with ACLF who are potential candidates for LT should be admitted to the intensive care unit and closely monitored until validated prognostic scores are assessed (CLIF-C ACLF organ failure score at d 3–7).	1C	43,44
4.3	Screening of occult infections, including blood and urinary cultures, is paramount in ACLF patients.	1A	45,46
4.4	When ACLF is triggered by an active infection, LT may be contraindicated until the responsible microbiologic agent is identified, the appropriate therapy is administered, and subsequent cultures are negative.	1A	42,47
4.5	Futility criteria are not established for ACLF patients. For LT purposes, severe and unresponsive extrahepatic organ failure (particularly cardiovascular or respiratory) would be a contraindication.	1C	43,46,48
4.6	Patients with ACLF-2 or ACLF-3 awaiting LT should be managed by expert transplant hepatologists and intensivists depending on the logistics and organization of the institution until transplantation or significant improvement. In the latter situation, the need of early LT should be reassessed by a multidisciplinary team.	1B	41,49,50
4.7	MELD score may not fully capture the severity of patients with ACLF-2 and ACLF-3. Given the dismal short-term prognosis without LT, a regional urgency priority should be granted.	2C	49,51

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TABLE 1. (Continued)

	Recommendations	GRADE	Ref.
5. Unresectable hilar cholangiocarcinoma			
5.1	LT may be considered in patients with unresectable hilar cholangiocarcinoma who fulfill the Mayo Clinic protocol (tumor diameter ≤ 3 cm without lymph node or distant metastases in the staging laparotomy, after external beam radiation, chemotherapy based in 5-fluorouracil, intrabiliary radiation, and oral capecitabine until LT).	2B	52
5.2	Prioritization within the waiting list should mirror the exception points for HCC in each region.	2C	N/A
5.3	The type of donor would be at the discretion of each transplant center according to local experience and length of the waiting list.	2C	N/A
5.4	Retransplantation is allowed whenever needed, except in patients with tumor recurrence.	1C	N/A
6. Intrahepatic cholangiocarcinoma in patients with liver cirrhosis			
6.1	In selected patients with portal hypertension and intrahepatic cholangiocarcinoma, LT could be considered only in the context of well-designed randomized trials	2B	53,54
6.2	The diameter of the tumor is tightly associated with post-LT recurrence. Only single-nodule tumors ≤ 2 cm without vascular invasion would be acceptable.	1B	53,55
6.3	Management of patients within the waiting list concerning prioritization and surveillance should mirror established protocols for hepatocellular carcinoma.	2C	N/A
6.4	Tumor progression (an increase of diameter beyond 2 cm, new nodules, vascular invasion, and significant elevation of Ca19.9 or extrahepatic spread) should motivate exclusion from the waiting list.	1C	N/A
6.5	Retransplantation is contraindicated in patients with tumor recurrence.	1C	N/A
7. Unresectable liver metastases of colorectal cancer			
7.1	In selected patients with unresectable liver metastases of colorectal cancer, LT could be considered only in the context of well-designed clinical trials and after a close evaluation by a multidisciplinary team composed by oncologists, hepatologists, and surgeons.	2B	56-59
7.2	The optimal strategy for waiting list prioritization is not established and should be tailored according to the composition and length of the waiting list in each region.	2C	N/A
7.3	The type of donor would be at the discretion of each transplant center according to local experience and length of stay in the waiting list.	2C	N/A

ACLF, acute-on-chronic liver failure; AFP, alpha-fetoprotein; CLIF-C, chronic liver failure; HCC, hepatocellular carcinoma; LT, liver transplantation; MELD, model for end-stage liver disease; RECIST, response evaluation criteria in solid tumors; SALT, sustained alcohol use post-LT; UCLA, University of California Los Angeles.

liver failure, hilar and intrahepatic cholangiocarcinoma, and unresectable liver metastases of colorectal cancer. A modified Delphi approach⁴ was used as summarized in Figure 2. Each topic was assigned to a pair of coordinators who were responsible to conduct independently a comprehensive literature search. MEDLINE, Google Scholar, Pubmed, The Cochrane Library, and resources of international societies of transplantation and hepatology were searched in order to gather the most robust scientific evidence available. The Spanish Transplant Organization (ONT) provided historical data of transplantation and outcomes whenever needed. This information was organized into an initial conceptual document, which was used to delineate the preliminary recommendations within each topic. The whole consensus panel agreed to avoid recommendations regarding regional prioritization, as such logistics aspects should be tailored to each clinical scenario.

In the first Delphi-like survey, the preliminary document was internally validated by the topic coordinators and then distributed among the consensus panel members, who were encouraged to provide feedback for each recommendation. In addition, to explore the agreement regarding situations with less supporting evidence, dedicated multiple-choice questions were distributed by using an online platform. The document was modified accordingly for discussion within the consensus meeting held in Madrid in September 2019. The summary of recommendations was presented at the 27th Congress of the SETH, held in Seville in October 2019. A second Delphi-like round was

conducted for minor remarks. The final version of the document was approved by the whole consensus panel.

The scientific evidence and strength of recommendations were evaluated by using the “Grading of Recommendations Assessment, Development and Evaluation” system,⁵ which rates 2 dimensions: (a) strength of the recommendation: classified as “1” (if strong) or as “2” (if weak) and (b) quality of the evidence: classified as “A” (high-quality evidence coming from well-designed randomized trials or overwhelming evidence from other sources, which is not expected to change in the future), “B” (moderate-quality evidence from randomized trials with methodological limitations or well-designed observational studies), or “C” (low-quality evidence from observational studies or unsystematic clinical experience, which may change in the future in light of new studies). This study was exempt from approval from an ethics board.

The implementation of the consensus statement will take place immediately upon the publication of the present manuscript. The “Registro Español de Trasplante Hepático-RETH” managed by the ONT, has been modified to identify new inclusions under the new expanded criteria. The annual report of the ONT will allow to monitor the impact of the consensus on the waiting list length and composition. Appropriate actions will be implemented to counteract significant changes in waiting list length and composition.

RESULTS

The consensus statements according to the Grading of Recommendations Assessment, Development and Evaluation

system and the supporting key references are included in Table 1. A total of 40 recommendations were issued for the 7 topics: recipient's age, hepatocellular carcinoma, alcoholic hepatitis, acute-on-chronic liver failure, hilar cholangiocarcinoma, intrahepatic cholangiocarcinoma, and unresectable liver metastases of colorectal cancer.

CONCLUSIONS

The consensus of SETH to expand indications for LT may increase the number of potential candidates for LT in Spain homogeneously. The implementation of these expansion criteria will be closely monitored to study the impact on the waiting list length and composition in order to implement the appropriate actions to preserve the ethical principles of utility and justice in LT. Although the present document could be a guidance for other countries or institutions facing a shortage of the waiting list, the decision to implement each recommendation should be taken after a close analysis of the regional scenario.

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APPENDIX

Consensus panel delegates of the Spanish Society of Liver Transplantation (SETH) listed in alphabetic order: Carme Baliellas, H. U. de Bellvitge; Gerardo Blanco, H. U. Infanta Cristina; Javier Briceño, H. U. Reina Sofía; Fernando Casafont, H. U. Marqués de Valdecilla; Constantino Fondevila, H. U. Clinic i Provincial; Félix García Pajares, H.U. Río Hortega; Mikel Gastaca, H. U. de Cruces; Rocío González Grande, H. Reg. U. de Málaga; Ignacio González-Pinto, H. U. Central de Asturias; Antonio González Rodríguez, H. U. N. Señora de la Candelaria; Ernest Hidalgo, H. U. Vall d'Hebrón; José Luis Lledó, H. U. Ramón y Cajal; Carmelo Loinaz, H. U. 12 de Octubre; José Luis Lucena de la Poza, H. U. Puerta de Hierro; Juan Manuel Pascasio, H. U. Virgen del Rocío; Sonia Pascual, H. Gral. U. de Alicante; Martín Prieto, H. U. La Fe; Fernando Rotellar, Clínica Universitaria de Navarra; Magdalena Salcedo, H. Gral. U. Gregorio Marañón; Trinidad Serrano, H. Clínico U. Lozano Blesa; Angel Manuel Vargas, H. U. Virgen de la Arrixaca; Evaristo Varo, H. Clínico U. de Santiago; M^a Trinidad Villegas, H. U. Virgen de la Nieves. The consensus group greatly appreciates the continuous support by Paloma Bellés from AOPC for her contribution in secretariat and logistic aspects.

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