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REVIEWS

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# Current challenges and future directions for liver transplantation

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## Abstract

Liver transplantation is an effective and widely used therapy for several patients with acute and chronic liver diseases. The discrepancy between the number of patients on the waiting list and available donors remains the key issue and is responsible for the high rate of waiting list mortality. The recent news is that the majority of patients with hepatitis C virus related liver disease will be cured by new antivirals therefore we should expect soon a reduction in the need of liver transplantation for these recipients. This review aims to highlight, in two different sections, the main open issues of liver transplantation concerning the current and future strategies to the best use of limited number of organs. The first section cover the strategies to increase the donor pool, discussing the use of older donors, split grafts, living donation and donation after cardiac death and mechanical perfusion systems to improve the preservation of organs before liver transplantation. Challenges in immunosuppressive therapy and operational tolerance induction will be evaluated as potential tools to increase the survival in liver transplant recipients and to reducing the need of re-transplantation. The second section is devoted to the evaluation of possible new indications to liver transplantation, where the availability of organs by implementing the strategies mentioned in the first section and the reduction in the number of waiting transplants for HCV disease is realized. Among these new potential indications for transplantation, the expansion of the Milan criteria for hepatocellular cancer is certainly the most open to question.

**KEYWORDS**

hepatocellular carcinoma, liver transplantation, machine perfusion, steatosis

**Abbreviations:** AAH, acute alcoholic hepatitis; AFP, alpha foetoprotein; ALD, alcoholic liver disease; BMI, body mass index; CCA, cholangiocarcinoma; CIT, cold ischaemia time; CNI, calcineurin inhibitors; CRCM, colorectal cancer metastases; DAAs, directed antiviral agent; DBD, brain dead donor; DCD, deceased cardiac donor; DDLT, deceased donor liver transplantation; HCC, hepatocellular carcinoma; HCVD+, HCV positive donor; HCV, hepatitis C virus; HCVR+, HCV positive recipient; HPM, hypothermic machine perfusion; IS, immunosuppression; LDLT, living donor liver transplantation; LT, liver transplantation; MC, milan criteria; MDF, maddrey discriminant function; MELD, model for end stage liver disease; MP, machine perfusion; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholicsteatohepatitis; NODAT, new onset diabetes after transplantation; PNF, primary non-function; PTMS, post-transplant metabolic syndrome; SNMP, sub-normothermic machine perfusion; WIT, warm ischaemia time.

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## 1 | INTRODUCTION

Candidates to LT are increasing, leading to a progressive discrepancy between the number of patients on the waiting list and the number of available donors.[1]

Strategies to minimize the impact of the donor shortage are being evaluated. The use of organs from donors infected by hepatitis C (HCV) or donors after cardiac death (DCD) are expected to increase while the use of older liver grafts and splitted livers already contributed to expand the organ pool. An additional issue to improve graft

**TABLE 1** Current and future strategies to reduce the donor organ shortage

| Strategies | | |
|---|---|---|
| **Increase the donor pool** | **Improve the preservation of the graft** | **Maximize the post-transplant long-term survival** |
| • Use of older donors<br>• Consider systematic splitting graft procedure in cadaveric organs<br>• Living donor LT<br>• Use of HCV positive grafts<br>• Use of DCD donors | • Use of machine perfusion systems | • Reduce or avoid immunosuppression after LT to minimize side effects |

LT, liver transplantation; HCV, hepatitis C virus; DCD, donor after cardiac death.

**Key points**

- Donor shortage is the key issue in liver transplantation.
- Strategies to overcome donor shortage are to increase the use of older donors, split grafts and living donors as well as the donors after cardiac death.
- New antivirals for treating hepatitis C will reduce the need of transplantation in HCV positive patients, allowing to save organs.
- The expansion of Milan criteria for liver transplantation in patients with HCC will become the hottest topic if more donors will be available.
- Liver transplants in NAFLD and NASH-related cirrhosis are expected to rise.

**TABLE 2** Future trends in the indications for LT

| Future indications for LT | | |
|---|---|---|
| **Expected** | **Controversial** | **Questionable** |
| NAFLD/NASH<br>• Decompensated cirrhosis<br>• HCC<br>HCC beyond Milan criteria | Acute alcoholic hepatitis<br>Acute on chronic liver failure | Non-HCC liver tumours<br>Liver metastases from colorectal cancer |

NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; HCC, hepatocellular carcinoma.

utilization is to expand the knowledge of technologies such as the machine perfusion (MP) systems. Protocols to reduce or avoid immunosuppression after LT will be crucial to minimize side effects and improve long-term survival.

This review aims to highlight the main open issues that presumably will change the scenario of LT in the near future.

The first section (Table 1) covers the strategies to overcome donor shortage and to maximize post-LT survival. The second section (Table 2) is devoted to the evaluation of potential new indications to LT, supposing that the availability of organs will increase by implementing the strategies mentioned in the first section and by the reduction in the number of waiting transplants for HCV disease due to the great efficacy of new direct antiviral agents (DAAs) in curing these patients.

## 2 | STRATEGIES TO OVERCOME DONOR SHORTAGE

### 2.1 | Use of older donors

Older donors presented frequently comorbidities such as obesity and metabolic syndrome, which are associated with liver steatosis and the increased risk of graft failure after transplantation as well as with biliary, vascular, infective and immunological complications.[1-10]

These observations raise the question whether older liver grafts might be offered to the sickest candidates that are at urgent need for LT. Considering the difference between life expectancy with and without transplantation in patients with high MELD scores, the so-called transplant benefit, it remains very high using older donors.[11] There is a strong debate in defining threshold of transplant benefit and how to predict it on the bases of older donor–recipient match. It has been suggested that to ensure a similar post-LT outcome obtained using young donors, it would be preferred to allocate liver grafts >70 years of age in first time recipients >45 years, with body mass index (BMI) <35 kg/m$^2$, non-status 1 registration, cold ischaemia time <8 h and either with hepatocellular carcinoma (HCC) or alcoholic cirrhosis.[10] Although many transplant centres agreed with these allocation criteria, they are not yet validated prospectively.

Several scores to objectively predict the transplant benefit have been developed and validated.[11-14] The BAR score [11] included 2 variables related to the donor (age and cold ischaemia time) and four variables related to the recipient (age, MELD score, re-transplantation status and the need of mechanical ventilation). This score identified a threshold of 18 points that predict a post-LT mortality ≤20%. Although this score could help in the decision to perform the best donor–recipient match, additional donor factors such as graft steatosis and cold ischaemia time imply a reduction in the BAR score threshold of mortality from 18 to 9 points.[11]

In refusing to allocate an older organ to a patient with severe liver disease on the waiting list, it should be carefully considered the risk of mortality of this patient while waiting for the next organ. This aspect makes the use of older organs with different criteria among liver transplant centres, depending on the volume of transplants and on the relationship between the number of transplants performed and the number of patients on the waiting list.

### 2.2 | Splitting grafts and living donor liver transplantation

Liver transplantation performed with splitted grafts in Europe and in USA accounted about 6% in the past decade[15,16] while in Asia comprised more than 90% of the transplant activity.[17]

Although outcomes of LT performed using partial grafts are good, there are specific complications associated with this technique. The small for size syndrome, related to a reduced ratio between graft and recipient body weight, is characterized by prolonged jaundice, graft dysfunction and sometimes graft failure. Moreover, biliary and vascular complications are more frequent, especially in recipients with high MELD scores.[16]

Living donor liver transplantation (LDLT) has emerged as a promising alternative to overcome donor shortage.[18]

The improvements in LDLT have led to the expansion of the recipient criteria to include patients previously considered not suitable for LT because of older age or comorbidities. Living donors older than 45 years are often discarded since the risks of these LDLT remains controversial. Goldaracena et al.[19] compared patients receiving a LDLT from 91 donors aged ≥50 years with 378 younger than 50 years. The incidence of biliary complications as well as graft and patients survival at 1, 5 and 10 years were similar between both groups. The use of LDLT in recipients older than 70 years has been evaluated by Oezcelik et al.[20] enrolling 469 patients. No significant differences in complications, hospital stay, perioperative mortality or median survival compared to the younger group were found.

The morbidity of LDLT donors ranges from 8.6% to 59%[21-24] and the overall mortality was about 0.2%.[21] The commonest complications were leaks and biliary strictures with an incidence of 9%.[25] Some donors may suffer from psychiatric problems though most of them believe that they had benefited from the donation experience.[24,26,27]

Although LDLT in Europe and USA decreased after 2011 due to the reports of donor deaths,[28] the understanding of the biochemical mechanisms of graft injury and the possibility to promote liver regeneration will be the key issues for the improvement of the use of partial liver grafts.

## 2.3 | Use of hepatitis C virus positive grafts

Liver grafts from donors infected with hepatitis C (HCVD+) transplanted in HCV positive recipients (HCVR+) demonstrated that it was not associated with a worse outcome.[29] In a recent study, among 694 HCVR+, 76 (11%) received a graft from HCVD+. Sixty-three of these patients were compared with 63 patients that received an HCVD− graft. Although HCV recurrence was more rapid in the HCVD+ grafts recipients, this difference did not reach statistical significance.[30] Other studies showed that in HCVR+, donor HCV positivity did not affect graft and patient survival or the severity of HCV recurrence when compared with grafts from HCVD−.[31-35] It should be taken into account that these results were obtained after a careful selection of HCVD+, performing LT in HCVR+ with low MELD scores.

Although some issues still have to be addressed (i.e. more effective treatment options in HCV genotype 3, drug–drug interactions), new DAAs against HCV permit to cure more than 90% of HCV positive liver transplanted patients.[36-39] Thus, when transmitted during LT from HCVD+, recurrent hepatitis could be easily cured, contributing to the further expansion of the use of HCVD+.

It is estimated that about 2% of donors are HCV positive but the number of usable liver grafts is reduced considering other quality criteria as age, steatosis and fibrosis.[40] As a result of widespread adoption of DAA in HCV+ patients.[41] HCVD+ will be more frequently HCV-RNA negative. Even if the number of potential HCVD+ seem to be small, policies approving the use of HCVD+ for HCVR+ in solid organ transplants different from the liver could represent a new tool in improving the donor pool. This strategy has been already associated with a reduction in time on the waiting list in kidney transplantation.[42]

## 2.4 | Donors after cardiac death

The use of Maastricht type 3 donors after cardiac death (DCD) represents a widely extended practice to increase the pool of organs.[43] In the past 10 years in the USA, 2.710 liver donors have been DCD organ donors, with the largest numbers used in the last 2 years.[44] Although previous series of DCD LT demonstrated a greater risk of graft failure related to non-anastomotic biliary strictures,[45-48] more recent reports showed similar outcomes between DCD and DBD.[49,50]

A first question concerns the criteria that can be used to properly select DCD for LT. Younger DCD with short warm (DWIT) and cold (CIT) ischaemia times resulted in graft survival rates similar to those associated with DBD.[51,52] Similarly, the risk of ischaemic cholangiopathy has been associated with older donor age, prolonged CIT[53] and total ischaemia time and increased donor weight.[54]

The second question is if these parameters are good enough to determine if a DCD liver graft should be considered suitable for transplantation. Although prolonged DWIT is the main determinant in conditioning a worse graft survival, the duration of donor hypotension or hypoxaemia may be better predictors of poor outcomes after DCD LT.[55]

A further question is to identify the ideal candidate to receive a DCD donor.[56] Previous reports demonstrated that DCD livers were used more frequently than DBD livers in patients with HCC.[50,57] This is likely due to increasing tendency to use extended criteria organs in recipients with lower MELD scores because of the perception that these recipients can tolerate better a graft dysfunction after LT.[58] In this study by Croome et al.[59] 397 HCC patients underwent LT, 340 with DBD and 57 with DCD. HCC recurrence in DBD and DCD group was 12.1% and 12.3%, respectively, without differences in recurrence-free survival. Interestingly, a recent report by the same Author raised some concerns about the use of DCD for LT recipients with HCC.[60] In this study, both patient and graft survival was lower for recipients of DCD compared to DBD allografts. In this paper, the percentage of recipients with alpha foetoprotein (AFP) serum levels >400 ng/ml and treated with trans-arterial chemoembolization was significantly higher in those received DCD compared to those received DBD donors. Thus, a possible explanation of a significant reduced survival of HCC recipients transplanted with DCD donors could derive from the potentiation of the effect of inferior survival combining simultaneously two determinants of worse outcome, that is, DCD and HCC, as demonstrated by the significant statistical interaction between these two factors.

The improvement of the ability to perform *ante mortem* interventions that may improve the likelihood of successful donation and the graft outcomes should take into account the delicate aspects related to the ethics and to the laws among different countries.

### 2.5 | Machine perfusion

Machine perfusion (MP) indicates dynamic strategies applied ex vivo of organs for transplantation aiming to improve the static cold storage preservation. MP can be applied at the donor site before cold storage, at the receiving hospital after cold storage prior to implantation or throughout the preservation period.[61] The configuration of MP is related to three parameters: the timing and the duration of its application and the perfusion temperature. Perfusion through the portal vein is only feasible at low temperatures[62] while, considering the biliary preservation, arterial perfusion and the oxygen supply to the biliary tree seem to be crucial because the biliary system depends mainly to arterial circulation.[63]

Hypothermic (0–10°C) machine perfusion (HMP) has the advantage that if the pump fails the organ falls back on the previous static cold storage. The main limitation is that under the perfusion at low temperatures it is impossible to assess the liver functions such as the bile production.[64] Guarrera et al.[62] reported the outcome of the first 31 cases of LT using HMP. The number of biliary strictures in the HMP preserved group was significantly lower compared to controls preserved with cold static storage. Dutkowski et al.[65] applied an oxygenated version of HMP (HOPE) to verify the outcomes in eight LT from DCD compared to DCD not treated with HOPE. The rates of biliary strictures were similar in the two groups.

Sub-normothermic (20-30°C) MP (SNMP) has the advantage to be simple to use and by inducing a metabolic rate of approximately 25% of physiological levels, allows for a better assessment of liver function compared to HMP.[66] SNMP needs the use of a nutrient enriched perfusate to avoid depletion of nutrients for the liver metabolism while is under debate if the use of an oxygen carrier should be essential.[67,68] Knaak et al.[69] compared SNMP with static cold storage in DCD pig livers. Cold stored grafts presented several bile duct necrosis 7 days after LT but those preserved with SNMP did not, suggesting a protective effect of SNMP on the biliary ducts in DCD model of pig transplantation.

Several authors suggest that NMP is superior to cold perfusion because it provides the closest metabolic condition to the normal physiological situation of the liver in vivo,[70] leading to perform functional tests of liver function during the preservation time.[71] The limitation of NMP is that interruption of the perfusion or insufficient oxygen delivery exposes immediately the graft to warm ischaemia damage. The efficacy of NPM in preserving the biliary tree from the ischaemic damage was demonstrated in 12 discarded human livers and the bile production during NPM was used as a predictor graft function, enabling viability testing.[71,72]

Data obtained in the animal models and in discarded human livers provide convincing evidence that MP is very effective in protecting biliary three from ischaemic damage. It could be anticipated that the extensive use of MP can lead to a significant increase in the availability of transplant livers as well as a significant reduction in several types of graft dysfunction and biliary complications.

## 3 | STRATEGIES TO MAXIMIZE LONG-TERM SURVIVAL

### 3.1 | Tolerance induction

Side effects of calcineurin inhibitors (CNI) are associated with several complications[73,74] that are responsible for long-term mortality in LT patients.[75] Thus, assess whether the reduction or suspension of IS can be implemented and its effect in the long term appears of great interest.

Tolerance is defined as a state of immune non-reactivity towards a specific set of antigens that is indefinitely maintained in the absence of ongoing immunosuppression (IS). LT can be considered as a peculiar clinical setting since the rate of long-term tolerant liver patients may reach 20%.[76,77]

The question is how to promote the natural propensity of the liver graft to be accepted and which type of IS should be used for its maintenance. Different approaches to attain allograft tolerance are being clinically explored.

One approach consists in the administration of induction therapies. The infusion of donor hematopoietic cells (DHC) after aggressive recipient immune-conditioning has been proposed.[78-81] Donckler et al. conducted two trials using DHC infusions after living donor LT and non-myeloablative conditioning reaching the tolerance state in some patients,[82,83] however, these studies have some significant limitations: the toxicity of the peri-transplant conditioning regimens apart from the fact that these protocols are almost exclusively reserved for LDLT. The liver itself may serve as a source of donor cells that may migrate to recipient hematopoietic sites, promoting tolerogenic effects.[84] Accordingly, an acceptable strategy for tolerance could take into account the natural propensity of a liver graft to be accepted forcing induction treatment with depleting agents[85] as performed in renal transplantation with polyclonal[86,87] or monoclonal antibodies.[88] The limitation of these protocols may be that polyclonal or monoclonal antibodies do not affect all T-cell subsets. T-cell populations escaping or rapidly reemerging after initial depletion may be responsible for acute allograft rejection upon drug withdrawal.[89,90]

A further strategy to promote tolerance involved the regulatory T cells (Tregs).[91] Recent developments in generating and expanding Tregs ex vivo and in vitro,[92] support the potential use of Treg-based therapies to induce tolerance. Based on experiments in rodents, two major strategies have been designed for the therapeutic use of Tregs in humans: adoptive transfer of ex vivo expanded Tregs and de novo induction or conversion of non-Tregs cells into Tregs in vivo. The current major limitation to Treg cellular therapy is not related to the safety, but rather generating sufficient numbers of Tregs for therapeutic use.[93]

Mammalian target of rapamycin (mTOR) inhibitors may promote immune tolerance. Conversion to mTOR inhibitors could have an additional beneficial effect by favouring the expansion of immune-regulatory

T cells,[94,95] which in animal models has been linked to transplantation tolerance. Whether these data would favour successful discontinuation of immunosuppression in humans is still unknown.

Nevertheless, few of the studies performed so far have provided a convincing benefit of IS withdrawal on pre-existing complications derived from the long-term administration of immunosuppressive drugs.[93,96,97]

## 4 | EMERGING INDICATIONS FOR LIVER TRANSPLANTATION

### 4.1 | Non-alcoholic fatty liver disease

Non-alcoholic fatty liver disease (NAFLD) is a rising cause of liver disease in Western countries. About 30% of patients with NAFLD can develop non-alcoholic steato-hepatitis (NASH), progressing to cirrhosis in up to 30%.[98] The prevalence of HCC seems to be higher in NASH than in patients with cholestatic (17.3% vs 7.1%) and similar (17.3% vs 13.6%) compared to patients with alcoholic liver disease (ALD).[99] Cirrhosis and HCC due to NAFLD/NASH have become the second leading indication for LT in USA, increasing by 170% from 2004 to 2013.[100]

The clinical evaluation of NAFLD/NASH candidates to LT represents a challenging issue for the transplant hepatologist, since overweight, obesity, diabetes, hypertension, cardiovascular diseases and dyslipidemia associated with NAFLD/NASH should be carefully identified in the clinical work-up. Dynamic cardiac tests should be performed to discover asymptomatic cardiovascular diseases, especially for diabetic and smokers recipients older than 50 years.[101]

Morbid obesity has been considered a contraindication for LT due to the high risk of postoperative surgical complications, infections and length of hospitalization.[102] In these candidates, after a strict evaluation by expert dietitians and psychologists to rule out eating disorders,[101] bariatric surgery before LT or sleeve gastrectomy during LT has been adopted.[103]

In selected NAFLD recipients, 1 and 3-year patient survival after LT[104] is better compared to HCV or ALD recipients.[105] Conversely, data on survival after LT for NASH-related HCC are controversial. In a study conducted in 17 patients, 5 years survival was 88.8%, even though in 6 recipients HCC was incidentally diagnosed at time of explant.[106] On the contrary, the metanalysis of 2 studies reported a potential unfavourable survival in patients with NAFLD and HCC, compared with non-NAFLD HCC cohorts.[107]

Non alcoholic fatty liver disease and non alcoholicsteatohepatitis may recur after LT in about 50% and 30% of recipients respectively. New onset diabetes after LT (NODAT), dyslipidemia and metabolic syndrome were independent risk factors for NASH recurrence but, at a mean follow-up of over 3 years, it seems not influence graft failure or mortality.[106,108]

Prevalence of Post-Transplant Metabolic Syndrome (PTMS) defined according to International Criteria,[109] ranged from 44% to 58%[110] and is expected to rise in the next years.[100] Identified risk factors for PTMS are male gender, higher pre-LT BMI and pre-LT diabetes.[111]

Despite NODAT, hypertension, dyslipidemia and other metabolic complication are treatable by drugs, overweight should be treated through lifestyle interventions including dietitians and physiotherapists.

### 4.2 | HCC beyond Milan criteria

About 20 years ago, the Milan criteria (MC; 3 nodules <3 cm or a single nodule <5 cm without vascular invasion) have been proposed to select patients with HCC achieving the best survival after LT. Patients within MC had 5-year survival of about 70% with tumour recurrence <10%.[112] This survival matches post-transplant survival of most other indications for LT, therefore MC still represent the globally accepted score system to consider patients with HCC suitable for LT.

There are several reports indicating that a modest expansion of the MC could increase the number of selected candidates to LT without negative impact on survival.[113] A potential extension of the criteria for LT in HCC must take into account the benefit for individual with HCC as well as the consequences for all potential liver recipients. Since post-transplant survival could be reduced due to higher HCC recurrence by expanding MC, it has been accepted that any proposal to expand MC must be associated with a predicted 5 years survival post-LT higher than 60%.[114] To obtain that, the benefit achievable in HCC beyond MC must be adjusted to acceptable levels of post-transplant utility, avoiding any harm to the prioritization for LT in patients without HCC still in the waiting list.

Multiple metrics criteria exceeding the MC have been proposed. The University of San Francisco (UCSF) criteria (single tumour <6.5 cm, or up to three nodules <4.5 cm and a total sum <8 cm)[115] and the Up-to-Seven criteria (HCC with seven as the sum of size of the largest nodule and the number of nodules)[116] determined a modest enlargement of patient selection beyond MC. Moreover, the Metroticket concept[116] stated that the further HCC staging criteria for LT are expanded, the greater the cost will be in terms of recurrence after LT and poorer overall survival.[117]

All the aforementioned criteria based on pure pre-transplant morphological evaluation of the tumour. These approaches suffer heavily the diagnostic accuracy of the imaging methods and, more importantly, do not consider aspects determining cancer prognosis such as the tumour biological characteristics and response to treatment.

To overcome these drawbacks, new selection criteria, adding to morphological characteristics of HCC, AFP serum levels has been proposed . Duvoux et al.,[118] analysing 537 LT recipients, showed that among patients exceeding MC, those with serum AFP<100 ng/mL presented the same risk of recurrence to patients within MC. Furthermore, Toso et al.,[119] validated prospectively a model that combined the total tumour volume ≤115 $cm^3$/serum AFP ≤400 ng/mL (TTV/AFP) to evaluate the drop out risk during waiting time and 4 years survival after LT in 38 patients with HCC beyond MC, compared to 195 patients within MC. Although the risk of drop out was higher in patients beyond MC but within TTV/AFP compared to those within MC (42.1% vs 25.1%), no significant differences in terms of HCC recurrence (9.4% vs 4.5%) and 4 years survival post-transplant (74.6% vs 78.7%) were recorded.

This study demonstrated that patients beyond MC but within TTV/AFP criteria could be considered good HCC candidates for LT, particularly in liver transplant centres with at least 8 month waiting time. Given this, the risk of waiting list dropout may be considered in the selection process for LT in HCC. In fact, in this study, the waiting time selected patients with a more aggressive tumour phenotype, avoiding their futile candidacy to LT.

The attractive concept to identify biological markers to predict HCC phenotype influencing its progression as well as response to treatments has been extensively investigated.[117] Unfortunately the molecular heterogeneity of HCC represents the impassable obstacle to the introduction of molecular or genetic signatures that could help the management of patients with HCC in clinical practice.[120]

More feasible, on the clinical point of view, is to evaluate the tumour behaviour merging the tumour stage and response to treatments. This approach has been recently adopted for selecting patients with HCC beyond MC for LT in Italy[121] and in many European transplant centres. This approach derived from observations indicating that post-LT survival in patients with HCC beyond MC who achieved objective and sustained response to pre-LT treatments was not significantly different compared to those obtained transplanting patients with HCC within MC.[113] Based on these assumptions, a current interesting approach to explore the feasibility to expand MC can be done following several steps of patient evaluation. Firstly, HCC patients should be selected at presentation with criteria able to ensure 5 years post-LT survival at least of 60%. These patients are considered to have a "transplantable tumour" (TT). Either MC or extended criteria (i.e. UCSF, up-to-seven, TTV/AFP) may be used to select patients with TT. Secondly, patients who have TT should be classified using a more dynamic process, including not only the first presentation characteristics of HCC but the type of response to bridging therapies, the achievement of objective down-staging within MC and the time of recurrence after treatment.[121] Classes of progression within TT will include patients with HCC completely removed by curative treatments, patients experiencing late recurrence (>2 years from a previous curative treatment) and patients with early recurrence or incomplete response to treatment who presented within conventional MC at the time of recurrence or after partial treatment response.[122] After this evaluation process, a stratification to prioritize for LT can be made in patients with HCC, taking into account both the urgency principle (risk of drop out) and the utility principle (maximum survival post-LT). The dynamic definition of TT based on treatment response is able to delay the priority for LT in HCC patients who can wait in favour of those who are still within transplant criteria but are at increased risk of drop out due to tumour progression or incomplete treatment response. These aspects emphasized that this approach really select HCC patients for LT with the best transplant benefit not precluding the access to LT to those presenting at baseline a tumour beyond MC.

Although this approach seems to be innovative and clinically sustainable, any decision to consider an expansion of MC should take into account the mortality on the waiting list in each liver transplant centre and should not be applied if it is expected to rise by additional expanded criteria.

Even though MC remain the preferred model to allocate organs to patients with HCC, due to the excellent post-LT survival,[112] a modest expansion of these criteria is reasonable and feasible in the case of strategies to implement the availability of organs are effective.

## 5 | CONTROVERSIAL INDICATIONS TO LT

### 5.1 | Acute alcoholic hepatitis

Acute alcoholic hepatitis (AAH) is associated with 1, 3 and 6 months mortality of 16%, 27%, and 40% respectively.[123]

Among the validated prognostic scores, the Maddrey Discriminant Function (MDF) is the most used. MDF score>32 is considered a strong predictor of short-term mortality in AAH.[124]

Steroids are accepted treatment for severe AAH although their use is still matter of debate. A meta-analysis by Rambaldi et al.,[125] including 721 patients, showed that steroids did not reduce mortality compared with placebo or no intervention. In another meta-analysis by Mathurin et al.,[126] steroid treatment was associated with better short-term survival than no treatment (79.9% vs 65.7%).

The Lille model[127] has been developed to predict the efficacy of steroid therapy. A Lille model ≥0.45 seven days after steroid therapy is highly predictive of treatment failure and justify the treatment withdrawal.

In a very selected group of patients with AAH not responding to steroids LT has been experimentally proposed after a selection process based on a multidisciplinary approach. Twenty-six patients at their first episode of liver decompensation with biopsy proven AAH, not responders to steroids, underwent LT.[128] The 6 and 24 months survival after LT were significantly higher than not transplanted matched controls with severe AAH (77% vs 23%). Recently, Im et al.[129] confirmed the favourable outcome of early LT in a US cohort of 94 patients with AAH. The strict selection process, considering psychosocial evaluation as the primary "next-step" following identification of nonresponse to medical therapy, determined a reduced access to early LT (9.6% of patients evaluated) but 6 months survival extremely better than matched controls (89% vs 11%).

The main concern is the risk of recidivism when transplantation is performed in patients who were still drinking during the onset of AAH. In the study by Mathurin et al.,[128] 11.5% of patients resumed alcohol consumption up to more than 3 years after LT.

Giving a graft to these patients could be considered disrespectful, with a potential negative impact on donation rate. However, a recent survey revealed that early LT for AAH would not influence the will to organ donation in the majority of people.[130]

Potential candidates to LT for AAH have to be carefully selected through absolute consensus multidisciplinary staff, absence of serious morbidities, social integration and supportive family members. The next steps should include transparent communication with the society, prevention of an a priori exclusion to the evaluation for LT and the identification of accepted selection criteria that provide the best long-term outcomes.[131]

### 5.2 | Acute-on-chronic liver failure

Acute-on-chronic liver failure (ACLF) is a clinical syndrome characterized by a rapid onset of liver decompensation and a poor prognosis. Moreau et al.[132] defined ACLF in the presence of the 3 major characteristics: acute decompensation, organ failure and high short-term mortality (32.8% and 51.2% at 28 and 90-day respectively).

Main causes of ACLF are alcoholic hepatitis, drug-induced liver injury, superimposed viral hepatitis, portal vein thrombosis and bacterial infections.[133] ACLF may be also caused by extra-hepatic insults such as ischaemic hepatitis and trauma or surgery, while in a substantial proportion of patients no identifiable precipitating factors are identified.[134]

Despite ACLF is now considered a defined syndrome, several aspects have to be taken into account to consider ACLF patients as candidates to LT. First, the tools adopted to make a prognosis were not specific since they derived from other clinical conditions. The majority of studies that explored the prognosis of ALCF adopted the CLIF-SOFA score,[132] which was considered a good predictor of early survival for patients admitted to intensive care unit even if in other studies an increase >5 points of MELD score within 4 weeks is considered enough for prognosis.[135] Furthermore, ACLF patients with MELD >35 showed worse prognosis than patients with acute liver failure (ALF) listed with UNOS Status 1.[136]

Secondly, the unclear criteria for prioritization to LT since these patients usually present with a multi-organ involvement or severely impaired general conditions that are not always revealed by MELD score.

Third point refers to the absence of solid and validated tools to identify the threshold of futility of LT. According to data provided by Gustot et al.,[137] resolution of ACLF is observed in 42.5% of patients, who will not benefit of LT. On the contrary, those patients who can be potential candidates for LT, often present several contraindications to LT as bacterial infections or haemodynamic instability. Due to the rapid deterioration of clinical conditions in several patients with ACLF there is not enough time to give a global evaluation of the candidate. Given that, in the CANONIC study, only 9% of ACLF patients underwent LT within 28 days of admission and 15% at 90 days.[132]

Acute-on-chronic liver failure will represent a challenge for transplant hepatologists, in terms of accurate diagnosis, correct treatment of trigger factors and adequate prognosis. Despite the increasing number of patients with ACLF, larger prospective studies are needed to correctly identify the best prognostic markers and the optimal timing for LT.

### 5.3 | Non-HCC liver tumours

Cholangiocarcinoma (CCA) accounts for 5% to 20% of liver malignances. For unresectable peri-hilar CCA at early stage (I-II), LT has been considered an experimental therapeutic option. It comes from the results obtained by Mayo Clinic multi-step protocol, which includes external beam radiation, brachytherapy and oral chemotherapy before abdominal exploration for tumour staging.[138] This protocol applied in 12 US LT centres determined 5 years recurrence-free survival of 65%.[139]

Few LT for from colorectal cancer metastases (CRCM) were performed with a discouraging 1 and 5-year survival.[140] More recently, Hagness et al.[141] proposed LT to 21 patients with unresectable CRCM, providing 1, 3 and 5 year survival of 95%, 68% and 60% respectively, which can be considered comparable or even better than liver resection.

Although these results may appear encouraging, it must remember that they derived from experimental protocols enrolling few and very selected patients. At present, it is not possible to consider these indications to transplant sufficiently solid in order to enter into clinical practice.

## 6 | CONCLUSIONS AND PERSPECTIVES

The future scenario of LT will focus as a priority on the lookout for the donor pool expansion methods and systems available through the use of older donors and DCD. The development of more sophisticated techniques for organ preservation and perfusion will help to significantly reduce the damage induced by ischaemia. The current availability of DAAs against HCV will reduce the need for LT in HCV positive patients, opening the issues to evaluate for LT new indications as HCC beyond MC.

The ability to increase the survival of liver transplanted patients will further challenge for the future, through research of immunological markers adapted to select immune-tolerant recipients in whom the immunosuppressive drugs can be minimized or suspended permanently.

The search for ethical principles as well as clinical proper allocation of organs will still have a major role in the choice of decisions in a context of rapid and constant evolution.

### CONFLICT OF INTEREST

The authors do not have any disclosures to report.

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