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REVIEW ARTICLE

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Specific issues concerning the management of patients on the waiting list and after liver transplantation

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Abstract

The present document is a second contribution collecting the recommendations of an expert panel of transplant hepatologists appointed by the Italian Association for the Study of the Liver (AISF) concerning the management of certain aspects of liver transplantation, including: the issue of prompt referral; the management of difficult candidates; malnutrition; living related liver transplants; hepatocellular carcinoma; and the role of direct acting antiviral agents before and after transplantation. The statements on each topic were approved by participants at the AISF Transplant Hepatology Expert Meeting organized by the Permanent Liver Transplant Commission in Mondello on 12-13 May 2017. They are graded according to the GRADE grading system.

KEYWORDS

end stage liver disease management, hepatocellular carcinoma, patient referral, transplant hepatologist

1 | INTRODUCTION

The present document is a second contribution collecting the recommendations of an expert panel of transplant hepatologists appointed by the Italian Association for the Study of the Liver (AISF) concerning the management of some of the most common aspects of liver transplantation (LT). The method adopted to produce these recommendations involved the following steps: the six current members of the AISF Permanent Liver Transplant Commission (CPT) and one previous AISF CPT member jointly selected six topics of major interest. One concerns the interaction between hepatologists and transplant centres: how can the referral of candidates for LT be improved? The second topic concerns the management of difficult candidates for LT. The third relates to nutrition before and after transplantation. The fourth aimed to provide an update on living donor LT, and its prospects. The fifth focuses on hepatocellular

Abbreviations: [99m]Tc-MAA, macro-aggregated albumin lung perfusion scan; AaO_2, alveolar-arterial oxygen gradient; ABM, French National Agency for Organ Sharing and Transplantation; ACLF, acute on chronic liver failure; AFP, alpha-foetoprotein; AISF, Italian Association for the Study of the Liver; AKI, acute kidney injury; ALF, acute liver failure; BMI, body mass index; BTS, British Transplantation Society; CKD, chronic kidney disease; CPT, Permanent Liver Transplant Commission; CT, computed tomography; DAAs, direct acting antiviral agents; DDLT, deceased donor LT; ESLD, end-stage liver disease; GFR, estimated glomerular filtration rate; GRBWR, graft to body weight ratio; HCV, hepatitis C virus; HPS, hepatopulmonary syndrome; HRS, hepatorenal syndrome; ICA, International Ascites Club; ILTS, International Liver Transplant Society; KDIGO, Kidney Disease, Improving Global Outcomes; L3 SMI, L3 skeletal muscle index; LDLT, living donor liver transplantation; LKT, liver-kidney transplant; LT, liver transplantation; MDRD6, modification of diet in renal disease 6; MDT, multidisciplinary team; MPAP, mean pulmonary artery pressure; MRI, magnetic resonance imaging; PAPs, systolic pulmonary arterial pressure; PMA, psoas muscle area; PPH, portopulmonary hypertension; QoL, quality of life; RFH-GA, Royal Free Hospital-Global Assessment; SVR, sustained virological response; TIPS, transjugular intrahepatic portosystemic shunt.

carcinoma (HCC) and LT: is it time to expand the criteria adopted in Italy? The sixth topic of interest concerns how to deal with the failure of DAA treatment before and after LT.

As in the preparation of a previous position paper, the AISF CPT members appointed a working group for each of these topics, and one of the six AISF CPT members each chaired one of these groups of experts. A total of 49 transplant hepatologists (experts), identified on the grounds of their competence, role, expertise and publications/research in the field of end-stage liver disease and LT, were invited to join the working groups. The composition of the six groups is given in the Appendix. The chairman of each group selected the relevant clinical questions, relating both to clinical practice and to controversial issues.[1]

Key points

- Patient eligible for liver transplantation should be referred to a transplant hepatologist, evaluated and managed with transparency and consistency among different centres.
- Patients awaiting liver transplantation may have extra hepatic comorbidities and impaired nutritional status, therefore a multidisciplinary approach aimed to implement candidate selection, balanced calorie intake, physical activity and behavioural changes, is needed.
- Living donor liver transplant is challenging because of donor and recipient issues and requires professionals working in multidisciplinary team.
- Indications to liver transplantation are changing with decreasing burden of HCV-related end stage liver disease, and HCC will become the leading indication.

2 | INTERACTION BETWEEN HEPATOLOGISTS AND TRANSPLANT CENTRES: HOW CAN THE REFERRAL OF CANDIDATES FOR LT BE IMPROVED?

End-stage liver disease (ESLD) is an increasingly common cause of death worldwide. In the USA, the years of life lost before the age of 75 because of ESLD has risen from 164.1 per 100 000 in 2000 to 190.3 in 2015, exceeding the life years lost because of cerebrovascular disease (161.0), colorectal cancer (123.3) and HIV (50.4).[2] LT is the best treatment for selected patients with ESLD, including those with decompensated cirrhosis and HCC. There are several barriers, however, that make it difficult for potentially eligible patients with ESLD to access LT at various stages. The obstacles may relate to: (a) referral to a LT centre for hospitalized cases or outpatients, by primary care physicians or specialists; (b) screening activities conducted by LT centres to confirm a patient's eligibility for LT, and exclude contraindications; (c) patient listing, and patient management to enable them to survive while on the waiting list; and (d) organ allocation.

All patients with ESLD who are potentially eligible for LT should have equal access to waiting lists according to principles of equity, justice, and consistently managed within each centre, according to transparency. Failure to refer patients to LT centres, or delaying their referral, and/or excessively selective screening practices at LT centres are possible reasons why potentially eligible LT candidates with ESLD have limited access to waiting lists. Although the estimates are only approximate (because of methodological bias), there is published evidence of such omitted referrals and low rates of ESLD patients on waiting listing.[3-12] Data on the prevalence of referrals to LT centres coming too late are scarce, and limited to patients with HCC.[13] To avoid their excessively late referral, it is strongly recommended that the initial referral of potentially eligible ESLD patients to LT centres be optimally timed, i.e, before the disease reaches the stage when the patient's listing for LT is actually indicated.[14-16] This is partly because it takes time for such potential candidates for LT to undergo the necessary multidisciplinary assessment before they can join the waiting list, and partly because the condition of some patients with ESLD may deteriorate rapidly, soon preventing them from accessing a LT. Few data are available on LT centres' selection procedures for including candidates with ESLD on their LT waiting lists.[10,13]

2.1 | Question 1

Is there any evidence of inadequacies in the referral of ESLD patients who are potential candidates for LT and/or their access to waiting lists (worldwide vs Italy)?

2.1.1 | Statement

Referral is defined as the first contact with a transplant hepatologist. In Italy there is a low referral rate for ESLD patients, but referral patterns and LT waiting list accessibility to potentially eligible candidates with ESLD should be monitored, clarifying the causes of suboptimal access and taking action to improve it. **(B, I)**

2.1.2 | Comment

Although the estimates are scarcely accurate because of methodological bias, evidence published in the USA and France points to a low rate of access to LT waiting lists for potentially eligible candidates with ESLD. In particular, retrospective studies comparing the number of adult patients with ESLD actually listed with the number potentially eligible, or with the number of deaths among such potentially eligible candidates for LT, showed they accounted for relatively small proportions of the patients listed from 1999 to 2014, in the range of 5%-29%.[3-6,9] It is also clear from retrospective studies performed in the USA, France and Germany, especially those focusing on alcoholic-related liver diseases, and enrolling patients from 2002 to 2013, that the small proportions of patients with ESLD on waiting lists was largely because of the low rate of referral of such potential candidates for LT to transplant

centres.[7,8,10-12] No published data are available on the rates of arrival on the waiting list, referral patterns, or LT centre selection procedures in Italy.

Based on unpublished data drawn from several countries' death and transplant registries in 2014, it was estimated that the rate of access to LT waiting lists for adults with ESLD potentially eligible for LT was similar in Italy to the situation in the USA, but 1.7 times lower than in Spain.[17-22] Thus, there is a need to monitor the referral patterns and the access to the waiting lists in Italy. This could be achieved in the future at two levels. Firstly, by comparing disease-specific death registries of potential LT candidates and detailed reports of all the LT candidates referred to the Italian liver transplant centres. Secondly, the outcomes of all the referred patients (listed or not listed, including reasons for not listing) should be monitored overtime and compared among different centres.

2.2 | Question 2

Do patients with or without HCC have the same chances of being referred to a transplant centre and accessing the waiting lists for LT (worldwide vs Italy)?

2.2.1 | Statement

In Italy, indirect data suggest a difference in the referral of patients with or without HCC, and their access to a waiting list for LT, in favour of patients with HCC. We should measure the accessibility of LT for potentially eligible cirrhotic candidates with and without HCC, to clarify the reasons behind any suboptimal access for such patients, and take action to improve it. **(B, I)**

2.2.2 | Comment

In the USA there is evidence of a marked difference in the numbers of cirrhotic patients with vs without HCC accessing a waiting list for LT.[4] A retrospective study using two large databases in the USA, and enrolling more than 84 000 patients, showed that 29% of patients with HCC potentially eligible for LT, but only 11.9% of patients with stage 4 cirrhosis (ascites), and 12.6% of those with stage 5 cirrhosis (ascites and variceal bleeding) were placed on the waiting list over a 2 year period. Among patients divided by stage of cirrhosis, those with HCC were significantly more likely to be listed for LT, with adjusted sub-hazard ratios ranging from 1.7 (for patients with stage 5 cirrhosis with vs without HCC) to 5.8 (for patients with stage 1 cirrhosis with vs without HCC). This disproportionate access to LT waiting lists in favour of patients with HCC is likely to be even more pronounced in Italy, where the percentage of transplants performed in patients with HCC is almost twice as high as in the USA.[20,23]

2.3 | Question 3

Is there a need to improve the referral of candidates for LT and in which particular aspects?

2.3.1 | Statement

Every effort should be made to increase the rate of referral to a transplant centre and access to a transplant program, because all potentially eligible candidates with ESLD should have the same chances of being assessed for a LT, and should receive optimal pre-transplant treatment. **(B, I)**

2.3.2 | Comment

All potential candidates for LT with ESLD should have the same chances of being assessed for a transplant according to principles of justice and equity with a transparent evaluation, consistent among the different centres. Recent retrospective data from the USA suggest that being listed per se, even for patients who never receive a transplant, affords a survival benefit: the adjusted survival from the diagnosis of ESLD in patients with decompensated cirrhosis and/or HCC was significantly longer for those listed for LT but not transplanted than in potentially eligible candidates who were never listed, in the absence of different medical comorbidities between the two groups.[6]

2.4 | Question 4

When is the best time to refer potential candidates for LT with severe acute hepatitis, acute liver failure (ALF) or acute on chronic liver failure (ACLF)?

2.4.1 | Statement

All patients with severe acute hepatitis, ALF or ACLF should be referred immediately to a liver centre with access to a transplant program. **(B, I)**

2.4.2 | Comment

A retrospective study comparing the number of adult patients with ALF placed on a waiting list for LT with the number of deaths among ALF patients potentially eligible for LT showed a low rate of listing (25%) for patients enrolled in the USA from 1999 to 2006.[9] Since late referral is probably the main reason for such low listing rates for such patients, it is important to refer them to a liver centre as soon as possible, even those with a diagnosis of severe acute hepatitis (i.e, without encephalopathy). The same early referral strategy should be applied to potentially eligible candidates with ACLF too.

2.5 | Question 5

When is the best time to refer patients with HCC who are candidates for a LT?

2.5.1 | Statement

All patients with a suspected or confirmed diagnosis of HCC should be promptly assessed by a multidisciplinary team (MDT) that includes a transplant hepatologist. **(C, I)**

2.5.2 | Comment

Liver transplantation is indicated in patients with HCC meeting the maximum criteria for transplant eligibility, i.e, no evidence of macrovascular invasion or metastasis, and a limited tumour size. The Milan criteria are the most generally accepted, but some centres use expanded criteria for tumour size (San Francisco, Up to seven, etc.). Locoregional treatments may also enable tumours initially exceeding the size restrictions to be downstaged to meet these criteria. It is therefore very important for patients with newly diagnosed HCC to be promptly discussed by a MDT that includes a transplant hepatologist, a liver and transplant surgeon, a liver radiologist, an oncologist and a specialist nurse in HCC. This also applies to patients with very small or even only suspected HCC because LT centres may vary in their approach and the criteria they adopt.[15] Thus, all patients with HCCs and without obvious absolute contra-indication to transplant should be referred to a MDT in a specialized centre with access to all treatments for HCC, including transplantation to reduce the rate of late referrals for transplantation and the risk of biases in treatments.

2.6 | Question 6

When is the best time to refer patients with cirrhosis without HCC for assessment for LT?

2.6.1 | Statement

Patients with cirrhosis unrelated to any cholestatic chronic liver disease and without obvious absolute contra-indication to transplant should be referred to a transplant hepatologist at their first decompensating event, when their MELD score is ≥10 and/or their Child Pugh score is ≥7. **(B, I)**

Patients with cirrhosis because of a chronic cholestatic liver disease and without obvious absolute contra-indication to transplant should be referred to a transplant hepatologist at their first decompensating event and/or when their Mayo score is ≥6.5 for primary biliary cholangitis, or ≥1 for primary sclerosing cholangitis. A dominant biliary stricture, severe metabolic bone disease and symptoms associated with a poor quality of life (QoL), such as intractable pruritus, recurrent cholangitis or xanthomatous neuropathy should also be independent reasons for prompt referral. **(B, I)**

2.6.2 | Comment

Referral to a transplant hepatologist is strongly recommended when a patient with cirrhosis is still well enough to be assessed and listed, but ill enough to have a reduced survival and/or poor QoL. Given the time it takes to complete an assessment before a patient can be listed for LT, and the risk of some patients' conditions deteriorating rapidly to the point where a transplant is no longer feasible, the optimal timing for initial referral to a transplant hepatologist of patients with cirrhosis potentially eligible for LT should be before their disease reaches the stage when their listing for a transplant is actually indicated.[14-16] In the case of non-cholestatic cirrhosis, patients should be referred when their MELD score is ≥10, even in the absence of MELD exceptions, while the minimum MELD score for listing a patient is 15. Similarly, it has been suggested that a Mayo risk score predicting more than 10% mortality at 1 year without LT should prompt referral for patients with cholestatic disease. Recurrent cholangitis, intractable pruritus, severe metabolic bone disease, and xanthomatous neuropathy should also prompt referral for patients with cholestatic diseases.[15]

2.7 | Question 7

Can we design a study to investigate how to improve the referral for assessment of potential candidates for LT?

2.7.1 | Statement

The design of a study aiming to improve the referral of patients with ESLD potentially eligible for LT to transplant centres should envisage:

1. A baseline survey addressed to transplant hepatologists at all Italian LT centres to obtain details of the number of LT candidates referred and their outcomes (listed or not listed, including reasons for not listing) in the last 2 years.
2. An intervention to improve cooperation with referring physicians by providing a simple web-based patient referral tool (a system of electronic referral, or *e*Referral for LT) and a regional network for hepatic diseases based on educational activities promoted by the tertiary transplant centre in conjunction with the secondary centres and with outreach clinics to increase awareness, improve communication and optimize patient referrals at a more appropriate time and an earlier stage for LT.
3. Repetition of the same survey 1 year after the intervention. **(C, IIb)**

2.7.2 | Comment

A study conducted in Germany demonstrated that referral patterns can be substantially improved by intervention using an interdisciplinary approach, based especially on the activity of dedicated transplant hepatologists, and with the involvement of referring physicians and patient organizations at meetings and symposia.[10] The "*e*Referral (electronic referral) web-based system for LT" is a simple tool for referring patients with ESLD who are non-urgent candidates for LT (excluding patients with severe acute hepatitis, ALF or ACLF). It was developed in Italy and initially used by three transplant centres in the Lazio Region. It will be tested for the purposes of changing referral and listing patterns over time. The *e*Referral website also enables patients' first visit to be scheduled appropriately according to their urgency (based on recent clinical

data), and their comanagement by the transplant hepatologist and the referring physician, as well as providing educational links for the latter.

3 | THE "DIFFICULT CANDIDATE" FOR LT

Liver transplantation technique has improved dramatically over the years. A successful outcome requires optimal patient selection and timing, so deciding which patients to list for LT remains a key issue that continues to generate debate and controversies. At present, there are few absolute contraindications to LT, and they generally refer to situations for which enough experience has been gained to establish that the transplanted patients' outcome is not acceptable.[14,24] It is important to emphasize, however, that the contraindications to LT are always changing, and they may also vary between different transplant centres, reflecting local expertise. Meanwhile, progress has been made in our understanding of pre- and post-LT physiology, and the introduction of newer, more effective immunosuppressants to prevent graft rejection has resulted in increasing the 5-year patient and graft survival rates by >80% in Europe and the USA.[25,26] On the other hand, the transplant community is currently facing a major organ shortage.[27] This has put a great deal of pressure on organ allocation programs, and many patients become seriously ill or die while on the waiting list for LT.

Taking all these aspects into account, some patients have one or more clinical conditions that place them at the limit for safely indicating LT: these are the so-called "difficult candidates" for LT. The purpose of this section is to explore several demographic and clinical conditions that identify these "difficult candidates," then a panel of experts advances some recommendations to orient the decision-making process to apply in such cases.

3.1 | Question 1

Is there an age limit above which LT is contraindicated?

3.1.1 | Statement

Although there are no age limits for LT recipients, patients between 65 and 70 years old should be carefully assessed in terms of transplant benefit because of the high prevalence of comorbidities in the more elderly. **(A, I)**

3.1.2 | Comment

Patients over the age of 60-65 years have been shown to have lower 1- and 5-year survival rates after LT than younger patients.[28] Some transplant teams consider physiological age more important than chronological age, however,[29,30] centres that have come to accept 70 years as the age limit for transplantation have reported obtaining good results with this policy.[31] It is largely accepted that, when questions about a potential recipient's age arise, they should be carefully discussed by the transplant team.

3.2 | Question 2

Which cardiovascular diseases negatively influence a patient's eligibility for LT?

3.2.1 | Statement

It is advisable to involve an expert cardiologist in assessing the cardiac risk of candidates for LT. **(C, IIb)**

A basic physical examination, electrocardiography and echocardiography are required for all LT candidates. **(A, I)**

More specific cardiac tests and a systemic vascular assessment with Doppler ultrasound are recommended for LT candidates with a history of cardiovascular diseases and/or known risk factors (diabetes mellitus, hypertension, pre-existing coronary artery disease, dyslipidaemia, age >60 years). **(A, IIa)**

Severe cardiac dysfunction or major electrophysiological abnormalities not amenable to medical or surgical treatment specifically contraindicate LT. **(A, IIa)**

Candidates with a systolic pulmonary arterial pressure >45 mm Hg on echocardiography should undergo right cardiac catheterization. **(A, I)**

3.2.2 | Comment

Cardiac abnormalities relating to an abnormal systolic contractile response to stress, a diastolic dysfunction at rest, and several electrophysiological anomalies have been demonstrated in patients with advanced cirrhosis, irrespective of the etiology of their liver disease. The condition is termed cirrhotic cardiomyopathy.[32]

Perioperative cardiovascular complications are a leading cause of morbidity and mortality after LT.[33] While it is generally agreed that cardiac function warrants careful assessment in LT candidates, there is no standardized way to do so. Patients with multiple cardiovascular risk factors should first have a cardiopulmonary exercise test to identify any signs of coronary artery disease. The recommended second-line tests in patients with tense ascites, sarcopenia and/or severe motility impairment whose target heart rate cannot be achieved during a standard exercise test, a pharmacological stress test[14,24] or coronary artery assessment with contrast-enhanced computed tomography (CT) scan or cardiac magnetic resonance imaging (MRI),[34] or coronary angiography.[35] When clinically relevant coronary artery disease is identified, candidates can be reconsidered for LT following a successful bypass surgery or angioplasty, since survival after LT does not differ significantly between patients with and without obstructive coronary artery disease providing the former have been properly treated before LT.[36]

Liver transplantation should be considered with caution for patients with a left ventricular ejection fraction <55% on echocardiography, taking into account any other cardiac abnormalities

contributing to the picture of cirrhotic cardiomyopathy.[32] There are no clear recommendations against LT for patients with cardiac electrophysiological abnormalities because prolonged QT intervals, electromechanical dyssynchronies and chronotropic incontinence generally disappear after the transplant.[32] In the event of major, severe electrophysiological abnormalities not amenable to medical or surgical treatment, the risk/benefit ratio of LT should be assessed case by case with a cardiologist who has demonstrable expertise in the management of complex cardiac arrhythmias.

Portopulmonary hypertension (PPH) is defined as a mean pulmonary artery pressure (MPAP) >25 mm Hg at rest, a pulmonary vascular resistance >240 dyn s cm^{-5}, and a normal left atrial pressure (<15 mm Hg), measured by means of a right cardiac catheterization procedure.[37] Identifying PPH and properly assessing its severity prior to LT is of paramount importance because it influences the clinical outcome after LT: if the MPAP is <35 mm Hg, the outcome after LT is good, whereas MPAP values between 35 and 50 mm Hg, or >50 mm Hg are associated with post-LT mortality rates of 50% and 100% respectively.[38] Pharmacological treatments such as epoprostenol (prostacyclin), or prostacyclin analogues (iloprost, treprostinil), endothelin receptor antagonists, or phosphodiesterase inhibitor type 5 (sildenafil) have recently been used to treat PPH and found to improve pulmonary hemodynamics in some patients. Although LT has sometimes been performed in patients treated with these agents, the long-term results are still under evaluation.[39] There is a general agreement that patients with PPH who achieve a MPAP ≤35 mm Hg in response to medical therapy with the above-mentioned drugs could be considered suitable for LT.[14,40]

3.3 | Question 3

What is the best way to establish a sufficient degree of respiratory function in LT candidates?

3.3.1 | Statements

Respiratory function should be assessed by means of: lung function tests, measuring the diffusion capacity of the lung for carbon monoxide, arterial blood gas analysis, and a chest X-ray. If hepatopulmonary syndrome (HPS) is suspected, further investigations are warranted. **(A, I)**

Hepatopulmonary syndrome can be an isolated indication for LT. Recipients with a PaO_2 ≤50 mm Hg and no reversibility to 100% oxygen risk irreversible respiratory failure in the post-LT period, and are at high risk of perioperative mortality. **(B, IIa)**

3.3.2 | Comment

Hepatopulmonary syndrome is a liver-related respiratory complication affecting about 10%-17% of patients with cirrhosis. It is caused by abnormal intrapulmonary vascular dilations, mainly in the basal parts of the lung, which lead to hypoxaemia, and patients with HPS often need oxygen therapy. The diagnosis is established if an arterial blood gas sample taken from a seated patient reveals an alveolar-arterial oxygen gradient (AaO_2) ≥15 or ≥20 mm Hg in patients over 64 years old. Other parameters previously used to diagnose HPS were: an AaO_2 >20 mm Hg (regardless of age) and/or a pO_2 <70 mm Hg with the patient in any supine, sitting or standing position.[41] Intrapulmonary shunts are identified on transthoracic contrast-enhanced echocardiography,[42] or a macro-aggregated albumin lung perfusion scan ([99m]Tc-MAA).[43]

The severity of HPS is graded according to the level of hypoxaemia as: mild (PaO_2 ≥ 80 mm Hg), moderate (PaO_2 <80 and ≥60 mm Hg), severe (PaO_2 <60 and ≥50 mm Hg) or very severe (PaO_2 <50 mm Hg); very severe HPS is often associated with a PaO_2 <300 mm Hg when the patient is given 100% oxygen.[42]

Liver transplantation has been shown to reverse the syndrome and improve survival rates, even in severe cases. It is essential to assess the severity of HPS properly, however, because patients with a PaO_2 < 50 mm Hg and no reversibility to 100% oxygen may risk irreversible respiratory failure after LT and carry a high risk of perioperative mortality.[44] It is also important to remember that it may be several months after LT before any improvement or reversibility of HPS becomes apparent.[45]

3.4 | Question 4

Which kidney diseases justify a combined liver-kidney transplant (LKT)?

3.4.1 | Statements

Patients with renal dysfunction require accurate pre-LT evaluation to establish the etiology and prognosis of their kidney disease. **(A, I)**

A hepatorenal syndrome (HRS) associated with acute kidney injury (AKI), or type II HRS, is not an indication for combined LKT. **(A, I)**

For stage IV chronic kidney disease (CKD), chronic hemodialysis or sustained AKI (≥6 weeks), combined LKT is an option that should be discussed with nephrologists and surgeons. **(B, IIb)**

3.4.2 | Comment

The choice of a combined LKT is generally driven by concern over the chances of recovery of a patient's renal function, and the higher patient mortality associated with renal function failing to recover after LT alone.[46]

The definition of AKI in patients with cirrhosis was recently revised by a panel of experts for the International Ascites Club (ICA). AKI is now defined as an increase in serum creatinine of at least 0.3 mg/dL within 48 hours, or a 50% (1.5-fold) increase from the baseline within 7 days.[47] Three stages of AKI have been identified on the basis of the increase in serum creatinine levels and the need for renal replacement therapy.[47] The change made to the definition of AKI in patients with cirrhosis highlights the need to revise the criteria for defining HRS type 1. The current criteria include a 2-week period over which serum creatinine should double to >2.5 mg/dL.[48]

Adopting the proposed new ICA algorithm to manage AKI in patients with cirrhosis, patients who have AKI stages 2 or 3, or AKI progressing from its initial stage despite general therapeutic measures, and who meet all the other criteria for a diagnosis of HRS according to the previous definition, should receive vasoconstrictors and albumin irrespective of their final serum creatinine level.[47] HRS type 2 is characterized by moderate renal failure (serum creatinine 1.5-2.5 mg/dL) with a steady or slowly progressive course, and is typically associated with refractory ascites. The survival of patients with HRS type 2 is better than for patients with HRS type 1.[48]

Chronic kidney disease is defined as an estimated glomerular filtration rate of <60 mL/min, calculated using the Modification of Diet in Renal Disease 6 (MDRD6) formula, persisting for more than 3 months.[49]

It can be difficult to assess renal clearance in patients with cirrhosis, so testing the clearance of inulin or other exogenous markers might facilitate decision-making.[50] When feasible, renal biopsy can help to detect any severe kidney disease, and establish whether it can be ameliorated after LT. Renal biopsy specimens demonstrating >30% glomerulosclerosis, or >30% fibrosis can be used to identify patients who require LKT.[24]

3.5 | Question 5

How can a history of non-hepatic cancer negatively affect a patient's eligibility for LT?

3.5.1 | Statements

Liver transplantation candidates with a history of extra-hepatic tumours should have received a curative treatment, and be tumour-free at the time of their assessment for listing them for LT. **(A, I)**

Recipients with a history of cured extra-hepatic malignancies can be considered for LT to a recurrence-free interval that depends on the type of tumour involved (Israel Penn International Transplant Tumor Registry). **(B, I)**

3.5.2 | Comment

Immunosuppressant treatment after LT is associated with a higher risk of recipients developing extra-hepatic malignancies,[51] so it is strongly recommended that all candidates for LT be accurately screened for malignancies before they join the waiting list.

The issue regarding the eligibility for LT of patients with a history of extra-hepatic cancer is more complex. The success of oncological treatments depends on the type and spread of the neoplastic disease involved, and these factors crucially influence the prognosis. In this setting, it is therefore essential to identify the type of extra-hepatic tumour and the treatment a patient received. An expected outcome should be calculated, and sufficient time should have elapsed to minimize the risk of recurrence. The Israel Penn International Transplant Tumor Registry (www.ipittr.uc.edu/registry) is a large database of outcomes after LT in recipients with a variety of tumours that can be helpful in planning an appropriate strategy for LT candidates with a history of extra-hepatic malignancies.[24] It is generally accepted that such patients are eligible for LT if the risk of tumour recurrence is estimated to be less than 10%. A 5-year recurrence-free interval is often required too, though this may vary considerably depending on the type of malignancy.[14]

It is still unclear whether LT recipients with a history of successfully treated extra-hepatic cancer should be assigned to a personalized oncological surveillance program after LT.

3.6 | Question 6

Which psychiatric conditions and types of substance abuse could contraindicate LT?

3.6.1 | Statements

All LT candidates should undergo an accurate psychosocial evaluation to assess their compliance and adherence to medical directives and the stability of their mental health before and after LT. **(A, IIa)**

Most psychiatric disorders make patients relatively unsuitable for LT, and warrant psychological and psychiatric assessment and monitoring before and after any transplant is undertaken. **(B, IIb)**

Repeated suicide attempts and active psychosis not controlled with pharmacological therapy in patients without social and family support, should be considered psychiatric disorders that absolutely contraindicate LT. **(B, I)**

Non-therapeutic use of opioids or active and continuative cocaine or synthetic drug abuse make LT absolutely contraindicated. **(B, I)**

3.6.2 | Comment

The main aspects to consider in the psychosocial evaluation of candidates for LT include: evidence of compliance with medical directives; adequate support from capable caregivers; and absence of active psychiatric disorders liable to affect compliance or induce behaviour harmful to health.[24] Patients with chronic hepatic encephalopathy should undergo neuropsychological testing, brain CT scan or MRI, and electroencephalography to ascertain the reversibility of their neuropsychiatric conditions.[14]

Active drug or alcohol abuse, or the non-therapeutic use of opioids, cocaine or synthetic drugs, are considered a contraindication to LT for numerous reasons, including the related risks of recidivism, non-compliance and graft injury.[14]

On the other hand, stably abstinent, methadone-maintained, opiate-dependent patients may be eligible for LT because they show low relapse rates. There is also no conclusive evidence to suggest that patients with ESLD being treated with methadone have worse outcomes.[52] Whether patients who regularly use marijuana should be excluded from the waiting list for LT is debatable:[53] In a US survey conducted at 102 adult LT centres, 46.7% of the centres considered

the daily consumption of marijuana an absolute contraindication, whereas 43% judged it a relative contraindication, and 10.3% considered it irrelevant.[54] Although it was suggested that patients who use compared to those who do not use marijuana are less likely to be transplanted, there was no significant difference in post-LT survival between the two groups.[55] Furthermore, unlike illicit drug use, marijuana use was not associated with worse outcomes on the LT waitlist.[56]

In addition to addressing psychiatric and substance abuse issues, the evaluation process should include assessing the patient's social support network. Caring for a transplant recipient involves frequent medical check-ups and tests, so a caregiver needs to be identified who can manage the patient's transport and other logistic requirements, especially in the early period after LT.[24]

4 | THE MANAGEMENT OF NUTRITION BEFORE AND AFTER TRANSPLANTATION

Malnutrition, sarcopenia and obesity are common comorbidities associated with poor pre- and post-transplant outcomes and a heavy burden on healthcare resources.

Malnutrition (or undernutrition) is a disorder resulting from an inadequate intake or uptake of nutrients that leads to an altered body composition (a reduction in fat free mass) and body cell mass, diminished physical and mental functioning, and a worse clinical outcome in the event of disease.[57] *Sarcopenia* is a separate syndrome characterized by a progressive, generalized loss of skeletal muscle mass, strength and function (performance) with a consequent risk of adverse outcomes.[57] *Obesity* is an abnormal or excessive fat accumulation that may impair health.[57] These different conditions may coexist in the same patient with cirrhosis. An association between malnutrition and sarcopenia can be expected, but obese patients can be sarcopenic too, or even malnourished, because of an imbalance between their energy intake and expenditure, and to the quality of their nutrient intake.[57] As nutritional disorders are potentially modifiable, transplant physicians have recently been paying more attention to recognizing them, understanding their impact on transplant patient mortality and morbidity, and developing appropriate treatment strategies.

4.1 | Question 1

Is nutritional status clinically relevant in patients with cirrhosis awaiting LT?

4.1.1 | Statements

Sarcopenia is an independent risk factor for mortality both before and after LT. **(A)**

Malnutrition is associated with a higher risk of poor outcomes. **(B)**

Moderate-severe obesity (body mass index—BMI > 35), combined with comorbidities, such as diabetes or cardiovascular risk factors, is associated with a higher risk of morbidity and mortality. The risk increases with the grade of obesity. **(A)**

Nutritional disorders should not per se be considered absolute contraindications to LT. They are conditions that need to be recognized, however, in order to plan nutritional intervention, and they contribute to an individual's risk profile. **(C, I)**

Nutritional assessments should be performed in all patients awaiting LT. **(A, I)**

4.1.2 | Comments

The prevalence of malnutrition, sarcopenia and obesity is consistently high in studies on patients with cirrhosis on the waiting list for LT, albeit with a broad variability because of different diagnostic methods and criteria being used. *Malnutrition* develops in 20%-90% of patients with cirrhosis,[58] and *sarcopenia* in 40%-70% of cases.[59] The impact of *obesity* has been increasing in recent decades, reaching a prevalence of almost 35% among patients awaiting LT in the USA.[60] *Sarcopenic obesity* is identified in about 20% of patients with cirrhosis.[61]

Nutritional disorders clearly affect the prognosis of patients with cirrhosis and/or awaiting LT, even though the available studies reveal several flaws relating to their design (often retrospective and/or on small samples), methods, diagnostic criteria and prognostic cut-offs.

Malnutrition (undernutrition) is associated with a higher risk of in-hospital mortality and clinical complications in patients with cirrhosis.[62,63] In the transplantation setting, it has been associated with increased post-transplant mortality and morbidity rates, and especially a higher incidence of bacterial and fungal infections, longer stays in the intensive care unit (ICU) and in hospital, and higher healthcare costs.[64-66] A BMI <18.5, as a simple, rough indicator of malnutrition, also identifies patients at higher risk of increased post-transplant mortality, as emerged from an analysis of the UNOS database.[67]

Sarcopenia is objectively measureable and represents the nutritional variable most strongly associated with a patient's prognosis after LT. Loss of muscle mass has been found to independently predict pre- and post-transplant mortality and morbidity, related mainly to a higher incidence of infections.[64,68,69] Interestingly, the prediction of mortality after LT appears to be more accurate in patients with low MELD scores (<15), and adding sarcopenia to the MELD variables (MELD-sarcopenia) improves the prognostic capacity of MELD alone in this group of patients.[68] This explains why the ICU and hospital stays are longer, and the related costs are higher for patients with sarcopenia.[64]

Patients with *severe obesity (BMI > 40)* appear to be at higher risk of post-transplant mortality and morbidity, as well as longer hospital stays and higher costs,[60,67,70] but this picture has not always been confirmed.[71] *Moderate obesity (BMI 35-40)* carries an adverse impact on post-transplant outcomes when associated with comorbidities, such as diabetes and cardiovascular disease.[72] The prognosis after LT is not affected in patients who are *overweight (BMI 25-30)* or *mildly obese (BMI 30-35)*.[60,67,70]

4.2 | Question 2

How can we assess nutritional disorders in patients with cirrhosis awaiting LT?

4.2.1 | Statements

There is no standardized diagnostic algorithm for assessing the nutritional status of patients with cirrhosis awaiting LT transplantation. A *pragmatic strategy* applicable in daily clinical practice should be based on a compromise between simplicity, reproducibility, and accuracy. **(C, I)**

Since sarcopenia is the strongest predictor of pre- and post-transplant outcomes, it should be assessed in all patients awaiting LT. **(A, I)**

Muscle mass should preferably be quantified by means of cross-sectional imaging studies, using the L3 skeletal muscle index (L3 SMI), for instance, or the psoas muscle area (PMA), given that CT scans or MRI are commonly used in the assessment of patients for listing purposes. These measurements also correlate strongly with whole body muscle area, even in the case of fluid overload or obesity. **(A, I)**

Measuring gait speed and hand-grip strength could be useful to assess *muscle strength* and *function* as an indicator of physical frailty, and for longitudinal reassessment purposes. **(B, I)**

4.2.2 | Comments

The first step of a nutritional assessment usually involves administering a screening tool, so that patients can be stratified by their risk of malnutrition. Tools such as the Royal Free Hospital—Global Assessment (RFH-GA),[73] or the Royal Free Hospital—Nutritional Prioritizing Tool[74,75] have been developed and applied, but not extensively validated, in patients with cirrhosis. There are several reasons why it seems reasonable to consider all patients awaiting LT potentially at risk of malnutrition, however. For instance: (a) the prevalence of nutritional changes, alone or in combination, and their impact on outcome are very high; (b) nutritional disorders are potentially modifiable factors; and (c) patients with cirrhosis often have concomitant clinical complications that require different, and sometimes conflicting, nutritional approaches.

The criteria for diagnosing nutritional disorders developed by international scientific societies depend on how they are adopted.[57,75] Unfortunately, the accuracy of methods developed for the general population is often limited by the changes in body composition that coincide with advanced cirrhosis. In the last decade sarcopenia has emerged as the "core issue" in the nutritional assessment of such patients because it can be objectively measured and quantified.[75,76]

Measuring muscle mass on CT scans or MRI is currently the gold standard for assessing a patient for sarcopenia. Among the several techniques proposed,[75] calculating the cross-sectional PMA normalized by height squared or body surface area,[77] or the third lumbar vertebra skeletal muscle index normalized by height squared (L3SMI)[78] have been validated for use in patients with cirrhosis awaiting LT (PMA cut-off: 1561 mm^2 in men, 1464 mm^2 in women;[77] L3SMI cut-off: <50 cm^2/m^2 in men and <39 cm^2/m^2 in women[78]).

Since abdominal CT scan or MRI are part of the assessment of potential candidates for LT, these measurements can be obtained without having to perform additional tests (though they may demand the use of specific software).

Sarcopenia is also characterized by impaired muscle function, and thus contributes heavily to physical frailty, which has recently been identified as an independent risk factor of poor outcomes before and after LT.[79] Muscle function is easy to assess with the hand-grip strength test and a few physical exercises (4-m walking test, chair standing test, 6-minute walking test). The results of these tests correlate positively with the degree of sarcopenia. The tests are easy to perform and reproducible, and consequently suitable for use in longitudinal assessments to monitor the efficacy of nutritional interventions.[80]

4.3 | Question 3

How can we manage the nutritional care of patients with cirrhosis awaiting LT?

4.3.1 | Statements

Patients awaiting LT should follow a *nutritional care pathway*, systematically involving a global nutritional assessment, the planning of a nutritional care program and the monitoring of nutritional outcomes. **(B, I)**

Nutritional care should be customized to meet the needs of individual patients, and preferably managed by a *dedicated dietitian/nutritionist*, in close collaboration with the patient's hepatologist. **(B, I)**

Regular counselling is recommended to ensure patients' adherence to their nutritional recommendations. **(B, I)**

The *general recommendations regarding energy and dietary intake*, based on the international guidelines, can be summarized as follows: **(A, I)**

1. Provide 30-35 kcal/kg of dry body weight a day (50%-60% of calories as carbohydrates; 20%-30% as fat).
2. Avoid unnecessary dietary restrictions.
3. Provide 1-1.5 g of protein per kg of body weight a day (in patients with hepatic encephalopathy, consider reaching the protein intake needed by including vegetable proteins, dairy proteins, and/or oral branched chain amino acid supplementation).
4. Distribute the dietary intake over 4-6 meals a day, including a late evening snack.
5. Consider the need for vitamins and trace elements, depending on patients' symptoms and/or serum levels.
6. Patients who are severely malnourished and/or unable to achieve a sufficient intake from their diet or oral supplementation may require enteral (preferably) or parenteral nutrition.

Sarcopenia should be treated using a combined approach based on an adequate intake of proteins, including supplementation with oral branched chain amino acids, and vitamins, especially vitamin D (see general recommendations above), and regular suitably adapted physical exercise. **(B, I)**

Obesity should be controlled by means of a comprehensive lifestyle management, including three key components: a lower calorie intake, more physical activity and behavioural intervention. **(A, I)**

In patients with morbid obesity not adhering and/or responding to a lifestyle management approach, *bariatric surgery* can be considered *prior to LT*, but this option suffers from a higher mortality rate in patients with decompensated cirrhosis (Child B/C) and portal hypertension. **(B, IIa)** *Combined LT and sleeve gastrectomy* may be an option for managing patients with morbid obesity. **(B, IIb)**

4.3.2 | Comments

Patients awaiting LT form a very heterogeneous population in terms of their clinical conditions and nutritional status. As an example, the spectrum can go from a normal-weight Child A patient with HCC to a sarcopenic Child C patient with ascites and/or hepatic encephalopathy with diabetes. The management of nutritional disorders at individual patient level should therefore always take into account the concomitant clinical manifestations of the disease, which often require apparently conflicting dietary approaches. For instance, how do we establish an adequate protein intake for a sarcopenic patient with hepatic encephalopathy and/or renal failure?

As well as a very often low calorie intake because of anorexia, nausea and vomiting, early satiety, and an inadequate digestion and absorption of nutrients, patients with cirrhosis tend to have a very poor adherence to general nutritional recommendations. There are several reasons for this behaviour, including patients' and physicians' poor knowledge of the content of food and drink, low socioeconomic conditions, lack of family support, physicians spending too little time on explaining dietary recommendations in routine clinical practice and poor compliance with prescribed diets.[81]

Hence, the need for nutritional interventions to be based on the specific needs of individual transplant candidates, and provided wherever possible by certified nutritionists or dieticians, as part of a multidisciplinary approach that takes all the above factors into account, and assures regular counselling and monitoring of adherence and results.

Our statements regarding the general nutritional indications for patients with cirrhosis, and for the treatment of sarcopenia and obesity, reflect the recommendations of the major international scientific associations and experts in the field.[82-84]

Finally, bariatric surgery has been proposed as a novel approach to treating severely obese patients listed for LT and failing to respond to a controlled diet and physical exercise. Patient selection issues and the timing of such surgery are still debated. For now, the option of bariatric surgery prior to LT appears to be limited to Child A patients because of the high mortality and morbidity rates in Child B and C patients.[85] A promising alternative is to combine a sleeve gastrectomy with the transplant surgery, but only a few such cases have been described so far.[86]

4.4 | Question 4

Can physical activity improve the nutritional status of patients awaiting LT?

4.4.1 | Statements

Regular physical activity has a positive effect on aerobic capacity, muscle loss and strength, and QoL in patients with cirrhosis awaiting LT. It also helps obese patients to lose weight. **(A)**

The *general recommendations* on physical activity available for adults aged 50-64 with clinically significant chronic conditions or functional limitations affecting their mobility, fitness or physical activity can be applied to cirrhotic patients. **(C, IIa)** A personalized program of physical activity may be useful in patients awaiting LT. **(B, IIa)**

Particular caution is needed for *patients with decompensated cirrhosis*: physical activity should always be associated with adequate dietary intake; and assessing their aerobic capacity can orient the customization of their activity programs. **(B, IIa)**

4.4.2 | Comments

Patients with cirrhosis awaiting LT are scarcely active physically, severely out of condition, with an impaired aerobic capacity, and these factors increase their risk of frailty.[87] A reduced maximal exercise capacity is associated with a high risk of 90-day and 1-year post-transplant mortality, perioperative complications and early in-hospital mortality.[88-90]

Regular physical activity is thought to be important to avoid frailty, improve QoL, and maintain an adequate physical condition.[87] Randomized clinical trials, on albeit small samples of patients with cirrhosis awaiting LT, have demonstrated that adapted physical activity programs are effective in increasing maximal oxygen uptake, 6-minute walking distance, and muscle strength, with no significant side effects.[91-93] A recent study showed that an intensive lifestyle intervention is also effective in obese/overweight patients with compensated cirrhosis, since diet and moderate physical exercise favour weight loss and, most notably, reduce portal pressure.[94]

The international recommendations for physical activity in adults aged 50-64 with clinically significant chronic conditions or functional limitations affecting their mobility, fitness or physical activity levels[95] can generally be adopted, given that no guidelines have been developed specifically for patients with cirrhosis. It is nonetheless important to emphasize that physical activity in patients with decompensated cirrhosis should be customized, and always coupled with appropriate nutritional supplementation because exercising under an insufficient nutritional intake can paradoxically accelerate protein catabolism and consequent muscle loss in patients with advanced cirrhosis.[87] A multidisciplinary approach thus seems particularly useful for patients with more advanced disease.

4.5 | Question 5

Is nutritional status and its management clinically relevant to the long-term outcome of patients after LT?

4.5.1 | Statements

Weight gain, *obesity* and *metabolic syndrome* are very common after LT, posing a major risk in terms of a higher incidence of cardiovascular disease in long-term survivors. *Sarcopenia* can persist, or even become worse, in the early months after LT. *Physical activity* is usually insufficient. **(A)**

Metabolic syndrome and/or obesity should be managed taking a comprehensive lifestyle approach, including three key components: a lower calorie intake, more physical activity and behavioural intervention. **(A, I)** *Sarcopenia* could be managed according the indications provided for patients on the waiting list for LT. **(C, I)**

Patients should be assessed soon after LT by a *MDT* in order to plan a personalized, long-term program of nutritional counselling and exercise training. (B, I)

4.5.2 | Comments

Cardiovascular diseases are a major cause of long-term morbidity and mortality after LT. This is hardly surprising, given the very high prevalence of risk factors among transplant recipients, who have obesity in 25%-30% of cases; type 2 diabetes in 30%-40%; and hyperlipidaemia in 45%-70%.[96,97] Overall, the diagnosis of metabolic syndrome can be established in 40%-60% of LT recipients, judging from different studies.[96,97] The onset of metabolic syndrome also seems to correlate inversely with the amount of physical activity.[98]

The maximal rate of increase in fat mass usually coincides with the first year after LT. Meanwhile, sarcopenia may persist or even become worse. This combination can lead to a condition of sarcopenic obesity, which may easily go misdiagnosed because of the concomitant increase in BMI.[99]

Studies on whether diet and physical exercise can improve long-term post-LT outcomes are few,[100,101] but multidisciplinary lifestyle intervention programs can plausibly produce positive results in this population at high risk of cardiovascular events.[87]

5 | LIVING DONOR LIVER TRANSPLANTATION: UPDATE AND PERSPECTIVES

All transplants from living donors to be performed in Italy must comply with the requirements of primary Italian legislation (Legge 16/12/1999, n. 483 "*Norme per consentire il trapianto parziale di fegato*" [G.U. n. 297 del 20/12/1999] e Decreto Ministeriale della Salute del 16/04/2010, n. 116 "*Regolamento per lo svolgimento delle attività di trapianto di organi da donatore vivente*" [G.U. n. 172 del 26/07/2010]). All health professionals involved in living donor liver transplantation (LDLT) should acknowledge the broad array of complex moral issues in this field and ensure that good ethics consistently underpin their clinical practice.[102,103] Regardless of the benefit to the potential recipient, the safety and welfare of the potential living donor should always take precedence over the needs of the recipient.

The key preoperative, operative and post-operative aspects surrounding liver donations from a living donor have been developed and published in two recent reports by the International Liver Transplant Society, and the British Transplantation Society, and they have been adopted as practical guidelines in the USA and UK respectively.[104,105]

5.1 | The donor

5.1.1 | Question

Which general donor selection criteria are accepted to obtain an adequate partial allograft while also ensuring an acceptable donor safety?

Statements

In Italy donors must be from 18 to 60 years old.

The medical work-up for older donors should be particularly strict (not graded). All potential donors should be screened for cardiovascular disease, and there should be a low threshold for their exclusion if significant risk factors are found. **(B, I)**

The goals of donor assessment are to ensure that: (a) an adequate partial allograft can be safely procured; (b) there is no risk of disease transmission from donor to recipient; and (c) the donor understands the process and would be able to overcome any psychological consequences. **(C, I)**

It is generally recommended that the recipient's graft to body weight ratio (GRBWR) be no lower than 0.8%, though a lower GRBWR can be considered in selected cases. **(C, IIa)**

The donor's remnant liver volume should be no less than 30%–35% of the initial volume of the whole liver. **(C, I)**

If fatty liver is suspected, a biopsy is needed: macrovesicular steatosis greater than 30% is an absolute contraindication for liver donation. **(C, I)**

Any disease transmissible from donor to recipient contraindicates LDLT. **(C, I)**

A multidisciplinary approach is needed for the donor's psychological assessment. **(C, IIa)**

Hospitals and teams involved in LDLT should devise a framework on how to respond to a potential living donor severe issue.

In the event of the donor's death, a root cause analysis should be conducted and the centre's LDLT program should be suspended pending the outcome of the investigation. **(B, IIa)**

A documented national disaster and media communication plan agreed by all centres performing LDLT should be adopted. **(B, IIa)**

Comments

Donor safety is the core issue, and the goals of donor assessment are to ensure that: (a) an adequate partial allograft can be safely procured; (b) there is no risk of disease transmission from donor to recipient; and (c) the donor understands the process and would be able to overcome possible psychological consequences. The donor's remnant liver volume should be no less than 30%-35% of the initial volume of the whole liver to avoid post-operative hepatic insufficiency, remnant loss, and death.[106-108] For the recipient, it is generally recommended that the GRBWR be no lower than 0.8% to avoid small for size *syndrome* and early post-operative graft failure.[105,109] A lower GRBWR can be considered for selected recipients with a good functional status and minimal portal hypertension.[109,110]

Donors should be checked for any chronic liver disease. Macrovesicular steatosis greater than 10% is a concern; and beyond 30% it becomes an absolute contraindication for donation and raises the risk of graft failure in the recipient.[111-114] Potential donors with predisposing factors for fatty liver (obesity, diabetes, dyslipidaemia) and/or imaging findings consistent with fatty liver should undergo biopsy during the pretransplant assessment to clearly ascertain the extent of macrovesicular steatosis.[114]

Living liver donation carries a significant donor mortality estimated at between 0.1% and 0.5% for left and right liver donors respectively.[115-118] A morbidity rate of 20%-35% is also expected.[115,116,119,120] Complications such as pulmonary embolism, myocardial infarction, peptic ulcer and liver failure[121,122] have resulted in donor deaths. It is therefore crucial to provide for intensive monitoring and the early identification of any post-operative complications.

5.1.2 | Question

Which specific process should be used to inform donors appropriately, arrange for donor advocates and obtain donors' consent?

Statements

The living donor should be offered the best possible environment in which to make a voluntary and informed choice about donation (not graded).

Separate clinical teams for donors and recipients are usually considered best practice, and a donor advocacy team should be assigned to every potential living liver donor.

Informed consent should include full information about the potential surgical, medical, financial and psychological risks (including death) of a hepatectomy. **(C, I)**

All potential donors should be assessed by a mental health professional, preferably a member of the donor advocacy team. **(B, I)**

Donor safety and the availability of sufficient time for informed consent should drive the pace of the donor work-up, even when the recipient is very ill. **(A, I)**

Comments

From a psychological viewpoint, living donation can be challenging. Donors are aware that the chances of extending the recipient's life depend on their decision to donate, but they should also be aware that post-transplant outcomes cannot be assured. Donors also need to understand that donation itself carries a potential risk of mortality and complications. That is why assessing the donor's psychological status and stability is essential.

The process of obtaining appropriate donor consent is summarized well by Gordon,[117] and includes: (a) assessment of donor's competence to make decisions; (b) disclosure of information; (c) donor's comprehension of the information; (d) a voluntary decision by the donor to donate, free from coercion; and (e) donor's agreement to undergo the procedure.

5.1.3 | Question

What is involved in the recommended presurgical donor work-up?

Statements

A CT scan or MRI of the donor's liver should be performed with an intravascular contrast. **(A, I)**

Three-dimensional reconstructions, using either in-house or proprietary software, are recommended to obtain detailed 3D models of the donor's liver for volumetric analysis and to ascertain its vascular/biliary anatomy. **(B, I)**

Conventional arteriography and hepatic venography should only be used in exceptional circumstances, when conventional contrast-enhanced CT fails to provide adequate imaging information. **(B, I)**

Magnetic resonance cholangiopancreatography is the gold standard for biliary anatomy. Endoscopic retrograde cholangiopancreatography as well as intraoperative cholangiography should not be anymore used to assess biliary anatomy. **(B, I)**

Steatosis assessment:

1. Ultrasound can be used as a screening tool. MRI provides a better picture than CT for grading steatosis, and is the preferred option. **(A, I)**
2. With CT, the liver-to-spleen attenuation ratio (difference between hepatic and splenic attenuation) and blood-free hepatic parenchymal attenuation should be used. The maximum amount of steatosis is not well-defined, but acceptable limits range from 10% to 30%. **(B, I)**

To calculate the liver volume, the percentage of steatosis should be subtracted from the estimated liver mass available for the graft. **(C, IIa)**

Liver biopsy is reserved for the potential donor with unexplained abnormalities on liver function tests, a BMI approaching 30 kg/m^2, or aspartate aminotransferase > alanine transaminase. **(B, IIa)**

Donors initially rejected because of steatosis can be considered for a low-calorie "defatting diet" and reassessment with new volumetric tests. Fibroscan can be a useful method to monitor

such defatting process, potentially reducing the need for a re-biopsy. **(B, I)**

To calculate the donor graft volume, software-assisted image post-processing is recommended because it is the most accurate assessment method. **(A, I)**

Published formulas with error rates of less than 10% should be used to calculate the recipient's standard liver volume. **(B, I)**

Comments

Any past or present condition carrying a significant risk of perioperative complications in the donor makes living donation contraindicated unless it can be corrected. The donor's pretransplant work-up should therefore include an exhaustive cardiovascular assessment. Echocardiography should be routine. Additional investigations, such as stress echocardiography and/or coronary angiography, may be needed. Transmissible disease is another contraindication for living donation. Appropriate blood tests should be used to screen systematically for asymptomatic inherited coagulation disorders involving liver synthesis (e.g, Leiden factor V, protein C/protein S deficiency, anti-thrombin deficiency).[118]

5.1.4 | Question

What is involved in the recommended donor aftercare program and clinical follow-up?

Statements

Laboratory tests for liver function and platelet counts should be conducted during the follow-up for at least 1 year. **(C, IIa)**

All donors should be advised to have annual checkups with primary care providers for the rest of their lives. **(C, I)**

Comments

Most living donors will return to a previous level of physical performance and psychological status over the course of 1 year.[123,124] With only 25 years of experience of LDLT, the long-term consequences of living donation have yet to be fully understood.

5.2 | The recipient

5.2.1 | Question

What should be the specific approach to the management of recipients of a living donation?

Statements

Living donor liver transplantation should only be performed at specialist centres by a multidisciplinary transplant team. **(A, I)**

Decision-making should be multidisciplinary and meet the standards for transplant services in European countries. **(A, I)**

The Italian standard for transplant benefit, an overall graft and patient survival of more than 50% at 5 years, is the recommended standard for both deceased donor LT (DDLT) and LDLT. **(B, I)**

Following similar current policies of western countries, potential recipients with HCC need to fall inside the currently accepted guidelines for DDLT. **(B, I)**

Following similar current policies of western countries, as in the case of DDLT, only recipients with a more than 50% chance of survival at 5 years should be considered for LDLT. **(A, IIa)**

Adult-to-adult LDLT is associated with a significant learning curve within the first 20 cases. All emerging centres should have access to mentoring over this period. **(B, I)**

There is a 40% risk of complications in the first year after right liver lobectomy. **(B, I)**

The incidence of donor death is not well defined, but in the USA and Europe it is approximately 0.2%. **(B, IIa)**

Reporting of donor death and morbidity is mandatory via the National Transplant Centre (CNT) incident reporting process. **(A, IIa)**

Recipient outcome and graft survival 12 months after LDLT should be at least as good as after DDLT. Graft survival crucially depends on case mix, but averages around 80% at 1 year after LT. **(B, I)**

It is accepted that the frequency of biliary complications in LDLT recipients is 25%-35%, which is higher than after DDLT. **(B, I)**

Comments

In a 10-year follow-up study that objectively graded 36 categories of complications (including time to their resolution) in 471 cases of DDLT and 565 of LDLT, the risk of graft loss and death (hazard ratio 0.89, $P = .60$), the time to resolution of complications, and the overall incidence of complications (70%) did not differ between LDLT and DDLT.[125] The rates of biliary-related complications and hepatic artery thrombosis were higher in LDLT (6% vs 4% in DDLT). On the other hand, DDLT was more likely to associated with ascites, intraperitoneal hemorrhage, cardiac morbidity, and pulmonary oedema, and with a 2.5-fold higher chance of CKD in stages 4 and 5 according to the Kidney Disease, Improving Global Outcomes (KDIGO) scale.[125] Whereas the survival benefit of LDLT relative to DDLT at 10 years has been confirmed,[126,127] the detrimental effect of severe renal dysfunction on mortality after LT will continue to negatively affect survival after DDLT.[128] The future is bright for LDLT recipients: with experience gained worldwide, not only has the related morbidity dropped to below the thresholds for LT established in national studies like the US A2ALL cohort, but underserved recipients who would never be eligible for DDLT have been added to the pool of successful LT recipients.[129-133] There is now strong evidence, magnified at experienced centres, of LDLT providing a sustained benefit to recipients with low MELD scores (<15), and a lower mortality on the waiting list is only part of the reason.[126,134] Candidates who have decompensated cirrhosis but are otherwise transplantable, and those whose low MELD scores underestimate their risk of death, as in patients with hyponatremia,[135,136] refractory ascites,[137] or recurrent variceal bleeding and contraindications to transjugular intrahepatic portosystemic shunt[138] are just a few of the subgroups of recipients benefiting from LDLT.[127] A prospective, long-term study on HCC treatment with the intention to transplant with

either type of graft further clarified the art and science of tumour biology and liver-directed ablative HCC treatment in preventing post-LT HCC recurrence from interfering with the choice of LDLT or DDLT for optimal care.[139] A Japanese study found that, within programmed criteria, and inside or outside the Milan criteria, the Kyushu criteria included the largest number of patients with HCC (95.6% of those meeting the Milan criteria, and 41.2% of those outside them).[140,141] The Kyoto criteria included the next highest number of patients with HCC (65.7% inside and 17.6% outside the Milan criteria), but with a 5-year survival of 91.7%, and a low HCC recurrence rate (4.6% at 5 years for patients outside the Milan criteria).[140] In patients with HCC undergoing ablation or resection followed by LT, the largest and longest prospective study (including DDLT and LDLT) found the lowest rate of HCC recurrence in patients with ≥3 months elapsing from HCC ablation to LT.[139] Validating this finding, an interval <3 months since the last treatment (P = .01), and serum PIVKA-II levels ≥300 mAU/mL (P = .03) were independent predictors of a shorter recurrence-free survival in a multivariate analysis conducted as part of a retrospective study on 114 patients undergoing LDLT for recurrent HCC.[142]

6 | HEPATOCELLULAR CARCINOMA AND LT: IS IT TIME TO EXPAND THE CRITERIA IN ITALY?

In Italy, 44.4% of patients who underwent LT between June 2007 and May 2009 had HCC as their primary indication for transplantation. Much the same picture emerges from more recent series from the Unites States, where HCC was the most common indication for both joining the waiting list and LT.[23,143] The advent of antiviral treatment for hepatitis C virus (HCV) infection capable of halting or slowing the progression of chronic liver disease (but not of abolishing the risk of HCC) has revolutionized the population that might need LT. This is particularly true in Italy, where chronic HCV infection, with or without HCC, was the main etiological factor in patients transplanted between 2007 and 2009.[23,144] With a projected further increase in the cases of HCC, the pressure to expand the criteria for LT in patients with HCC is consequently significant. The fact that the pool of liver donors has not expanded poses important questions, however, regarding: the appropriate (upper) limit for considering LT for HCC; and, if the currently recommended limits are expanded, the best way to establish new boundaries that can avoid any misuse of a limited resource. Other as yet unanswered questions concern how to assess response to tumour downstaging treatments and, more importantly, how to judge the efficacy of any expanded criteria.

6.1 | Question 1

What are the minimal outcome requirements for potentially expanded criteria for LT in patients with HCC?

6.1.1 | Statement

Any expansion of the criteria for LT in patients with HCC beyond the Milan criteria should ensure a 5-year survival rate of at least 61%, which is the figure needed for the benefit of LT in such patients to outweigh the possible harm caused to other patients on the waiting list. **(A, I)**

6.1.2 | Comment

As well as complying with the currently accepted overall and recurrence-free survival rates (i.e, the Milan criteria), expanded criteria for LT in patients with HCC should allow for the population that can be listed for LT to grow only to a level that is reasonably acceptable in terms of organ availability and transplant waiting time.[145] More importantly, this expansion should not be detrimental to the chances of a transplant for patients on the waiting list who have ESLD without HCC. According to studies based on Markov models and using data from the USA, patients outside the Milan criteria would need to achieve a 5-year survival rate of at least 61% to prevent a substantial drop in the life-years available to the whole population of candidates for LT.[146] The effect on non-HCC patients could vary widely, depending on the composition of the population on the waiting list, and on the availability of donor livers at a given centre and in a given transplant region. Theoretically, any decision made by transplant centres to expand their criteria for HCC should take into account the current mortality on their waiting list, and only be adopted if it is low and will not be substantially increased by adding the expanded-criteria cases. In Italy, the widespread application of the "HCC-MELD" score has been proposed by the Italian Board of Expert in the Field of LT as a means to allow equity of allocation between HCC and ESLD patients on a common liver transplant waiting list, and therefore to obviate this potential inequality even considering expanded criteria for transplantation for HCC patients.[147]

6.2 | Question 2

Which parameters should be used to define expanded criteria: morphology, biomarkers, histology?

6.2.1 | Statements

Combining morphometric measurements and biochemical markers seems to produce better results than including either of these parameters alone in expanded criteria for LT in HCC patients. **(B, IIa)**

Among the models that combine morphometric parameters and biomarkers, the alpha-foetoprotein (AFP) model is reproducible and accurate, and retains its prognostic capability even when patients' scores change, so it can be proposed as a model for expanding the current criteria for listing HCC patients. **(B, IIa)**

6.2.2 | Comment

In most of the proposed criteria for expanding the current limits for LT in HCC patients, morphometric considerations (size or number of nodules, or both), biomarkers (AFP), and HCC differentiation on preoperative tumour biopsy (tumour grade), alone or in various combinations, are used to judge whether the 5-year survival rate would remain much the same if the Milan criteria were exceeded.[148]

The French National Agency for Organ Sharing and Transplantation (ABM) recently adopted the AFP model to select HCC patients for LT.[149] This model was identified using multivariate analysis on a training cohort, and validated in a more recent cohort. It includes AFP with various cut-offs (10-100-1000 ng/mL) to provide a greater degree of granularity, as well as tumour number and size.[149,150] A scoring system that includes these three parameters, using a simplification to obtain a two-tiered classification (low vs high risk of recurrence) was able to differentiate between 5-year recurrence rates (8.8% vs 50.6%, $P < .001$), and survival rates (67.8% vs 47.5%, $P = .002$). The impact of the three parameters on recurrence and survival was evident and statistically significant, in patients both within and outside the Milan criteria. It is noteworthy that an estimation of the net reclassification improvement indicated that the AFP model significantly improved the prediction of recurrence. Among those exceeding the Milan criteria, 38.4% of patients in the training cohort and 74.0% in the validation cohort whose HCC did not recur were classified as low-risk using the AFP model. Similarly, of the patients meeting the Milan criteria whose cancer recurred, 21.6% and 21.4% in the training and validation cohorts, respectively, would have been classified as high-risk using the AFP model. The predictive capacity of the AFP model was consistent when it was applied to patients re-assessed after down-staging, and in the transition from a high- to a low-risk score. The model's predictive power was recently validated independently in a multicentre Italian study, in which the AFP model confirmed its ability to differentiate between patients at low- and high-risk of recurrence, and their 5-year survival in a population with mainly post-viral cirrhosis.[150] A competing risk analysis taking the competing risk of death unrelated to HCC showed that the AFP model performed better than the Milan criteria. The study also showed a closer association of the AFP model with predictors of recurrence on pathology of the explanted liver, such as the presence of microvascular invasion and poor differentiation.[150] A further external validation of this model came from a study in Latin America, where the predictive capability of the AFP model was replicated, though in this population (as in the Italian population) the model was less accurate for patients with HCC and chronic HBV infection.[151] At a recent consensus meeting of the Liver Advisory Group of the UK National Health Service, Blood and Transplant section, the AFP model was included in the pre-existing UK criteria.[152]

6.3 | Question 3

Are there upper limits for rejecting a patient with HCC for LT, and starting HCC downstaging?

6.3.1 | Statements

Macrovascular invasion and extrahepatic spread are conditions that preclude patients with HCC from downstaging with a view to LT because they are associated with unsatisfactory post-LT survival and recurrence rates. **(A, IIb)**

Apart from any absolute contraindications to LT, there is no definite "upper limit" to HCC downstaging. **(B, IIb)**

Transplant centres should periodically review the outcome of downstaged patients to ensure adequate post-transplant survival rates. **(C, I)**

6.3.2 | Comment

It seems crucial to set a threshold beyond which a patient cannot be considered a candidate for LT because their HCC has reached a stage that would make the transplant futile, while harming other patients on the waiting list. On the other hand, there is debate about whether tumour burden (size and number of nodules) actually influences liver transplantability. It may be that any patient without absolute contraindications (such as macrovascular invasion or extrahepatic spread) is potentially transplantable irrespective of tumour burden, pending successful downstaging to locally or regionally preset transplant criteria. This latter approach has recently been endorsed by the Italian community of liver transplant surgeons and transplant hepatologists. Going a step further, instituting downstaging treatments, then assessing response to such treatment in terms of reconciling HCC stage with accepted boundaries (e.g, Milan criteria; AFP model), using other available means that may help us to assess tumour response to treatment or progression during the wait, and monitoring the dynamics of these parameters while awaiting LT as a "test of time" may help us to identify rapidly progressing tumours, and thus enable us to make appropriate decisions.[147]

6.4 | Question 4

Are there any predictors of successful downstaging? If so, can they be used to modify the indication for LT?

6.4.1 | Statements

Tumour burden (number and diameter of nodules, total tumour volume, and HCC growth pattern) is associated with:

1. The success of downstaging treatments, in terms of the reduction in this burden; **(C, IIb)**
2. Post-LT recurrence; **(B, IIa)**

3. Overall survival after LT. **(C, IIb)**

Serum AFP levels before or on completing downstaging treatments, or at the time of LT, are associated with:

1. Downstaging efficacy; **(C, IIb)**
2. Waiting list drop-out; **(B, IIa)**
3. HCC recurrence after LT; **(B, IIa)**
4. Time to recurrence; **(C, IIb)**
5. Disease-free survival; **(B, IIa)**
6. Overall survival. **(C, IIb)**

Response to treatment, and its stability over time predict post-transplant HCC recurrence, and are associated with time to recurrence. **(C, IIb)** Complete response to downstaging is associated with overall survival. **(B, IIa)**

The use of heterogeneous inclusion criteria, a shortage of randomized studies, the adoption of different characteristics/thresholds for the same parameter, and the lack of standardized measures of downstaging treatment efficacy make it impossible to identify parameters capable of unequivocally predicting the success of downstaging, or provide consistent and clear-cut indications for LT on the basis of response to downstaging treatment. **(C, I)**

It is strongly recommended that centres establish well-defined written parameters (to be verified and updated in the light of outcomes) in terms of initial criteria, response to treatment, and maintenance of response over time for transplantability. **(C, I)**

6.4.2 | Comment

Patients with HCC listed for LT while exceeding the currently accepted criteria for transplantation usually undergo procedures aiming to reduce their tumour burden, and thus avoid waiting list drop-out because of tumour progression beyond transplantability. When using expanded criteria, one of the most relevant issues concerns the need to identify parameters capable of predicting which patients will fail to respond to measures to reduce their tumour burden, and therefore benefit from other downstaging treatments. Several studies tried to establish which parameters best predicted successful downstaging, but their value is limited by differences, for instance in: the numbers of patients involved (ranging from 22 to 271); the populations considered (with some reports including patients with macrovascular invasion); the criteria for defining successful downstaging; the cut-offs used for the same parameter (e.g, AFP levels); the types of downstaging treatment; the radiological criteria used to assess response to treatment; and the duration of the follow-up to establish a consolidated response to downstaging.[153-158] Lastly, and most importantly, no randomized controlled trials have examined this issue, and very few of the published studies were prospective. All these shortcomings clearly limit the chances of drawing any firm conclusions regarding this important issue.

6.5 | Question 5

How should we assess the efficacy of expanded criteria, in terms of intention-to-treat or post-transplant survival?

6.5.1 | Statements

In transplantable patients who undergo downstaging, survival should be assessed by means of an intention-to-treat analysis. **(C, IIb)**

In transplanted patients, survival should be expressed at 5 years using a per-protocol analysis. **(A, I)**

6.5.2 | Comment

When assessing the efficacy, in terms of survival, of adopting expanded criteria for transplanting HCC patients, we should consider "oncological survival" (for all patients with HCC who receive a transplant), and "transplant survival" (considering transplanted patients with and without HCC). Judging the efficacy of the expanded criteria should thus avoid the "double mortality" of patients with HCC whose tumour recurs and who die after LT, and of potential LT recipients without HCC who do not receive a transplant.[148,159,160] Excess waiting list mortality because of the listing of patients who cannot wait and who have to drop out as a result of uncontrollable HCC progression should be taken into account as well. In this regard, the thresholds for initiating downstaging, and for considering it successful should be clearly defined at each transplant centre, and preferably the same across centres. The intention-to-treat criterion seems to be more pertinent to patients who may be eligible for downstaging because it assesses patients who have reached the downstaging threshold and are waiting for a transplant, thus reflecting the performance of the listing criteria adopted (e.g, risk of overtreatment and drop-out because of uncontrollable liver failure; risk of drop-out because of inadequate expansion of transplant criteria and consequent uncontrollable progression of HCC). On the other hand, per-protocol criteria only consider the survival of patients who have had a transplant, with the risk of evaluating survival in favour of patients with a disease that has a benign biological behaviour, excluding mortality on the waiting list among patients with aggressive disease or an excess tumour burden.

7 | HOW TO DEAL WITH DIRECT-ACTING ANTIVIRAL TREATMENT FAILURE BEFORE AND AFTER LT

Infection with HCV is the most common indication for LT worldwide.[161,162] In viraemic patients, HCV infection nearly always recurs after transplantation, with a significant impact on patient and graft survival. HCV patients on the waiting list generally belong to one of two different clinical scenarios of HCV disease, i.e, liver decompensation (Dec-HCV, with or without HCC), or HCC in compensated disease (HCC-HCV). Historically, attempts to eradicate HCV before

LT had been disappointing, due largely to significant safety concerns relating to the use of interferon. The treatment of HCV recurrences after LT also suffered from a very low applicability rate, safety concerns and a limited efficacy.[163]

The approval of safe and effective DAAs has substantially changed the landscape of treatment for patients with decompensated cirrhosis, as well as for transplanted patients. The most important reasons for treating Dec-HCV patients on the waiting list for LT are: to improve their liver function, aiming for "delisting"; to improve their QoL; and to reduce mortality on the waiting list. The data supporting this strategy come from various sources. In the European study promoted by ELITA 20% of patients with Dec-HCV could be delisted thanks to their clinical improvement.[164] A recent Italian study on the real-life compassionate use of sofosbuvir in HCV patients listed for LT found that MELD scores could be brought down to satisfy a delisting rule in 17.4% of 47 patients with severely impaired liver function.[165] There is also evidence of a longer survival and better QoL while on the waiting list.[166,167] Negativization of viraemia prior to LT has also been associated with lower rates of early allograft dysfunction in HCV-positive LT recipients.[168]

In the treatment of patients with HCC and HCV, the main goal of DAA has been to prevent HCV reinfection after LT.[169] Pre-LT DAA therapy effectively prevented HCV recurrence in 95% of 61 Child-Pugh A patients, providing a minimum 30-day period of viral suppression elapsed before LT. A bridging strategy enabled graft reinfection to be prevented in most of the patients enrolled in the Italian ITACOPS study.[165,170] No solid data exist at present on whether preventing decompensation by eradicating the virus would enable the use of downstaging therapies for HCC.

7.1 | Question 1

What is the rate of DAA failure and its clinical impact in the pretransplant setting?

7.1.1 | Statement

The overall HCV eradication rate in cirrhotic patients is high, but always lower in those with advanced cirrhosis. The rate of failure in this patient population is due mainly to viral relapse, and ranges between 11% and 17% in trials and real-life cohort studies. **(A, I)**

Treatment failures should be minimized by identifying predictors of a negative response. This could prompt the adoption of a prolonged scheme including Ribavirin within current Italian regulatory agency rules. **(B, IIa)**

If there is a strong likelihood of DAA failing in patients with high MELD scores, the treatment could be delayed until after LT, **(B, IIa)** bearing in mind that therapeutic schemes including protease inhibitors are not appropriate as a retreatment strategy in decompensated patients. **(A, I)**

Resistance testing is mandatory after treatment failure in NS3, NS5A, NS5B, and it can orient the retreatment strategy. **(A, I)**

7.1.2 | Comment

Among various other clinical and transplant-specific considerations (expected time on the waiting list, etc.), the decision to treat a patient with Dec-HCV should take the risk of DAA failure into account. This points to the need for a precise definition of the predictors of a negative response (very advanced liver disease, presence of ascites, hepatic encephalopathy, albumin <2.8 g/dL, INR >1.7 and bilirubin >2 mg/dL) in order to optimize first-line treatment strategies to prevent resistance efficiently. The retreatment schemes available in this setting are limited, as protease inhibitors are contraindicated in decompensated liver disease, and the safety of multiple drug combinations in compensated HCC-HCV is unknown.[171] It is important to reassess the genotype involved in the event of DAA failure, especially in countries where pan-genotyping regimens are unavailable.[172]

7.2 | Question 2

Is the improvement in liver function following HCV eradication enough to balance the risk of DAA failure? In other words, should the treatment be given before or after transplantation?

7.2.1 | Statement

The clinical benefit of DAA treatment exceeds the risk of failure. **(B, IIa)** A significant reduction in Child-Pugh or MELD scores has been reported in 20%-40% of patients with decompensated cirrhosis treated with DAA, and one in four of them could be delisted. There have been no warnings about a negative impact of failed viral eradication treatments on any further decompensation.

As baseline MELD scores predict the likelihood of clinical improvement and of being delisted, any treatment of patients with a high MELD cut-off should be discussed case by case. **(B, IIb)**

7.2.2 | Comment

There is an abundance of data on the clinical improvement of Dec-HCV patients following HCV eradication. Overall, a sustained virological response (SVR) is associated with a median 2-point reduction in MELD score, a lower incidence of decompensation over 12 months post-SVR, and a 30% chance of delisting.[172-178] In the European study coordinated by Belli et al., and involving 11 European centres, 38/142 treated patients were delisted.[165] In the Italian ITACOPS study, viral eradication was associated with a better liver function in about half of 224 patients treated. High basal MELD scores (≥18), severe portal hypertension,[179] older age, albumin <3.5 g/dL, and hepatic encephalopathy are all associated with a lower chance of improvement.

7.3 | Question 3

Based on the magnitude of virological failure in transplanted patients, what policies are used to minimize DAA failure after LT?

7.3.1 | Statement

Direct acting antiviral agent (DAA) treatment should be administered as soon as possible after LT to avoid graft damage and optimize SVR rates. **(A, IIa)**

If negative predictors are identified, longer treatments and the use of ribavirin should be considered, as in the general population, and according to Italian regulatory agency rules. **(C, IIb)**

7.3.2 | Comment

The treatment failure rate with 2nd-generation DAA in HCV patients after LT ranges between 4% and 12%. In recent "real-world" studies, excluding those in which only the suboptimal sofosbuvir and ribavirin scheme was used, the rate of virological failure dropped to 0%-6%.[178,180-183] The factors associated with a poor response are the same as in immunocompetent patients (advanced disease stage, genotype 3, and a shorter treatment duration). Genotyping should be done (unless it has been done only recently, or a reliable report is available), and serum storage should be recommended for retrospective testing.[172]

No data are available on the best timing to start treatment after LT, but treatments in pre- and post-LT patients with advanced fibrosis and decompensated cirrhosis achieve lower SVR rates, as low as 60%.[171] Several studies have also demonstrated a lower SVR rate in patients with genotype 1a and advanced fibrosis (F3-F4 METAVIR). HCV treatment should be started as soon as feasible, not only to optimize SVR, but also and especially to reduce the risk of graft damage. Treatment with ribavirin, and its duration, after LT is still a concern.

Based on the available data, the recommendations are no different from the general guidelines for cirrhotic or non-cirrhotic patients, except for a close monitoring of immunosuppression levels in view of the drug interactions between calcineurin and m-TOR inhibitors, and DAA.

8 | CONCLUSION

Although LT is the best treatment for ESLD, there is published evidence of very low rates of access to LT for potentially eligible candidates with ESLD around the world, largely because they are either not referred to liver transplant centres for assessment, or their referral comes too late. Even if the organ donor pool is scarce, every patient potentially eligible for LT should be referred—at the appropriate time—to a transplant hepatologist on principles of justice and equity, and evaluated and managed with transparency and consistency among different centres, to improve their survival—even for patients who ultimately do not receive a transplant. In Italy, a strong effort should be made to: (a) prospectively measure referral rates to liver transplant centres, and the latter's selection of patients to place on the waiting list for LT; (b) engage with primary care physicians and specialists who manage potential LT candidates at meetings and symposia to reinforce the concept of the optimal timing for initial referral to a transplant hepatologist, and to spread the use of telehealth technologies, such as the "*e*Referral" website, to improve referral to transplant hepatologists and optimize patient comanagement.

The growing success of LT over the years has enabled us to gradually expand the indications for its use, including patients with increasingly severe liver diseases, and refining the selection of appropriate recipient and donor characteristics. Increasingly elderly patients, and those with numerous comorbidities are accessing LT nowadays. The age of donors is increasing too, along with the need to choose the right combination of donor and recipient ever more accurately to ensure an acceptable transplant benefit. Although the absolute contraindications to LT are few today, there are growing numbers of potential candidates with extra-hepatic comorbidities that are not always easy to quantify in terms of their impact on survival and QoL after LT. This type of scenario is destined to become more and more common in future, and will probably make it necessary to combine current organ allocation models with the preparation and validation of more complex prognostic scores than those used today in order to calculate the transplant benefit for "difficult candidates" for LT.

Sarcopenia, obesity and malnutrition, alone or in combination, are common comorbidities in LT candidates and are associated with poor outcomes before and after LT, as well as a higher burden on healthcare resources. Since these disorders are potentially modifiable factors, a nutritional assessment should be conducted on all patients on the waiting list for LT.

Criteria for diagnosing nutritional disorders have been developed by various scientific societies, but their accuracy in cases of advanced cirrhosis is often limited by the related changes in body composition. Testing for sarcopenia has emerged as the mainstay of nutritional assessments, however: it is objectively measureable and the most important nutritional variable associated with prognosis.

Patients awaiting LT can differ considerably in terms of their clinical conditions and nutritional status. Dietary interventions should consequently be based on the specific needs of individual transplant candidates, and preferably managed by a certified nutritionist/dietician as part of a multidisciplinary approach. Any intervention should also include adapted physical activity and regular counselling.

Metabolic syndrome is very common in transplant recipients, and cardiovascular diseases are a major cause of long-term morbidity and mortality after LT. Implementing programs based on a comprehensive lifestyle management, a lower calorie intake, more physical activity and behavioural changes are believed to have a clear benefit in reducing this cardiovascular risk.

In Italy, as in other parts of the world, LDLT continues to be a small but important source of grafts to help address the shortage of liver donors. LDLT reduces the mortality of recipients on the waiting list and affords the same short-term, and better long-term allograft and patient survival rates than DDLT. Recipients of LDLT have more short-term morbidity, however, and biliary complications in particular.

Since donor safety remains the first priority, only a minority (around 30%) of potential donors are acceptable candidates after a thorough psychosocial, medical and anatomical evaluation. The donor characteristics identified as maximizing safety and efficacy for both donors and recipients have include the transplant team's experience, younger donor age, healthy donor BMI, an adequate remnant volume of the native liver for the living donor, and accurate preoperative donor and recipient preparation. LDLT is now an established therapy at some transplant centres in Italy, with a well-documented 40% perioperative donor morbidity, but also with disabling complications in <1% of cases, and an ongoing 0.2% risk of death. The QoL for donor and recipient is generally excellent. Continued advocacy is required to reduce social, financial and emotional roadblocks to optimal LDLT practice. LDLT is more challenging than DDLT because of ethical issues concerning both donor and recipient. As a specialty, it therefore requires full-time professionals working in MDTs, with a strong emphasis on the importance of teamwork.

In the imminent future, there is likely to be a proportional decrease in the number or LT procedures performed because of ESLD. HCC will probably increasingly become the leading indication for LT, and the time may be ripe for an expansion of the Milan criteria currently used to select appropriate candidates. Expanding the criteria for LT in patients with HCC should not be detrimental to other patients with ESLD, however, and 5-year survival has to be adequate. A combination of morphological (tumour size and number) and biochemical (serum AFP) parameters has been proposed and independently validated as a broader criterion for transplanting patients with HCC outside the Milan criteria. Macrovascular invasion or extrahepatic spread are still regarded as a contraindication to transplantation in these patients, however. When applying expanded criteria, it is crucially important to ensure that transplant centres periodically review the outcome of downstaged patients in order to maximize patient survival. In this regard, assessing tumour aggressiveness *in itinere* (for example, response to downstaging treatment, biochemical expression changes) should serve as a "test-of-time" and facilitate the choice of the best candidates for LT. The survival of patients who undergo downstaging treatment should also be expressed on an intention-to-treat basis, as this gives an accurate measure of the actual benefit gained by applying expanded criteria.

The approval of safe and effective DAAs has prompted substantial changes in the landscape of treatments for patients with decompensated cirrhosis, as well as for transplanted patients. Among several clinical and transplant-specific considerations, the decision to treat a decompensated patient should be balanced against the risk of DAA failure in order to optimize treatment strategies with a view to preventing resistance efficiently. Re-treatment options are limited in this setting because protease inhibitors are contraindicated in decompensated liver disease, and the safety of multiple drug combinations in compensated HCC-HCV is unknown. Overall, SVR is associated with a median 2-point reduction in MELD score, and a lower incidence of decompensation over 12 months thereafter. Few data are available on the best time after the transplant to start treatment. HCV treatment should be started as soon as feasible, not only to optimize SVR, but also and especially to reduce the risk of damage to the graft. The rate of treatment failure with 2nd-generation DAAs in HCV patients after transplantation ranges between 4% and 12%. Close monitoring of patients' immunosuppression levels should be recommended in view of the drug interactions between DAAs and calcineurin or m-TOR inhibitors.

9 | SUMMARY OF THE CONTENT

1. This position paper states that every patient potentially eligible for LT should be referred to a transplant hepatologist even for patients who ultimately do not receive a transplant.
2. Sarcopenia, obesity, and malnutrition, alone or in combination, are common comorbidities in liver transplant candidates and are associated with poor outcomes as well as a higher burden on healthcare resources. A nutritional assessment should be conducted on all patients on the waiting list for liver transplant.
3. In Italy, as in other parts of the world, liver donor LT continues to be a small but important source of grafts to help address the shortage of liver donors. It is more challenging than deceased donor liver transplant because of ethical issues concerning both donor and recipient.
4. In the imminent future, HCC will probably increasingly become the leading indication for LT, and the time may be ripe for an expansion of the Milan criteria currently used to select appropriate candidates. Expanding the criteria for LT in patients with HCC should not be detrimental to other patients with ESLD.
5. The approval of safe and effective DAAs has prompted substantial changes in the landscape of treatments for patients with decompensated cirrhosis, as well as for transplanted patients. Close monitoring of patients' immunosuppression levels should be recommended in view of the drug interactions between some antiviral and some immunosuppressive drugs.

CONFLICT OF INTEREST

Patrizia Burra, Edoardo G. Giannini, Paolo Caraceni, Stefano Ginanni Corradini, Riccardo Volpes, Pierluigi Toniutto: none in the last 24 months. Maria Rendina: Gilead, Abbvie, BMS, Merck.

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REFERENCES

1. Burra P, Belli LS, Ginanni Corradini S, et al. Common issues in the management of patients in the waiting list and after liver transplantation. *Dig Liver Dis*. 2017;49:241-253.
2. U.S. Government Printing Office. *Health, United States, 2016: With Chartbook on Long-term Trends in Health*. Hyattsville, MD: U.S. Government Printing Office; 2017.
3. Adler JT, Dong N, Markmann JF, Schoenfeld D, Yeh H. Role of patient factors and practice patterns in determining access to liver waitlist. *Am J Transplant*. 2015;15:1836-1842.
4. Goldberg D, French B, Newcomb C, et al. Patients with hepatocellular carcinoma have highest rates of wait-listing for liver transplantation among patients with end-stage liver disease. *Clin Gastroenterol Hepatol*. 2016;14:1638-1646. e2.
5. Goldberg DS, French B, Forde KA, et al. Association of distance from a transplant center with access to waitlist placement, receipt of liver transplantation, and survival among US veterans. *JAMA*. 2014;311:1234-1243.
6. Goldberg DS, French B, Sahota G, Wallace AE, Lewis JD, Halpern SD. Use of population-based data to demonstrate how waitlist-based metrics overestimate geographic disparities in access to liver transplant care. *Am J Transplant*. 2016;16:2903-2911.
7. Julapalli VR, Kramer JR, El-Serag HB; American Association for the Study of Liver Diseases. Evaluation for liver transplantation: adherence to AASLD referral guidelines in a large Veterans Affairs center. *Liver Transpl*. 2005;11:1370-1378.
8. Kotlyar DS, Burke A, Campbell MS, Weinrieb RM. A critical review of candidacy for orthotopic liver transplantation in alcoholic liver disease. *Am J Gastroenterol*. 2008;103:734-743; quiz 44.
9. Mathur AK, Ashby VB, Fuller DS, et al. Variation in access to the liver transplant waiting list in the United States. *Transplantation*. 2014;98:94-99.
10. Schmied BM, Mehrabi A, Schallert C, et al. Evolution of liver transplantation at the University of Heidelberg: interventions influencing patient referral. *Transplantation*. 2005;80(1 Suppl):S147-S150.
11. Vidal-Trecan G, Kone V, Pilette C, et al. Subjective parameters markedly limit the referral of transplantation candidates to liver transplant centres. *Liver Int*. 2016;36(4):555-562.
12. Wilder JM, Oloruntoba OO, Muir AJ, Moylan CA. Role of patient factors, preferences, and distrust in health care and access to liver transplantation and organ donation. *Liver Transpl*. 2016;22:895-905.
13. Lim SG, Wai CT, Da Costa M, et al. Referral patterns and waiting times for liver transplantation in Singapore. *Singapore Med J*. 2006;47:599-603.
14. European Association for the Study of the Liver. Electronic Address E E E. EASL Clinical Practice Guidelines: Liver transplantation. *J Hepatol*. 2016;64:433-485.
15. Fox RK. When to consider liver transplant during the management of chronic liver disease. *Med Clin North Am*. 2014;98(1):153-168.
16. Murray KF, Carithers RL Jr; AASLD. AASLD practice guidelines: evaluation of the patient for liver transplantation. *Hepatology*. 2005;41:1407-1432.
17. http://dati.istat.it/.
18. https://trapianti.sanita.it/statistiche/home.asp.
19. https://www.cdc.gov/nchs/data/nvsr/nvsr65/nvsr65_04.pdf.
20. https://www.srtr.org/reports-tools/srtroptn-annual-data-report/.
21. https://www.msssi.gob.es/estadEstudios/estadisticas/estadisticas/estMinisterio/mortalidad/docs/PatronesMortalidadEspana2014.1.pdf.
22. http://www.irodat.org/.
23. Angelico M, Cillo U, Fagiuoli S, et al. Liver Match, a prospective observational cohort study on liver transplantation in Italy: study design and current practice of donor-recipient matching. *Dig Liver Dis*. 2011;43(2):155-164.
24. Martin P, Dimartini A, Feng S, Brown R Jr, Fallon M. Evaluation for liver transplantation in adults: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. *Hepatology*. 2014;59(3):1144-1165.
25. Adam R, Karam V, Delvart V, et al. Improved survival in liver transplant recipients receiving prolonged-release tacrolimus in the European Liver Transplant Registry. *Am J Transplant*. 2015;15(5):1267-1282.
26. Scheuher C. A review of organ transplantation: heart, lung, kidney, liver, and simultaneous liver-kidney. *Crit Care Nurs Q*. 2016;39(3):199-206.
27. Toniutto P, Zanetto A, Ferrarese A, Burra P. Current challenges and future directions for liver transplantation. *Liver Int*. 2017;37(3):317-327.
28. Keswani RN, Ahmed A, Keeffe EB. Older age and liver transplantation: a review. *Liver Transpl*. 2004;10:957-967.
29. Cross TJ, Antoniades CG, Muiesan P, et al. Liver transplantation in patients over 60 and 65 years: an evaluation of long-term outcomes and survival. *Liver Transpl*. 2007;13:1382-1388.
30. Garcia CE, Garcia RF, Mayer AD, Neuberger J. Liver transplantation in patients over sixty years of age. *Transplantation*. 2001;72:679-684.
31. Lipshutz GS, Hiatt J, Ghobrial RM, et al. Outcome of liver transplantation in septuagenarians: a single-center experience. *Arch Surg*. 2007;142:775-781; discussion 81-84.
32. Liu H, Jayakumar S, Traboulsi M, Lee SS. Cirrhotic cardiomyopathy: implications for liver transplantation. *Liver Transpl*. 2017;23(6):826-835.
33. Fede G, Privitera G, Tomaselli T, Spadaro L, Purrello F. Cardiovascular dysfunction in patients with liver cirrhosis. *Ann Gastroenterol*. 2015;28(1):31-40.
34. Ehtisham J, Altieri M, Salame E, Saloux E, Ollivier I, Hamon M. Coronary artery disease in orthotopic liver transplantation: pretransplant assessment and management. *Liver Transpl*. 2010;16(5):550-557.
35. Sharma M, Yong C, Majure D, et al. Safety of cardiac catheterization in patients with end-stage liver disease awaiting liver transplantation. *Am J Cardiol*. 2009;103(5):742-746.
36. Wray C, Scovotti JC, Tobis J, et al. Liver transplantation outcome in patients with angiographically proven coronary artery disease: a multi-institutional study. *Am J Transplant*. 2013;13:184-191.
37. Porres-Aguilar M, Mukherjee D. Portopulmonary hypertension: an update. *Respirology*. 2015;20(2):235-242.
38. Ayoub T. Pulmonary hypertension in liver transplant. *Curr Opin Organ Transplant*. 2011;16(3):331-337.
39. Hoeper MM, Krowka MJ, Strassburg CP. Portopulmonary hypertension and hepatopulmonary syndrome. *Lancet*. 2004;363:1461-1468.
40. Krowka MJ, Plevak DJ, Findlay JY, Rosen CB, Wiesner RH, Krom RA. Pulmonary hemodynamics and perioperative cardiopulmonary-related mortality in patients with portopulmonary hypertension undergoing liver transplantation. *Liver Transpl*. 2000;6:443-450.
41. Martinez GP, Barbera JA, Visa J, et al. Hepatopulmonary syndrome in candidates for liver transplantation. *J Hepatol*. 2001;34:651-657.
42. Rodriguez-Roisin R, Krowka MJ. Hepatopulmonary syndrome – a liver-induced lung vascular disorder. *N Engl J Med*. 2008;358(22):2378-2387.
43. Abrams GA, Nanda NC, Dubovsky EV, Krowka MJ, Fallon MB. Use of macroaggregated albumin lung perfusion scan to diagnose

hepatopulmonary syndrome: a new approach. *Gastroenterology*. 1998;114:305-310.
44. Arguedas MR, Abrams GA, Krowka MJ, Fallon MB. Prospective evaluation of outcomes and predictors of mortality in patients with hepatopulmonary syndrome undergoing liver transplantation. *Hepatology*. 2003;37:192-197.
45. Pastor CM, Schiffer E. Therapy Insight: hepatopulmonary syndrome and orthotopic liver transplantation. *Nat Clin Pract Gastroenterol Hepatol*. 2007;4:614-621.
46. Nadim MK, Sung RS, Davis CL, et al. Simultaneous liver-kidney transplantation summit: current state and future directions. *Am J Transplant*. 2012;12:2901-2908.
47. Angeli P, Gines P, Wong F, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. *Gut*. 2015;64(4):531-537.
48. Salerno F, Gerbes A, Gines P, Wong F, Arroyo V. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. *Gut*. 2007;56(9):1310-1318.
49. Wong F, Nadim MK, Kellum JA, et al. Working Party proposal for a revised classification system of renal dysfunction in patients with cirrhosis. *Gut*. 2011;60:702-709.
50. Francoz C, Glotz D, Moreau R, Durand F. The evaluation of renal function and disease in patients with cirrhosis. *J Hepatol*. 2010;52(4):605-613.
51. Chandok N, Watt KD. Burden of de novo malignancy in the liver transplant recipient. *Liver Transpl*. 2012;18(11):1277-1289.
52. Lucey MR; Weinrieb RM. Alcohol and substance abuse. *Semin Liver Dis*. 2009;29(1):66-73.
53. Coffman KL. The debate about marijuana usage in transplant candidates: recent medical evidence on marijuana health effects. *Curr Opin Organ Transplant*. 2008;13(2):189-195.
54. Secunda K, Gordon EJ, Sohn MW, et al. National survey of provider opinions on controversial characteristics of liver transplant candidates. *Liver Transpl*. 2013;19:395-403.
55. Ranney DN, Acker WB, Al-Holou SN, et al. Marijuana use in potential liver transplant candidates. *Am J Transplant*. 2009;9:280-285.
56. Kotwani P, Saxena V, Dodge JL, Roberts J, Yao F, Hameed B. History of marijuana use does not affect outcomes on the liver transplant waitlist. *Transplantation*. 2018; https://doi.org/10.1097/TP.0000000000002045.
57. Cederholm T, Barazzoni R, Austin P, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. *Clin Nutr*. 2017;36(1):49-64.
58. Bakshi N, Singh K. Nutrition assessment and its effect on various clinical variables among patients undergoing liver transplant. *Hepatobiliary Surg Nutr*. 2016;5(4):358-371.
59. Sinclair M, Gow PJ, Grossmann M, Angus PW. Review article: sarcopenia in cirrhosis–aetiology, implications and potential therapeutic interventions. *Aliment Pharmacol Ther*. 2016;43(7):765-777.
60. Ayloo S, Hurton S, Cwinn M, Molinari M. Impact of body mass index on outcomes of 48281 patients undergoing first time cadaveric liver transplantation. *World J Transplant*. 2016;6(2):356-369.
61. Montano-Loza AJ, Angulo P, Meza-Junco J, et al. Sarcopenic obesity and myosteatosis are associated with higher mortality in patients with cirrhosis. *J Cachexia Sarcopenia Muscle*. 2016;7:126-135.
62. Merli M, Nicolini G, Angeloni S, Riggio O. Malnutrition is a risk factor in cirrhotic patients undergoing surgery. *Nutrition*. 2002;18(11–12):978-986.
63. Sam J, Nguyen GC. Protein-calorie malnutrition as a prognostic indicator of mortality among patients hospitalized with cirrhosis and portal hypertension. *Liver Int*. 2009;29(9):1396-1402.
64. Kalafateli M, Mantzoukis K, Choi Yau Y, et al. Malnutrition and sarcopenia predict post-liver transplantation outcomes independently of the Model for End-stage Liver Disease score. *J Cachexia Sarcopenia Muscle*. 2017;8(1):113-121.
65. Merli M, Giusto M, Gentili F, et al. Nutritional status: its influence on the outcome of patients undergoing liver transplantation. *Liver Int*. 2010;30(2):208-214.
66. Merli M, Giusto M, Giannelli V, Lucidi C, Riggio O. Nutritional status and liver transplantation. *J Clin Exp Hepatol*. 2011;1(3):190-198.
67. Dick AA, Spitzer AL, Seifert CF, et al. Liver transplantation at the extremes of the body mass index. *Liver Transpl*. 2009;15:968-977.
68. Montano-Loza AJ, Duarte-Rojo A, Meza-Junco J, et al. Inclusion of sarcopenia within MELD (MELD-sarcopenia) and the prediction of mortality in patients with cirrhosis. *Clin Transl Gastroenterol*. 2015;6:e102.
69. van Vugt JL, Levolger S, de Bruin RW, van Rosmalen J, Metselaar HJ, IJzermans JN. Systematic review and meta-analysis of the impact of computed tomography-assessed skeletal muscle mass on outcome in patients awaiting or undergoing liver transplantation. *Am J Transplant*. 2016;16:2277-2292.
70. Lamattina JC, Foley DP, Fernandez LA, et al. Complications associated with liver transplantation in the obese recipient. *Clin Transplant*. 2012;26:910-918.
71. Saab S, Lalezari D, Pruthi P, Alper T, Tong MJ. The impact of obesity on patient survival in liver transplant recipients: a meta-analysis. *Liver Int*. 2015;35(1):164-170.
72. Wong RJ, Cheung R, Perumpail RB, Holt EW, Ahmed A. Diabetes mellitus, and not obesity, is associated with lower survival following liver transplantation. *Dig Dis Sci*. 2015;60:1036-1044.
73. Morgan MY, Madden AM, Soulsby CT, Morris RW. Derivation and validation of a new global method for assessing nutritional status in patients with cirrhosis. *Hepatology*. 2006;44:823-835.
74. Borhofen SM, Gerner C, Lehmann J, et al. The Royal Free Hospital – nutritional prioritizing tool is an independent predictor of deterioration of liver function and survival in cirrhosis. *Dig Dis Sci*. 2016;61:1735-1743.
75. Tandon P, Raman M, Mourtzakis M, Merli M. A practical approach to nutritional screening and assessment in cirrhosis. *Hepatology*. 2017;65(3):1044-1057.
76. Mazurak VC, Tandon P, Montano-Loza AJ. Nutrition and the transplant candidate. *Liver Transpl*. 2017;23:1451-1464.
77. Golse N, Bucur PO, Ciacio O, et al. A new definition of sarcopenia in patients with cirrhosis undergoing liver transplantation. *Liver Transpl*. 2017;23:143-154.
78. Carey EJ, Lai JC, Wang CW, et al. A multicenter study to define sarcopenia in patients with end-stage liver disease. *Liver Transpl*. 2017;23:625-633.
79. Lai JC, Dodge JL, Sen S, Covinsky K, Feng S. Functional decline in patients with cirrhosis awaiting liver transplantation: results from the functional assessment in liver transplantation (FrAILT) study. *Hepatology*. 2016;63:574-580.
80. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European Working Group on Sarcopenia in Older People. *Age Ageing*. 2010;39:412-423.
81. Ney M, Gramlich L, Mathiesen V, et al. Patient-perceived barriers to lifestyle interventions in cirrhosis. *Saudi J Gastroenterol*. 2017;23(2):97-104.
82. Amodio P, Bemeur C, Butterworth R, et al. The nutritional management of hepatic encephalopathy in patients with cirrhosis: International Society for Hepatic Encephalopathy and Nitrogen Metabolism Consensus. *Hepatology*. 2013;58(1):325-336.
83. Dasarathy S, Merli M. Sarcopenia from mechanism to diagnosis and treatment in liver disease. *J Hepatol*. 2016;65(6):1232-1244.

84. Newsome PN, Allison ME, Andrews PA, et al. Guidelines for liver transplantation for patients with non-alcoholic steatohepatitis. *Gut*. 2012;61:484-500.
85. Mosko JD, NGUYEN GC. Increased perioperative mortality following bariatric surgery among patients with cirrhosis. *Clin Gastroenterol Hepatol*. 2011;9(10):897-901.
86. Heimbach JK, Watt KD, Poterucha JJ, et al. Combined liver transplantation and gastric sleeve resection for patients with medically complicated obesity and end-stage liver disease. *Am J Transplant*. 2013;13:363-368.
87. Berzigotti A, Saran U, Dufour JF. Physical activity and liver diseases. *Hepatology*. 2016;63(3):1026-1040.
88. Dharancy S, Lemyze M, Boleslawski E, et al. Impact of impaired aerobic capacity on liver transplant candidates. *Transplantation*. 2008;86(8):1077-1083.
89. Epstein SK, Freeman RB, Khayat A, Unterborn JN, Pratt DS, Kaplan MM. Aerobic capacity is associated with 100-day outcome after hepatic transplantation. *Liver Transpl*. 2004;10:418-424.
90. Neviere R, Edme JL, Montaigne D, Boleslawski E, Pruvot FR, Dharancy S. Prognostic implications of preoperative aerobic capacity and exercise oscillatory ventilation after liver transplantation. *Am J Transplant*. 2014;14:88-95.
91. Debette-Gratien M, Tabouret T, Antonini MT, et al. Personalized adapted physical activity before liver transplantation: acceptability and results. *Transplantation*. 2015;99(1):145-150.
92. Roman E, Torrades MT, Nadal MJ, et al. Randomized pilot study: effects of an exercise programme and leucine supplementation in patients with cirrhosis. *Dig Dis Sci*. 2014;59:1966-1975.
93. Zenith L, Meena N, Ramadi A, et al. Eight weeks of exercise training increases aerobic capacity and muscle mass and reduces fatigue in patients with cirrhosis. *Clin Gastroenterol Hepatol*. 2014;12:1920-1926. e2.
94. Berzigotti A, Albillos A, Villanueva C, et al. Effects of an intensive lifestyle intervention program on portal hypertension in patients with cirrhosis and obesity: the SportDiet study. *Hepatology*. 2017;65(4):1293-1305.
95. Chodzko-Zajko WJ, Proctor DN, Fiatarone Singh MA, et al. American College of Sports Medicine position stand. Exercise and physical activity for older adults. *Med Sci Sports Exerc*. 2009;41:1510-1530.
96. Davis BC, Shadab Siddiqui M. Liver transplantation: the role of metabolic syndrome. *Curr Treat Options Gastroenterol*. 2017;15(2):316-331.
97. Gitto S, Vukotic R, Vitale G, Pirillo M, Villa E, Andreone P. Non-alcoholic steatohepatitis and liver transplantation. *Dig Liver Dis*. 2016;48(6):587-591.
98. Kallwitz ER, Loy V, Mettu P, von Roenn N, Berkes J, Cotler SJ. Physical activity and metabolic syndrome in liver transplant recipients. *Liver Transpl*. 2013;19:1125-1131.
99. Giusto M, Lattanzi B, di Gregorio V, Giannelli V, Lucidi C, Merli M. Changes in nutritional status after liver transplantation. *World J Gastroenterol*. 2014;20(31):10682-10690.
100. Garcia AM, Veneroso CE, Soares DD, Lima AS, Correia MI. Effect of a physical exercise program on the functional capacity of liver transplant patients. *Transplant Proc*. 2014;46:1807-1808.
101. Krasnoff JB, Vintro AQ, Ascher NL, et al. A randomized trial of exercise and dietary counseling after liver transplantation. *Am J Transplant*. 2006;6:1896-1905.
102. Kahn J, Matas A. What's special about the ethics of living donors? Reply to Ross et al. *Transplantation*. 2002;74:421-422.
103. Truog RD. The ethics of organ donation by living donors. *N Engl J Med*. 2005;353(5):444-446.
104. Manas D, Burnapp L, Andrews PA. Summary of the British Transplantation Society UK guidelines for living donor liver transplantation. *Transplantation*. 2016;100(6):1184-1190.
105. Miller CM, Durand F, Heimbach JK, et al. The International Liver Transplant Society guideline on living liver donation. *Transplantation*. 2016;100:1238-1243.
106. Cho JY, Suh KS, Kwon CH, et al. Outcome of donors with a remnant liver volume of less than 35% after right hepatectomy. *Liver Transpl*. 2006;12:201-206.
107. Reichman TW, Sandroussi C, Azouz SM, et al. Living donor hepatectomy: the importance of the residual liver volume. *Liver Transpl*. 2011;17:1404-1411.
108. Taner CB, Dayangac M, Akin B, et al. Donor safety and remnant liver volume in living donor liver transplantation. *Liver Transpl*. 2008;14:1174-1179.
109. Li C, Mi K, Wen TF, Yan LN, Li B. Safety of patients with a graft to body weight ratio less than 0.8% in living donor liver transplantation using right hepatic lobe without middle hepatic vein. *Hepatogastroenterology*. 2012;59(114):469-472.
110. Troisi R, de Hemptinne B. Clinical relevance of adapting portal vein flow in living donor liver transplantation in adult patients. *Liver Transpl*. 2003;9(9):S36-S41.
111. Hwang S, Lee SG, Lee YJ, et al. Lessons learned from 1,000 living donor liver transplantations in a single center: how to make living donations safe. *Liver Transpl*. 2006;12:920-927.
112. Iwasaki M, Takada Y, Hayashi M, et al. Noninvasive evaluation of graft steatosis in living donor liver transplantation. *Transplantation*. 2004;78(10):1501-1505.
113. Jun MJ, Shim JH, Kim SY, et al. Clinical implications of preoperative and intraoperative liver biopsies for evaluating donor steatosis in living related liver transplantation. *Liver Transpl*. 2014;20:437-445.
114. Rinella ME, Alonso E, Rao S, et al. Body mass index as a predictor of hepatic steatosis in living liver donors. *Liver Transpl*. 2001;7:409-414.
115. Barr ML, Belghiti J, Villamil FG, et al. A report of the Vancouver Forum on the care of the live organ donor: lung, liver, pancreas, and intestine data and medical guidelines. *Transplantation*. 2006;81:1373-1385.
116. Cheah YL, Simpson MA, Pomposelli JJ, Pomfret EA. Incidence of death and potentially life-threatening near-miss events in living donor hepatic lobectomy: a world-wide survey. *Liver Transpl*. 2013;19:499-506.
117. Gordon EJ. Informed consent for living donation: a review of key empirical studies, ethical challenges and future research. *Am J Transplant*. 2012;12(9):2273-2280.
118. Hougardy L, Stephenne X, Reding R, et al. Acquired antithrombin type IIb deficiency after liver transplantation: a case report. *Am J Transplant*. 2012;12(5):1329-1332.
119. Abecassis MM, Fisher RA, Olthoff KM, et al. Complications of living donor hepatic lobectomy – a comprehensive report. *Am J Transplant*. 2012;12:1208-1217.
120. Chan SC, Fan ST, Lo CM, Liu CL, Wong J. Toward current standards of donor right hepatectomy for adult-to-adult live donor liver transplantation through the experience of 200 cases. *Ann Surg*. 2007;245:110-117.
121. Akabayashi A, Slingsby BT, Fujita M. The first donor death after living-related liver transplantation in Japan. *Transplantation*. 2004;77(4):634.
122. Trotter JF, Adam R, Lo CM, Kenison J. Documented deaths of hepatic lobe donors for living donor liver transplantation. *Liver Transpl*. 2006;12:1485-1488.
123. Chan SC, Liu CL, Lo CM, Lam BK, Lee EW, Fan ST. Donor quality of life before and after adult-to-adult right liver live donor liver transplantation. *Liver Transpl*. 2006;12:1529-1536.
124. Humar A, Carolan E, Ibrahim H, et al. A comparison of surgical outcomes and quality of life surveys in right lobe vs. left lateral segment liver donors. *Am J Transplant*. 2005;5(4 Pt 1):805-809.

125. Samstein B, Smith AR, Freise CE, et al. Complications and their resolution in recipients of deceased and living donor liver transplants: findings from the A2ALL cohort study. *Am J Transplant*. 2016;16:594-602.
126. Berg CL, Merion RM, Shearon TH, et al. Liver transplant recipient survival benefit with living donation in the model for endstage liver disease allocation era. *Hepatology*. 2011;54:1313-1321.
127. Olthoff KM, Smith AR, Abecassis M, et al. Defining long-term outcomes with living donor liver transplantation in North America. *Ann Surg*. 2015;262:465-475; discussion 73-5.
128. Ojo AO, Held PJ, Port FK, et al. Chronic renal failure after transplantation of a nonrenal organ. *N Engl J Med*. 2003;349:931-940.
129. Fisher RA, Cotterell AH, Maluf DG, et al. Adult living donor versus deceased donor liver transplantation: a 10-year prospective single center experience. *Ann Hepatol*. 2009;8:298-307.
130. Kim SH, Kim YK, Lee SD, Park SJ. Successful living donor liver transplantation between septuagenarians. *Am J Transplant*. 2015;15:274-277.
131. Lee SG. A complete treatment of adult living donor liver transplantation: a review of surgical technique and current challenges to expand indication of patients. *Am J Transplant*. 2015;15(1):17-38.
132. Selzner M, Kashfi A, Cattral MS, et al. A graft to body weight ratio less than 0.8 does not exclude adult-to-adult right-lobe living donor liver transplantation. *Liver Transpl*. 2009;15(12):1776-1782.
133. Wan P, Yu X, Xia Q. Operative outcomes of adult living donor liver transplantation and deceased donor liver transplantation: a systematic review and meta-analysis. *Liver Transpl*. 2014;20(4):425-436.
134. Berg CL, Gillespie BW, Merion RM, et al. Improvement in survival associated with adult-to-adult living donor liver transplantation. *Gastroenterology*. 2007;133:1806-1813.
135. Fisher RA, Heuman DM, Harper AM, et al. Region 11 MELD Na exception prospective study. *Ann Hepatol*. 2012;11:62-67.
136. Heuman DM, Abou-Assi SG, Habib A, et al. Persistent ascites and low serum sodium identify patients with cirrhosis and low MELD scores who are at high risk for early death. *Hepatology*. 2004;40:802-810.
137. Somsouk M, Kornfield R, Vittinghoff E, Inadomi JM, Biggins SW. Moderate ascites identifies patients with low model for end-stage liver disease scores awaiting liver transplantation who have a high mortality risk. *Liver Transpl*. 2011;17(2):129-136.
138. Patidar KR, Thacker LR, Wade JB, et al. Covert hepatic encephalopathy is independently associated with poor survival and increased risk of hospitalization. *Am J Gastroenterol*. 2014;109:1757-1763.
139. Ramanathan R, Sharma A, Lee DD, et al. Multimodality therapy and liver transplantation for hepatocellular carcinoma: a 14-year prospective analysis of outcomes. *Transplantation*. 2014;98(1):100-106.
140. Kaido T, Takada Y, Uemoto S. Usefulness of the Kyoto criteria as selection criteria for living donor liver transplantation for hepatocellular carcinoma. *Liver Transpl*. 2010;16(4):538-540.
141. Soejima Y, Taketomi A, Yoshizumi T, et al. Extended indication for living donor liver transplantation in patients with hepatocellular carcinoma. *Transplantation*. 2007;83(7):893-899.
142. Harimoto N, Yoshida Y, Kurihara T, et al. Prognostic impact of des-gamma-carboxyl prothrombin in living-donor liver transplantation for recurrent hepatocellular carcinoma. *Transplant Proc*. 2015;47(3):703-704.
143. Yang JD, Larson JJ, Watt KD, et al. Hepatocellular carcinoma is the most common indication for liver transplantation and placement on the waitlist in the United States. *Clin Gastroenterol Hepatol*. 2017;15:767-775. e3.
144. Goldberg D, Ditah IC, Saeian K, et al. Changes in the prevalence of hepatitis C virus infection, nonalcoholic steatohepatitis, and alcoholic liver disease among patients with cirrhosis or liver failure on the waitlist for liver transplantation. *Gastroenterology*. 2017;152:1090-1099. e1.
145. Clavien PA, Lesurtel M, Bossuyt PM, et al. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. *Lancet Oncol*. 2012;13:e11-e22.
146. Volk ML, Vijan S, Marrero JA. A novel model measuring the harm of transplanting hepatocellular carcinoma exceeding Milan criteria. *Am J Transplant*. 2008;8:839-846.
147. Cillo U, Burra P, Mazzaferro V, et al. A multistep, consensus-based approach to organ allocation in liver transplantation: toward a "blended principle model". *Am J Transplant*. 2015;15(10):2552-2561.
148. Silva MF, Sherman M. Criteria for liver transplantation for HCC: what should the limits be? *J Hepatol*. 2011;55(5):1137-1147.
149. Duvoux C, Roudot-Thoraval F, Decaens T, et al. Liver transplantation for hepatocellular carcinoma: a model including alpha-fetoprotein improves the performance of Milan criteria. *Gastroenterology*. 2012;143:986-994. e3; quiz e14-5.
150. Notarpaolo A, Layese R, Magistri P, et al. Validation of the AFP model as a predictor of HCC recurrence in patients with viral hepatitis-related cirrhosis who had received a liver transplant for HCC. *J Hepatol*. 2017;66(3):552-559.
151. Pinero F, Tisi Bana M, de Ataide EC, et al. Liver transplantation for hepatocellular carcinoma: evaluation of the alpha-fetoprotein model in a multicenter cohort from Latin America. *Liver Int*. 2016;36:1657-1667.
152. Liver transplantation for hepatocellular carcinoma in the UK – report from a national consensus meeting (Birmingham January 2014) http://odt.nhs.uk/pdf/advisory_group_papers/LAG/HCC_recommendations_IR_TS_b_NAS_Work_in_Progress.pdf. Accessed April 27, 2018.
153. Agopian VG, Morshedi MM, McWilliams J, et al. Complete pathologic response to pretransplant locoregional therapy for hepatocellular carcinoma defines cancer cure after liver transplantation: analysis of 501 consecutively treated patients. *Ann Surg*. 2015;262:536-545; discussion 43-5.
154. Chapman WC, Garcia-Aroz S, Vachharajani N, et al. Liver transplantation for advanced hepatocellular carcinoma after downstaging without up-front stage restrictions. *J Am Coll Surg*. 2017;224:610-621.
155. Kim HD, Shim JH, Kim GA, et al. Optimal methods for measuring eligibility for liver transplant in hepatocellular carcinoma patients undergoing transarterial chemoembolization. *J Hepatol*. 2015;62:1076-1084.
156. Murali AR, Romero-Marrero C, Miller C, et al. Predictors of successful downstaging of hepatocellular carcinoma outside milan criteria. *Transplantation*. 2016;100:2391-2397.
157. Parikh ND, Waljee AK, Singal AG. Downstaging hepatocellular carcinoma: a systematic review and pooled analysis. *Liver Transpl*. 2015;21:1142-1152.
158. Yao FY, Mehta N, Flemming J, et al. Downstaging of hepatocellular cancer before liver transplant: long-term outcome compared to tumors within Milan criteria. *Hepatology*. 2015;61:1968-1977.
159. Prasad KR, Young RS, Burra P, et al. Summary of candidate selection and expanded criteria for liver transplantation for hepatocellular carcinoma: a review and consensus statement. *Liver Transpl*. 2011;17(Suppl 2):S81-S89.
160. Sharr WW, Chan SC, Lo CM. Section 3. Current status of downstaging of hepatocellular carcinoma before liver transplantation. *Transplantation*. 2014;97(Suppl 8):S10-S17.

161. European Liver Transplant Registry. 2017. www.eltr.org/. Accessed March 15, 2017.
162. United Network for Organ Sharing-US. 2017. https://www.unos.org/. Accessed March 15, 2017
163. Belli LS, Volpes R, Graziadei I, et al. Antiviral therapy and fibrosis progression in patients with mild-moderate hepatitis C recurrence after liver transplantation. A randomized controlled study. *Dig Liver Dis*. 2012;44:603-609.
164. Belli LS, Berenguer M, Cortesi PA, et al. Delisting of liver transplant candidates with chronic hepatitis C after viral eradication: a European study. *J Hepatol*. 2016;65:524-531.
165. Martini S, Donato MF, Mazzarelli C, et al. The Italian compassionate use of sofosbuvir in HCV patients waitlisted for liver transplantation: a national real-life experience. *Liver Int*. 2018;38(4):733-741.
166. Cholankeril G, Li AA, March KL, et al. Improved outcomes in HCV patients following liver transplantation during the era of direct-acting antiviral agents. *Clin Gastroenterol Hepatol*. 2018;16(3):452-453.
167. Dusheiko G. The impact of antiviral therapy for hepatitis C on the quality of life: a perspective. *Liver Int*. 2017;37(Suppl 1):7-12.
168. Martini S, Tandoi F, Terzi di Bergamo L, et al. Negativization of viremia prior to liver transplant reduces early allograft dysfunction in hepatitis C-positive recipients. *Liver Transpl*. 2017;23:915-924.
169. Curry MP, Forns X, Chung RT, et al. Sofosbuvir and ribavirin prevent recurrence of HCV infection after liver transplantation: an open-label study. *Gastroenterology*. 2015;148:100-107. e1.
170. Donato MF, Morelli C, Romagnoli R, et al. Prevention of hepatitis C recurrence by bridging sofosbuvir/ribavirin from pre- to post-liver transplant: a real-life strategy. *Liver Int*. 2017;37:678-683.
171. Pawlotsky JM. Hepatitis C virus resistance to direct-acting antiviral drugs in interferon-free regimens. *Gastroenterology*. 2016;151(1):70-86.
172. Di Maio VC, Cento V, Lenci I, et al. Multiclass HCV resistance to direct-acting antiviral failure in real-life patients advocates for tailored second-line therapies. *Liver Int*. 2017;37:514-528.
173. Cheung MCM, Walker AJ, Hudson BE, et al. Outcomes after successful direct-acting antiviral therapy for patients with chronic hepatitis C and decompensated cirrhosis. *J Hepatol*. 2016;65:741-747.
174. Fernandez Carrillo C, Lens S, Llop E, et al. Treatment of hepatitis C virus infection in patients with cirrhosis and predictive value of model for end-stage liver disease: analysis of data from the Hepa-C registry. *Hepatology*. 2017;65:1810-1822.
175. Lawitz E, Poordad F, Gutierrez JA, et al. Simeprevir, daclatasvir and sofosbuvir for hepatitis C virus-infected patients with decompensated liver disease. *J Viral Hepat*. 2017;24(4):287-294.
176. Mandorfer M, Kozbial K, Schwabl P, et al. Sustained virologic response to interferon-free therapies ameliorates HCV-induced portal hypertension. *J Hepatol*. 2016;65(4):692-699.
177. Manns M, Samuel D, Gane EJ, et al. Ledipasvir and sofosbuvir plus ribavirin in patients with genotype 1 or 4 hepatitis C virus infection and advanced liver disease: a multicentre, open-label, randomised, phase 2 trial. *Lancet Infect Dis*. 2016;16(6):685-697.
178. Poordad F, Schiff ER, Vierling JM, et al. Daclatasvir with sofosbuvir and ribavirin for hepatitis C virus infection with advanced cirrhosis or post-liver transplantation recurrence. *Hepatology*. 2016;63:1493-1505.
179. Afdhal N, Everson GT, Calleja JL, et al. Effect of viral suppression on hepatic venous pressure gradient in hepatitis C with cirrhosis and portal hypertension. *J Viral Hepat*. 2017;24:823-831.
180. Coilly A, Fougerou-Leurent C, de Ledinghen V, et al. Multicentre experience using daclatasvir and sofosbuvir to treat hepatitis C recurrence – the ANRS CUPILT study. *J Hepatol*. 2016;65(4):711-718.
181. Elfeki MA, Abou Mrad R, Modaresi Esfeh J, et al. Sofosbuvir/ledipasvir without ribavirin achieved high sustained virologic response for hepatitis C recurrence after liver transplantation: two-center experience. *Transplantation*. 2017;101:996-1000.
182. Forns X, Berenguer M, Herzer K, et al. Efficacy, safety, and pharmacokinetics of simeprevir, daclatasvir, and ribavirin in patients with recurrent hepatitis C virus genotype 1b infection after orthotopic liver transplantation: the Phase II SATURN study. *Transpl Infect Dis*. 2017;19.
183. Pungpapong S, Aqel B, Leise M, et al. Multicenter experience using simeprevir and sofosbuvir with or without ribavirin to treat hepatitis C genotype 1 after liver transplant. *Hepatology*. 2015;61(6):1880-1886.

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APPENDIX

Working Group 1

Interaction between hepatologists and transplant centres: how can the referral of candidates for liver transplantation be improved?

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Working Group 2

The "difficult candidate" for liver transplantation

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Working Group 3

The management of nutrition before and after transplantation

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Working Group 4

Living donor liver transplantation (LDLT): update and perspectives

Coordinator:

Riccardo Volpes

Participants:

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Working Group 5

Hepatocellular carcinoma and liver transplantation: is it time to expand the criteria in Italy?

Coordinator:

Edoardo G. Giannini

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Working Group 6

How to deal with direct-acting antiviral (DAA) treatment failure before and after LT

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