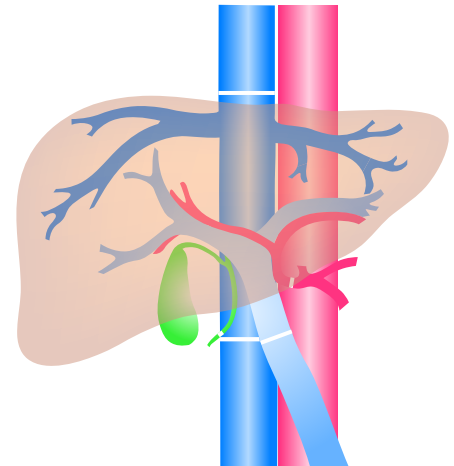


# Mistakes in liver transplantation and how to avoid them

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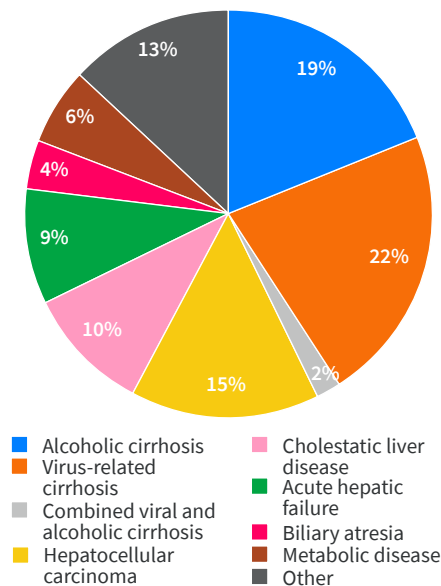
Since it was first performed by Thomas Starlz in 1963, liver transplantation has become a viable treatment option for patients with acute and chronic liver failure whatever the aetiology (figure 1).<sup>1-3</sup> Over the years, the outcomes of liver transplant recipients have improved significantly,<sup>1</sup> owing to continuous advances in surgical techniques and organ preservation, optimization of intensive care, and management of immunosuppressive therapy.<sup>4</sup> New strategies to enlarge the donor pool and to maximize survival after liver transplantation have also been introduced, which is essential particularly given the rise in cases of nonalcoholic steatohepatitis (NASH) and its emergence as a leading indication for liver transplantation.<sup>5</sup> That the field is continually evolving poses unique challenges to clinical practice, and these challenges may increase the risk of making mistakes. By definition, patients on the waiting list for liver transplantation do not have a therapeutic alternative, so any mistakes can have an ominous impact on their prognosis.

Here, we highlight 10 mistakes that can frequently be made when managing liver transplant candidates or recipients, and provide an evidence- and experience-based approach to avoiding them. Much of the discussion is based on the European Association for the Study of the Liver (EASL) clinical practice guidelines.<sup>2,6-12</sup>



## Mistake 1 Basing eligibility for transplantation in patients with alcohol-related liver disease solely on duration of pre-transplant abstinence

Gastroenterologists and hepatologists frequently encounter patients with alcoholic liver disease (ALD), and those with decompensated cirrhosis



**Figure 1 |** Main indications for liver transplantation in Europe. Data from the 2008 Annual Report of the European Liver Transplant Registry (ELTR).<sup>1</sup>

or with acute-on-chronic liver failure due to alcoholic hepatitis may be candidates for a new liver. Indeed, ALD is one of the main indications for liver transplantation.<sup>13</sup> Outcomes for ALD patients are excellent and comparable to other indications, with a 5-year survival rate of 76–86%.<sup>14</sup> Nonetheless, liver transplantation for patients with ALD still generates a lot of discussion, due to the perception that ALD is self inflicted and concerns regarding alcohol relapse after liver transplantation. As patients with a history of alcohol abuse are believed to be poor transplant candidates, many of those eligible for referral for liver transplantation are not referred. In the United States alone, lack of referral may be associated with as many as 12,000 deaths per year.<sup>15</sup>

In our opinion, patients should not be excluded from liver transplantation based on preconceived ideas, lack of evidence and presumed lack of resources, even if they are actively drinking at the time of decompensation.<sup>16</sup> Most important is the selection of candidates, balancing the needs of the individual and the claim that other potential recipients may have on each donated organ.<sup>17</sup> In our experience, this balance can be achieved via a strict selection process that takes a multidisciplinary approach, involving transplant hepatologists and surgeons, psychiatrists, addiction specialists, psychologists and/or social workers (figure 2). Identifying patients at risk of severe alcohol relapse after transplantation is of utmost importance, as only severe relapse has

been shown to have a negative impact on long-term survival.<sup>18,19</sup>

Traditionally, most transplant centres require a 6-month period of abstinence before considering a patient with ALD suitable for liver transplantation. The so-called 6-month rule was introduced more than 20 years ago, when a group of experts formulated the minimal criteria for listing patients with ALD.<sup>20</sup> The rationale behind this rule was twofold—to prevent liver transplantation in patients whose liver function will recover with abstinence alone and to identify patients at high risk of relapse after liver transplantation (for whom liver transplantation should be contraindicated).

Although some studies have demonstrated that the maximum benefit of abstinence is observed within the first 3–6 months, it's very hard to establish whether the length of pre-transplantation abstinence is really helpful when assessing the risk of post-transplantation relapse.<sup>2,9,21,22</sup> Assessing the real likelihood of abstinence post-transplantation is extremely complex, and both the European and American guidelines state that the 6-month rule should no longer be used to assess whether a patient can be accepted as a liver transplantation candidate.<sup>2,3,9</sup> In particular, liver transplantation may be indicated even without 6 months of abstinence when liver function deteriorates rapidly.<sup>23</sup>

The seminal study by Mathurin et al. provides further evidence that good results can be achieved in patients transplanted for alcoholic

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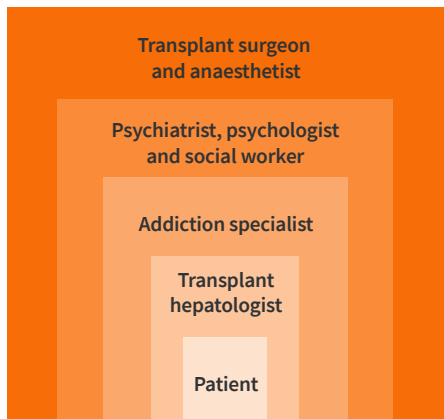
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**Figure 2** | The transplant evaluation process in patients with alcohol-related liver disease.

hepatitis when they are selected via a strict multidisciplinary consensus (2-year survival of 77%, risk of relapse of 11.5%).<sup>24</sup> Under the umbrella of the Italian Association for the Study of the Liver, our centre in Padova started a program of early liver transplantation in patients with alcoholic hepatitis who are not responding to medical therapy. Our protocol mimics that conceived by Mathurin et al.,<sup>24</sup> as we believe this approach can bring transparency and consensus when making such difficult decisions.

**Mistake 2 Assuming the patient is too old or too obese for liver transplantation**

Liver transplant candidates may have demographic (e.g. age) and/or clinical (e.g. obesity) characteristics that make it borderline whether or not it is safe for them to undergo liver transplantation.

A patient may ask if being 70 is too old to get a new liver. Although it is unclear whether there is an age above which liver transplantation should be contraindicated, it's clear that liver transplantation should not be ruled out just because the patient is a certain age. A few preliminary reports have suggested that recipients over 65 years old may have a worse outcome than their younger counterparts, but physiological age seems more important than chronological age.<sup>2</sup> Indeed, excellent results have been reported in recipients older than 65 as long as they are selected carefully (especially with regard to cardiovascular and pulmonary comorbidities).<sup>25,26</sup>

The proportion of registrants older than 65 years of age has increased considerably both in Europe and the United States,<sup>27</sup> and it is expected to increase further due both to the aging population present in Western societies and to changes in liver transplantation indications (i.e. the decrease in liver transplantation for HCV-decompensated cirrhosis and its increase for NASH-related cirrhosis and/or NASH-related hepatocellular carcinoma [HCC]). Age per se must not, therefore, disqualify candidates for liver

transplantation, and the final decision for listing an 'old' candidate (70 years of age or older) should be taken after a multidisciplinary discussion with the transplant team.<sup>2</sup>

Another frequent dilemma is whether a patient is too obese for transplantation. A very high body mass index (BMI) presents technical challenges when performing transplant surgery, but it's unclear whether it is associated with an increased risk of complications or death.<sup>28</sup> Class III obesity (BMI ≥40) at the time of liver transplantation was associated with worse outcomes in a recent analysis of the United Network for Organ Sharing database,<sup>29</sup> but high BMI was not associated with an increased risk of death in two other studies when adjusted for ascites.<sup>30,31</sup> So far, no upper limit of BMI that makes a candidate too 'difficult' to be transplanted has been identified.

As with older patients, obese patients do need particularly careful assessment prior to listing.<sup>28</sup> Expertise in selection and post-operative management of obese patients who undergo abdominal surgery is increasing, and we hope this will improve the outcome of obese patients undergoing liver transplantation. To ensure a balanced evaluation of the benefits and risks, as well as to evaluate the indication for bariatric surgery as an adjunct to liver transplantation, obese patients should be referred to tertiary centres with extensive experience in the field.

**Mistake 3 Not paying enough attention to sarcopenia in patients awaiting liver transplantation**

The management of patients awaiting liver transplantation can be very challenging. Treatment of complications related to portal hypertension, bridging treatments for HCC, frequent hospitalizations, real-time updates of patient status, and so on, make it easy to forget about skeletal muscle abnormalities, including sarcopenia. In the past few years, however, particular emphasis has been given to this issue by the transplant community, as sarcopenia was found to be an independent predictor of clinical outcomes. Sarcopenia—defined as a “generalized and progressive loss of skeletal muscle mass, strength, and function”—is present in up to 70% of patients with decompensated cirrhosis,<sup>32</sup> and is associated with an increased risk of liver decompensation, increasing morbidity and mortality both before and after liver transplantation.<sup>33,34</sup>

Evaluation of muscle mass should be performed in the work-up of all patients with cirrhosis at the time of listing.<sup>2,3</sup> In the transplant setting, the diagnosis of sarcopenia is particularly easy, as the quantification of muscle mass can be obtained by looking at the CT scan required for liver transplantation evaluation. In our clinical practice, we calculate the skeletal muscle index (SMI) at the L3 level, and we define a patient as

sarcopenic if they have an SMI <50cm<sup>2</sup>/m<sup>2</sup> (male) or <39cm<sup>2</sup>/m<sup>2</sup> (female).

Although a CT scan is the gold standard for the diagnosis of sarcopenia,<sup>35</sup> there are other simple tests that are immediately available in daily practice and that can be used to stratify patient risk, including the “Liver Frailty Index” (grip strength, chair stands, and balance). This index evaluates residual physical function, thus being a surrogate of sarcopenia, and independently correlates with the risk of death.<sup>36</sup>

Treatment of sarcopenia is based on dietary intervention. Patients should consume 30–35kcal/kg of dry body weight/day (with 50–60% of calories as carbohydrates and 20–30% as fat), including 1.2–1.5g of protein/kg of dry body weight/day. Meat consumption is not prohibited for patients with hepatic encephalopathy, but vegetables and/or dairy proteins may be more beneficial for the removal of ammonia via the glutamine pathway. It is important to shorten the duration of the fasting period, as prolonged fasting is associated with enhanced and uncontrolled proteolysis. In patients with cirrhosis, the inclusion of a long-acting energy source containing complex carbohydrates (e.g. pasta, bread, rice, potatoes) in the late evening followed by an early morning protein supplement provides great benefit for the prevention of muscle loss. In our practice, we recommend that patients with decompensated cirrhosis have 5–6 meals per day, including a late dinner and an early breakfast.

Strong evidence supporting the utility of physical exercise in reversing sarcopenia in patients with cirrhosis is lacking, but it is reasonable to expect that gentle physical therapy may prevent further muscle loss. Physical exercise should be customized and always coupled with appropriate nutritional supplementation.<sup>37</sup> If it can be tolerated, we encourage our patients to walk for 40–50 minutes three to four times per week.

**Mistake 4 Thinking that patients with cirrhosis and HCC can be transplanted only if the tumour is within the Milan criteria**

For patients with HCC, recipient selection is of the utmost importance for determining the risk of HCC recurrence and patient survival. Morphological criteria based on tumour size and number were introduced in 1996—the Milan criteria—and quickly became the ‘conventional criteria’ after being incorporated in the Barcelona Clinic Liver Cancer and United Network for Organ Sharing systems.<sup>38</sup> According to the EASL guidelines,<sup>2,11</sup> liver transplantation is the first-line option for HCC that is within the Milan criteria (a single HCC ≤5cm or multiple HCCs ≤3 nodules ≤3cm in size, without vascular invasion) but unsuitable for resection. Patients with HCC beyond the Milan criteria can

be considered for liver transplantation after successful downstaging to within the Milan criteria.<sup>11</sup>

Although the Milan criteria remain the benchmark for allocation of liver grafts to candidates with HCC due to the excellent outcomes post-liver transplantation,<sup>38</sup> a modest expansion of these criteria is reasonable and feasible. Many proposals for how to expand the Milan criteria have been made but consensus has not yet been reached.<sup>39</sup> Optimal identification of candidates who will have a poor oncological outcome is an ongoing issue, because HCC has a complex biological behaviour than cannot be determined accurately by just the number and size of the nodules. There is evidence that composite criteria including surrogates of HCC biology, such as  $\alpha$ -fetoprotein (AFP) and response to treatment, in combination with tumour size and number, are superior to conventional criteria for defining suitability for transplantation.<sup>11</sup> France, for instance, has already replaced the Milan criteria with the 'AFP model', which includes the number of nodules, the largest nodule diameter and the level of AFP.<sup>40</sup>

In our clinical practice, we classify HCC aggressiveness according to stage and response to treatment.<sup>41</sup> Patients who have a transplantable tumour are divided into different classes of progression (that have a different priority in the waiting list), according to three elements: response to bridging therapies; achievement of downstaging to within the Milan criteria; and time of HCC recurrence after treatment. Any selection criteria can be used for defining a transplantable tumour, provided a 5-year survival post-liver transplantation of at least 60% is ensured.<sup>2,11,38</sup> This model allows us to prioritize patients according to both 'urgency' (risk of drop-out during the waiting-list time) and 'utility' (survival post-liver transplantation) principles.

### **Mistake 5 Withholding treatment for portal vein thrombosis in patients with cirrhosis awaiting transplantation**

Portal vein thrombosis (PVT) is the most frequent thrombotic complication in patients with cirrhosis who are awaiting liver transplantation, with a prevalence of up to 23%.<sup>42</sup>

The clinical impact of PVT depends on both the extent of the thrombosis and the severity of the underlying cirrhosis.<sup>43</sup> Clinical manifestations of PVT may vary from asymptomatic disease to life-threatening complications (e.g. variceal bleeding and/or intestinal infarction due to the extension of thrombosis into the mesenteric vein). In compensated patients, PVT may not be predictive of decompensation.<sup>44</sup> The effect of PVT on the course of patients with decompensated cirrhosis is not as clear, but PVT has been associated with higher risk of failure to control variceal bleeding<sup>45</sup> and increased risk of death.<sup>43</sup>

For several reasons, the occurrence of PVT is perhaps even more important when the patient is a candidate for liver transplantation. First, complete PVT extending to the superior mesenteric vein significantly increases both morbidity and mortality after liver transplantation.<sup>42</sup> Second, these patients may have or develop HCC, and HCC further increases the risk of PVT (1-year incidence of 25%).<sup>46</sup> In those cases, complete PVT reduces the chance to perform transarterial chemoembolization (TACE).

Timely therapy is important, as anticoagulation is more effective when given within 6 months of the estimated diagnosis.<sup>47</sup> Treatment of PVT in liver transplant candidates, however, is often delayed—and sometimes even denied—due to fear of bleeding complications. Anticoagulation in patients who have cirrhosis is safe,<sup>48</sup> and a recent meta-analysis including 257 patients with cirrhosis and PVT confirmed the risk of bleeding in patients with cirrhosis and PVT is comparable for those who are treated versus those who are not.<sup>49</sup> The same meta-analysis showed that the risk of variceal haemorrhage was lower in patients who were receiving anticoagulation (which would have potentially resolved the thrombus) versus those who were not anticoagulated.<sup>49</sup>

In our centre, all patients on the waiting list undergo regular screening for PVT and receive prompt anticoagulant treatment if they develop PVT.<sup>7</sup> When there is no response or progression is observed during therapy, or if there is an absolute contraindication to anticoagulation, we consider using a transjugular intrahepatic portosystemic shunt (TIPS).<sup>7,50</sup>

### **Mistake 6 Assuming that patients with decompensated cirrhosis always need prophylactic transfusions before invasive procedures**

Cirrhosis is characterized by multiple alterations of haemostasis.<sup>51</sup> These alterations include thrombocytopenia and platelet function defects, an increased level of von Willebrand factor, a concomitant decrease of both clotting factors and inhibitors, and altered fibrinolysis.<sup>52–54</sup> Historically, patients with decompensated cirrhosis were considered to be at high risk of bleeding from invasive procedures. This belief was because most of these patients are thrombocytopenic (platelet count  $<50 \times 10^9/L$ ) with a prolonged international normalized ratio (INR). However, recent studies have shown a lack of correlation between haemostatic alterations and bleeding risk.<sup>55</sup> In parallel, the thrombin generation assay has demonstrated that the capacity to generate thrombin (e.g. how coagulation 'works') in patients with cirrhosis is similar or even increased compared with that in healthy subjects.<sup>51</sup> It is now generally accepted that patients with cirrhosis are not 'naturally

anticoagulated', but rather have a 'rebalanced' haemostatic system. This precarious balance, however, can easily be unbalanced by superimposed factors, such as infection.<sup>56</sup>

When assessing the risk of post-procedural bleeding in patients with cirrhosis, the first thing to look at is the patient's condition. Is cirrhosis compensated or decompensated? Is there any factor that can tip the balance towards hypocoagulability, such as infection? Abnormalities of INR and platelet count should not be interpreted as single measurements, but more as trends. A chronically prolonged INR (even if profoundly altered, e.g. 2.7) in a patient awaiting liver transplantation for refractory ascites does not necessarily imply there is an increased risk of haemoperitoneum or that it should be corrected prior to large-volume paracentesis. On the other hand, a patient whose INR is usually 1.2 but now presents with an INR of 2 may have an increased risk of bleeding, as that prolongation may be an indicator of instability in their haemostatic balance (i.e. presence of hyperfibrinolysis).<sup>57</sup>

It's also important to stratify procedures according to the bleeding risk. Low-risk procedures (e.g. paracentesis using a <5-F gauge catheter) may be performed in patients who have any laboratory abnormality depending on operator skill. High-risk procedures require a different approach and that may include the correction of INR and/or platelet count.<sup>57,58</sup>

Thromboelastography (TEG) and rotational thromboelastometry (ROTEM) are whole-blood viscoelastic tests that assess clot formation and stability.<sup>59,60</sup> They may be useful to prevent unnecessary transfusions before procedures in patients who have cirrhosis and coagulopathy,<sup>61</sup> but more studies are needed to establish specific thresholds for when transfusions are warranted in this population.

### **Mistake 7 Thinking that a past history of extrahepatic cancer is a contraindication to liver transplantation**

Consider the following two cases. Mr Smith is a 59-year-old man with HCV cirrhosis that is decompensated by ascites and variceal bleeding. His Model for End-Stage Liver Disease (MELD) score is 22. In his medical history, he reports a left hemicolectomy for stage I colon cancer in 2008. So far, he has shown no sign of recurrence. Mrs. Christie is a 49-year-old woman with NASH cirrhosis complicated by multifocal HCC within the Milan criteria that is not suitable for resection. She had melanoma in 2017 (locoregional disease), for which she underwent surgical resection plus adjuvant chemotherapy. There has been no sign of recurrence so far. Is liver transplantation contraindicated for neither patient, one patient or both patients?

A past history of nonhepatic tumours should not disqualify candidates for liver transplantation.<sup>2</sup>

Such patients can be considered for liver transplantation provided they received a curative treatment, are tumour free at the time of evaluation, and have observed an appropriate recurrence-free interval (determined by the type of tumour involved). Survival and risk of recurrence under immunosuppressive therapy should be estimated, on a case-by-case basis, with an oncologist.<sup>2</sup> Common practice is to consider a patient suitable for liver transplantation if the risk of recurrence is estimated to be less than 10% and to require an interval time of 5 years recurrence-free to exclude potential recurrence, though this varies by tumour type.

Although no robust data have been published on the optimal management of liver transplantation candidates who have a history of extrahepatic tumours, the Israel Penn International Transplant Tumor Registry ([www.ipittr.uc.edu/registry](http://www.ipittr.uc.edu/registry)) is a large free online database of outcomes after liver transplantation in recipients with pre-existing tumours, and it can be helpful in planning an appropriate strategy.

Returning to the cases of Mr Smith and Mrs Christie, liver transplantation is contraindicated for one but not the other. Mrs Christie is not a candidate for liver transplantation because the time that has passed since her melanoma was treated is too short, melanoma is an aggressive type of cancer and the tumour was locally advanced at diagnosis. By contrast, Mr Smith is a candidate for liver transplantation because the interval time is long enough, the tumour was at an early stage and it was completely removed.

### **Mistake 8 Not paying enough attention to hypertension, hyperlipidaemia and diabetes in liver transplant recipients**

Liver transplant recipients frequently have one or more features of metabolic syndrome, which includes hypertension (40–85%), hyperlipidaemia (40–70%), and diabetes mellitus (10–65%).<sup>2,62</sup> Overall, the prevalence of metabolic syndrome in liver transplant recipients is approximately 50–60%.<sup>63</sup> The features of metabolic syndrome can pre-exist (liver transplantation does not cure the pre-existing conditions) or be caused and/or worsened by liver transplantation (immobilization, use of steroids, and long-term immunosuppressive therapy). Owing to the high prevalence of metabolic risk factors, the cumulative risk of cardiovascular events is approximately 25% at 10 years post-liver transplantation, which is significantly elevated compared with the age- and gender-matched general population.<sup>64</sup> Cardiovascular complications are a leading cause of post-liver transplantation morbidity and mortality, and account for a third of deaths in the long-term follow-up.<sup>65</sup>

Gastroenterologists and hepatologists tend to focus very carefully on the management of

liver-related issues in transplant recipients (symptoms and signs of liver diseases, recurrence and treatment of primary liver disease, management of immunosuppressive therapy and its complications, HCC recurrence, etc.), but often overlook metabolic comorbidities. A good evaluation of liver transplant recipients should always include analysis of their metabolic profile. Primary care teams should perform a meticulous cardiovascular risk assessment, and treat each of the components of metabolic syndrome aggressively to improve patient outcomes. The timing of the interval follow-up should be based on general population guidelines, as there is no specific guidance for transplanted patients.

European and American guidelines state that management of metabolic complications in liver transplant recipients should start with prevention, as interventions to prevent weight gain and its sequelae (i.e. diet, lifestyle and physical exercise) are more successful than attempts to induce weight loss afterwards.<sup>2,62</sup> These interventions should be implemented as soon as possible after liver transplantation, as the biggest weight gain occurs within the first year after transplantation.

The multidisciplinary approach to metabolic syndrome in liver transplant recipients targets different elements.<sup>2,62</sup> First is the introduction of a Mediterranean diet (<60g/day of complex carbohydrates and a reduction of dietary fructose are correlated with a lower risk of insulin resistance and obesity) and physical exercise. Second is pharmacological therapy, including calcium-channel blockers or ACE inhibitors to treat hypertension, statins ± ezetimibe for hypercholesterolaemia, fish oil and fibric acid derivatives for isolated hyperlipidaemia, and insulin and/or other agents for diabetes. Third are changes in immunosuppressive therapy, including conversion of ciclosporin to tacrolimus or vice versa, reduction of calcineurin inhibitors with the addition of other drugs (e.g. mycophenolate mofetil), and discontinuation of sirolimus. Fourth is evaluation of the potential benefit of bariatric surgery for those recipients who are, or who become, morbidly obese despite multiple other attempts to lose weight.

Our team usually involves a metabolic disease specialist in the management of liver transplantation recipients with diabetes, especially once insulin therapy is started. From a study from our unit, we have seen that mycophenolate mofetil is protective versus the development of diabetes (Becchetti and Burra, abstract accepted for ILC 2020). New drugs for the treatment of diabetes have recently been approved, and they have shown good results in terms of safety and efficacy in the general population. Hopefully, these drugs will also prove helpful for the treatment of diabetes in liver transplant recipients.

### **Mistake 9 Late referral of patients with decompensated cirrhosis and a possible indication for transplantation**

The evaluation of patients with cirrhosis for liver transplantation should be considered once the patient has experienced a major complication of portal hypertension, such as ascites, hepatic encephalopathy or variceal haemorrhage, or when hepatocellular dysfunction results in a MELD score  $\geq 15$ .<sup>2,3</sup> The evaluation process starts once the patient is referred, which means the patient is evaluated by a specialist transplant hepatologist.

It is important that potential candidates are referred early, before the underlying liver disease reaches the stage at which listing is actually indicated. This is because multidisciplinary assessment to evaluate transplantability is a multistep process that takes time. From head to foot, the assessment includes hepatology and surgical evaluation, laboratory testing, general health and dental assessment, nutritional evaluation, psychology with or without psychiatric evaluation, and cardiac and anaesthesia evaluation.<sup>2,3</sup> Depending on the patient's condition and the presence of one or more comorbidities, second-level tests may be needed.

To ensure that all potential candidates have the same chance of being evaluated for liver transplantation according to the principles of justice and equity, they need to be referred when they are ill enough to have reduced survival and/or a poor quality of life, but are well enough to be assessed and listed. In practical terms, this is at the first decompensation event, when the MELD score is  $\geq 10$  and/or the Child-Pugh is  $\geq B-7$ . In our experience, more than one third of patients referred to our unit need to be transferred to the intensive care unit because they are too sick—the mortality rate in these patients is very high.<sup>66</sup>

In our practice, we regularly communicate with referring centres via phone calls and emails (we have a dedicated phone number and a dedicated email address that both operate 24/7). Referring physicians can ask us to be involved in liver transplantation evaluation in different ways, according to the patient's condition. Non-urgent outpatient evaluation takes place within 4 weeks. Urgent outpatient evaluation takes place within 1–2 weeks. Urgent inpatient evaluation takes place within a few days for hospitalized patients who are transferred to our service. Communication with referring centres works both ways, and patients can be transferred back in case of clinical improvement.

### **Mistake 10 Assuming that liver transplantation in patients with subacute liver failure is indicated only once hepatic encephalopathy occurs**

Acute liver failure (ALF) is a specific syndrome defined by acute abnormality of liver function in



a patient who has no pre-existing chronic liver disease.<sup>8</sup> ALF is characterized by the development of both coagulopathy (INR >1.5) and hepatic encephalopathy. The condition of patients who develop coagulopathy, but not hepatic encephalopathy, is defined as acute liver injury (ALI).

The clinical course of ALF usually starts with a severe ALI. The ALI is characterized by a 2–3-fold elevation of transaminase levels, associated with impaired liver function (jaundice and coagulopathy), in a patient with no prior evidence of liver disease. Considering jaundice as the first sign, ‘hyperacute liver failure’ describes patients who develop hepatic encephalopathy within 7 days, ‘acute liver failure’ describes patients who develop hepatic encephalopathy between 8 and 28 days, and ‘subacute liver failure’ describes patients who develop hepatic encephalopathy within 5–12 weeks.

These ALF phenotypes have distinct presentations and prognosis.<sup>8</sup> Patients with a hyperacute presentation have severe coagulopathy, extremely elevated transaminase levels, and only moderate (if any) increase in their bilirubin levels.<sup>67,68</sup> By contrast, patients who have a subacute presentation have a severe jaundice, mild-to-moderate coagulopathy, and only a mild increase in transaminase levels. These patients frequently have splenomegaly and ascites, and a shrinking liver viewed on imaging. Hepatic encephalopathy occurs very late, and is often a manifestation of bacterial infection. Once hepatic encephalopathy occurs, these patients have a very short window, if any, in which to undergo liver transplantation.<sup>69</sup>

In ALF, early identification of patients who will not survive with medical support alone is of utmost importance, as they will be priority candidates for liver transplantation. Even at an early stage, there are clinical features (i.e. development of hepatic encephalopathy) that may be helpful for risk stratification. As a general rule, the development of hepatic encephalopathy prompts critical care assessment and transfer to a transplant centre.<sup>8</sup>

The adoption of a single threshold of hepatic encephalopathy severity across the three phenotypes of ALF does, however, seem too simplistic. In patients with a subacute presentation, even low-grade hepatic encephalopathy may indicate poor prognosis, whereas survival with medical support may be excellent in the hyperacute setting with concomitant hepatic encephalopathy of equal severity. Recent proposals suggest that, in an appropriate clinical context accompanied by a decreasing liver volume, super urgent listing could be undertaken in patients with subacute liver failure even without the presence of clinically overt hepatic encephalopathy.<sup>8</sup>

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## Your liver transplantation briefing

### Online courses

'Malignant liver lesions' from UEG [<https://www.ueg.eu/education/online-courses/malignant-liver-lesions/>].

### UEG week

- 'Liver transplantation' presentation in the 'From guidelines to clinical practice: Hepatocellular carcinoma' session at UEG Week 2019 [<https://www.ueg.eu/education/document/liver-transplantation/211612/>].
- 'DILI: when is the optimal time for liver transplantation' presentation in the 'Management of patients with drug-induced liver disease (DILI)' session at UEG Week 2019 [<https://www.ueg.eu/education/document/dili-when-is-the-optimal-timing-for-liver-transplantation/211339/>].
- 'Open questions on the role of liver transplantation' presentation in the 'Liver cancer: New guidelines' session at UEG Week 2018 [<https://www.ueg.eu/education/document/>].

open-questions-on-the-role-of-liver-transplantation/184272/].

- 'Surgery and liver transplantation for HCC' presentation in the 'Therapy update: Hepatocellular carcinoma (HCC) in 2017' at 25th UEG Week 2017 [<https://www.ueg.eu/education/document/surgery-and-liver-transplantation-for-hcc/155605/>].
- 'Fulminant hepatitis and liver transplantation' session at UEG Week 2016 [<https://ueg.eu/library/session/fulminant-hepatitis-and-liver-transplantation/144/1571/>].

### Standards and Guidelines

- European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Liver Transplantation. *J Hepatol* 2016; 64: 433–485 [<https://www.ueg.eu/education/document/easl-clinical-practice-guidelines-liver-transplantation/125960/>].