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Baishideng Publishing Group Inc  
7901 Stoneridge Drive, Suite 501,  
Pleasanton, CA 94588, USA  
Telephone: +1-925-2238242  
Fax: +1-925-2238243  
E-mail: [editorialoffice@wjgnet.com](mailto:editorialoffice@wjgnet.com)  
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Telephone: +1-925-2238242  
Fax: +1-925-2238243  
E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
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## Liver transplantation for critically ill cirrhotic patients: Overview and pragmatic proposals

Thierry Artzner, Baptiste Michard, Camille Besch, Eric Levesque, François Faitot

Thierry Artzner, Baptiste Michard, Service de Réanimation Médicale, Hôpital de Haute-pierre, Hôpitaux Universitaires de Strasbourg, Strasbourg 67000, France

Baptiste Michard, Camille Besch, François Faitot, Service de Chirurgie Hépatobiliaire et Transplantation, Hôpital de Haute-pierre, Hôpitaux Universitaires de Strasbourg, Strasbourg 67000, France

Eric Levesque, Service d'Anesthésie et Réanimation Chirurgicale, Hôpital Henri Mondor, Créteil 94000, France

ORCID number: Thierry Artzner (0000-0001-6077-5148); Baptiste Michard (0000-0001-5605-9229); Camille Besch (0000-0002-7992-1595); Eric Levesque (0000-0002-9026-7715); François Faitot (0000-0001-6514-0774).

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**Corresponding author to:** Baptiste Michard, MD, Doctor, Service de Réanimation Médicale, Hôpital de Haute-pierre, Hôpitaux Universitaires de Strasbourg, 1 Avenue Molière, Strasbourg 67000, France. [michard.baptiste@gmail.com](mailto:michard.baptiste@gmail.com)  
Telephone: +33-388-128269  
Fax: +33-388-127908

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### Abstract

Liver transplantation for critically ill cirrhotic patients with acute deterioration of liver function associated with extrahepatic organ failures is controversial. While transplantation has been shown to be beneficial on an individual basis, the potentially poorer post-transplant outcome of these patients taken as a group can be held as an argument against allocating livers to them. Although this issue concerns only a minority of liver transplants, it calls into question the very heart of the allocation paradigms in place. Indeed, most allocation algorithms have been centered on prioritizing the sickest patients by using the model for end-stage liver disease score. This has led to allocating increasing numbers of livers to increasingly critically ill patients without setting objective or consensual limits on how sick patients can be when they receive an organ. Today, finding robust criteria to deem certain cirrhotic patients too sick to be transplanted seems urgent in order to ensure the fairness of our organ allocation protocols. This review starts by fleshing out the argument that finding such criteria is essential. It examines five types of difficulties that have hindered the progress of recent literature on this issue and identifies various strategies that could be followed to move forward on this topic, taking into account the recent discussion on acute on chronic liver failure. We move on to review the literature along four axes that could guide clinicians in their decision-making process regarding transplantation of critically ill cirrhotic patients.

**Key words:** Liver transplantation; Cirrhosis; Acute on chronic liver failure; Critical; Intensive; Ethical; Intubation; Organ failure; Sepsis



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**Core tip:** Liver transplantation (LT) for critically ill cirrhotic patients is a controversial topic. While transplantation benefits these patients individually, the post-transplant mortality rate of this population taken as a whole is an argument against transplanting them. This issue is particularly pressing in a time when the paradigm dominating LT algorithms is based on the model for end-stage liver disease score, which prioritizes the sickest patients. Balancing individual benefits against collective utility is complex, especially given the absence of guidelines. This review examines the literature that can guide clinicians who treat critically ill patients and who decide to transplant them or not.

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## INTRODUCTION

The model for end-stage liver disease (MELD) score, which has proven to be a good predictor of transplant-free mortality for patients with cirrhosis<sup>[1]</sup>, has been widely used to prioritize liver transplantation (LT) candidates around the world since 2002, when it was first introduced by the United Network For Organ Sharing (UNOS) in the United States. This simple, celebrated score is the cornerstone of the allocation paradigm that prevails today. This paradigm is based on the ideas that patients with the highest MELD scores have the highest 3-mo waitlist mortality rate and that they receive the greatest benefit from LT. It helps to ensure that the sickest patients are transplanted first and prevents “deleterious” LT in patients with low MELD scores<sup>[2]</sup>.

This strategy has led to allocating transplants to increasingly severe patients<sup>[3]</sup> and some authors have argued that such a practice leads to poorer post-transplant results<sup>[4]</sup>. To this day, and apart from the specific context of hepatocellular carcinoma, there is no robust or consensual limit beyond which patients can be declared to be “too sick to be transplanted”.

The absence of evidence-based guidelines and consensus concerning the allocation of organs to critically ill cirrhotic patients with organ failure, defined recently by the term of acute on chronic liver failure (ACLF) is, in this respect, particularly glaring. Some teams believe that critically ill patients with ACLF should not have access to LT when they suffer from multiple-organ failure and therefore sometimes do not even admit them to their intensive care unit (ICU) given how somber their global

prognosis is<sup>[5]</sup>. Other teams, probably focusing primarily on the interest of individual patients, transplant critically ill patients with global post-transplant mortality results that are not acceptable in view of the current organ shortage. This has raised ethical issues, notably concerning the notions of transplant futility and organ rationing<sup>[6]</sup>, which have been mindfully dissected in a recent review<sup>[7]</sup>.

Various studies have proved beyond a doubt that critically ill patients benefit from LT on an individual level<sup>[8-10]</sup>. What remains a subject of debate is the optimal way of setting a limit to how sick cirrhotic patients can be and still undergo a LT with an outcome that is acceptable in the context of organ shortage.

## IN SEARCH OF A CONSENSUS FOR FUTURE STUDIES

A call to determine an upper limit on how sick patients can be and still have access to LT has been repeated on numerous occasions in the past decade<sup>[11-13]</sup>, but relatively little progress has been made in the way of achieving this goal. We have identified four reasons that help to explain this standstill.

### A polarizing issue

While some pathologies, in particular hepatocellular carcinoma have clearly identified limits based on tumoral staging beyond which LT is not performed<sup>[14]</sup>, there are no limits agreed upon for critically ill patients. This situation may be considered unfair and sometimes leads to an urge to impose equally strict limits on critically ill patients. However, while there is plenty of evidence available to set consensual limits for patients with hepatocellular carcinoma based on post-transplant mortality targets, the lack of evidence leads teams to set individual, arbitrary limits for critically ill patients<sup>[7,15]</sup>.

Moving forward on this divisive topic requires transplant teams to recognize that it is in patients’ best interests to open this discussion and try to be as transparent and rational as possible concerning the limits set for transplanting critically ill patients. Indeed, this should allow these patients to individually benefit from LT while setting outcome standards as high as those set for other pathologies and therefore allocate transplants as justly and transparently as possible between different pathologies.

### The problem of comparing heterogeneous cohorts

The literature devoted to the question of LT in critically ill patients has focused on various subgroups of patients, in particular: high MELD patients<sup>[13]</sup>, ICU patients<sup>[16]</sup>, and intubated patients<sup>[15]</sup>. The introduction of the European Association for the Study of the Liver (EASL)-ACLF classification in 2013 finally allows for the grouping of patients according to a common classification and identifies various groups of increasing severities. This will enable studies to use single criteria to focus on the patients who are

**Table 1** Main retrospective studies on critically ill cirrhotic patients and liver transplant

Author	Study period	n	Defined exclusion criteria for LT	General severity at LT	MELD at LT	Prognostic factors of post-transplant mortality	Post-transplant survival
Umgelter <i>et al</i> <sup>[12]</sup>	2007-2009	13	Subjective	SOFA19	38	Increasing MELD during first 48 h and longer ICU stay	46% at 1 yr
Karvellas <i>et al</i> <sup>[16]</sup>	2000-2009	198	No	SOFA 14	34	Not SOFA	62% at 3 yr
Duan <i>et al</i> <sup>[27]</sup>	2004-2012	100	No	SOFA 9	32	Recipient age > 60 yr	78% at 1 yr
Finkenstedt <i>et al</i> <sup>[9]</sup>	2002-2010	33	Subjective	RRT 30% MV 9%	28	LDLT = DDLT No	87% at 1 yr
Petrowsky <i>et al</i> <sup>[13]</sup>	2002-2010	133	No	RRT 90% MV 66%	> 40	MELD Age adjusted-Charlson index Cardiac risk Septic shock	64% at 3 yr
Knaak <i>et al</i> <sup>[15]</sup>	2000-2013	122	FiO <sub>2</sub> > 40% Norepinephrine > 0.1 µg/kg per min	SOFA 15	32	Glasgow Coma Score < 7 before intubation	76% at 3 yr
Levesque <i>et al</i> <sup>[19]</sup>	2008-2013	30	No	SOFA 16	37	No	43% at 1 yr
Moon <i>et al</i> <sup>[45]</sup>	1998-2010	190	No	RRT 43% MV 36%	38	No	70% at 5 yr
Artru <i>et al</i> <sup>[10]</sup>	2008-2014	73	No active GI bleeding Norepinephrine < 3 mg/h PaO <sub>2</sub> /FiO <sub>2</sub> < 150 mmHg	SOFA 16	38	No	84% at 1 yr
Michard <i>et al</i> <sup>[44]</sup>	2007-2015	55	No	SOFA 16	42	Lactate > 5 mmol/L ARDS with PaO <sub>2</sub> /FiO <sub>2</sub> < 200 mmHg	60% at 1 yr
Thuluvath <i>et al</i> <sup>[43]</sup>	2002-2016	677	No	5 or 6 OF	40	Age, intubation	81% at 1 yr

LT: Liver transplant; SOFA: Sequential organ failure assessment; ICU: Intensive care unit; RRT: Renal replacement therapy; MV: Mechanical ventilation; ARDS: Acute respiratory distress syndrome; DDLT/LDLT: Deceased/living donor liver transplantation; GI: Gastro intestinal; MELD: Model for end-stage liver disease; OF: Organ failure according to CLIF-SOFA.

most critically ill (ACLF 3) in future studies.

### Which post-transplant outcome is relevant?

There is no single or straightforward solution to determining the most meaningful outcome evaluation endpoint. On the one hand, it makes sense to analyze post-transplant survival of patients with multiple-organ failure on a short-term basis to assess individual benefit of LT, for example 3 mo<sup>[17]</sup>. On the other hand, maximizing organ utility with the interest of the wider community of waiting list patients in mind probably requires a 5-year endpoint<sup>[18]</sup>. In practice, the endpoint of most studies for critically ill patients and LT is usually one year (Table 1). This seems a reasonable compromise, given that mortality beyond this endpoint is less attributable to immediate pre-transplant clinical characteristics. Particular attention should be given to the number of retransplantations in order to assess not only patient survival but also organ utility.

### Finding significant risk factors of futile transplantation requires large cohorts with significant mortality and survival rates

The literature specifically devoted to the post-transplant prognosis of critically ill patients with ACLF (ACLF 3 patients) reports drastically different one-year survival results ranging from 84%<sup>[10]</sup> to 43%<sup>[19]</sup>. Interestingly, these studies do not identify significant risk factors of mortality within their cohorts of ACLF 3 patients. Two

conclusions can be drawn from these observations. First, team-specific practices probably lead to selecting patients for LT that are quite different (despite being all classified as ACLF 3), which helps explaining the gap in post-transplant outcome. Second, both studies lack statistical power to identify mortality risk factors. This is due both to the size of their cohorts and to the fact that the cohorts lack significant numbers of mortality events<sup>[10]</sup> or survival events<sup>[19]</sup>.

In practice, we need to pool different cohorts together, with enough patients and significant mortality and survival rates in order to be able to identify independent prognostic factors.

We have selected references (Table 1) and organized this review along 4 axes (Table 2) on the basis of their ability to provide insight into potential prognosis factors that can guide clinicians in the sensitive and taxing process of deciding whether to list critically ill patients for LT, and whether to transplant them.

## PRE-TRANSPLANT ORGAN FAILURES: QUANTITATIVE AND QUALITATIVE APPROACHES

### Pre-transplant MELD score in critically ill patients does not predict post-transplant outcome

Since its implementation, there has been much debate over the MELD's potential use as a post-transplant

**Table 2 Potential pre-transplant prognosis factors of critically ill cirrhotic patients requiring liver transplantation**

Pre-transplant organ failures	None of the existing organ failure scores used in liver transplant (MELD, BAR, SOFT, UCLA) or in ICU (SOFA, CLIF SOFA) are capable of predicting post-transplant survival of critically ill ACLF patients Individual organ failures should be precisely examined. Severe acute respiratory distress syndrome, high lactate level and coma have each been shown to be associated with poor post-transplant outcome
Dynamic perspective on ACLF and optimal timing for LT	Patients with ACLF have very different evolutive profiles during their first week of treatment. Admission criteria in ICU should therefore be lenient in order to re-evaluate patients 3 to 7 d after admission and their evolutive profile should be taken into consideration when deciding to transplant them or not.
Sepsis	The link between pre-transplant bacterial infection and post-transplant mortality is controversial but sepsis does not seem to be sufficient to exclude patients from LT <i>per se</i> . In some circumstances, sepsis and septic shock can be difficult to distinguish from SIRS in patients with severe ACLF. By contrast, there is a consensus regarding invasive fungal infections, which constitutes a strict contraindication to LT.
General medical condition and risk factors of patients	There is little data on the effect of age, comorbidities and alcohol abuse history on the post-transplant prognosis of patients with severe ACLF, in part because different transplant teams apply center-specific selection criteria on patients prior to listing. The attitude described in the literature on LT in alcoholic hepatitis is, to date, the best guide to decide as early as possible whether to (de) list patients admitted for severe ACLF or not.

LT: Liver transplantation; MELD: Model for end-stage liver disease; BAR: Balance of risk; SOFT: Survival outcome following liver transplantation; UCLA: University of California, Los Angeles; ICU: Intensive care unit; SOFA: Sequential organ failure assessment; ACLF: Acute-on-chronic liver failure; SIRS: Systemic inflammatory response syndrome.

mortality predictor and, consequently, its potential use to identify those patients who are too sick to be transplanted by setting an upper limit beyond which patients should not have access to LT.

In 2013, Petrowsky's single center cohort of 169 patients with MELD scores > 40 showed that the MELD score, along with the Charlson comorbidity index, cardiac risk and the presence of a septic shock, was significantly associated with poor post-transplant prognosis. This relation between the MELD score and post-transplant survival among patients with high MELD scores has not been confirmed by other studies. In 2013, a general, systematic review of the literature<sup>[20]</sup> concluded that the MELD score could not serve as a reliable predictor of post-transplant survival. Large studies have confirmed this in the context of patients with high MELD scores. Looking back at the 34975 LT that have taken place in the United States since the introduction of the Share 35 policy in 2013, Kwong *et al*<sup>[21]</sup> found that although this policy had increased the proportion of recipients with > 35 MELD scores, the one-year mortality had not increased, suggesting that transplanting patients with very high MELD scores did not increase mortality *per se*.

Among patients hospitalized in the ICU, the effect of higher MELD scores on post-transplant mortality has been questioned repeatedly. A small German study from 2011<sup>[12]</sup> found that, among the 13 patients who received LT from their ICU (all of whom were intubated and received norepinephrine), there was, surprisingly, an inverse relation between the probability of post-transplant mortality at 90 d and the severity of the MELD score. In a much larger study compiling all the results from the UNOS database from 2002 to 2013, Bitterman *et al*<sup>[22]</sup> found that a higher MELD score was associated with higher post-transplant mortality only among patients who were transplanted from their home. For the subgroup of patients who received LT from the ICU (4095 patients in their cohort), the MELD score could not discriminate

between the patients with good or poor post-transplant prognosis. Multiple variations of the MELD score have been tested in other studies with disappointing results for critically ill patients<sup>[23-26]</sup>.

In summary, the MELD score is a reliable tool for predicting short-term mortality of patients without LT and holds a key role in prioritizing the access of the sickest patients to LT. By contrast, it is not reliable to predict post-transplant outcome, especially in the context of patients whose severe clinical state draws them to the ICU. For those patients, post-transplant prognosis may be significantly altered by an array of organ failures (neurologic, circulatory, pulmonary) that are not taken into account by the MELD score.

### **Pre-transplant SOFA, SOFT and BAR scores do not predict post-transplant outcomes for ACLF patients**

Other pre-transplant scores have not proved to be useful in predicting post-transplant outcome of critically ill patients with ACLF. First and foremost, the sequential organ failure assessment (SOFA) score, widely used in the ICU and from which the CLIF scores are derived, is not associated with post-transplant mortality<sup>[15,16,25,27]</sup>.

In 2008, Rana *et al*<sup>[17]</sup> introduced the survival outcomes following LT (SOFT) score, which includes 18 risk factors. In a follow-up study, Rana found that this score was useful for high-risk patients (labMELD > 40 and/or patients hospitalized in the ICU pre-transplant) with a C statistic at 0.67 and 0.65<sup>[28]</sup>. This finding was not confirmed in a cohort of patients with a labMELD > 30<sup>[23]</sup> or in the multicenter study of patients with ACLF by Artru *et al*<sup>[10]</sup> in 2017.

The balance of risk (BAR) score<sup>[29]</sup> was introduced in 2011 and includes 6 predictive factors. Some reports have validated this score<sup>[26,30]</sup> while others have denied its discriminative power<sup>[31,32]</sup>. In the specific context of candidates with ACLF, this score has not proved to be useful<sup>[10]</sup>.



### **Does being hospitalized in the ICU before transplantation matter?**

The literature devoted to analyzing the impact of the hospitalization status of patients on their post-transplant outcome is ambiguous. Three large studies from the UNOS database<sup>[17,33]</sup> and one study in the United Kingdom and Ireland<sup>[34]</sup> found a markedly increased mortality rate for transplant recipients who were in the ICU prior to LT. On the other hand, a study devoted specifically to this issue did not identify hospitalization in the ICU as a significant mortality risk factor<sup>[15]</sup>. Moreover, the ACLF 3 patients from the Artru study, all of whom were hospitalized in the ICU, did not have a significantly different outcome from the patients with lower ACLF grades who were, for the most part, not hospitalized in the ICU<sup>[10]</sup>.

At the heart of this question lies the inescapable fact that admission criteria in the ICU are subjective and center-dependent. Consequently, it does not seem sound that such criteria, in and of itself, should constitute a substantive argument against transplantation for ACLF patients and even less an argument against admitting critically ill ACLF patients in the ICU.

### **Pros and cons of the ACLF classification**

There are two leading definitions of ACLF: one created by the Asia-Pacific Association for the Study of the Liver (APASL)<sup>[35]</sup>, the other by the EASL<sup>[36,37]</sup>. Both definitions distinguish ACLF from acute liver failure and from decompensated cirrhosis<sup>[38]</sup>. Using the APASL-ACLF definition, three Chinese studies<sup>[39-41]</sup> have shown that ACLF patients could have post-transplant survival rates similar to those of non-ACLF patients. But these studies have a number of distinctive features that are not directly translatable to either the European or the American context: the majority of the patients were transplanted for hepatitis B-induced cirrhosis (rather than alcohol or hepatitis C virus) and they include a large proportion of living donors.

The discriminative power of the EASL-ACLF classification is debated in terms of post-transplant survival. This entity, based on the assessment of 6 organ functions, distinguishes only 3 grades (from one organ failure to 3 or more organ failures). Each grade is associated with increasing transplant-free short-term mortality rate, ranging from 14.6% (for ACLF 1) to 78.6% (for ACLF 3) at 28 d<sup>[36]</sup>. The individual benefit of LT for patients with ACLF 3 has been demonstrated in the CANONIC cohort<sup>[42]</sup> and confirmed subsequently<sup>[10,43]</sup>. What remains under debate is the extent to which the severity of ACLF patients affects their post-transplant outcome. In fact, whether ACLF patients (all grades considered) suffer from significantly worse post-transplant outcomes than non-ACLF patients is in itself controversial. In 2017, a single-center study showed that ACLF was associated with a significantly higher post-transplant mortality than that shown in non-ACLF patients<sup>[19]</sup>. The 30 patients with ACLF 3 who were transplanted in that cohort had a remarkably low one-year survival rate of 43.3%. The same year, a multi-center study reported

opposite results, with a one-year survival rate of 83.6% for ACLF 3 patients, which was not significantly different from the survival rates of ACLF 1 and 2 patients and even from patients without ACLF<sup>[10]</sup>. Our own study, also published in 2017, with 55 ACLF patients in the ICU prior to transplantation, reports an "intermediate" one-year survival rate of 60%<sup>[44]</sup>. A South Korean study, focusing exclusively living donors but using the EASL-ACLF definition did not find significantly different post-transplant patient survival between the various ACLF grades<sup>[45]</sup>. Finally, a large UNOS retrospective study found an 81% one-year survival rate for patients with 5-6 organ failures<sup>[43]</sup>.

An overall picture emerges from these studies. First, the grade of ACLF can reliably be used to assess the transplant-free prognosis of patients. Second, patients with ACLF 3 individually benefit from LT. Third, the grade of ACLF cannot be used to gain insight into the post-transplant outcome of the highest-acuity patients. This observation leads to two pragmatic points concerning future research on LT for ACLF 3 patients. First, the exact number of organ failures should be considered when reporting outcomes of patients transplanted with ACLF 3 (*i.e.* whether patients have 3, 4, 5 or 6 organ failures). Second, the nature of the organ failure should be investigated to determine which organ failures are most relevant in determining post-transplant outcome<sup>[46,47]</sup>.

### **Considering organ failures individually**

Some isolated studies have shown that acute kidney injury<sup>[48]</sup> has an effect on post-transplant mortality but this has not been investigated in the specific context of ACLF. Pre-transplant encephalopathy has been proved to lead to poorer post-transplant outcomes in general<sup>[49]</sup> and in the particular context of critically ill patients<sup>[15]</sup>. Our own work<sup>[44]</sup> has shown that pre-transplant moderate or severe acute respiratory distress syndrome (with PaO<sub>2</sub>/FiO<sub>2</sub> < 200 mmHg) and elevated lactate levels (> 5 mmol/L) were significantly associated with higher post-transplant mortality in ACLF patients. This qualitative approach, based on precise individual organ dysfunctions, could be promising in identifying robust and reproducible exclusion criteria for LT.

The nature of each organ failure should be defined precisely. For example, intubation is considered, in and of itself, as a pejorative prognostic factor<sup>[43]</sup>. However, one should distinguish between intubation for neurological failure and for respiratory failure, which has been shown to be an independent prognostic factor in critically ill patients (Knaak *et al*<sup>[15]</sup>).

## **A DYNAMIC PERSPECTIVE ON ACLF: WHAT IS THE OPTIMAL TIMING FOR LT IN CRITICALLY ILL PATIENTS?**

Gustot's 2015 analysis<sup>[42]</sup> of the CANONIC cohort has shown that ACLF is a dynamic process and that some patients' conditions can improve without transplantation. In particular, 40% of the patients who were initially

diagnosed with ACLF 2 or 3 improved in the course of their hospital stay to ACLF 0 or 1. He also showed that the transplant-free prognosis of patients was determined more by their evolution and by their ACLF grade between day 3 and day 7 than by their initial ACLF grade. These important observations have been confirmed in other cohorts<sup>[50]</sup>. Only 9 patients with ACLF 3 were transplanted in Gustot's study, which does not allow him to draw conclusions concerning the optimal management of critically ill ACLF patients with regard to transplantation.

A number of pragmatic points can nevertheless be drawn from this important study. First, there is a growing consensus that more patients with ACLF whose condition was considered desperate should be admitted to the ICU for initial organ support and monitoring<sup>[38]</sup>. Second, an expedited pre-transplant assessment [computed tomography (CT) scan to eliminate a tumor, cardiovascular screening, psychiatric history] should be completed within the first 2 or 3 d after admission in order to decide whether or not to place (or maintain) the patient on the transplant waiting list. Third, patients' conditions should be carefully monitored and a complete assessment of their condition should be done between day 3 and day 7, in order to gain a better picture of their prognosis.

Gustot's insight concerning the dynamic nature of ACLF also raises an important question: how does the patients' evolution before LT affect their post-transplant prognosis? Artru reports a remarkably high one-year survival rate for his multicenter cohort of patients with ACLF 3 (83.6%) and underlines that there was an improvement in the number of organ failures in the patients who were transplanted from the ICU in his study<sup>[10]</sup>.

Different strategies can be followed in terms of transplantation timing. One attitude consists in limiting access to LT for patients whose clinical condition is improving while they are in the ICU, or even to transplant them after they have left the ICU. This guarantees better post-transplant results but relies on a selectivity that could sacrifice a substantial number of patients with relatively good post-transplant outcome expectancy<sup>[51]</sup>. Another attitude consists in transplanting patients more rapidly if their clinical state is deteriorating. This attitude could nevertheless lead to potentially worse post-transplant outcome<sup>[12]</sup>.

Once again, there is not enough data to answer this thorny question. Future studies will have to consider both the clinical state of patients (in particular their ACLF grade) not only on admission and on the day of transplant, but also between day 3 and day 7. Such studies will have to try to differentiate patients according to the short-term evolution of their condition in the ICU in order to determine the impact of their clinical trajectory on post-transplant outcome.

## SEPSIS

Uncontrolled sepsis is put forward as a contraindication of LT in a large number of studies focusing on critically ill patients<sup>[7,10,12,13,15]</sup>. Apart from invasive fungal infec-

tions<sup>[52]</sup>, this seems problematic for several reasons, which are detailed below.

### **Sepsis and septic shock are often difficult to identify in ACLF critically ill patients**

ACLF is characterized by the presence of systemic inflammation which is proportional to the severity of the syndrome<sup>[53]</sup>. Sepsis is one of the triggers of ACLF<sup>[36,54]</sup>, but only in an estimated 30% of cases<sup>[53]</sup>. While the majority of ACLF triggers are not infectious, it is possible that there exists a continuum between gut bacterial translocation and severe infection<sup>[55]</sup>.

Determining whether the inflammation associated with ACLF is related to sepsis or not is not straightforward. Fever, for example, is often masked by renal replacement therapy due to extra corporal circulation. Biological markers such as CRP or high blood count are not specific of sepsis in ACLF<sup>[53]</sup> and encephalopathy can be a sign of both liver failure and severe sepsis.

The diagnosis of septic shock is even more problematic in the case of ACLF, given the major systemic vasoplegia that patients with decompensated cirrhosis can have<sup>[56,57]</sup>. In the absence of unambiguous signs of infection (bacteremia, clinical or radiological abscess), it therefore seems particularly delicate to distinguish non-infectious systemic inflammatory response syndrome (SIRS) from septic shock.

Our point is not to deny the evident existence of sepsis or septic shock in patients with ACLF but to highlight the difficulty of diagnosing the presence of sepsis in patients with ACLF.

### **There is not enough evidence to exclude septic patients from LT systematically**

Two studies on critically ill patients have found a link between septic shock and poor post-transplant prognosis. Petrowsky's study<sup>[13]</sup> on patients with MELD scores > 40 finds that septic shock is significantly associated with post-transplant mortality. But he does not detail the diagnosis criteria or the types of infections (germs/sites), pointing out the subjective character of this diagnosis. In the cohort published in 2017, Levesque describes in detail the criteria used to establish the diagnosis of infection and shows that it is an independent risk factor of post-transplant mortality in a general cohort, which includes patients with and without ACLF<sup>[19]</sup>.

Other studies have not found a link between pre-transplant bacterial infection and post-transplant mortality in the general population of LT patients<sup>[58,59]</sup>. In critically ill patients, one case-control study did not find a significant link between pre-transplant infection and post-transplant mortality<sup>[60]</sup> and our own work, which includes 13 ACLF patients with bacteremia in the 15 d prior to transplant, did not find a significantly worse one-year post-transplant outcome<sup>[44]</sup>. In both cases, this could be due to insufficient statistical power. Finally, a much larger, multicenter study of critically ill patients in the ICU has found no link between the SOFA score and post-transplant mortality in spite of this score's robust mortality predictive power for patients with sepsis in the

ICU<sup>[16]</sup>.

We can hope that future studies will describe in more detail the criteria used to establish a diagnosis of infection and that they will attempt to provide a finer analysis of the link between infection and outcome. In particular, it would be interesting to distinguish the differential effects of various pathogens and infectious sites on post-transplant outcome. For example, it is generally accepted that uncontrolled sepsis due to diffuse biliary disease is not an absolute contraindication for LT, and that hepatectomy can in fact help resolve sepsis<sup>[7]</sup>.

## GENERAL MEDICAL CONDITION AND RISK FACTORS OF PATIENTS

While a significant number of articles have been published concerning the effect of patients' overall general medical condition and various risk factors on their post-transplant outcome, the literature devoted to this question in the context of critically ill patients is relatively scarce. Apart from obvious contraindications (high cardiac risk, extrahepatic tumors and age > 70), there is no consensus and very little evidence concerning the way the general medical condition and risk factors of patients should guide clinicians when deciding whether to transplant them or not. One of the limits to collecting evidence on this topic seems to lie in the fact that transplant teams select critically ill patients who may be eligible to transplant according to varying criteria. These inter-center differences certainly contribute to explaining the scarcity of the literature on this question, which nevertheless seems central.

### Age and comorbidities

The median age of patients undergoing LT has risen in the past decades, along with the comorbidities that come with older age. Recipient age has been proved to be associated with poorer post-transplant prognosis both in the general population of recipients<sup>[61]</sup>, and in the sub-population of critically ill recipients<sup>[16]</sup>. It has recently been proved to be associated with higher post-transplant mortality<sup>[43]</sup>.

The composite Charlson comorbidity index has been shown (with some modifications) to be a useful prognostic tool in a general cohort of 624 patients<sup>[62]</sup> and only once in a cohort of critically ill patients<sup>[13]</sup>.

A study based on the UNOS registry has shown that a body mass index (BMI) > 50 kg·m<sup>-2</sup> is significantly associated with higher post-transplant mortality<sup>[63]</sup>. At the other end of the BMI spectrum, cachexia is also associated with poorer outcomes<sup>[64]</sup> and so is frailty, as defined by Lai *et al.*<sup>[65]</sup> in her composite index published in 2017. These findings probably hold true for critically ill patients, for whom the evaluation of frailty is unfortunately more difficult to undertake (especially the grip test).

Pre-transplant cardiovascular risk is a post-transplant mortality risk factor in the general population<sup>[66]</sup> and in one cohort of critically ill patients with MELD scores >

40<sup>[13]</sup>. This finding has nevertheless not been validated in other studies of critically ill patients. Other cardiovascular markers, such as pre-transplant cardiac troponin levels, which has been shown to be correlated to post-transplant outcome<sup>[67]</sup>, could potentially be useful in evaluating the cardiovascular risk of critically ill patients.

### Pre-transplant evaluation, alcohol abstinence and psychiatric evaluation

One of the striking characteristics of ACLF is that, in half of the cases, the diagnosis of ACLF is either inaugural or made within three months of the patients' underlying liver disease<sup>[53]</sup>. This naturally implies that, in a large number of cases, pre-transplant evaluation has not been completed when patients are hospitalized with ACLF. In addition, patients with ACLF who have not presented a previous acute decompensation tend to be younger and active alcohol drinkers, and have more severe grades of ACLF<sup>[36,53]</sup>.

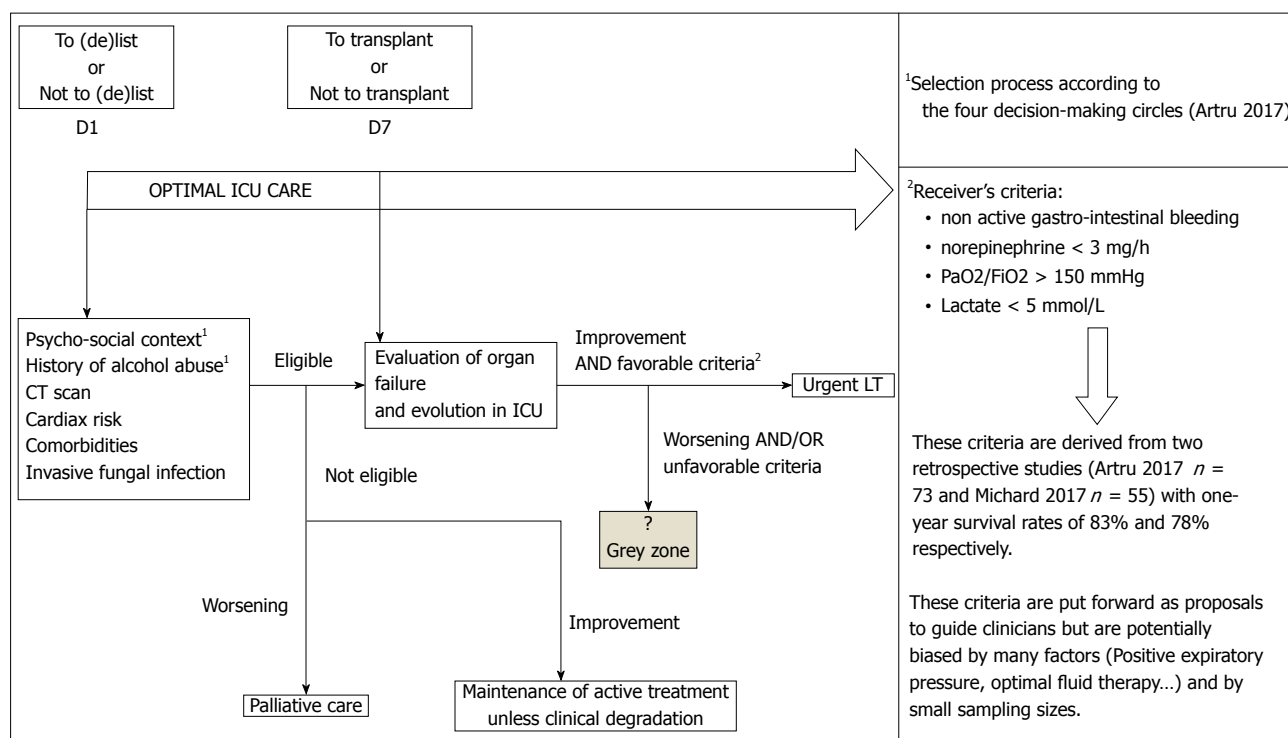
Some studies report the positive effects of close pre-transplant social and psychological evaluation and care on post-transplant outcome<sup>[68,69]</sup>, and it seems reasonable to assume that prolonged alcohol abstinence is a prerequisite for LT. Nevertheless, the question of allocating livers to a set of carefully selected patients who are still actively drinking is open. Indeed, 3 studies have proved the relevance of LT for patients whose alcoholic hepatitis does not respond to medical therapy<sup>[70-72]</sup>. These studies nonetheless underline the difficulty of finding reliable criteria that can predict future abstinence<sup>[73]</sup>.

There is no evidence published in the literature so far concerning the question of abstinence or the effect of pre-transplant social and psychiatric evaluation on post-transplant outcome. In particular, it is not clear whether, in the case of critically ill patients, a prolonged and thorough evaluation (one that would have been conducted before the chronic decompensation) is an absolute prerequisite for LT or if a minimal medical, social and psychiatric screening conducted within the ICU for critically ill patients with no previous decompensation or regular medical check-ups could potentially suffice to put patients on a transplant waiting list. The complexity of this medical and ethical puzzle defies simple answers and straightforward protocols. We can only recommend following Mathurin *et al.*<sup>[72]</sup>'s approach: evaluate critically ill patients in multi-disciplinary meetings and through discussions with the patients' relatives and assess the history and degree of addiction, the duration of abstinence and the potential relapses in order to estimate subjectively the risk of future relapse.

## PRACTICAL PROPOSALS AND FUTURE PERSPECTIVES

### Inherent limitations

Transplant centers apply different criteria to decide whether or not to list critically ill patients for LT. This center-dependent preselection implies that it is impossible to retrospectively extract post-transplant mortality risk



**Figure 1** Algorithm proposal for liver transplantation critically ill cirrhotic patients. CT: Computed tomography; ICU: Intensive care unit; LT: Liver transplantation.

factors with a perfectly rigorous methodology.

### Practical proposals and remaining uncertainties

We propose an algorithm (Figure 1) that takes into account the evidence that has been described above in a two-step process, which distinguishes the question “to list or not to list” and “to transplant or not to transplant”<sup>[75]</sup>. We have combined the criteria that have been shown to predict post-transplant mortality for critically ill ACLF patients in our own work (lactate level > 5 mmol/L and PaO<sub>2</sub>/FiO<sub>2</sub> < 200 mmHg)<sup>[44]</sup> and those used by Artru *et al.*<sup>[10]</sup> to select the ACLF 3 patients that were not eligible for LT in his recent multicentric study: patients with active gastrointestinal bleeding, or doses of norepinephrine > 3 mg/h (patients with PaO<sub>2</sub>/FiO<sub>2</sub> < 150 mmHg were also excluded). Given the excellent one-year survival of these cohorts (78% for ACLF patients without these criteria in our cohort and 84% in Artru’s cohort), we believe that these criteria should be given particular weight in the decision to transplant critically ill patients with cirrhosis.

These four criteria obviously have limitations. They were derived from retrospective studies and have not been validated in other cohorts. In addition, they are potentially altered by many factors (PaO<sub>2</sub>/FiO<sub>2</sub> can vary rapidly and depends on levels of positive expiratory pressure; doses of norepinephrine depend on fluid therapy and blood pressure targets). These criteria are therefore put forward in the absence of better evidence in the literature so far. In addition, the question of whether these criteria should be used to exclude patients from transplantation or to include them is not fully answered yet. Finally, many uncertainties remain and the algorithm

put forward leaves large gray areas, in particular concerning the role of renal failure, neurologic failure or sarcopenia that have all proved to have an impact on post-transplant outcome.

A specific group poses particular ethical and medical problems: patients who do not have initial contraindication to LT but whose clinical condition deteriorates at day 7 after admission and/or who are in critical hemodynamic or respiratory condition. There is not enough evidence in the literature to definitely exclude these patients from LT. Another group of patients raises important: patients with ACLF 2 or 3 whose clinical condition improves to ACLF 1 or 2 without LT. These patients could require some form of prioritization insofar as an episode of ACLF substantially increases medium-term mortality<sup>[38]</sup>.

### What type of criteria are we looking for?

There are three possible ways of conceiving a score for critically ill ACLF patients. First, a specific score in order to prioritize patients with ACLF<sup>[51]</sup>. Such a score would take into account extra hepatic organ failures but might lead to prioritizing patients with poorer, if not unacceptably low, post-transplant survival. Second, a general score that could be applied to all patients, including ACLF patients. This would probably be quite complex to implement in a single score and might lack discrimination for the small number of patients with severe ACLF. Third, a set of criteria that could be used to set an upper limit beyond which LT could reasonably be contraindicated. This solution, probably the most simple and pragmatic one, would be modeled on the score used for LT in



hepatocellular carcinoma. It would not replace the MELD but would complement it.

### LT in critically ill ACLF patients: looking beyond the score

A number of research perspectives concerning the management of severe ACLF patients will potentially transform the issue of organ allocation for these patients in the future. First, the continuum between liver failure and multi-organ failure implies that treating liver failure precociously could, in principle, prevent severe ACLF. Some studies have detailed promising results using granulocyte colony-stimulating factors in decompensated liver failure in order to avoid transplantation but they remain at exploratory phases<sup>[76]</sup>.

The potential use of extracorporeal liver support devices has not been fully examined in the specific context of ACLF patients. Non-biological<sup>[77-79,80,81]</sup> and biological<sup>[82]</sup> liver support systems do not improve overall survival, but they could potentially play a role as a bridge to transplant therapy for patients with severe ACLF.

Donor/receiver matching is a particularly complex technical and ethical puzzle in critically ill patients<sup>[83]</sup>. For example, transplanting critically ill patients with poor-quality organs has been reported to lead to significantly poor outcomes<sup>[26]</sup>. This could encourage transplanting critically ill patients with high-quality organs. On the other hand, if the post-transplant outcome of critically ill cirrhotic patients is known to be lower than that of other groups of patients, such a strategy would give rise to lower organ utility and potentially unfair access to high-quality organs. Some authors have suggested using artificial intelligence to optimize the allocation of organs to recipients<sup>[84]</sup>. In the meantime, technical points concerning the allocation of organs from non-heart-beating donors and expanded criteria donors as well as the use of organ preservation devices<sup>[85,86]</sup> in the specific context of ACLF have not been examined yet.

Finally, several markers of oxidative and cellular injury are emerging in ACLF patients, along with factors that reflect organ-specific injury. Most of these still require validation in heterogeneous populations of ACLF<sup>[80]</sup>. Markers at the time of LT, such as donor metabolomic profiles, have been shown to accurately predict graft dysfunction and could be used to refine donor-recipients matching according to identified prognostic factors such as sarcopenia<sup>[81]</sup>.

## CONCLUSION

This review offers a tentative algorithm to guide clinicians who treat critically ill patients with ACLF and have to decide whether to transplant them or not. It highlights the large grey area that surrounds this issue and identifies a number of steps that could be followed in the future to elucidate the key points that remain unclear in this controversial area of liver transplant.

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