



# Approaches for patients with very high MELD scores

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## Summary

**In the era of the “sickest first” policy, patients with very high model for end-stage liver disease (MELD) scores have been increasingly admitted to the intensive care unit with the expectation that they will receive a liver transplant (LT) in the absence of improvement on supportive therapies. Such patients are often admitted in a context of acute-on-chronic liver failure with extrahepatic failures. Sequential assessment of scores or classification based on organ failures within the first days after admission help to stratify the risk of mortality in this population. Although the prognosis of severely ill cirrhotic patients has recently improved, transplant-free mortality remains high. LT is still the only curative treatment in this population. Yet, the increased relative scarcity of graft resource must be considered alongside the increased risk of losing a graft in the initial postoperative period when performing LT in “too sick to transplant” patients. Variables associated with poor immediate post-LT outcomes have been identified in large studies. Despite this, the performance of scores based on these variables is still insufficient. Consideration of a patient’s comorbidities and frailty is an appealing predictive approach in this population that has proven of great value in many other diseases. So far, local expertise remains the last safeguard to LT. Using this expertise, data are accumulating on favourable post-LT outcomes in very high MELD populations, particularly when LT is performed in a situation of stabilization/improvement of organ failures in selected candidates. The absence of “definitive” contraindications and the control of “dynamic” contraindications allow a “transplantation window” to be defined. This window must be identified swiftly after admission given the poor short-term survival of patients with very high MELD scores. In the absence of any prospect of LT, withdrawal of care could be discussed to ensure respect of patient life, dignity and wishes.**

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## Introduction

Since the first experiment by Thomas E Starzl in the 1960s,<sup>1</sup> liver transplants (LTs) have revolutionized the treatment of patients with severe liver disease, dramatically improving outcomes. Illustrating the success of the procedure, around 23,000 transplants were performed around the world in 2017.<sup>2</sup> However, access to LT is limited. A stagnant pool of donor organs contrasts with an increasing number of candidates. In France, for instance, the overall number of newly listed patients increased by 24% between 2011 and 2017 with an average 2.4 transplant candidates per available graft.<sup>3</sup> Regulation regarding the allocation system has led to grafts being offered to the patients with the highest risk of short-term mortality. As a consequence, severely ill patients with end-stage liver disease (ESLD), prioritized for LT, have been increasingly admitted to the intensive care unit (ICU).<sup>4</sup> Outcomes of patients with ESLD in the ICU used to concern intensivists due to their outcomes compared to the general population.<sup>5,6</sup> However, improved practices have led to an outstanding 30 point short-term survival gain between 2000 and 2010 in a liver-specific ICU.<sup>7</sup> The reasons for such

improvements are fourfold: better identification of candidates for ICU admission based on specific prognosis scores,<sup>8,9</sup> better understanding of the pathophysiology of complications in chronic liver diseases, general improvement in ICU care,<sup>10,11</sup> and development of specific management for patients with advanced liver disease. Indeed, in the last decades, there have been numerous medical improvements in the management of precipitating events and complications of ESLD. For instance, improvement in administration of antimicrobial therapy and bundle of care in sepsis resulted in better outcomes in both sepsis and septic shock.<sup>12–14</sup> Among others, the use of vasopressors, antibiotic prophylaxis and endoscopic management resulted in significant improvements in prognosis for patients admitted in the context of acute variceal bleeding.<sup>15–18</sup> In the setting of hepatorenal syndrome (HRS), the combination of using albumin infusions, and vasopressors alongside clearer disease definitions has led to significant improvements in terms of outcome.<sup>19–22</sup> Despite these improvements, LT remains the only life-saving procedure in patients that fail to recover adequate liver function. In order to illustrate the

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importance of “urgent” LT in this situation, the “share 35” policy has recently been implemented in the US to improve equity in access to LT, based on the comparable outcomes observed in patients with very high MELD scores without LT as in patients with fulminant hepatic failure (FHF).<sup>23–25</sup> With Share 35, patients with ESLD are now given the same geographic access to organs as patients with FHF, while the latter group is still granted higher allocation status in a given region.<sup>24</sup> Several unmet medical and ethical issues have to be faced by clinicians in order to optimize management of patients with very high MELD scores from the perspective of LT, such as: How should these patients be categorized in the era of the dual concepts of acute-on-chronic liver failure (ACLF) and “mere” acute decompensation? Which prognosis assessment should be used? In the context of permanent scarcity of resource, how should the priority access to LT be managed in the most severely ill patients given the potential increased risk of post-LT mortality? Can upper limits of sickness be identified beyond which a patient should not be listed for an LT? How should we deal with patients already listed with less severe disease who are exposed to brutal deterioration of liver function and death due to restricted access to LT? Finally, how to identify and manage patients that are not candidates for LT and who do not recover adequate liver function?

We hereby offer to discuss all these important questions and review the literature in order to shed light on the management of patients with very high MELD scores.

### Very high MELD and relationship to Acute-on-Chronic Liver Failure

#### Acute-on-chronic liver failure or “mere” acute decompensation?

Patients with very high MELD scores are often admitted in the context of acute decompensation (*i.e.* ascites, gastrointestinal bleeding, hepatic encephalopathy and/or acute bacterial infections). Distinctions have been made between “mere” acute decompensation and ACLF regarding their respective outcomes. “Mere” acute decompensation is associated with an acceptable 28-day and 3-month mortality (5% and 14% respectively)<sup>26</sup> and is defined by either the absence of organ failures (OFs) or the presence of cerebral failure with a serum creatinine level <1.5 mg/dl or the presence of 1 “non-kidney” OF with serum creatinine level <1.5 mg/dl and no encephalopathy (Table 1). The median MELD of patients hospitalized in this setting is 16.<sup>27</sup> Patients with very high MELD scores are more likely to be admitted in the context of ACLF. The World Gastroenterology Organization defined ACLF as a syndrome in patients with chronic liver disease with or without previously diagnosed cirrhosis which is characterized by acute hepatic decompensation resulting in liver failure (jaundice and prolongation of the

#### Key points

Patients with very high MELD scores have prioritized access to LT and are therefore increasingly admitted to the ICU, as a bridging option, in the context of ACLF.

The prognosis of such patients is accurately assessed by sequential evaluation of ACLF grade at admission and after 3 to 7 days.

General management of patients with very high MELD scores is based on organ support, treatment of precipitating events and prevention of complications, with a particular focus on prevention of infectious events.

In case of recovery of liver function, patients should be referred to an LT centre when considering the risk of liver-related complications in this population.

In case of non-recovery, LT is the only curative treatment that can be performed, with good outcome in selected patients transplanted within a “transplantation window”.

Withdrawal of care can be suggested in patients who are not candidates for LT and who have persistent multiorgan failure after several days of optimal medical management.

international normalized ratio) and 1 or more extrahepatic OFs that is associated with increased mortality within a period of 28 days and up to 3 months from onset.<sup>28</sup> By definition, 28-day and 3-month mortality in this setting is high (respectively around 35% and 50%).<sup>26,29</sup> Three types of ACLF were defined according to absence (Type A) or presence (Type B) of cirrhosis and history of previous hepatic decompensation (Type C). The latter 2 are the most prevalent in western countries.<sup>28</sup> Despite agreement on the definition, exact implications of concepts such as “acute” and “failure” remain debated among the different learned societies.<sup>26,30–32</sup>

#### Which prognostic score to use and how to use them?

In cases of ACLF, standard liver disease prognostic scores underestimate short-term mortality, which is more closely associated with the number of OFs than with liver failure *per se*.<sup>33–35</sup> It is well established that, in such patients often hospitalized in the ICU, ICU scores (simplified acute physiology score II, sequential organ failure assessment [SOFA], acute physiology and chronic health evaluation score [APACHE]) evaluating

**Table 1. ACLF grading according to EASL-CLIF consortium.**<sup>26</sup>

ACLF grade	Definition
No ACLF	Absence of organ failure OR Presence of one “non-kidney” failure + creatinine <1.5 mg/dl + absence of encephalopathy OR Cerebral failure + creatinine <1.5 mg/dl
Grade 1	Kidney failure OR Presence of one non-kidney failure + creatinine between 1.5 to 1.9 mg/dl and/or mild to moderate encephalopathy OR Cerebral failure + creatinine between 1.5 to 1.9 mg/dl
Grade 2	Two organ failures
Grade 3	Three organ failures or more

extrahepatic OFs are better predictors of mortality than the MELD and other scores.<sup>33,35–37</sup>

The Chronic Liver Failure Consortium (CLIF-C) of the European Association for the Study of the Liver Disease (EASL) has led a European prospective multicentre (29 centres) study involving 1,343 patients hospitalized for acute deterioration of hepatocellular function in order to establish diagnostic criteria for ACLF and assess the natural history of the syndrome (CANONIC cohort). In this cohort, OF was defined by CLIF-SOFA<sup>26</sup> (adapted from the SOFA)<sup>38</sup> and then by the CLIF-C OF score.<sup>39</sup> The authors proposed arbitrarily 6 thresholds (identical in the 2 scores) to define OFs according to the 6 organ systems included (liver, coagulation, kidney, brain, respiration, circulation) and a subsequent grading ranging from 0 (absence of ACLF) to 3 depending on the number of OFs (Tables 1 and 2). This classification identifies 3 populations with different prognoses at 28-days, illustrated by mortality rates of 22% 32% and 76.7% in patients with ACLF grade 1, 2, and 3, respectively.<sup>26</sup> ACLF is a dynamic process in which the rapid evolution after the first days of medical care is associated with clinical outcome (Fig. 1). Identification of an early non-severe course (resolution of ACLF or ACLF grade 1 after day 3 to 7) is associated with low to moderate 28-day transplant-free mortality ranging from 6–18%. On the contrary, early severe course (ACLF grade 2 or 3 at day 3 to 7) is associated with a high 28-day transplant-free mortality ranging from 42–92%.<sup>29</sup> Therefore, sequential evaluation during the first days of care is required in order to optimize prediction of outcome and subsequent medical management in this population. A score derived from CLIF-C OF, named CLIF-C ACLF, which additionally included age and log-transformed white-blood cell count was initially reported to have the best performance in predicting short-term mortality in this population. These results were not confirmed in a recent study of more than 800 patients with ACLF. In this work, CLIF-C ACLF failed to show better performance in prediction of 90 days mortality compared to MELD (AUROC 0.68 vs. 0.67,  $p=0.3$ ).<sup>39,40</sup> Moreover, its daily use seems less convenient than the evaluation of OF number by the CLIF-C OF. Lactate levels were independently associated with short-term mortality in critically ill patients with liver cirrhosis and were shown to significantly improve performance of CLIF-C ACLF. The modified called CLIF-C ACLFsLact score remains to be evaluated in an external cohort<sup>41</sup> together with the numerous biomarkers that have recently been associated with outcomes in this population.<sup>42–47</sup> Combining available scores with biomarkers could optimize prediction of events in this population with a high short-term mortality.

According to the North American Consortium for the Study of Liver Disease (NACSELD), ACLF syndrome is defined by 2 or more extrahepatic

**Table 2. Organ failures as defined by CLIF-C OF score.<sup>39</sup>**

Organ failure	Definition
Liver	Bilirubin level $\geq 12$ mg/dl
Kidney	Serum creatinine level $\geq 2.0$ mg/dl or renal replacement therapy
Brain	Grade 3 or 4 hepatic encephalopathy* (WH scale)
Circulatory	Use of vasopressors
Respiratory	$\text{PaO}_2/\text{FiO}_2 \leq 200$ <sup>#</sup> OR $\text{SpO}_2/\text{FiO}_2 \leq 214$ <sup>#</sup>

FiO<sub>2</sub>, fraction of inspired oxygen; PaO<sub>2</sub>, partial pressure of arterial oxygen; SpO<sub>2</sub>, pulse oximetric saturation; WH, West-Haven.

\*Patients submitted to mechanical ventilation (MV) due to HE and not due to a respiratory failure were considered as presenting a cerebral failure.

<sup>#</sup>Other patients with MV were considered as presenting a respiratory failure.

OFs among the following: circulatory failure defined by a shock, brain failure by grade III/IV hepatic encephalopathy, renal failure by requiring renal replacement therapy and respiratory failure by requiring mechanical ventilation.<sup>32,48</sup> The main difference between this definition and EASL-CLIF consortium is the stringent definition of renal failure restricted to requirements of renal replacement therapy and the absence of liver-related variables (*i.e.* bilirubin and international normalized ratio). While 22.6% (303/1,343) of patients fulfilled the ACLF definition of the EASL-CLIF consortium at enrolment in the *princeps* European study,<sup>26</sup> only 10% (264/2,675) fulfilled the NACSELD's definition in a large study published recently.<sup>48</sup> In the latter, including a large multinational cohort of infected and non-infected cirrhotic patients, NACSELD-ACLF was an independent prognostic factor of 30-day survival and the number of OFs (1, 2, 3 or 4) was also associated with 30-day survival (respectively around 85%, 73%, 53% and 12%). A substantial proportion of patients with very high MELD scores were excluded from the NACSELD-ACLF definition due to the stringent definition of renal failure. Moreover, excluding liver-related variables could include patients without very high MELD scores. We shall therefore hereafter focus on the patients with very high MELD scores, hospitalized in a context of ACLF according to the EASL-CLIF consortium classification as recommended in the 2018 published guidelines (the diagnosis and the grading of ACLF should be based on the assessment of organ function as defined by the CLIF-C OF score).<sup>49</sup>

According to these data, in daily practice, the prognosis of patients with very high MELD scores, hospitalized in the context of ACLF, can be assessed by the grade of ACLF on admission. Sequential evaluation at day 3 to day 7 appears critical in order to characterize the course of ACLF (severe vs. non-severe) and optimize medical management.

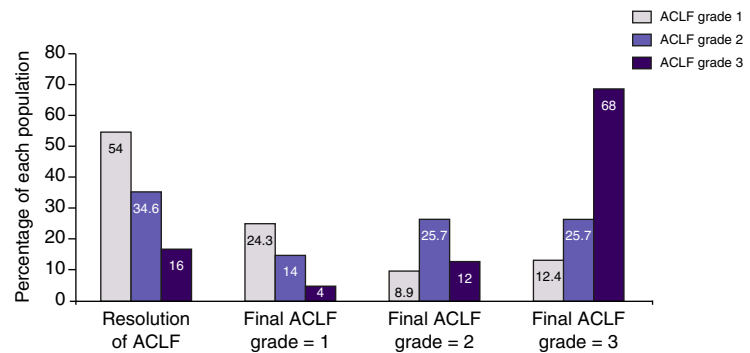
### **Type of organ failure, precipitating events and association with outcome**

#### *Prognosis by type of organ failure*

Kidney failure (55.8% of patients) was the most common failure reported in the CANONIC cohort

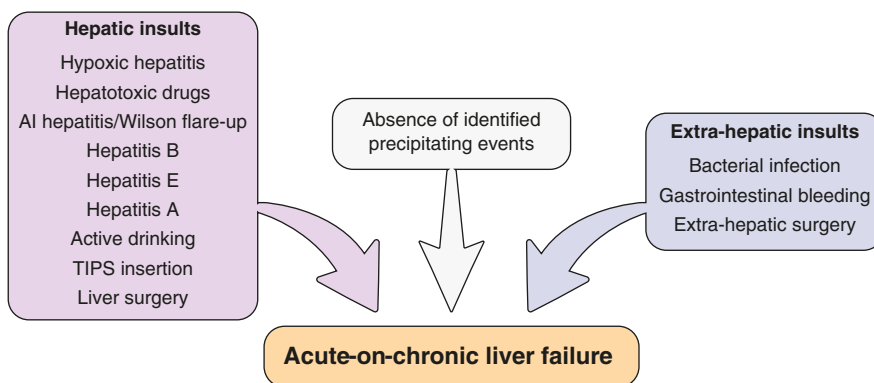
followed by liver failure (43.6% of patients), coagulation (27.7% of patients), brain (24.1% of patients), circulation (16.8% of patients) and the lungs (9.2% of patients). The impact of the type of failure on short-term outcome remains debated. Requirements for vasopressors and mechanical ventilation were identified as the failures associated with the worst outcomes in some studies<sup>32,48,50</sup> whereas this was not reported in a large recent international study.<sup>40</sup> Liver failure, as defined by a total bilirubin  $\geq 12$  mg/dl in the CANONIC study, was an independent predictor of a severe life-threatening course of ACLF, suggesting a central role as a trigger or perpetuating factor of multi-organ failure.<sup>29</sup>

*Do precipitating events have an impact on outcome?* In the *princeps* study on ACLF, precipitating events were sepsis (33%), alcohol consumption (25%), gastrointestinal bleeding (13%) or others (8% transjugular portosystemic intrahepatic shunt insertion, surgery, viral hepatitis).<sup>26</sup> Multiple precipitating events were reported in 13% of the population whereas no precipitating events were identified in around 44% of patients.<sup>26</sup> The absence of a precipitating event was not associated with a different clinical course.<sup>26,51</sup> An absence of precipitating events was thought to be linked with either the lack of sensitivity of diagnostic tests for bacterial infections, spontaneous resolution of events, or bacterial translocation episodes.<sup>52-55</sup> The type and distribution of precipitating events varies according to the regions of the world. For instance, if viral hepatitis represented a minority of identified precipitating events in the CANONIC cohort, it represented more than 40% of events in a large Chinese study.<sup>56</sup> The type of precipitating events was not related to 28-day mortality but could be related to 3-month mortality when divided into



**Fig. 1. Histograms illustration of clinical course of ACLF depending on initial ACLF grade.** Around 80% of patients with initial ACLF grade 1 will observe resolution of ACLF or will be stabilized at grade 1. On the other side, only a small proportion (but non-null - 20%) of patients with initial ACLF grade 3 will observe final ACLF grade 1 or resolution of ACLF. ACLF, acute-on-chronic liver failure.

“hepatic” or “extrahepatic” events<sup>26,56</sup> (Fig. 2). In a subset of the CANONIC database, bacterial infection as the trigger of ACLF was associated with poorer outcome than ACLF not triggered by sepsis, with a 3-month transplant-free mortality of 50.7% vs. 38.4%,  $p < 0.05$ . In the same study, infections with multidrug resistant bacteria that triggered ACLF and/or severe sepsis/septic shock at diagnosis were associated with worse prognosis.<sup>57</sup> Therefore, according to the recent recommendations from EASL, potential precipitating factor(s), either hepatic (*i.e.* heavy alcohol intake, viral hepatitis, drug-induced liver injury, autoimmune hepatitis) and/or extrahepatic (*i.e.* infections, haemodynamic changes following haemorrhage, surgery) should be investigated. Early identification and treatment, particularly bacterial infections, are recommended.<sup>49</sup>



**Fig. 2. Illustration of most listed precipitating events leading to ACLF and classified as intrinsic (hepatic), extrinsic (extra-hepatic) and non-identified ones.** The latter ones are mainly sought to be related with bacterial translocation not documented due to a lack of sensitivity of bacterial tests. Distribution of these events varies significantly according to the region of the world. Association of type of events on outcomes is still a controversial issue that needs further exploration. ACLF, acute-on-chronic liver failure.

## Management and therapies

### General management

In the population of patients with very high MELD scores, no specific treatment is available aside from antiviral therapy in patients with ACLF due to reactivation of HBV infection.<sup>49,55,57</sup> The management is mainly based on organ support together with the prevention and the treatment of associated complications. Such medical care requires a multidisciplinary approach that includes intensivists, specialists in infectious diseases, and a transplant team made up of hepatologists, surgeons and anaesthesiologists.<sup>59</sup> Because of the severe prognosis particularly observed in ACLF grade 2 or 3 (corresponding to patients with very high MELD scores), patients should preferably be managed in the ICU of an LT centre as recommended by EASL guidelines (early referral of patients with ACLF to LT centres for immediate evaluation is recommended).<sup>49,57</sup> Major improvements in prognosis of critically ill cirrhotic patients have been observed over the past decades.<sup>7</sup> In parallel, outcomes of patients with ACLF have been shown to be similar to those of patients without liver disease who are admitted to the ICU with sepsis or with other critical conditions.<sup>60</sup> Therefore, in our opinion, access to the ICU for this population should not be denied without strong evidence of futility of care assessed by a multidisciplinary evaluation.

Among the specific bundle of care in this population, a particular effort should be made to time initial resuscitation in order to control the extension of multi-organ failure. For instance, each hour delay in appropriate antimicrobial therapy is associated with significantly increased hospital mortality.<sup>61,62</sup> Moreover, prophylactic strategies should be used to prevent bacterial infection, considering its deleterious influence on prognosis in the setting of ACLF triggered by non-infectious factors.<sup>57</sup>

General management of such patients should be made in accordance with recent guidelines and expert reviews on critically ill cirrhotic patients.<sup>55,59,63–65</sup> This review will then focus only on the few different alternative strategies available in this population.

### Therapies

#### Liver transplantation

*Who to transplant?* In the absence of effective alternative strategies, LT remains the unique curative treatment available in this population who has been granted priority access. Indeed, the MELD score was first proposed to predict the 3-month mortality in cirrhotic patients after transjugular portosystemic intrahepatic shunt insertion.<sup>66</sup> Later on, this score was widely implemented in graft allocation scores to prioritize patients disclosing the highest risk of waiting list mortality, thus leading to the “sickest first” policy.<sup>67–70</sup> The survival benefit conferred to recipients of LTs increases progressively with MELD score when compared

to candidates on the LT waiting list. The lower threshold of MELD identifying patients who will benefit from LT is not well established (around 15) and could vary according to the aetiology of underlying liver disease.<sup>71,72</sup> Nevertheless, the maximum benefit of LT is constantly observed in the sickest patients with the highest MELD scores (i.e.  $\geq 40$ ).<sup>71–73</sup> The MELD is currently capped at 40 while waiting list mortality continues to increase over this score, penalizing transplant candidates with a capped score.<sup>74</sup> Despite the obvious theoretical benefit of this procedure, performing LT in patients with very high MELD scores hospitalized in the context of ACLF remains controversial. Indeed, some studies reported an increased mortality and morbidity after LT in recipients with very high MELD scores compared to populations with lower MELD scores<sup>75–77</sup> whereas others did not.<sup>78,79</sup> In the context of a global organ shortage in LT, the concept of utility has therefore been opposed to the one of equity.<sup>80</sup> This raises several unsolved issues linked to the question of results of LT in patients with very high MELD scores, identification of “too sick to transplant” patients and the associated upper limits of the “sickest first” policy.

In recent years, the notion of “futility” of LT has been used if post-transplant mortality was higher than waiting list mortality<sup>81,82</sup> or in case of 3-month or in-hospital mortality after LT.<sup>76,83</sup> However, authors of a recent review preferred to correct “futile” LT to “potentially inappropriate” LT, thus reducing the value judgment inherent to the term “futile”.<sup>80</sup> This semantic change follows the adoption of these new terms by a multisociety statement that provided guidance for clinicians to prevent and manage disputes regarding patients with advanced critical illnesses.<sup>84</sup> This change introduces an element of uncertainty in this area (i.e. “potentially”) when considering the fact that medicine is always evolving and upper limits always repelled.<sup>85</sup>

The terms of “potentially inappropriate LT” should therefore be preferred to “futile LT”. Identification of variables associated with post-LT outcomes in the setting of patients with very high MELD should help identify clinical situations where LT is potentially inappropriate.

*Pretransplant variables vs. post-transplant outcomes.* MELD alone does not show good enough performance in identifying patients with high rates of short-term post-LT mortality even in the most severe patients using uncapped MELD with scores  $>40$ .<sup>74,86</sup> Therefore, many authors have searched for recipient factors associated with 3-month mortality or in-hospital mortality. Thirteen variables were identified in a retrospective study from 21,673 patients in the United Network for Organ Sharing (UNOS) database<sup>81</sup> leading to the development of the P-SOFT (for Preallocation

Survival Outcomes Following Liver Transplantation) and SOFT scores (after inclusion of graft related variables) which show good performances in prediction of 3-month post-LT mortality with a c-statistic at 0.69 and 0.70 respectively. The BAR (BALance of Risk) score was developed based on the 37,255 patients from the UNOS database after identification of 4 simple recipient variables (age, MELD, life support pretransplantation and retransplantation) and 2 donor-related variables associated with 3-month post-LT mortality.<sup>76</sup> This score showed similar performance in predicting 3-month post-LT mortality (c-statistic of 0.7). The ACLF-score identified 5 recipient characteristics (age, gender, ESLD or hepatocellular carcinoma, recent infection and presence of ACLF) and 1 donor characteristic (gender) as independently associated with mortality 3 months after LT.<sup>87</sup> This score also showed comparable predictive performance with a c-statistic test at 0.71.

Apart from age, none of these scores contain variables evaluating comorbidities. Through various diseases, comorbidities have been associated with outcome.<sup>88-92</sup> Screening of significant extrahepatic comorbid conditions is the cornerstone of the health assessment required before placement on a waiting list. The UCLA score was developed with the aim of identifying variables associated with 3-month or in-hospital mortality after LT in patients with very high MELD scores ( $\geq 40$ ). Among the evaluated variables, authors chose the Charlson-comorbidity index (CCI)<sup>93</sup> that had already been proven in a recalibrated form to be efficient in determining outcome in an LT population.<sup>94</sup> Another score named the “cardiac risk score” was defined by the presence of at least 1 of the following variables: severe valvular disease, coronary artery disease with more than 70% stenosis or previous revascularization, history of myocardial infarction, history of ventricular and/or atrial arrhythmias, elevated pre-orthotopic LT troponin I ( $> 0.2$  ng/ml), and/or new wall motion abnormalities on echocardiography. Indeed,

cardiovascular disease was shown to be associated with short-term outcome, particularly in the first month following LT (mortality or cardiovascular events).<sup>95,96</sup> MELD score, pretransplant septic shock, but also age-adjusted CCI and cardiac risk score were associated with outcomes using a multivariate analysis. In the final score named UCLA futility risk score (UCLA-FRS) an important weight was given to comorbidity including the cardiac risk index and the CCI:  $UCLA-FRS = 0.5 \times (MELD\ score) + 5 \times (1 = CCI \geq 6; 0 = CCI < 6) + 4 \times (1 = cardiac\ risk; 0 = no\ cardiac\ risk) + 3 \times (1 = septic\ shock; 0 = no\ septic\ shock)$ .<sup>97</sup> In a recent study reporting results of LT in patients with OFs, this score seemed to be helpful in selecting candidates for LT when considering predicted and observed post-LT survival rates.<sup>98</sup> Another study aimed to compare available scores in 2 independent cohorts of transplanted patients with high MELD scores (Swiss and UNOS cohort). Most prediction scores showed low positive predictive values for post-transplant mortality despite good specificity. Among these scores, the BAR score was the only score linearly associated with complications.<sup>99</sup> The usefulness of this score, which was designed for the more critically ill patients, seems restricted to this population based on its performance in other cohorts<sup>100</sup> (Table 3).

An emerging concept in hepatology is frailty. Frailty corresponds to a validated geriatric construct of increased vulnerability to physiologic stressors. Frailty represents the conditions in a given patient that are unlikely to reverse after liver function returns or will take so long to reverse that the patient will be highly vulnerable to postoperative complications.<sup>101,102</sup> Many tools assessing frailty have been proposed and evaluated in ESLD, particularly in patients awaiting LT: Fried frailty index, short physical performance battery,<sup>102,103</sup> 6 minute walk test,<sup>104</sup> activity of daily living.<sup>105,106</sup> A Karnofsky performance status-based score has recently been proposed for the prediction of death after hospital discharge

**Table 3. Available scores predicting early post-LT outcome and including recipient variables, adapted from <sup>77</sup>.**

Score	Recipient variables	Graft variables	C-stat 3-month post-LT mortality*
P-SOFT# and SOFT <sup>79</sup>	Age, BMI, previous transplant, previous abdominal surgery albumin, dialysis prior to transplantation, intensive care unit pretransplant, admitted to hospital pretransplant, MELD score, life support pretransplant, encephalopathy, portal vein thrombosis, ascites pretransplant, portal bleed 48 h pretransplant	Age, cause of death, creatinine, allocation, CIT	0.69 and 0.70
BAR score <sup>73</sup>	MELD score, previous LT, life support, recipient age	Donor age, CIT	0.70
UCLA-FRS <sup>94</sup>	MELD score, septic shock, cardiac risk, age-adjusted Charlson comorbidity index	None	0.75
ACLF-Score <sup>84</sup>	Gender, ESLD or HCC, ongoing infection, age, presence of ACLF	Gender	0.71

SOFT, survival outcome following liver transplantation score; P-SOFT, preallocation-SOFT; BMI, body mass index; MELD, model for end-stage liver disease; CIT, cold-ischemia time; BAR, balance of risk; UCLA-FRS, University of California, Los Angeles-futility risk score; ACLF, acute-on-chronic liver failure, ESLD, end-stage liver disease, HCC, hepatocellular carcinoma

\*C-stat for 3-month and/or in-hospital mortality for the UCLA-FRS score.

#P-SOFT includes only recipient variables whereas SOFT score includes recipient and graft variables.

in cirrhosis.<sup>107</sup> The subgroup of patients with low MELD scores and high frailty may derive the greatest benefit from implementation of these measures.<sup>102</sup> However, functional tests evaluating frailty could be not enough discriminant in the homogeneous population of very high MELD patients. Moreover, it may not be possible to perform such tests because of patients' clinical condition. An interesting approach will be the use of alternative tests to evaluate frailty, which are better adapted for an ICU population and do not require functional assessment.<sup>108,109</sup> Evaluation of surrogate markers of frailty, such as sarcopenia, which can be assessed by imaging, represent an alternative option. When associated with MELD, CT-scan assessed sarcopenia has been demonstrated to be useful in the identification of patients with the highest risk of mortality on waiting lists.<sup>110</sup> Moreover, sarcopenia was associated with post-LT mortality independently of the MELD score.<sup>111</sup> These results were confirmed recently with different thresholds for women and men.<sup>112</sup> Fat-free muscle mass assessed by MRI in decompensated patients was associated with mortality and also with the development of ACLF<sup>113</sup>. However, data are lacking regarding the impact of sarcopenia on post-transplant outcome in patients with very high MELD scores in the context of ACLF. Sarcopenia is an evolving process and evaluation should be readily performed. In this view, assessment of sarcopenia by ultrasonography seems to be an easy and reliable option, but it is yet to be evaluated in cirrhotic patients.<sup>114</sup>

At the present time, identification of potentially inappropriate LT candidates should not be based solely on available scores considering their statistical performance. However, a combination of scores, as well as evaluation of frailty, could improve the clinical management of patients with very high MELD scores who are candidates for LT.

*What is the outcome of ACLF transplanted patients?* Data on outcomes in patients with ACLF treated with liver LT are less scarce. Post-LT 3-month survival of recipients is about 80–90% and much higher than that anticipated if patients were not transplanted.<sup>29,50,87,98,115–117</sup> Indeed, in the CANONIC study, patients transplanted with an ACLF grade 2 and 3 between day 3 and day 7 ( $n = 21$ ) had a better 6-month survival than the non-transplanted patients (80.9 vs. 10%,  $p < 0.001$ ).<sup>29</sup> Similarly, in our reported experience, the 73 patients transplanted with ACLF grade 3 at the time of LT had better 1-year survival than matched controls (83.9 vs. 7.9%,  $p < 0.0001$ ).<sup>98</sup> In a very large cohort study from the UNOS, performed in more than 11,000 patients transplanted with 1 or more OFs, a good 1-year survival ranging from 88% (1 OF) to 80% (5/6 OFs) was reported. Moreover, recipient's long-term survival (5-year)

was acceptable, ranging from 65% to 74% with similar results for liver graft survival.<sup>116</sup> Regarding the impact of the type of OFs on post-LT outcomes, there was a lower post-LT survival among intubated patients or patients with circulatory failure than for other types of OF (1-year patient survival 79–81% vs. 84–87%).<sup>116</sup> Levesque *et al.* recently reported a worse outcome following LT for patients with ACLF grade 3 compared to our cohort (43.3% survival at 1 year).<sup>87</sup> The main difference in patient characteristics between this study and our collaborative work was the incidence of respiratory failure between the 2 groups of patients with ACLF grade 3 (76.7 vs. 15.8%).<sup>98</sup> Together, these data suggest that severe and uncontrolled respiratory failure may be viewed as a contraindication for LT. This is in line with a recent report that identified severe acute respiratory distress syndrome as an independent factor associated with post-transplant mortality.<sup>118</sup> Improvement or stabilization in OFs in the immediate pretransplant period has been associated with favourable post-LT outcomes in patients with ACLF, suggesting that the evolution of OFs should at least be controlled, if not improved, before considering an LT.<sup>98,115</sup>

Another important point to consider is the timeframe of LT. In most studies reporting favourable post-LT outcomes in these severely ill patients, an "early" LT has been performed (time between placement on the waiting list and LT ranging from 3–9 days).<sup>98,116,119</sup> This very short timeframe is required because of the natural history of these patients. Indeed, around 50% of them will die in the first 10 days.<sup>116</sup> A significant proportion of patients are not placed on the waiting list before acute deterioration of their condition. As an example, in our study, 45/73 patients transplanted with ACLF grade 3 were placed on waiting lists during the immediate pre-LT hospitalization (median time to LT: 8 days).<sup>98</sup> Therefore, pretransplant evaluation must be performed in a timely fashion, precluding a number of clinical tests usually required in LT programmes. To our knowledge, the potential impact on post-LT outcomes of this "truncated" evaluation has yet to be studied extensively in patients with very high MELD scores.<sup>50</sup> Such a "truncated" evaluation, involving the performance of only a few necessary screening tests, could lead to potential contraindications for LT (active neoplasia, severe alcohol dependence, or still significant coronary artery disease) being overlooked. In addition to the potential impact on outcomes, this raises some degree of unfairness with regard to less severe patients undergoing the recommended exhaustive evaluation (routinely responsible for not listing patients after the discovery of a contraindication).<sup>117</sup> There is an urgent need to evaluate the various international LT centre practices in this setting. A prospective study validating a standardized assessment for patients

with very high MELD scores, who have not yet been listed, should be put forward in order to optimize selection of candidates and decrease inequity.

While LT seems to confer favourable survival outcomes in these very sick patients, it is associated with longer total stay in both the ICU and the hospital. This also leads to a high rate of complications observed in this population, who therefore require attentive screening for complications, particularly of an infectious nature.<sup>87,98,115,117</sup>

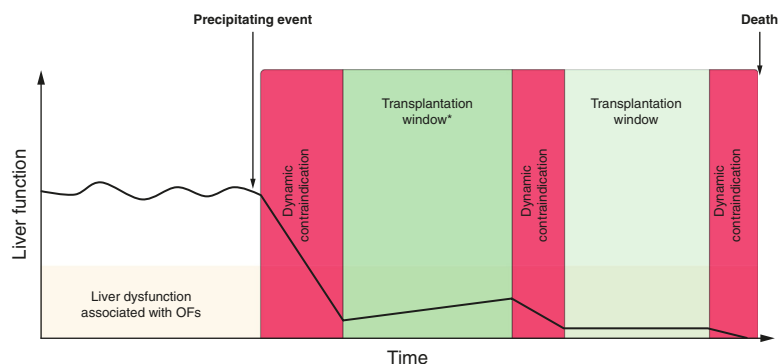
The current knowledge suggests that transplant outcomes in selected patients with ACLF could be favourable, even in patients with multi-organ failure at the time of LT. However, in order to optimize post-LT outcomes, LT should be performed in a timely manner after admission, within a window of improvement or at least stabilization of OFs.

*When to transplant? The concept of a “transplantation window”.* In order to identify the transplantation window, 2 classes of contraindications have to be separated. First, the “definitive” contraindications responsible for an immediate and irreversible arrest in the LT process at the local level. Some contraindications are widely accepted and might be illustrated by metastatic solid neoplasia, severe cardiac or pulmonary insufficiency (not related to liver disease), or even pre-hospitalization bedridden states. However, these “definitive” contraindications are definitive at a specific time in a specific transplant centre as their appreciation varies between LT centres depending on local expertise and the potential change over time within each centre.<sup>117</sup> Second, the “dynamic” contraindications are responsible for a short temporary inability to perform liver transplantation. These “dynamic” contraindications are represented by numbers of diseases or failures that could evolve positively after appropriate therapeutic management: uncontrolled bacterial infection, active fungal infection, active gastrointestinal bleeding, severe acute respiratory distress syndrome, severe haemodynamic instability, severe coagulopathy. The “dynamic” contraindications are often represented by precipitating events of ACLF syndrome.<sup>26,56</sup> Occurrence and resolution (or control) of “dynamic” contraindications in the context of stabilization or improvement of OFs define the “transplantation window”<sup>98</sup> (Fig. 3). As discussed earlier, the optimal transplantation window should be identified as soon as possible after the admission of patients with very high MELD scores, considering their poor expected outcome and the risk of them developing adverse events (other “dynamic” contraindications in a short timeframe).<sup>29,120</sup> Due to the lack of data in this field, the exact timeframes within which LT is contraindicated by “dynamic”

contraindications are often transplant centre and local expertise dependant.

The concept of a transplantation window for LT in a patient without a “definitive” contraindication is based on the absence of “dynamic contraindications” that allow for LTs to be performed in a context of stabilization or improvement of OFs. The transplantation window should be rapidly identified following admission in order to optimize post-LT outcomes.

*What to do in patients who are not transplanted because of recovery of liver function?* Studies reporting outcomes in cirrhotic patients after ICU discharge are scarce. However, after recovery from critical illness, cirrhotic patients are at higher risk of 1-year mortality (between 27.5% to 68%) compared to the general population.<sup>121–124</sup> Predictors associated with 1-year mortality after ICU discharge are not clearly reported but could be related to the number and type of OFs that patients experienced in the ICU, as well as the severity of liver disease at admission to and discharge from the ICU.<sup>123</sup> There are currently no reliable tools that identify populations with a very low risk of mortality after initial effective ICU care and discharge from the ICU. Therefore, such patients should be referred to liver transplant centres during the same hospitalization or closely thereafter, in order to be evaluated for LT.



**Fig. 3. Illustration of “transplantation window” and “dynamic contraindication” relationship.** Y axis illustrates “liver function” and X axis “time”. In this scenario, the onset of a precipitating event (bacterial pneumonia for example) leads to a rapid deterioration of liver function and ACLF in a patient with chronic liver disease. The “dynamic” contraindications (red boxes) illustrate a timeframe in which LT should not be performed due to uncontrolled clinical condition (e.g. severe acute respiratory syndrome with hemodynamic instability). After their resolution (or at least control – depending on local expertise) “dynamic” contraindications are separated by transplantation windows (green boxes) if LT is indicated. In these (often) short elapsed time in patient who were not already listed health assessment should be performed in order to exclude “definitive” contraindication to LT (e.g. metastatic neoplasia, severe cardiac insufficiency). If, the opportunity to transplant is not taken during the firsts transplantation windows, other events (e.g. other bacterial infection such as ventilation associated pneumonia, GI bleeding) can occur and lead patient to death. ACLF, acute-on-chronic liver failure; LT, liver transplantation; GI, gastrointestinal.



Even in cases of recovery of liver function, patients with very high MELD scores admitted in the context of ACLF should be referred to LT centres as soon as possible, considering the risk of events at 1-year in this population.

#### *Is there a place for extracorporeal liver support as bridging therapy to LT?*

Modalities that can serve as a “bridge” to LT or that can confer sufficient clinical improvement to enable patients to be discharged from the ICU/hospital can positively impact outcomes in patients with very high MELD scores. These modalities aim to replace the functions of the failing liver, allowing hepatic recovery or stabilizing clinical state to enable transplantation.<sup>55,59</sup> The key concepts of such therapies are to remove harmful toxins, support the liver for spontaneous regeneration and to reduce the ongoing inflammatory injury.<sup>59</sup> Based on albumin dialysis, the molecular adsorbent recirculating system (MARS®) and plasma separation and absorption system (Prometheus®) are the most studied devices. MARS therapy has been reported to improve bilirubin levels, hepatic encephalopathy, haemodynamic parameters and kidney function in patients with decompensated cirrhosis<sup>125,126</sup> without improving survival. In the RELIEF trial, including patients with ACLF, no improvement in transplant-free survival at 28 and 90 days was observed.<sup>127</sup> In the Helios study, despite a well-tolerated treatment, Prometheus therapy was not reported to improve short-term survival in patients with ACLF.<sup>128</sup> Of note, these results have to be interpreted with caution due to the heterogeneous population of patients with decompensated cirrhosis associated with different degrees of OFs and different definitions of ACLF.<sup>58</sup> Results of a large prospective multicentre study evaluating a bioartificial device (extracorporeal cellular therapy) in patients with severe alcoholic hepatitis showed that it conferred no overall survival benefit compared to standard of care. However, among other limitations, patients were not stratified according to response to medical treatment and definitive conclusions on the efficacy of this device cannot, as of this date, be drawn.<sup>129</sup> A second study in younger patients with lower MELD scores is therefore ongoing (NCT02612428).

Currently, 2 trials involving extracorporeal liver support are recruiting in the setting of ACLF. The first is evaluating the efficacy of high-volume plasma exchange and G-CSF vs. G-CSF alone in patients with ACLF (Clinicaltrials.gov identifier: NCT03162419). The second is a multicentre, randomized, controlled, study evaluating the safety and performance of a new liver support device called DIALIVE in 24 patients with ACLF vs. standard of care (NCT03065699).

Based on the results of available RCTs, EASL guidelines state that extracorporeal liver support

systems do not improve survival of patients with ACLF and should therefore not be recommended for this indication.<sup>49</sup>

#### *Other medical treatment*

Among the medical treatments offered in this setting, G-CSF seems to be the most promising treatment, with accumulating evidence of its potential efficacy, albeit with only a small number of patients treated to date. G-CSF promotes mobilization of hematopoietic stem cells and induces proliferation of hepatic progenitor cells in animal models of liver failure but also in human alcoholic hepatitis.<sup>130,131</sup> A few small-randomized clinical trials have demonstrated not only improvement in liver function with G-CSF but also significant survival benefit compared with standard medical therapy for ACLF.<sup>132–135</sup>

Nonetheless, at this time, there is insufficient evidence for such therapies to be recommended in patients with very high MELD scores. This decision is essentially performed according to local expertise and beliefs. On this specific point EASL guidelines state that despite promising results, the administration of G-CSF cannot be recommended at present.<sup>49</sup>

#### **What management to offer patients who do not receive a transplant given either their poor predicted survival or failure to receive a transplant within the target window?**

The survival probability of patients with very high MELD scores is efficiently calculated by the available scores of ACLF (ACLF grade or CLIF-C ACLF).<sup>29</sup> In the absence of alternative treatments for LT, due to the severe course observed in this population without LT, withdrawal of care could be a reasonable option in some patients presenting with a “definitive” contraindication. In the CANONIC cohort, sequential calculation of the scores was reported to identify a group of patients with the most severe outcome, with a 100% transplant-free mortality.<sup>29</sup> These patients were identified as those with  $\geq 4$  OFs and/or CLIF-C ACLF  $\geq 64$  between day 3 and day 7. Based on these results, an algorithmic approach has proposed withdrawal of care to these patients.<sup>29</sup> A retrospective analysis performed in the King’s College cohort<sup>7</sup> using these thresholds reported that 10% of the patients survived at 90 days.<sup>136</sup> This highlights that prediction scores perform differently in different cohorts and that medical management related to algorithm-based scores cannot be adopted widely without caution. It is important to recognize that any decision regarding withdrawal is irrevocable and small survival probabilities can be perceived differently by caregivers and patient’s families. Balancing these aspects while maintaining patient life, dignity, and wishes is fraught with statistical and ethical difficulties, and a single score is an

unlikely final referee.<sup>136</sup> Regarding the decision to withdraw care, data from the literature, as well as data from local experience should be considered, alongside the potential for improvement in OFs and qualitative factors (frailty and patient's wishes).<sup>136–139</sup> Finally, in our opinion, these scores are useful in identifying situations in which it could be reasonable to initiate discussion around withdrawal of care.

The EASL guidelines state that withdrawal of ongoing intensive care support can be suggested in patients who are not candidates for LT and who have 4 or more OFs after 1 week of adequate intensive treatment.<sup>49</sup>

Accurate identification of variables associated with mortality in patients with cirrhosis and the

permanent scarcity of liver grafts has led to LT being recommended to an increasing number of severely ill patients. As a consequence, physicians in LT centres routinely face medical, surgical and ethical challenges. Nonetheless, data are accumulating on the pretransplant management of such patients and refined disease assessments based on variables such as clinical course, and the determination of risk factors for poor outcome after LT, may be made and help define a “too sick for transplant” upper-limit. However, while awaiting devices or treatment that will delay (or avoid) LT, there is an urgent need, based on robust data, to offer a consensual definition of “definitive” contraindications and the “transplantation window”.

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