Review

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Potentially inappropriate liver transplantation in the era of the "sickest first" policy – A search for the upper limits

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Summary

Liver transplantation has emerged as a highly efficient treatment for a variety of acute and chronic liver diseases. However, organ shortage is becoming an increasing problem globally, limiting the applicability of liver transplantation. In addition, potential recipients are becoming sicker, thereby increasing the risk of losing the graft during transplantation or in the initial postoperative period after liver transplantation (three months). This trend is challenging the model for end-stage liver disease allocation system, where the sickest candidates are prioritised and no delisting criteria are given. The weighting of the deontological demand for "equity", trying to save every patient, regardless of the overall utility; and "efficiency", rooted in utilitarianism, trying to save as many patients as possible and increase the overall quality of life of patients facing the same problem, has to be reconsidered. In this article we are aiming to overcome the widespread concept of futility in liver transplantation, providing a definition of potentially inappropriate liver transplantation and giving guidance on situations where it is best not to proceed with liver transplantation, to decrease the mortality rate in the first three months after transplantation. We propose "absolute" and "relative" conditions, where early post-transplant mortality is highly probable, which are not usually captured in risk scores predicting post-transplant survival. Withholding liver transplantation for listed patients in cases where liver transplant is not deemed clearly futile, but is potentially inappropriate, is a far-reaching decision. Until now, this decision had to be discussed extensively on an individual basis, applying explicit communication and conflict resolution processes, since the model for end-stage liver disease score and most international allocation systems do not include explicit delisting criteria to support a fair delisting process. More work is needed to better identify cases where transplantation is potentially inappropriate and to integrate and discuss these delisting criteria in allocation systems, following a societal debate on what we owe to all liver transplant candidates.

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Key point

Shortage of donor livers is an increasing global problem resulting in an ethical dilemma between prioritising the sickest first "equity" and trying to save as many as possible "efficiency".

Introduction

Liver transplantation (LT) has been a tremendous success since its inception in the 1960s[1] offering many patients with end-stage liver disease (ESLD) or acute liver failure a chance of cure and survival. The worldwide demand for this life-saving procedure is steadily rising as its success leads to an increasing number of patients being deemed suitable for transplantation. Over 25,000 liver transplants were performed globally in 2013, while the pool of donor organs remains stagnant.[2] Many transplant candidates die while waiting for LT because of organ shortages.

This imbalance means that organ allocation policies must be reconsidered. To better predict the mortality of patients on the waiting list, the model of end-stage liver disease (MELD) was introduced.[3,4] This model is based on three laboratory values including serum creatinine, bilirubin, and international normalized ratio (INR), and has been used in the United States since February 2002 to prioritise organ allocation to the sickest patients on the LT waiting list.[4–7] Meanwhile, MELD allocation has been adopted by many LT programmes worldwide.[8] In the case of global organ shortage, an inevitable consequence of this allocation policy is the prioritisation of high MELD patients awaiting LT. This trend has triggered numerous medical, ethical and socio-economic debates, challenging the merits of the "sickest first" allocation policy. In contrast to well defined criteria to activate patients on the waiting list, criteria to declare patients as "too sick for transplant" are rare and are not captured by most allocation systems. The lack of a transparent, commonly shared, decision guidance framework, means that the decision to withhold LT falls to transplant physicians caring for individual patients.

Before going into detail on the upper limits of disease severity, their consequences for allocation, and the question of appropriate delisting, we first aim to critically discuss the concept of "futility", which has been the historical basis of withholding treatment in specific conditions (Table 1). However, we argue that the use of the futility concept beyond a very narrow definition of physiologic futility is fundamentally flawed[9,10] and should be replaced by a definition of potentially inappropriate treatment based on evidence-driven

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Table 1. General definitions of futility.

Futility category	Definition	Possible scenarios in medicine	Possible scenarios in LT
Physiological futility	Treatment which fails to trigger an improved physiological response	Cardiac arrest or brain death on ventilator	LT in patients too sick to survive the operation LT performed too early in patients PNF after LT
Imminent-demise futility	Death can be anticipated in the very near future despite the intervention	"Bridges to nowhere" (e.g. ECMO) Chronic dependency on ICU care Dying before discharge after CPR	Failure of life support treatment in pre-transplant patients requiring delisting and withdraw of care LT in a recipient who will not be able to leave ICU or hospital alive
Lethal-condition futility	Death can be anticipated in the not too distant future (months, years) due to terminal illness despite the intervention	End-stage metastatic cancer	LT in patients with HCC/CCC above accepted criteria who have a post-transplant tumor recurrence
Qualitative futility	No acceptable quality of life can be achieved with the intervention	Terminal dementia Persistent coma	Severe failure to thrive after LT LT in patients with acute liver failure and irreversible brain injury resulting in post-transplant persistent vegetative state

LT, liver transplantation; PNF, primary nonfunction; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; CPR, cardiopulmonary resuscitation; HCC, hepatocellular carcinoma; CCC, cholangiocarcinoma.

assessments of risks and benefits (Table 2–4) which, we hope, will trigger transparent and structured communication and help to develop conflict-resolving skills and strategies in LT.[11]

Of note, living donor LT is embedded in a much more complex ethical and medical decision making process, involving consideration of the healthy donor. Therefore, this review does not cover the topic of living donor LT and disease severity.

Definitions of medical futility

"Futility" is a concept which has accompanied medical practice from its beginning. The *Hippocratic Corpus*, the first known codification of the medical ethos, included a definition of futility, stating that medicine is powerless for those who are overmastered by their diseases, suggesting that physicians withhold treatment in such cases.[12] Such concepts are becoming more important, particularly in times of rapid medical advances. Modern medicine puts some patients in a situation where neither cure nor acceptable quality of life is possible. In these situations, cessation or withholding of a life-prolonging therapy and maximisation of palliative treatment is a reasonable and humane consideration. Currently, most in-hospital deaths in intensive care units (ICU) are accompanied by withholding or withdrawing life-prolonging treatments (most according to patients wishes, and few based on so called "futility" assessments of medical staff[13]).

The aim of defining futility was to offer criteria for specific situations in which stopping or not starting treatment can be undertaken based on a unilateral medical judgment, without a patient's or family's consent, in order to define limits of a patient's autonomous choice or surrogate's requests for a specific medical treatment.[14] Besides avoiding unnecessary suffering and harm to a patient, the reason for its application in modern medicine has been closely linked to questions about allocation of resources.[15,16]

Quantitative *vs.* qualitative futility

Futility was often defined as a treatment that does not "serve its purpose" or "cannot benefit the patient" [17] based on assessment of odds (prognosis of chances – *quantitative* aspect) and ends (observed or prognosticated outcome regardless of odds – *qualitative* aspect). One of the most frequently used definitions was proposed by Schneiderman *et al.*[14,18], stating that treatment should be considered as futile if:

a) it has been useless in the last 100 cases (<1%);
b) it merely preserves permanent unconsciousness, or
c) it fails to end total dependence on intensive medical care

In this definition, (a) delineates quantitative futility describing a numerical probability that a treatment will almost have no effect, whereas (b) and (c) are based upon an independent qualitative evaluation of utility.

Key point

The definition of "futile" LT represents a too narrow concept for when LT should be avoided. More appropriately, we propose the concept of "potentially inappropriate" LT when risk profiling of conditions indicates a high probability of not surviving the early post-transplant period.

Table 2. Specific definitions of post-transplant futile outcome in LT.

Author, yr	Patient population	Definition of futility
Rana, 2008/2013	Adult recipients	Post-transplant mortality >waiting list mortality
Lao, 2010	Paediatric re-transplant recipients	One-year mortality
Petrowsky, 2014	Adult recipients with MELD ≥40	90-day or in-hospital mortality
Panchal, 2015	Adult recipients with MELD ≥40	90-day mortality
Asrani, 2015	Adult recipients	>50% mortality at five years

MELD, model of end-stage liver disease.

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Table 3. Scores predicting waiting list mortality.

Score	Author, year	Prediction	*c*-statistic	Variables
CTP	Child, Turcotte, 1964 Pugh, 1973	Mortality rates 1–10 years, perioperative mortality	n/a	Bilirubin, albumin, quick, hepatic encephalopathy, ascites
MELD	Wiesner, 2001	Three-month mortality	0.78–0.87	Bilirubin, creatinine, INR
Delta MELD	Merion, 2003	Three-month mortality	0.85	Bilirubin, creatinine, INR change within 30 days
Re-weighted MELD	Sharma, 2008	Three-month mortality	0.70	Bilirubin, creatinine, INR
MELDNa	Kim, 2008	Three-month mortality	0.87	Bilirubin, creatinine, INR, sodium (bound between 125–140 mmol/L)
UKELD	Barber, 2008	One-year mortality	0.76	MELD, bilirubin, creatinine, INR, sodium
MELDNa + frailty index	Lai, 2017	Three-month mortality	0.82	MELDNa, frailty index

CTP, Child-Turcotte-Pugh; MELD, model of end-stage liver disease; INR, International normalized ratio; model of end-stage liver disease; UKELD, United Kingdom model for end-stage liver disease.

Key point

Patients who have a high risk of not surviving LT during the early postoperative period (three months) are widely accepted to be inappropriate candidates for LT.

Four qualitative categories of medical futility

Brody and Halevy have proposed four qualitative categories of medical futility (Table 1) defined as not reaching specific goals.[19] The first, *physiological futility* describes a treatment which fails to trigger an improved physiological response. This definition is the most narrow description of futility and has been applied to LT when a patient is either too sick or too healthy for LT. For instance, high acuity or extremely ill recipients who are too sick might not respond to LT even in the scenario of receiving the best possible donor organ.[20] Conversely, in patients with ESLD and MELD scores below 15, who have no hepatocellular carcinoma (HCC) or other conditions requiring exception points, the risk of mortality is higher in patients after LT than in those not receiving LT.[6,21] In this scenario, when the patient is too healthy, LT can also be considered futile. Another example of physiological futility in LT is the scenario of patients with acute liver failure who develop irreversible brain injury before or during LT. Here, liver function might be restored but irreversible brain injury results in a persistent vegetative state after LT. Of note, the prevalence of cerebral oedema and intracranial hypertension in acute liver failure has decreased over the years,[22] whereas rapid multiorgan failure is now the leading cause of death in acute liver failure, sometimes even occurring in patients receiving a fully functioning graft. This situation often reflects physiological futility.

The second, *imminent-demise futility* describes a situation where death can be anticipated in the very near future. In the context of LT, this kind of futility can be applied to pre-transplant patients in whom treatment fails to restore a transplantable condition, leading to delisting and withdrawal of life support. For example, patients without the chance of weaning from an extracorporeal membrane oxygenation would fall into this category.

The third, *lethal-condition futility* describes the situation where a patient is suffering from terminal illness, which will lead to death in months to years despite any intervention. Examples in medicine are bedfast metastatic cancer and HIV infection with repeated opportunistic infections of PCP pneumonia.[23] The same definition also applies to patients undergoing LT for HCC or cholangiocarcinoma who experience recurrence of the primary liver cancer.

The fourth, *qualitative futility* defines a health state where no acceptable quality of life can be achieved by further treatment. It is important to emphazise that this criterion has not been related to a longer or shorter life expectancy, but to quality of life which is externally assessed as being too low to justify the life-prolonging intervention. Examples are life-prolonging treatments in patients with persistent vegetative state or severe dementia requiring long-term care. In LT, this definition may be translated to post-transplant patients with failure to thrive because of severe weight loss, diminished appetite, malnutrition, and physically inactivity.

From futility to potentially inappropriate treatment

Reviewing various definitions of futility and their use during the last 20 years, it became more and more obvious that wider concepts of futility beyond a narrow definition of physiologic futility are highly warranted. All futility definitions are value judgments despite asserting they are "objective",[15,24] thus reflecting "the same confused fallacy of the generalisation of expertise as did the earlier tradition of unjustified paternalism".[10] Futility always implies that a decision can be made unilaterally by individual physicians or medical teams. If wider concepts of futility are applied, life-prolonging treatments are unilaterally denied even in cases where a treatment might have success. If this is considered in a patient incapable of decision making who objectively suffers, the principle of "do no harm" is a good reason to try and convince the surrogates that the treatment is not in the patients best interest, following best conflict resolution practices.[11]

The discussion on futility has always been closely linked to allocation of scarce resources, especially in transplantation. It was used as an ethical argument for rationing treatment while not only applying the "rule of rescue",[25] but also utilitarian principles in a balanced way. In LT, it is ethically worth discussing whether donor organs should be given to a patient with a very low chance of survival or a very low quality of life (*e.g.* in a

Table 4. Scores predicting post-transplant outcome.

Score	Author, yr	Prediction	c-statistic	Recipient variables	Donor variables
DRI	Feng, 2006	Graft loss (time to graft failure)	n/a	None	Age, cause of death, ethnic origin, DCD, partial/split, height, allocation*, CIT
SOFT	Rana, 2008	Three-month mortality	0.70	Age, gender, height, BMI, diagnosis, number of previous LT, ICU or in-hospital pre-LT, diabetes, ALT, albumin, diabetes, dialysis, UNOS status 1, MELD, life support, encephalopathy, portal vein thrombosis, incidental tumor found at LT, ABO incompatible, ventilator dependent, portal bleeding 48 h pre-LT, variceal bleeding within 2 weeks of registration, ascites pre-LT, SBP pre-LT, PE within 6 months of registration	Age, height, weight, cause of death, creatinine, cocaine use, allocation*, CIT, WIT
D-MELD	Halldorson, 2009	Four-year mortality	n/a	MELD	Donor age
Net-benefit model	Schaubel, 2009	Five-year mean lifetime	n/a	Creatinine, albumin, sodium, age, diagnosis, diabetes, dialysis, hospitalisation status, previous LT, mechanical support, portal vein thrombosis, previous abdominal surgery, hepatitis C	Age, cause of death, DCD, CIT, allocation*
BAR	Dutkowski, 2011	Three-month mortality	0.70	MELD, Re-LT, life support, recipient age, CIT	Donor age, CIT
ET-DRI	Braat, 2012	Three-month to one year mortality	0.62	None	Age, cause of death, GGT (U/L), DCD, partial/split, allocation*, rescue LT, CIT
UCLA score	Petrowsky, 2014	Three-month and/or in–hospital mortality	0.75	MELD score, septic shock, cardiac risk, comorbidities (CCI ≥6)	None
Pedi-SOFT	Rana, 2015	Three-month mortality	0.74	Previous LT, life support, renal insufficiency, weight <6 kg	Cadaveric technical variant allograft
ACLF score	Levesque, 2017	Three-month mortality	0.71	Gender, ESLD or HCC, ongoing infection, age, ACLF	Gender

ACLF, acute-on-chronic liver failure; ALT, alanine transaminase; BAR, balance of risk score; BMI, body mass index; CCI, Charlson comorbidity index; CIT, cold ischaemia time; DCD, donation after cardiac death; D-MELD, donor age × recipient MELD; DRI, donor risk index; ESLD, end-stage liver disease; ET-DRI, Eurotransplant donor risk index; GGT, gamma glutamyltransferase; HCC, hepatocellular carcinoma; ICU, intensive care unit; LT, liver transplantation; MELD, model of end-stage liver disease; PE, pulmonary embolism; SBP, spontaneous bacterial peritonitis; SOFT, survival outcome following liver transplantation score; UCLA, University of California, Los Angeles; UNOS, United Network of Organ Sharing; WIT, warm ischaemia time.

vegetative state) or to another patient who is less sick but more likely to benefit (Fig. 1).

This is a different and, in our view, more appropriate reflection of the futility debate in LT, hinting to the core delisting dilemma and justice problem:

Due to the "sickest first" policy and the lack of widely accepted delisting criteria in most allocation systems, we not only face more and more cases of "real futility", where a patient is literally too sick to be transplanted, meaning that we prognosticate that he or she will not survive the operation; but increasingly more cases of very low utility, where there is a high risk of post-transplant death or chronic dependency on intensive medical care after LT. In low utility, LT "does work" in a few cases and can therefore not be considered futile. In this scenario, LT might be better considered as a potentially inappropriate treatment, which is associated with high opportunity costs and lower overall utility of LT for all patients on the waiting list.

In LT, the term futility is still widely applied to decisions to forgo LT despite few studies using "futile outcome" as a primary endpoint of post-transplant outcome in LT.[20,26–28] Many LT studies that use the term futility fail to provide a clear definition of the concept, which obscures the value judgments underlying its use. Therefore, we further define and scrutinise the concept of potentially inappropriate LT.

Potentially inappropriate liver transplantation

For the reasons mentioned above "potentially inappropriate LT" better addresses the medically driven decision process to forgo the life-saving transplant procedure. This applies in situations where a patient:

a) will certainly die before or despite LT (recipient too sick)
b) has a low chance of survival after LT (*e.g.* rapid tumour recurrence due to LT beyond accepted tumour criteria)
c) will be ICU dependent or permanently unconscious after LT
d) will have a very low quality of life or will be permanently institutionalised after LT.

In LT or in transplantation in general, there are other good reasons to deny transplantation based on medical judgments. Firstly, transplantation always involves donor organ shortages and opportunity costs. The principle of rescuing a single identified endangered life, regardless of cost, at the expense of the "nameless faces" who will be denied health care is becoming less prominent.[29]

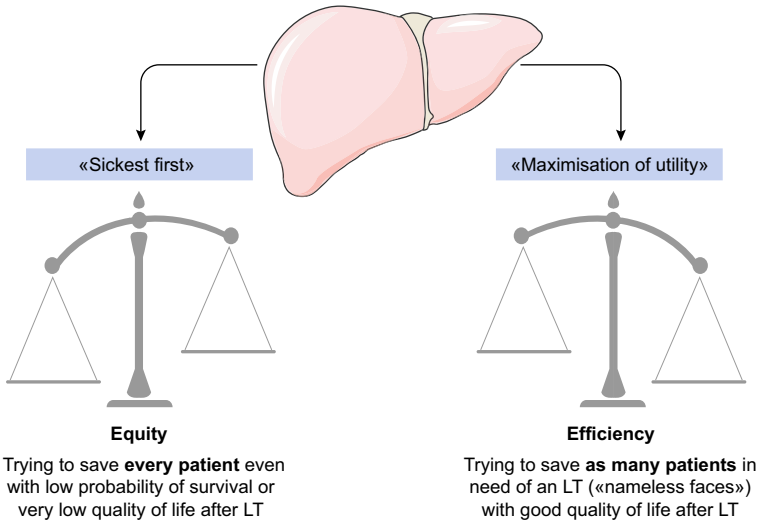


Fig. 1. Central ethical aspects weighing the "delisting dilemma". In an attempt to achieve the "best possible" allocation of liver grafts we face two conflicting scenarios. Aiming to rescue every patient, can mean transplanting the sickest first, which consequently on average leads to lower survival rates and quality of life. Conversely, trying to save as many patients as possible, we have to consider denying LT in some patients in favour of patients who have a higher probabilitiy of survival. LT, liver transplantation.

Therefore, LT in patients irrespective of the severity of liver disease is closely related to rationing.[30] Secondly, rationing of scarce donor organs is always associated with uncertainties. It makes sense to guide our rationing decisions with risk models that predict prognosis.[26,27,31–36] The individual risk of a patient should be discussed transparently with that patient and/or surrogate decision maker, and the decision shared by all involved medical disciplines (Fig. 1).

To better estimate the chance of benefit *vs.* no benefit from LT, many studies suggest risk models that predict the likelihood of inappropriate LT to help transplant physicians to estimate early failure of LT in extreme recipient populations (Table 2). Rana *et al.* defined futile LT as the case where the three-month probability of post-transplant mortality exceeds that of waiting list mortality.[26,27] This approach has the advantage that it does not exclusively focus on potential transplant status, but also balances this against the waitlist status. However, this definition might be challenged by the fact that this high-risk group of patients would die anyway on the waiting list without LT. Others defined futile LT as three-month and/or in-hospital mortality or one-year mortality.[20,28,37] Both definitions primarily focus on the recipient and do not take waitlist characteristics into account.

Allocation – prioritising the sickest first

Before the introduction of the National Organ Transplant Act in 1984, LT prioritisation was based on waiting time, like kidney transplantation.[38] The next step towards a more disease severity oriented allocation policy was the definition of Status 1 for high urgency transplantation, followed by the introduction of Child-Turcotte-Pugh score. Despite these modifications, waiting time remained the leading criterion for liver graft allocation for many years. The drawback of the early allocation policies based on waiting time was that sick patients on the waiting list would not have a realistic chance of surviving long enough to receive a life-saving organ (Fig. 2).

In 2000, a simple score was proposed to predict the three-month mortality in 231 patients with cirrhosis undergoing elective transjugular intrahepatic portosystemic shunts.[39] Serum bilirubin, INR, serum creatinine, and the cause of liver disease were identified as the best predictors of mortality in an ESLD cohort.[39] This score, named MELD, has been validated and demonstrated a good model performance with a *c*-statistic of 0.83.[6] The MELD system was first adopted for adult liver allocation by the United Network of Organ Sharing (UNOS) in 2002,[3,4,6,39,40] followed by many other countries including the Eurotransplant region in 2003. The MELD score is calculated by a logarithmic transformation of bilirubin, INR, and creatinine according to the following formula:

$$\text{MELD score} = 3.78 \times \ln(\text{bilirubin in mg/dl}) + 11.2 \times \ln(\text{INR}) + 9.57 \times \ln(\text{creatinine in mg/dl}) + 6.43.$$

To prevent negative values, the minimum value for all three variables is one; the maximum possible value of creatinine is 4 mg/dl which applies to patients on dialysis.

Although MELD scores greater than 40 can be calculated, the score is capped at 40 for allocation. Patients with ESLD and MELD scores of 40 and higher have the greatest transplant survival benefit but are also the sickest candidates with the highest risk of early mortality (Fig. 4A). Of note, there is documented evidence that patients with laboratory MELD score greater than 40 have a higher mortality on the waiting list than patients with MELD of 40.[4,6,41] Conversely, patients with ESLD without HCC who have MELD scores <15 should not undergo liver transplantation, because the associated mortality after LT exceeds the risk of dying from ESLD.[6,42]

For paediatric patients with ESLD, organ allocation follows the principle of sickest first as well. For paediatric patients aged 11 years or younger, organ allocation is based on a modified version of the MELD score, the paediatric end-stage liver disease (PELD) score.[4,43] The PELD score additionally includes age, serum albumin, and growth failure giving an accurate prediction of mortality in children with ESLD.[4,43] In contrast to the MELD score, PELD does not have upper and lower limits. Organ allocation for children aged >12 years follows the same MELD rules as for adult recipients.

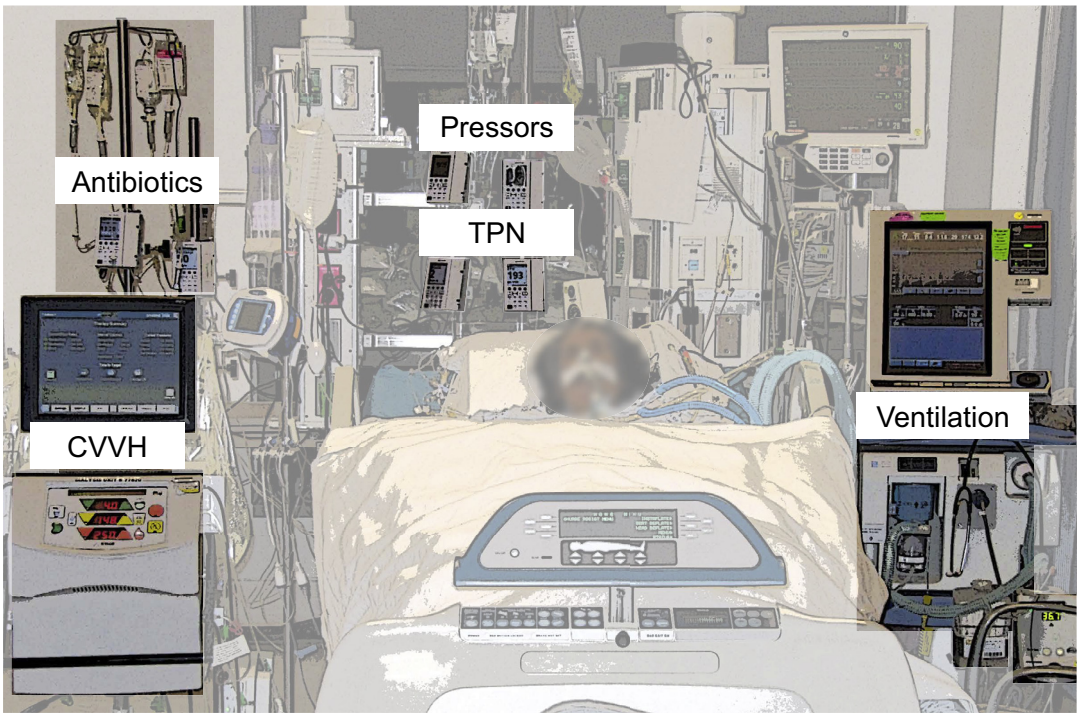


Fig. 2. Common clinical scenario in the ICU of referral centres for ESLD. As many patients on the waiting list for LT are presenting with MELD scores ≥40, life support (CVVH, vasopressors and ventilation) is required frequently. The prognosis for these patients without LT is poor, and often reduced even after LT. The consideration whether to proceed with LT or not seems adequate in such scenarios, to optimally allocate liver grafts. CVVH, continuous veno-venous haemofiltration; ESLD, end-stage liver disease; ICU, intensive care unit; LT, liver transplantation; MELD, model for end-stage liver disease.

MELD-based allocation resulted in a considerable reduction of patients on the waiting list,[6] as well as waiting list mortality.[21] Therefore, MELD-based allocation became widely adopted and is currently the number-one system for liver allocation worldwide. However, prioritising the sickest patients has led to more difficult and demanding LT, especially in transplant centres where more patients have high MELD scores.[20] In a more recent approach to reduce waiting list mortality of critically ill patients with high MELD scores, UNOS implemented the "Regional Share 35 Policy" in 2013 which allocates livers to local and regional waiting list patients with MELD scores of 35 and higher.[44] By regional donor organ sharing, a higher proportion of patients with MELD scores ≥35 undergo LT and the waiting list mortality of this group has been reduced.[45,46] Meanwhile, liver allocation in the United States has adopted the MELDNa score in 2016 as a further approach to reduce waiting list mortality (Table 3).

Nonetheless, high MELD recipients have an elevated risk of early post-transplant mortality. In order to avoid wasting sparse organs which might save other patients, LT needs to be carefully considered, particularly in recipients at the extremes. This represents not only a medical but also an ethical challenge, since the greatest benefit for a single patient must be weighed against the greatest benefit for aggregate liver failure patients.

Recipient factors determine medical acuity

Medical acuity in patients awaiting LT describes the level of global liver-related and liver-unrelated illness. Initially, the term was used in patient classification systems assigning allocation of nursing staff, to justify staffing decisions in health care systems. Often, characteristics of medical acuity are associated with attributes such as severity or intensity.[47] In LT, pre-transplant medical acuity can be divided into two clinical components: acute and chronic conditions. The level of medical acuity is determined by the impact of the severity of each of the two clinical components. Patients listed for LT can present with a wide range of medical acuity from ambulatory patients with low MELD scores to hospitalised patients with high MELD scores requiring life support treatment.

Severity of acute liver failure

The American Association for the Study of Liver Diseases defines acute liver failure (ALF) as rapid onset of liver failure within a period of 26 weeks, an INR ≥1.5, jaundice, and the presence of hepatic encephalopathy.[48] The aetiology of ALF varies

Key point

MELD-based allocation is the most commonly applied allocation system worldwide and captures hepatic and renal organ function.

Key point

Acute and chronic liver failure may result in varying numbers of organ failures which determine the prognosis of liver transplant candidates.

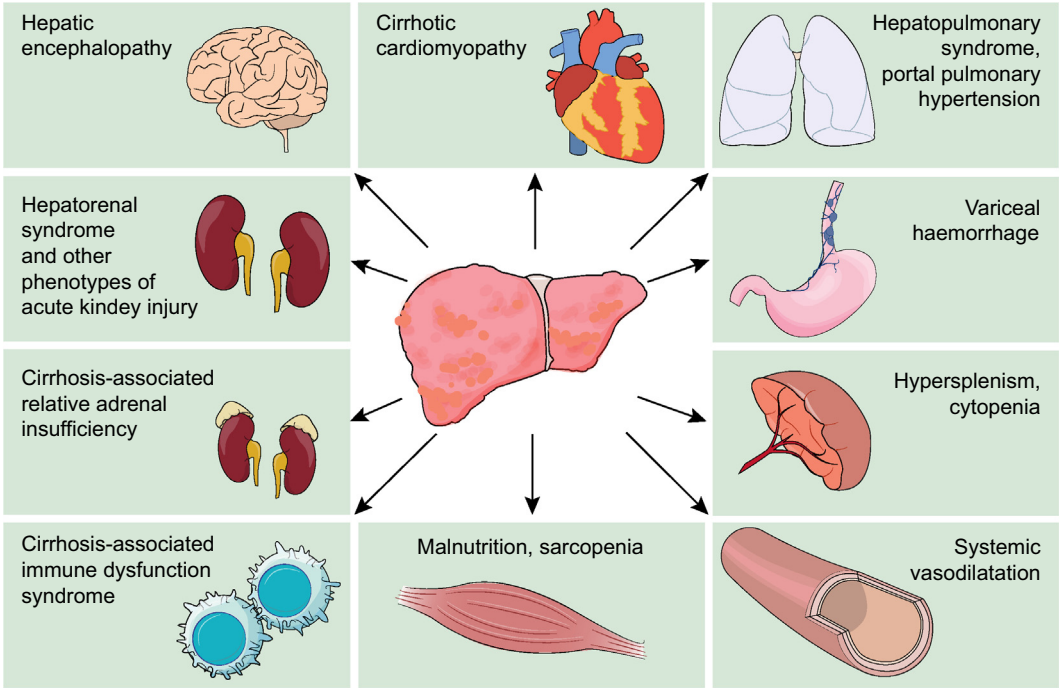


Fig. 3. Liver cirrhosis needs to be considered a systemic disease leading to dysregulation of various organ systems. The presence of one or more organ failure markedly increases the risk of mortality without LT.

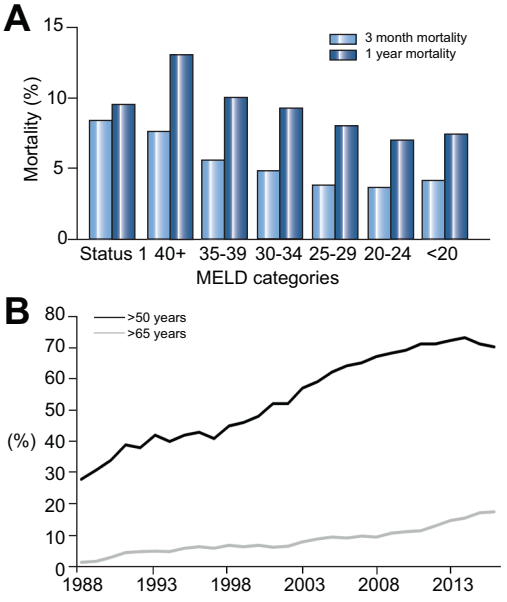


Fig. 4. Three-month and one-year mortality rates of 11,086 adult LT recipients excluding re-LT according to MELD category including Status 1. Status 1 listed patients had the lowest survival rate, followed by the MELD ≥40 category, one-year survival rates, however were much better in Status 1 transplanted patients as opposed to MELD ≥40 patients. (A) The data was kindly provided by the SRTR covering the year 2013–2014. (B) Displays liver transplants in the US by recipient age in the time period between 1988 and 2016 based on OPTN data as of May 27, 2016. There is a clear trend towards an elderly recipient population, in 2016 nearly 20% of recipients were older than 65 years of age. LT, liver transplantation; MELD, model for end-stage liver disease; OPTN, Organ Procurement and Transplantation Network; SRTR, Scientific Registry of Transplant Recipients.

considerably around the world, with hepatotoxic drugs (acetaminophen), hepatitis A and E the leading causes in developed countries[49] and hepatitis B the leading cause in South American and Asian countries.[50,51] The proportion of ALF among all liver failure is around 7% in Europe[52] and 8% in the United States.[53]

ALF has a worse prognosis than chronic liver failure before and, interestingly, also after LT[49,54,55]. The short-time window of opportunity for LT is a particular challenge in ALF (Fig. 5). As multiorgan failure usually develops rapidly, the decision to list a patient as "status 1" in the US or "high or super urgent" in Europe needs to be taken in a timely manner after admission, to avoid poor outcomes. While the King's College Hospital[56] and the Clichy criteria[57] are scores that predict the clinical course of ALF before LT, Barshes *et al.* proposed a prediction model for post-LT outcome based on a large UNOS cohort of 1,457 patients. Four predictors of adverse outcome were identified, including body mass index ≥30 kg/m^2, serum creatinine >2.0 mg/dl, recipient age >50 years, and requirement for life support.[58] In this model, each risk factor increases the relative risk of post-LT mortality by approximately 150%.[58] An analysis from the European Transplant Registry (ELTR)[55] identified that male recipient gender, recipient age >50 years, incompatible ABO transplantation, donor age >60 years, and reduced size graft were risk factors for death or graft loss in ALF.[55] Similarly, a single centre study from the King's College Hospital identified recipient age >45 years, vasopressor support, and the

use of high-risk grafts as predictors of adverse outcome.[59]

The acute onset and severe course of hepatic encephalopathy and brain oedema represents a serious event of ALF, potentially leading to irreversible brain injury or even brain death as a result of brain herniation.[60] The exact mechanism of this fatal complication has not yet been fully understood and therapeutic possibilities are limited. Irreversible brain injury in patients with ALF represents a situation where LT can be considered as inappropriate, even in the setting of a fully functioning liver graft.

Systemic clinical features of chronic liver failure

Chronic liver failure (CLF) or ESLD needs to be assessed as a systemic disease involving various organ systems (Fig. 3), and not just as a liver disease in isolation. In many CLF-associated organ failures, the main pathophysiologic driver is portal hypertension and the associated pathophysiologic changes resulting from dysfunctional interplay between different organ systems.[61] Furthermore, CLF can cause other acute and chronic systemic conditions, including cirrhosis-induced immune dysfunction (CAIDS) predisposing patients to bacterial and fungal infections,[62] kidney failure due to hepatorenal syndrome,[63] circulatory failure including cirrhotic cardiomyopathy with increased cardiac output and systemic vasodilation,[64,65] pulmonary complications including hepatopulmonary syndrome, portopulmonary hypertension, and volume overload with pulmonary oedema and/or pulmonary hypertension,[66] mental status changes with hepatic encephalopathy, endocrine dysfunction in cirrhosis-associated relative adrenal insufficieny[67,68] and malnutrition with sacropenia[69] (Fig. 3).

Candidates experiencing uncontrolled infection or septic shock are at high risk of early post-transplant mortality and need to be on hold on the waiting list or delisted until the infection is cleared.[70] However, it is generally accepted that uncontrolled sepsis due to diffuse infected biliary disease is not an absolute contraindication for LT; hepatectomy might be the only option to resolve the septic focus. Pathophysiological components of sepsis or septic shock might also be present in patients with CLF, without underlying infection. This systemic hyperdynamic vasodilated syndrome, often called "hepsis", is not always easy to differentiate from infection and is not a contraindication for LT.

The MELD allocation does address patients with CLF according to their liver and kidney disease severity as represented by INR, bilirubin and creatinine. However, other organ systems affected (Fig. 3) are not considered. In addition, severity of acute deterioration of CLF triggered by external or internal events, *e.g.* trauma or sepsis cannot be predicted by the MELD score (see acute-on-chronic liver failure).

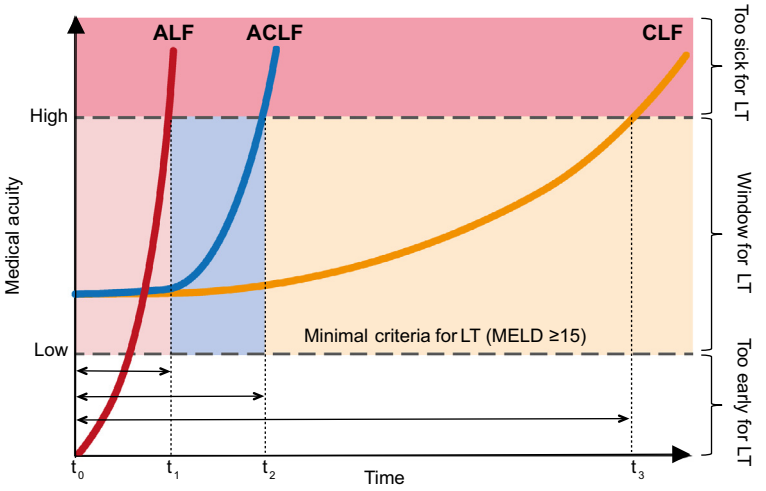


Fig. 5. Principle courses of three types of liver failure (ALF, ACLF, and CLF) plotted as function of medical acuity over time. Patients with MELD scores <15 are widely accepted not to qualify for LT, as the operative risk exceeds their predicted mortality on the waiting list. Conversely, patients with a high medical acuity might already be too sick to benefit from LT. The major course-determining factor in this setting is time. The rapid onset of sequential organ failure as it occurs in ALF and ACLF leads to a short window of opportunity for LT (t_0-t_1 and t_0-t_2). ACLF, acute-on-chronic liver failure; ALF, acute liver failure; CLF, chronic liver failure; LT, liver transplantation; MELD, model for end-stage liver disease.

Pulmonary complications of CLF – hepatopulmonary syndrome and portopulmonary hypertension

The presence of pulmonary complications of CLF including hepatopulmonary syndrome and portal pulmonary hypertension can particularly affect mortality.[71] The European Respiratory Society (ERS) diagnostic criteria for hepatopulmonary syndrome (HPS) includes the triad of liver disease, increased alveolar-arterial oxygen gradient (room air PaO_2 <70 mmHg or A-a PO_2 gradient ≥20 mmHg supine) and intrapulmonary vascular dilatations (IPVD), as demonstrated by positive contrast echocardiography.[72] The prevalence is 15–30% in various studies depending on the population and criteria used for the diagnosis.[73] Most patients are asymptomatic and the severity of hypoxaemia does not correlate with the severity of liver disease, as measured by the CPT or MELD score.[74,75] Multiple studies suggest that patients with HPS have a higher mortality rate awaiting LT than non-HPS transplant candidates. Pre-transplant mortality correlates with the severity of hypoxaemia.[76,77] LT is the only known therapy for HPS. Although no intraoperative deaths have been directly attributed to HPS, oxygenation may worsen post-LT because of volume overload and postoperative infections. Post-transplant mechanical ventilation is often prolonged in patients with severe preoperative hypoxaemia and these patients often require extended critical care.[78] Since 2002, patients with HPS and PaO_2 <60 mmHg received MELD exception points in an attempt to improve survival. In a study of 106 patients with HPS, those receiving MELD exception points had favourable post-transplant survival compared to patients treated before the era

of MELD exception points. However, post-transplant survival did not differ based upon pre-transplant PaO_2 values.[79] Post-transplantation oxygenation improves in most patients with HPS, within a year.[80] However, the small percentage of patients with type 2 IPVD (macroscopic and discrete) who do not respond to LT might be candidates for coil embolization.[81] The results of medical treatments for HPS that target vasodilation and angiogenesis have been disappointing. Therefore, HPS – regardless of the severity of hypoxaemia – does not represent a condition where LT should be considered inappropriate. LT is the definitive treatment and should be offered as soon as possible after the diagnosis of HPS. In recognition of this, MELD exception points are awarded in many countries, which prioritise HPS patients for transplantation.

Key point

Screening for pulmonary complications should be independent of the MELD score and ongoing while the patient is on the waitlist.

Diagnostic criteria for portopulmonary hypertension (POPH) are well defined and are based on right heart catheterisation (RHC). In the absence of other causes of pulmonary hypertension the following criteria need to be fulfilled: portal hypertension, mean pulmonary arterial pressure (mPAP) >25 mmHg, pulmonary vascular resistance >240 dynes/s per cm^{-5}, and pulmonary artery wedge pressure <15 mmHg.[82] The ERS task force also grades the severity of POPH into mild (mPAP ≤25–<35), moderate (mPAP ≤35–<45), and severe (mPAP ≥45), in the presence of elevated pulmonary vascular resistance.[83] However, transthoracic Doppler echocardiography, is used as a screening tool not only in symptomatic patients but increasingly in all patients that are evaluated for LT. Several different estimated pulmonary systolic arterial pressure cut offs (mostly between 30–40 mmHg) have been used to proceed to RHC. Similarly, as with HPS, the severity of liver disease or portal hypertension is not predictive for POPH. Portopulmonary hypertension constitutes approximately 5–10% of all diagnosed cases of pulmonary hypertension.[84] MELD exception points have been allowed for select patients with at least moderate POPH, who have been responsive to medical therapy.[85] However, a considerable number of patients that are incorrectly diagnosed with POPH receive MELD exception points.[86] Determination of the transpulmonary gradient can help distinguish pulmonary venous hypertension from POPH.[82] Untreated POPH is poorly tolerated and leads to poor survival, which is generally less than 50% at one year.[87] Perioperative mortality is also well described and POPH resolution remains unpredictable even after LT, which is somewhat in contrast to HPS. However, recent advances in medical treatment have allowed successful bridging to LT. In particular, endothelin receptor antagonists, phosphodiesterase inhibitors type 5, and prostacyclin analogues have been successfully used, albeit evidence is largely limited to single centre studies or small case series. Calcium channel blockers should not be used for POPH.[88] Importantly, medical therapy should be continued during the perioperative phase and postoperatively weaned only when serial transthoracic Doppler echocardiography demonstrates maintained or improved cardiac function.

There is a lack of data from definitive prospective trials on medical treatment efficacy and long-term outcomes in patients with POPH undergoing LT. A recent single centre study reported favourable one-year outcomes in their patients with POPH who maintained cardiac function.[89] Emphasis should be placed on accurate screening and detection of POPH in patients evaluated for LT, initiation of medical therapy as a bridge to LT in patients with at least moderate disease, and appropriate counselling of patients with moderate or more severe disease. These patients remain at elevated risk of perioperative mortality.

Acute-on-chronic liver failure

A distinct dynamic category of liver failure which does not follow the prognostic modelling of acute or chronic liver failure is commonly referred to as acute-on-chronic liver failure" (ACLF).[90] Since the first description of this syndrome in 1995,[91] a variety of definitions have been proposed.[92–94] Today, ACLF is defined by the occurrence of extrahepatic organ failure in a patient with cirrhosis.[90] Regardless of the exact cause, the common feature of ACLF is the high risk of mortality,[95–97] frequently leading to the dilemma of whether to proceed with LT or not.

In an attempt to reach a consensus definition, the Chronic Liver Failure Consortium (CLIF-C) of the European Association for the Study of the Liver Disease prompted a prospective multicentre trial investigating patients admitted for decompensated cirrhosis (DC). The so called "CLIF acute-on-chronic liver failure in cirrhosis (CANONIC)" study enrolled 1,343 patients hospitalised for acute decompensation from 29 liver centres. The study proposed diagnostic criteria for ACLF based on the presence of organ failure, age, precipitating events, and systemic inflammation.[90] Organ failure in this setting was initially defined by an adapted sequential organ failure assessment (SOFA)[98] score (CLIF-SOFA) and subsequently simplified to the CLIF organ failure consortium score (CLIF-C OF score).[99] This score, which considers six organ systems (liver, kidney, brain, coagulation, circulation, respiration), has a significantly better prognostic ability than the MELD score in this setting.[99]

According to the findings of the CANONIC study, ACLF was graded in four categories: DC alone in the absence of ACLF and three grades of ACLF. DC depicts no renal failure or a single non-renal failure in the absence of hepatic encephalopathy, grade 1 represents a single renal failure and/or hepatic encephalopathy, grade 2 represents two organ failures and grade 3 represents three or more organ failures. ACLF grade 1,

2, and 3 were associated with a 28-day and 90-day mortality rate of 22%, 32%, and 79% and 41%, 52%, and 79% without LT, respectively.[90]

ACLF can be triggered by hepatic or extrahepatic stimuli.[100] Hepatic stimuli include viral exacerbation of hepatic disease, hepatotoxic drugs, alcohol, flare up of autoimmune hepatitis or Wilson's disease. Meanwhile infection (sepsis), gastrointestinal bleeding, and surgery are the main extrahepatic stimuli for acute decompensation. Both hepatic and extrahepatic ACLF had a similar 28-day transplant-free mortality rate of 48 *vs.* 51%, whereas the 90-day and one-year mortality rates were significantly better for hepatic ACLF (90-day: 59% *vs.* 68%; one-year: 64% *vs.* 75%).[100]

LT for ACLF represents a challenge since these patients are deteriorating very fast, as shown by the poor short-term transplant-free survival (Fig. 5). Therefore, it is essential to transplant these patients in the window of opportunity. Gustot *et al.* suggested that the clinical course between day 3 and 7 after ACLF diagnosis is crucial to further direct clinical management, including LT.[101] The authors propose that patients with four or more organ failures, or ACLF grade 3, within this timeframe are very likely to have futile outcomes.[101] Unfortunately, this can be the case in up to 75% of cases, making LT only amenable in one-quarter of patients presenting with ACLF because of the prevalence of multiorgan failure.[102] Conversely, Artru *et al.* recently reported a multicentre study in 73 patients with ACLF-3 undergoing LT in specialised liver units in France.[103] One-year survival for patients with LT and non-transplanted controls was 84% *vs.* 7.9%.[103] Interestingly, matched controls with no ACLF, ACLF-1 and ACLF-2 showed one-year survival rates of 90%, 82%, and 86%, suggesting only marginally inferior survival of patients with ACLF-3.[103] In an attempt to include ACLF in the prediction of 90-day mortality after LT, Levesque *et al.*[104] recently proposed a risk score which includes independent predictors such as presence of ACLF, infection shortly before LT, recipient age >57 years, male recipient gender, and female donor gender. Overall 90-day mortality was 11%, the predominant cause of death was multiorgan failure because of infection. Patients with ACLF grade 1 or 2, ACLF grade 3, and non-ACLF patients had 90-day mortality rates of 16%, 40%, and 8%, respectively.[104] Optimal organ support in the ICU, including mechanical ventilation, renal replacement therapy, and vasopressor support offers life-saving bridging therapy, enabling LT in many critically ill patients. One-year survival in patients with ACLF after LT is between 73%[105] and 96%,[106] not specifying the grade of ACLF. However, this data suggests an acceptable mortality rate after the critical period immediately after LT. Despite this acceptable prognosis, the rapid onset of multiorgan dysfunction in ACLF is not given additional priority in the MELD allocation system and therefore patients with high-grade ACLF need to be carefully evaluated in the decision process for forgoing LT.

Impact of age and prevalent comorbidities

To more accurately predict post-LT survival, it seems worthwhile to also consider prevalent comorbidities which are not evaluated in the MELD system. Comorbidities may significantly aggravate the medical acuity of critically ill transplant recipients. Comorbidities are considered for any medical intervention and are a mandatory element in the assessment of the health status of liver transplant candidates.

Key point

Allocation of donor livers to rapidly deteriorating patients with ACLF is not well presented by the MELD system. Objective criteria of listing and de-listing are lacking for this group of patients.

Of note, the continuous trend of increasing age of LT recipients (Fig. 4b) is parallelled by a rise in pre-existing comorbidities, with negative effects on LT outcome. LT in elderly recipients, often over the age of 70, is now becoming clinical routine,[107] often because these recipients have spent years on the waiting list.[108] LT above an age of 65 has repeatedly been reported to have inferior outcomes than LT performed in younger recipients.[109–112] Aside from comorbidities, age is certainly an important prognostic factor which has to be considered in the decision process of whether to transplant, particularly in the presence of other adverse factors.

Cardiovascular disease (CVD) was shown to significantly impact on short-[113,114] and long-term mortality[114–116] after LT.[117] Pre-existing CVD turns out to be the leading cause of early mortality (30 days post LT) followed by infection, graft failure, haemorrhage and renal failure in an Organ Procurement and Transplantation Network analysis of 54,697 LT.[113] But pre-existing CVD *per se* is also an important risk factor for developing new CVD events after LT.[118] The importance of CVD has been demonstrated by another study showing that elevated serum troponin levels were highly predictive of post-LT mortality.[119] In a recently published cohort of recipients with MELD scores of 40 and higher at the time of LT, significant cardiac disease was the second strongest predictor of 90-day or in-hospital mortality.[20] The importance of cardiac comorbidities needs to be highlighted since various medical conditions which present in high acuity patients, such as volume overload, cirrhotic cardiomyopathy, *etc.* can further increase the chance of short-term mortality.

Being either under- or overweight (BMI <18.5 and ≥40) has been identified to increase the risk of death after LT.[120,121] In an UNOS analysis of 73,538 patients, patients with a BMI <18.5 had more bleeding complications and cerebrovascular accidents, whereas obese patients with a BMI ≥40 had a higher risk of infectious complications.[121]

Key point

Advanced age, severe comorbidities, and physical frailty represent significant prognosis-determining factors, which are not captured by the MELD allocation system, but must be considered when LT is an option.

In an attempt to integrate various comorbidities, the Charlson Comorbidity Index (CCI)[122] has been applied to the LT population.[20,123] The CCI proved to have a good prognostic performance when applied to patients undergoing LT.[123] Volk *et al.* identified CVD, diabetes, chronic obstructive

pulmonary disease, connective tissue disease and renal failure as independent predictors of post-LT survival.[123] Furthermore, a high age-adjusted CCI, which considers age and aggravation of comorbidities, was a risk factor of futile LT in recipients with MELD scores greater than 40.[20] The combination of comorbidities may have a particularly deleterious effect on outcome after LT; however, this "combined effect" has not yet been sufficiently investigated.

Key point

In ACLF, the number of organ failures rather than MELD score alone determines the prognosis of LT candidates.

Physical frailty and failure to rescue

An increasingly used term in the assessment of the performance status in ESLD is "physical frailty".[124] The term originates from geriatric medicine describing a biological syndrome with the common outcome of increased vulnerability.[125] In contrast, comorbidity is an aetiological risk factor leading to frailty. This concept has also been adopted for LT candidates[126] and several tests have been proposed[124] including the Fried frailty index,[126] the short physical performance battery,[126] the six minute walk test,[127] the activity of daily living[128] and the frailty index[129] to objectively assess physical frailty of patients on the waiting list for LT. To our knowledge these functional tests have not yet been shown to be predictive of worse performance post LT, although there is evidence that patients with sarcopenia, which is probably a good morphological correlate of frailty, do perform worse after major surgery.[130] The failure to recover after a complication is often referred to as failure to rescue[130] and has been shown to significantly increase the risk of mortality in LT recipients.[131]

The frailty concept can be used as an additional tool to guide futility decision making, particularly in ACLF. Frail patients who experience an insult like sepsis, leading to hepatic decompensation or even higher grade ACLF, do not have the reserve to recover in the way non-frail patients do, reflecting a much higher risk and faster progress to multiorgan failure.

Donor organ quality and recipient medical acuity

The choice of the appropriate liver graft, particularly for critically ill candidates is a major challenge in LT.[132] Organ shortage has led to an increase of patients with advanced ESLD at the time of LT in many transplant centres. To overcome this shortage, transplant centres utilise more extended criteria donor organs (ECD). ECD are grafts with impaired quality because of the presence of macrosteatosis >30%,[33,133,134] cold ischaemia time >12 h,[135] donor warm ischaemia time >30 min, donation after cardiac death (DCD),[136,137] and grafts >70 years of age.[138] A number of risk scores and models essentially matching high-risk liver grafts (ECD) with low-risk recipients and vice versa have been proposed. Among them are the DRI,[31] ET-DRI,[32] SOFT,[26,27] BAR,[139] D-MELD,[34] Delta MELD[35] and the Net benefit model[36] (Table 4).

For critically ill recipients, the applicability of most scores might be limited since all of them are validated in large patient populations with only marginal numbers of critically ill recipients with, for example, fulminant ALF with (multi-) organ failure, ACLF I-III, or MELD ≥40 with sarcopenia and/or major comorbidities. As the risk profile of these patients is not included in most prediction models, the decision around when to proceed with LT is challenging. It seems important to avoid the allocation of an ECD graft to a high-risk recipient because of the imminent risk of short-term mortality. The UCLA experience of high acuity candidates[20] showed that such patient populations benefit from high quality grafts. While donor factors are not accounted for in the proposed futility prediction score,[20] it is widely accepted practice that ECD organs should be avoided in critically ill patients with high MELD scores because of the high risk of poor outcomes.

When is sick too sick for transplant

"Too sick for transplant" describes a critically ill recipient who has a high risk of three-month mortality after LT, even when receiving the best-quality donor organ. In contrast to non-transplant treatments, utility and opportunity costs have more weight in transplantation since medical decisions must focus not only on individual candidates but also on the pool of other potential transplant candidates who might not receive a life-saving graft. In LT, organ allocation follows the policy of prioritising the sickest candidates first, which results in an increase of critically ill candidates on the waiting list in many metropolitan areas. The judgment of a patient as too sick for LT needs to consider if early mortality after liver transplantation is highly likely. Therefore, three-month or in-hospital post-transplant mortality might serve as the best outcome measures for potentially inappropriate LT.[20,37] This short-term measure has the advantage over long-term survival metrics (*e.g.* five-year survival) because it does not take general life expectancy into account.

Deciding how much risk is too much and when LT should be denied remains the challenge in daily clinical practice. A definition of these upper limits would be an essential step towards an objectifiable decision process. A survey among 35 transplant centres in the U.S. attempted to identify current practice in such high risk situations.[140] The authors created various clinical scenarios of patients with high MELD scores and asked transplant surgeons and hepatologists whether candidates should proceed with transplantation or should be removed from the transplant list because of futile conditions. The vast majority of clinicians would proceed with LT in candidates with high MELD scores, who require dialysis and

Table 5. Proposed absolute and relative pre-transplant conditions when potentially inappropriate LT has to be considered.

Absolute	Relative
Multiorgan failure with 4 or more organ systems failing (liver, kidney, lungs, circulation, brain)	Increased ventilation support (FiO_2 ≥0.5)
Brain oedema plus herniation or absence of cerebral circulation	Intestinal ischaemia
Circulatory failure requiring 2 vasopressors both with limited responsiveness to further dose escalation	Severe frailty secondary to muscle waisting and malnutrition
Pulmonary hypertension with: - mPAP >50 mmHg, - mPAP 35–50 mmHg with elevated PVR - >250 dyn/s/cm^5, or - high PVR >400 dyn/s/cm^5	Aggregated severe chronic comorbidities
Severe respiratory failure requiring maximal ventilation support (FiO_2 ≥0.8, high PEEP) or on ECMO	
Ongoing infections with following features: septic bacteraemia/fungaemia, septic shock, active spontaneous bacterial/fungal peritonitis, tissue invasive fungal infection	
Ongoing severe/necrotising pancreatitis	
Aggregation of several relative conditions	

mPAP, mean pulmonary artery pressure; PVR, pulmonary vascular resistance; LT, liver transplantation; ECMO, extracorporeal membrane oxygenation; FiO_2, fraction of inspired oxygen; PEEP, positive end expiratory pressure.

mechanical ventilation, but would not proceed when high vasopressor dose is required to maintain a sufficient MAP, a high FiO_2 of 70% for ventilation is needed, or sputum cultures reveal gram negative rods (unhappy triad). In addition, frailty characterised by non-ambulatory or wheelchair-bound condition was a criterion for 56% of transplant clinicians to delist patients.

As demonstrated by the survey, the majority of transplant clinicians would proceed with LT in candidates with high MELD scores, in the presence of dual organ failure (liver, kidney) but they would be reticent when additional organ failures (circulatory, respiratory, or cerebral failure) occur.[140] There is growing evidence that the number of organ failures determines delisting of patients and early mortality after LT[104,141] rather than high MELD score alone, which captures hepatic and renal organ function only.[3,4] The risk of short-term mortality is extraordinarily high when multi-organ failure occurs in an ACLF setting.[104] Therefore, patients with four or more organ failures in an ACLF setting are not candidates for LT. Also, upper limits of circulatory (two vasopressors with limited responsiveness to further dose escalation) and respiratory (maximal ventilation support: FiO_2 ≥0.7, high PEEP) failure demonstrate criteria where LT needs to be withheld (Table 5).

Pulmonary hypertension in the setting of confirmed portal hypertension is associated with a high intraoperative and early postoperative mortality risk. Whether of primary or secondary aetiology, pulmonary hypertension results in right ventricular enlargement with potential right heart failure, usually occurring within the first few post-operative days. A previous study showed that a mean PAP >50 mmHg resulted in a mortality rate of 100%, which makes LT futile under this condition.[75] Patients with a mean PAP of 35–50 mmHg and high pulmonary vascular resistance (>250 dyn/s/cm^5) had a 50% mortality rate, while those with <250 dyn/s/cm^5 had no mortality. Therefore, many transplant centres use these criteria of pulmonary haemodynamics to avoid futile and potentially inappropriate LT (Table 5), although these guidelines are not based on solid data. Of note, patients may be reconsidered for LT after successful treatment of pulmonary hypertension.

The clinical impact of infections on outcome of patients on the waiting list or after LT is well documented.[20,104,141–143] Ongoing septic bacteraemia and fungaemia, as well as active spontaneous bacterial[143] or fungal[142,143] peritonitis, in critically ill patients with ESLD are conditions associated with high mortality in this population and are widely accepted criteria for delisting or denying LT.[70] However, relisting or proceeding with LT might be reconsidered after complete resolution of infection, often demonstrated by repeat negative microbiological cultures.[70] Especially for spontaneous bacterial peritonitis, it has been shown that previous infectious episodes had no impact on post-transplant survival when the infection was completely resolved at the time of LT.[144] However, tissue-invasive fungal infections remain an absolute contraindication for LT[145] and are often resistant to treatment.

The negative impact of other chronic comorbidities[114] including cardiac risk[113–117] as well as pre-transplant malnutrition[121] and frailty[146] on post-transplant outcome has repeatedly been reported in the literature. In particular, when these conditions are present in patients with advanced age, selection of LT candidates needs to be carefully considered in a multidisciplinary transplant team setting. Although these conditions demonstrate no absolute barriers to transplantation, the presence of two conditions such as chronic comorbidities and frailty might become the critical threshold of denying LT in candidates with high MELD scores, with additional extrahepatic/extrarenal organ failure.

High medical acuity in critically ill patients with CLF/ESLD is not only a selection criteria to

Key point

Considering high-acuity patients as too sick for LT has serious consequences. Future directions should include the definition of solid criteria when high-acuity patients need to be on hold or de-listed for LT.

avoid inappropriate LT, but also needs to be considered in patients with high MELD scores undergoing simultaneous liver and kidney transplantation to avoid futile loss of scarce donor kidneys.[147] In a large cohort study of 145 patients undergoing simultaneous liver and kidney transplantation, 20% of renal grafts were lost early after LT either as a result of early post-transplant death or primary nonfunction.[147,148] The authors of this study identified predictors of renal allograft futility (RAF) which was defined as patient death or need for renal replacement therapy at three months post LT. Among various predictors, MELD score, retransplantation, and renal variables were associated with RAF in simultaneous liver and kidney transplantation. Although simultaneous allocation of kidneys to patients with irreversibly failing liver and kidney function serves the principle of the maximum benefit of post-transplant life expectancy, the study suggests that renal transplantation should be deferred in liver transplant recipients with a high risk for RAF. It is important to note that early patient death after simultaneous liver and kidney transplantation affects not only a potential liver recipient who did not recieve the life-saving organ, but also applies to the loss of a scarce donor kidney for a potential kidney recipient. Therefore, simultaneous liver and kidney transplantation in critical ill patients should not only focus on medical acuity of the patient, but consider the ethical implication for other potential recipients on the liver and kidney waiting list.

The aim of the proposed concept is to highlight the need for shared decision making that not only considers factors identifying the upper limits of futile LT, but also of inappropriate LT. Because clear criteria to deny LT are currently missing, decisions have to be carried out on an individual basis taking the proposed factors into account. Nevertheless, this proposal should be regarded as a first step towards more generally applicable guidance for clinicians to decide when LT is potentially inappropriate. Implementation of delisting criteria in allocation systems for candidates that are too sick for LT would make the decision much more objectifiable, would take the pressure off the treating physicians, and would make thorough evaluation of the results possible.

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Conflict of interest

The authors declare no conflicts of interest that pertain to this work.

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Supplementary data

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