Review

JOURNAL OF HEPATOLOGY

Limitations of current liver donor allocation systems and the impact of newer indications for liver transplantation

Patrizia Burra[1,*,a], Didier Samuel[2,a], Vinay Sundaram[3,a], Christophe Duvoux[4,a], Henrik Petrowsky[5,a], Norah Terrault[6,a], Rajiv Jalan[7,a]

Keywords: Liver transplantation; Acute-on-chronic liver failure; Non-alcoholic steatohepatitis; Alcohol-associated acute hepatitis; Allocation models; Futility; Waiting list.

Received 22 October 2020; received in revised form 4 January 2021; accepted 5 January 2021

Summary

Liver transplantation represents a life-saving treatment for patients with decompensated cirrhosis, a severe condition associated with a high risk of waiting list mortality. When decompensation occurs rapidly in the presence of extrahepatic organ failures, the condition is called acute-on-chronic liver failure, which is associated with an even higher risk of death, though liver transplantation can also markedly improve survival in affected patients. However, there are still gaps in our understanding of how to optimise prioritisation and organ allocation, as well as survival among patients with acute-on-chronic liver failure (both before and after transplant). Moreover, it is urgent to address inequalities in access to liver transplantation in patients with severe alcoholic hepatitis and non-alcoholic steatohepatitis. Several controversies still exist regarding gender and regional disparities, as well as the use of suboptimal donor grafts. In this review, we aim to provide a critical perspective on the role of liver transplantation in patients with decompensated cirrhosis and address areas of ongoing uncertainty.

Introduction

Although there have been continued improvements in survival since the first liver transplant 50 years ago, there remain areas of uncertainty related to priority on the waiting list, liver disease severity score(s), and the management of severe decompensation of cirrhosis while waiting for a suitable graft. Whether transplantation is always viable (concept of futility) and whether donors with non-optimal characteristics can always (or should) be used independently of (or depending on) the clinical condition of the recipient are both topics of continued discussion. Lastly, faced with a constantly evolving plethora of indications for transplantation, the question – and common thread of this article – is how do we standardise access at the European and international level?

Key point

There is an urgent need to modify the MELD-based models to reduce waiting list mortality in patients with severe decompensation of cirrhosis and acute-on-chronic liver failure.

[1]*Multivisceral Transplant Unit, Department of Surgery, Oncology and Gastroenterology, Padua University Hospital, Padua, Italy;* [2]*Centre Hépato-Biliaire, Paris-Saclay University, Inserm research unit 1193, Hôpital Paul Brousse, Villejuif, France;*

Prognostic models

Prognostic models for allocation and new scoring systems

Liver transplantation (LT) represents a potentially life-saving treatment for patients with decompensated cirrhosis (DC). DC is a severe condition and is associated with a 15% risk of dying while on the waiting list (WL). When decompensation occurs rapidly in the presence of extrahepatic organ failure(s), a condition termed acute-on-chronic liver failure (ACLF), the risk of death on the WL is even higher.[1] In these rapidly deteriorating scenarios, timely LT needs to be considered. However, there is an ongoing debate about which allocation model serves the best interest of patients with DC.

Allocation models for predicting WL mortality or drop out need to be based on unbiased criteria including objectiveness, simplicity, repeated reproducibility, and short- (3 months) and mid-term (1 year) risk of death. Under this consideration, the Child-Pugh score is compromised due to the subjective interpretation of ascites and encephalopathy.[2] The first allocation model to overcome the limitation of non-objectivity was the model for end-stage liver disease (MELD) system.[2] Initially, MELD was developed to predict mortality after placement of a transjugular intrahepatic portosystemic shunt.[3] First introduced in 2002 in the USA and subsequently in most other countries, the majority of LT programmes practice MELD-based allocation which prioritises the sickest patients on the WL. Despite the advantages of the MELD score as a more objective decision tool, the initially reported discriminatory model performance (c-statistic of 0.78–0.87[4]) has recently been revised down in European patients with DC (c-statistics 0.65–0.68)[5,6] (Table 1). The declining accuracy of the MELD score was also reported in patients with DC listed for LT. In a recent study based on UNOS data,[7] the c-index of MELD was 0.7 in patients listed between 2014 and 2016. This observation probably reflects major epidemiological changes on the WL over the last decade, with more DC patients listed with very advanced liver

disease, and an increasing proportion of patients listed for HCC, fiercely competing with DC for organ allocation. Furthermore, 2 groups of listed patients with DC might have additional disadvantages under an MELD-based allocation policy. Decompensated patients with MELD scores <15 have almost no chance of access to LT, while patients with intermediate scores of 25–30 have a higher risk of WL mortality (20–25%). Therefore, there is an urgent need to modify the MELD-based models to improve prediction of WL mortality. Although the MELD score reflects dual organ function of liver and kidney, other important conditions and/or organ functions impacting the medical acuity of decompensated patients are not captured by the score.[8] Some biomarkers reflecting inflammation (ferritin, C-reactive protein, white blood cell count), cardiac (copeptin, pro-brain natriuretic peptide) or renal dysfunction (neutrophil gelatinase-associated lipocalin, cystatin C), and portal hypertension (sCD 163, von Willebrand factor) have recently been identified as adding some independent predictive value to MELD (Table 1). Another important consideration relates to malnutrition and sarcopenia. Sarcopenia, which is a loss of muscle mass, is the main clinical result of malnutrition. A recent study of 630 patients awaiting LT demonstrated that insufficient protein intake was associated with an increased risk of mortality while on the WL.[9] Another recently published study found that sarcopenia was associated with WL mortality, especially in low-MELD patients (MELD score ≤15).[10] These findings highlight the need to include nutritional assessment data in allocation models.

Attempts have been made to combine such predictors with MELD to improve prediction. Examples are the MELD-sodium (MELD-Na) score,[11] the combination of MELD-Na and frailty index[12] or MELD and sarcopenia score,[10,13] which, notably, seems to outperform MELD in patients with MELD <15.[13] Supporting this approach, the USA adopted the MELD-Na score in 2016 as a further tool to reduce WL mortality. Also, in acute DC, the CANONIC-driven, Chronic Liver Failure Consortium (CLIF-C) AD model, combining white blood cell count, as a marker of systemic inflammation, with age and some MELD-Na components (INR, serum sodium and creatinine) has recently proven more accurate than MELD for prediction of 3-month mortality in patients with DC.[5]

In patients who fall into the dynamic category of ACLF with rapid decompensation and associated organ failures new models based on extrahepatic organ failures associated with liver disease appear to perform better for prognostic prediction. The pioneering CLIF-C-driven CANONIC study[14] proposed diagnostic ACLF criteria that included the presence of organ failures. In this study, patients with ACLF had a 3-month mortality rate of 51%. In a subsequent follow-up study, a 6-organ failure assessment of liver, kidney, brain, coagulation, circulation, and respiration (CLIF-C organ failure score) performed significantly better for prognostic prediction than the MELD score in patients with ACLF[5] (Table 1).

We anticipate that a future super allocation score should capture important recipient factors such as organ failures or dysfunctions (Table 1), global nutrition (sarcopenia) and physical performance (frailty), as well as chronic conditions (comorbidities) and should be directed towards a more personalised allocation approach. Further refinement of allocation models needs to take both donor and recipient factors into account in order to optimise organ allocation by serving both principles of equity (sickest first) and efficiency (maximisation of utility). Although such models have been developed,[15–18] the vast majority of the current allocation models do not include donor factors. The transplant benefit[15] may also be considered to prevent futile use of organs. A very specific model integrating transplant benefit, with expected survival on the WL weighed against mortality post-LT, has recently been adopted in the UK. This model, called the Transplant Benefit Model, deserves careful evaluation but may pave the way for other innovative allocation approaches.

Outcome of liver transplantation in patients with ACLF

LT can markedly improve survival in patients with ACLF, with 1-year post-transplant survival exceeding 80%.[1,19,20] However, there remain gaps in our understanding of how to optimise survival

[3]*Karsh Division of Gastroenterology and Comprehensive Transplant Center, Cedars-Sinai Medical Center, Los Angeles, CA, USA;*
[4]*Department of Hepatology and Medical Liver Transplant Unit Henri Mondor Hospital-APHP, Paris Est University (UPEC), Créteil, France;*
[5]*Swiss HPB and Transplantation Center Department of Surgery and Transplantation University Hospital Zürich, Zürich, Switzerland;*
[6]*Keck School of Medicine of University of Southern California, Los Angeles CA, United States;*
[7]*Liver Failure Group, Institute for Liver and Digestive Health, University College London, London and European Foundation for the Study of Chronic Liver Failure, Barcelona, Spain*

[a]All authors contributed to the paper.

* Corresponding author. Address: Multivisceral Transplant Unit, Gastroenterology, Department of Surgery, Oncology and Gastroenterology, University Hospital of Padua, Via Giustiniani 2, Padua, 35128 Italy. Tel.: +39 0498212892.

E-mail address: burra@unipd.it (P. Burra).

https://dx.doi.org/10.1016/j.jhep.2021.01.007

Key point

Liver transplantation can significantly improve survival in patients with acute-on-chronic liver failure.

Key point

Gaps remain regarding our understanding of how to optimise survival among patients with severe decompensation of cirrhosis and acute-on-chronic liver failure, both before and after liver transplantation.

Table 1. Biomarkers and predictive models with added predictive value of mortality compared to MELD.

Predictor	Author (Ref)	Pts, n	End-point	Cut-off	HR	C-index	95% CI	*p* value
Nutrition								
Protein intake	Ney *et al.*[9]	630	Waitlist mortality	Protein intake <0.8 g/kg	1.8		1.2–2.7	0.006
Sarcopenia	Montano-Loza *et al.*[13]	669	Waitlist mortality	L3 skeletal muscle index	2.26		1.73–2.94	<0.001
				MELD *vs.* MELD-sarcopenia		0.73 *vs.* 0.77		0.03
	Durand *et al.*[81]	376	Waitlist mortality	Psoas diameter/height >16.8 mm/m	0.86		0.78–0.94	0.001
Encephalopathy								
Minimal encephalopathy	Ampuero *et al.*[82]	117	Death		4.36		1.67–11.37	0.003
Serum ammonia	Patwardhan *et al.*[83]	494	3-month mortality or LT	Ammonia >60 μmol/L	1.22		1.03–1.38	<0.01
Inflammation								
Neutrophil to lymphocyte ratio	Leithead *et al.*[84]	570	3-month mortality	2< neutrophil/ lymphocyte <4.9	3.17		0.70–14.37	
				Neutrophil/lymphocyte ≥5	6.02		1.28–28.41	0.043
	Kalra *et al.*[85]	107	Death	Neutrophil /lymphocyte ≥4	4.4			0.023
CRP	Cervoni *et al.*[86]	583	6-month mortality	CRP >29 mg/L	1.65		1.04–2.64	0.035
				MELD *vs.* MELD + CRP		0.769 *vs.* 0.796		0.019
25 Hydroxyvitamin D	Trepo *et al.*[87]	324	12-month mortality	25(OH)D3 <10 ng/ml	4.33		1.47–12.78	0.008
	Finkelmeier *et al.*[88]	251	Death	25(OH)D3 <6 ng/ml	1.703		1.038–2.794	0.035
	Stokes *et al.*[89]	65	24-month mortality	25(OH)D3 <6 ng/ml	6.32		1.28–31.18	0.012
Ferritin	Walker *et al.*[90]	191	6-month mortality	Ferritin >200 μg/L	4.62		1.17–18.2	0.03
				MELD *vs.* MELD-Ferritin		0.7 *vs.* 0.86		0.001
% Transferrin saturation	Maras *et al.*[91]	120	1-month mortality	TSC >20%	3.34		1.58–7.03	0.002
Portal hypertension								
sCD163	Waidmann *et al.*[92]	244	Survival	sCD163 <4,100 ng/l	0.237		0.134–0.419	<0.001
vWF:Ag	Ferlitsch *et al.*[93]	286	Death	vWF :Ag >315%	2.92		1.72–4.97	<0.001
	Kalambokis *et al.*[94]	102	Death	vWF :Ag >321%	1.006		1.002–1.01	0.002
Haemodynamics								
Copeptin	Kerbert *et al.*[95]	184	6-month death or LT	Copeptin >12.3 pmol/L	3.36		1.26–8.98	0.016
	Sola *et al.*[96]	265	6-month death or LT	Copeptin >14 pmol/L	1.66		1.14–2.43	0.008
ProBNP	Pimenta *et al.*[97]	83	6-month mortality	BNP >130.3 pg/ml	2.86		1.11–7.38	0.03
Renal function								
Urine NGAL	Ariza *et al.*[98]	716	1-month mortality		1.77		1.42–2.21	
				MELD *vs.* MELD + urine NGAL		0.81 *vs.* 0.86		0.017
	Barreto *et al.*[99]	132	3-month mortality		1.1		1.06–1.13	0.04
Cystatin C	Seo *et al.*[100]	78	Death		6.09		1.41–26.4	<0.001
	Markwardt *et al.*[101]	429	3-month mortality or LT	Cystatin C >1.5 mg/L	3.1		2.1–4.7	
New statistical models						**C-index for 3-month mortality**		
CLIF-C AD model (CANONIC cohort without organ failure)	Jalan *et al.*[6]	1,016	**CLIF-C AD**			**0.743**	**0.704–0.783**	
			vs. Child-Pugh score			0.651	0.601–0.701	<0.001
			vs. MELD score			0.649	0.602–0.697	<0.001
			vs. MELD-Na			0.681	0.633–0.728	<0.001
CLIF-C ACLF model CANONIC cohort	Jalan *et al.*[5]	275	**CLIF-C ACLF**			**0.732**	**0.691–0.773**	
			vs. Child-Pugh score			0.655	0.605–0.705	<0.001
			vs. MELD score			0.659	0.615–0.710	<0.001
			vs. MELD-Na			0.663	0.617–0.709	<0.001
Validation cohort		225	**CLIF-C ACLF**			**0.736**	**0.696–0.776**	
			vs. Child-Pugh score			0.647	0.599–0.695	<0.001
			vs. MELD score			0.635	0.585–0.684	<0.001
			vs. MELD-Na			0.637	0.588–0.686	<0.001
MELD-Na + frailty	Lai *et al.*[12]	536	**MELD-Na + frailty**			**0.82**		
			vs. MELD-Na			0.80		<0.001
			Frailty index			0.76		
MELD-sarcopenia	Montano-Loza *et al.*[13]	669	**MELD-sarcopenia***			**0.85**	0.81–0.88	
			In MELD <15 only**			**0.85**	0.77–0.92	
			vs. MELD overall*			0.82	078-0.87	0.1
			vs. MELD <15 only**			0.69	0.56-0.82	0.02

(*continued on next page*)

Table 1. (*continued*)

Predictor	Author (Ref)	Pts, n	End-point	Cut-off	HR	C-index	95% CI	*p* value
MELD-sarcopenia encephalopathy score	Van Vugt *et al.*[10]	585	**MELD + sarcopenia$_{M}$* + encephalopathy + Age**			**0.851**		
			MELD sarcopenia$_{M}$***			0.834		
			vs. MELD			0.839		n.a.
			MELD-Na			0.824		

ACLF, acute-on-chronic liver failure; AD, acute decompensation; BNP, brain natriuretic peptide; CRP, C-reactive protein; MELD, model for end-stage liver disease; MELD-Na, MELD-sodium; NGAL, neutrophil gelatinase-associated lipocalin; Pts, patients; TSC, transferrin saturation coefficient; vWF, von Willebrand factor.
*MELD-sarcopenia in the whole population.
**MELD-sarcopenia in patients with MELD <15.
***Sarcopenia as defined by Martin *et al.*[102]

among patients with ACLF, both before and after LT.

Organ allocation policy among candidates with ACLF

The current organ allocation policy gives highest priority to candidates with status-1A designation, while subsequent classification is based on the MELD-Na score. However, this may not fully account for mortality in patients with ACLF-3, partly because the MELD-Na score does not capture several of the extrahepatic organ failures that may be present in the ACLF-3 setting (Table 2).[1,21,22] One study from UNOS database demonstrated that patients with ACLF-3 and a MELD-Na score <25 have greater 90-day mortality than patients without ACLF and a MELD-Na score ≥35 (Fig. 1A).[1] This discrepancy may be related to a combination of mortality risk associated with the development of circulatory or respiratory failure, along with a perceived futility in full supportive care due to lower priority for transplantation. A follow-up study from the same database demonstrated that in a cohort of transplant candidates with a MELD-Na score ≥35, mortality was still higher among patients with ACLF-3, particularly those with 4-6 organ system failures, despite having similar priority for LT as patients with lower ACLF grades[22] (Fig. 1B). Recently, data from an investigation of the Veterans Administration database corroborated these findings.[21] Utilising a standardised mortality ratio (SMR) to compare observed and expected mortality, the authors determined that the SMR was significantly higher for patients with ACLF *vs.* decompensated cirrhosis, and furthermore, the SMR increased with rising grade of ACLF.[21] Finally, another study indicated that patients with ACLF-3 have a greater risk of 14-day mortality relative to status-1A candidates, again independent of MELD-Na score.[23] Further investigation is therefore warranted regarding whether the presence of extrahepatic organ failures should be incorporated into organ allocation policy to reduce WL mortality.

Outcomes after liver transplantation

Outcomes for patients with ACLF at transplantation are variable due to heterogeneity among studied populations. Initial data from the CANONIC study revealed 1-year post-LT survival of 75% among 25 patients transplanted with ACLF, of whom 38% had ACLF-3 and none had respiratory failure.[24] In another single centre retrospective study of 140 transplanted patients with ACLF, of whom 30 had ACLF-3 at transplantation, 90-day post-LT survival was 84.5% for those transplanted with ACLF-1, 77.2% for patients with ACLF-2, and 60% among recipients with ACLF-3. Multivariable analysis determined the presence of ACLF at LT to be the strongest risk factor for post-transplant mortality.[25] More recent studies have demonstrated better outcomes. In a multicentre European study of over 250 patients transplanted with ACLF, of whom 73 patients had ACLF-3, 1-year survival was above 83% among all grades of ACLF.[19] It should be noted that individuals in this study who were transplanted with ACLF-3 were selected carefully, and those who had haemodynamic instability, acute respiratory distress syndrome (ARDS), active gastrointestinal bleeding or uncontrolled sepsis were denied LT.[19] In a separate multicentre investigation of 152 patients in Europe, the following variables indicated high risk of 1-year mortality for patients transplanted with ACLF-3: age ≥53, leukocyte count ≤10G/L, lactate level 4 and the presence of mechanical ventilation with ARDS.[26] The authors derived the transplantation and multiorgan failure (TAM) score, allocating 1 point for the presence of each of these variables. A TAM score >2 indicated post-LT survival of <10% at 1 year, while a score ≤2 was associated with a 1-year survival of 83.9%.[26]

Key point

To optimise patient survival after liver transplantation for acute-on-chronic liver failure we should determine how to prioritise those on the waiting list based on a scoring system able to predict futility.

Table 2. Summary of studies regarding transplantation for ACLF-3.

Study (Year)	Type of study	Total patients with ACLF-3	Waitlist outcomes	Post-LT outcomes	Significance	Limitations
Artru (2017)[19]	Three centres from January 1, 2008 to December 31, 2014	73 transplanted	n.a.	1-year survival 83.6%	Found LT can improve survival of ACLF-3 (with similar rates to lower ACLF grades)	Lack of power for multivariate analysis Case-control study with control cases from one single centre
Levesque (2017)[25]	A single centre from January 2008 to December 2013	30 transplanted	n.a.	1-year survival 43.3%	Confirmed ACLF as independent predictor of 90-day mortality Proposed scoring system to identify potentially futile LT	Small sample Limited variables used to build statistical propensity score
Thuluvath (2018)[20]	UNOS database from February 27, 2002 to September 30, 2016	2,515 at listing 3,556* transplanted	30-day mortality >92%	1-year survival >81.0%	Identified number of organ failures, age, and mechanical ventilation as independent predictors of post-LT survival	Short time to LT (up to 5 days after listing in >3 organ failures) Unable to identify cause of decompensation
Sundaram (2019)[1]	UNOS database from 2005 to 2016	5,355 at listing 6,381 transplanted	28-day mortality 43.8%	1-year survival 78.9%	Demonstrated waitlist mortality is highest among ACLF-3 patients regardless of MELD-Na Identified presence of mechanical ventilation as strongest predictor of post-LT mortality	Potential for misclassification of decompensating event in database Unclear indications for use of mechanical ventilation
Sundaram (2019)[23]	UNOS database from 2002 to 2014	5,099 at listing	21-day mortality 32.7%	n.a.	Demonstrated 14-day waitlist mortality is greater in ACLF-3 patients compared to status-1a listed patients	Potential for misclassification of decompensating event in database Excludes patients listed status-1a with exception points
Artzner (2020)[26]	Five centres, years 2007-2017	152 transplanted	n.a.	1-year survival 83.9% *vs.* 8.3% depending on TAM score	Developed TAM score to help determine futility of LT for ACLF-3	TAM score derived from 22 patients with ACLF-3 and mortality within 1 year. Minimal information on donor organs

ACLF, acute-on-chronic liver failure; LT, liver transplantation; MELD, model for end-stage liver disease; TAM score, transplantation and multiorgan failure score.
*Study separately analysed number of organ failures by 3, 4, and 5-6 organ failures. Data shown in table reflect combination of 3 or more organ failures.

Key point

NASH-related acute-on-chronic liver failure is an emerging issue which will require particular attention and prospective studies to understand the mechanisms leading to it, and to develop specific prevention and management strategies.

Several large studies from the UNOS registry have supported these findings, demonstrating a 1-year post-LT survival above 80%, even among recipients with 4-6 organ system failures at transplantation. In 2 studies from the UNOS registry, the requirement for mechanical ventilation at the time of LT was one of the strongest risk factors for 1-year post-transplant mortality among patients with ACLF-3 at the time of transplantation,[1,20] yielding a 10% decrease in survival rate (75.3% *vs.* 85.4%), with only marginal improvement if utilising a higher quality donor organ (76.5%) or transplanting within 30 days of listing (76.5%).[1] A separate study of the UNOS database has revealed age to be a strong prognosticator for post-transplant survival among patients with ACLF-3, as transplantation of patients with ACLF-3 above the age of 60 yields a 1-year survival of 74.9%.[27] Regarding long-term survival outcomes after transplantation, one study reported a 5-year post-LT survival rate of 67% for transplanted patients with ACLF-3.[28] Furthermore, after the first year post-LT, the percentage decrease in survival was similar among all ACLF grades.[28]

Emerging and special subgroups

NASH and ACLF

NASH is an emerging disease and is becoming one of the leading indications for LT in the USA and a growing one for LT in Europe. NASH is strongly, but not-exclusively, associated with the epidemic of dysmetabolic syndrome and is commonly associated with obesity, type 2 diabetes, hypertension and dyslipidaemia. These cofactors of NASH are also associated with cardiovascular diseases, particularity in patients with NASH. The natural history of NASH is well described and its evolution can lead to DC and HCC. There is limited information on the development of ACLF in patients with NASH. A recent study from the USA reported increasing admissions for ACLF among patients with cirrhosis (+5.9% between 2006 and 2014). There was a 63% increase of ACLF in patients with NASH (3.5% in

2006-2008 to 5.7% in 2012-2014) *vs.* a 28% increase in patients with alcohol-related cirrhosis (5.6% in 2006-2008 to 7.2% in 2012-2014) and a 25% increase in patients with other aetiologies of liver disease (5.2% in 2006-2008 to 6.5% in 2012-2014). Patients with NASH-related ACLF had longer mean length of stay, and more frequent use of dialysis.[29] Obesity and type 2 diabetes were associated with liver disease progression.[30]

In a recent study of LT in Europe, NASH represented 4% of the indications for LT between 2002 and 2016, increasing to 8.4% of indications for LT in 2016.[31] In a study from the USA, the number of new registrants with NASH increased by 170% between 2004 and 2013, with NASH becoming the second leading indication for LT. Patients with NASH on the WL were significantly younger, had significantly higher BMI, higher frequency of diabetes, and were more frequently female in comparison to patients listed with other indications.[32,33] In a recent study from the USA, looking at all LT recipients from 2005 to 2016 in the UNOS database, NASH accounted for 21.9%, 18.9% and 17.8% of recipients with ACLF-1, ACLF-2, and ACLF-3, respectively.[1] Interestingly, NASH accounted for 20.8% of the LT recipients without ACLF. This suggests that the percentage of NASH among LT recipients is quite stable according to the presence of ACLF or not. An important factor in patients with NASH is the risk of associated severe type 2 diabetes, of severe or morbid obesity, and of cardiovascular disease. This will require a rapid and intensive work-up in these patients. Obesity and type 2 diabetes have been associated with a higher risk of infection and a higher rate of drop out from the WL for LT. Prophylactic antibiotics may be required in patients with NASH and ACLF. The management of morbid obesity is quite complex. Performing a sleeve gastrectomy during surgery for LT appears to be beneficial in some patients, however, this has been limited to expert centres and has not been performed in patients with ACLF.[34] Therefore, it appears that NASH-related ACLF is an emerging issue which will require particular attention and prospective studies to understand the mechanisms leading to ACLF in patients with NASH, and to develop specific prevention and management strategies.

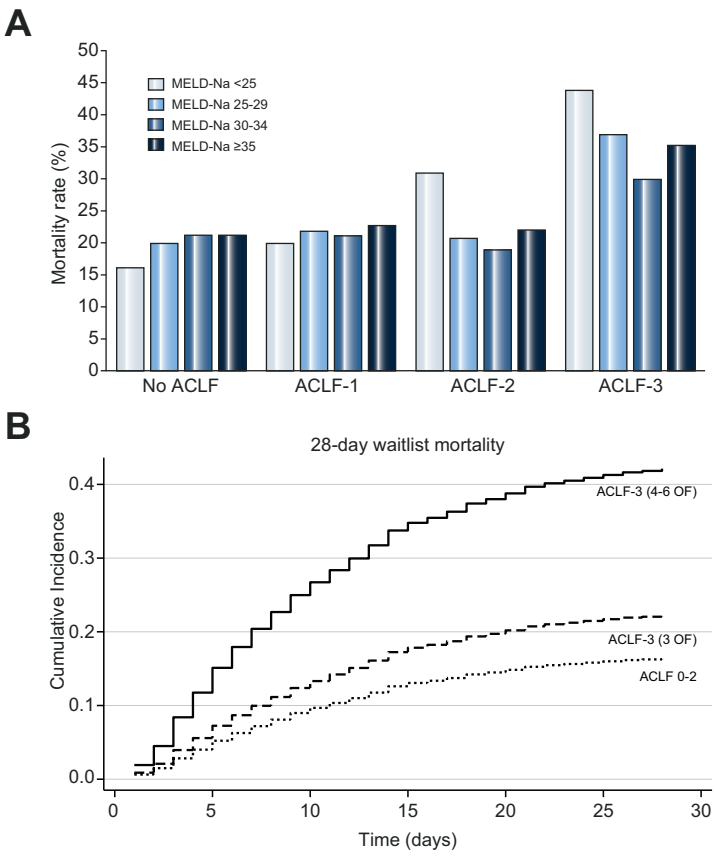

Fig.1. Waitlist mortality in ACLF patients. (A) Waitlist mortality across different grades of ACLF and MELD-Na score categories. (B) Waitlist mortality across different grades of ACLF, in a cohort of patients with MELD-Na score ≥35 (p <0.001, Chi-Square Test). ACLF, acute-on-chronic liver failure; MELD-Na, model for end-stage liver disease-sodium.

Severe acute alcoholic hepatitis

An increasing incidence of hospitalisation for alcoholic hepatitis (AH) has been seen both in the USA[35] and in Europe, with a parallel increase in mortality rates in recent years.[36]

Severe cases (Maddrey discriminant function ≥32) not responding to corticosteroid therapy (according to the Lille score) are associated with a 6-month mortality rate of 75%.[37] However, despite the lack of effective therapies and high mortality rates, AH has for a long time been considered an absolute contraindication for LT by most transplant centres worldwide, mainly due to the lack of pre-transplant abstinence and the potential high risk of post-transplant alcohol relapse.[37–40] Therefore, LT for severe AH remains controversial owing to concerns about the limited organ supply. Recognising an increasing body of favourable evidence, a convergence of practice guideline recommendations from leading hepatology and gastroenterology societies have suggested that the length of abstinence should not be a sole criterion for LT selection.[41]

In 2011, a multicentre French-Belgian study demonstrated that early LT (eLT), if performed under stringent selection criteria, significantly increases survival rates in patients with severe AH not responding to steroid therapy.[42] However, eLT without requiring a minimum period of sobriety for severe AH is controversial: many centres delay eligibility until a specific period of sobriety (such as 6 months) has been achieved.[43] Mathurin *et al.*

recently published an abstract reporting long-term results from their 2011 cohort, with the addition of more recently transplanted patients, in the same 7 centres and according to the same inclusion criteria. Sixty-eight patients who had failed to respond to medical therapy underwent eLT, with severe alcohol relapse reported in 10.3% of cases in just under 5 years. However, overall patient survival was 82.6±5% at 1 year, 70±6% at 5 years and 56±7% at 10 years, confirming that AH could be a good indication for LT in selected patients.[44]

Another multicentre study has been published,[45] performed at 12 LT centres in the USA, confirming the high survival rates after eLT for severe AH (94% and 84% at 1 and 3 years) with rates of alcohol relapse ranging between 10% and 17% between 1 and 3 years of follow-up. In this study, it seems that almost all (96%) of the 147 patients included with the diagnosis of AH had underlying alcohol-related cirrhosis and the point of onset of liver disease may be different from experience in other centres. Patients with AH who undergo eLT are usually admitted to hospital with a high MELD score. They consequently go to the top of the WL, opening the discussion on equity regarding the priority of patients already listed for different liver diseases. Only very restrictive criteria, which should be comparable among different centres and different countries, could allow us to compare indications, contraindications and outcomes. AH, in most cases, develops on the background of existing liver disease; therefore, it is quite unusual to see patients with pure AH. Another issue that is raised when proposing eLT in patients with acute decompensation is the rate of relapse to alcohol consumption after LT. The study by Lee *et al.*[45] reported a 3-year relapse rate of 17%, which is acceptable. However, in a European study, a 2-year relapse rate of 33.8% was reported.[46] In general, if the rate of alcohol relapse is similar with or without the 6-month abstinence rule, we believe the rate of relapse is also acceptable after eLT, but it is crucial that the studied populations are comparable, in terms of inclusion criteria and the definition of AH in different studies.

To inform ongoing debate and policy, a mathematical model has recently been proposed to simulate early *vs.* delayed LT for patients with AH and different amounts of alcohol use after transplantation: abstinence, slip (alcohol use followed by sobriety), or sustained use. The study estimated life expectancies of patients receiving early *vs.* delayed LT (6-month wait before placement on the WL) and life years lost attributable to alcohol use after receiving the LT. Patients offered eLT were estimated to have an average life expectancy of 6.55 years, compared with an average life expectancy of 1.46 years for patients offered delayed LT. Patients who were offered eLT and had no alcohol use afterward were predicted to survive 10.85 years compared with 3.62 years for patients with sustained alcohol use after LT. Compared with delayed transplantation, eLT increased survival times in all simulated scenarios. However, the net increase in life expectancy should be confirmed in prospective studies.[47]

Another pilot study on eLT was performed in Italy in patients with AH who had a first episode of decompensation of chronic liver disease, were non-responders to medical therapies and had no comorbidities. eLT was only performed after obtaining consensus from paramedical and medical staff, as well as supportive family members, and following an assessment of patients' psychiatric and addiction profile. Preliminary data confirmed excellent patient survival, as all patients were alive with no alcohol relapse at a median follow-up of 17 months (range 9–41 months); this was significantly higher than in patients not responding to medical therapy who were denied transplantation.[48] A prognostic score, the SALT (sustained alcohol use post-LT) score (Table 3), using 4 objective pre-transplant variables, was proposed in order to predict alcohol use after eLT; the latter identifies candidates with AH for eLT who are at low risk of sustained alcohol use post-transplant. This tool may assist in the selection of patients with AH for eLT or in guiding risk-based interventions post-LT.[49]

There is an ongoing discussion about using the ACLF classification in patients with AH to define the risk of death. It is well known that alcohol abuse is the precipitating event in about 25% of cases of ACLF.[14] That said, there are differences in the underlying pathophysiology of the diseases. In AH, hepatic inflammation is thought to be predominant, while multiorgan failure is a key component of ACLF-3 that is often infection-related. The key issue remains how best to prioritise patients with these diseases based on current risk scores and predicted survival after LT.[19,24,25,37]

Key point

Early liver transplantation in patients with severe acute alcoholic hepatitis significantly increases survival rates compared to patients who are denied transplantation, if performed under stringent selection criteria.

Table 3. SALT score and sustained alcohol use post-LT.[49]

Variable	Points
>10 drinks/day at presentation	+4
≥2 prior failed rehabilitation attempts	+4
Any history of prior alcohol-related legal issues	+2
History of non-THC illicit substance abuse	+1

LT, liver transplantation; SALT, sustained alcohol use post-LT; THC, tetrahydrocannabinol.

Areas of uncertainty and adequate timing regarding LT for DC and severe ACLF

Adoption of MELD almost 2 decades ago dramatically changed our perspective on allocation. Yet, there is an increasing body of evidence that the efficiency of MELD-based systems is now

hampered by intrinsic limitations, notably because MELD does not adequately capture organ failures/dysfunctions and inflammation in patients with DC, and because of the increasing number of patients listed for HCC. Large-scale prospective cohort studies are therefore urgently needed, first to test recently developed predictive models integrating new predictors of mortality and second to look for next generation predictive biomarkers and statistical models, prompting the LT community to move from the MELD to the post-MELD era, based on robust evidence.

Moreover, given the high mortality associated with ACLF-3, candidates who have developed this condition would likely benefit from eLT. However, the potential advantages of rapid transplantation may also include improved post-transplant survival when transplantation occurs in less than 30 days compared to more than 30 days (82.2% *vs.* 78.7%).[1] However, findings from other studies have indicated that transplantation after clinical improvement yields better post-LT survival than eLT. A single centre proof-of-concept study revealed that patients transplanted after improvement of ACLF, defined as recovery of at least 1 organ system failure, had similar 90-day post-transplant survival as patients without ACLF prior to transplantation.[50] In a larger registry study, 1-year post-transplant survival substantially increased in patients with ACLF-3 who improved ACLF grades to 0-2 (88.2%) *vs.* those who remained at ACLF-3 at LT (82.0%).[27] In particular, improvement in circulatory failure, brain failure, and requirement for mechanical ventilation were associated with greater post-LT survival. This study also compared the effect of timing of transplantation *vs.* improvement in organ failures on post-LT survival. The findings demonstrated that compared to transplantation in patients with ACLF-3 within 7 days of listing, improvement from ACLF-3 to ACLF 0-2 resulted in greater post-transplant survival (87.6 *vs.* 82.7%, p <0.001) even if performed after 7 days from listing.[27] The question of the "transplantation window" and the precise criteria for deciding on a transplant have not yet been determined. There are no consolidated data on the best time for transplantation. Should patients be transplanted during their stay in the ICU or after recovery from ICU? What criteria should be used to determine indication, timing or contraindication for LT? Although there has been significant progress in intensive care management, outcomes in patients with ACLF remain poor without transplantation and the proportion of patients with ACLF who are transplanted is still too low. In the future, we should work to improve the transplantation rates of these patients without negatively influencing results.

Although progress has been made regarding the safety of LT in patients with severe ACLF, there are 2 primary areas that need to be addressed to optimise survival. First is determining how to prioritise patients with severe ACLF, particularly ACLF-3, on the WL to both minimise WL and post-LT mortality. Second, is creating a scoring system to determine in whom transplantation would be futile. Although studies to date have demonstrated excellent post-LT survival even among patients with 4-6 organ failures, these data may reflect a selection bias which does not account for factors such as sarcopenia, frailty, or uncontrolled infection. Prospective investigations are therefore imperative to establish reliable determinants of futility, such that WL priority can be allotted to patients with severe ACLF who would benefit from LT.

Potentially inappropriate vs. life-saving liver transplantation in critically ill patients

Under the sickest-first allocation policy, many transplant centres face an increased proportion of critically ill patients on the WL.[51]

Despite LT being the “only rescue option” in many cases, futile outcomes must be avoided because of donor organ shortages and limited health care resources. Most studies define a futile outcome as 90-day[51,52] or 1-year[53,54] post-transplant mortality. Alternatively, futile treatment can be understood as an almost zero-chance of surviving despite LT. Many aspects of organ allocation are highly regulated, but widely accepted delisting criteria – when a patient is literally too sick for transplantation – are lacking. Therefore, determining when post-transplant mortality risk is too high in severely decompensated patients is still a challenge.[8] A recent study in high acuity recipients with ACLF or acute liver failure found that ARDS (defined as a PaO_2/FiO_2 ratio <200) and pre-transplant lactatemia were independently associated with poor 90-day prognosis after LT.[55] Furthermore, high vasopressor requirement and ongoing sepsis are often reasons for deferring or denying LT in order to avoid futile outcomes.[8,19] A multidisciplinary expert panel study explored criteria for when not to proceed with LT due to high severity of critical illness.[53] Experts from anaesthesiology, critical care, hepatology and transplant surgery suggested thresholds contradicting LT in the presence of severe ARDS (PaO_2/FiO_2 ratio <150), high vasopressor requirement (norepinephrine dose >1 μg/kg/min), and lactatemia (>9 mmol/L). Another study identified MELD score, pre-transplant septic shock,

cardiac risk and comorbidities as independent predictors of futile outcome (90-day mortality) after LT in patients with MELD scores >40.[51] Therefore, a model predicting 90-day mortality that integrates risk factors of ACLF would be a helpful tool to address potential futility in this high-risk population of LT candidates.

However, the medical challenge of undesired futile LT outcomes also extends to ethical issues since the potential rescue of a single critically ill patient, regardless of costs, must be weighed against the benefits of aggregated patients on the WL. In extreme recipients with low utility, LT may work in a few cases and thus cannot be considered as futile treatment. Therefore, these scenarios are beyond the narrow definition of physiological futility and are better described by potentially inappropriate LT.[8] Even with a perfect risk prediction of 90-day mortality after LT, it remains a matter of debate how much predicted risk of death defines futile or potentially inappropriate LT in patients with ACLF. We anticipate that a future personalised allocation system should not only prioritise patients based on recipient and donor criteria but also needs to integrate criteria when LT is highly likely to be potentially inappropriate in patients with ACLF.

Key point

Gender, geographical disparity, and the use of donors positive for different viruses remain the main areas of controversy in the liver transplant setting.

Areas of controversy in the liver transplant setting

Gender disparity

Disparities in access to LT by sex, documented more than 20 years ago,[56] continue to persist. The introduction of the MELD-Na score worsened the sex disparity.[57] Women have a lower likelihood of LT than men at the same MELD-Na score,[57] and are thus more likely to be delisted due to death or becoming too sick,[58] with higher hospitalisation rates after listing.[59] This difference is accounted for by shorter stature, fewer MELD exceptions and the underestimation of renal dysfunction by creatinine among women.[57,60] Modelling suggests that adding 1 or 2 MELD points for women would provide more equitable access to LT.[57]

Geographic disparity

Geographic disparities are well-recognised, with many countries considering rules for broader sharing of organs.[61–64] Patients living in rural areas, lower income and education settings and those with public (*vs.* private) insurance are particularly affected.[65,66] The USA recently implemented an acuity circle approach (using 150-mile radius of the donor hospital) in an attempt to reduce geographic disparities. However, reconfiguring organ distribution is a challenging issue. For example, a modelling study evaluating the use of distance and population density "circles" to define organ distribution in the USA found little improvement over the older donor service area system.[67] The complexity of addressing geographical barriers to LT is further highlighted by a recent USA survey that found strong public support for maximising outcomes after LT, but also for keeping organs local, and considering cost in allocation decisions.[68]

HIV-, HBV-, HCV-positive donors

Maximising available donors is an additional means by which to address disparities in access to LT; the use of donors positive for hepatitis C, hepatitis B and HIV has increased in many countries.

- Use of HIV-positive donors was made possible in the USA by the Hope Act and countries without restrictions have used HIV-positive donors in HIV-positive recipients (D+/R+).[69] Superinfection appears to be rare in this context and graft and patient outcomes (with modest duration follow-up) are comparable to those in recipients of HIV-negative organs. A case report on LT of HIV D+/R- in a mother-child pair suggests this is possible with the use of antiretroviral therapy in donor and recipient, but long-term follow-up is needed.[70] This may be relevant in countries with high rates of HIV among donors.
- For donors positive for HBsAg, only recipients with HBV should be offered these organs due to the known persistence of covalently closed circular DNA in the liver and the certainty of HBV transmission.[71,72] Donors must be carefully assessed for liver disease pre-implantation. No significant HBV-related disease has been observed in HBsAg D+/R+ recipients treated with life-long antiviral therapy, except in patients co-infected with hepatitis D virus,[73] so the latter should be considered a contraindication to the use of HBsAg-positive donors. Whether there are long-term consequences (beyond 5 years), such as risk of liver cancer, is unknown.
- HCV-viraemic donors have traditionally been used for HCV-positive LT recipients (D+/R+) with outcomes shown to be comparable to those receiving from HCV-uninfected donors. However, the use of HCV-viraemic donors in HCV-negative recipients (D+/R-) has rapidly increased, fuelled by the availability of safe and effective direct-acting antivirals (DAAs) for HCV.[74–77] Early results with HCV D+/R- transplants are encouraging, with high rates of sustained virologic response achieved post-LT. Early treatment is preferred, typically starting DAAs within days to 1–2 weeks of LT, rather than delaying for weeks or months, to minimise the risk of hepatic and extrahepatic complications.[78] A higher risk of acute and

chronic rejection has been reported when DAA therapy is delayed,[76,77] highlighting the importance of monitoring for immune-mediated events in the context of DAA therapy.[79,80]

Conclusions

In conclusion, although more than 50 years have now passed since the first liver transplant was performed, there remain major differences in perspective between countries and transplant centres. There are several controversies related to transplantation timing in patients with severe liver disease decompensation, particularly when organs other than the liver are involved. Early transplantation in AH is performed in several centres, but ethical questions persist, while the use of donors that are positive for different viruses sits on the cusp of science and ethics. Finally, the right approach to transplantation in very sick patients remains a delicate balance between utility, benefit and justice.

Abbreviations

AH, alcoholic hepatitis; ACLF, acute-on-chronic liver failure; ARDS, acute respiratory distress syndrome; CLIF-C, Chronic Liver Failure Consortium; DC, decompensated cirrhosis; eLT, early liver transplantation; HCC, hepatocellular carcinoma; LT, liver transplantation; MELD, model of end-stage liver disease; NASH, non-alcoholic steatohepatitis; SMR, standardised mortality ratio; TAM, transplantation and multiorgan failure; WL, waiting list.

Financial statement

The authors declare that no financial support was provided for the preparation of the manuscript.

Conflict of interest

PB declares no conflict of interest with any financial organization regarding the manuscript, however she received fees from Biotest, Germany, Kedrion, Italy and Chiesi Farmaceutici, Italy. DS declares no conflict of interest with any financial organization regarding the manuscript, however he received fees from Biotest, Germany and Goliver Therapeutics, France. CD declares no conflict of interest with any commercial organization regarding the manuscript, however he received fees from Biotest, Germany. NT has institutional grant support from Gilead Sciences, USA and Genentech/Roche, USA. RJ has research collaborations with Yaqrit Limited, UK and Takeda, Japan. He is the inventor of OPA, which has been patented by UCL and licensed to Mallinckrodt Pharma, UK. He is also the founder of Yaqrit Limited, a spin out company from University College London. VS, HP declare no conflict of interest with any commercial organization.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

All authors participated in drafting the manuscript, read and approved the final version.

Acknowledgments

The authors thank Dr Jean Philippe Richardet for performing a comprehensive review of the predictors of mortality in cirrhotics independent of MELD.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2021.01.007.

Transparency declaration

This article is published as part of a supplement entitled New Concepts and Perspectives in Decompensated Cirrhosis. Publication of the supplement was supported financially by CSL Behring. The sponsor had no involvement in content development, the decision to submit the manuscript or in the acceptance of the manuscript for publication.

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Author names in bold designate shared co-first authorship

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