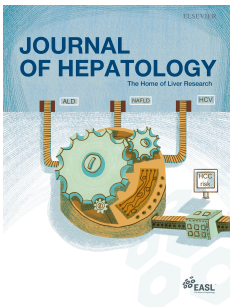

‘Equity’ and ‘justice’ for patients with acute-on chronic liver failure: A call to action

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INVITED EXPERT OPINION.

'Equity' and 'Justice' for patients with acute-on chronic liver failure: A call to action

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Conflicts of interest.

Rajiv Jalan has research collaborations with Yaqrit and Takeda. Rajiv Jalan is the inventor of OPA, which has been patented by UCL and licensed to Mallinckrodt Pharma. He is also the founder of Yaqrit Ltd, a spin out company from University College London.

Thierry Gustot is on the advisory board for Promethera Biosciences, GoLiver Therapeutics and Abbvie and has a Grant from Gilead

Javier Fernandez has received grant and research support from Grifols, speaker honorarium from MSD and educational grant from Pfizer

William Bernal is on the advisory board, Versantis AG and has Research funding from Synapse Research Institute

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ABSTRACT

Acute-on chronic liver failure (ACLF) occurs in hospitalised patients with cirrhosis and is characterised by multiorgan failures and high rates of short-term mortality. Without liver transplantation (LT), the 28-day mortality of patients with ACLF ranges between 18-25% in those with ACLF Grade 1 to 68-89% in those with ACLF Grade 3. It has become clear that there is lack of equity of access to LT for patients with ACLF across the world due to the current allocation policies, which are based on prognostic scores that underestimate the risk of death of these patients and lack of appreciation that there is clear evidence of transplant benefit for carefully selected patients as they can have excellent post-LT outcomes. This expert opinion provides evidence supporting the argument that patients with ACLF should be given priority for LT using prognostic models that define the risk of death for these patients, pinpoint risk factors for poor post-LT outcomes, identify unanswered questions and describe the design of a global study, the CHANCE study, which will provide answers to the outstanding issues. It also suggests widespread adoption of pilot programmes across the world as have been initiated in the UK and recommended in Spain to introduce new policies for organ allocation for patients with ACLF.

KEY POINTS

1. Data from the ECLIS study shows that patients with acute-on chronic liver failure do not have equity of access for liver transplantation, which is the only life-saving therapy available to these patients.
2. Currently used allocation systems that are based on MELD scoring system underestimate the death of patients with acute-on chronic liver failure.
3. Data confirm that carefully selected patients with severe acute-on chronic liver patients can have excellent clinical outcomes providing evidence of transplant benefit.
4. Absolute and relative contraindications include severe respiratory and circulatory failure, severe frailty and high lactate levels.
5. The UK regulators have implemented a new strategy to allow prioritisation of patients with acute-on chronic liver failure and Spain has made recommendations to do so.

Acute on chronic liver failure (ACLF) is a well-defined disease entity that occurs in cirrhotic patients and is characterised by precipitating events, multiorgan failures, systemic inflammation and high rates of short-term mortality. Data from across the globe in over 100,000 patients has validated the diagnostic and prognostic criteria that were developed in the CANONIC study, referred to as the EASL-CLIF criteria (Figure 1) [1]. Without liver transplantation, the 28-day mortality of patients with ACLF ranges between 18-25% in those with ACLF Grade 1 to 68-89% in those with ACLF Grade 3 [2]. The available data indicate that about 30% cirrhotic patients who are hospitalised for liver-related complication will have ACLF or develop it during the hospitalisation [1,2]. Emerging data from retrospective studies and those from large organ transplantation databases provide robust information that liver transplantation (LT) can save the lives of these patients [3]. However, the lack of widespread recognition of the transplant benefit that these patients with severe ACLF obtain, absence of strategies to prioritise ACLF patients for earlier access to donor organs, pre-conceived ideas that patients with ACLF will have poor post-LT outcomes and the fear that higher post-transplant death rates may disadvantage smaller centers, provide the perfect setting for lack of equity of access to LT [4].

Current organ allocation around the world is based on a prognostic model, referred to as the Model for End-Stage Liver Disease (MELD) score. Although the model was developed in the US, it is used for organ allocation in most European countries that are in the Eurotransplant organ sharing program. There are no specific priority points for ACLF patients. The only option for transplanting ACLF patients is to stay on the waiting list until an organ is allocated or use organs from deceased donors or use marginal donors. In many Asian countries, living donors provide the organs. As is evident from Table 1, rates of access to LT for ACLF patients varies widely across Europe [4]. In recognition of this, new policies for organ transplantation for patients with ACLF have been implemented in Spain and UK.

Recommendations of the Spanish Society of Liver Transplantation (SETH)

In a recently published Consensus statement, SETH has recommended an expedited organ allocation programme to allow patients with ACLF to be transplanted (Table 2) [5]. In brief, they suggest that LT should be considered in patients with ACLF. They recommend the use of the EASL-CLIF criteria to assess prognosis and suggest that MELD score does not recognise the severity of illness in those

with ACLF Grades 2 or 3. In these patients, they suggest prioritization given the poor short-term survival.

Recommendations of the NHS Blood and Transplant, UK

A new allocation tier referred to as ACLF Transplantation Tier (ACLFLT) has been created in the UK and came into force in May 2021. The ACLFLT priority tier is below that of the superurgent listed patients, hepatoblastoma, split-able organs and critically ill paediatric patients. The criteria for selection of patients to be eligible for expedited transplantation includes the presence of cirrhosis, significant liver failure manifested by jaundice and coagulopathy, organ failures necessitating organ support in the intensive care unit (ICU) or equivalent and a risk of 28-day mortality of >50%. This group of patients will usually fulfil the EASL-CLIF criteria for ACLF Grade 2 or 3 (www.nhsbt.nhs.uk).

This expert opinion follows the above mentioned recommendations of the Spanish and the UK societies to allow priority of organs for LT for ACLF patients and focusses on discussing the evidence that the current allocation policy based on MELD scoring is inadequate and LT saves the lives of ACLF patients. The limits, potential futility and contraindications of transplantation are then addressed. Finally, the design of a global study assessing the role of LT to address remaining questions and refine criteria is described.

MELD-based allocation systems disadvantage patients with ACLF

Data from the CANONIC study published about 7-years back confirmed that the risk of short-term mortality was better identified by the EASL-CLIF based organ failure (OF) grading system than the MELD score, which also validated the scoring system for sequential use [2]. The EASL-CLIF predictive model reached an AUROC of 0.8 by Day 3-7 from the time the cirrhotic patient was hospitalised [6]. The superior performance of the ACLF classification over MELD has been validated by many investigators. The study from Hernaez et al., which included over 70,000 patients from 127 VA hospitals showed that at each MELD decile, the EASL-CLIF model was able to identify patients at risk of death. The data suggest that the MELD scoring system underestimates the risk of death of ACLF patients (Figure 2a) [7].

In an important study using data from the United Network for Organ Sharing (UNOS) database, mortality on the waiting list was assessed in about 79,000 patients. The data confirmed that patients with relatively low MELD scores (<25) had high mortality rates, ranging between 30-40%, if they had ACLF grades 2 or 3 (Figure 2b) [8]. In order to allow more equitable distribution of organs, a share-35 rule was introduced in the US in 2014. In a study of the UNOS database between 2010-2017, including only patients with MELD≥35, mortality rate of patients on the waiting list was 16% if they had ACLF grade 2 and 30% if they had ACLF grade 3. In studying the impact of share-35, the data suggested increased transplantation rate for ACLF patients, but no impact was observed in those with ACLF grade 3, particularly patients with 4-6 OFs [9]. In another study, the interaction between MELD and EASL-CLIF classification was explored and a new scoring system including age, MELDs, etiology, ACLF grade, ethnicity, obesity, sex and Karnofsky score has been proposed [10]. This requires further validation.

Taken together, the overwhelming evidence points to replacing the MELD-based allocation system with the EASL-CLIF classification for patients with ACLF. This is not surprising as the MELD score fails to recognise the importance of brain, circulation and respiratory failures in defining the short-term mortality of ACLF patients. The UK and the Spanish pilot programmes will provide information on areas that need further refinement.

Evidence of transplant benefit in patients with ACLF

Although there is ongoing debate on the detail of the definitions used to categorise the stages of ACLF, there is unequivocal evidence of a close relationship between the number and severity of organ system failures and survival. The EASL-CLIF diagnostic and prognostic criteria have been shown to be superior to APASL or NACSELD criteria in various studies [11,12]. In patients with cirrhosis with the failure of three or more organ systems the 90-day mortality consistently exceeds 60% despite the best available medical therapies [1]. Experimental extra-corporeal liver assist devices are yet to demonstrate consistent and convincing improvements in survival. In contrast, there are consistent and strong indications of a survival benefit from LT in carefully selected patients.

Post-LT patient survival for recipients transplanted from the ICU has shown progressive improvement over time and in many series, now approaches that of elective surgery [13,14]. Comparison with transplantation for non-ACLF indications does however indicate that ACLF transplants are associated with longer post-operative ICU and hospital stay [15]. Though the use of LT for ACLF has not been – and probably never will be – tested in randomised controlled trials, patient survival in recent series reporting the outcome of LT of recipients with ACLF consistently exceeds that expected with medical therapies alone (Table 3). In a recently published collaborative study between EFCLIF and ELITA (ECLIS study), the outcomes of LT for ACLF was evaluated in 20 centres from 8 European countries. Patients on the waiting list over 18 months between 2018 and 2019 were included. Only 234 (19%) patients with decompensated cirrhosis had ACLF at listing. Mortality on the waiting list even in this very carefully selected group was 31.6% but the 1-year post-LT survival was 81% providing clear evidence of transplant benefit [4]. Data from other single and multicenter studies and also from large registries support this more granular observation in the ECLIS study [3].

There are few studies of patients with ACLF that have directly compared survival with and without transplantation. To date, retrospective comparison with matched, non-transplanted controls has been made in 3 studies which combined in meta-analysis have shown 'huge benefit of LT for select ACLF patients.'(Figure 3) [16]. Importantly, this meta-analysis also confirmed key features required in future research to determine standardised criteria for LT selection and facilitate analysis of outcome in this patient group – with need for robust prospective multi-centre data collection using standardised definitions of ACLF.

Limits, Futility and Contraindications

Despite clear evidence of transplant benefit in carefully selected patients with ACLF, the limits and contraindications for proceeding or denying LT in these patients have not been well defined [3,4,8,17]. LT should be cautiously considered in the following situations.

1. Higher grades of ACLF in cirrhotic patients has been suggested as a possible pre-transplant condition that defines potentially futile LT. Patients with 4 to 6 OFs, especially if they require renal, vascular and ventilatory support, have traditionally been considered too sick for LT due

to their expected poor prognosis after surgery [18]. However, recent studies show that although mortality increases with the number of OFs, the price to pay is minor with just a 9% reduction in 1-year survival after LT in patients with 5-6 OFs compared to those without ACLF [19]. The type of OF also has a minor impact on post-LT survival with only mechanical ventilation being identified as independent predictor of mortality (HR 1.5-1.7) [3,8,19]. Patients requiring full organ support at LT (dialysis, mechanical ventilation and vasopressors) also show excellent survival at 1-year (77%) [19]. Severity of specific OFs and overall clinical course of the syndrome are therefore clinically more relevant than the number or type of OFs [20]. Three OFs are of major importance in the decision to delay or deny LT: respiratory, circulatory and metabolic failures. Moderate or severe respiratory failure (Pa02/Fi02 <150), refractory shock (noradrenaline >0.6-1 µg/Kg/min or need for 2 vasopressors) and high arterial lactate levels (>9 mmol/L) should be considered major contraindications to proceed to LT as they are indicative of poor post-LT outcome [16,17,20].

2. Other conditions that should delay or deny LT are the following [16,17,20]:
    a. active gastrointestinal bleeding
    b. severe pancreatitis and
    c. suspicion of ongoing infection identified by presence of one of the following; (i) persistent fever >39ºC (ii) leucopenia <0.5 g/L (iii) appropriate antibiotic therapy of severe infections for <72h (iv) infection by pandrug-resistant bacteria and invasive fungal infections.

3. Poor functional status and severe frailty (clinical frailty score >6) is also considered a major contraindication for LT in ACLF. Additionally, severe sarcopenia and advanced age (>60yr in the UK recommendations but need to be considered on a case by case basis) are factors with major prognostic impact in critical care and should be considered as potential contraindications for LT in this setting [20].

Finally, there is firm evidence that early LT is crucial to ensure the success of LT in patients with ACLF-3. The median time between listing and LT in studies reporting good outcomes in these

patients ranged from 4 to 8 days, indicating that the window for LT in this setting is extremely narrow and that the decision to transplant must be taken rapidly [3,8,16,19]. After initial stabilization and adequate control of infections, patients should have a quick assessment for LT. Standard evaluations will delay LT in frail patients at very high risk of new infections, myopathy and further OFs.

Further prospective studies will objectively define the limits and contraindications for LT in ACLF-3 and therefore, when transplantation should be considered futile or inappropriate in the era of the "sickest first "policy.

Unanswered questions and the CHANCE study

All published data on liver transplantation (LT) in ACLF comes from relatively small mono/multi-centric cohort [3,4,15,16] or large national database (UNOS) [8,19] with several limitations: potential misclassification of organ failures and ACLF definition, selection bias, absence of detailed data about clinical trajectory, infectious complications, management, donor organ selection, short and long-term post-LT outcomes. Numerous unanswered questions remain in specific populations of patients with severe ACLF (ACLF-2 or 3) such as:

- lack of intention-to-treat results of LT from the time of wait listing
- detailed information about waiting list outcomes
- best organ allocation system for this specific population
- objective limits to define futile LT
- ideal timing
- characteristics of donor organ to ensure acceptable post-LT outcomes
- long-term post-LT survival rates and impact on the quality of life (QoL)
- resource utilization of performing LT and
- the overall results across the different continents

The answers to these questions are an urgent medical need to ensure a 'justice' among LT candidates. Indeed, due to the scarcity of liver donors, we need a strategy of rationing where the

success of LT will be maximized among different indications with the best equilibrium to limit mortality on the waiting list.

In this context, the EASL-CLIF Consortium in collaboration with the International Liver Transplantation Society (ILTS) and the European Liver and Intestine Transplant Association (ELITA) have designed a prospective non-interventional observational global study (*CHANCE, liver transplantation in patients with CirrHosis and severe ACLF: iNdications and outcome, ClinicalTrials.gov: NCT04613921*). The primary objective of the study is to compare 1-year graft and patient survival rates after LT in patients with ACLF-2 or 3 at the time of LT with patients with decompensated cirrhosis without ACLF 2-3 and transplant-free survival of patients with ACLF-2 or 3 not listed for LT. The project plans to recruit 3,000 patients of whom 2,000 will have ACLF-2 or 3 (based on the EASL-CLIF definition) and will be registered on the LT waiting list around the world (Figure 3). With detailed follow-up on the waiting list and during the first year after LT and precise graft and surgical data collection, we expect to accumulate sufficient data to answer the challenging questions described above. Up-to-date validated scores/questionnaires will be used to assess the impact of frailty and sarcopenia on post-LT outcomes and the effect of LT on QoL.

The international nature of the CHANCE study will allow deep assessments of the potential impact of different precipitating factors of ACLF (e.g. alcohol vs. HBV flare), different types of LT (deceased donor LT vs. living donor LT) and different regional/national allocation systems on transplant outcomes. Beside these clinical objectives, the CHANCE study aims to build a repository of biological samples to explore new biomarkers to predict prognosis on the waiting list and after LT, and mechanisms of liver and extrahepatic organ recovery after LT. The recruitment of patients is expected to start in the second half of 2021.

Conclusions

We believe that the current organ allocation system disadvantages patients with ACLF and clear evidence of transplant benefit for these patients is overwhelming. We therefore suggest that the widespread inequity of access to transplantation should be addressed urgently with ACLF patients having priority for organs. The recent recommendations from the SETH to consider priortisation and

UK LT regulators implementing strategies to prioritise organs for patients with ACLF in a special category allows other countries to follow their lead.

References

[1] Arroyo V, Moreau R, Jalan R. Acute-on-Chronic Liver Failure. N Engl J Med. 2020;382:2137-2145.

[2] Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology 2013;144:1426-37

[3] Burra P, Samuel D, Sundaram V, Duvoux C, Petrowsky H, Terrault N, Jalan R, Limitations of current liver donor allocation systems and the impact of newer indications for liver transplantation. J Hepatol (in press)

[4] **Belli LS, Duvoux C, Artzner T, Bernal W**, Conti S, Cortesi PA, et al. Liver transplantation for patients with acute-on-chronic liver failure (ACLF) in Europe: results of the ELITA/EF-CLIF collaborative study (ECLIS). J Hepatol. 2021 (in press)

[5] Rodríguez-Perálvarez M, Miguel Ángel Gómez-Bravo MA, Sánchez-Antolín G, De la Rosa G, Bilbao I, et al. Expanding Indications of Liver Transplantation in Spain: Consensus Statement and Recommendations by the Spanish Society of Liver Transplantation. Transplantation 2021 (in press).

[6] **Jalan R, Saliba F**, Pavesi M, Amoros A, Moreau R, Ginès P, et al. Development and validation of a prognostic score to predict mortality in patients with acute-on-chronic liver failure. J Hepatol. 2014;61:1038-47.

[7] Hernaez R, Liu Y, Kramer JR, Rana A, El-Serag HB, Kanwal F. Model for end-stage liver disease-sodium underestimates 90-day mortality risk in patients with acute-on-chronic liver failure. J Hepatol. 2020;73:1425-1433.

[8] **Sundaram V, Jalan R**, Wu T, Volk ML, Asrani SK, Klein AS, Wong RJ. Factors Associated with Survival of Patients With Severe Acute-On-Chronic Liver Failure Before and After Liver Transplantation. Gastroenterology 2019;156:1381-1391.

[9] Sundaram V, Shah P, Mahmud N, Lindenmeyer CC, Klein AS, Wong RJ, et al. Patients with severe acute-on-chronic liver failure are disadvantaged by model for end-stage liver disease-based organ allocation policy. Aliment Pharmacol Ther 2020;52:1204-1213.

[10] Abdallah MA, Kuo YF, Asrani S, Wong RJ, Ahmed A, Kwo P, et al. Validating a novel score based on interaction between ACLF grade and MELD score to predict waitlist mortality. J Hepatol 2020 (in press)

[11] Mahmud N, Kaplan DE, Taddei TH, Goldberg DS. Incidence and Mortality of Acute-on-Chronic Liver Failure Using Two Definitions in Patients with Compensated Cirrhosis. Hepatology 2019;69:2150-2163.

[12] Li F, Thuluvath PJ. EASL-CLIF criteria perform better than NACSELD to diagnose and prognosticate ACLF. J Hepatol 2021 (in press)

[13] Bernal W. Improving Outcomes forTransplantation of Critically Ill Patients With Cirrhosis? Clinical Liver Disease 2017;10:25-28.

[14] Moon DB, Lee SG, Kang WH, Song GW, Jung DH, Park GC, et al. Adult Living Donor Liver Transplantation for Acute-on-Chronic Liver Failure in High-Model for End-Stage Liver Disease Score Patients. American Journal of Transplantation. 2017;17:1833-1842.

[15] Karvellas CJ, Lescot T, Goldberg P, Sharpe MD, Ronco JJ, Renner EL, et al. Liver transplantation in the critically ill: a multicenter Canadian retrospective cohort study. Critical Care 2013;17:R28.

[16] Abdallah MA, Waleed M, Bell MG, Nelson M, Wong R, Sundaram V, et al. Systematic review with meta-analysis: liver transplant provides survival benefit in patients with acute on chronic liver failure. Alimentary Pharmacol Ther 2020;52:222-232.

[17] Artru F, Louvet A, Ruiz I, Levesque E, Labreuche J, Ursic-Bedoya J, et al. Liver transplantation in the most severely ill cirrhotic patients: A multicenter study in acute-on-chronic liver failure grade 3. J Hepatol 2017;67:708-71.

[18] Linecker M, Krones T, Berg T, Niemann CU, Steadman RH, Dutkowski P, et al. Potentially inappropriate liver transplantation in the era of the "sickest first" policy. A search for the upper limits. J Hepatol 2018;68:798-813.

[19] Thuluvath PJ, Thuluvath AJ, Hanish S, Savva Y. Liver transplantation in patients with multiple organ failures: feasibility and outcomes. J Hepatol 2018;69:047-56.

[20] Weiss E, Saner F, Asrani SK, Biancofiore G, Blasi A, Lerut J, Durand F, et al. When is a critically ill cirrhotic patient too sick to transplant? Development of consensus criteria by a multidisciplinary panel of 35 international experts. Transplantation 2021;105:561-68.

Legends to Figures.

Figure 1. (a) CLIF-organ failure score. The dark shaded areas define criteria to diagnose organ failure. (b) Criteria to diagnose different Grades of ACLF using the CLIF-organ failure scoring system. MAP. Mean arterial pressure; INR: international normalized ratio; OF: organ failure; KD: kidney dysfunction; BD: brain dysfunction. *Data from Jalan and Saliba et al. J Hepatol 2014 (ref 5).*

Figure 2. (a) The data here show that at each MELD decile, the EASL-CLIF model was able to identify patients at risk of death. (b) The data show that patients with relatively low MELD scores (<25) had high mortality rates, ranging between 30-40% if they had ACLF grades 2 or 3. *Data from Hernaez et al. J Hepatol. 2020;73:1425-1433 and Sundaram and Jalan et al. Gastroenterology 2019;156:1381-1391 (refs 7 and 8 respectively).*

Figure 3. Forest Plots of 30-day and one-year patient survival of ACLF patients who did or did not receive liver transplantation. ACLF: Acute on Chronic Liver Failure, LT: Liver Transplantation. Data from *Abdallah et al. Alimentary Pharmacology & Therapeutics. 2020;52:222-232 (ref 16)*.

Figure 4. Design of the CHANCE study. The patients with (Acute-on-Chronic Liver Failure) ACLF-2 or 3 referred to the Liver Transplant (LT) team will be screened and included in either the group of transplant candidates at the time of listing (n=2,000) or in the group of non-listed patients (n=500). Patients with decompensated cirrhosis without ACLF-2 or 3 but MELD ≥ 20 listed for transplantation (n=500) will be also included as a control group. The follow-up will end 12 months (M12) either after LT or M12 after decision of non-listing. *ClinicalTrials.gov: NCT04613921.*

Table 1. Evidence of lack of equity of access to LT for patients with ACLF across Europe.

	Sites	No. of LTs	DCC*	ACLF1 at LT	ACLF2 at LT	ACLF3 at LT
FRANCE	4	613	316	19 (6%)	27(8.5%)	60 (19%)
GERMANY	2	85	41	10 (24%)	10 (24%)	7 (17%)
ITALY	7	891	353	14 (3.9%)	31 (8.8%)	18 (5%)
SWITZERLAND	1	66	26	1 (3.8%)	2 (7.6%)	2 (7.6%)
POLAND	1	184	45	2 (4.4%)	3 (6.6%)	1 (2.2%)
NETHERLANDS	1	114	59	0	1 (1.7%)	3 (5%)
UK	2	495	275	4 (1.4%)	1 (0.3%)	6 (2.1%)
SPAIN	2	229	101	8 (7.9%)	4 (4%)	1 (1%)
TOTAL	**20**	**2.677**	**1216**	**56 (4.6%)**	**79 (6.5%)**	**98 (8%)**

2.677/9.000= 29.7% of all LTs registered in ELTR between January 2018 and June 2019; * DCC = Decompensated Cirrhosis. LT: Liver transplant. Yellow: low transplant rates, Blue: Intermediate; Green: High. *Data from Belli et al. J Hepatol 2021 (in press)*

Table 2. Recommendations of *Spanish Society of Liver Transplantation*

- LT should always be considered in patients with ACLF unless otherwise contraindicated.
- Patients with ACLF who are potential candidates for LT should be admitted to the intensive care unit and closely monitored until validated prognostic scores are assessed (CLIF-C ACLF organ failure score at d 3–7).
- Screening of occult infections, including blood and urinary cultures, is paramount in ACLF patients.
- When ACLF is triggered by an active infection, LT may be contraindicated until the responsible microbiologic agent is identified, the appropriate therapy is administered, and subsequent cultures are negative.
- Futility criteria are not established for ACLF patients. For LT purposes, severe and unresponsive extrahepatic organ failure (particularly cardiovascular or respiratory) would be a contraindication.
- Patients with ACLF-2 or ACLF-3 awaiting LT should be managed by expert transplant hepatologists and intensivists depending on the logistics and organization of the institution until transplantation or significant improvement. In the latter situation, the need of early LT should be reassessed by a multidisciplinary team.
- MELD score may not fully capture the severity of patients with ACLF-2 and ACLF-3. Given the dismal short-term prognosis without LT, a regional urgency priority should be granted.

Data from Transplantation 2021;105: 602–607

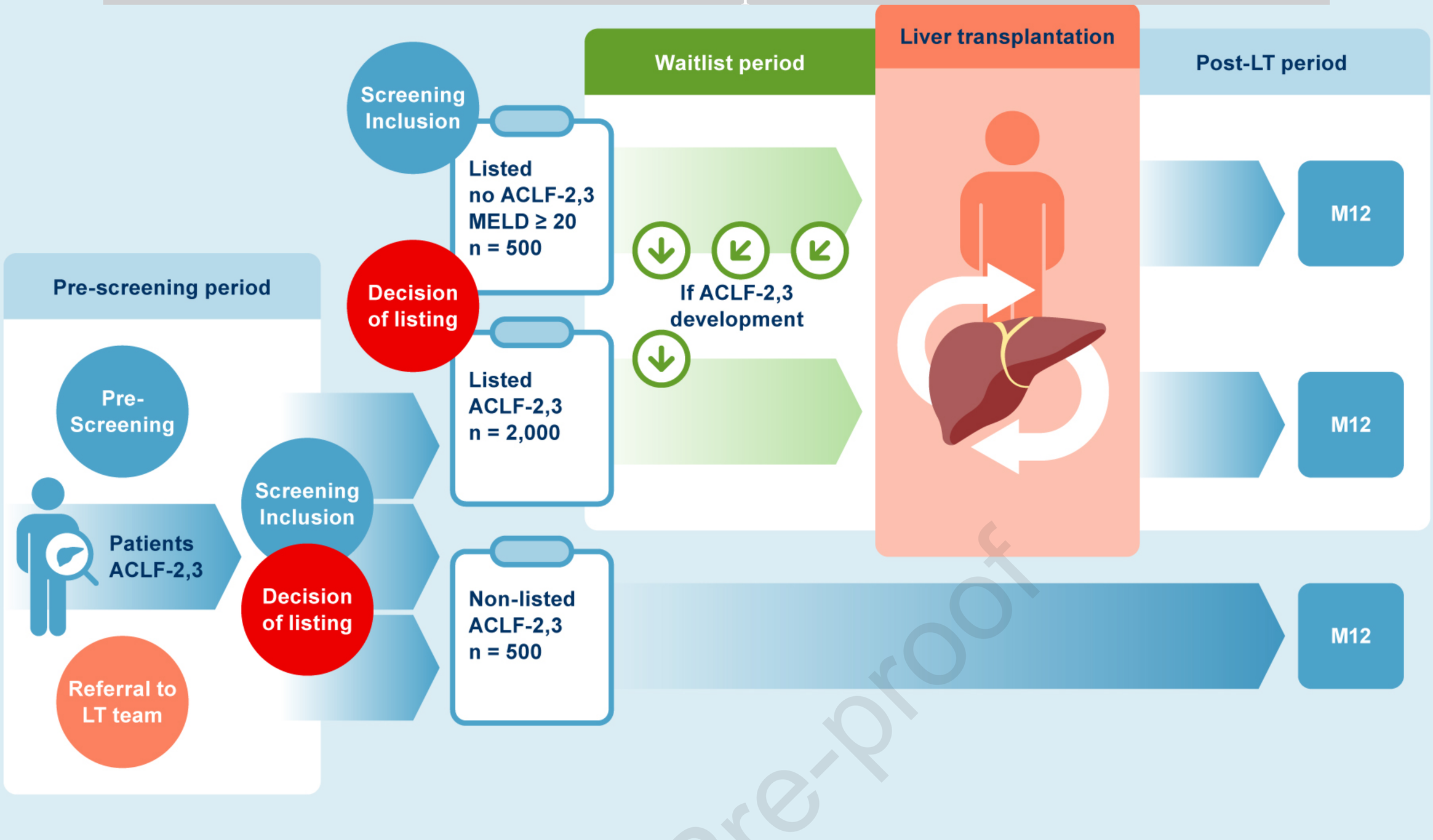
Table 3. Reports of patient survival after liver transplantation with ACLF

Site	Cohort	N	Era	Patient survival	Illness Severity	Reference
Korea	Single site	190	1998-2015	1-year 72%	ACLF 1-3	Moon et al. 2017 [14]
Canada	Multi-site	198	2000-09	1-year 74%	Median SOFA 14	Karvellas et al. 2013[15]
USA	Registry	3556	2002-16	1-year 81-84%	3+ Organ failures	Thuluvath et al. 2018 [19]
Austria	Single site	33	2002-10	1- year 87%	ACLF: APASL classification	Finkensetdt et al. 2013
USA	Registry	6381	2005-16	1-year 81.8%	ACLF-3 only	Sundaram et al. 2019 [8]
USA	Single Site	101	2006-13	1-year 82%	ACLF 1-3	Agbim et al. 2020
France	Single Site	55	2007-14	1-year 60%	Median SOFA 13	Michard et al. 2017
France	Single Site	140	2008-13	1-year 70%	ACLF 1-3	Levesque et al. 2017
France	Multi-site	73	2008-14	1-year 84%	ACLF-3 only	Artru et al. 2017; [15]
Germany	Single Site	98	2009-14	1-year 62%	ACLF 1-3	Huebner et al. 2018
UK	Registry	65	2011-16	1-year 90%	3+ Organ failures	Bernal W. 2017
N. America	Multi-site	57	2015-17	6-month 93%	ACLF NACSELD classification	O'Leary et al.
Pakistan	Single Site	60	2012-16	1-year 92%	ACLF 1-3	Bhatti et al. 2018

France / UK	Multi-site	152	2007-17	1-year 67%	ACLF-3 only	Artzner et al. 2020
Korea	Single site	44	2011-14	1-year 84%	ACLF 1-3	Hong et al. 2016

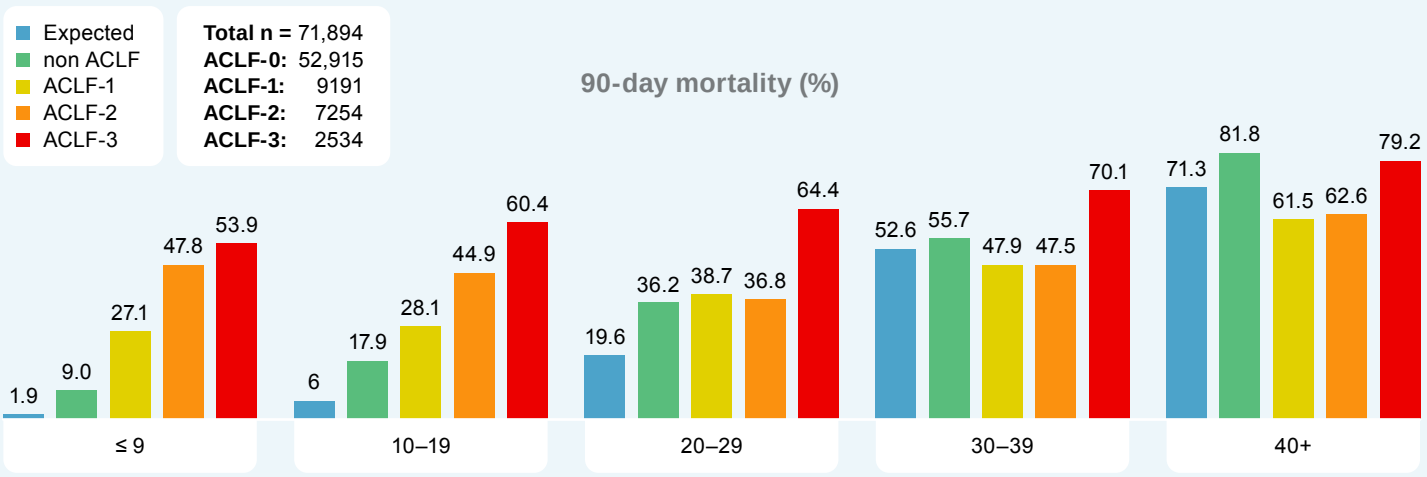
Note; ACLF; Acute on Chronic Liver Failure, APASL: Asian Pacific Association for the Study of the Liver, NACSELD: North American Consortium for the Study of End Stage Liver Disease, SOFA: Sequential Organ failure Assessment, USA; United States of America, UK: United Kingdom.

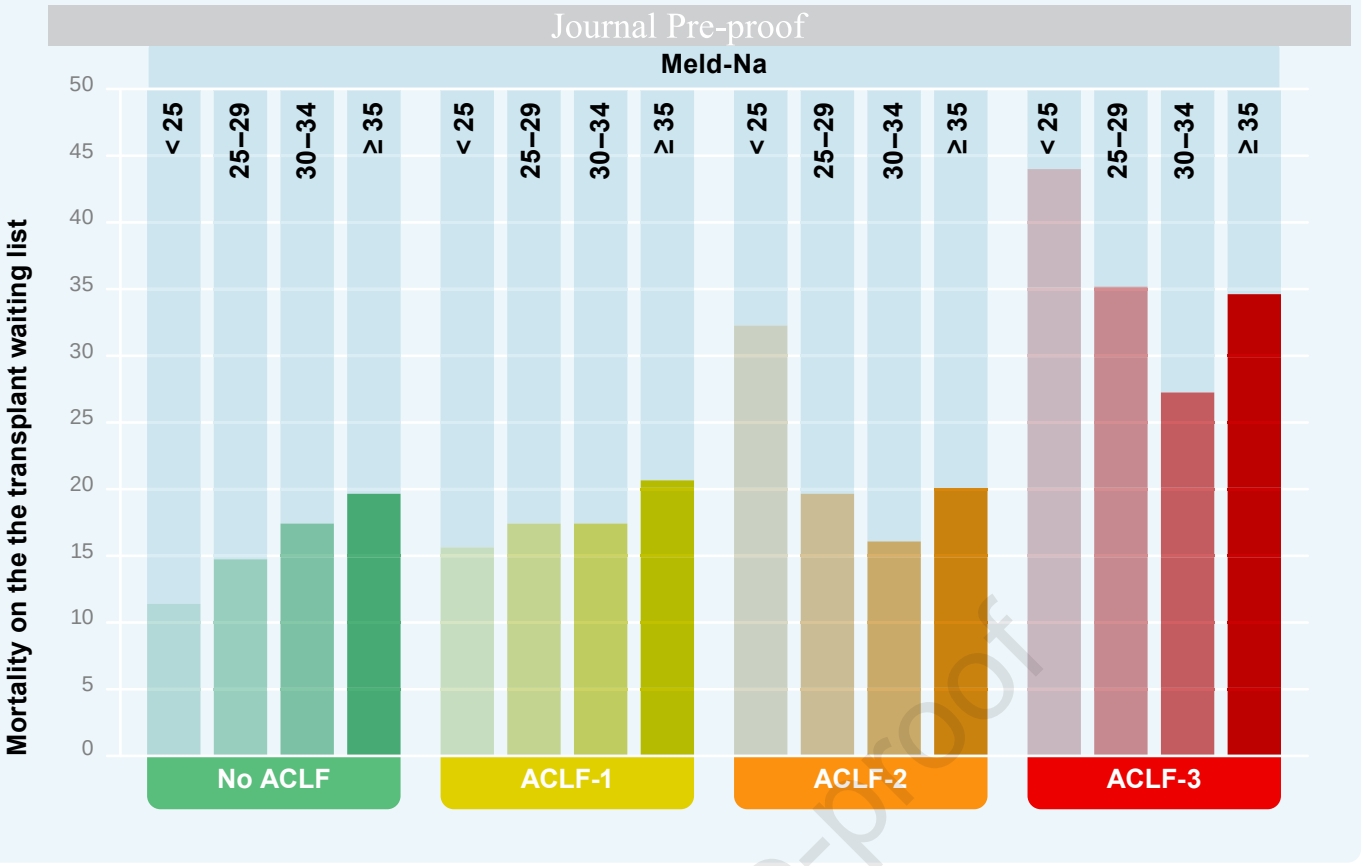
Refs: Finkenstedt et al. Liver Transplantation 2013;19:879-886; Agbim et al. Transplant Direct 2020;6:e544; Michard et al. Clinical Transplantation 2017;31; Levesque et al. Liver International 2017;37:684-693; Huebner et al. Alimentary Pharmacology & Therapeutics 2018;02:02; Bernal W. Clinical Liver Disease 2017;10:25-28; O'Leary et al. Liver Transplantation 2019;25:571-579; Bhatti et al. Journal of Clinical & Experimental Hepatology 2018;8:136-143; Artzner et al. American Journal of Transplantation 2020;20:2437-2448; Hong et al. World Journal of Gastroenterology 2016;22:3785-3792



Organ s			
Liver	Bilirubin < 6 mg/dL	Bilirubin 6–11.9 mg/dL	Bilirubin ≥ 12 mg/dL
Kidney	Creatinine < 1.5 mg/dL	Creatinine 2–3.4 mg/dL	Creatinine ≥ 3.5 mg/dL or RRT
	Creatinine 1.5–1.9 mg/dL		
Brain (West Haven Score)	Grade 0	Grade 1–2	Grade 3–4
Coagulation	INR < 2.0	INR 2.0–2.4	INR ≥ 2.5
Circulation respiratory	MAP ≥ 70 mmHg	MAP < 70 mmHg	Vasopressor requirement
	PaO_2 / FiO_2 > 300 SpO_2 / FiO_2 > 357	PaO_2 / FiO_2 201–300 SpO_2 / FiO_2 215–357	PaO_2 / FiO_2 ≤ 200 SpO_2 / FiO_2 ≤ 214

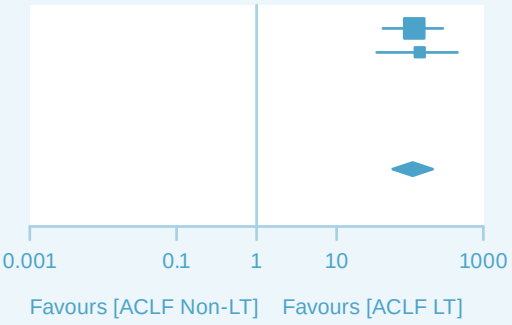
Patient	1287 patients (%)	Mortality (%)	Category
Absence of OF	68.3	4.4	Absence of ACLF
Single non kidney OF without KD or BD	9.9	6.3	
Single KF	6.7	18.6	ACLF-1
Single non kidney OF with KD or BD	4.2	27.8	ACLF-1
Two OFs	7.5	32.0	ACLF-2
Three OFs	1.9	68.0	ACLF-3
Four to six OFs	1.4	88.9	ACLF-3





(B) 90-day mortality

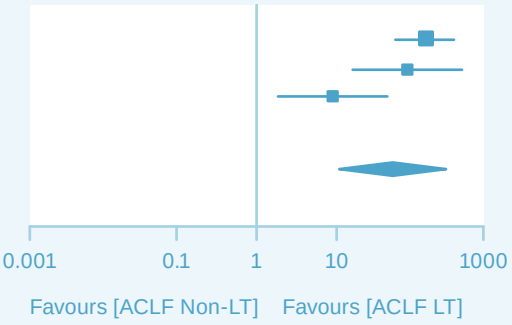
	ACLF LT		ACLF Non-LT			Odds ratio	Odds ratio
Study or subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
Artru	284	337	9	119	72.7%	65.49 [31.24, 137.28]	
Bhatti	55	60	7	59	27.3%	81.71 [24.40, 273.65]	
Hong	37	44	69	124		Not estimable	
Total (95% CI)		397		178	100.0%	69.57 [37.01, 130.77]	
Total events	339		16				



Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.09$, df = 1 (P = 0.76); $I^2 = 0\%$
Test for overall effect: Z = 13.17 (P < 0.00001)

(A) 30-day mortality

	ACLF LT		ACLF Non-LT			Odds ratio	Odds ratio
Study or subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
Artru	318	337	23	119	40.1%	69.86 [36.50, 133.69]	
Bhatti	57	60	17	59	31.2%	46.94 [12.92, 170.61]	
Hong	42	44	92	123	28.6%	7.08 [1.62, 30.95]	
Total (95% CI)		441		301	100.0%	32.02 [8.50, 120.66]	
Total events	417		132				



Heterogeneity: $Tau^2 = 1.03$; $Chi^2 = 8.45$, df = 2 (P = 0.01); $I^2 = 76\%$
Test for overall effect: Z = 5.12 (P < 0.00001)