Proposal for a Pilot of Liver Transplantation

for

Critically Ill Patients with Cirrhosis

Fixed Term Working Group

Core Members

Dr William Bernal – Kings College Hospital, London

Dr Ian Rowe – St James's University Hospital, Leeds

Dr Alexander Gimson – Addenbrookes Hospital, Cambridge

Mr James Powell – Royal Infirmary, Edinburgh

Full Membership below:

11th November 2019

Draft 10 – Circulation to Liver Advisory Group.

Participants in Fixed Term Working Group

Name	Affiliation
Alexander Gimson	Addenbrooke's Hospital
Joanna Leithead	Addenbrooke's Hospital
Andrew Holt	Birmingham
Nick Murphy	Birmingham
Kenneth Simpson	Edinburgh
James Powell	Edinburgh
Steven Masson	Freeman Hospital
William Bernal (Chair)	King's College Hospital
Brian Hogan	King's College Hospital
Ian Rowe	Leeds
Robert Mitchell-Thain	PBC Foundation
Richard Aspinall	Portsmouth
David Patch	Royal Free Hospital
Rajiv Jalan	Royal Free Hospital

Part 1. Background

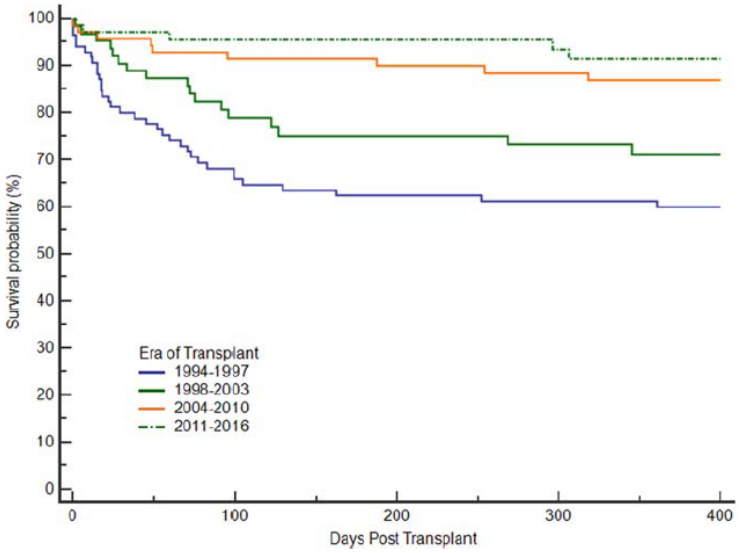
In the natural history of cirrhotic chronic liver disease (CLD) the eventual development of severe end-organ complications may result in critical illness with extra-hepatic multi-organ failure (MOF), which requires critical care based organ support with high short term mortality. Now often termed 'Acute On Chronic Liver Failure' (ACLF), this condition can be phenotypically characterised, illness severity assessed and defined using specific organ failure scoring systems (Appendix A for EASL endorsed systems) [1]. It is well established that there is clear relation between the severity of MOF measured in this way and survival with medical management alone, and accurate early prognostic evaluation may be possible [2 3]. Though recent series suggest that some improvements in outcome have occurred over time, for patients with ACLF and severe MOF survival remains poor [4 5].

In selected critically ill patients with Acute Liver Failure (ALF) who may also have severe MOF, 'rescue' though emergency liver transplantation (ELT) is an established and successful intervention. Using predetermined criteria indicative of a poor survival with medical management alone, with prioritised access to liver grafts - and with the accumulated experience of use of ELT in this setting - outcomes for patients undergoing ELT have been transformed, with survival now approaching that of elective LT for CLD.

However, this approach has not been adopted for critically ill patients with CLD, for a number of reasons. Principal amongst these is the historically high post-transplant mortality seen in patients with CLD transplanted whilst critically ill. ELT places enormous strain on the physiologic reserve of recipients and in this respect patients with CLD differ importantly from patients with ALF. The latter usually become ill in the setting of previous good health, whilst those with CLD are usually older, often with comorbidity, and have become critically ill in the setting of chronic and debilitating illness with significant underlying physiologic compromise. Further, the time window of opportunity for successful ELT may be very narrow and using standard wait-listing mechanisms only a minority of patients who develop ACLF undergo transplantation, even when they have undergone the LT assessment process prior to its development [6 7]. Consequent upon these factors very few patients with ACLF undergo LT from ICU; in a UNOS series from 2002-2013 of first transplants with cirrhosis only 8% were in ICU at the time of LT and in the NHSBT dataset from 1994-1996 only 4% [8].

The longstanding dogma of poor survival for patients with ACLF undergoing transplantation in the setting of active critical illness has been challenged by the results of recent studies. There is now good evidence to suggest that the outcome of patients undergoing ELT in this clinical setting has markedly improved over time. Review of the NHSBT outcomes for patients with cirrhosis and MOF undergoing first liver transplant between 1994 and 2016 has shown progressive improvement in survival over time, with most recent patient survival >90% and not statistically different from hospitalised patients with CLD without MOF (Figure 1) [8].

Figure 1 Post-transplant Patient survival in cirrhotic patients hospitalised with organ failure or support at time of transplant by era of transplant.

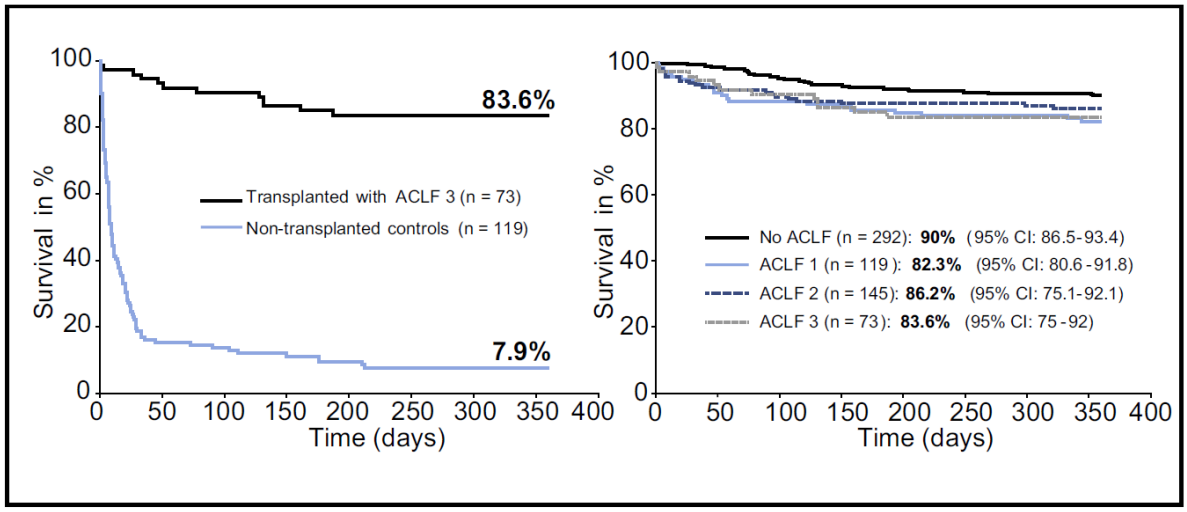


Note; NHSBT dataset, first elective transplant for cirrhosis 1994-2016. n=276. P<0.001

Source [8]. Organ failure: Renal replacement therapy, Ventilation or HE grade ≥3.

Other single centre and national datasets have reported 1-year patient survival of >80% [6,7 9]and have confirmed that survival for some patients with ACLF undergoing ELT is dramatically better than that seen with medical management alone (Figure 2) [10].

Figure 2. Survival with and without Transplantation in patients with EASL ACLF Grade 3 and by ACLF Grade.



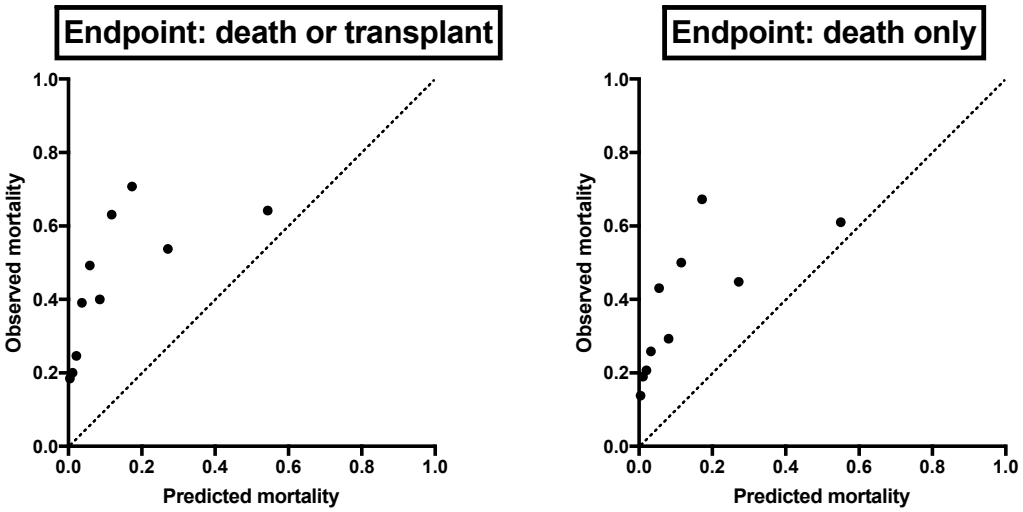
Note: 3 French centres, 2004-2014. Source: [10]

Acute liver failure and ACLF do however share an important commonality in that in both clinical settings the time 'window' for successful transplantation is days rather than weeks, with both waitlist and post-LT mortality increasing with duration on wait listing [11]. In a single centre series, patients waitlisted with ACLF had a median wait time of 24 days with more than half of the patients dying before LT [6]. Nonetheless, in those patients who did undergo LT outcomes were good: 1-year patient survival 87% [6].

Patients with ACLF may be disadvantaged by restriction to standard approaches to transplantation wait-listing, even following the fundamental advances resulting from the introduction of the national offering scheme (NOS). Clinical experience and new statistical analysis suggest that survival for patients with ACLF is not accurately predicted using the NOS wait-list survival model. Though this was derived from analysis of a patient cohort of nearly 5,000 registrations, fewer than 770 were inpatients and only a small proportion of these were critically ill. We have examined the predictive accuracy of the NOS model in an independent cohort of 680 critically ill patients with cirrhosis

managed in the Liver Intensive Therapy Unit at Kings College Hospital. In this dataset, death or transplantation occurs in 45% at 30 days and 54% at 90 days. This analysis has demonstrated that the model consistently underestimates both the 30- and 90-day mortality of this patient group and thus would fail to apply sufficient priority to allow transplantation within an appropriate timeframe (Figure 3).

Figure 3: Calibration Plots for 30-day mortality in 680 cirrhotic patients in ICU using National Allocation System M1 model.



Note: Predicted mortality from M1 (survival without transplant) against Observed mortality. Each dot describes the mean value for each decile o

f the predicted and observed values.

Source; Unpublished 2019 Rowe/Bernal/Gimson.

Summary.

1. In recent years there have been fundamental changes in the understanding and classification of critically ill patients with cirrhosis, with accurate individual prognostic evaluation now possible.

2. The outcome of patients with ACLF undergoing ELT in this clinical setting has markedly improved, with survival for some patients undergoing ELT is markedly better than with medical management alone.

3. There is evidence to suggest that the time window for successful transplantation is narrow and in addition existing graft allocation systems fail to accurately assess illness severity and survival in critically patients with cirrhosis.

The second part of this document presents a proposal for a national evaluation of prioritised transplantation for critically ill patients with cirrhosis. It aims to deliver an intervention to patients for whom with existing treatment options there would otherwise be an unacceptably high mortality. In parallel there will be data collection for a detailed prospective assessment of outcomes for these patients managed with medical care alone, with the aim of refining future ACLF transplant selection processes and organ allocation models. A prospective analysis will be undertaken to assess the impact of the program upon resource use and elective waitlist outcomes.

References

1. Arroyo V, Moreau R, Jalan R, Gines P, Study E-CCC. Acute-on-chronic liver failure: A new syndrome that will re-classify cirrhosis. *Journal of Hepatology* 2015; **62**(1 Suppl): S131-43.

2. Jalan R, Saliba F, Pavesi M, et al. Development and validation of a prognostic score to predict mortality in patients with acute-on-chronic liver failure. *Journal of Hepatology* 2014; **61**(5): 1038-47.

3. McPhail MJ, Shawcross DL, Abeles RD, et al. Increased Survival for Patients With Cirrhosis and Organ Failure in Liver Intensive Care and Validation of the Chronic Liver Failure-Sequential Organ Failure Scoring System. *Clinical Gastroenterology & Hepatology* 2015; **13**(7): 1353-60.e8.

4. McPhail MJW, Parrott F, Wendon JA, Harrison DA, Rowan KA, Bernal W. Incidence and Outcomes for Patients With Cirrhosis Admitted to the United Kingdom Critical Care Units. *Critical Care Medicine* 2018; **05**: 05.

5. Weil D, Levesque E, McPhail M, et al. Prognosis of cirrhotic patients admitted to intensive care unit: a meta-analysis. *Ann Intensive Care* 2017; **7**(1): 33.

6. Finkenstedt A, Nachbaur K, Zoller H, et al. Acute-on-chronic liver failure: excellent outcomes after liver transplantation but high mortality on the wait list. *Liver Transplantation* 2013; **19**(8): 879-86.

7. O'Leary JG, Bajaj JS, Tandon P, et al. Outcomes After Listing for Liver Transplant in Patients With Acute-on-Chronic Liver Failure: The Multicenter North American Consortium for the Study of End-Stage Liver Disease Experience. *Liver Transplantation* 2019; **25**(4): 571-9.

8. Bernal W. Improving Outcomes forTransplantation of Critically Ill Patients With Cirrhosis? *Clinical Liver Disease* 2017; **10**(1): 25-8.

9. Thuluvath PJ, Thuluvath AJ, Hanish S, Savva Y. Liver transplantation in patients with multiple organ failures: Feasibility and outcomes. *Journal of Hepatology* 2018; **69**(5): 1047-56.

10. Artru F, Louvet A, Ruiz I, et al. Liver transplantation in the most severely ill cirrhotic patients: A multicenter study in acute-on-chronic liver failure grade 3. *Journal of Hepatology* 2017; **67**(4): 708-15.

11. Sundaram V, Shah P, Wong RJ, et al. Patients with acute on chronic liver failure grade three have greater 14-day waitlist mortality than status-1a patients. *Hepatology* 2019; **25**: 25.

Part 2. Pilot Evaluation Proposal.

1. Phase 1; A Pilot Evaluation of transplantation for Critically Ill Cirrhotic patients in the United Kingdom.

   Overview:

   A pilot will be undertaken of expedited liver transplantation in a cohort of critically ill patients with cirrhosis. For the purposes of this pilot, guidance only will be offered for the selection of potential transplant recipients. Specific individual decision-making will be at the discretion of each transplant centre until models can be adequately refined. Cases selected for transplantation as detailed below will receive prioritised donor offers because of the relative high short term mortality compared to non-critically ill cirrhotic patients on the Elective transplant list. Eventually it is anticipated that transplantation would be offered on a basis of transplant benefit, once accurate models of waiting list and post-transplant outcomes have been developed.

   1.1. Defining the Intervention Cohort

   All critically ill cirrhotic cases admitted to ITU or HDU of Liver transplantation centres can be considered. Data collection will be undertaken for both liver and other end organ failures, and with changes over time to define 'windows' of transplant applicability. Absolute exclusion criteria will be limited and local clinical judgement supported so that a real outcome can be assessed. Cases will be followed until discharge from hospital, 30, 60, 90 day and 1-year survival or OLT

   1.2. A Pilot Evaluation of the feasibility, outcomes and resource utilisation of liver transplantation for ACLF.

   1.2.1. Entry criteria; unplanned admissions to ICU/HDU of cases with cirrhotic chronic liver disease and qualifying clinical scenario and with an ACLF grade consistently predicting 28-day survival of less than 50%: ACLF 3 (See appendix B; ACLF Selection Thresholds)

   1.2.2. Exclusion criteria; Upper limit of age of 60 years (see appendix C; Age thresholds) active bacterial or fungal sepsis, EBV or CMV viraemia, severe irreversible brain injury,

MOF of such a severity and with adverse trajectory to realistically preclude successful organ transplantation; use of ECMO, excessive comorbidity, gross frailty and likely inability to rehabilitate; active malignancy, acute pancreatitis or intestinal ischemia. Guidance on assessment of futility of transplantation is presented in Appendix D.

1.2.3. Selection for the Intervention. Cases to be reviewed by a Hepatologist, Intensivist, Transplant Anaesthetist and Transplant Surgeon and accepted by consensus as meeting the entry criteria and having physical reserve sufficient to survive transplantation. Where cases with alcohol-related liver disease are being considered the standard guidelines for acceptance of such cases will apply (Liver Transplantation: Selection Criteria and Recipient Registration Policy POL195/10 (2/5/19)), and it is not considered that alcohol itself was the precipitant of the ACLF.

1.2.4. Notification of NHSBT. CLD Registration Form to be filled out and submitted if not already completed for patients who have already been assessed prior to developing ACLF. Additional information kept within each unit for later central analysis.

1.2.5. Donor Offering; recipient will be eligible for both DBD and DCD (+/- NRP/machine perfusion) organ as each unit wishes. Potential recipients will be prioritised by time on the waiting list. Donor offering under NOS formulae would not be appropriate (Fig 3). Allocation mechanism will be through a new 'ACLF' category inserted after hepatoblastoma and before multi-visceral cases or Elective/Variants for the duration of the pilot (figure 1). This would result in 2.2 offers per day for these cases. Allocation will be by time on the 'ACLF' waiting list. Recipients would not, at this stage be offered split livers, but Unit may wish to consider using good quality DCDs.

1.2.7 Post-operative management. Management as dictated within each transplant centre, including immunosuppression (+/- renal sparing protocols), antibiotic/anti-fungal policy, nutritional support.

1.2.6. Assessment of Intervention

A specific dataset will be collected for the detailed prospective assessment of the intervention; will include detail of graft and recipient factors and measures of pre- and post-transplant organ failure. Principal outcomes assessed will include:

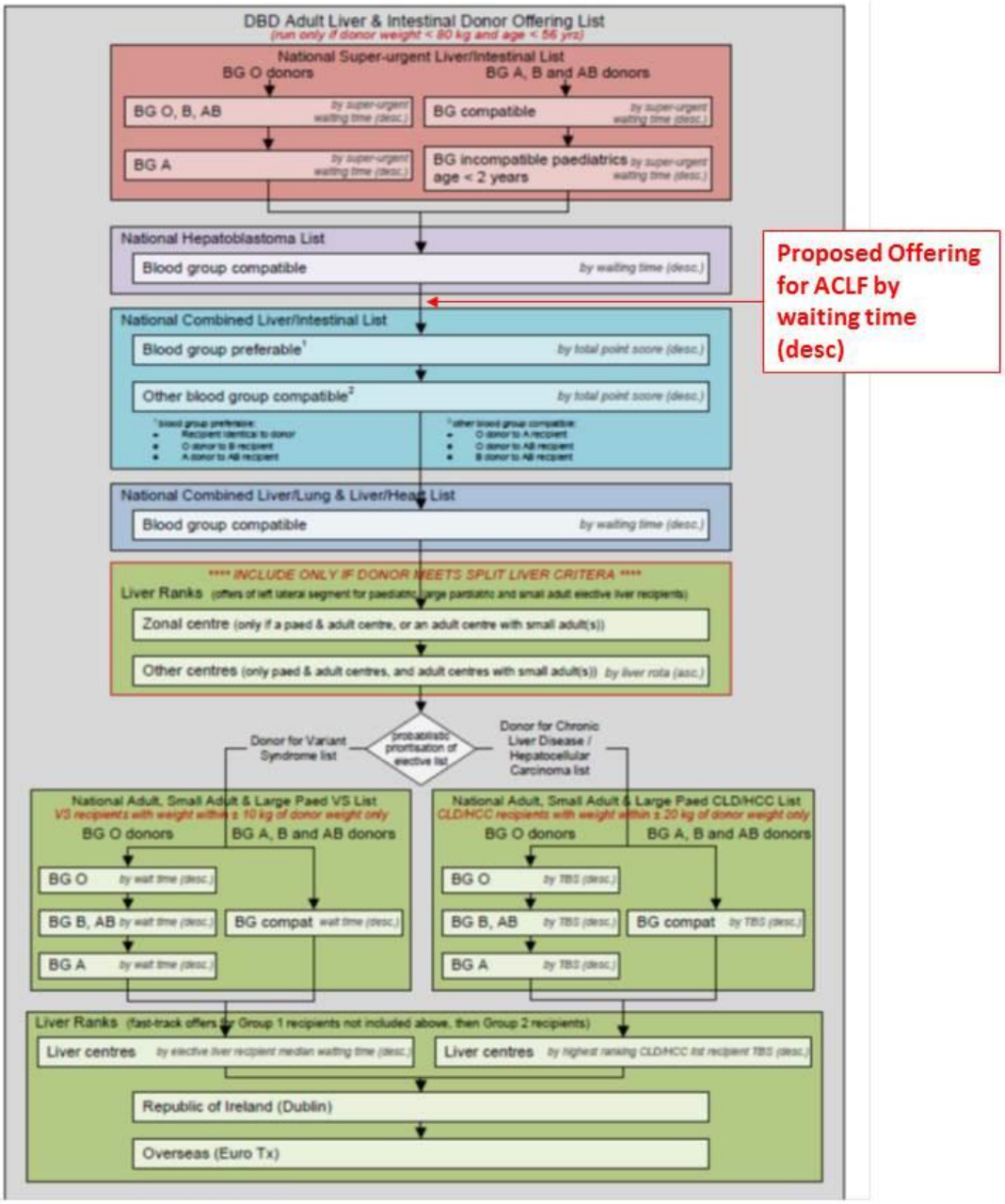
- Time to OLT or death on waiting list or removal from list; reason for removal.
- Survival time-post OLT, risk-adjusted survival from point of registration.
- Resource utilisation: days in ITU, hospital, re-operations, nature and grade of complications, use and duration of renal replacement therapy, re-admissions.

1.3. NHS BT reporting forms. As for all transplants with additional data kept within each unit for central analysis.

1.4. Governance; if accepted by LAG and TPRG, we propose setting up an ACLF/OLT review group comprising all participating Units to further refine the protocol; there will be monthly reviews of outcomes and time to transplantation or death; monthly activity reports to Chair LAG; 6 monthly activity and outcome reports to LAG;.

1.5. Final Assessment of the Pilot Intervention ; a one year survival of greater than 60% at one year will be defined as a successful outcome.

Figure 1: Proposed place of graft offering for ACLF within existing offering scheme.



2. Phase 2; modelling survival of cirrhotic patients in ITU in UK

Phase two will seek to review the outcomes of Phase 1 transplants, critically assessing the overall impact of this pilot on the NOS and on the increase in resource use that may follow an increase in transplantation of critically ill recipients. Utilising the data collected from phase one, transplant models will be refined in combination with a parallel prospective dataset of patients with ACLF managed in the participating centres without the use of transplantation. Phase 2 will aim to:

2.1. Accumulate a prospective cohort of ACLF cases in ITU/HDU on which to model outcomes with and without transplantation in combination with other retrospective cohorts from participating transplant centres.

2.2. Use newly derived models to inform better selection criteria for potential OLT recipient amongst ACLF cohort.

2.3. Use prospectively collected data to delineate the current clinical trajectory of patients with ACLF to refine the practical time windows of opportunity for liver transplantation. In doing so a firm basis for understanding the necessary degree of prioritisation for this patient group can be established.

2.4. Assess predictive factors for outcome after transplantation for ACLF and whether transplant benefit models may also apply to this population

WB/IR/IP/AG 11/11/19

Appendix A

EASL / CLIF Classification Systems for Acute on Chronic Liver failure

Table 9. CLIF-Sequential Organ Failure Assessment (SOFA) score (adapted from Ref. n° 3).

The CLIF-Sequential Organ Failure Assessment (SOFA) score					
Organ/system	**0**	**1**	**2**	**3**	**4**
Liver (bilirubin mg/dl)	<1.2	≥1.2–<2.0	≥2.0–<6.0	≥6.0–<12.0	**≥12.0**
Kidney (creatinine, mg/dl)	<1.2	≥1.2–<2.0	**≥2.0–<3.5**	**≥3.5–<5.0**	**≥5.0**
Cerebral (HE grade)	No HE	Grade I	Grade II	**Grade III**	**Grade IV**
Coagulation (INR and PLT count)	<1.1	≥1.1–<1.25	≥1.25–<1.5	≥1.5–<2.5	**≥2.5 or PLT ≤ 20.000/mm^3**
Circulation (MAP, mmHg and vasopressors)	≥70	<70	**Dopamine ≤5* or dobutamine or terlipressin**	**Dopamine >5* or E ≤0.1* or NE ≤0.1***	**Dopamine >15* or E >0.1* or NE >0.1***
Lungs					
PaO_2/FiO_2, or	>400	>300–≤400	>200–≤300	>100–≤200	**≤100**
SpO_2/FiO_2	>512	>357–≤512	>214–≤357	>89- ≤214	**≤89**

E, epinephrine; FiO_2, fraction of inspired oxygen; HE, hepatic encephalopathy; NE, norepinephrine; PaO_2, partial pressure of arterial oxygen; SpO_2, pulse oximetric saturation. The bold text indicates the diagnostic criteria for organ failures.
* µg/kg/min.

Table 10. Classification and grades of ACLF (adapted from Ref. 3).

Grades of ACLF	Clinical characteristics
No ACLF	No organ failure, or single non-kidney organ failure, creatinine <1.5 mg/dl, no HE
ACLF Ia	Single renal failure
ACLF Ib	Single non-kidney organ failure, creatinine 1.5–1.9 mg/dl and/or HE grade 1–2
ACLF II	Two organ failures
ACLF III	Three or more organ failures

ACLF, acute-on-chronic liver failure; HE, hepatic encephalopathy.

Source: EASL Clinical Practice Guidelines for the management of Patients with decompensated Cirrhosis Journal of Hepatology 2018 69 (2) 406-460,

Appendix B.

Selection Thresholds for Expedited Transplantation.

Overarching Selection Criteria

1. All patients considered for expedited transplantation under this scheme should have cirrhosis, significant liver failure as manifest by jaundice and coagulopathy and thus an illness that will be corrected by restoration of liver function by transplantation.

2. All patients should also have physiologic instability and organ dysfunction or failure that mandates care in a critical care environment and of severity such that a 28-day survival is consistently expected to be below 50%.

Discussion

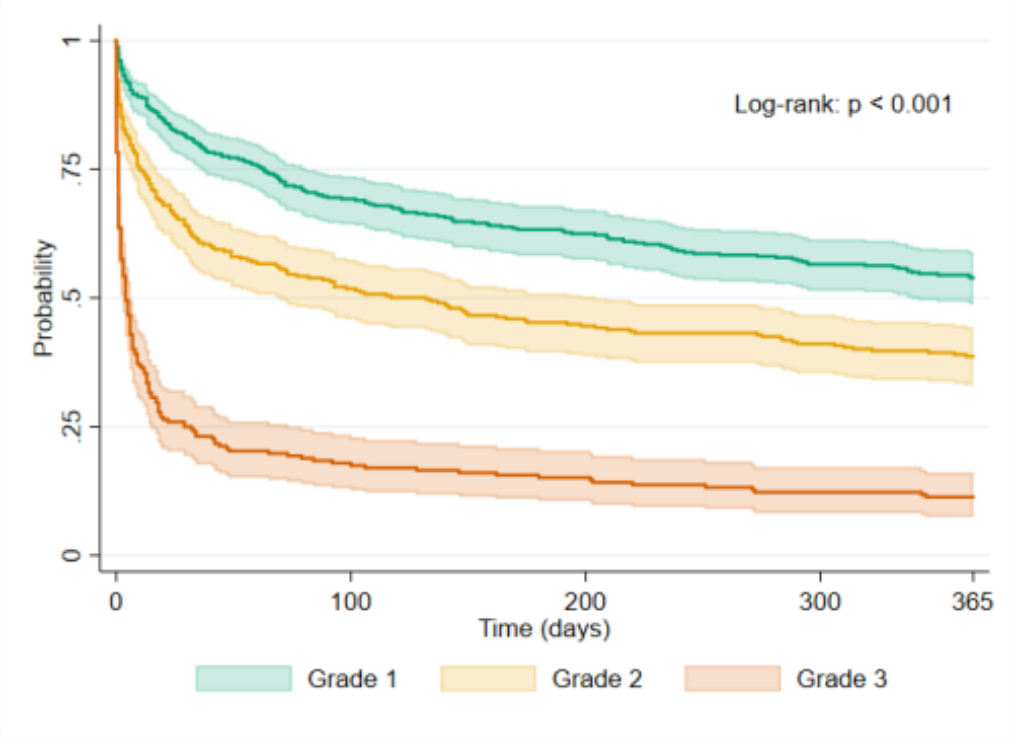
The recent report of Mahmud et al (Hepatology 2019;69:2150-2163) is one of the largest recent independent assessments of the prognostic associations of the EASL ACLF grading system (Table 1). The study cohort is recent (2008-2016) and from an overall cohort of 80,383 subjects identified 4,296 with EASL ACLF. Most of those classified as ACLF 1 did not have liver failure (as defined by a Bilirubin of <12 mg/dl or <204 µMol/l) and thus would not fulfil criterion 1 above.

Non-transplanted Survival for the study cohort with ACLF is shown in figure 1 (figure S3 in original publication). The rapidity of deterioration of patients with ACLF 3 is evident with fewer than 25% remain alive at 28 days. It is thus suggested that survival at 28- rather than 90- days should be the principal consideration for expedited transplantation, and this should be recognised in the organ allocation system applied.

Patient survival according to ACLF grade from the Mahmud report is shown in detail in table 1 below (Table S11 in the original publication). It compares survival with and without an additional bilirubin criterion of 5 mg/dl (85 µMol/l). Using the <50% survival at 28 days proposal of criterion 2 this suggests that appropriate thresholds would be ACLF Grade 2 and a bilirubin of > 5 mg/dl, or all cases with ACLF 3.

Review of this and other larger recent assessments of short-term mortality in patients with ACLF is summarised in table 2. Almost all report 28-day non-transplanted survival of <50% for patients with ACLF 3 and this consistency suggests this to be an appropriate inclusion threshold for criterion 2 above. The 28 day survival for patients with ACLF 2 is >50% and approaches 50% at 90-days; it is suggested that the unadjusted ACLF 2 grade would not consistently fulfil criterion 2. and that as indicated in the Mahmud report, this grade be utilised only with a concurrently elevated bilirubin. For simplicity, currently only the ACLF 3 threshold will be adopted.

Figure 1. Non-transplanted survival in 4296 Veterans Health Administration patients with cirrhosis according to ACLF grade.



Source: Hepatology 2019;69:2150-2163.

Table 1. Mortality in 4296 Veterans Health Administration patients with cirrhosis according to ACLF grade.

HEP-18-1608

Supplemental Table 11– Short-term Mortality of EASL ACLF by Total Bilirubin Threshold

	<5mg/dL		≥5mg/dL	
EASL Grade	**28-day**	**90-day**	**28-day**	**90-day**
Overall	**26.4%**	**39.4%**	**63.7%**	**76.3%**
Infection	32.8%	42.5%	67.8%	77.7%
Ascites	27.3%	48.7%	59.2%	77.1%
GI bleed	25.1%	35.7%	62.8%	74.7%
Hepatic encephalopathy	20.3%	36.9%	57.1%	71.5%
Grade 1	**16.2%**	**29.2%**	**43.2%**	**57.5%**
Infection	16.5%	25.6%	34.2%	48.3%
Ascites	23.5%	43.9%	51.6%	67.2%
GI bleed	13.7%	25.0%	53.5%	74.4%
Hepatic encephalopathy	11.8%	26.8%	45.0%	58.3%
Grade 2	**31.2%**	**45.0%**	**51.3%**	**68.2%**
Infection	43.9%	55.0%	55.3%	67.6%
Ascites	31.9%	55.6%	55.1%	75.1%
GI bleed	28.3%	40.1%	46.2%	57.7%
Hepatic encephalopathy	21.3%	39.5%	41.9%	61.0%
Grade 3	**62.8%**	**73.2%**	**81.9%**	**90.2%**
Infection	66.2%	75.8%	86.7%	92.9%
Ascites	51.5%	76.5%	70.6%	87.5%
GI bleed	65.9%	70.7%	79.2%	88.5%
Hepatic encephalopathy	52.6%	69.0%	74.8%	84.7%

Source: Hepatology 2019;69:2150-2163.

Table 2. Short Term non-transplanted Survival in larger series of ACLF patients.

			Survival	
Canonic	**ACLF Grade**	**n**	**28 day**	**90 day**
n=303	1	148	77.9	59.3
Gastro 2013 144 1426-37	2	108	68	47.7
	3	47	23.3	20.9
Mahmud*	**ACLF Grade**	**n**	**28 day**	**90 day**
n=4296	1	2365	80.7	67.5
Hepatol 2019 69:2150-63	2	1564	61.6	46.7
+Unpublished	3	1150	25.7	16.6
Sundaram	**ACLF Grade**	**n**	**28 day**	**90 day**
n=143759	0	116439	95.5	87.7
Gastro 2019 156 1381-91	1	13643	84.8	81.4
+Unpublished	2	7225	80.2	80.3
	3	6452	65.8	65.4
Hernaez*	**ACLF Grade**	**n**	**28 day**	**90 day**
n=19082	1	9239	83.1	69.2
J Hep 2019 70 639-47	2	7298	73.2	58.4
	3	2545	46.7	31.2
Bernal	**ACLF Grade**	**n**	**28 day**	**90 day**
n=623	0	187	87.7	85
Unpublished	1	73	79.4	65.7
	2	144	66.7	57
	3	219	37.8	29.7

Note: The ACLF2 / Bilirubin > 5 mg/dl criterion as per Mahmud et al is difficult to extract from other studies but many report 28-day survival according to unmodified ACLF grade and are shown above.

*Study cohorts derived from overlapping VHA patient dataset with varying derivation methodology.

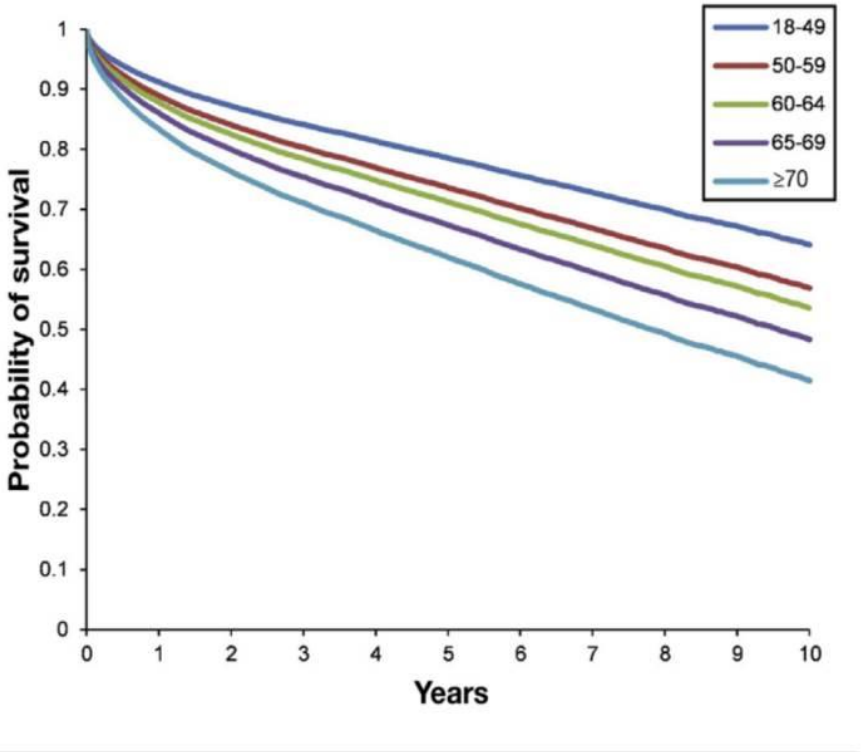
WB 28/10/19

Appendix C

Age Thresholds as Exclusion Criteria for Liver Transplantation for ACLF.

1. Evaluation of both single centre and national liver transplantation programmes have confirmed that increasing age is consistently associated with impaired post-transplant patient survival.

Figure 1. Kaplan-Meir Post transplant patient survival by age group (years) in UNOS dataset (n=60,820) USA, 2002-2014.

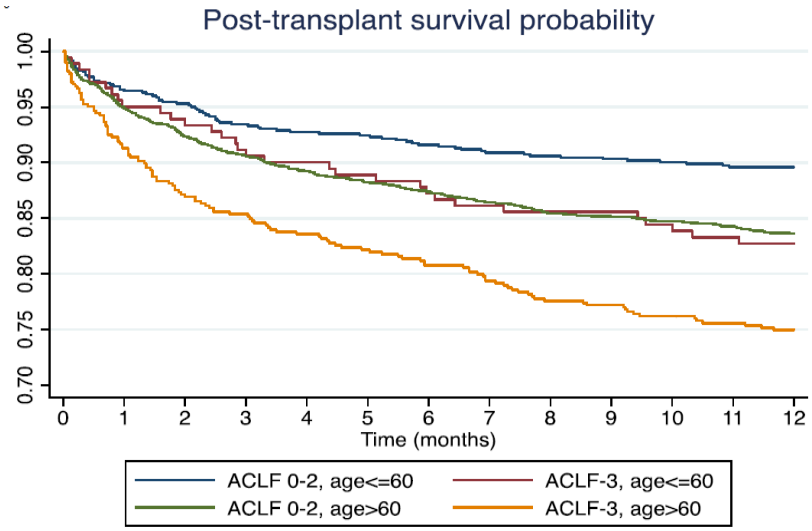


Source: Su et al Gastroenterology 2016 150 (2):441-453.

2. Other studies have suggested that in elective transplantation there may be a synergistic adverse effect upon survival of increasing age and higher MELD score, with increased early mortality seen in older patients with MELD scores >25-28 (Durand et al Journal of Hepatology 2019 70(4) 745-758).

3. Retrospective database studies also suggest close interaction between age and severity of MOF, with an additive adverse effect seen on post-transplant mortality. (Sundaram et al Journal of Hepatology 2019 (in press), Figure 2)

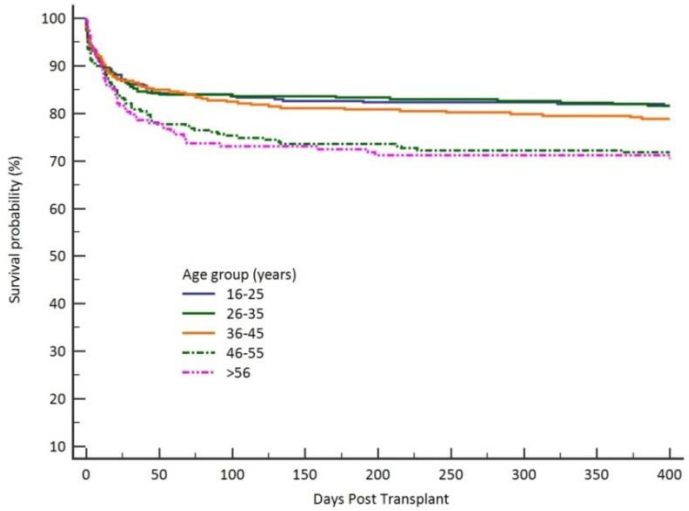
Figure 2. One-year post-transplant survival of UNOS patients with ACLF-3 at listing (n=3636), categorized by ACLF grade and age at transplantation.



Source: Sundaram et al Journal of Hepatology 2019 (in press) UNOS database 2004-2017 At transplantation ACLF 0-2 n=892 ACLF 3 n=2744

4. Parallels may be drawn from experience in emergency transplantation in patients with ALF where there may be an equivalent severity of multi-organ failure. Clinical experience and the analyses to date suggest the factor most consistently associated with recipient mortality is age, with markedly inferior outcomes seen in recipients older than 50 years, a low threshold reflecting the extreme physiologic stress associated with emergency transplantation.

Figure 3. Patient Survival after super-urgent transplantation for ALF by recipient age: UK & Ireland. 1995-2016 n=1375



Source: NHSBT dataset; Bernal et al Unpublished 2019.

5. Such an effect is likely to be even more pronounced in patients with CLD where unlike in ALF, chronic illness preceding the development of ACLF will likely have resulted in greater compromise of underlying physical reserve.

6. Age is a key consideration in the potential use of expedited transplantation for patients with ACLF. It is suggested that whilst individualised judgements are made on the basis of underlying physical condition and the severity of acute illness, the age of 60 is the upper limit considered.

WB 28/10/19

Appendix D. Clinical Assessment of Futility of Transplantation

Overview

A key judgement that will need to be made in the practical utilisation of expedited liver transplantation (ELT) for critically ill patients with cirrhosis is when proceeding with liver transplantation is associated with an unacceptably high recipient mortality. There is limited data available to inform this decision, and most of that is derived either from case series of limited size, or from the secondary analysis of retrospective datasets not constructed for this purpose. It is anticipated that the results of the current pilot and similar undertakings in other national LT programmes will provide detailed data in this regard. A synthesis of current data is provided below to provide practical support clinicians in making this challenging assessment.

1. Age, Comorbidity and Hospitalisation.

Recipient age and comorbidity already form key considerations when selecting patients for ELT and it is assumed that all those waitlisted will be below 60 years of age and have only minimal comorbid conditions.

Factors about which there is very limited data to inform decision-making include the impact of prolonged hospitalisation and sarcopenia prior to transplantation, on post-ELT survival. It must be assumed that both are clearly adverse factors to be included in the overall assessment process, but that it is not currently possible to specify thresholds or weighting that should be applied to transplantation decisions. It is very likely that the impact of these factors will be greater in older recipients, even within the age range planned.

2. Multiple Organ Failure

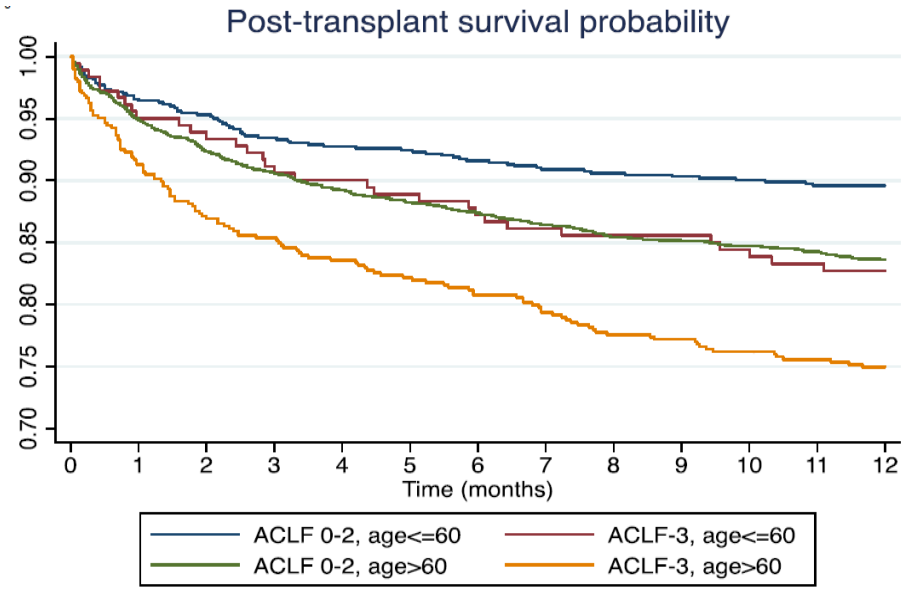
All patients in this pilot will by definition have multiple extra-hepatic organ systems dysfunction and / or failure (MOF), and some guidance can be offered on the pattern and severity of multiple organ failure and how it relates to likely ELT outcome. The worse the MOF, the worse the survival; there is close interaction between MOF severity and recipient age. As compared to younger recipients with MOF of equivalent severity, older recipients have markedly worse survival (figure 1).

2.1 Dynamics

a. A minority – perhaps 20% - of patients waitlisted for ELT will show improvement in OF whilst awaiting ELT. This pattern of change is associated with better post-ELT survival, particularly in older recipients (figure 1). Improvements in respiratory function are most strongly linked to better patient survival, with significant but less strong association also

seen with improvement in cardiovascular and neurologic function (Sundaram et al Journal of Hepatology 2019 (in press)).

Figure 1. One-year post-transplant survival of patients with ACLF-3 at listing (n=3636), categorized by ACLF grade and age at transplantation.



Source: Sundaram et al Journal of Hepatology 2019 (in press) UNOS database 2004-2017 At transplantation ACLF 0-2 n=892 ACLF 3 n=2744

b. The greater proportion of potential recipients can be expected to have initially static and then worsening MOF. If such worsening is clearly related to the development of bacterial or fungal sepsis, then this would represent an absolute contra-indication to proceeding with ELT.

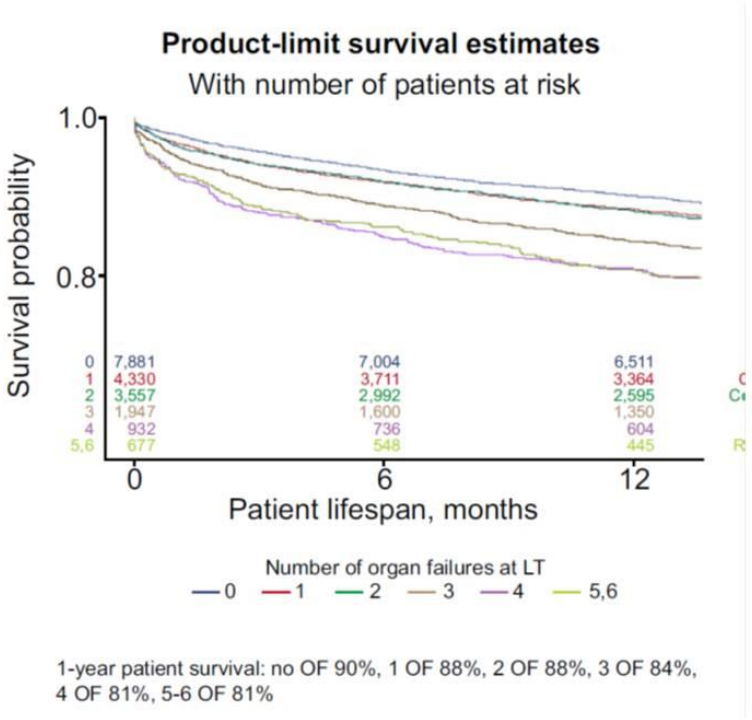
2.2 MOF and Waitlist Duration.

The relationship between duration of time on the waitlist and post-ELT recipient survival is complex. Though some series suggest that wait time prolonged >7 days is associated with impaired survival, the impact of wait-list time appears to be interrelated with the dynamics of MOF. In UNOS ACLF 3 recipients in whom the severity of MOF fell between listing and ELT, there was no increase in mortality when those transplanted within 7 days of listing were compared to those transplanted between 7 and 28 days. However, in those in whose MOF remained static at ACLF 3 on the waitlist, an increase in mortality seen in those transplanted after 7 days (Sundaram et al Journal of Hepatology 2019 (in press)).

2.3 MOF thresholds

Thresholds for cumulative and individual OF are more difficult to specify, and assessments must be placed in the context of recipient age, duration of illness and general debility. In multi-centre studies, recipient survival after ELT was worse in those patients transplanted with increasing organ failures (figure 2). However, in this analysis no MOF threshold for 'futile' ELT was identified as 1-year survival was still >75% in the selected patients transplanted in 5-6 OF.

Figure 2. UNOS Patient survival probability by the number of OFs for those transplanted within the first 30-days based on the number of OFs at the time of LT.



Source: UNOS 2002-16 . *Journal of Hepatology* 2018; **69**(5): 1047-56

Another multicentre study of 150 European ACLF 3 patients who underwent ELT identified 4 independent risk factors for mortality, 3 of which related to MOF severity (Artzner et al 2019 MS submitted)

- Age >53 years (OR 5.79 (95% CI 1.05-32))
- Respiratory compromise such that PF ratio was ≤200mmHg (OR 8.6 (1.3-57)
- Arterial blood lactate level >4 mMol/l (OR 10 (1.6-61))
- Leukopenia and count <1 x 10^9/l (OR 12.9 (2.3-74))

There is less data to inform thresholds for Cardiovascular OF beyond which ELT should not be proceeded with, and clearly this will need to be placed into context of the dynamics of changes in levels of support required and whether there is suspicion that sepsis is evolving. It is suggested that a caution be applied if the requirement for norepinephrine to maintain a mean arterial pressure of >65 mmHg is greater than 0.3 micrograms / kg / min, and that ELT should not be proceeded with if it exceeds 0.5 micrograms / kg / min.

Consultation with other United Kingdom Liver Intensivists and Anaesthetists suggests that thresholds for respiratory dysfunction should be low, with a required FiO2 of >45-50% with PEEP ≥5 should be regarded as a significant concern. Any radiologic indication of evolving pulmonary sepsis, particularly if suggestive of possible fungal infection, should also be regarded as contra-indication to proceeding with ELT.

WB 11/11/19