Liver transplantation for critically ill patients with acute on chronic liver failure: a prospective national programme of waitlist prioritisation

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Summary

Background Acute on Chronic Liver Failure (ACLF) complicates chronic liver disease (CLD) combining rapidly progressive hepatic with extra-hepatic multiple organ failure and high short-term mortality. Effective therapeutic options are very limited, and liver transplantation (LT) seldom utilised through concerns of high recipient mortality and resource use. Retrospective reports suggest recent outcomes may have improved, but use of LT for ACLF has not been prospectively assessed.

Methods A prospective programme of prioritised liver graft allocation for selected recipients with ACLF through registration on a new national tier, initiated in May 2021 in all 7 United Kingdom LT centres. Candidates were selected by centre multidisciplinary teams, with inclusion criteria mandating cirrhotic CLD with ACLF requiring critical care (CC) organ support and expected 1-month mortality >50%. Exclusion criteria included age ≥60 years, previous LT, comorbidity or substance misuse profile precluding elective LT. A pilot 50 registrations were planned, with pre-specified futility criteria of a 1-year post-LT survival of 60%.

Findings Fifty-two patients were registered on the ACLF tier, median (IQR) age 46 (39–52) years, ACLF grade 3 (3–3) and Model for End-stage Liver Disease (MELD) 39 (35–40). At registration 32 (62%) required mechanical ventilation, 44 (85%) vasopressors and 46 (89%) renal replacement. Forty-two (81%) underwent LT 2 (2–5) days after registration: 10 (19%) did not. All non-transplanted died at median 7 (4–13) days after registration ($p < 0.0001$ vs. LT). Post-LT follow-up was 212 (119–530) days and patient survival 81% (95% CI 66–91): 28-, 90-day and 1-year survival after registration 93%, 86% and 77%. Median length of CC and hospital stay in LT recipients was 16 (8–28) and 35 (23–54) days respectively.

Interpretation We report the first prospective national series of prioritised liver transplantation for critically ill patients with ACLF. For selected recipients LT is a practical and highly effective treatment option where no other similarly effective interventions exist.

Funding There was no funding for the study.

Keywords: Acute on chronic liver failure; Liver transplantation; Critical care

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Research in context

Evidence before this study

In planning the acute on chronic liver failure (ACLF) transplant prioritisation tier we assessed evidence available at that time relating to the survival of people with cirrhosis and ACLF with non-transplant interventions, survival and resource use after liver transplantation (LT), and risk factors for post-transplant mortality. The findings confirmed the need for the tier and informed the inclusion and exclusion criteria utilised. Initial searches were conducted using PubMed and MEDLINE and the search terms 'Liver Transplantation', 'acute on chronic liver failure' and 'ACLF'. No language restrictions were applied. Subsequent searches used the reference lists from the sources identified, and were informed by discussion with subject matter experts, including people with lived experience of the condition. Meta-analyses and prospective case series of ACLF confirmed close relation between severity of multi-organ failure and survival, reporting 28-day mortality >70% in severely ill patients. Few patients with ACLF undergo LT from intensive Care (ICU); on meta-analysis 3.8% of all people with cirrhosis admitted to critical care underwent LT within 6 months of admission. In a United States national registry series from 2002 to 2013 of first transplants with cirrhosis, 8% were in ICU at the time of LT, and in the United Kingdom national registry from 1994 to 2016 only 4%. Registry data and retrospective case series suggest progressive improvement over time in post-LT survival of severely ill LT recipients but no prospective national reports were identified.

Added value of this study

We report the results of the first prospective national series of prioritised LT for patients with very severe ACLF. All those registered for LT but not transplanted died at median of 7 days after registration, whilst survival in LT recipients was 81% (95% CI 66–91) at median follow up 212 days, with 88% of post-LT deaths occurring in the immediate post-LT hospitalisation. Survival was related to severity of illness at time of registration, and post-LT hospitalisation was prolonged at a median 35 days. Post-transplant renal dysfunction was common in surviving recipients late after LT, and three of 10 cases transplanted with underlying Primary Sclerosing Cholangitis were later found to have unexpected Cholangiocarcinoma.

Implications of all the available evidence

The findings of this study confirm that for selected recipients with severe ACLF, expedited LT is a practical and highly effective treatment option where no other similarly effective interventions exist. They support expansion of prioritised LT for this indication, with prospective investigation of the practical clinical issues identified. Future research should focus on optimisation of LT candidate assessment to avoid LT with an unacceptably high mortality, including means for quantification of pre-LT illness severity, and reduction of post-LT infection and renal dysfunction. Post transplantation quality of life in ACLF LT recipients requires further investigation. The ACLF prioritisation tier has now been adopted as part of the United Kingdom national liver graft allocation policy.

Introduction

Acute on Chronic Liver Failure (ACLF) represents a final stage in the natural history of cirrhotic chronic liver disease (CLD). It combines the presence of liver failure, manifest as jaundice and coagulopathy, with the development of extra-hepatic organ failures including encephalopathy, renal and cardiovascular failure.[1] The severity of illness is such that management in a critical care setting is frequently required, with high short- and medium-term mortality.[2]

Effective therapeutic options are very limited in patients with advanced ACLF. With current approaches to care, mortality 28-days after illness onset often exceeds 70%.[1,2] To date, when tested in randomised controlled trials (RCT) the theoretical potential of extra-corporeal liver assist devices has not translated into meaningful clinical benefit, and immune-modulatory medical therapies have been similarly unsuccessful.[3,4] There is urgent unmet clinical need for interventions to improve survival in a condition responsible for many of the two million deaths from CLD world-wide each year.[2,5]

For selected patients with advanced ACLF, Liver Transplantation (LT) could offer that opportunity. It is now an established treatment for other critically-ill patients with liver disease. Acute Liver Failure (ALF) is a rare critical illness most commonly affecting younger adults with both liver and multiple extra-hepatic organ failure (MOF) but is distinct from ACLF as it occurs in people with normal pre-morbid liver function in the absence of underlying CLD.[6] The refinement over time of use of LT in people with ALF is such that post-transplant outcomes of prioritised emergency liver transplantation (ELT) now approaches that of elective LT for other 'standard' indications.[7]

Extending the use of LT to ACLF presents significant practical challenges. Patients with ACLF are not only critically ill with MOF but are commonly older than those with ALF, and its onset is often in the setting of prolonged chronic illness with debility and sarcopenia, factors established as having major negative effects upon post-LT patient survival.[8,9] The time 'window' for successful LT may be very short given the rapidity of illness progression to overwhelming MOF that contra-indicates LT. This paired with their incapacity limits psychological and physiological assessment of underlying comorbidity while necessitating prioritisation of

ACLF candidates on the LT waitlist, above those with CLD and elective indications.[10–13]

These factors and a historical presumption of poor recipient survival and very prolonged post-LT hospitalisation and resource use have resulted in a reticence for the use of LT for ACLF.[14] In the United Kingdom (UK) fewer than 5% of LT are performed for this indication, and the existing National Liver Offering Scheme (NLOS) introduced in March 2018 for deceased donors after brain death (DBD) does not provide waitlist prioritisation.[15–17]

However, recent retrospective series and one single centre prospective series suggest that post-LT survival and resource use may in fact be at acceptable levels, and this and the lack of alternative effective interventions have resulted in increased interest in its use.[10,11,15,18] In recognition of these reports and following analysis indicating that the NLOS mortality prediction and organ allocation model underestimated the pre-LT mortality of critically-ill patients with CLD, the Liver Advisory Group (LAG) of NHS Blood and Transplant (NHSBT) initiated a national pilot programme in May of 2021 of prioritised LT for adults with ACLF with a new 'tier' of graft offering, above that for standard 'elective' NLOS-based allocation[19] (Supplemental Materials 1). Here we report the results of this, the first national prospective initiative of prioritised LT for this indication, with an assessment of the practicality of this approach, patient survival with and without LT, post-LT resource use and complications.

Methods

Inclusion and exclusion criteria

Criteria for inclusion and exclusion from the ACLF tier were determined in 2021 by the ACLF Fixed Term Working Group (FTWG) of LAG on the basis of clinical experience and review of case series reporting outcome of LT for ACLF and are shown in Text Box 1. Criteria specified that all cases should have cirrhosis without other comorbidity that would preclude standard LT, be requiring critical care support and have ACLF defined using European Foundation for the Study of Chronic Liver Failure (EF-CLIF) criteria with expected 1-month mortality exceeding 50%; most were expected to be ACLF Grade 3.[1] All cases had to have evidence of severe liver failure manifested by clinically significant jaundice and coagulopathy, and thus an illness that would be corrected by LT. All cases must be below 60 years of age, a consistent threshold for poor post-LT survival in retrospective series, and patients who previously underwent LT were not eligible for consideration. Only cases whose alcohol and/or substance misuse profile were compatible with existing UK criteria for elective LT were considered for the Tier, and for this reason active high-level alcohol consumption and Severe Alcoholic Hepatitis were specifically excluded.[3,20]

Box 1.
Inclusion and exclusion criteria for United Kingdom prioritised ACLF tier.

Inclusion criteria:
Cirrhosis and liver failure with jaundice and coagulopathy.
Severe organ dysfunction or failure requiring intensive care support.
Illness severity with expected 28-day survival of <50%, usually ACLF-3.

Exclusion criteria:
Age >60 years.
Comorbidity or alcohol use precluding standard LT.
Previous liver transplantation.
Active bacterial or fungal sepsis.
CMV viraemia.
Severe irreversible brain injury.
Multi-organ failure of severity and/or with adverse trajectory precluding successful LT.
Use of ECMO.
Gross frailty and likely inability to rehabilitate.
Active malignancy.
Severe acute pancreatitis or intestinal ischaemia.

Review and selection process

Candidates for ELT were selected by clinicians at the seven UK LT centres and could include cases who had previously undergone LT assessment and wait-listing, and those presenting for in ACLF without prior asessment. All underwent review by members of a local multi-disciplinary team comprising a Transplant Hepatologist and Surgeon, Anaesthetist and Intensivist and were selected only if all members were supportive. No threshold values for pre-LT individual or cumulative organ systems failure excluding LT were mandated. Cases were then proposed for final review to the FTWG at LAG which included a Transplant Hepatologist, Surgeon and Intensivist who confirmed eligibility through review of inclusion and exclusion criteria and were placed on the ACLF tier on the same day. The decision to proceed with transplantation and pre-, intra-operative and post-transplantation care, including immunosuppression and antimicrobial therapies were at the transplanting centres discretion. Detail of the supportive care utilised in different participating LT centres is presented in Supplementary Materials 2.

Prioritisation

The NLOS comprises 6 tiers of liver graft allocation, with greatest priority and highest tier assigned to 'Super-Urgent' (SU) indications—principally ALF–and the lowest assigned to 'standard' elective indications.[17] The ACLF tier was placed below the SU tier and those tiers allocating grafts for critically ill paediatric recipients and those with Hepatoblastoma, with estimations that this would result in an interval from ACLF tier registration to graft availability of 2–3 days. A pragmatic 50 ACLF

tier registrations was planned, with interim review of outcomes after 25 had been registered. Pre-specified futility criteria for the pilot of the tier were of a 1-year post-LT survival of 60% or below equating to an anticipated 5-year outcome of 50%, the accepted measure of futility within the UK (Supplemental Materials).[20]

Scoring and statistical analysis

Acute on Chronic Liver Failure grade was assigned as previously published, with ACLF grade 3 (ACLF-3) assigned when 3 or more organ failures (OF) were present.[1] Critical Illness severity assessment at ACLF tier registration utilised CLIF Organ Failure Scores (CLIF-OF) to assess global severity of multiple organ failure, with derivation of the number of specific OF using the CLIF-OF thresholds.[1] Organ failure scoring was repeated in those patients who remained on the waitlist for more than 48 h. Other scores calculated included the CLIF-C ACLF score which combines the CLIF-OF with patient age and leucocyte count to generate a short-term survival prediction, and the MELD-Sodium score to assess liver disease severity.[21,22] Determination of severity of frailty was at the centres discretion and was principally by subjective clinical assessment. We also determined the Sundaram ACLF-LT-Mortality (SALT-M) and Transplantation for ACLF-3 (TAM) scores proposed to identify ACLF LT recipients with poor 1-year post-LT survival.[23,24] These two scores were not used in decision-making in relation to selection for or proceeding with LT. Post-transplant renal dysfunction was categorised by Kidney Disease: Improving Global Outcomes (KDIGO) eGlomerular Filtration Rate (eGFR).[25] The primary outcome assessed was patient survival, with descriptive exploration of resource use and recipient morbidity. Donor, recipient and transplant characteristics were compared, stratified by registration outcome using non-parametric tests with chi-square and fisher's exact tests for categorical data and mann-whitney U and Wilcoxon rank-sum tests for continuous data as appropriate. Statistical analysis utilised SPSS v29.01 and MEDCALC v23 and data is presented as median (interquartile range) or n (%).

The programme was initiated as a service evaluation rather than a research study and consent beyond that standard for LT with high mortality risk was not obtained. No randomisation or procedures beyond that required for standard care were undertaken. Consent for the use of anonymised data for outcome analysis is obtained from all UK patients at registration onto the national transplant waiting list.

Role of the funding source

There was no funding for this study.

Results

By November of 2023 a total of 52 patients had been registered on the ACLF tier. Clinical and laboratory features are shown in Table 1. Median (IQR) age was 46 (39–52) years, 24 (46%) were female and ACLF grade was 3 (3–3), MELD 39 (35–40), CLIF-OF score 15 (13–16) and CLIF-C ACLF score was 64 (54–69). Causes of CLD were Cholestatic disease in 13 (25%: Primary Biliary Cholangitis (PBC) n = 3, Primary Sclerosing Cholangitis (PSC) n = 10), Alcohol in 13 (25%), Viral in 6 (12%) and Other in 20 (Autoimmune Hepatitis (n = 3), Biliary Atresia (n = 3), Congenital hepatic fibrosis (n = 3), Indeterminate (n = 5), Metabolic dysfunction-associated steatotic liver disease (n = 3), cystic fibrosis/alpha-1 anti-trypsin deficiency (n = 2), Secondary Sclerosing Cholangitis (n = 1)). Thirty-two (62%) of those registered had been previously waitlisted for elective LT and had deteriorated with development of ACLF, at a median of 53 (10–161) days after initial wait-listing. All were in Intensive Care at the time of ACLF tier registration having been admitted at a median of 6 (2–13) days previously. At registration 32 (62%) were intubated and ventilated, 44 (85%) were requiring vasopressors and 46 (89%) continuous renal replacement therapy (RRT). The precipitant of ACLF was bleeding in 18 (35%) cases and sepsis in 16 (31%) with no definitive precipitant identified in the others. Thirty-nine (75%) had never smoked, 9 (17%) were former and 4 (8%) active smokers at time of LT. Seven (13%) and 8 (15%) had pre-LT hypertension and diabetes respectively.

Four cases were discussed with the central review team and not registered on the tier. In two cases the review group suggested that severity of illness was such that LT was felt to be inadvisable and both died very soon after, and in two cases the review group felt acute illness to be of insufficient severity to justify ACLF registration. In both of the latter cases LT was subsequently and successfully undertaken under standard NLOS mechanisms.[20]

ACLF tier outcomes

Forty-two (81%) patients underwent LT at a median of 2 (2–5) days after ACLF tier registration. Ten (19%) did not, and all died at a median of 7 (4–13) days after registration (Fig. 1). Seven had deteriorated with worsening MOF on the waitlist and were removed and 3 died with MOF whilst active on the waitlist. Whilst on the ACLF tier, 7 of the 10 (70%) had graft offers (median 2 (range 1–3)) which were declined at the LT Centre due to recipient condition or donor unsuitability.

Comparison of transplanted and non-transplanted cases

Comparison of cases registered who did and did not undergo LT is shown in Table 1. Non-transplanted cases tended to have higher Body-Mass Index, a longer time on the ACLF Tier and higher organ failure scores at registration, although these differences did not reach statistical significance (Supplemental Materials 3).

	All		Transplanted		Not transplanted		p
n	52		42		10		
Age (years)	46	(39–52)	47	(38–53)	45	(40–51)	
Sex (F)	24	46%	20	48%	4	40%	
BMI (kg/m^2)	28.5	(22.1–34.3)	27.4	(22–32.6)	36.1	(22.3–39.3)	0.14
Aetiology							
Alcohol	13	25%	8	19%	5	50%	0.28
Cholestatic	13	25%	11	26%	2	20%	
Viral	6	12%	5	12%	1	10%	
Other	20	38%	18	43%	2	20%	
ACLF precipitant							
Bleeding	18	35%	16	38%	2	20%	0.28
Sepsis	16	31%	12	29%	4	40%	0.48
Other	10	19%	7	17%	3	30%	
Timing of ACLF Tier registration							
Previously waitlisted	32	62%	25	60%	7	70%	
Time in ICU Prior (days)	6	(2–13)	5	(1–14)	8	(4–12)	0.50
ACLF tier wait (days)	3	(2–5)	2	(2–5)	4	(3–7)	0.11
Laboratory findings at ACLF tier registration							
HB (g/l)	83.5	(72–91)	85	(73–91)	76	(70–93)	
WBC (x10^9/l)	11.4	(7.7–17.2)	11	(6.7–17.1)	14.5	(10.5–22.5)	0.13
PLT (x10^9/l)	62	(41–93)	66	(42–97)	51	(35–72)	0.10
INR	2.1	(1.7–2.9)	2	(1.6–2.7)	2.8	(1.9–4.2)	0.04
Bilirubin (µMol/l)	423	(271–581)	419	(255–542)	536	(393–648)	0.14
Urea (mMol/)	11.5	(7.4–18.2)	10.8	(7.2–18.4)	12.7	(8.9–18.4)	
Creatinine (µMol/l)	124	(86–181)	121	(81–184)	129	(105–146)	0.79
Sodium (mMol/l)	136	(131–140)	138	(133–140)	135	(128–137)	0.07
Arterial PO_2 (kPa)	10.6	(9.6–12.6)	11	(9.7–12.9)	10.2	(9.6–10.8)	
Arterial lactate (mMol/l)	2.2	(1.5–2.8)	2.1	(1.4–2.8)	2.7	(1.7–4.5)	0.14
Illness severity at ACLF tier registration							
Encephalopathy grade	3	(1–3)	3	(2–4)	2	(1–4)	
PaO2/FiO2 ratio	260	(201–363)	287	(208–393)	253	(195–313)	0.21
ACLF grade	3	(3–3)	3	(3–3)	3	(3–3)	0.48
CLIF OF score	15	(13–16)	14	(13–16)	16	(15–17)	0.07
CLIF organ failures (n)	4	(3–5)	4	(3–4)	5	(4–5)	
MELD score	39	(35–40)	38	(34–40)	40	(38–40)	0.08
CLIF-C ACLF Score	64	(54–69)	61	(54–68)	69	(64–71)	0.05
Organ support at ACLF tier registration							
Vasopressors	44	85%	35	83%	9	90%	
No. of vasopressors	1	(1–2)	1	(1–1)	2	(1–2)	0.14
Renal replacement	46	88%	36	86%	10	100%	0.21
Ventilation	32	62%	27	64%	5	50%	0.41
Inspired oxygen (%)	30	(24–35)	30	(24–35)	30	(25–38)	0.16

Note: data is median (IQR) or n (%). p for comparison of transplanted and non-transplanted patients with values shown only when $p \leq 0.5$. Abbreviations: BMI: body mass index, ACLF: acute on chronic liver failure, ICU: intensive care unit, HB: haemoglobin, WBC: white blood cell count, PLT: platelet count, INR: International Normalised Ratio, CLIF OF: chronic liver failure organ failure score, MELD: model for end-stage liver disease.

Table 1: **Clinical and laboratory features at time of ACLF registration according to transplant status.**

Cases transplanted

Grafts and immunosuppression

All grafts were whole, and with one exception from DBD donors, and were ABO matched (14 compatible, 28 identical). Median donor age was 54 (48–63) years and Cold Ischemic Time (CIT) 508 (409–615) minutes. All centres utilised Tacrolimus based immunosuppression, with a low dose Calcineurin-Inhibitor (CNI) regimen with Basiliximab induction adopted in 13 (31%) recipients (Supplemental Materials 2).

Survival

Median follow-up in those transplanted was 212 (119–530) days and current patient survival is 81%

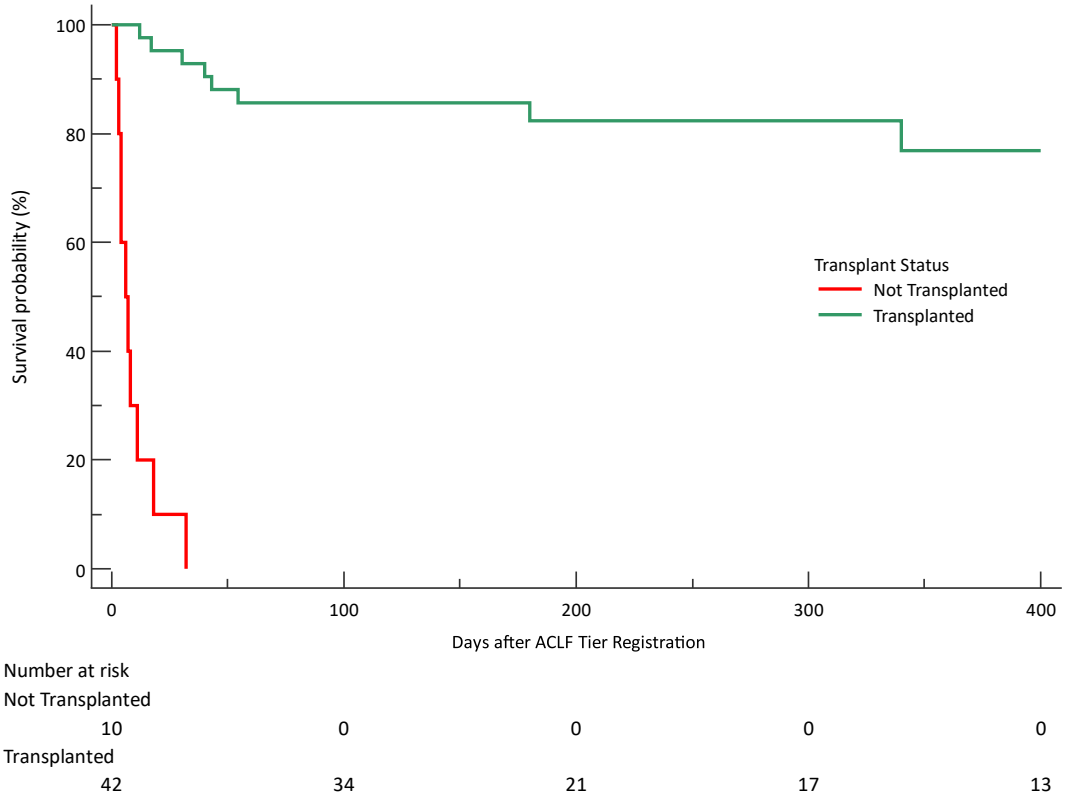

Fig. 1: Survival after ACLF tier registration according to Transplant Status. Note: p < 0.001 Log-rank.

(95% CI 66–91): 28-, 90-day and 1-year survival after registration was 93%, 86% and 77% respectively (Fig. 1). No recipient was lost to follow-up. Eight recipients died at a median of 42 (20–149) days after LT, 7 (88%) during their initial post-LT hospitalisation at a median of 32 (12–38) days after LT, one of an early intracranial haemorrhage and the remainder of later sepsis-related MOF. One recipient who died received a whole ABO-identical graft from a deceased after cardiac death (DCD) donor outside of the ACLF tier. One recipient with PSC died more than 9 months after LT with metastatic cholangio-carcinoma (CCA).

Resource use and morbidity

Median intraoperative blood transfusion requirement was 7 (5–11) units, Fresh frozen plasma 6 (4–9) and Platelets 3 (1–5). Length of ICU and hospital stay in LT recipients was 16 (8–28) and 35 (23–54) days respectively. All surviving recipients are now living at home. One recipient required retransplantation for primary non-function at day 2 after first transplant, and another who died with MOF had developed hepatic artery thrombosis at post-LT day 6. Eight (19%) had post-LT biliary issues, of whom 3 required surgical reconstruction and 5 were managed endoscopically. Three (7%) cases were treated for episodes of acute cellular rejection. Pre-LT 3 patients had Vancomycin resistant enterococcus (VRE) colonisation and one was later identified as having pulmonary aspergillus colonisation. Post-LT a further 3 were identified with VRE, 2 with Carbapenem-resistant Enterobacteriaceae, one with multi-resistant Pseudomonas and one with Candidaemia.

Three patients were diagnosed with CCA after LT, not identified on pre-LT imaging. Pre-transplant CA19.9 was 38, 47 and 328 kU/l (normal <37). All had PSC and two were first presentations with ACLF and not been previously waitlisted. All were deeply jaundiced at presentation (Bilirubin >400 μMol/l) and 2 had presented with sepsis—one with a *klebsiella* bacateraemia and one with spontaneous bacterial peritonitis. One patient died (as above) and the other two remain well, one having undergone a later Pancreato-duodenectomy and the other with limited intrahepatic disease at LT, showing no evidence of recurrence at 484 and 335 days post-LT respectively.

Post-transplant renal dysfunction was common in surviving recipients: at latest follow-up 13 of 34 (38%) had CKD Categories G1 and G2 (normal or mild reduction of GFR with eGFR >60 ml/min/1.73 m^2), 13 (38%) G3a/G3b (eGFR 59–30) and 8 (24%) G4/G5 (severe reduction/kidney failure: eGFR <29). Two (6%) are

currently dialysis dependent. There was no significant association between G4/5 CKD at follow-up with requirement for pre-LT RRT, graft characteristics or use of CNI sparing immunosuppression (data not shown).

Comparison of survivors and non-survivors of transplantation

Comparison of survivors and non-survivors of transplantation is shown in Table 2. Non-survivors were more often first presentations with ACLF, tended to have a longer wait time on the ACLF tier and as evidenced by organ failure scores, significantly more severe MOF at registration. In those recipients waitlisted for more than 2 days, there was no significant difference in CLIF-OF score at day 3 or change from day 1 to 3 when survivors and non-survivors were compared (Supplemental Materials 3). There were no significant differences in donor age, ABO compatibility or CIT, though the only recipient of a DCD graft died.

Discussion

We report the first prospective national series of prioritised liver transplantation for critically ill patients with ACLF. Using a pragmatic approach to candidate selection that was centrally guided but transplant centre driven, cases selected by local consensus were very severely ill. Even with waitlist prioritisation and transplantation a median of 2 days after registration, nearly 20% died before transplantation was possible. Waitlist deaths were characterised by a longer wait time, higher body mass index and more severe multi-organ failure at registration. Transplant recipients received near-optimal deceased donor grafts, with prolonged post-LT hospitalisation, but more than three quarters were alive one year after transplantation. Non-survivors of transplantation also had a longer wait-time and more severe multi-organ failure at registration.

Acute on chronic liver failure represents a final stage in the natural history of chronic liver disease and is a condition that patients may reach through a number of clinical routes. Our 'real-world' cohort included both those who had both been previously waitlisted and those presenting 'de-novo'. As time zero in the analysis presented is registration for transplantation on the ACLF Tier, there is no immortal time in the design of the analysis of the intervention.[26] Our results parallel those of retrospective series, confirming that for carefully selected recipients liver transplantation is a practical and highly effective treatment option where no other similarly effective interventions exist. It is however clear that as compared to elective transplantation, resource use is increased, as evidenced by prolonged post-LT ICU and hospital stay. Median length of hospital stay in the ACLF recipients at 35 days was more than double that seen nationally for elective first LT (15 days: personal communication NHSBT). Further, though recipient survival was above the pre-specified 1-year futility threshold, it remains numerically inferior to that now commonly reported for both elective LT for CLD and prioritised LT for ALF.[3,7] If LT is to be more widely applied for ACLF with graft utility maintained and resource utilisation optimised, then a key requirement is to improve recipient selection and survival to avoid 'futile' transplantation. Our results suggest that this may be possible. The principal differences we identified between LT survivors and non-survivors related to severity of multi-organ failure at time of ACLF tier registration, suggesting that beyond specific measured thresholds anticipated levels of recipient survival may not justify LT. Using ACLF *grade* alone to do this will not have the granularity to inform decision-making in respect of futility. Other scoring systems for MOF severity such as the CLIF-OF and TAM score, or those additionally assessing relevant comorbidity such as the SALT-M score may provide standardised and objective mechanisms to identify cases in whom LT will have an unacceptably low survival, and large-scale pro- and retrospective studies are seeking to clarify the optimal approach.[18,23,24] It is likely that such decision making will not rely on a single scoring system as the arbiter: our experience with the use of the tier is that clinical decisions are nuanced and multifactorial considerations are required for individual candidates—whether to wait list, and in the waitlisted patient, whether to proceed with LT with the available graft.

Our data also confirm the need for waitlist prioritisation of transplant candidates with severe ACLF. Multiple organ failure is not considered in the NLOS or MELD and MELD-Na based organ allocation systems, and mortality risk in ACLF underestimated by these scoring systems[27](Supplemental Materials 1). Even with prioritisation such that LT occurred within days, a fifth of patients deteriorated such that LT was not possible despite the majority receiving timely offers of donor organs, and non-survivors of LT were characterised by longer wait-times for an appropriate graft. If transplantation is to be effectively employed as an intervention in ACLF, to ensure equity of access and maintain post-LT patient survival at levels acceptable to a national transplant program, a degree of prioritisation will be required for severely ill ACLF candidates–potentially greater than that utilised in this programme.

The short time window for successful transplantation inevitably constrains the usually rigorous pre-transplantation assessment undertaken in elective transplant candidates—though in practice the majority of those registered on the tier had already undergone such elective assessment. With these and the assessments employed on the 'de-novo' presentations with ACLF in this series by the transplanting centres we did not find that this resulted in transplantation of patients with unexpected underlying cardio-respiratory comorbidity—a principal concern–but after LT did identify

	All		Survived		Died		p
n	42	(38–53)	34		8		
Age (years)	46	(38–53)	47	(39–53)	45	(40–51)	
Sex (F)	20	42%	16	47%	4	50%	
BMI (kg/m^2)	27.4	(22–32.6)	27	(22.2–31.4)	36.2	(22.3–39)	
Aetiology							
Alcohol	8	19%	7	21%	1	13%	
Cholestatic	11	26%	8	24%	3	38%	
Viral	5	12%	4	12%	1	13%	
Other	18	43%	15	44%	3	38%	
ACLF precipitant							
Bleeding	16	38%	12	35%	4	50%	0.44
Sepsis	12	29%	9	26%	3	38%	
Other	7	17%	6	18%	1	13%	
Timing of ACLF Tier Registration							
Previously waitlisted	25	60%	23	68%	2	25%	0.03
Time in ICU Prior (days)	5	(1–14)	5	(1–17)	6	(2–11)	
ACLF tier wait (days)	2	(2–5)	2	(2–5)	5	(3–10)	0.08
ICU admission to LT (days)	10	(5–19)	8	(4–22)	11	(6–18)	
Laboratory findings at ACLF tier registration							
HB (g/l)	84.5	(73–91)	84	(73–90)	86.5	(82–99)	0.35
WBC (x10^9/l)	11	(6.7–17)	10.7	(5.6–16.4)	12.8	(9.7–21.5)	0.28
PLT (x10^9/l)	66	(42–97)	65	(40–104)	66	(50–77)	
INR	2	(1.6–2.7)	1.9	(1.6–2.5)	2.1	(1.6–3.4)	
Bilirubin (µMol/l)	419	(255–541)	407	(208–528)	476	(324–591)	
Urea (mMol/)	10.8	(7.2–18.4)	10.8	(7.3–17.3)	11.2	(3.8–28)	
Creatinine (µMol/l)	121	(81–184)	120	(74–184)	126	(90–234)	
Sodium (mMol/)	138	(133–140)	138	(133–140)	136	(130–145)	
Arterial PO_2 (kPa)	11	(9.7–12.9)	11.5	(10–13.2)	9.4	(9.2–10.5)	0.12
Arterial lactate (mMol/l)	2.1	(1.4–2.8)	2.1	(1.3–2.8)	2.2	(1.6–3.0)	0.49
Illness severity at ACLF tier registration							
Encephalopathy grade	3	(2–4)	3	(2–4)	3	(1–4)	
Inspired oxygen (%)	30	(24–35)	28	(24–35)	35	(33–39)	0.06
PaO_2/FiO_2 ratio	286	(208–393)	310	(223–395)	201	(176–246)	0.07
ACLF Grade	3	(3–3)	3	(3–3)	3	(3–3)	
CLIF OF Score	14	(13–16)	14	(13–16)	16	(14–18)	0.03
CLIF organ failures (n)	4	(3–5)	3	(3–4)	4	(3–5)	0.16
MELD score	38	(34–40)	38	(34–40)	40	(37–40)	0.05
CLIF-C ACLF score	61	(54–68)	61	(53–66)	70	(62–73)	0.04
SALT-M score	14.7	(11–19)	13.8	(12–26)	19.8	(12–26)	0.07
TAM score	1	(0–1)	1	(0–1)	1	(1–1)	
Organ support at ACLF tier registration							
Vasopressors	35	83%	28	82%	7	88%	
Renal replacement	36	86%	26	76%	8	100%	0.19
Ventilation	27	64%	21	62%	6	75%	0.48
Donor and graft features							
Donor age (years)	55	(49–63)	56	(49–66)	55	(49–58)	
CIT (minutes)	508	(409–615)	507	(401–658)	532	(410–567)	
ABO identical	28	67%	23	68%	5	63%	
DCD graft	1	2%	0	0%	1	13%	0.19
Intra-operative blood product use							
Red blood cells (units)	7	(5–11)	6	(5–10)	8	(7–11)	0.20
Fresh frozen plasma (units)	6	(4–9)	6	(4–8)	6	(4–16)	
Platelets (Units)	3	(1–5)	2	(1–4)	3	(3–7)	0.07

Note: figures are median (IQR) or n (%). p for comparison of survivors and non-survivors of transplantation with values shown only when $p \leq 0.5$. Abbreviations: BMI: body mass index, ACLF: acute on chronic liver failure, ICU: intensive care unit, LT: Liver transplantation, HB: haemoglobin, WBC: white blood cell count, PLT: platelet count, INR: International Normalised Ratio, CLIF OF: chronic liver failure organ failure score, MELD: model for end-stage liver disease, SALT-M: Sundaram ACLF-LT-Mortality Score, TAM Score: Transplantation for ACLF-3 score, CIT: Cold ischemic time, DCD: deceased cardiac death.

Table 2: **Comparison of transplant survivors and non-survivors.**

cholangiocarcinoma (CCA) in three of ten recipients with Primary Sclerosing Cholangitis, one of whom later died. Of note, this case was one of two with CCA who were not previously registered for elective LT, but all were under active follow up including surveillance for CCA. None of the three cases had shown evidence of CCA on immediately pre-LT cross sectional imaging. In a non-emergency setting detection of CCA is complex and challenging and current detection methods have limited performance with CCA often identified only when advanced.[28] The optimal techniques utilised in the elective setting cannot be applied in the acutely ill patient with ACLF. Our experience reflects the challenges involved in pre-LT assessment in ACLF and reinforces the need for rigorous pre-LT evaluation for exclusion of comorbidity contra-indicating LT, with a heightened suspicion of disease or therapy-related complications manifest in patients with very advanced end stage CLD presenting in ACLF.

Given current excellent short- and medium-term survival for recipients of elective LT, clinical focus is now on optimisation of longer-term survival and quality of life, and for some indications for LT thresholds of >70% 5-year survival have been proposed for recipient selection.[29] The limited data on long term outcomes in ACLF recipients suggests stepwise worsening of longer-term survival with increasing ACLF grade at the time of LT—with the worst survival seen in patients with ACLF-3, in whom 5-year patient survival from registry and retrospective single centre studies is reported as 60–70%.[30,31] Much of this survival difference results for the excess mortality seen in ACLF recipients in the first months after LT, principally from infection. However, later mortality also remains higher than elective recipients. Renal impairment was very common in our surviving ACLF recipients, and in those reported in retrospective series.[30] Its presence is closely associated with worse long-term survival in LT recipients transplanted for other indications, and this is also likely to be the case in ACLF recipients.[32,33] Determining the optimal means for its prevention and if present, best management to prevent progression are important research questions. Early calcineurin-sparing regimens were utilised in only a minority of the cases transplanted and it may be that this approach was underutilised; this is an aspect of management that needs further investigation. In the longer term, other post-transplant comorbidities including arterial hypertension, diabetes, dyslipidaemia and obesity commonly occur in both ACLF and elective recipients, and improving their long-term management is also likely to be of importance.[32]

A further consideration is that of quality of life in ACLF transplant recipients. After solid organ transplantation this is generally good but may be impacted by factors including comorbidities, side effects of medication, particularly immunosuppression, and psychological and socioeconomic factors.[34] Pre- and peri-operative clinical course and complications may also have an effect. The impact on survivors of other critical illness, particularly if prolonged, is well established, with negative effects on physical and psychological health and socioeconomic status.[35] The very limited current data on ACLF recipients suggests that though many have post-LT quality of life similar to elective LT recipients, many also experience long term impaired health and pronounced anxiety and depression, particularly after prolonged ICU admission.[31,36] A better understanding of these issues is clearly needed—evaluated using tools appropriate to this specific setting,[31,36] and additional psychological and social support likely to be required improve quality of life beyond simple survival.

Though our programme was developed and applied in a specific geographic and organisational setting, and with a UK case-mix and is of limited scale, the key aspects of the prioritisation process we applied may be extrapolated to other settings. Internationally, few organ allocation schemes recognise the impact of critical illness on survival in patients with cirrhosis, and the criteria we derived were principally drawn from experience and the results of studies conducted outside the UK (Text Box 1 and Supplemental Materials 1). However, the UK has a highly developed and responsive organ allocation system with optimal grafts available for use within a very short time frame, and the centres participating had mature high volume LT programmes. Extrapolation to other settings where these are not present may not deliver equivalent outcomes.

Use of Liver transplantation for ACLF is at a relatively early stage of development and it remains a controversial indication that is currently utilised in only a small proportion of patients with severe ACLF.[12,15] There are clear parallels with the early experience of its first application to ALF in the 1980s and 90s. First results were poor, but in the years after its introduction there has been a progressive, incremental improvement in recipient survival, reflecting refinement of case selection, improvements in pre-, intra- and post-operative care including a better understanding of graft/recipient matching and use of immunosuppression.[6,7] Outcomes now closely parallel those of elective transplantation and it forms a standard part of clinical management. The same may be expected for ACLF, though it is clear that many challenges are yet to be overcome. The ACLF tier of prioritised graft allocation as presented has now been adopted a part of standard practice in the United Kingdom, but to improve pre-and post-LT outcomes its refinement over time is highly likely.

Contributors

WB, DT, IAR and AG conceived and operationalised the Tier. WB, RT and IAR did the statistical analysis and WB wrote the first draft of the report with input from DT and RT. All authors contributed to the final version of the manuscript. WB and RT accessed and verified the data and all authors had access to the data in the study.

Data sharing statement

Data collected for the UK Transplant Registry can be accessed on application to NHSBT. Further information can be found at: https://www.odt.nhs.uk/statistics-and-reports/access-data/.

Declaration of interests

WB: Consulting Fees: Sana Biotech/Flagship Pioneering, RT: none, IAR: Consulting Fees: Roche, Novo Nordisk, Boehringer Ingelheim, Honoraria: Norgine, Research Committee Chair, British Association for the Study of the Liver, AC: none, MJA: none, MEDA: Payment or honoraria: GSK: made to CUHFT as part of research collaboration, GW: Support for attending meetings from NHS Blood and Transplant, TP: none, JM: none, LB: none, SM: none, DC: none, BJH: none, RW: none, RJ: Royalties or Licenses: Co-Founder (with stock options): Yaqrit Ltd, Cyberliver Limited, Hepyx, Limited, Payment or honoraria: Grifols, Committee evaluating grants, Patents planned, issued or pending: Patent Families: DIALIVE, CARBALIVE, TLR4 antagonists, Targeting Pyroptosis; Targeting Necroptosis; Ornithine Phenylacetate, KJS: none, JI: none, DT: none.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanepe.2024.101067.

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