Proposal for a study of Liver Transplantation

for

Critically Ill Patients with Cirrhosis

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Part 1. Background

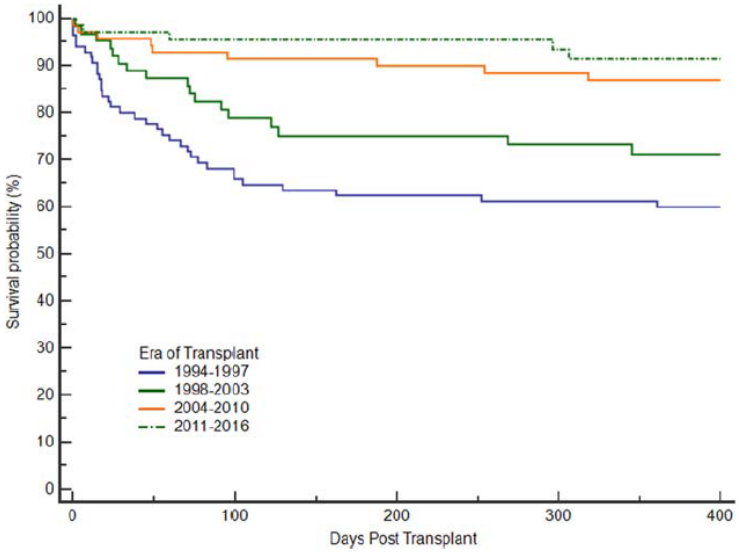
In the natural history of cirrhotic chronic liver disease (CLD) the eventual development of severe end-organ complications may result in critical illness with extra-hepatic multi-organ failure (MOF), which requires critical care based organ support with high short term mortality. Now often termed 'Acute On Chronic Liver Failure' (ACLF), this condition can be phenotypically characterised, illness severity assessed and defined using specific organ failure scoring systems [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.

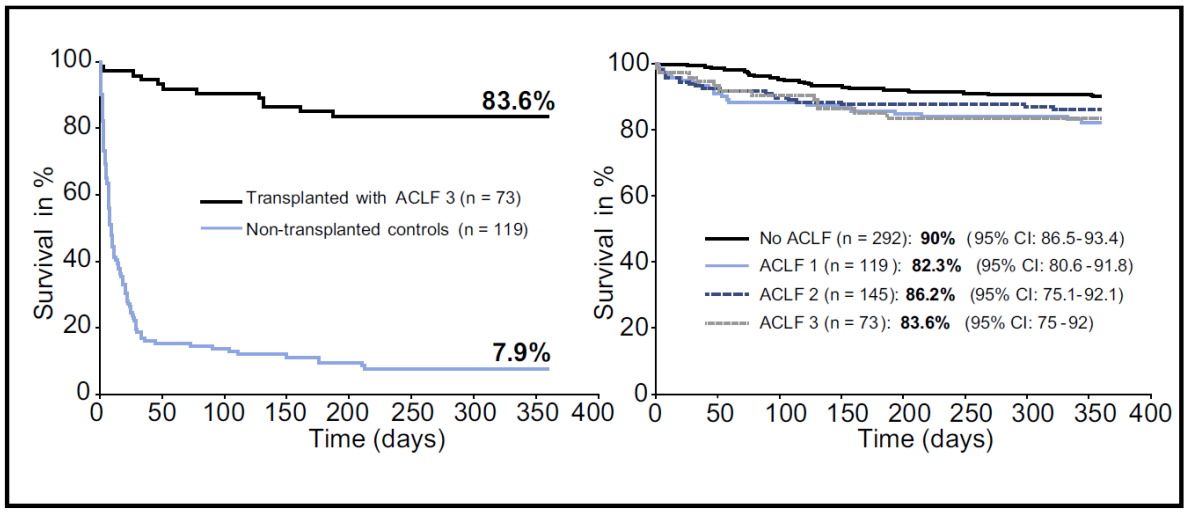


Note; NHSBT dataset, first elective transplant for cirrhosis 1994-2016. n=276. P<0.001

Source [8].

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 ACLF Grade 3 and by ACLF Grade.



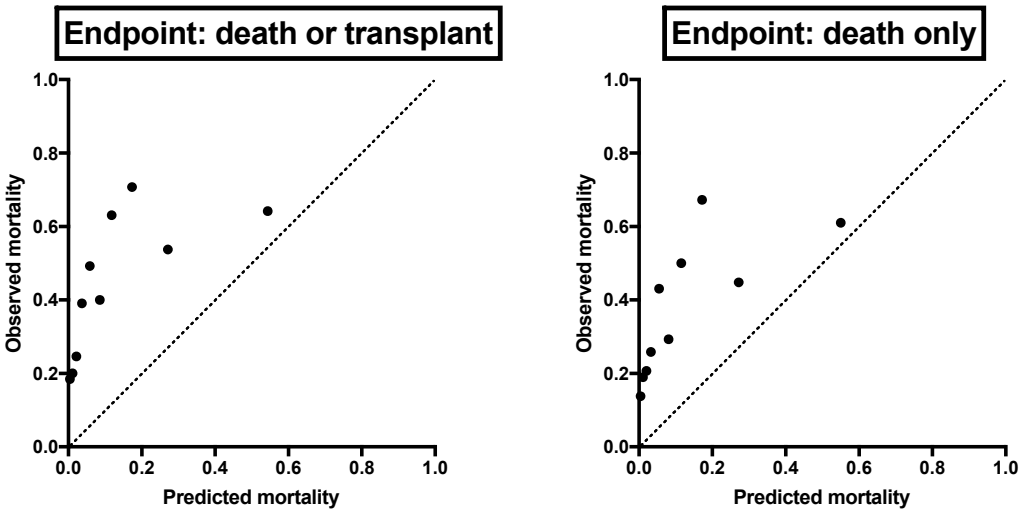
Note: 3 French centres, 2004-2014. Source: [10]

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 of 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 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.

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Part 2. Study Proposal.

1. Phase 1; A preliminary study of ACLF outcomes in UK intensive care units and the potential role of liver transplantation.

Overview:

Phase 1 of the study will comprise two parallel workstreams. It will collect specific data on critically ill un-transplanted patients with cirrhosis that will inform future modelling of both organ allocation and prioritisation. In those who do undergo transplantation data collection will also focus upon outcomes of surgery to assist in defining likely thresholds for futile transplantation.

A pilot study will be undertaken of prioritised liver transplantation in a cohort of critically ill patients with cirrhosis (referred to as ACLF). For the purposes of this phase, 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 within the NOS rather than the Super-Urgent scheme. Two possible mechanism are suggested below.

1.1. Defining the Study Cohort

All cases with ACLF (from consensus definition) admitted to ITU or HDU of Liver transplantation centres. Data collection for both liver and other end organ failures, and with changes over time to define 'windows' of transplant applicability. No exclusion criteria will be applied 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 study of the feasibility, outcomes and resource utilisation of liver transplantation for ACLF.

1.2.1. Entry criteria; unplanned admissions to ICU/HDU of CLD cases with an ACLF score predicting 90-day survival of less than 50%, and ACLF grade 2 or 3.

1.2.2. Exclusion criteria; active sepsis, MOF of such a severity and with adverse trajectory to realistically preclude successful organ transplantation; use of ECMO, excessive comorbidity, frailty and likely inability to rehabilitate; active malignancy. Age is a key predictor of post-transplant outcome in ALF and is likely to be very important in outcome for ACLF as well - a possible upper threshold of 50 years is suggested. These specific aspects of selection to be considered by individual centres.

1.2.3. Selection for the study. Cases to be reviewed by a Hepatologist, Intensivist 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.

1.2.4. Notification of NHS BT. CLD Registration Form to be filled out and submitted. Additional information kept within each unit for central analysis.

1.2.5. Donor Offering; 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 would not be appropriate (Fig 3). There are two further options for offering donors to this group.

- Proportional allocation; Liver offers could be on a proportional allocation basis; assuming 50 ACLF registrants in the first year and 989 total adult registrants offer 5% of all donors ahead of Elective/variants. With 809 DBC or DCD transplantable liver offers in a year (excluding super-urgent/hepatoblastoma/multivisceral offers), there will on average be a liver offer to this group once every 9 days. This is unlikely to be quick enough for this cohort of severely ill cases
- A new ACLF category inserted after multivisceral cases, before Elective/Variants for the duration of the study. This would result in 2.2 offers per day for these cases.

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

1.2.6. Outcome metrics

- Graft details.
- Time to OLT or death on waiting list or removal from list; reason for removal
- Survival time-post OLT
- Organ failures and scores over time, pre- and post-OLT.
- Days in ITU, hospital, subsequent operations, complications, re-admissions
- Resource utilisation.
- Risk adjusted survival from point of registration

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

1.4. <u>Governance</u>; 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;.

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

Phase two will seek to review the outcomes of Phase 1 transplants, critically assessing the overall impact of this study 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.

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 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 determine 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

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