

Outcome after wait-listing for emergency liver transplantation in acute liver failure: A single centre experience[☆]

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Background/Aims: Though emergency liver transplantation (ELT) is an established treatment for severe acute liver failure (ALF), outcomes are inferior to elective surgery. Despite prioritization, many patients deteriorate, becoming unsuitable for ELT.

Methods: We examined a single-centre experience of 310 adult patients with ALF registered for ELT over a 10-year period to determine factors associated with failure to transplant, and in those patients undergoing ELT, those associated with 90-day mortality.

Results: One hundred and thirty-two (43%) patients had ALF resulting from paracetamol and 178 (57%) from non-paracetamol causes. Seventy-four patients (24%) did not undergo surgery; 92% of these died. Failure to transplant was more likely in patients requiring vasopressors at listing (hazard ratio 1.9 (95% CI 1.1–3.6)) paracetamol aetiology (2.5 (1.4–4.6)) but less likely in blood group A (0.5 (0.3–0.9)). Post-ELT survival at 90-days and one-year increased from 66% and 63% in 1994–1999 to 81% and 79% in 2000–2004 ($p < 0.01$). Four variables were associated with post-ELT mortality; age >45 years (3 (1.7–5.3)), vasopressor requirement (2.2 (1.3–3.8)), transplantation before 2000 (1.9 (1.1–3.3)) and use of high-risk grafts (2.3 (1.3–4.2)).

Conclusions: The data indicate improved outcomes in the later era, despite higher level patient dependency and greater use of high-risk grafts, through improved graft/recipient matching.

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Abbreviations: ELT, emergency liver transplantation; ALF, acute liver failure; HR, hazard ratio; BMI, body mass index; UKT, United Kingdom transplant; LITU, liver intensive therapy unit; INR, international normalised ratio; KCH, King’s College Hospital; RRT, renal replacement therapy; AUROC, area under receiver operating characteristic curve; HE, hepatic encephalopathy; ICH, intra-cranial Hypertension; CLD, chronic liver disease; MOF, multiple organ failure; HAT, hepatic artery thrombosis.

1. Introduction

Emergency liver transplantation (ELT) plays a pivotal role in the management of acute liver failure (ALF), with little impact to date from alternative therapies including liver support devices and cell transplants [1,2]. While survival rates appear acceptable, outcomes are consistently worse than for patients undergoing elective transplantation for chronic liver disease (CLD) [3–5]. The gap in the US is seven percentage points and in Europe it is up to 15 percentage points [4,6]. Understanding the issues driving this survival differential would be beneficial for selection and management of candidates for ELT.

Key factors that influence patient survival include the timeliness of organ availability, clinical condition of the patient at time of transplantation, quality of the donor organ and standard of intra- and post-operative care [7–9]. Organ allocation systems prioritize patients with ALF with no obvious opportunity to accelerate progression to transplantation. Supportive care protocols are sophisticated and, again, immediate significant improvement is not anticipated. Therefore, the opportunity to improve results of ELT appears to rest on an ability to recognise futility of intervention and manipulate patient/organ matching to achieve optimal results.

The most comprehensive attempt to date to address some of these issues was a study of outcomes in 1457 patients transplanted for ALF between 1998 and 2004 in the US [10]. The overall mortality was 23%, and factors identified as correlating with outcome were body mass index (BMI), serum creatinine, age and the need for assisted ventilation. Survival decreased progressively with increasing number of adverse factors present but the worst observed outcome was 42% survival in a cohort that accounted for only 2% of the study population. This study did not consider the cumulative effects of adverse graft factors of likely importance in this setting [5,11].

We report a single-centre experience of ELT in ALF over a 10-year period with specific aims of understanding why patients listed for ELT succumbed without being transplanted, and what factors were predictive of early death once transplantation had been performed.

2. Patients and methods

This study examined all patients aged >16 years at King's College Hospital (KCH) who were registered for ELT for the first time between January 1, 1994 and December 31, 2004. ALF was defined using criteria previously described [12], and in all patients the time from onset of jaundice to encephalopathy was less than 12 weeks. With the exception of patients with Wilson's disease, histopathological examination of explants or post mortem samples excluded the presence of CLD. The listing criteria used nationally during the study period were standardised and were based on the KCH criteria [12]. Amended criteria were implemented in 2005 but were not pertinent to this study [13]. Patients registered for ELT received absolute priority for ABO compatible grafts.

Patients were managed in a specialist liver intensive therapy unit (LITU) to standardised protocols [14,15]. Those developing encephalopathy of grade 3 or above were sedated and ventilated, with supportive care designed to minimise risks of intra-cranial hypertension (ICH) [15]. Norepinephrine was used as the primary vasopressor, and continuous veno-venous haemofiltration for renal replacement therapy (RRT). Intravenous N-acetyl-cysteine was infused at a rate of 150 mg/kg for 24 h until the INR was <2 or for a maximum of 7 days. All listed patients received broad-spectrum antimicrobial and antifungal therapy.

Potential recipients were removed from the ELT list if there was evidence of irreversible brain-stem dysfunction, refractory escalating vasopressor requirement, or culture positive systemic sepsis with deteriorating clinical status despite 48 h of anti-microbial therapy. The decision to accept an allocated organ and the details of the operation were made by the duty transplant surgeon. Primary immunosuppres-

sion consisted of methylprednisolone given at hepatectomy and a subsequent tacrolimus and low dose corticosteroid regimen with steroids typically withdrawn within 3 months of transplantation.

2.1. Data analysis

Two retrospective analyses were performed. The first related to risk factors associated with failure to proceed to ELT in patients who were wait-listed. The second addressed factors influencing 90-day mortality after ELT. Data were obtained from the clinical and electronic records at KCH and UKT (UK Transplant). Variables studied comprised patient age, gender, aetiology of ALF (paracetamol/non-paracetamol), ethnicity (caucasian/non-caucasian), blood group and era of listing (1994–1999/2000–2004). Clinical parameters at time of listing (requirement for intubation, vasopressors and RRT, severity of encephalopathy) and waiting time before ELT or removal from the list were also analyzed.

In those patients who underwent ELT the variables relating to surgery and the graft were; donor age, gender, blood group, cold ischemic time, use of 'non-whole' (split, reduced or auxiliary) grafts and presence of significant graft steatosis as assessed by surgical inspection. A pre-specified composite variable for graft risk was created using graft factors repeatedly associated with poor patient and graft outcomes in elective and emergency transplantation, [5,11]. Grafts were classified as high-risk if more than one previously determined risk factor was present; donor age >60 years, non-whole status, ABO non-identical or macroscopic steatosis.

Chi-square or Fisher's exact tests were used for categorical variables and Mann-Whitney U test for continuous variables to compare various outcome measures and variables between groups. Optimal threshold values for continuous variables were determined using receiver-operator characteristic techniques. Each potential risk factor was first analysed separately by the Kaplan-Meier method to estimate survival, by univariate Cox regression to estimate the hazard ratios and by log-rank to test survival differences between groups. These analyses were followed by a multiple Cox regression analysis to model the simultaneous effect of covariates and possible interactions. Models were generated from variables with $p < 0.20$ from the univariate Cox regression analyses. Analysis of data was performed using SPSS version 14.0 (SPSS Inc., Chicago, IL).

3. Results

3.1. Study cohort

During the study period 1379 patients were admitted to the LITU with acute severe hepatic dysfunction, of whom 783 (57%) developed ALF with encephalopathy (HE) of grade 3 or above requiring intubation and mechanical ventilation. Three hundred and ten patients were registered for ELT. Median age of those listed was 34 years (Inter-quartile range 23–43) and 67% of the cohort were female. Two hundred and thirty-six (76%) underwent LT at a median of 1 day (IQ range 1–2, range 1–7) after listing.

Overall, 132 (43%) listed patients had disease resulting from paracetamol-induced hepatotoxicity and 178 (57%) from non-paracetamol causes. Non-paracetamol causes were seronegative or indeterminate in $n = 92$, non-paracetamol drug induced $n = 26$, viral $n = 21$, Budd-Chiari syndrome $n = 15$, autoimmune $n = 8$, pregnancy related $n = 8$, Wilson's disease $n = 5$, mushroom poisoning $n = 2$ and trauma $n = 1$.

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