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Retrospective Study

Long-term Outcomes of Paediatric Liver Transplantation in Acute Liver Failure *vs* End-Stage Chronic Liver Disease: Retrospective Observational Study

Alnagar AM *et al*, ALF *vs* ESCLD in PLT

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Abstract

BACKGROUND

Children with acute liver failure (ALF) who meet the criteria are eligible for super-urgent transplantation while children with end-stage chronic liver disease (ESCLD) are usually transplanted electively. Paediatric liver transplantation (PLT) in ALF and ESCLD settings has been well described in the literature, but there are no studies comparing the outcomes in these two groups.

AIM

To identify if there is a difference in postoperative complications and survival outcomes between the ALF and ESCLD in PLT.

METHODS

This is a retrospective observational study of all primary PLTs performed at a single centre between 2000 and 2019. ALF and ESCLD groups were compared for pre-transplant recipient, donor and operative parameters, and postoperative outcomes including graft and patient survival.

RESULTS

Over the 20-year study period, 232 primary PLTs were performed at our centre; 195 were transplanted for ESCLD and 37 were transplanted for ALF. The ALF recipients were significantly older (median 8 vs. 5.4 years; $P = 0.031$) and heavier (31 vs. 21 kgs; $P = 0.011$). Living donor grafts were used more in ESCLD group (34 vs. 0; $P = 0.006$). There was no difference between the two groups concerning vascular complications and rejection, but there were more bile leaks in the ESCLD group. Post-transplant patient survival was significantly higher in the ESCLD group: 1-, 5- and 10-year survival rates were 97.9%, 93.9%, and 89.4% respectively compared to 78.3%, 78.3%, 78.3% in the ALF group ($P = 0.007$). However, there was no difference in 1-, 5- and 10-

year graft survival between ESCLD and ALF groups - 90.7%, 82.9%, 77.3% vs. 75.6%, 72.4%, and 66.9% (P = 0.119).

CONCLUSION

Patient survival is inferior in ALF compared to ESCLD recipients; the main reason is death in the first year post-PLT in ALF group. Once the ALF children overcome the first year after transplant, their survival stabilizes, and they have good long-term outcomes.

Key Words: Paediatric liver transplantation; acute liver failure; end-stage chronic liver disease; graft failure; patient survival; complications

Alnagar A, Hakeem A, Daradka K, Kyrana E, Methga M, Palaniswamy K, Rajwal S, Mulla J, o'meara M, Upasani V, dhakshina V, Prasad R, Attia M. Long-term Outcomes of Paediatric Liver Transplantation in Acute Liver Failure *vs* End-Stage Chronic Liver Disease: Retrospective Observational Study. *World J Transplant* 2023; In press

Core Tip: To our experience, this research is the first to compare the complications and survival outcomes in ALF and ESCLD children post-PLT. This study has not only shown that survival in the ALF group is significantly inferior post-PLT but also showed a different pattern of survival where ALF survival is mostly affected in the first year post-transplant and then stabilizes, while ESCLD survival declines steadily over time.

INTRODUCTION

Liver disease is a leading cause of morbidity and mortality in children. The spectrum of liver pathologies in this age group includes infectious, genetic, metabolic, and drug-induced disorders that may eventually progress to either acute liver failure (ALF) or end-stage chronic liver failure (ESCLD). Paediatric liver transplantation (PLT) is the only treatment option for children with ALF or ESCLD [1].

The diagnosis of ALF in children can be challenging, as hepatic encephalopathy in this age group is usually difficult to define, particularly in its early stages and sometimes it may not be clinically evident until the ALF becomes advanced [2-4]. Also in some cases, accurate diagnosis of the aetiology of ALF may not possible, chiefly in candidates who present with unrecognized metabolic diseases shortly after birth or those who clinically deteriorate over a short period not allowing enough room for full biochemical and radiological testing [3].

Managing children suffering from ALF is a dynamic process, with the decision to list for PLT made in an emergent manner, when the probability of spontaneous recovery is low but also before any irreversible neurological or respiratory sequalae take place [2]. At times, the window from presentation to PLT may span from only few hours up to a small number of days, posing significant challenges for the clinical team [5]. Optimum clinical and logistical management is essential as successful PLT in this special group has a dramatic effect on their survival [4-6]. Hence at the National level, the graft allocation system gives ALF children the highest priority being labelled as "super-urgent".

In comparison, the clinical and logistic dynamics are completely different in the case of children with ESCLD as PLT is usually performed on an elective basis, as candidates are usually in less critical clinical condition and the transplant team has enough time for evaluation and planning, aiming for optimum timing and potentially improved outcomes.

Both groups were discussed among other categories in publications describing PLT centres' experience but to the best of our knowledge, no previous studies had directly compared the outcomes of PLT in ALF and ESCLD settings. This study was carried out to identify if there is a difference in post-PLT complications between the ALF and ESCLD groups, and to describe any variance in survival between the two cohorts. The importance of this comparison is to give insight for transplant centres and organ allocation systems dealing with these two divergent groups to make the best use of limited resources including a limited graft pool and to anticipate differences in

behaviour between candidates in each group to tailor their clinical care accordingly. This comparison also meant to open the door for future research to overcome obstacles and improve PLT outcomes, especially in the ALF group where the underlying cause of the liver failure remains unknown in a considerable number of children.

MATERIALS AND METHODS

This is a retrospective cross-sectional observational study of the long-term outcomes of PLT performed at Leeds Teaching Hospitals NHS Trust between 2000 to 2019. Hospital documents and electronic records were used to retrieve donor and recipient data. Ethical approval was not required for this retrospective analysis of already collected data and the study was registered as a service improvement project within the hospital clinical governance department, with no patient identifiable information stored while collecting and analysing the data for this project.

Eligibility:

The inclusion criteria was all PLT recipients of the first liver transplant in our centre aged less than or equal to 18 years with either ALF or ESCLD as the recorded indication for PLT. Exclusion criteria were re-transplants, primary PLTs for liver tumours, or metabolic disorders without underlying liver disease. Re-transplants were excluded as they represent a heterogenous group with well-reported inferior outcomes compared to primary transplants. Children with liver tumours are unique with a well-defined transplant indication, and their disease may be complicated by the burden of chemotherapy before undergoing a liver transplant, although they tend to be systemically well with no effects of acute or chronic liver disease. So, we think they should be ideally studied separately. PLT for metabolic diseases usually has excellent patient and graft survival than PLT for other indications. In addition to this, genotypic and phenotypic diversity in metabolic disorders complicate the possibility of forecasting long-term outcomes in this group of children, hence they were excluded from the study.

Definitions:

For the objective of this article, ALF was specified to match the Paediatric Acute Liver Failure Study Group (PALFSG)[6] definition, as biochemical proof of liver injury, excluding records of recognized chronic liver illness, international normalized ratio (INR) greater than 1.5 if the patient had encephalopathy or greater than 2.0 if the patient does not have encephalopathy, and coagulopathy not rectified by vitamin K use.

End-stage chronic liver disease (ESCLD) was specified as an enduring hepatic inflammation identified by biochemical investigations and clinical examination, spanning over more than six months causing cirrhosis or permanent liver injury [7].

Data collected and outcomes studied:

Data were collected through retrospective case note review. We recorded 24 peri-transplant parameters for this study, which were grouped into four classes: pre-transplant recipient as well as donor parameters, operative parameters, and post-transplant recipient observations. Pre-transplant recipient variables were gender, age, weight, liver failure category (ALF and ESCLD), fundamental liver illness aetiology, time on the transplant waiting list, and patient location when graft became available (an indirect marker of recipient sickness instantly pre-transplant). Donor parameters were gender, age, weight, type of graft (living and deceased), and type of graft (whole or variant graft such as split or reduced). The intra-operative parameters studied were warm ischaemia time (WIT) and cold ischaemia time (CIT). The postoperative outcomes studied were the incidence of vascular and biliary complications, post-transplant paediatric intensive care unit (PICU) and overall hospital stay, the incidence of biopsy-proven acute/chronic rejection, re-transplantation, causes of graft and patient loss, and 1-,5- and 10-year graft as well as patient survival.

The primary outcome of this article was to identify if there is a distinction in patient and graft survival in PLT recipients transplanted for ALF or ESCLD. The

secondary outcome was to compare the incidence of vascular, biliary complications, and biopsy-proven rejection in PLT for both groups.

Statistical analysis of the data

Data were supplied to the computer and evaluated using IBM SPSS software version 20.0. (Armonk, NY: IBM Corp). The Kolmogorov-Smirnov was employed to validate the normality of variables allocation, Assessments for categorical variables were reviewed employing the Chi-square test (Fisher's Exact adjustment). Student t-test was applied to assess two normally distributed quantitative variables between two cohorts whilst the Mann-Whitney test was applied to assess not normally distributed quantitative data. Missing data were taken into account through statistical evaluation. Kaplan-Meier survival curve was employed to examine the graft and patient survival. The significance of the recorded outcomes was determined at the 5% level.

RESULTS

Over the interval between November 2000 to August 2019, 322 PLTs were operated in our centre. We excluded re-transplants, transplants for children with liver tumours, or metabolic disorders without underlying liver disease (90 PLTs) from the final analysis. The remaining 232 PLTs were classified into 195 PLTs due to ESCLD and 37 PLTs as emergency management of ALF **(figure 1)**. The median follow-up for the ALF group was 8.3 years (1–19.3 years), while the median follow-up for the ESCLD group was 8.1 years (1–19.6 years).

During the study period, 232 children presented to our institute with ALF, unfortunately, 58 (25.0%) of them did not survive to undergo transplantation, 37 (15.9%) underwent transplantation, and 137 (59.1%) recovered without transplantation.

Pre-transplant recipient parameters:

Both groups were homogenous in terms of recipients' gender (P = 0.312) while recipients' age and weight were significantly higher in the ALF group. Further analysis of the ALF group showed that 6 patients were transplanted at the age below 1 year, 10

patients were transplanted at the age of 1 to 4 years, 3 patients were transplanted at the age above 4 to 10 years and 18 patients were more than 10 years old at the time of transplant. Biliary atresia and progressive familial intrahepatic cholestasis (PFIC) were the most common causes of liver failure in the ESCLD group while seronegative hepatitis and auto-immune hepatitis were the most common causes in the ALF group **(table 1).** There was a significant difference in the waiting time on the transplant list between both groups; the median waiting time for the ALF group was 3 days (1 – 41 days), while the median waiting time for ESCLD patients was 60.5 days (1 - 560 days; $p<0.001$). The location of the recipient when the liver graft became available also showed a significant difference as the home locality was greater in the ESCLD group, while in the ALF group, hospital, as well as PICU locality (with or without invasive ventilation), were significantly higher **(table 1)**.

Donor parameters:

There was no statistically significant difference in terms of donor gender or weight, however, donors in the ALF group were significantly older than the ESCLD group **(table 1)**. Concerning the graft resource, living donors were considerably superior in the ESCLD cohort (34 donors) than the ALF cohort which did not receive any graft from living donors ($P = 0.006$).

Operative parameters:

Technical variant (reduced and split) grafts were used significantly more in the ESCLD group **(table 1)**. There was no difference in cold ischaemia time (CIT) between the two groups, but the warm ischaemia time (WIT) time was significantly longer in the ALF group (median 55 minutes; 32 – 81 minutes) than ESCLD group (median 45.5 minutes; 29 – 81 minutes; $P = 0.004$).

Post-transplant recipient variables:

Vascular complications occurrence:

There was no distinction among the groups regarding vascular complications. Five patients in the ALF group and 41 patients in the ESCLD group had at least one post-transplant vascular event **(table 2)**. Some patients in the ESCLD group had more than one vascular complication; two recipients had both HAT and PVT, two recipients developed both HAS and PVS, and one patient had PVS then PVT **(table 2)**.

Incidence of biliary complications:

Bile leak was significantly higher in the ESCLD group, while biliary stricture and common hepatic duct (CHD) sludge showed no significant difference between the two groups. It was also of note that 3 of the ESCLD recipients developed both bile leakage and biliary stricture **(table 2)**.

Incidence of Rejection:

There was no difference in biopsy-proven acute or chronic rejection between the two groups. 17 (45.9%) ALF patients had one or more episodes of rejection and 62 patients (31.8%) in the ESCLD group had experienced rejection ($P = 0.096$).

Post-transplant stay:

Paediatric intensive care unit (PICU) stay post-PLT was longer in the ALF group by a median of half a day (2.5 vs. 2 days), but this difference was not statistically significant ($P = 0.112$). In keeping with their sick status before the transplant, the ALF patients had a longer median hospital stay (29 vs. 21 days) when compared to ESCLD patients ($P = 0.013$).

Re-transplantation rate:

There was no distinction among the studied groups in terms of the need for re-transplantation; 5 (13.5%) ALF group and 27 (13.8%) ESCLD group; $P = 0.957$.

Patient survival:

During the follow-up period, 17 (8.7%) of the ESCLD recipients died while in the ALF group, 9 (24.3%) recipients died ($P = 0.011$) **(Table 3) (figure 2A)**. Sepsis and liver failure were the two most common causes of death in PLT recipients but there was no

statistically significant difference between the two groups **(Table 2).** Analysis of ALF group survival in conjunction with the age of transplant (less than 1 year, 1-4 years, 4-10 years, as well as more than 10 years) showed 5-year patient survival of 50%, 90%, 100%, and 77.8% respectively.

Graft survival:

The median graft survival was longer in the ESCLD group (2412 days) when compared to the ALF group (2292 days), but this difference was not statistically significant (P = 0.587**) (figure 2B) (tables 3)**. Despite some causes of graft failure being more frequent in one group than the other, there was no statistically significant difference **(Table 2).**

DISCUSSION

In the UK, children with ALF or ESCLD who are candidates for PLT are referred to one of the three centres in the country including our centre for evaluation. When the indication for PLT is established, patients would be offered transplantation if there is more than 50% survival likelihood at 5 years after PLT with an acceptable quality of life. But the dynamics of PLT are completely divergent between ALF and ESCLD settings leading to separate selection criteria for candidates needful of emergency transplantation measure up to those who need an elective procedure.

The studied cohorts have diverse aetiology with distinctly short-term prognosis difference. Similarly, graft allocation procedures are unique for elective and emergency transplantation, showing that those cohorts have a distinct probability of mortality without PLT. In our study the percentage of PLTs performed as emergency management for ALF was 11.5%, this is consistent with studies from other centres [8-10] while some other authors reported higher rates of PLT in ALF patients that may reach up to 35%[11, 12], this difference reflects the absence of a reliable prognostic model for ALF patients that can accurately predict ALF candidates who would not survive without PLT.

Identifying ALF patients who would be saved by successful PLT and differentiating them from those who may recover spontaneously or those who will eventually die with or without PLT cannot be guided by currently available data[13-16]. Using isolated biomarkers like ammonia, actin-free Gc-globulin and lactate is not reliable and cannot be applied to all ALF patients without being sufficiently studied in the paediatric population[17-19]. Prognostic scoring models applying clinical and laboratory variables such as King's college criteria and liver injury unit score cannot be confidently used to anticipate ALF patient death[19-21].

In terms of the aetiology of liver failure, biliary atresia has been the most common indication for PLT in ESCLD patients in our study (47.2%), this has been consistently reported in the literature [1, 8, 11, 22, 23]. On the other hand, aetiology of the underlying liver disease could not be identified in 45.9% of our ALF recipients. Most of the literature concerned with PLT in ALF patients have shown the same observation [3, 12, 24, 25]. Failure to identify the aetiology of ALF is probably multifactorial, first, most of the data concerned with ALF in children and infants are retrieved from case reports, exploration of adult data, individual practice, and retrospective studies of single centres [2], second, the rapid progression of liver failure to transplant or death that doesn't give enough room for extensive work up required [4]. The inability to identify the cause of ALF is always stressful for the treating physicians as it may affect the outcome of this group of patients because of its effect on prognosis, therapy, and prevention.

Until 2008, we were using molecular adsorbent recirculating system (MARS) as bridging therapy for ALF patients, but we haven't found it helpful in terms of changing outcomes for patients. We use plasmapheresis in selected patients, as we did use it in a paracetamol overdose patient in the last 3 years. Such bridging therapies are not commonly used in our program for ALF children, due to the lack of evidence for survival benefits. Time on the transplant waiting list was significantly shorter in the ALF group, this is the outcome of labeling such patients as "super-urgent" which puts them on top of the national waiting list. Receiving a timely PLT in this group is vital as prolonged waiting can lead to the development or progression of respiratory and

neurological complications, which can eventually result in the de-listing of the child who becomes "too sick" for transplantation and eventually patient mortality.

The location of the recipient when the graft became available showed a significant difference between the two groups, ALF patients are mostly located in the hospital ward or PICU while ESCLD patients are usually admitted to our centre from home. This is explained by the fact that ALF patients are usually sicker in the immediate pre-transplant period thus they are usually hospitalized or even admitted to PICU if multiple organ support is needed while ESCLD patients are mostly less critical and thus usually followed up in out-patient clinics and admitted to the transplant centre only when the graft becomes available. This was also reflected in the post-transplant hospital stay that was significantly longer in ALF patients who are expected to require a longer time to recover before discharge.

In contrast to the ESCLD group, ALF candidates in our study did not receive a living donor graft, this is possibly linked to a brief window that does not provide sufficient time for meticulous assessment of possible living donors. Living donation intended for ALF candidates has constantly been a matter of discussion.[26]Various studies expressed concerns about the ultra-short period utilized for radiological and clinical assessment of the living donor along with the emotional element in PLT that might affect the outcomes.[27] Other reports claim that PLT using living donor grafts has a possible better outcome owing to a briefer waiting period as the unwell child does not have to wait for the liver graft allocation system to receive a suitable graft in addition to the presumed better-quality graft due to limited CIT as shown by the inferior primary non-function (PNF) incidence in grafts from living donors.[28]

Technical variant grafts were used significantly higher in the ESCLD group, this is explained by the significantly lower age at transplant of this group in comparison to the ALF group so smaller grafts were needed to match recipient size. This can also explain higher rates of bile leakage in the ESCLD group from the cut surface of reduced or split grafts.

ALF recipients in our study have a significantly lower survival rate than ESCLD recipients, which has been reported in multiple studies[11, 22], while only one study to our knowledge has reported similar patient survival in both groups[25]. This can be explained by multiple factors: first, the more critical condition of ALF patients in the pre-transplant period that was reflected in our study by significantly higher PICU location of these patients when the graft becomes available and that was linked in some reports to low post-transplant survival[11]. Second is the scarcity of suitable grafts for the paediatric population[29] which prolongs the waiting time of ALF patients and may put pressure on the transplant centres to accept marginal grafts as survival of this critical group is largely dependent on receiving a PLT within a short window of opportunity[28]. The third is the fact that the aetiology is unknown in most cases of ALF, and this will surely affect post-transplant disease management and progression.

Interestingly, we noticed that the recipient's survival in the ALF group is most affected in the first-year post-transplant and remained almost stable after that while survival in the ESCLD group continued to decline gradually over the years. This observation is probably related to how unwell the ALF recipients were at the time of transplant (a considerable proportion were in intensive care), but after the first year, survival stabilizes. Whereas in ESCLD, the first-year outcomes are better, probably because most of these patients were stable and were admitted for transplant from home, but after that, there seems to be a steady decrease in their survival, possibly because of the effects of disease chronicity where ESCLD itself or its underlying aetiology like cystic fibrosis or alpha-1-antitrypsin deficiency would have affected other systems like lungs and kidneys and this effect would reflect on patient survival over the years.

There are some limitations to this study. The larger study cohort, the longer follow-up duration, the single centre population with uniform pre-transplant and post-transplant protocol, and the careful retrieval of data allow us to overcome the limitation of the retrospective nature of the study. More importantly, no such studies are comparing ALF with ESCLD in the paediatric transplant literature.

CONCLUSION

This is a retrospective study to compare the long-term outcomes of PLT in ALF and ESCLD settings. Survival of PLT recipients was significantly higher in the ESCLD group due to multiple factors like the critical general condition of ALF patients in the peri-transplant time, scarcity of suitable grafts for paediatric recipients, and the obscure aetiology of ALF in most of the cases. The rate of complications did not show a significant difference apart from higher rates of bile leak in the ESCLD group.

ARTICLE HIGHLIGHTS

Research background

Settings of paediatric liver transplantation (PLT) in end-stage chronic liver disease (ESCLD) and acute liver failure (ALF) are divergent. ALF recipients are transplanted within a narrow window of opportunity while ESCLD recipients are usually transplanted electively.

Research motivation

Outcomes of PLT in ALF and ESCLD were described before by different centres but to the best of our knowledge, they were not compared to establish if there is a difference in post-PLT survival and complication rates between these two groups.

Research objectives

To identify if there is a difference in postoperative complications and survival outcomes between the ALF and ESCLD in PLT.

Research methods

This is a retrospective observational study of all primary PLTs performed at a single centre between 2000 and 2019. ALF and ESCLD groups were compared for the pre-transplant recipient, donor and operative parameters, and postoperative outcomes including graft and patient survival.

Research results

During the 20-year study period, 232 primary PLTs were performed at our centre; 195 were transplanted for ESCLD and 37 were transplanted for ALF. The ALF recipients were significantly older (median 8 vs. 5.4 years; $P = 0.031$) and heavier (31 vs. 21 kgs; $P = 0.011$). Living donor grafts were used more in the ESCLD group (34 vs. 0; $P = 0.006$). There was no difference between the two groups concerning vascular complications and rejection, but there were more bile leaks in the ESCLD group. Post-transplant patient survival was considerably superior in the ESCLD group: 1-, 5- and 10-year survival figures were 97.9%, 93.9%, and 89.4% correspondingly compared to 78.3%, 78.3%, 78.3% in the ALF group ($P = 0.007$). However, there was no difference in 1-, 5- and 10-year graft survival between ESCLD and ALF groups - 90.7%, 82.9%, 77.3% vs. 75.6%, 72.4%, and 66.9% ($P = 0.119$).

Research conclusions

Post-PLT survival in ALF patients is inferior to ESCLD patients. This can be due to several factors including uncertainty of the underlying pathology in most ALF patients and the more critical clinical status of ALF candidates in the immediate pre-transplant period. Survival post-PLT in the ALF group was adversely affected in the first year then it stabilized while post-PLT survival in the ESCLD group showed a gradual decline over the study period.

Research perspectives

Future research should address the dilemma of identifying the underlying pathology in a considerable portion of ALF candidates and should also try to overcome liver graft shortage by identifying methods to widen the graft pool.

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