BILIARY ATRESIA: CLINICAL PROFILES, RISK FACTORS, AND OUTCOMES OF 755 PATIENTS LISTED FOR LIVER TRANSPLANTATION

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Objectives To test the hypothesis that risk analysis from the time of listing for liver transplantation (LT) focuses attention on areas where outcomes can be improved.

Study design Competing outcomes and multivariate models were used to determine significant risk factors for pretransplantation and posttransplantation mortality and graft failure in patients with biliary atresia (BA) listed for LT and enrolled in the Studies of Pediatric Liver Transplantation (SPLIT) registry.

Results Of 755 patients, most were infants (age < 1 year). Significant waiting list mortality risk factors included infancy and pediatric end-stage liver disease (PELD) score ≥ 20, whose components were also continuous risk factors. Survival posttransplantation (n = 567) was 88% at 3 years. Most deaths were from infection (37%). Posttransplantation mortality risk factors included infant recipients, height/weight < −2 standard deviations (SD), use of cyclosporine versus tacrolimus and retransplantation. Graft failure risks included height/weight < −2 SD, cadaveric partial donors, donor age ≤ 5 months, use of cyclosporine versus tacrolimus, and rejection.

Conclusions Referral for LT should be anticipatory for infants with BA with failed portoenterostomies. Failing nutrition should prompt aggressive support. Post-LT risk factors are mainly nonsurgical, including nutrition, the relative risk of infection over rejection, and the choice of immunosuppression. *(J Pediatr 2005;147:180-5)*

See editorial, p 142.

Biliary atresia (BA), a neonatal progressive cholangiopathy of unknown etiology, is the most common reason for liver transplantation (LT) in children.[1,2] Left untreated, BA leads to death by age 2 years.[1,2] Timely Kasai portoenterostomy (KP) improves survival of the native liver, although LT remains the only ultimate treatment for most (> 70%) patients.[1,2]

Although both short and long-term outcomes after KP and LT have been well documented for patients with BA, the experience is based mainly on single-center data.[3-10] Moreover, the clinical course after evaluation and listing for LT and the predictors of outcome after this important clinical event have not yet been carefully evaluated.[11]

We report outcomes and a risk analysis using competing-risk analysis methodology for patients with BA listed for their first LT and recorded in the Studies of Pediatric Liver Transplantation (SPLIT) registry.[12,13] These data provide a broad view of outcomes across centers in North America. Such information may help focus clinicians' attention on areas of management where improvements in outcomes might be realized and better inform physicians and parents of children with BA who are faced with the challenge of LT.

METHODS

Patient Population

The study group comprised all 755 children < age 18 years with BA listed for their first LT and enrolled in the SPLIT registry from May 1995 to June 2003. As described

BA	Biliary atresia	PELD	Pediatric end-stage liver disease
INR	International normalized ratio	SD	Standard deviation
KP	Kasai portoenterostomy	SPLIT	Studies of Pediatric Liver Transplantation
LT	Liver transplantation		

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previously, all of the 39 SPLIT centers had Institutional Review Board approval or a waiver for data collection and analysis.[14-16] Individual informed consent was obtained from parents and/or guardians. Coded information was submitted to the SPLIT data-coordination center at the time of listing for LT. Follow-up data were submitted on a biannual basis pre-and post-LT. There was separate reporting of data related to events such as LT, death, allograft rejection, infection, and posttransplantation complications. (In this analysis, "infant" refers to a child age < 1 year.)

Data Analysis

Clinical profiles and outcomes were analyzed according to the effect of separate risk factors and the cumulative effect of potential risk factors. After listing, 1 of the following outcomes occurs at any time point: death while waiting, living while waiting, removal from the list (improved or too ill for LT), or transplantation. Factors that might influence pre-LT outcomes include 10 discrete factors—recipient's age, sex, blood type, race, era of listing (before versus after 1999), parents' marital status, pediatric end-stage liver disease (PELD) score,[14] hospitalization status, and height/weight standard deviations (SD) at listing—and 6 continuous factors—height/weight SD, PELD score, bilirubin (log), international normalized ratio (INR) (log) and albumin (log) trends. The components of the PELD score include age, growth parameters, total serum bilirubin, INR, and albumin values. After LT, the analyses included the aforementioned factors for pre-LT outcomes (era and marital status excluded), plus PELD components at the time of LT, donor organ type, donor age, donor–recipient sex match, donor–recipient race match, primary immunosuppression (cyclosporine vs tacrolimus), and previous KP, rejection, or retransplantation. Data on the presence or absence of a KP were recorded at the time of LT (not listing). Cadaveric reduced and split donor livers were considered cadaveric technical variants. Graft failure included death and retransplantation.

Statistical Methods

Patients were grouped into proportions experiencing each event. A competing-risk analysis was used to assess the likelihood of pre-LT outcomes on the waiting list.[12] Kaplan-Meier probability estimates were used to predict patient and graft survival after LT. Univariate and multivariate analyses were performed using the aforementioned risk factors from listing and LT, and outcome groups were compared. The Cox proportional hazards model was used to test univariate and multivariate associations. Factors significant at a P value of .15 in the univariate analyses were used in the multivariate model. Next, a backward-elimination procedure was performed to obtain those risk factors that were significant at a P value of .05 from the multivariate analysis. The partial likelihood ratio test was used to test significance, and model simplification continued until the reduced model yielded significant worsening of fit at a P value of .05 (SAS System for Windows, v 8.02; SAS Institute, Cary, NC).

RESULTS

Characteristics of Patients With BA Listed for LT

Clinical and demographic details of the 755 patients with BA at the time of listing for LT are summarized in Table I (available online at www.mosby.com/jpeds). More than 70% of the patients were < 1 year of age, and 60% were female. Most (82%) were not hospitalized at the time of listing. Most had PELD scores between 10 and 20 (mean, 11.7; median, 12.1). More than 40% of patients had growth failure, although only 16% received nasogastric supplements. The mean height z-score at listing was -1.3 ± 1.8, and the mean weight z-score at listing was -1.4 ± 1.8 SD (data not shown).

Course After Listing for LT

As shown in Figure 1, after listing for LT, 24 patients (3%) died while awaiting LT, 164 (22%) were alive without LT at the last follow-up, and 567 (75%) underwent transplantation. After LT, outcomes included death (6%), survival (83%), and retransplantation (11%). Of 65 patients who received a second LT, 38% died. Overall, 81 patients died, approximately 1/3 while waiting, 1/3 after the first LT, and 1/3 after retransplantation.

From the time of listing, the probability of survival was 91% at 6 months, 89% at 1 year, and 86% at 3 years, although these data include those alive on the waiting list. The competing-risk probability of receiving LT over time was 40% at 3 months after listing, 60% at 6 months and almost 80% by 12 months (Figure 2). From the time of transplantation, patient survival rates were 92%, 90% and 88% and graft survival rates were 88% at 6 months, 86% at 1 year, and 79% at 3 years (Figure 3).

Waiting List Mortality

The majority of deaths (40%) occurred within the first 3 months after listing for LT (Figure 2; bar chart), at a time when 60% of patients were still on the waiting list (Figure 2). The most common causes of death while waiting were multiorgan failure (21%), cardiopulmonary complications (21%), and liver failure (17%), with gastrointestinal hemorrhage, cerebral edema, and bacterial infection recorded as the causes of death for the remainder (data not shown). Comparing those who died with those who were alive on the waiting list at last follow-up (Table I; available online at www.us.elsevierhealth.com/jpeds), 20% of the patients who died versus 10% of those alive had blood type B ($P < .05$). In addition, most of the patients who died had PELD scores ≥ 20 ($P < .05$) and height/weight deficits. At the time of listing, 42% of those who died were at home and 54% were receiving nutritional supplementation.

Table II gives a risk analysis for death on the waiting list. By univariate analysis, age < 1 year, PELD ≥ 10, hospitalization status and the need for nasogastric/intravenous nutrition were significant risk factors. Continuous predictors of death included the individual PELD components, namely height/weight parameters, bilirubin, INR, and albumin trends

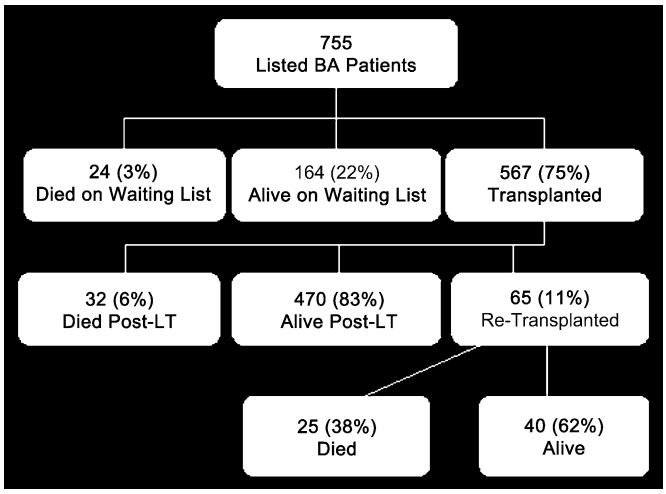

Figure 1. Flow chart of the competing outcomes for 755 biliary atresia patients listed for first LT. "Alive on waiting list" refers to patients who were alive at the last follow-up before June 2003.

(Table II). Importantly, race, sex, and year of listing were not significant. In the multivariate model, the need for nasogastric/intravenous nutrition and the trends of bilirubin, INR, and albumin were each significant predictors of death.

Characteristics of Patients With BA Receiving LT

The 567 patients who received a LT had similar age, sex, racial, and blood type characteristics as those 164 living patients who had not received a LT as of June 2003 (Table II). But at the time of LT, approximately 20% had PELD scores $\geq$ 20, 34% had scores between 10 and 20, and 36% had scores < 10. Most were orally fed (76%), and 55% had height/weight < -2 SD below the mean. Between listing and LT, mean height *z*-score decreased from -1.3 ± 0.2 to -1.5 ± 0.3 and mean weight *z*-score changed from -1.4 ± 0.4 to -1.5 ± 0.4.

Posttransplantation Mortality

Of the 567 patients who underwent LT, 57 (10%) died. Actuarial survival from LT was 90% at 6 months and 88% at 3 years (Figure 3). The most common cause of death after LT was infection (n = 21 [37%]), both bacterial and viral. Multiorgan failure accounted for 16 deaths (31%), most occurring within 30 days of LT. Although approximately 50% of patients experienced at least 1 episode of rejection, only 2 patients died from acute or chronic rejection. Other, less common causes of death included hepatic and portal vein thromboses, intra-abdominal hemorrhage, pancreatitis, and central nervous system abnormalities.

Risk factors for death post-LT (Table II) included infant recipient, use of cyclosporine versus tacrolimus, growth deficit, and retransplantation. Sex, race, donor type, donor age, previous KP, era (before or after 1999), PELD score at LT, and rejection were not significant predictors of death. In the multivariate model, infant recipients, use of cyclosporine versus tacrolimus, growth failure, and retransplantation remained significant predictors of post-LT mortality.

Graft Failure After Transplantation

Graft survival was 80% at 3 years post-LT (Figure 3). Significant factors predicting poor graft outcome (Table II) included the use of cadaveric technical variant donors, use of cyclosporine versus tacrolimus, growth failure, and rejection. In the multivariate analysis, predictors included growth failure, use of cyclosporine versus tacrolimus, cadaveric technical variant donors, rejection, and donor age $\leq$ 5 months.

Surgical Considerations and Retransplantation

Previous KP had been performed in 86% of patients who underwent LT. This was not a risk factor for poor outcome after LT. Nonsurgical factors, such as recipient age < 1 year, nutrition, infection, and type of immunosuppression, were significant risk factors for post-LT mortality. At LT, 44% of patients received whole cadaveric livers, 31% received cadaveric technical variants, and 24% received living donor partial organ transplants. Donor type was not a factor in mortality. Although not risk factors for mortality, the use of cadaveric technical variants and the use of very small donor livers (age $\leq$ 5 months) were risk factors for graft failure (Table II). Donor ages ranged from 2 months to 55 years; 50% were children. Retransplantation was performed in 65 patients (11%), within 30 days of the first transplantation in 41 patients and beyond 30 days in 24 patients. Retransplantation was a risk factor for mortality (relative risk = 12.0; 95% confidence interval = 6.75 to 21.45). Reoperations were necessary in 48% of the transplanted patients, with 26% undergoing 1 reoperation and 12% undergoing 2 or more reoperations.

DISCUSSION

These data, the largest cumulative dataset available to date describing outcomes from the time of listing for LT in patients with BA needing such therapy, reflect the current state of the art in the United States and Canada. Special considerations regarding LT for BA apply, including the predominance of infant recipients, difficulties in predicting outcomes, and timing of donor acquisition. To date, clinical profiles, likelihood of living or dying while on the LT waiting list, and donor availability/waiting time have been deduced by clinicians with limited support from the literature.[6,9,10] The present study was designed to describe the clinical profiles of a large group of patients with BA listed for LT and to provide risk analysis for poor outcomes. Improvements in management are clearly needed, underscored by the fact that there is a predicted mortality of 10% by 6 months after listing. Some 30% of the overall deaths occurred in persons waiting for LT. Among persons who undergo LT, there is a 10% mortality rate and an 11% retransplantation rate, which in turn carries a 33% mortality rate.

These data define the major predictors of poor outcome, both pre-LT and post-LT, for patients with BA who are listed for LT. The majority of deaths occurred in infants. A failed KP, manifesting as persisting or rising hyperbilirubinemia (a component of the PELD score), should be a clear indication to

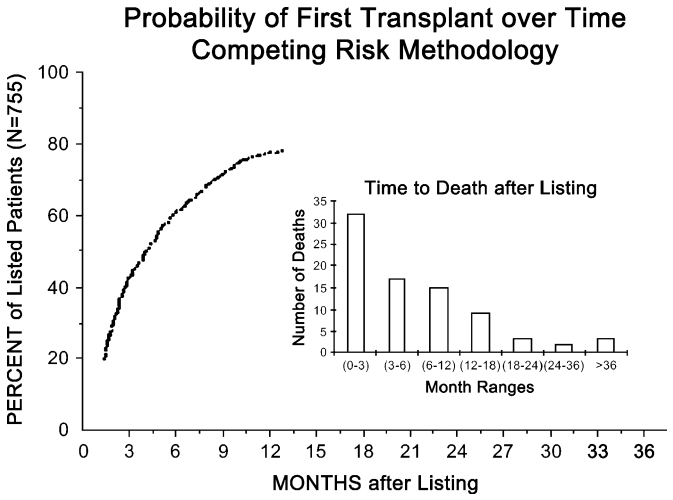

Figure 2. Competing-risk probability curve of the time to LT after listing. The accompanying bar chart shows time to death after listing for liver transplantation. Predicted survival from listing was 84% at 6 months and 81% at 1 year (data not shown).

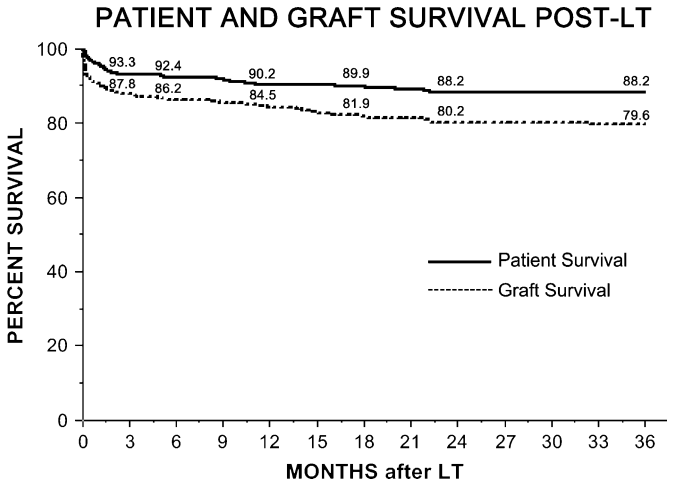

Figure 3. Actuarial patient and graft survival after LT for BA. The solid black line denotes patient survival after LT; the dashed red line denotes graft survival after LT.

refer a patient for LT. An increasing PELD score over time is directly associated with an increased mortality risk, confirming the usefulness of the PELD score for this disease. Based on the data presented here, waiting for synthetic defects or nutritional deficits to occur before listing will result in more deaths of patients on the waiting list, particularly infants. Infants are particularly suited to consideration for a scheduled living donor LT or a left-lateral (split) segment of an adult cadaver donor because of their greater risk of dying while waiting for LT, particularly infants with blood type B. Cadaveric technical variant donors do carry an increased risk of graft problems, but this may be outweighed by the benefits of receiving a timely LT. These data also reemphasize the significance of nutritional deficit as an important risk factor for poor outcome,[17-21] pointing to another area of management in which improvement may be possible.[18,20]

Table II. Significant Factors Predicting Death Pre- & Post-LT and Graft Failure Post-LT

	Relative Risk Ratio	95% CI
Death Pre-LT		
Univariate Factors		
Age ≤ 11 months[a]	4.2	(1.23, 14.05)
PELD ≥ 10[b]	18.9	(2.34, 152.27)
Hospitalization/ICU[c]	10.0	(2.38, 52.36)
NG/IV nutrition[d]	12.4	(4.00, 48.47)
*Decreasing Ht/Lt Z	1.2	(1.00, 1.50)
*Decreasing Wt Z	1.4	(1.20, 1.70)
*Increasing Bilirubin	6.8	(3.42, 13.71)
*Increasing INR	5.0	(2.49, 9.92)
*Decreasing Albumin	5.0	(3.20, 12.50)
Multivariate Factors		
NG/IV nutrition[d]	5.8	(1.89, 32.23)
*Increasing Bilirubin	3.2	(1.62, 6.09)
*Increasing INR	5.5	(2.13, 13.99)
*Decreasing Albumin	50.0	(5.56, 333.33)
Death Post-LT		
Univariate Factors		
Growth failure (Ht or Wt)[e]	2.3	(1.32, 4.14)
Recipient age ≤ 11 months[a]	2.5	(1.36, 4.55)
Cyclosporine[f]	2.1	(1.15, 3.71)
+ Re-transplantation[g]	12.0	(7.04, 20.60)
Multivariate Factors		
Recipient age ≤ 11 months[a]	2.1	(1.07, 4.08)
Cyclosporine[f]	2.0	(1.08, 3.52)
+ Re-transplantation[g]	12.0	(6.75, 21.45)
Graft Failure Post-LT		
Univariate Factors		
Growth failure (Ht or Wt)[e]	1.9	(1.27, 2.95)
Cadaveric technical variant donor[h]	1.6	(1.04, 2.59)
Cyclosporine[f]	1.6	(1.06, 2.55)
+ Rejection[i]	1.7	(1.03, 2.80)
Multivariate Factors		
Growth failure (Ht or Wt)[a]	1.9	(1.04, 2.54)
Cadaveric technical variant donor[h]	1.9	(1.07, 3.54)
Cyclosporine[f]	1.6	(1.05, 2.55)
+ Rejection[i]	1.8	(1.07, 2.98)
Donor age ≤ 5 months[j]	2.3	(1.02, 5.12)

All factors listed had $P < .05$. Univariate factors with $P \leq .15$ were included in the multivariate analyses. The final results of the multivariate analysis were obtained via a backward elimination procedure. CI = Confidence Interval; * = continuous variables (representing a trend or change in the factor, not a minimum or maximum value). Letter superscripts denote the reference group to which the discrete significant factors were compared: a = A ≥ 1 year, b = PELD < 10, c = Not hospitalized, d = Oral, e = > −2 SD below mean, f = Tacrolimus, g = Absence of re-transplantation, h = Cadaveric whole donor, i = Absence of rejection and j = Donor age 1-17 years.

After LT, infants remain at greater risk, with nonsurgical factors, such as nutritional status, choice of primary immunosuppression, and infection, the major contributors to mortality

and graft loss. Early deaths were caused by multiorgan failure in sick, undernourished infants, emphasizing the importance of good timing and selection of donor organs. Later deaths were related primarily to infection. Although rejection episodes occurred in a significant proportion of patients (~ 50% within 6 months post-LT), rejection was not a significant risk factor for mortality, suggesting that current methods for treating rejection are adequate. The choice of the primary calcineurin inhibitor immunosuppression regimen affected both patient and graft outcome, favoring tacrolimus over cyclosporine. These results support previous findings of improved clinical outcomes from using tacrolimus versus cyclosporine for primary immunosuppression in adult recipients.[22] Although the present study is not a comparative controlled study of immunosuppression regimens, the observed imbalance between the number of deaths due to infection and the lack of deaths from rejection suggests that these children are in general over-immunosuppressed, giving support to current attempts to study the effects of minimization of immunosuppression regimens in children post-LT.[23,24]

Interestingly, other risk factors that did not predict poor patient and graft outcome included previous KP surgery, donor organ type, sex, and race. The finding in this study that previous KP surgery did not predict patient survival post-LT substantiates the current recommendations for staged treatment of BA, starting with KP and progressing to LT if necessary. Race was not a factor predicting patient or graft survival. This finding contrasts with data from kidney transplant recipients, among whom African-American patients in the United States have a higher mortality rate than other racial groups.[25,26]

The present analysis was not without limitations. First, the SPLIT database is incomplete in some aspects of BA care, such as the age at KP, the presence or absence of cirrhosis at the time of KP, and histological changes occurring between KP and the listing for LT. Second, multicenter registries exhibit between-center variations in interpreting and recording patients' clinical data, as well as in clinical management. We did not evaluate the impact of center effect, because the large number of centers and the relatively small number of patients per center limited adequate interpretation. Third, this study is observational and does not include a control population. We did attempt to assess an era effect over the 8 years of data collection but found none. Nevertheless, these limitations are offset by the size and dynamic nature of the dataset, the fact that the SPLIT database includes most pediatric LTs performed in the United States and Canada, and the strength of using a competing-outcomes analysis for this large cohort.

From these analyses, several conclusions can be made concerning the care of patients with BA once they are listed for LT. An overriding conclusion is that progressive or persisting cholestasis after KP (indicating failure of the KP to reestablish bile flow) mandates early referral for consideration for LT and institution of aggressive supportive management. Specifically, aggressive nutritional support with correction of nutritional deficits while awaiting LT is likely to improve outcome.[17-23] Infants with BA awaiting LT are hypermetabolic in general and catabolic during fasting,[27] and trials of nocturnal enteral nutrition, specifically with branched-chain amino acid–supplemented formula, have demonstrated significant nutritional benefits.[17,18] Attention to post-LT nutritional support, particularly in patients who are already undernourished, would also seem advisable.[17] Next, an increasing PELD score, regardless of its starting or maximum value, should stimulate earlier referral for LT. With respect to the imbalance between deaths from infection and the low risk of allograft rejection found in this study, rigorous evaluation of immunosuppression regimens is indicated, including the potential benefits of the use of tacrolimus versus cyclosporine, early withdrawal of steroids, and avoiding over-immunosuppression by carefully monitoring calcinuerin inhibitor dosage and blood levels. In addition, research into chimerism and tolerance in transplantation holds the prospect of future immunosuppression-free regimes, which clearly merit study in young children, in whom induction of tolerance may indeed be possible.[28] Anticipatory management and aggressive control of infection are also indicated. Finally, future analyses are warranted, such as those arising from the Biliary Atresia Research Consortium,[29] concerning the outcomes of specific BA subtypes and the influence of KP surgery and its timing on the survival of patients with BA.

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