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)*

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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