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Improved Outcomes for Liver Transplantation in Patients with Biliary Atresia Since Pediatric End-Stage Liver Disease Implementation: Analysis of the Society of Pediatric Liver Transplantation Registry

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Objective To identify changes in demographics, outcomes, and risk factors for patient and graft loss in patients with biliary atresia undergoing liver transplantation since Pediatric End-Stage Liver Disease implementation (2002).

Study design Demographics and outcomes were compared between patients enrolled in the Society of Pediatric Liver Transplantation registry before (n = 547) and after (n = 1477) 2002. Kruskal-and χ^2 Wallis tests identified significant differences between eras. Risk factors for patient and graft loss after 2002 were determined by Cox regression model analysis of time to event data.

Results Significant patient differences after 2002 support increasing disease severity including more status 1 patients and those with a derived Model for End-Stage Liver Disease/Pediatric End-Stage Liver Disease score of greater than 30 awaiting transplant. Both patient and graft survival improved after 2002 from 90% to 97% and 81% to 90%, respectively (primary transplant; $P < .0001$). Significant differences in complications within 30 days included reduced relisting for transplant, rejection, culture-positive infection, repeat operation, hepatic artery thrombosis, portal vein thrombosis, and death/transplant before discharge. Multivariable analysis identified deceased technical variant vs whole graft and retransplantation predictive for patient death, hazard ratios of 4.041 and 8.308, respectively. Deceased technical variant vs whole graft (hazard ratio, 1.963) and donor age 0-5 months vs 1-17 years (hazard ratio, 5.525) were risk factors for graft loss.

Conclusions The overall outcomes of patients receiving liver transplantation for patients with biliary atresia have improved since 2002 despite evidence of increased disease severity at the time of transplant. Risk factors impacting post-transplant morbidity and mortality in patients with biliary atresia are now mainly surgical including donor variables. *(J Pediatr 2019;■:1-9)*.

Biliary atresia is a neonatal cholestatic liver disease that is the leading cause of pediatric liver transplantation.[1,2] Even when diagnosed promptly and a Kasai portoenterostomy is performed, the majority of patients ultimately receive a liver transplant before reaching adulthood.[1] Indications for liver transplantation in patients with biliary atresia include absence of biliary drainage after Kasai portoenterostomy, delayed diagnosis of biliary atresia resulting in primary liver transplantation without Kasai portoenterostomy, recurrent cholangitis, portal hypertension with significant complications, pulmonary vascular disorders such as hepatopulmonary syndrome or portopulmonary syndrome, hepatorenal syndrome, presence of hepatic malignancy, or intractable pruritus adversely affecting quality of life.[3] The 5- and 10-year survival rates of pediatric patients with biliary atresia after primary liver transplantation between 1998 and 2003 was 87.2% and 85.8%, respectively.[4] More recent data obtained on patients with biliary atresia after primary liver transplantation between 2002 and 2012 demonstrates overall improved patient survival at 5 years of 94.6%; however, patients transplanted before age 2 years have significantly lower patient and graft survival rates than older children.[5]

Risk factors for mortality and graft loss in patients with biliary atresia was previously evaluated by the Society of Pediatric Liver Transplantation (SPLIT) for 755 patients enrolled between 1995 and 2003.[6] Risk factors for post-transplant patient mortality in this cohort included infant recipients, nutritional deficit with height/weight z-score greater than 2 SD below the mean, use of cyclosporine, and retransplantation. In addition to nutritional deficit and use of cyclosporine, risk factors for graft failure included the use of deceased technical variant donors, donor age of 5 months or younger, and a history of rejection.

MELD	Model for End-stage Liver Disease
PELD	Pediatric end-stage liver disease
SPLIT	Society of Pediatric Liver Transplantation

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An evaluation of 1976 pediatric patients with biliary atresia undergoing primary liver transplantation in the United Network for Organ Sharing database between 1988 and 2003 demonstrated that deceased partial/reduced liver grafts, patients on life support at the time of liver transplantation, and lower recipient age were independent risk factors for post-transplant mortality.[4] Many medical advancements have occurred over the past 2 decades, including changes to immunosuppression, nutritional management, and infection prophylaxis as well as improved surgical techniques.[7] Although improved outcomes have been reported in the era after implementation of the pediatric end-stage liver disease (PELD) severity scores, there is a gap in knowledge on how these advances have specifically affected patients with biliary atresia.[8]

In the present study, we examined the characteristics of patients with biliary atresia enrolled in SPLIT longitudinally from 1995 to 2017. Analysis of data obtained over 2 decades will allow for comparison of patient and graft outcomes before and after implementation of the Model for End-stage Liver Disease (MELD) and PELD severity scores in February 2002.[9] We hypothesize that outcomes and predictors for graft loss and mortality for patients with biliary atresia have improved since 2002 in parallel with surgical and medical advances. Through univariable and multivariable analyses, we identify risk factors for patient and graft loss after 2002 to enhance risk assessment in this patient population and improve outcomes.

Methods

All patients with a diagnosis of biliary atresia enrolled in the SPLIT registry who underwent liver transplantation between January 13, 1995, and December 11, 2017, were included in the study. Each center participating in SPLIT obtained institutional review board approval for inclusion in the registry and data collection. Individual consent was obtained from the parents and/or participant at each participating center. Coded participant information was collected and submitted to the SPLIT data coordination center at the time of enrollment and listing for liver transplantation. Follow-up data were collected for each era (1995-2002 and 2002-2017) according to the SPLIT registry data forms until the last recorded follow-up visit.

Statistical Analyses

Pretransplant and post-transplant clinical characteristics of 2024 total patients were analyzed. Statistical comparisons between the pre-2002 and post-2002 eras were made using χ^2 test for categorical data and the nonparametric test Kruskal-Wallis test for continuous data. Significance was defined by a P value of less than .05. Patient and graft outcomes for each era were evaluated using Kaplan-Meier survival analysis. Univariable and multivariable Cox regression analysis was performed to identify risk factors for patient and graft loss after 2002. Factors that were significant at .15 level in the univariable analysis were included in the first step for stepwise multivariable model.

We performed univariable analysis to identify risk factors for patient and graft survival after 2002 using the following characteristics: age at transplant of less than 1 year, sex, race, history of previous Kasai portoenterostomy, derived PELD and MELD scores calculated from registry data, growth parameters (Z-weight, Z-height, and weight-height failure), laboratory values at the time of liver transplant (albumin <3 g/dL, total bilirubin, international normalized ratio), clinical status at transplantation (hospitalization status, patient in the intensive care unit, intubated before liver transplantation, presence of portal vein thrombosis in the native liver), donor factors (donor type, donor age, warm and cold ischemia times), immunosuppression agents used within the first week after liver transplantation, rejection episodes after transplantation, and a history of retransplantation. The type of transplant procedure was defined as either living, whole, or deceased technical variant. Additional characterization of technical variants included partial liver in which the remainder of the graft was not transplanted or graft from a living donor, or split liver in which both segments were transplanted. Status 1 listing at the time of transplant included United Network for Organ Sharing status 1a/b, Canadian 4/4f, and Transplantation Society of Australia and New Zealand 1/2a. Risk factors with a P value of .15 or less on univariable analysis were included in multivariable analysis for the post-2002 era. Comorbidities with a large proportion of missing data (>75%) before 2011 that were excluded from comparison between eras but used in the post-2002 univariable and multivariable analyses included use of renal replacement therapy before transplantation, presence of hepatopulmonary syndrome or congenital cardiac disease, and use of supplemental feeds. Significant risk factors on multivariable analysis ($P < .05$) were compared with prior analyses of the pre-2002 era.[6] We performed Schoenfeld test to evaluate the proportional hazards assumption in the Cox proportional hazard's model. Overall hazard ratios for factors significant in multivariable analysis were reported with the 95% CI in addition to hazard ratios with CI for these factors at 1-year after transplantation. Missing data were excluded from reported percentages and statistical analyses in all tables and factors with missing data of less than 5% or more than 5% of total patients are reported. The IQR is reported for laboratory values and range is reported for continuous variables.

Last, we compared outcomes within 30 days and more than 1 year after liver transplantation between the 2 time periods and determined significance by χ^2 and Kruskal-Wallis tests. Owing to the long time periods of comparison, a subanalysis of patient and graft outcomes and post-transplant complications was performed for patients transplanted between January 1, 2011, and December 31, 2017, to validate the results obtained from the larger post-2002 cohort.

Results

Patient Demographics

Recipient and donor characteristics for patients with biliary atresia in each era are shown in Table I. In both eras, approximately 50% of all patients with biliary atresia who underwent liver transplantation received the transplant before 1 year of age. The sex distribution remained similar across eras with a larger proportion of female transplant recipients. An increased proportion of patients with biliary atresia of Asian race were present in the patient cohort after 2002. More patients received a Kasai portoenterostomy before 2002 as compared with after 2002 ($P = .0054$). There was an increase in patients with derived PELD/MELD scores of 30 or greater in the post-2002 era. Despite this difference, the percentage of patients in the intensive care unit or intubated before transplant was similar between eras. Additionally, there was no significant difference in the median laboratory values for sodium, total bilirubin, and albumin at the time of transplant. Improvement in median Z-weight score in the post-2002 era approached statistical significance.

Although overall the use of technical variants was similar in both eras, the use of split liver technical variants significantly increased by 10% in the post-2002 era. There was a similar use of deceased (whole or technical variant) and living donors in both eras; however, fewer adult donors were used after 2002. Additionally, both warm and cold ischemia times improved after 2002. Significant differences in immunosuppression agents used within the first 7 days after liver transplantation after 2002 included increased use of antibody induction, tacrolimus, and mycophenolate mofetil, and decreased use of corticosteroids, cyclosporine, and azathioprine.

Patient and Graft Survival by Era

Of the total 2024 patients with biliary atresia in the study, 95% were alive at the time of last contact for the study period (Figure 1, A). Figure 1, B demonstrates significantly improved patient survival after 2002 ($P < .0001$). The most common cause of death in both eras was bacterial infection or sepsis comprising 20.2% of deaths before 2002 and 21.7% of deaths after 2002. Multiorgan failure was the second most common cause of death in both cohorts, comprising 18.1% and 15.9% of deaths before 2002 and after 2002, respectively. A comparison between the characteristics of patients who died after liver transplantation in the 2 eras demonstrated no significant difference in the proportion of patients who died awaiting a second liver transplant, patients on renal replacement therapy before death, intensive care unit status before death, or occurrence of intraoperative deaths.

Graft survival also significantly improved in the post-2002 era (Figure 1, B; $P < .0001$). Repeat liver transplantation was performed in 14.3% of patients in the pre-2002 era compared with only 6.6% of patients in the post-2002 era ($P = .0002$). In patients with biliary atresia receiving a second liver transplant, 42.3% lost their graft and 34.6% died before 2002 as compared with 18.4% graft loss and 14.3% mortality after 2002 (Figure 1, B; $P = .0122$ and .0229 respectively).

Risk Factors Impacting Patient and Graft Loss after 2002

We report variables in univariable analysis with a P value $< .05$ for patient death and graft loss after 2002 in Table II. Risk factors for patient death entered into the multivariable model included z-weight score, use of supplemental feeds, retransplantation, donor type of deceased technical variant vs whole liver graft, and a donor age of 5 months or younger. Risk factors for graft loss after 2002 entered into the multivariable model included z-weight score, presence of weight-height failure, recipient receiving supplemental feeds, presence of portal vein thrombosis in the native liver, use of living donor graft vs whole graft, and donor age of 5 months or less. Of the patients reported to receive supplemental feeds after 2002, 66% received tube feeds, 30% had parenteral nutritional support, and 4% received a combination of parenteral and tube feeds. Multivariable analysis for the post-2002 era identified 2 risk factors for patient death and 2 risk factors for graft loss (Table II). Retransplantation was a risk factor for patient mortality (HR, 8.308; 95% CI, 4.206-16.411) and donor age of 5 months or younger was a risk factor for graft loss (HR, 5.525; 95% CI, 3.048-10.017). The use of a deceased technical variant was a risk factor for both patient death (HR, 4.041; 95% CI, 1.992-8.196) and graft loss (HR, 1.963; 95% CI, 1.148-3.358). The mean recipient weight for a deceased technical variant was 10.8 $\pm$ 8.3 kg (data not shown).

We further evaluated the significant multivariable risk factors at 1-year after transplantation to determine the difference in risk at a shorter time interval after transplant. At 1 year after transplantation, the HR for retransplantation increased to 12.695 for patient death (95% CI, 5.231-30.808) and the HR for a donor age of 5 months or younger increased to 6.556 as a risk factor for graft loss (95% CI, 3.530-12.176). The use of a deceased technical variant had similar though reduced risk for both patient and graft loss at 1 year with a HR of 3.830 (95% CI, 1.537-9.543) and 1.854 (95% CI, 1.016-3.383), respectively. Schoenfeld test demonstrated adherence to the proportional hazard assumption for multivariable factors for graft loss ($P > .05$ for all factors). The patient survival model includes retransplantation as a time-dependent factor resulting in HR being a function of time and thereby no longer a proportional hazards model.

Outcomes After Primary Liver Transplantation

Changes in the rate of complications within 30 days of liver transplantation are shown in Figure 2. There was a significant improvement in the rate of hepatic artery thrombosis from 12.9% to 8.8% ($P = .0220$) and portal vein thrombosis from 14.2% to 6.5% ($P < .0001$). The

Table I. Demographic and descriptive characteristics of the patient cohorts

Variables	Before 2002 (n = 547)	After 2002 (n = 1477)	Total (n = 2024)	*P* value
Age at transplantation	n = 547	n = 1477	n = 2024	.0024
0-5 mo	68 (12.4%)	107 (7.2%)	175 (8.6%)	
6-11 mo	217 (39.7%)	633 (42.9%)	850 (42.0%)	
1-17 y	262 (47.9%)	735 (49.8%)	997 (49.3%)	
≥18 y	0	2 (0.1%)	2 (0.1%)	
Sex	n = 547	n = 1477	n = 2024	.1117
Male	194 (35.5%)	581 (39.3%)	775 (38.3%)	
Female	353 (64.5%)	896 (60.7%)	1249 (61.7%)	
Race*	n = 544	n = 1465	n = 2009	<.0001
American Indian/Alaska Native	9 (1.7%)	17 (1.2%)	26 (1.3%)	
Asian	7 (1.3%)	107 (7.3%)	114 (5.7%)	
Native Hawaiian or other Pacific Islander	4 (0.7%)	10 (0.7%)	14 (0.7%)	
Black or African American	99 (18.2%)	242 (16.5%)	341 (17.0%)	
White	322 (59.2%)	858 (58.6%)	1180 (58.7%)	
>1 race	26 (4.8%)	44 (3.0%)	70 (3.5%)	
Other	15 (2.8%)	40 (2.7%)	55 (2.7%)	
Not reported	62 (11.4%)	147 (10.0%)	209 (10.4%)	
Previous Kasai portoenterostomy*	n = 532	n = 1424	n = 1956	.0054
Yes	463 (87.0%)	1164 (81.7%)	1627 (83.2%)	
Organ allocation distribution				
Status 1	21 (n = 528, 4.0%)	121 (n = 1441, 8.4%)	142 (n = 1969, 7.2%)	<.0001
Derived PELD†	n = 383	n = 1308	n = 1691	.0187
≤15	186 (48.6%)	632 (48.3%)	818 (48.4%)	
PELD 15-30	174 (45.4%)	537 (41.1%)	711 (42.0%)	
PELD ≥30	23 (6.0%)	139 (10.6%)	162 (9.6%)	
Derived MELD†	n = 412	n = 1367	n = 1779	.0457
≤15	117 (28.4%)	448 (32.8%)	565 (31.8%)	
MELD 15-30	280 (68.0%)	843 (61.7%)	1123 (63.1%)	
MELD ≥30	15 (3.6%)	76 (5.6%)	91 (5.1%)	
Median wait time (d)	86 (n = 537)	91 (n = 1458)	90 (n = 1995)	.4932
Clinical status at transplantation				
Median Z-height (range)	−1.5 (n = 453, −7.5 to 2.9)	−1.5 (n = 1276, −7.6 to 4.8)	−1.5 (n = 1729, −7.6 to 4.8)	.7049
Median Z-weight (range)	−1.4 (n = 509, −7.9 to 4.6)	−1.2 (n = 1388, −7.8 to 5.6)	−1.3 (n = 1897, −7.9 to 5.6)	.0504
Hospitalized in ICU*	71 (n = 542, 13.1%)	220 (n = 1467, 15.0%)	291 (n = 2009, 14.5%)	.1491
Intubated before transplantation*	28 (n = 541, 5.2%)	105 (n = 1461, 7.2%)	133 (n = 2002, 6.6%)	.1086
Portal vein thrombosis*	23 (n = 519, 4.4%)	76 (n = 1420, 5.4%)	99 (n = 1939, 5.1%)	.4149
Median laboratory values at transplantation				
Na, mEq/L (n, IQR)	139.0 (n = 67, 136 to 141)	138.0 (n = 1255, 135 to 141)	138.0 (n = 1322, 135 to 141)	.3173
Total bilirubin, mg/dL (n, IQR)	9.8 (n = 533, 3.4 to 16.6)	8.4 (n = 1434, 2.4 to 16.8)	8.8 (n = 1967, 2.7 to 16.7)	.0702
Albumin, g/dL (n, IQR)	3.0 (n = 518, 2.5 to 3.5)	3.0 (n = 1427, 2.5 to 3.5)	3.0 (n = 1945, 2.5 to 3.5)	.3567
INR (N, IQR)	1.3 (n = 422, 1.1 to 1.6)	1.4 (n = 1399, 1.2 to 1.8)	1.4 (n = 1821, 1.2 to 1.7)	.0006
Donor and graft characteristics				
Procedure type*	n = 538	n = 1430	n = 1968	.2499
Living	131 (24.3%)	300 (21.0%)	431 (21.9%)	
Whole	244 (45.4%)	691 (48.3%)	935 (47.5%)	
Deceased technical variant	163 (30.3%)	439 (30.7%)	602 (30.6%)	
Donor age†	n = 506	n = 1343	n = 1849	.0167
0-5 mo	36 (7.1%)	100 (7.4%)	136 (7.4%)	
6-11 mo	25 (4.9%)	83 (6.2%)	108 (5.8%)	
1-17 y	254 (50.2%)	756 (56.3%)	1010 (54.6%)	
≥18 y	191 (37.7%)	404 (30.1%)	595 (32.2%)	
Warm ischemia time (min)				
Mean (n, SD)	53.0 (n = 498, 21.8)	44.8 (n = 1224, 21.4)	47.2 (n = 1722, 21.8)	<.0001
Cold ischemia time (h)				
Mean (n, SD)	7.2 (n = 482, 3.5)	6.5 (n = 1299, 3.3)	6.7 (n = 1781, 3.4)	.0003
Initial immunosuppression‡				
Antibody induction*	85 (n = 517, 16.4%)	454 (n = 1415, 32.1%)	539 (n = 1931, 27.9%)	<.0001
Corticosteroids*	515 (n = 527, 97.7%)	1314 (n = 1440, 91.3%)	1829 (n = 1967, 93.0%)	<.0001
Tacrolimus*	322 (n = 526, 61.2%)	1329 (n = 1441, 92.2%)	1651 (n = 1967, 83.9%)	<.0001
Cyclosporine*	210 (n = 519, 40.5%)	90 (n = 1423, 6.3%)	300 (n = 1942, 15.4%)	<.0001
Mycophenolate mofetil*	74 (n = 516, 14.3%)	455 (n = 1435, 31.7%)	529 (n = 1951, 27.1%)	<.0001
Azathioprine*	190 (n = 519, 36.6%)	61 (n = 1421, 4.3%)	251 (n = 1940, 12.9%)	<.0001
Sirolimus*	28 (n = 516, 5.4%)	27 (n = 1419, 1.9%)	55 (n = 1935, 2.8%)	<.0001
Everolimus†	0 (n = 3, 0%)	4 (n = 565, 0.7%)	4 (n = 568, 0.7%)	.8837
Graft outcomes				

(*continued*)

Table I. Continued

Variables	Before 2002 (n = 547)	After 2002 (n = 1477)	Total (n = 2024)	*P* value
Overall reported rejection	316 (n = 547, 57.8%)	585 (n = 1477, 39.6%)	901 (n = 2024, 44.5%)	<.0001
Graft loss (primary transplant)	113 (n = 547, 20.7%)	126 (n = 1477, 8.5%)	239 (n = 2024, 11.8%)	<.0001
Patient outcomes				
Death	62 (n = 547, 11.3%)	42 (n = 1477, 2.8%)	104 (n = 2024, 5.1%)	<.0001
Retransplantation	78 (n = 547, 14.3%)	98 (n = 1477, 6.6%)	176 (n = 2024, 8.5%)	.0002

ICU, intensive care unit; *INR*, international normalized ratio.
Statistical significance for differences in each factor by era was calculated and *P* value is reported. Missing data were excluded from calculation of percentages and statistical significance. Graft and patient outcomes include cumulative reports for all enrolled patients until their last recorded follow-up visit.
*Missing data <5% of total number.
†Missing data >5% of total number.
‡Initial immunosuppression is defined as immunosuppression given within the first 7 days after transplantation.

percent of patients with a culture-proven infection after 2002 remained high at 40.1%, but was significantly decreased from 51.7% before 2002 ($P < .0001$). In line with improved graft outcomes, there was also a decreased incidence of rejection within 30 days after transplantation by 15.9% after 2002 ($P < .0001$).

Greater variability was present for data collection at longer time interval from transplant. At 1-3 years of follow-up, more than 80% of all patients remained in the registry for each era and there was a similar proportion of patients lost to follow-up (10.8% before 2002 and 9.8% post-2002). More patients reached their 10-year visit with data collection on 25% of patients at this visit before 2002 compared with 7.7% after 2002; however, a greater amount of missing data was present in this era. Evaluation of complications between 1 and 3 years after primary liver transplantation demonstrated an increase in the occurrence of portal vein stenosis ($P = .0095$) and repeat hospitalization ($P = .0029$) in the post-2002 era. Reported cases of post-transplant lymphoproliferative disorder decreased from 6.8% before 2002 to 1.7% after 2002 at the 1- to 3-year follow-up. Rejection was most common in the 1- to 3-year follow-up period and was reported in 19% of patients. Over 10 years of follow-up data, skin cancer was reported in only 1 patient in either era. There were no reports of hepatocellular carcinoma or hepatoblastoma. Of patients with more than 10 years of follow-up after 2002, 43% of patients had had a liver biopsy. The median laboratory values for measures of liver injury, hepatic function, thrombocytopenia, insulin resistance, and renal function were with the normal range for both eras at 10 years after transplantation. This finding is similar to previously reported data of all patients in SPLIT who received a liver transplant before December 1999.[10]

We demonstrate a continued trend toward improved outcome over time in the subanalysis of patients transplanted after 2011 compared with our larger post-2002 cohort. Patient survival for first liver transplant was higher at 98.5% (n = 716) and only 5.6% of patients experienced graft loss. In comparison with the significant differences noted in the post-2002 cohort (**Figure 2**), after 2011, 1.8% of patients died or received a repeat liver transplant before discharge (vs 3.2%), 3.7% of patients were relisted for liver transplant (vs 6.2%), 4.6% of patients had a portal vein thrombosis (vs 6.5%), 6.4% had hepatic artery thrombosis (vs 8.8%), 35.5% had a repeat operation within the first 30 days (vs 37.0%), 34.1% had culture proven infection (vs 40.1%), and 15.1% had an episode of rejection within 30 days (vs 17.2%).

Discussion

Cumulative data from 1995 to 2017 demonstrate significantly improved patient and graft outcomes after 2002 for patients with biliary atresia in the SPLIT registry. In contrast with previously reported univariate analysis of patients in SPLIT before 2002 by Utterson et al, recipient age of 11 months or younger was no longer a risk factor for patient death after liver transplantation despite about 50% of infants undergoing liver transplant before 1 year of age in both eras.[6] This finding suggests that advances in surgical techniques and medical care of smaller recipients have contributed to improved post-transplant outcomes in patients with biliary atresia rather than disease-modifying interventions to prolong transplant-free survival. Additionally, the use of cyclosporine (patient and graft loss), history of rejection (graft loss only), and parameters of growth failure were no longer risk factors after 2002, supporting the premise that medical advancements in immunosuppressive therapy and nutritional support have helped to improve outcomes since 2002. Factors predictive of patient death after primary liver transplantation in both time periods included a history of retransplantation. Although the use of deceased technical variant was a risk factor only for graft failure in the pre-2002 era, the donor type influenced both patient and graft survival in the post-2002 era. A notable new risk factor for both patient and graft loss after 2002 included donor age of 0-5 months despite similar use of these donors between eras (7.1% before 2002 and 7.4% after 2002). Despite medical advances, surgical and technical factors continue to impact patient and graft outcomes.

In the current study, we demonstrate that the use of deceased technical variants (partial or split livers) are risk factors for patient and graft loss in biliary atresia. This finding significantly adds to current literature that has recently suggested comparable outcomes between split and whole liver

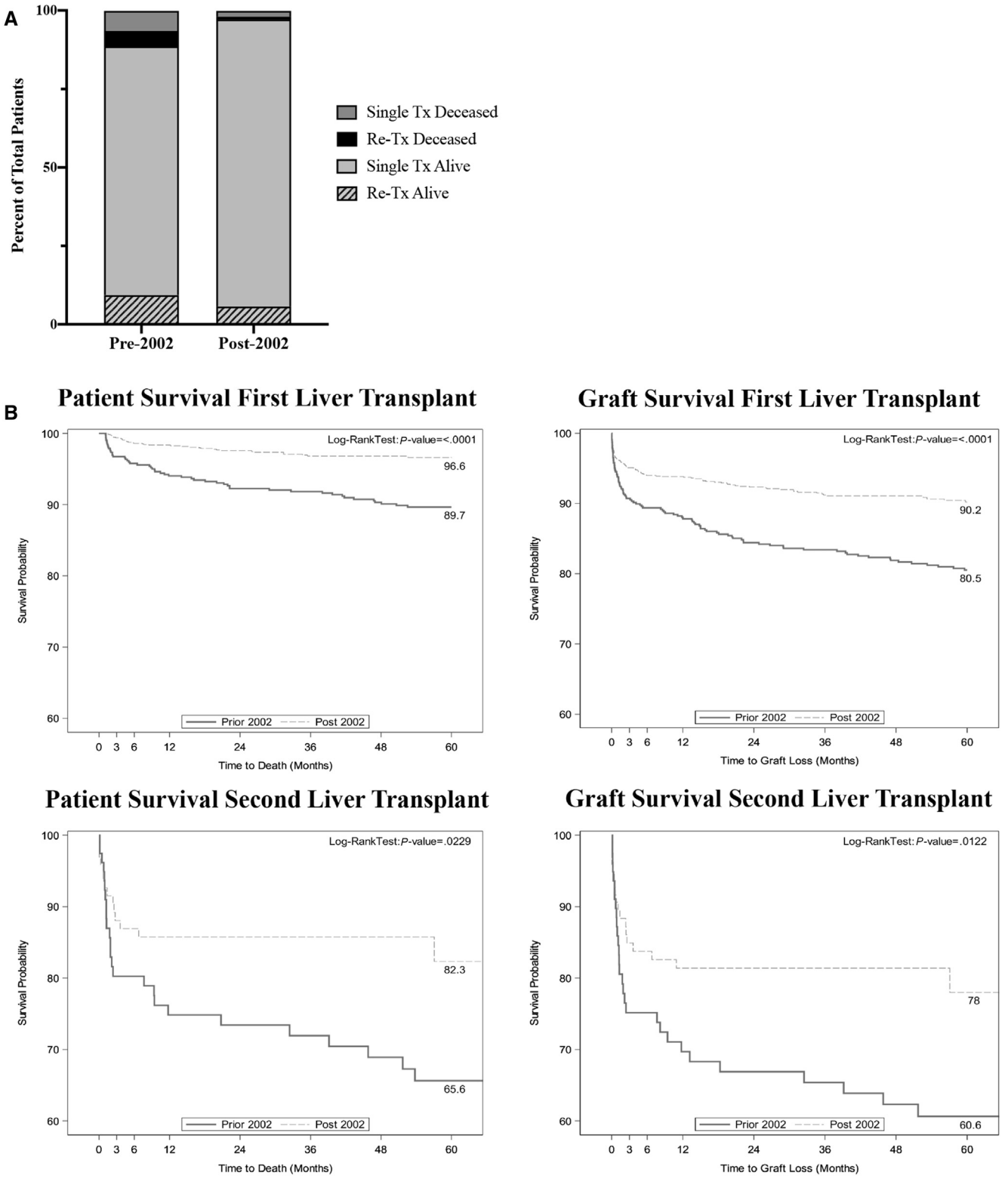

Figure 1. **A,** Summary of survival data by era. Rate of repeat liver transplantation and death decreased after 2002. **B,** Patient and graft survival curves by era for primary liver transplant and retransplantation. The solid line represents patient and graft survival before 2002, the dashed line represents patient and graft survival after 2002. The log-rank test was used for calculation of statistical significance between eras and *P* values are reported. *Tx*, transplantation.

Table II. Risk factors for patient and graft survival after 2002

Variables	Univariable analysis	Multivariable analysis
Patient survival after 2002		
Z-weight	0.781 (0.649-0.940)	NA
Supplemental feed: tube	3.682 (1.526-8.883)	NA
Supplemental feed: any	15.065 (2.034-111.578)	NA
Retransplantation	9.105 (4.779-17.349)	8.308 (4.206-16.411)
Donor type: deceased technical variant vs whole	3.487 (1.766-6.886)	4.041 (1.992-8.196)
Donor age: 0-5 mo vs 1-17 y	2.659 (1.066-6.633)	NA
Graft survival after 2002		
Z-weight	0.832 (0.746-0.927)	NA
Weight-height failure	1.517 (1.055-2.181)	NA
Supplemental feed: tube	1.789 (1.119-2.859)	NA
Supplemental feed: any	1.844 (1.078-3.154)	NA
PVT in native liver	1.937 (1.068-3.514)	NA
Donor type		
Living vs whole	0.358 (0.184-0.697)	NA
Deceased technical variant vs whole	NA	1.963 (1.148-3.358)
Donor age: 0-5 mo vs 1-17 y	4.177 (2.605-6.699)	5.525 (3.048-10.017)

NA, not applicable; *PVT*, portal vein thrombosis.
Univariable risk factors determined to have a pairwise *P* value of <.05 are reported. Risk factors with a *P* value of ≤.15 on univariable analysis were included in multivariable analysis. Significant risk factors in multivariable analysis were defined by a *P* value of <.05. Values are HR (95% CI).

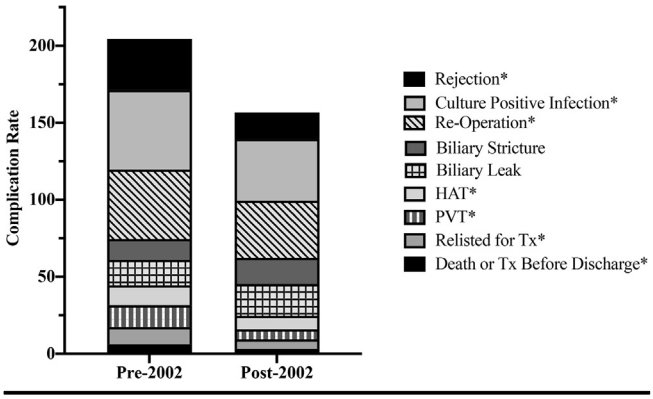

Figure 2. Complications occurring within 30 days after primary liver transplantation reported by era. Rate of vascular, biliary, operative, and rehospitalization events for patients after liver transplantation. Missing data was excluded from calculation of percentages. *Statistically significant complications between eras. Rate of hepatic outflow obstruction was less than 0.5% for each era (*P* = .3697, data not shown). *HAT*, hepatic artery thrombosis; *PVT*, portal vein thrombosis; *Tx*, transplantation.

allografts in pediatric transplant recipients.[11,12] Recent data in adult transplant recipients suggests the risk of split liver grafts may be falsely decreased in long-term studies in which the time-varying effect is abrogated.[13] Although the global risk for deceased technical variants was significant in our study despite concern for variance over time, we also evaluated the HR at 1 year after transplantation and demonstrate higher risk at this time interval. Prior reports in infants with biliary atresia demonstrate that partial liver allografts (deceased or living donor) have superior outcome to whole liver allografts in infants with biliary atresia who weigh 7 kg or less.[14] Although the average weight of patients receiving a deceased technical variant graft in our cohort was higher at 10.8 kg and may have contributed to increased risk, further studies are needed to define which liver transplant recipients with biliary atresia benefit most from technical variant grafts.

Advancing our knowledge of factors favorable for improved outcome after technical variant grafts is critical as disease severity of patients with biliary atresia awaiting liver transplant increases. The higher acuity of patients with biliary atresia undergoing liver transplantation since 2002 is supported by our data and an increase in patients listed as status 1 awaiting liver transplantation, higher derived PELD and MELD scores, and more episodes of repeat hospitalization during 1-3 years after transplant. This finding parallels data from the 2017 Organ Procurement and Transplantation Network annual report for all pediatric transplant recipients in which the proportion of patients listed as status 1a/1b increased to 26.9% from 16.7% in 2006.[15] Improved outcomes despite increased patient acuity highlights the positive impact of advancements in the modern era on pediatric candidates with biliary atresia awaiting transplantation. Furthermore, there was no difference in the median time on the wait list and greater use of split liver allografts was observed supporting improved strategies to increase the supply of donor grafts to match increasing demand and disease severity.[16] However, to avoid pediatric waitlist mortality, the increased use of split liver allografts remains important and does not adversely impact adult liver transplantation rates.[17]

A history of having a previous Kasai portoenterostomy was significantly different between eras; however, this factor was not predictive of outcome. As such, Kasai portoenterostomy remains standard of care to promote biliary drainage and prolong patient survival with their native liver. However, this finding may be in part due to low number of patients in our database that did not receive a Kasai portoenterostomy. A report of 626 patients with biliary atresia, of whom 50% underwent primary liver transplantation without Kasai portoenterostomy, demonstrated improved survival in patients undergoing primary liver transplantation.[18] Because failure to improve biliary drainage after Kasai portoenterostomy occurs in more than 30% of cases, further trials are needed to define patient factors that may predict improved response to primary liver transplantation and guide future surgical strategy.[19]

Although growth failure was no longer a significant risk factor on multivariable analysis, evidence of poor nutrition (as defined by requirement of supplemental feeds) was a significant risk factor for patient and graft loss on univariable analysis.[6] Growth failure in infants with biliary atresia after Kasai portoenterostomy has been recognized as a risk factor

for liver transplantation or mortality before 2 years of age.[20] Retrospective data in infants with biliary atresia awaiting liver transplant suggests improvement in nutritional status can be safely achieved using parenteral nutrition.[21,22] However, prospective studies are lacking to directly compare outcomes using enteral vs parenteral supplementation in this vulnerable patient population and it remains difficult to achieve adequate growth owing to increased metabolic demands. Insufficient nutritional supplementation leading to sarcopenia is associated with increased risk of infection in patients with cirrhosis and after transplantation, and sepsis is one of the most common precipitating factors to develop acute-on-chronic liver failure in patients with biliary atresia awaiting liver transplantation.[23-25] Infection remains an important post-transplant complication as illustrated by our data, with bacterial infection or sepsis as the leading causes of death. New measures of nutritional status in children such as psoas muscle surface area may help to identify patients before transplantation who will be most at risk for nutrition-associated post-transplant complications.[26] These findings suggest that malnutrition remains an important factor impacting prognosis, even though our study supports improvement in nutritional optimization over time.

Despite the strengths of the SPLIT registry database, limitations exist in the present study. First, our study is a retrospective observational study without a control population. However, biliary atresia is the leading indication for pediatric liver transplantation, thereby allowing for comparison between our findings and other published literature on pediatric liver transplant recipients. Second, although a multicenter study offers the benefit of accruing a large number of patients, data collection may differ between centers introducing bias in data reporting. Furthermore, SPLIT has transitioned from a research study funded by the National Institutes for Health to a collaborative society and data collection has evolved to document clinical changes and medical advances over time. Data are limited by the predefined forms of the SPLIT registry and cannot evaluate additional risk factors such as age at Kasai portoenterostomy, liver histology at Kasai portoenterostomy, or time to clearance of jaundice after Kasai portoenterostomy. Last, the sample size with full data collection at the 10-year follow-up is small and limits evaluation of these patients.

We demonstrate that both short-term and long-term outcomes after pediatric liver transplantation for biliary atresia have improved since 2002. Decreased vascular and biliary complications within the first 30 days after transplantation may contribute to improved patient and graft outcomes. Similarly, decreased rates of rejection and improved laboratory profiles at long-term follow-up in the modern era support more effective immunosuppression management. Despite these improvements, surgical variables remain risk factors for patient and graft loss. Further studies are needed to optimize continued use of split liver allografts and increase the donor pool to reduce wait list and post-transplant complications in parallel with the increasing disease severity of transplant recipients. ■

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