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REGISTRY REPORT

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# Society of pediatric liver transplantation: Current registry status 2011-2018

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## Abstract

**Background:** SPLIT was founded in 1995 in order to collect comprehensive prospective data on pediatric liver transplantation, including waiting list data, transplant, and early and late outcomes. Since 2011, data collection of the current registry has been refined to focus on prospective data and outcomes only after transplant to serve as a foundation for the future development of targeted clinical studies.

**Objective:** To report the outcomes of the SPLIT registry from 2011 to 2018.

**Methods:** This is a multicenter, cross-sectional analysis characterizing patients transplanted and enrolled in the SPLIT registry between 2011 and 2018. All patients, <18 years of age, received a first liver-only, a combined liver-kidney, or a combined liver-pancreas transplant during this study period.

**Results:** A total of 1911 recipients from 39 participating centers in North America were registered. Indications included biliary atresia (38.5%), metabolic disease (19.1%), tumors (11.7%), and fulminant liver failure (11.5%). Greater than 50% of recipients were transplanted as either Status 1A/1B or with a MELD/PELD exception score. Incompatible transplants were performed in 4.1%. Kaplan-Meier estimates of 1-year patient and graft survival were 97.3% and 96.6%. First 30 days of surgical complications included reoperation (31.7%), hepatic artery thrombosis (6.3%), and portal vein thrombosis (3.2%). In the first 90 days, biliary tract complications were reported in 13.6%. Acute cellular rejection during first year was 34.7%. At 1 and 2 years of follow-up, 39.2% and 50.6% had normal liver tests on monotherapy (tacrolimus or sirolimus). Further surgical, survival, allograft function, and complications are detailed.

KEYWORDS
liver transplantation, outcomes, pediatrics

**Abbreviations:** AASLD, American Association for the Study of Liver Diseases; ALT, alanine aminotransferase; CMV, cytomegalovirus; GGTP, gamma-glutamyl transpeptidase; IQR, interquartile range; IRB, institutional review board; MELD, model for end-stage liver disease; PELD, pediatric end-stage liver disease; PTLD, post-transplant lymphoproliferative disease; QI, quality initiative; REB, research ethics board; SPLIT, Society of Pediatric Liver Transplantation; SRTR, Scientific Registry of Transplant Recipients; TTS, The Transplantation Society; UNOS, United Network for Organ Sharing.

The Society of Pediatric Liver Transplantation Research Group are presented in Appendix 1.

## 1 | INTRODUCTION

In 1995, the Studies of Pediatric Liver Transplantation was designed as a multicenter, observational, longitudinal registry to collect prospective data on children receiving liver transplantation in the United States and Canada. It was specifically formed to help characterize patient outcomes before and after liver transplant. This registry served as the backbone for multiple major collaborative publications on pediatric liver transplantation and was instrumental for the development of the PELD score for organ allocation.[1-6]

Between 1995 and 2009, funding evolved from industry support to NIH (U01-DK061693-01A1) support. The SPLIT registry evolved to maintain its distinctive role in providing long-term outcome data at a more granular level than that available in other databases. In 2009, the registry came to a cross-road, requiring center-specific support to keep SPLIT and the registry moving forward. Given limited funding, there were strategic discussions to ensure that only the most important data be collected to limit the burden on participating centers. Registry design focused on specific participant data that would be needed to help complete our stated goals. In addition, there was a special focus on facilitating ancillary studies, with the SPLIT database being able to collect specific supplemental data elements for finite periods of time.

After being vetted and refined by participating SPLIT investigators, the updated registry began enrolling new transplant recipients in 2011. In addition, sites attempted to re-consent patients already followed in SPLIT before 2009 in order to collect their long-term data from 2011 onwards. The stated goal of this new registry was to improve outcomes in children receiving liver transplants by collecting specific data that could serve as a foundation for the development of targeted clinical studies.[7] Since 2011, the specific aims of the SPLIT registry are to collect prospective data to identify opportunities to improve 30-day and 90-day outcomes and prospectively collect data from pediatric liver transplant survivors more than 1 year after transplant so as to identify emerging outcomes, clarify predictors for these outcomes, and identify best practice. As part of this rejuvenated effort, the SPLIT Registry Committee oversaw the revision of a refined and streamlined database, ably managed by the same data coordinating center, Emmes. As part of this effort, Emmes generated improved static center-specific outcome reports that centers could access via web-based entry, with up-to-the-day information. In addition, the new registry has allowed for SPLIT, guided by our QI committee, to develop a web-based interactive benchmarking application. Centers are now able to ascertain specific outcome measures (graft/patient survival, rejection, vascular/biliary complications, reoperation, infection) as a function of customizable transplant variables (diagnosis, donor type, procedure type, recipient size, age, and transplant year) to benchmark their outcomes against the cohort of participating SPLIT centers in a more meaningful and fluid manner.

This report aims to describe the most current information about the new SPLIT registry population from 2011 to March 2018, highlighting the areas of opportunity for ongoing investigation.

## 2 | PATIENTS AND METHODS

Inclusion criteria were all patients, <18 years of age, who received a first liver-only, a combined liver-kidney, or a combined liver-pancreas transplant at a participating SPLIT center. Exclusion criteria were other multiple organ transplants or age 18 years or greater. All participating centers had IRB and/or REB approval for data collection

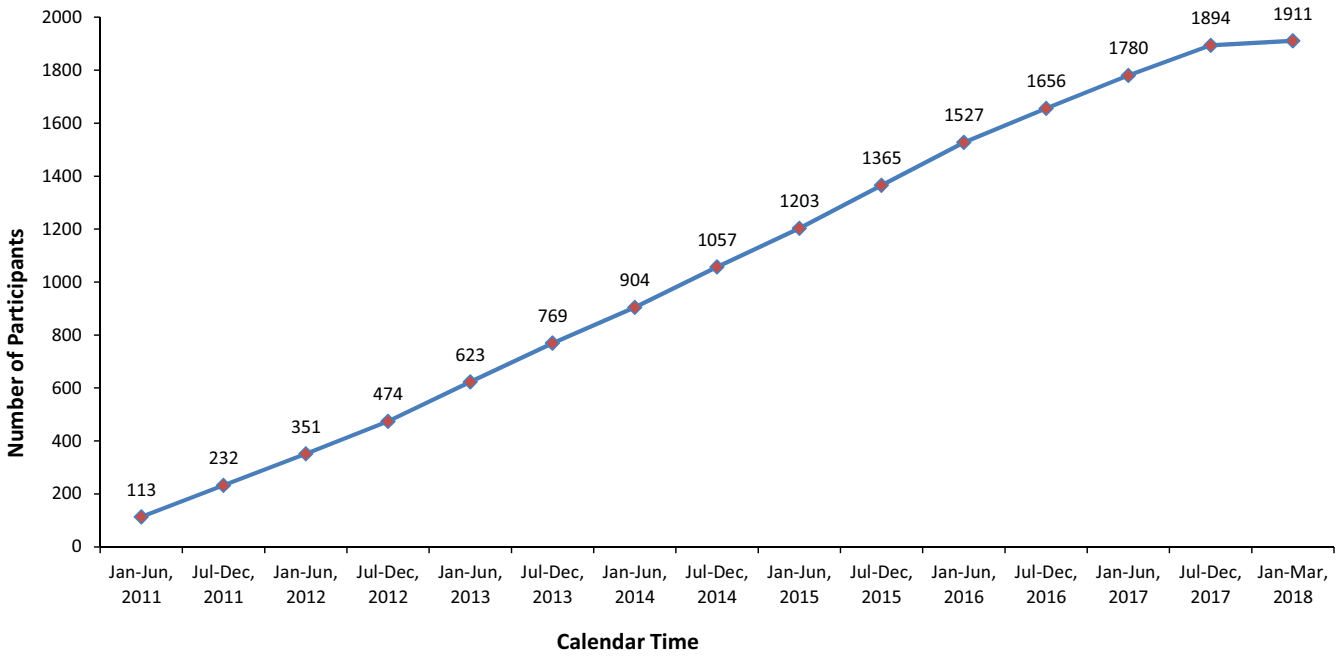



**FIGURE 1** Number of children receiving a first liver transplant in the SPLIT registry

and analysis. Individual informed consent was obtained from parents and/or guardians.

Data were submitted to the Data Coordinating Center, Emmes, through a secure Internet portal at specific time points including at first transplant, 30-day follow-up, 90-day follow-up, 1-year follow-up, and annually thereafter. If patients have graft failure requiring re-transplant, data were collected at the same time points for the new graft. Participants could be withdrawn from the study for any of the following reasons: receiving a bone marrow transplant, death, transferring care to a non-SPLIT center, transferring to an adult provider, or deciding to terminate participation by the participant, guardian, or investigator.

Data collected included patient demographics, donor characteristics, transplant surgery details, patient survival, graft survival, allograft function, immunosuppression, concomitant medications, rejection episodes, growth trends, early complications (readmissions, reoperations, infections, cancer, and laboratory assessments), late complications, blood pressure trends, laboratory assessments, cancer occurrence, and measures of renal function.

### 2.1 | Statistical analysis

Data are presented as percentage, mean, or median. The Kaplan-Meier method was used for estimating time to first rejection, as well as graft and patient survival. Log-rank test was used to compare survival outcomes between groups. The non-parametric Kruskal-Wallis test was used to compare the distribution of continuous variables, and Fisher's exact test was used to compare event rates between groups. All statistical analyses were performed using the SAS System for Windows version 9.4 (SAS Institute Inc.).

In addition to the data collected, two separate analyses were performed. The first analysis stratified data by program size to determine whether program volume affected clinical outcomes. Transplant volume was determined by the number of transplants per year reported to UNOS (or reported from Canadian sites) between 2011 and 2017. Center size was divided into two groups: <10 or ≥10 pediatric transplants per year. Secondly, to avoid selection bias due to underreporting, the investigators defined data quality. The data quality measures chosen were enrollment in SPLIT of ≤80% or >80% of total transplants reported by UNOS or Canadian data that occurred at participating centers.

## 3 | RESULTS

### 3.1 | Current status

As of March 2018, the SPLIT registry database contained data on 1911 children who had undergone a first-only liver transplant at one of the 39 SPLIT centers. Of these enrolled patients, 71 (3.7%) patients required a second liver transplant.

Accessing data from UNOS and Canadian centers, we determined that SPLIT centers transplanted 3002 of 3948 (76%) of all pediatric liver transplants in the United States and Canada between 2011 and 2018. Of these 3002 patients that were transplanted at SPLIT centers, 71.3% were enrolled by SPLIT investigators into the registry, representing 54.2% of all pediatric liver transplants in Canada and the United States during the 8 years studied. Accrual is shown in Figure 1.

### 3.2 | Demographics at first liver transplant

A total of 1911 patients have been enrolled to date. Table 1 summarizes the clinical demographic details of the study cohort. Within this group, 28.6% of recipients were <1 year of age, and 38.4% were between 1 and 5 years of age. Females and males were of equal proportion. The majority of children came from homes with married or domestic partnership (71.4%). White race was the majority.

**TABLE 1** Demographics at first liver transplant

| | Participants (n = 1911) (%) |
|---|---|
| Age at transplant (y) | |
| <1 y | 546 (28.6) |
| 1-5 y | 733 (38.4) |
| 6-10 y | 260 (13.6) |
| 11-17 y | 371 (19.4) |
| Gender | |
| Male | 945 (49.5) |
| Female | 966 (50.5) |
| Race | |
| Missing | 206 (10.8) |
| White | 1148 (60.1) |
| Black or African American | 257 (13.4) |
| Asian | 122 (6.4) |
| American Indian/Alaska Native | 19 (1.0) |
| Native Hawaiian or Other Pacific Islander | 9 (0.5) |
| More than one | 59 (3.1) |
| Other | 91 (4.8) |
| Primary caregiver marital status | |
| Missing | 59 (3.1) |
| Single parent | 305 (16.0) |
| Married | 1321 (69.1) |
| Divorced | 76 (4.0) |
| Domestic partnership | 44 (2.3) |
| Unknown | 100 (5.2) |
| Primary caregiver highest level of education | |
| Missing or unknown | 806 (42.2) |
| Some high school or less | 156 (8.2) |
| High school diploma/GED | 291 (15.2) |
| Vocational school | 212 (11.1) |
| College degree | 313 (16.4) |
| Professional or graduate degree | 133 (7.0) |

**TABLE 2** Primary diagnosis at the time of transplant

| Primary diagnosis | N = 1911 (%) |
|---|---|
| Cholestatic | 904 (47.3) |
| Biliary atresia | 733 (38.4) |
| Alagille syndrome | 78 (4.1) |
| TPN-induced cholestasis | 6 (0.3) |
| Neonatal hepatitis | 15 (0.7) |
| PFIC 1 | 12 (0.6) |
| PFIC2 | 28 (1.5) |
| PFIC3 | 15 (0.7) |
| Other biliary/cholestatic conditions | 17 (0.9) |
| Metabolic disease | 364 (19.0) |
| Alpha-1 antitrypsin | 58 (3.0) |
| Wilson's disease | 12 (0.6) |
| Tyrosinemia | 5 (0.3) |
| Primary hyperoxaluria | 11 (0.6) |
| Cystic fibrosis | 23 (1.2) |
| Crigler-Najjar | 13 (0.7) |
| Glycogen storage disease | 20 (1.0) |
| Urea cycle disorder | 113 (5.9) |
| Maple syrup urine disease | 48 (2.5) |
| Organic acidemia | 33 (1.7) |
| Familial hypercholesterolemia | 14 (0.7) |
| Niemann-Pick C | 2 (0.1) |
| Other metabolic diseases | 12 (0.6) |
| Tumor | 223 (11.7) |
| Hepatoblastoma | 175 (9.2) |
| Hepatocellular carcinoma | 24 (1.3) |
| Other tumors | 24 (1.3) |
| Fulminant liver failure | 219 (11.5) |
| Indeterminate | 140 (7.3) |
| Hepatitis A | 2 (0.1) |
| Hepatitis B | 1 (0.1) |
| Hepatitis C | 1 (0.1) |
| Herpes simplex | 2 (0.1) |
| Other viruses | 5 (0.3) |
| Autoimmune hepatitis | 17 (0.9) |
| Acetaminophen | 7 (0.4) |
| Wilson's disease | 10 (0.5) |
| Drug induced | 10 (0.5) |
| Gestational alloimmune liver disease | 7 (0.4) |
| Hemophagocytic syndrome | 4 (0.2) |
| Other liver failures | 13 (0.7) |
| Cirrhosis | 132 (6.9) |
| Autoimmune hepatitis | 35 (1.8) |
| Primary sclerosing cholangitis | 49 (2.6) |
| Hepatitis B | 1 (0.1) |
| Other cirrhosis | 47 (2.5) |
| Other | 61 (3.2) |
| Budd Chiari | 2 (0.1) |
| Abernethy malformation | 8 (0.4) |
| Congenital hepatic fibrosis/Caroli | 14 (0.7) |
| Choledochal cyst | 10 (0.5) |
| Other | 27 (1.4) |
| Missing | 7 (0.4) |

The primary diagnoses leading to liver transplant are presented in Table 2. Biliary atresia was the most common indication for liver transplantation (38.5%), though less than in previous reports,[8] followed by metabolic disease (19.1%), tumors (11.7%), and fulminant liver failure (11.5%) (Figure 2).

As for recipient size, 35.1% of children transplanted were <10 kg, with 2.4% of all recipients being <5 kg at the time of transplant.

Organ allocation in the United States is as follows: Status 1A: acute liver failure or hepatic artery thrombosis, and Status 1B: a) cirrhosis with heavy GI bleeding, intubation, dialysis, or coma; b) non-metastatic hepatoblastoma; or c) metabolic disease, after spending 30 days on the waitlist with an exception score of PELD/MELD 30, and finally, patients on list by MELD/PELD exception or natural score. At the time of transplant, 28.7% of recipients were either Status 1A/1B or the medical equivalent in their respective country. Another 29.6% of recipients were transplanted with a MELD/PELD exception score. In regard to PELD exception scores, 20% (93/464) were greater than 40, 32.5% were between 31 and 40, 38.1% were between 21 and 30, and 9% were <20. The majority (51%) of MELD exception scores were 30 or greater.

Donor organ type by recipient age is shown in Figure 3. For all transplants, 17.6% received a living donor graft, 54.4% received a deceased whole liver graft, and 25.2% received a deceased donor technical variant graft. Of the deceased donor technical variant grafts, 34.5% (166/481) were reduced grafts without utilizing the remaining liver segments in a second recipient. As recipient age increased, the use of whole grafts increased and technical variants decreased. Living donation was reported in 14.1% of recipients 11-17 years of age.

In regard to deceased donor age, over half (57.7%) were from pediatric donors (<18 years of age). Donors <1 year of age contributed 9.1% of transplant grafts, donors 1-4 years (21.1%), donors 5-17 years (27.5%), and donors ≥18 years (33.9%).

Donor-recipient blood type is shown in Table 3. Donor-recipient blood type match was most commonly identical (81.7%), followed by compatible (14.2%) and incompatible (4.1%). The most common incompatible transplant was donor A/recipient O (50.7%). Seventy-five incompatible transplants were performed.

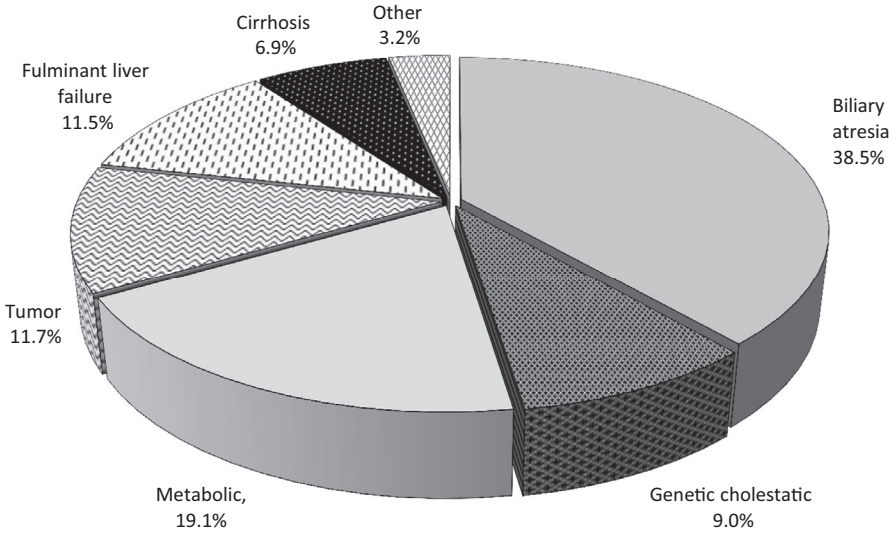



**FIGURE 2** Percent of children transplanted within diagnostic categories

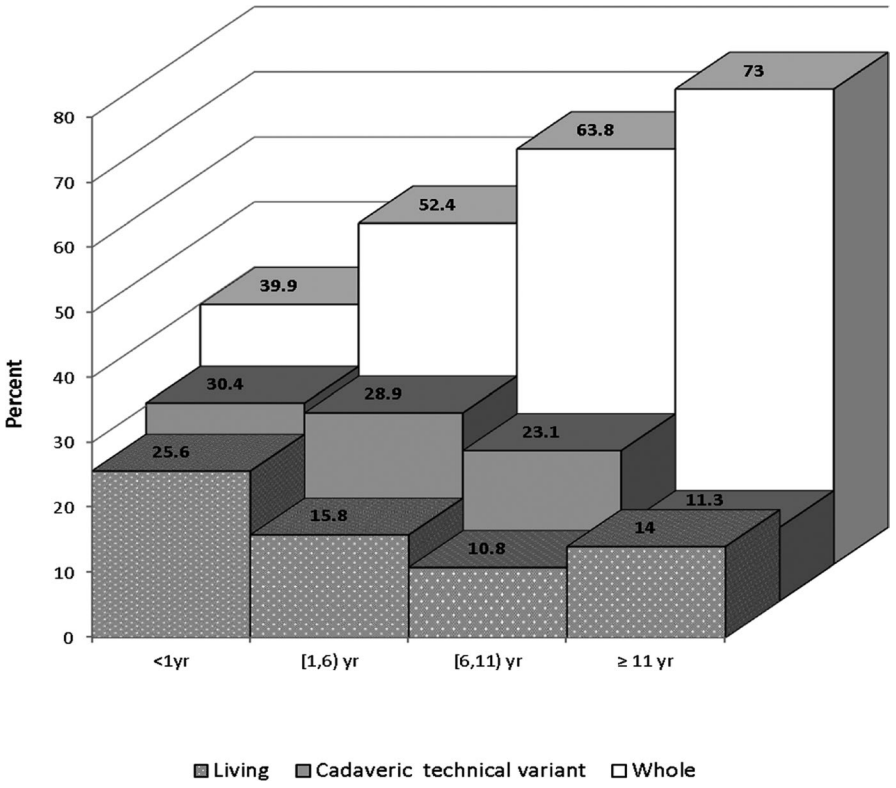



**FIGURE 3** Donor organ type shown for recipient age ranges

**TABLE 3** Donor-recipient ABO blood type matching at transplant

| Recipients | Donor A N = 535 | Donor B N = 182 | Donor AB N = 30 | Donor O N = 1064 |
|---|---|---|---|---|
| A | 469 (87.7%) | 7 (3.8%) | 4 (13.3%) | 117 (11.0%) |
| B | 5 (0.9%) | 141 (77.5%) | 2 (6.7%) | 89 (8.4%) |
| AB | 23 (4.3%) | 18 (9.9%) | 21 (70.0%) | 10 (0.9%) |
| O | 38 (7.1%) | 16 (8.8%) | 3 (10.0%) | 848 (79.7%) |

Median age at ABO-incompatible transplant was 10.9 months (range: 0.5 months-190.7 months). The leading indications for transplant in the 75 ABO-mismatched recipients were biliary atresia (41.3%), fulminant hepatic failure (17.3%), metabolic (10.7%), and tumor (9.3%). Medical status at transplant for this group included 41.3% Status 1A/1B or medical equivalent in their country. An additional 38.7% had either an exception score or calculated MELD/PELD ≥ 25.

### 3.3 | Patient and graft outcomes

In this cross-sectional cohort, 3.8% of participants have died (72/1911). The most commonly reported causes (could be multiple causes) were sepsis/infection (11.5%), multiorgan failure (10.8%), malignancy recurrence (7.4%), primary respiratory failure (7.3%), and hepatic artery thrombosis (6.1%). Participant Kaplan-Meier patient survival probability, at 90 days, 1 year, 3 years, and 5 years, was 98.8%, 97.3%, 95.2%, and 94.2%, respectively (Figure 4). Survival probability by center size (smaller vs larger) demonstrated no statistical difference when analyzed through 3 years (94.7% vs 95.2%). In addition, assessment by data quality compliance showed no significant difference at 3 years (95.8% vs 94.6%).

To date, 7.2% of all grafts reported have been lost secondary to death or retransplant (137/1911). Of the patients requiring retransplant, the indication reported was hepatic artery thrombosis (52.3%), other vascular thromboses (13.8%), primary graft dysfunction (9.2%), chronic rejection (9.2%), biliary complications (7.7%), hyperacute rejection (1.5%), recurrent primary disease (1.5%), and other (6.2%). The probability of first liver transplant graft survival recorded at 90 days, 1 year, 3 years, and 5 years was 98.4%, 96.6%, 92.2%, and 87.7%, respectively. Over half of these patients have been rescued via retransplantation (71/137), with 68 having 1 retransplant and only 3 having 2 retransplants. Once again, center size comparisons did not reveal statistical significance at similar time points. One-year graft survival probability (small vs large) was 92.4% vs 95.1%; 3 years 90.3% vs 91.9%. Graft survival by data quality compliance was also comparable without statistically significant differences.

Over the same time period, patients receiving ABO-incompatible grafts had worse outcomes than ABO-matched or ABO-compatible grafts (Figure 5). Seven of 75 patients have died (9.3%). The indications for transplant for these 7 patients included fulminant hepatic failure (3), gestational alloimmune liver disease (1), biliary atresia (1), and tumor (2). The two tumor patients died of recurrence, and the remaining 5 patients died of either multiorgan failure or cerebral edema as the cause of death. Graft loss by death or retransplant for this population was 12/75. After excluding the 7 deaths, the other 5 retransplanted patients had a vascular complication leading to graft loss. These vascular events leading to graft loss usually occurred early after transplant.

### 3.4 | Quality measures/complications

Data points gathered for the purpose of center benchmarking are shown in Table 4.

Length of intubation was very short; the median days of intubation post-surgery was 1 day (IQR: 0, 3). Initial hospitalization length of stay for the transplant was a median of 16 days (IQR: 11, 27).

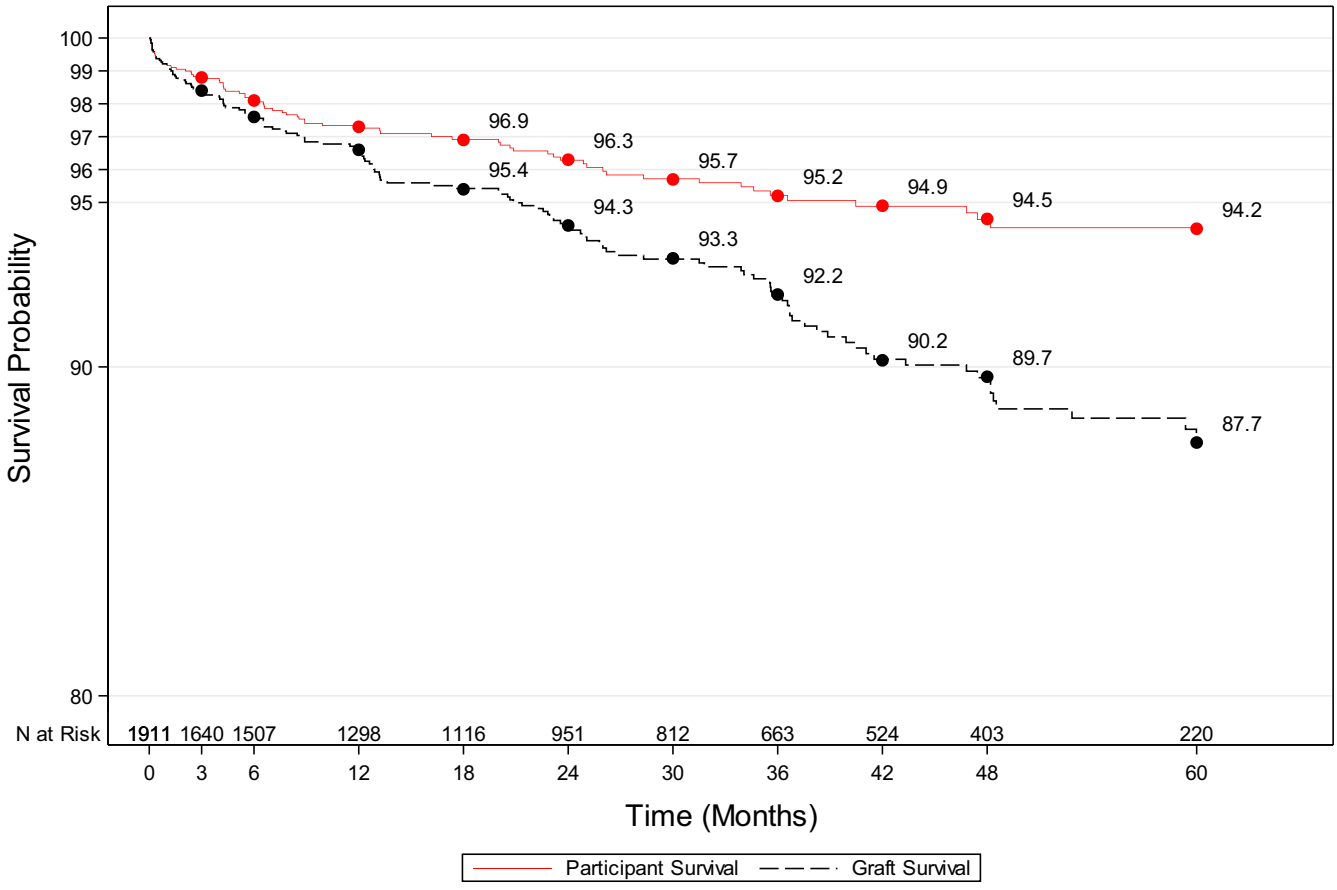
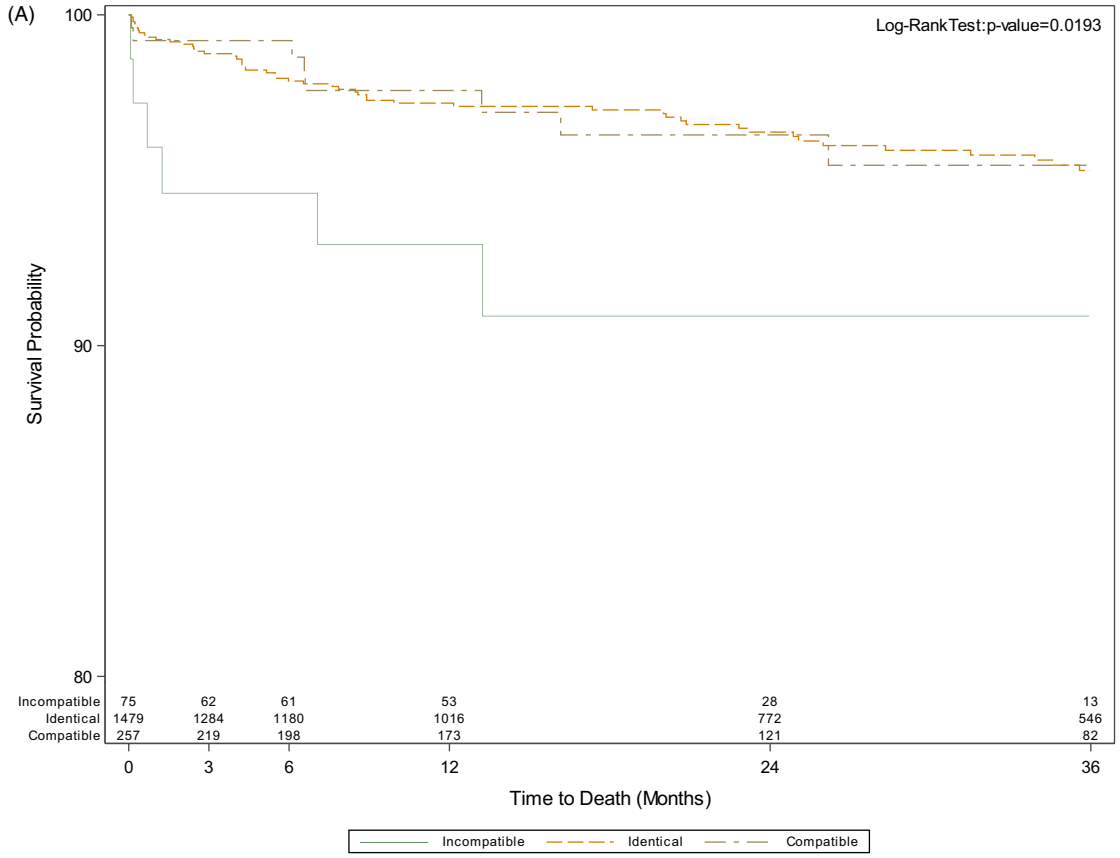



**FIGURE 4** Kaplan-Meier estimate for overall patient and graft survival over time, including the number of patients at risk



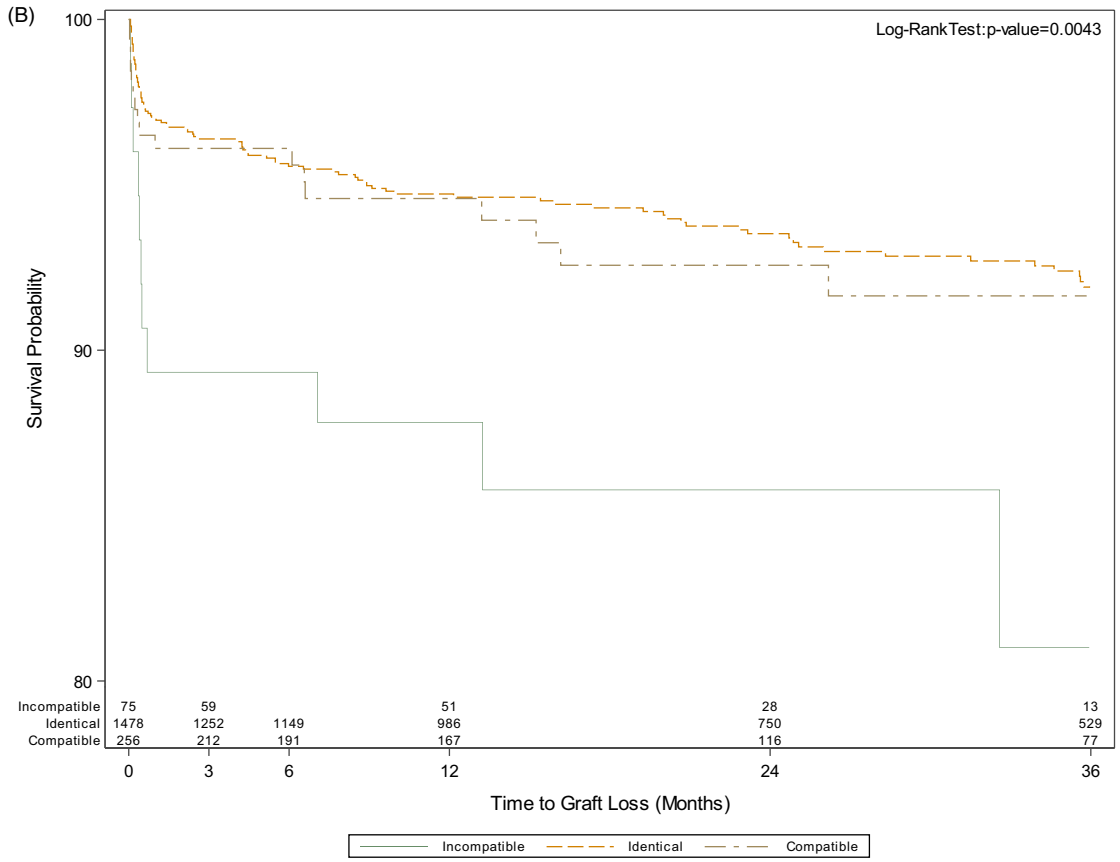




**FIGURE 5** (A) Kaplan-Meier estimate of patient survival over time, by ABO blood type compatibility. (B) Kaplan-Meier estimate of graft survival over time, by ABO blood type compatibility

**TABLE 4** Sentinel benchmarking data captured in the registry

| |
|---|
| Number of transplants |
| Patient survival at 30 d, 90 d, and 1 and 2 y |
| Graft survival at 30 d, 90 d, and 1 and 2 y |
| Rejection at 30 d, 90 d, and 1 and 2 y |
| Percentage of patients with monotherapy, ALT<50, GGT<50 at 30 d, 90 d, and 1 and 2 y |
| Initial hospitalization days |
| Primary intubation in days post-transplant |
| Hepatic artery thrombosis |
| Biliary tract complications |
| Portal vein thrombosis |
| Reoperation |
| Infections |
| Rehospitalizations |

Approximately one-third (31.7%) of patients required a reoperation within the first 30 days, with 71% (431/605) having one reoperation. The most common reasons cited for reoperation (could be multiple reasons) included exploratory laparotomy (45.8%), vascular complication (23.2%), biliary tract complication (18%), and intra-abdominal bleeding (17.5%).

Vascular and biliary surgical complications are summarized for the entire cohort as well as by center size. Hepatic artery thrombosis was detected in 6.3% of grafts in the first 30 days. Late hepatic arterial thrombosis (after 90 days) was rarely reported, with only 0.7% reporting this event. Portal vein thrombosis was reported in 3.2% of all transplants in the first 30 days. Late portal vein thrombosis (after 90 days) was reported in 1.1% of recipients. Biliary tract complications, within the first 90 days, were reported in 13.6% of recipients (250/1844). This included biliary leak, biloma, bile duct stricture, or other biliary complications requiring operative repair.

Culture-proven infections including either bacterial, viral, or fungal pathogens occurred in 27.6% (502/1911) of recipients during the first 30 days after transplant and 37.9% during the first 90 days. Of patients having an infection, approximately two-thirds were bacterial in nature. Leading types of bacterial infection during the first 30 days (could be multiple) included intra-abdominal infection (28.6%), bloodstream infection (20.2%), urinary tract infection (13.9%), and pneumonia (11.7%). Fungal infections accounted for 15% of all infections, and viral infection occurred in 37.7% of transplants.

Rehospitalization rates, a common QI measure at most transplant centers, have been captured as part of this registry. In the first 90 days post-transplant, 44.4% were rehospitalized. Of the patients rehospitalized, close to a third (28.6%) occurred within 7 days of discharge. The most common reasons reported for rehospitalization (could be multiple) were fever (30%), abnormal liver tests (16.5%), rejection (11.9%), and fluid-electrolyte imbalance (11.1%). An additional 16% were admitted 8-14 days post-discharge, 15.3% 15-30 days post-discharge, and 11.2% between 30 days and 90 days post-discharge.

Kaplan-Meier probability of being PTLD free over the first 2 years was calculated. The percentage of patients PTLD free at 1 year was 98.9% and 98.2% at 2 years.

Further outcome analyses were performed to determine whether center size had a significant effect on surgical outcomes. There were no statistically significant differences between large and small volume centers for initial hospitalization length of stay, reoperation rates, hepatic artery thrombosis, or portal vein thrombosis. However, there was a statistically significant difference in biliary complications within 90 days, with centers performing <10 transplants reporting 19.7% in comparison with 11.7% for centers with ≥10 transplants ($P < .001$). Although both groups had a median initial intubation of 1 day, using the Kruskal-Wallis test for continuous variables, intubation time tended to be longer in the larger centers ($P < .02$), but not clinically significant.

Evaluation for outcomes based on data quality compliance (>80% of UNOS transplants enrolled in SPLIT registry) was not statistically different in regard to initial hospitalization length of stay, hepatic artery thrombosis rates (5.9% vs 6.8%), or portal vein thrombosis rates (3% vs 3.3%). Reported biliary complications were less in the <80%

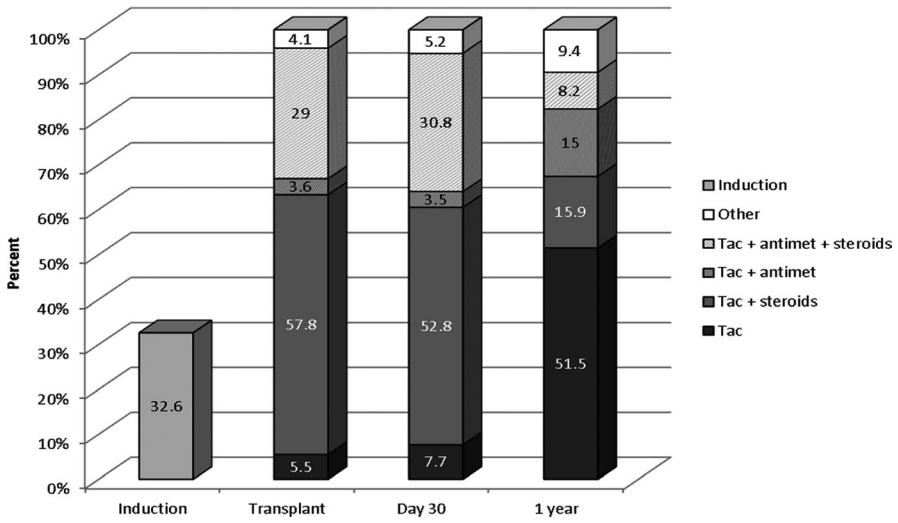



**FIGURE 6** Use of immunosuppression from time of transplant to 12 mo after transplant

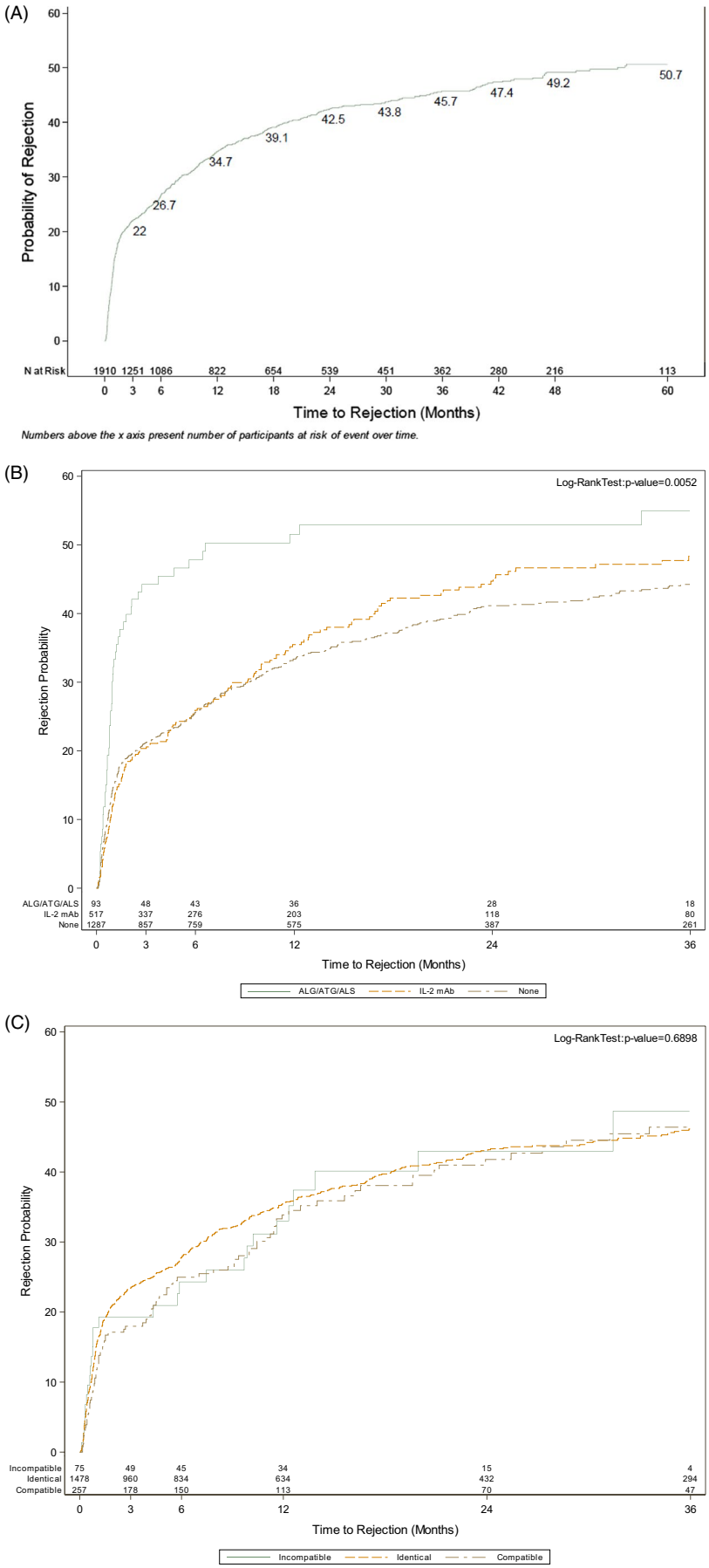



**FIGURE 7** (A) Kaplan-Meier estimate of acute cellular rejection over time for the entire registry. (B) Kaplan-Meier estimate of acute cellular rejection over time by induction strategy. Antithymocyte globulin (ATG), IL-2 monoclonal antibody (IL-2mAb). (C) Kaplan-Meier estimate of acute cellular rejection over time, by ABO blood type compatibility

group (11.1% vs 15.1%, $P < .02$), and reoperation rates were less in the <80% group (29.3% vs 33.6%, $P < .02$).

### 3.5 | Immunosuppression after first liver transplant

Figure 6 shows immunosuppression use after first transplant. In comparison with previous SPLIT publications a decade ago, tacrolimus has become the primary immunosuppressive agent in 97% percent of recipients after transplant. Immunosuppression regimens within 7 days of transplant included tacrolimus/steroids (57.8%), tacrolimus/antimetabolite/steroids (29%), tacrolimus/antimetabolite (3.6%), or tacrolimus alone (5.5%). Of the 39 SPLIT centers, 29 used antibody induction during this time period. Antibody induction was used in 32.6% of all transplants, with either IL-2 monoclonal antibodies (27.2%) or antithymocyte globulin (5%).

At day 30 post-transplant, the majority of patients (57.4%) were on dual immunosuppression, with 31.8% remaining on triple immunosuppression. Tacrolimus and steroids were the most common immunosuppression regimen at 30 days (52.8%). Antimetabolites were used in 34.3% of patients at the day 30 time point.

Of the 1448 patients with year 1 post-transplant immunosuppression data, 55.4% were using a single immunosuppressive agent with either tacrolimus or sirolimus; 34.1% were using two immunosuppressive agents (tacrolimus/metabolite or tacrolimus/steroids); and 9.2% were using three immunosuppressive medications. During this first year, tacrolimus use decreased to 92.8%, as the use of sirolimus rose to 7.1%. Antimetabolites were used in 23.2% of recipients at year 1, and 25% of recipients were still taking steroids at this time point.

An additional benchmarking end-point chosen in the registry was the number of recipients achieving maintenance with a single immunosuppressive agent with normal allograft function. This was defined as the percentage of patients on monotherapy, with an ALT (<50 IU/mL) and a GGTP (<50 IU/mL) at 1 and 2 years of follow-up. At 1-year follow-up, 37.1% (537/1448) were on tacrolimus monotherapy with normal allograft function. Sirolimus monotherapy with normal allograft function accounted for 2.1% of transplants. Of patients with 2-year follow-up data, 46.9% (500/1067) were on tacrolimus monotherapy with normal allograft function. Sirolimus monotherapy with normal allograft function accounted for 3.7% (40/1067) of transplants.

The probability of having biopsy-proven acute cellular rejection for the entire cohort was 22% at 3 months, 26.7% at 6 months, and 34.7% during the first year after transplant (Figure 7A). Biopsy-proven rejection rates were also compared by induction strategy (Figure 7B). Of patients using antithymocyte or other lymphocyte induction agents (n = 93), the probability of rejection by 1 year was 51.5%. For patients receiving IL-2 receptor monoclonal antibodies (n = 517), the probability of biopsy-proven rejection was 35.5% at 1 year, similar to that of the cohort not receiving antibody induction (33.4%). After accounting for the ABO-incompatible transplants that died early, rejection rates by donor-recipient blood group matching (identical, compatible, or incompatible) were not statistically different over a 36-month time period (Figure 7C).

### 3.6 | Growth

Weights were recorded for 1806/1364/970 children at transplant, 1 year, and 2 years post-transplant, respectively. Over this time period, median weight Z score increased steadily, from −0.6 to −0.1 to 0.2. Height/length was recorded for 1662/1354/954 children at transplant, 1 year, and 2 years post-transplant. Similarly, median *Z* scores increased from −1.1 to −0.8 to −0.6 over this time period (Figure 8).

## 4 | DISCUSSION

The current SPLIT registry has enrolled nearly 2000 pediatric liver transplant recipients. This volume provides the opportunity to characterize the latest cohort of pediatric recipients stratified by demographics, immunosuppression, and clinical outcomes.

Several important trends are identified in the current data set. Of note, the indications for liver transplant have changed since the last cohort was described. The percentage of patients transplanted for biliary atresia has decreased due to the broader acceptance of liver tumors and metabolic disease as indications for liver transplant.[4] The registry now follows longitudinal data for over 700 biliary atresia patients and 200 fulminant liver failure children after liver transplant.

As published in other reports, our data support that PELD/MELD exception scores account for a large proportion of organ allocation at the time of transplant. This percentage has increased to greater than 40% from the previous SRTR data rate of 24.3% in the 2004-2006 cohort.[9] The fact that this practice has been necessary to achieve liver transplant in children will need to be tracked continually in light of the implementation of the pediatric National Review Board and the new UNOS allocation schemes. Although 28.5% of all liver recipients are under 1 year of age, there are only 9.1% of donors coming from children <1 year.

Living donation still appears to be an important method to achieve transplant in young recipients. Interestingly, this cohort also has a high percentage of adolescents that received living donation. We hypothesize that the utilization of living donors in the adolescent population represents an attempt to address the challenge that adolescents face in organ allocation under MELD.

Liver transplantation with an ABO-incompatible graft was performed in over 4% of our cohort, higher than the 2.2% reported in SRTR reports from a decade ago.[9] This population's graft and patient survival percentages are inferior to other transplants, possibly related to the fact that the majority of these patients are quite small and very ill at the time of transplant, with close to 80% being either Status 1A/1B or having PELD/MELD ≥ 25. The death rate and graft failure rate are highest in the first 30 days. Interestingly, the rejection rates were similar to identical/compatible transplants, so there were probably other underlying factors and comorbid conditions that contributed to the inferior graft and patient survival in this population. Further analysis is required as outcomes following this practice are captured by the registry.

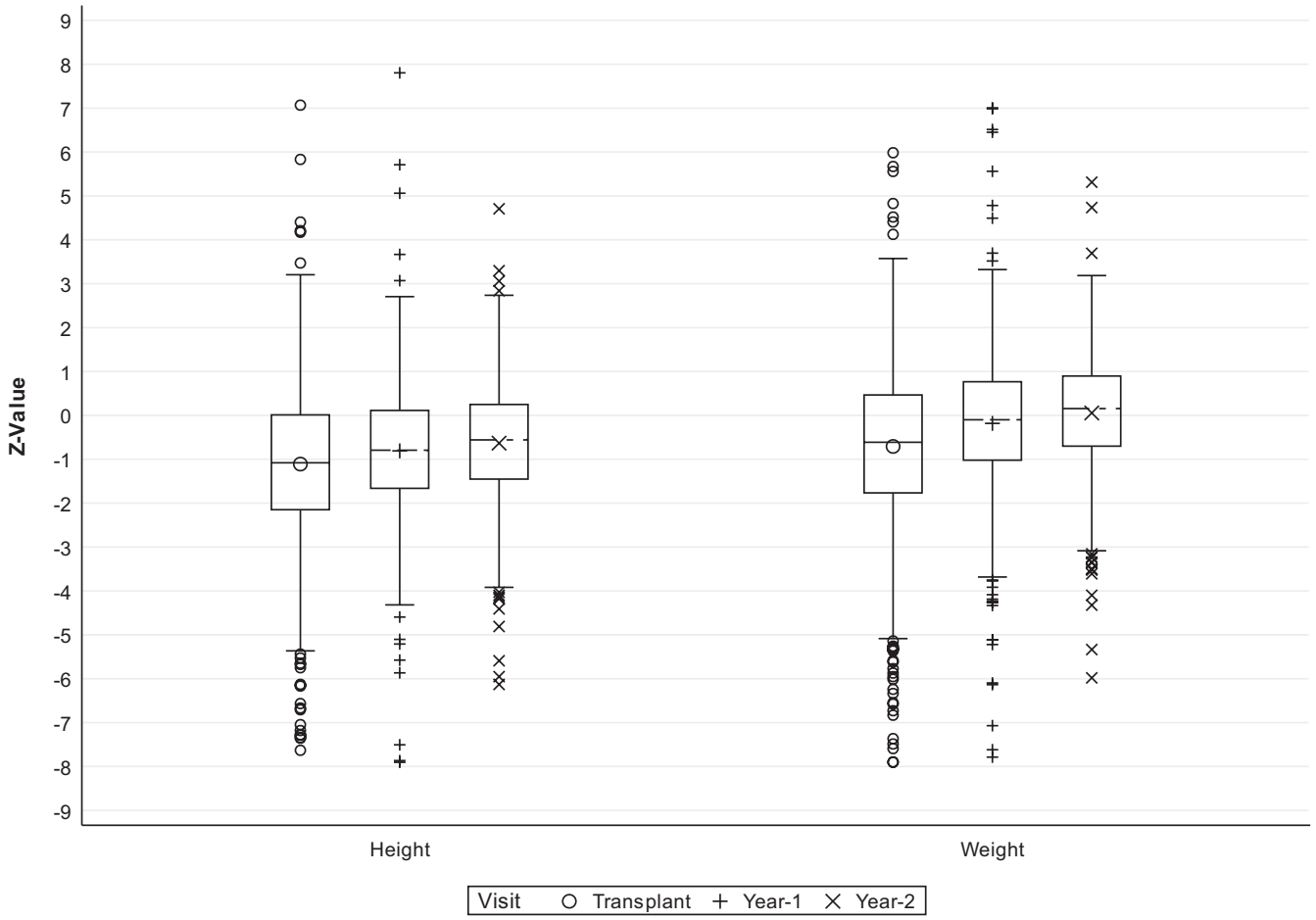



**FIGURE 8** Weight and height Z scores at transplant, and 1 and 2 y post-transplant

The registry not only continues to reveal the evolution of trends in immunosuppression over the decades, but also demonstrates the wide variability in immunosuppression practices among the centers at multiple time points. Still close to one-third of transplant centers follow protocols that use antibody induction; tacrolimus is initiated in 97% of transplants; sirolimus use is increasing, and cyclosporine use is almost non-existent. Interestingly, children receiving anti-lymphocyte agents have a higher observed rejection rates in the first year post-transplant in comparison with IL-2 monoclonal antibody induction or no antibody induction. The data set is not robust enough to assess causality at this time, but may do so in future reviews.

Quality measures including time to extubation appear quite short. There have been published studies that support the active engagement of anesthesiologists in the selection process to promote early extubation, even in the operating room.[10] Overall hospital length of stay after transplant for this cohort was around the national Organ Procurement and Transplantation Network data median of 15 days. Interestingly, despite many centers implementing specific efforts to avoid early readmissions to the hospital, almost one-third of patients were readmitted within 7 days of discharge. This is an important factor for payor reimbursement and could definitely be a future focus for quality initiatives. Complications after transplant appear similar to previous reports with re-exploration, vascular and biliary complications being areas of ongoing clinical focus.[11,12]

This new SPLIT registry has provided the opportunity to identify and answer new questions, as well as to affirm previous ones. The revised SPLIT database continues to be actively utilized as the backbone for newly developed ancillary studies, a goal of the new database. SPLIT generated ancillary studies include graft type outcomes, CMV prophylaxis strategies,[13] cirrhotic cardiomyopathy, biliary stricture management strategies, and hepatic artery thrombosis prevention/management with most currently in the manuscript preparation. The registry now provides data access through a new web-based QI benchmarking project developed by the SPLIT QI committee. Quality initiatives have always been important to SPLIT and may take on a greater role in the future as data-driven QI efforts to derive best practices receive increased visibility in the pediatric community.[6,14]

There a number of factors affecting the effectiveness of the SPLIT registry, including those relevant to registry-based research and analyses. Some high-volume US centers have simply decided not to participate in SPLIT. Fortunately, all 3 Canadian sites are participating. Close to 85% of all US centers averaging over 5 transplants per year are participating. Unfortunately, not all children at participating SPLIT centers have been enrolled due to various issues. The registry committee is currently attempting further analysis of

the reasons for no consent, in order to help centers optimize center enrollments moving forward. The lack of full center enrollment may introduce selection bias, weakening the power of the registry, especially if enrollment rates are <80% of UNOS/Canada reported transplants. Fortunately, over 97% of the data fields captured by SPLIT were complete for the patients that are enrolled. In addition, SPLIT data were quite comparable to that of the SRTR registry in terms of diagnosis, demographics, medical condition at transplant, MELD/PELD exception, ABO compatibility, and donor type.

In summary, the latest SPLIT registry is now comprised of close to 2000 pediatric patients with their first liver transplant. Data continue to be prospectively collected from 39 participating sites in the United States and Canada longitudinally. The data set captured is much more granular than other registries permitting analysis of factors affecting long-term outcomes in pediatric transplant recipients. The registry now has 5-year data for over 200 patients. With cooperative data collection from multiple centers, SPLIT remains poised to ask questions that are not easily answered by single-center reviews. The data captured continue to be used to generate further clinical and research hypotheses facilitated by a web-based interactive benchmarking tool. The data, outlined above, provide the backbone for ancillary studies. The flexibility of the collaborating centers and the data coordinating center has permitted the addition of new data elements collected to answer specific queries over specified time frames. In addition, the data sets provide for center QI benchmarking that is imperative for transplantation practices to evolve into the 21st century. As part of the evolution from a mere registry to a quality improvement, research, and advocacy collaborative, SPLIT has become a pediatric transplant society. In 2018, maintaining the same acronym for continuity purposes, SPLIT has now become the Society of Pediatric Liver Transplantation, an official subsection of The Transplantation Society (TTS).

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## AUTHORS' CONTRIBUTION

Elisofon, Magee, Ng, Horslen, and Mazariegos: provided substantial contributions to the conception and design, analyzed and interpreted the data, drafted and critically revised the manuscript, and approved the final version of the manuscript. Fioravanti, Economides, Erinjeri, and Anand: provided substantial contributions to the conception and design, collected the data, analyzed and interpreted the data, critically revised the manuscript, and approved the final version of the manuscript.

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## APPENDIX 1

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