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The Society of Pediatric Liver Transplantation (SPLIT): 2023 Registry Status

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Abbreviations: ABO-I, ABO-incompatible; ALG, anti-lymphocyte globulin; ALS, anti-lymphocyte serum; ATG, anti-thymocyte globulin; BA, biliary atresia; DCC, Data Coordinating Center; HAT, hepatic artery thrombosis; IQR, interquartile range; IS, immunosuppression; LT, liver transplantation; mAb, monoclonal antibody; MELD, Model for End-Stage Liver Disease; NLRB, National Liver Review Board; OKT3, Muromonab-CD3, brand name Orthoclone; OPTN, Organ Procurement and Transplantation Network; PELD, pediatric end-stage liver disease score; PFEP, Patient, Family, and Engaged Partners; PTLD, posttransplant lymphoproliferative disease; PVT, portal vein thrombosis; SPLIT, Society of Pediatric Liver Transplantation; U.S., United States.

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ABSTRACT

Background: The Society of Pediatric Liver Transplantation (SPLIT) has undergone tremendous growth with > 45 sites contributing data focusing on improving outcomes in pediatric liver transplantation (LT). We report and compare outcomes from the SPLIT Registry.

Methods: Patients < 18 years with first-time LT only enrolled into the SPLIT Registry between 2011 and 2023 were included. Data was stratified into eras from the last published registry update (era 1: 2011–2018, era 2: 2018–2023).

Results: Three thousand five hundred four participants from 47 centers were included (era 1: $n = 2159$; era 2: $n = 1345$). Age distribution differed with more children < 1 year. of age at LT in era 2 (era 1: 29% vs. era 2: 33%, $p = 0.01$). Indications for LT were similar, with biliary atresia (38.8%) and metabolic disease (16.0%) being most common. Exception point use was higher in era 2 (era 1: 45% vs. era 2: 56%, $p < 0.001$). No difference in graft type (deceased: 81% era 1 vs. 78% era 2, $p = 0.78$), patient survival at 90 days (era 1: 98.7% vs. era 2: 98.3%), 1 year (era 1: 97.2 vs. era 2: 96.8%), or 3 years (era 1: 95.3% vs. era 2: 95.2%) was noted. Rate of hepatic artery thrombosis was lower in era 2 (era 1: 7% vs. era 2: 5%, $p = 0.02$).

Conclusions: Trends in pediatric LT within SPLIT note similar LT indications and graft type, higher utilization of exception points, and lower HAT rates despite transplanting more children < 10 kg. This data underscores the evolution of pediatric LT toward higher survivability and overall patient outcomes.

1 | Introduction

The Studies of Pediatric Liver Transplantation (SPLIT) was developed as a multicenter, prospective registry of children in the United States (U.S.) and Canada who underwent liver transplantation (LT). From its inception in 1995 through 2003, the registry was a voluntary and cooperative research network of pediatric LT centers that allowed for hypothesis-generating studies and development of the pediatric end-stage liver disease score (PELD), the basis of organ allocation in the U.S. [1]. From 2004 to 2009, SPLIT received NIH funding with > 30 centers participating in the registry, resulting in numerous publications on survival, immunosuppression trends, and quality of life [1–14]. When NIH funding ended in 2010, center-driven support allowed SPLIT to continue to thrive as a community committed to advancing the care of pediatric LT recipients through key publications highlighting standards of care and clinical drivers of ideal outcomes [1–14].

In 2018, SPLIT entered a new phase with incorporation and rebranding with the formal name change to the Society of Pediatric Liver Transplantation and administrative/infrastructure support from The Transplantation Society (https://tts.org/split-home). This allowed SPLIT to expand its mission of inclusivity by fostering a greater sense of community as a member-driven, patient-centered collaborative society. SPLIT's mission includes being the international voice of expertise and advocacy. With over 450 individual members from 36 different countries and 47 individual centers actively contributing data in 2023, SPLIT has grown tremendously since incorporation as a society. Enhanced engagement with patients and family partners through the Patient, Family, and Engaged Partners (PFEP) committee, as well as educational initiatives for trainees and members, has expanded SPLIT's impact beyond its initial research/quality improvement agenda [15].

Since the last SPLIT Registry update published in 2018 [7], the network has undergone continued revitalization. During and after the COVID-19 pandemic in 2020, SPLIT continued to be a productive organization, providing significant education and support for the nationalization of the pediatric waiting list, revisions to the National Liver Review Board (NLRB) exceptions review process, and improvements in Model for End-Stage Liver Disease (MELD) allocation for adolescents [16]. The goal of this report is to provide an update on the SPLIT Registry data and compare outcomes across SPLIT eras (2011–2018, 2018–2023).

2 | Methods

The SPLIT Registry includes IRB-approved deidentified patient-level data prospectively and voluntarily submitted by 47 SPLIT sites. Although international sites now contribute data, only data from U.S. and Canadian sites are presented to allow for consistent comparison across eras. Data collected between 1/1/2011 and 3/24/2023 was analyzed. Inclusion criteria were participants < 18 years of age with a first-time liver-only transplant. Each individual SPLIT site submitted specific data to the Data Coordinating Center (DCC) (Emmes Inc.) at the time of transplant, and postoperative time points (30, 90, and 365 days) and annually thereafter. Data elements included patient demographics, donor and graft characteristics, allograft function, immunosuppression, rejection episodes, graft and patient survival, etc. (Table S1). For any graft failure requiring retransplant, the identical data elements were collected for the new LT at the same time points. The distribution of eras was determined based on the timing of the previously published SPLIT Registry update in 2018 with era 1 from 2011 to 3/19/2018 and era 2 from 3/20/2018 to 3/24/2023 [7].

3 | Statistical Analysis

The DCC serves as a data warehouse and statistical resource for patient-level data submitted by the secure portal. Data are

securely stored for purposes of individual site benchmarking as well as to facilitate collaborative research and quality improvement. For purpose of this analysis, data are presented as percentages, means, or medians with the appropriate accompanying variance and confidence intervals.

Kaplan–Meier analyses were conducted to estimate patient and graft survival, as well as time to first rejection episodes. The Log-rank test was used to compare survival outcomes between groups. The Kruskal–Wallis (nonparametric) test was used to compare the distribution of continuous variables, and the Fisher's exact test was used to compare event rates between groups. SAS v9.4 was the statistical package used for analysis.

4 | Results

A total of 47 SPLIT sites contributed data, with 5 new centers being represented in era 2. A total of 3504 participants were identified in the SPLIT Registry, with 2159 in era 1 (2011–2018) and 1345 in era 2 (2018–2023). Patient accrual is shown in Figure 1 and Figure S1. Of these participants, 3380 (96%) had only 1 LT, whereas 116 (3.3%) had 2 LTs, and a total of 3 participants (0.08%) had 3 LTs.

As of 09/17/2023 based on UNOS and Canadian center data, a total of 5324 pediatric LTs were performed and of these, 4141 (78%) were performed at SPLIT sites. Of the 4141 transplants at SPLIT sites by 9/17/2023, 96% (3975) were enrolled by SPLIT investigators, representing 74% of all pediatric LTs in the US and Canada since 2011 [17].

4.1 | Demographics at Time of First Liver Transplant

Table 1 summarizes the demographic characteristics across eras. The distribution of age was different, with a larger percentage of children < 1 year at the time of LT in era 2 (era 1: 29% vs. era 2: 33%, Table 1). There was no significant difference in the distribution of gender across eras, while the distribution of race was different, with a larger percentage of African Americans in era 2 (era 1: 13% vs. era 2: 16%), $p < 0.001$.

Overall, the primary diagnosis at LT was BA in 1361 (39%), followed by metabolic causes (16%), tumors (11%), other cholestatic disease (11%) and acute liver failure (11%). There was no significant difference in the distribution of diagnoses between eras (Table 1, Table S2). Only 1.3% of transplants in era 2 were < 5 kg, as compared to 2.4% in era 1, with a larger proportion of participants < 10 kg at the time of transplant in era 2 (38%) (Table 1).

4.2 | Organ Allocation and Donor Graft Characteristics

Organ allocation in the U.S. is prioritized based on Status 1A/1B followed by MELD/PELD exception and calculated scores. In May 2019, the Organ Procurement and Transplantation Network (OPTN) implemented the NLRB to improve and standardize the use of common exception point requests. The data presented regarding the use of exception scores includes time before and after NLRB implementation. During this time, liver allocation was also updated to be based on acuity circles and

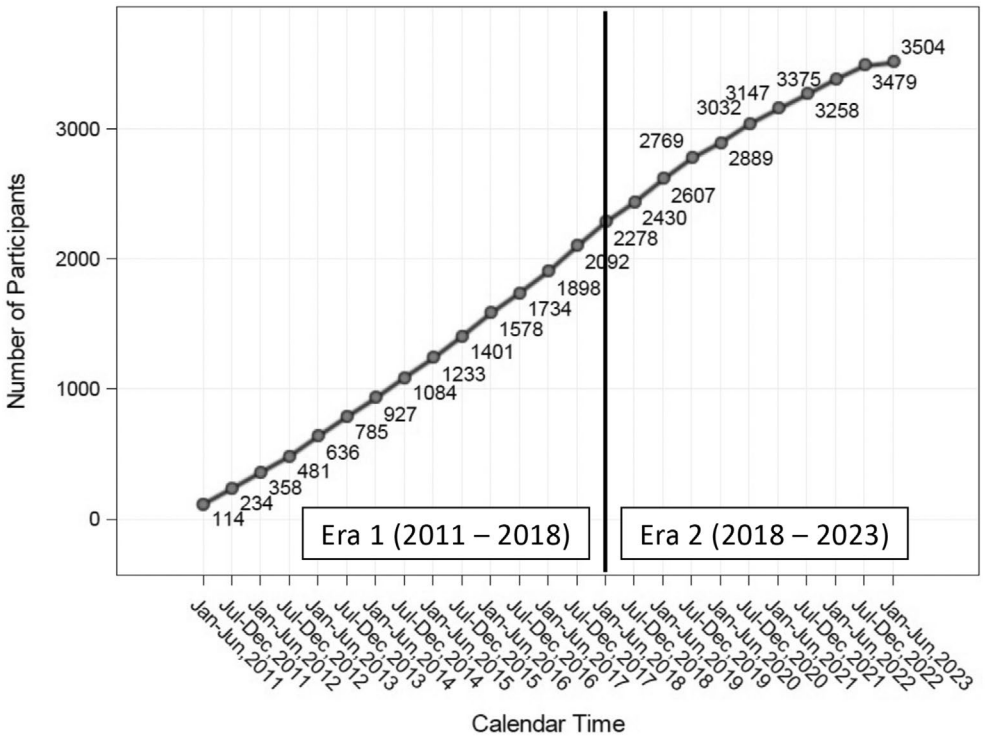


FIGURE 1 | Number of Transplants over time entered into SPLIT registry.

TABLE 1 | Patient demographics at time of liver transplant.

	Era 1 (2011–2018), $n = 2159$	Era 2 (2018–2023), $n = 1345$	Overall, $n = 3504$	p
Age at Transplant (years)				
< 1 year	615 (28.5%)	449 (33.4%)	1064 (30.4%)	0.01
1– < 6 year	828 (38.4%)	461 (34.3%)	1289 (36.8%)	
6– < 11 year	290 (13.4%)	167 (12.4%)	457 (13.0%)	
11– < 18 year	426 (19.7%)	268 (19.9%)	694 (19.8%)	
Gender				
Male	1058 (49.0%)	680 (50.6%)	1738 (49.6%)	0.37
Female	1101 (51.0%)	665 (49.4%)	1766 (50.4%)	
Race				
White	1277 (59.1%)	717 (53.3%)	1994 (56.9%)	< 0.001
Black or African American	283 (13.1%)	215 (16.0%)	498 (14.2%)	
Asian	148 (6.9%)	94 (7.0%)	242 (6.9%)	
American Indian/Alaska Native	21 (1.0%)	12 (0.9%)	33 (0.9%)	
Native Hawaiian or other Pacific Islander	12 (0.6%)	5 (0.4%)	17 (0.5%)	
More than one	75 (3.5%)	70 (5.2%)	145 (4.1%)	
Other	91 (4.2%)	0	91 (2.6%)	
Missing	252 (11.7%)	232 (17.2%)	484 (13.8%)	
Primary caregiver marital status				
Single parent	346 (16.0%)	187 (13.9%)	533 (15.2%)	< 0.001
Married	1463 (67.8%)	829 (61.6%)	2292 (65.4%)	
Divorced	81 (3.8%)	46 (3.4%)	127 (3.6%)	
Domestic partnership	70 (3.2%)	98 (7.3%)	168 (4.8%)	
Widowed	8 (0.4%)	9 (0.7%)	17 (0.5%)	
Unknown	135 (6.3%)	152 (11.3%)	287 (8.2%)	
Missing	56 (2.6%)	24 (1.8%)	80 (2.3%)	
Primary caregiver highest level of education				
Some high school or less	181 (8.4%)	76 (5.7%)	257 (7.3%)	0.13
High school diploma/GED	323 (15.0%)	171 (12.7%)	494 (14.1%)	
Vocational school or some college	241 (11.2%)	113 (8.4%)	354 (10.1%)	
College degree	360 (16.7%)	221 (16.4%)	581 (16.6%)	
Professional or graduate degree	140 (6.5%)	74 (5.5%)	214 (6.1%)	
Unknown	693 (32.1%)	642 (47.7%)	1335 (38.1%)	
Missing	221 (10.2%)	48 (3.6%)	269 (7.7%)	
Primary diagnosis for Transplant				
Biliary atresia	838 (38.8%)	523 (38.9%)	1361 (38.8%)	0.62
Other cholestatic	227 (10.5%)	141 (10.5%)	368 (10.5%)	

(Continues)

TABLE 1 | (Continued)

	Era 1 (2011–2018), $n=2159$	Era 2 (2018–2023), $n=1345$	Overall, $n=3504$	p
Fulminant Liver Failure	233 (10.8%)	134 (10.0%)	367 (10.5%)	
Metabolic	345 (16.0%)	214 (15.9%)	559 (16.0%)	
Cirrhosis	43 (2.0%)	40 (3.0%)	83 (2.4%)	
Tumor	234 (10.8%)	137 (10.2%)	371 (10.6%)	
Other	238 (11.0%)	155 (11.5%)	393 (11.2%)	
Missing	1 (0.0%)	1 (0.1%)	2 (0.1%)	
Weight at time of Transplant				
< 5 kg	51 (2.4%)	18 (1.3%)	69 (2.0%)	0.02
5–10 kg	723 (33.5%)	497 (37.0%)	1220 (34.8%)	
> 10 kg	1312 (60.8%)	783 (58.2%)	2095 (59.8%)	
Missing	73 (3.4%)	47 (3.5%)	120 (3.4%)	0

nautical mile distance from the donor hospital on February 4, 2020 [add reference 17 here][17].

At time of transplant, 29% of participants were listed Status 1A/1B without significant difference across eras (era 1: 30% vs. era 2: 28%, $p=0.87$, Table 2). About two-thirds of participants were listed with MELD/PELD score at time of transplant (Table 2). Distribution of how participants were listed at time of transplant (calculated vs. exception scores) was different across eras with a larger percentage of participants having a PELD/MELD exception at time of transplant in era 2 (57.5%) as compared to era 1 (45.4%) ($p<0.001$). Of these, 38% had PELD exception points in era 1% and 47% in era 2, whereas 7% had MELD exception points in era 1% and 10% in era 2. The distribution of PELD exception scores was also different across eras with a larger percentage in era 2 receiving exception scores between 30 and 40 (era 1: 35% vs. era 2: 54%) and a smaller percentage receiving scores > 40 (era 1: 18% vs. era 2: 12%, $p<0.001$). Most participants with PELD calculated scores had scores ≥ 20 (31% in era 1 vs. 37% in era 2, $p=0.3$). Meanwhile, 23% in era 1 as compared to 19% in era 2 had calculated PELD scores between 10 and 20 ($p=0.3$). Interestingly, many participants had MELD calculated scores between 10 and 20 with no significant difference across eras (era 1: 50% vs. era 2: 58%, $p=0.46$) and a smaller percentage had MELD calculated scores ≥ 20 (era 1: 27% vs. era 2: 19%).

The majority of participants received a deceased donor whole liver graft (54%), with 26% receiving a deceased donor technical variant graft and 18% receiving a living donor graft (Table 2). There was no significant difference in the distribution of graft types across eras ($p=0.78$, Table 2). Of the technical variant grafts, 305/904 (34%) were reduced grafts without utilization of remaining segments in a second recipient. Figure 2 depicts the distribution of graft types based on patient age across the two eras, with a significant difference seen ($p<0.001$). Pediatric donors (< 18 years) were used in 57% of participants (1999/3504) and this did not change between eras (era 1: 58% vs. era 2: 56%).

Donor age 0–5 months contributed to 5% of all transplants, 6–11 months of 4% of all transplants, 1–4 years 21% of all transplants, 5–17 years 27% of all transplants, and donors > 18 years 34% of all transplants.

Donor-recipient blood type match was most commonly identical 81%, followed by compatible 15% and incompatible 5% (Table 2). The distribution of ABO-incompatible (ABO-I) transplants was different across eras, with a larger percentage of ABO-I transplants occurring in the second era (era 1: 4% vs. era 2: 6%, $p=0.01$).

4.3 | Patient Survival and Graft Outcomes

Overall, 4.7% (166/3504) of participants died, with 118 participants in era 1 (5.5%) and 48 in era 2 (3.6%). The probability of overall patient survival at 90 days was 98.5%, at 1 year 97.1%, at 3 years 95.2%, and at 5 years 94.2% (Figure 3A). There was no significant difference in patient survival across eras (Figure 3B, $p=0.5$). The three most common causes of death were secondary to infections and sepsis (30%, 49/166), multiorgan failure (25%, 42/166), and malignancy including post-transplant lymphoproliferative disease (PTLD), primary or recurrent malignancy (21%, 34/166).

Overall, 8% (272/3504) of grafts were lost. The probability of graft survival at 90 days was 98.4%, at 1 year, 96.7%, at 3 years, 94.4%, and at 5 years, 92.1% (Figure 3A). There was no significant difference in graft survival across eras (Figure 3C, $p=0.42$). Almost half of the participants who experienced graft failure were rescued with retransplantation (46%, 124/272). The overall indication for retransplantation was reported as hepatic artery thrombosis (HAT, 47%), other (16%), followed by primary graft dysfunction (12%), chronic rejection (9%), biliary tract complications (7%), and portal vein thrombosis (PVT, 5%). Between eras, a larger proportion (61%) required retransplant for HAT in the second era as compared to 42% in the first era.

TABLE 2 | Perioperative Patient and Graft Characteristics.

	Era 1 (2011–2018), $n = 2159$	Era 2 (2018–2023), $n = 1345$	Overall, $n = 3504$	p
MELD/PELD at time of transplant				
Total number	1480 (100.0%)	872 (100.0%)	2352 (100.0%)	< 0.001
PELD/MELD exception	673 (45.4%)	501 (57.5%)	1174 (49.9%)	
PELD/MELD calculated	591 (39.9%)	303 (34.7%)	894 (38.0%)	
PELD allocation unknown	2 (0.1%)	5 (0.6%)	7 (0.3%)	
Canadian	203 (13.7%)	53 (6.1%)	256 (10.9%)	
Missing	11 (0.7%)	10 (1.1%)	21 (0.9%)	
UNOS Status (1a/1b), Canadian Status (4/4f)				
Yes	643 (29.8%)	374 (27.8%)	1017 (29.0%)	0.87
No	1480 (68.6%)	872 (64.5%)	2352 (67.1%)	
Missing	36 (1.7%)	99 (7.4%)	135 (3.9%)	
Donor graft type				
Living	379 (17.6%)	249 (18.5%)	628 (17.9%)	0.78
Deceased whole	1182 (54.7%)	710 (52.8%)	1892 (54.0%)	
Deceased reduced	192 (8.9%)	113 (8.4%)	305 (8.7%)	
Deceased split	368 (17.0%)	231 (17.2%)	599 (17.1%)	
Deceased missing	8 (0.4%)	2 (0.1%)	10 (0.3%)	
Missing	30 (1.4%)	40 (3.0%)	70 (2.0%)	
Donor age				
0–5 months	106 (4.9%)	55 (4.1%)	161 (4.6%)	0.69
6–11 months	93 (4.3%)	58 (4.3%)	151 (4.3%)	
1–4 years	456 (21.1%)	270 (20.1%)	726 (20.7%)	
5–17 years	593 (27.5%)	368 (27.4%)	961 (27.4%)	
18–35 years	560 (25.9%)	310 (23.0%)	870 (24.8%)	
36–49 years	186 (8.6%)	97 (7.2%)	283 (8.1%)	
≥ 50 years	25 (1.2%)	10 (0.7%)	35 (1.0%)	
Missing	140 (6.5%)	177 (13.2%)	317 (9.0%)	
Donor-recipient blood type match				
Incompatible	80 (3.8%)	79 (6.1%)	159 (4.7%)	0.01
Identical	1703 (81.5%)	1037 (79.5%)	2740 (80.7%)	
Compatible	307 (14.7%)	189 (14.5%)	496 (14.6%)	

Abbreviations: MELD, model for end-stage liver disease; PELD, pediatric end-stage liver disease.

Overall patient survival for ABO-I transplants was similar when compared to ABO-compatible (Figure S2A, $p = 0.23$). Probability of patient survival at 3 months was 96.1% for ABO-I vs. 98.6% for ABO-compatible; at 1 year, survival was 94.6% for ABO-I vs. 97.2% for ABO-compatible, and at 3 years, survival was 93.7% for ABO-I vs. 95.2% for ABO-compatible. A total of 10 of 159 participants receiving ABO-I transplants died (6%). When comparing ABO-I patient survival across eras, there was no significant difference noted (Figure S3B,C).

Overall graft survival for ABO-I transplants was worse when compared to ABO-compatible (Figure S2D, $p = 0.01$). Kaplan–Meier probability estimates of overall graft survival at 3 months were 92.4% for ABO-I vs. 96.4% for ABO-compatible, at 1 year were 89.4% for ABO-I vs. 95% for ABO-compatible, and at 3 years were 87.4% for ABO-I vs. 92.4% for ABO-compatible. When comparing ABO-I graft survival across eras, ABO-I participants in era 2 had worse graft survival (Figure S3E,F).

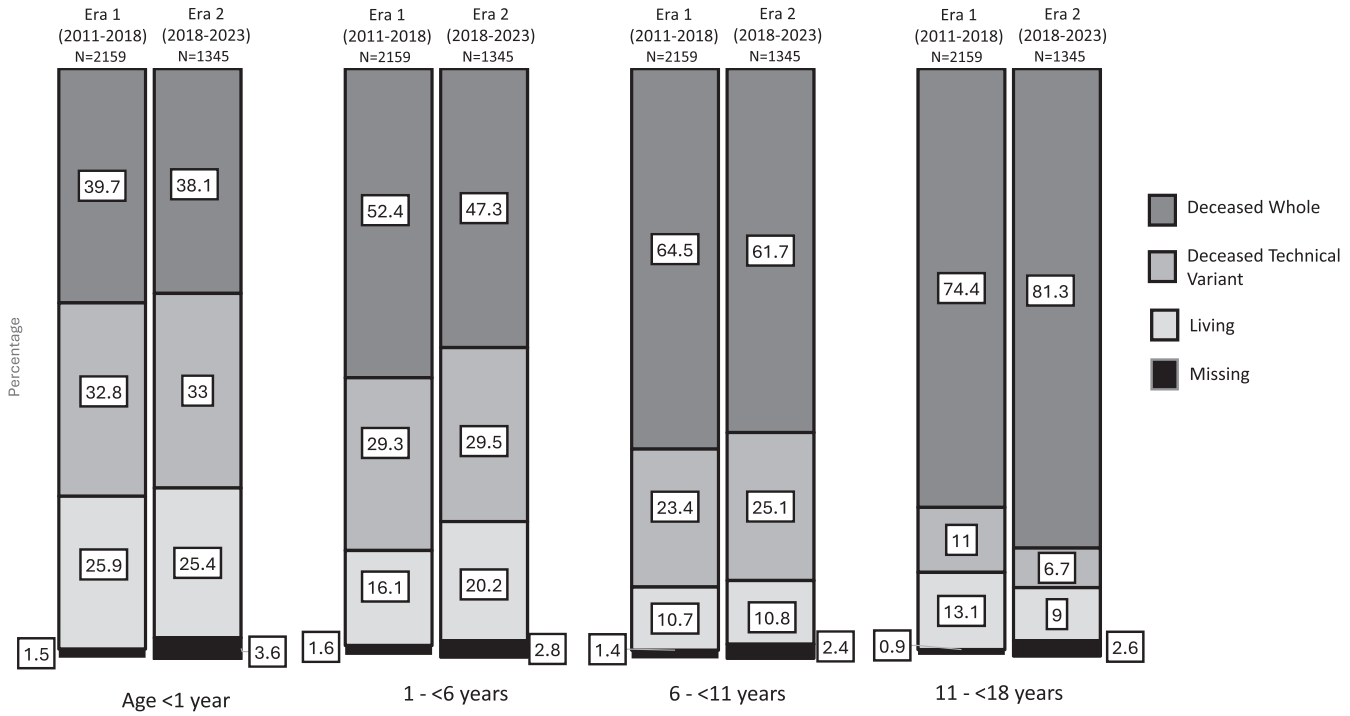


FIGURE 2 | Graft type distribution by age and era. There was a statistically significant difference when assessing different graft types across various age groups, $p < 0.001$.

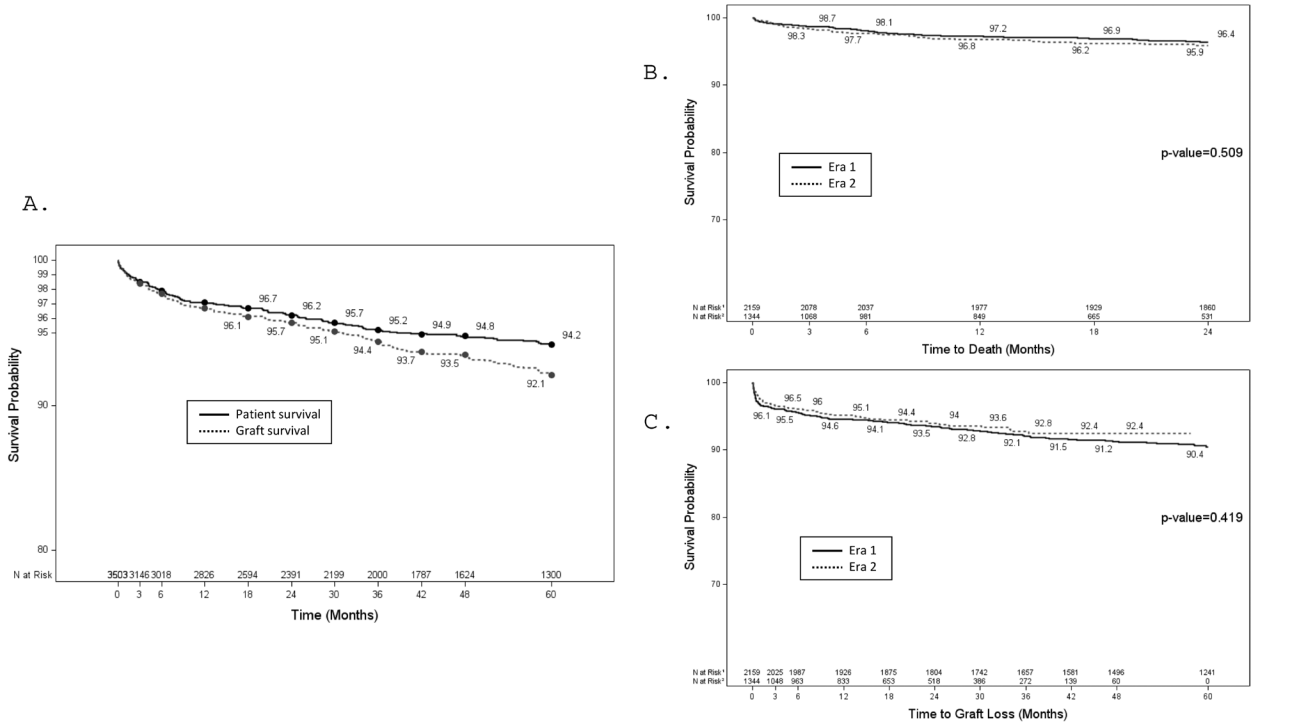


FIGURE 3 | Kaplan–Meier estimates for patient and graft survival. (A) Overall patient and graft survival. (B) Overall patient survival separated by era. (C) Overall graft survival separated by era.

4.4 | Quality Measures and Complications Following Liver Transplantation

The SPLIT Registry captures sentinel quality benchmarking data points that have been previously described [7, 18]. The overall median length of stay for the transplant hospitalization was 16 days (interquartile range [IQR] 11–27) with no significant difference across eras (Table 3). Overall, 33% (1141/3504) required unplanned reoperation with no significant difference between eras (era 1: 44% vs. era 2: 32%, $p = 0.99$). Of those requiring reoperation, 68% (777/1141) required only one reoperation, 6.2% (218/1141) required two reoperations, and only 2% required > 3

TABLE 3 | Post-operative complications.

	Era 1 (2011–2018), $n=2159$	Era 2 (2018–2023), $n=1345$	Overall, $n=3504$	p
Initial length of stay (days) (median, IQR), $n=3294$	16 (11.27)	16 (11.27)	16 (11.27)	0.96
Primary intubation (days) (median, IQR), $n=3301$	1 (0.3)	1 (0.3)	1 (0.3)	<0.001
Reoperation within 30 days (missing $n=171$)	715 (33.1%)	426 (31.7%)	1141 (32.6%)	0.99
Hepatic artery thrombosis in the first 30 days (missing $n=26$)	137 (6.5%)	58 (4.6%)	195 (5.8%)	0.02
Biliary complications cumulative until 90 days (missing $n=27$)	302 (14.3%)	196 (15.4%)	498 (14.7%)	0.41
Portal vein thrombosis in the first 30 days (missing $n=24$)	2 (3.0%)	42 (3.3%)	104 (3.1%)	0.52
Rehospitalization in the first 90 days (missing $n=139$)	973 (45.1%)	531 (39.5%)	1504 (42.9%)	0.30
Days to readmission from discharge				
Total number	$n=995$	$n=592$	$n=1587$	0.002
≤ 7 days	296 (29.7%)	184 (31.1%)	480 (30.2%)	
8–≤ 14 days	171 (17.2%)	111 (18.8%)	282 (17.8%)	
15–≤ 30 days	169 (17.0%)	139 (23.5%)	308 (19.4%)	
>30 days	135 (13.6%)	144 (24.3%)	279 (17.6%)	
Missing	224 (22.5%)	14 (2.4%)	238 (15.0%)	

Abbreviation: IQR, interquartile range.

reoperations, without any difference across eras ($p=0.94$). More patients required exploratory laparotomy in era 2 (era 1: 48% vs. era 2: 60%, $p<0.001$). Vascular complications (era 1: 23% vs. era 2: 22%, $p=0.51$), biliary tract complications (era 1: 19% vs. era 2: 19%, $p=0.89$), and intraabdominal bleeding (era 1: 19% vs. era 2: 22%, $p=0.20$) were the most common reasons for unplanned reoperation (Table S3).

The overall rate of HAT in the first 30 days was 5.8%. When comparing across eras, there were fewer HAT in era 2 at 5% (58/1345) as compared to era 1 at 7% (137/2159), $p=0.02$ (Table 3). Patient survival following HAT was improved in era 2 with 3-month survival at 95.8% as compared to 93.6% in era 1, $p=0.003$ (Figure S2). The overall rate of PVT in the first 30 days was 3% without significant difference across eras (era 1: 3% vs. era 2: 3%, $p=0.5$). Patient survival following PVT was no different between eras (Figure S2). Biliary complications in the first 90 days (leaks, strictures, bilomas, other biliary complications requiring operative repair) were seen in 15% (Table 3). There was no significant difference in rates of biliary complications across eras (era 1: 14% vs. era 2: 15%, $p=0.4$).

Culture-proven all-cause infections within the first 30 days were seen in 28% (954/3362) of participants without difference across eras (era 1: 28% [596/2098] vs. era 2: 28% [358/1264], $p=0.98$). Bacterial infections within the first 30 days were seen in 64% (614/954) with the most common being intraabdominal in 28% (172/614), bloodstream 22% (137/614), urinary tract infections 14% (86/614), and pneumonia 10% (63/614). When comparing across eras, bloodstream infections were more common in era 2 (era 1: 19% [74/391] vs. era 2: 22% [63/223], $p=0.008$) and pneumonia was less common (era 1: 12% [48/391] vs. era 2: 7% [15/223], $p=0.029$). Fungal infections accounted for 12% (117/954) of all culture-proven infections, with no era difference ($p=0.3$). Viral infections accounted for 40% (381/954) of all culture-proven infections, similarly with no era difference ($p=0.99$).

The cumulative frequency of culture-proven infections increased to 40% (1344/3381) by 90 days. Most of these culture-proven infections in the first 90 days were bacterial 62% (828/1344), fungal 11% (145/1344), and viral 53% (714/1344).

Almost half of all participants (43%, 1504/3504) required rehospitalization within the first 90 days after transplantation with no era difference ($p=0.3$). Up to 30% (480/1587) of participants required readmission within 7 days of discharge, with a higher percentage in era 2 (Table 3). The most common reasons for readmission within 7 days included fever (27%), abnormal liver tests (20%), rejection (10%) and fluid-electrolyte imbalance (8%) with no difference across eras. The most common reasons for readmission within 30 days included fever (18%), abnormal liver tests (16%) and rejection (10%).

Overall, PTLD was reported in 4% of participants (134/3504). The probability of being PTLD-free at 1 year was 98.1% and 96% at 3 years. There was a significant difference between the probability of being PTLD-free across eras (estimated 3-year 97% in era 1 vs. 93.2% in era 2, $p = < 0.001$). PTLD within 2 years was seen in 3% of overall participants (94/3504), with a higher proportion of participants in era 2 experiencing PTLD (era 1: 2% vs. era 2: 3%, $p < 0.001$). The most common treatment for PTLD within 2 years was a reduction of immunosuppression performed in 83% (78/94) of participants, followed by anti-B cell therapy in 51% (48/94), antivirals in 37% (35/94), resection in 26% (24/94), and chemotherapy in 25% (23/94).

4.5 | Immunosuppression Use Following First Liver Transplant

Immunosuppression (IS) practices at various time points following transplantation are summarized in Table 4 and Figure 4. Antibody-induction therapy was used in 32% of all participants, without any difference across eras (Figure 4). When assessing the use of antibody-induction therapy at the SPLIT center level, 75% of centers (35/47) reported using an induction protocol including agents in lieu of or in addition to steroids. The most common agent used is anti-IL-2 monoclonal antibody (mAb) at 66% of centers, followed by anti-thymocyte globulin (ATG) and similar agents at 34% of centers. Oddly, muromonab-CD3 (Orthoclone, OKT3)/mAb induction was reported by 15% of centers despite its lack of availability. Lymphocyte-depleting agents (ATG, etc.) were used in 6% (218/3504) of participants without a difference across eras, and nondepleting antibodies (anti-IL-2 mAb) were used in 26% (916/3504) of overall participants, with a statistically significant decrease in era 2 (24% [321/1345]) as compared to era 1 (28% [593/2159]), $p = 0.03$.

After induction, 61% of overall participants received two IS agents, while 31% received three agents. Interestingly, in era 2, there was a significantly larger percentage receiving 3 agents at LT as compared to era 1 (era 1: 29% vs. era 2: 35%, $p = 0.002$). Figure 4 demonstrates induction therapy and the combination of IS agents used at various transplant time points compared across eras. Tacrolimus with steroids was the most common initial maintenance IS regimen used at LT in 57% of all participants. However, when compared across eras, fewer participants received this combination in era 2 (54%) vs. era 1 (59%, $p < 0.001$). Additionally, more participants in era 2 received tacrolimus in combination with an antimetabolite and steroids (34%), as compared to only 29% in era 1 ($p < 0.001$).

At 30 days post-transplant, nearly half of all participants (57%) received double IS and almost one-third were still on triple IS. In era 2, a larger percentage of participants remained on triple IS (38%) as compared to 32% in era 1 ($p = 0.004$). Tacrolimus in combination with steroids was the most common regimen used in 52%. A larger percentage of participants remained on tacrolimus + antimetabolite + steroids at 30 days in era 2 (36%) as compared to era 1 (31%), $p = 0.003$. By 1 year, 51% of overall participants were reduced to single-agent tacrolimus, while 16% of participants remained on tacrolimus + antimetabolite, 15% on tacrolimus + steroids, and 9% on triple IS with tacrolimus + antimetabolite + steroids. There was no significant difference in IS regimens across eras at 1 year ($p = 0.1$). Monotherapy with sirolimus at 1 year was only employed in 82 participants and not at 30 days or 90 days post-LT.

One of the SPLIT's ideal outcome endpoints is the number of recipients achieving maintenance with single-agent IS and normal allograft function defined as ALT < 50 IU/L + GGT < 50 IU/L at 1 year and 2 years following LT. Only 37% (1088/2924) of participants achieved tacrolimus monotherapy with normal graft function by 1 year following LT, while 2% (51/2924) of overall participants were receiving sirolimus monotherapy with normal graft function. There was no significant difference across eras, with 37% of participants in era 1 (722/1969) and 38% (366/955) in era 2 achieving this metric ($p = 0.6$). By 2 years, 46% (1154/2505) achieved tacrolimus monotherapy with normal graft function and 3% (88/2505) with sirolimus monotherapy. Similarly, there was no difference in achieving monotherapy with normal graft function by 2 years across eras ($p = 0.7$).

The overall rate of rejection was 44% (1541/3504). Kaplan–Meier probability estimate of rejection at 3 months was 22%, at 6 months was 27%, and within the 1st year of transplant was 35% (Figure 5A). There was no significant difference when comparing the probability of rejection between eras, $p = 0.09$ (Figure 5B). The overall rate of rejection in ABO-I transplants was 44% (70/159). There was no significant difference in the probability of rejection in ABO-I grafts as compared to ABO-compatible, $p = 0.6$ (Figure 5C). There was also no significant difference in the rate of rejection in ABO-I transplants compared to ABO-compatible when comparing across eras (era 1: $p = 0.2$, era 2: $p = 0.5$). Participants receiving anti-IL2 receptor mAb had lower rates of rejection at 3 months (anti-IL-2 receptor mAb group 19% vs. ATG group 37%), 6 months (anti-IL-2 receptor mAb group 24% vs. ATG group 40%), and 1 year (anti-IL-2 receptor mAb group 34% vs. ATG group 44%) as compared to anti-lymphocyte globulin (ALG)/ATG/anti-lymphocyte serum (ALS) group, $p = 0.02$ (Figure 5D). When compared across eras, during era 1, rejection was less in participants receiving anti-IL-2 mAb at each time point as compared to ALG/ATG/ALS, $p = 0.005$, whereas there was no significant difference in the probability of rejection in era 2 when compared across induction types ($p = 0.4$).

5 | Discussion

Updates from the SPLIT Registry over the last 5 years highlight the changes in transplant trends for children and provide insight for future investigations. The SPLIT Registry represents the vast majority of pediatric LTs occurring in North America. It includes data from both large and small volume transplant centers capturing up to ~75% of all pediatric LTs since 2011. Total enrollment and data completion at each participating center remain high, with 96% of all eligible transplant participants at SPLIT sites being enrolled into the registry, despite disruptions in medical care delivery brought on by the COVID-19 pandemic. There were no significant differences in the underlying causes of liver disease for participants who received LT, specifically BA. This is encouraging as we did not observe an increase in transplant for BA, despite concerns for delayed medical care during the COVID-19 pandemic, which could have led to delays in BA diagnoses and Kasai-portoenterostomy. Results from the

TABLE 4 | Immunosuppression use after liver transplant.

	Era 1 (2011–2018) $n = 2159$	Era 2 (2018–2023) $n = 1345$	Overall $n = 3504$	p
Immunosuppression at time of transplant				
Number of agents				
None	16 (0.7%)	5 (0.4%)	21 (0.6%)	0.002
Single	125 (5.8%)	61 (4.5%)	186 (5.3%)	
Double	1360 (63.0%)	775 (57.6%)	2135 (60.9%)	
Triple	633 (29.3%)	468 (34.8%)	1101 (31.4%)	
Quadruple	6 (0.3%)	7 (0.5%) 1	3 (0.4%)	
Missing	19 (0.9%)	29 (2.2%)	48 (1.4%)	
Antibody therapy as induction				
No	1402 (64.9%)	895 (66.5%)	2297 (65.6%)	0.16
Yes	714 (33.1%)	410 (30.5%)	1124 (32.1%)	
Missing	43 (2.0%)	40 (3.0%)	83 (2.4%)	
ALG/ATG/ALS induction				
No	1996 (92.5%)	1223 (90.9%)	3219 (91.9%)	0.46
Yes	120 (5.6%)	82 (6.1%)	202 (5.8%)	
Missing	43 (2.0%)	40 (3.0%)	83 (2.4%)	
OKT3/Monoclonal induction				
No	2113 (97.9%)	1290 (95.9%)	3403 (97.1%)	< 0.001
Yes	3 (0.1%)	13 (1.0%)	16 (0.5%)	
Missing	43 (2.0%)	40 (3.0%)	83 (2.4%)	
IL-2 mAB induction				
No	1523 (70.5%)	983 (73.1%)	2506 (71.5%)	0.03
Yes	593 (27.5%)	321 (23.9%)	914 (26.1%)	
Missing	43 (2.0%)	40 (3.0%)	83 (2.4%)	
Immunosuppression at Day 30				
Total number	$n = 2098$	$n = 1264$	$n = 3362$	
Number of agents				
None	6 (0.3%)	5 (0.4%)	11 (0.3%)	0.004
Single	171 (8.2%)	77 (6.1%)	248 (7.4%)	
Double	1222 (58.2%)	695 (55.0%)	1917 (57.0%)	
Triple	677 (32.3%)	475 (37.6%)	1152 (34.3%)	
Quadruple	7 (0.3%)	2 (0.2%)	9 (0.3%)	
Quintuple	0	2 (0.2%)	2 (0.1%)	
Missing	15 (0.7%)	8 (0.6%)	23 (0.7%)	
Immunosuppression at 1 year				
Total number	$n = 1969$	$n = 955$	$n = 2924$	
Number of agents				
None	2 (0.1%)	0	2 (0.1%)	0.64

(Continues)

TABLE 4 | (Continued)

	Era 1 (2011–2018) $n = 2159$	Era 2 (2018–2023) $n = 1345$	Overall $n = 3504$	p
Single	1083 (55.0%)	514 (53.8%)	1597 (54.6%)	
Double	667 (33.9%)	337 (35.3%)	1004 (34.3%)	
Triple	198 (10.1%)	88 (9.2%)	286 (9.8%)	
Quadruple	2 (0.1%)	2 (0.2%)	4 (0.1%)	
Missing	17 (0.9%)	14 (1.5%)	31 (1.1%)	

Abbreviations: ALG, anti-lymphocyte globulin; ALS, anti-lymphocyte serum; ATG, anti-thymocyte globulin; mAb, monoclonal antibody; OKT3, Muromonab-CD3 (brand name Orthoclone OKT3).

NASPGHAN SARS-CoV2 Registry did not identify significant transplant complications apart from two patients with acute cellular rejection following IS reduction [16]. However, as the start of era 2 was 2 years prior to the COVID-19 pandemic, the current study could not evaluate the influence of immunosuppression management on the development of rejection.

This registry report evaluated data from the U.S. and Canada. When compared to Japanese and European Registries, which both also included retransplants, survival outcomes were similarly excellent. The graft survival rates reported most recently by the Registry of the Japanese LT Society were 88.9%, 85.9%, 82.2%, 77.1%, and 75.4% at 1, 5, 10, 20, and 30 years post-LT [19]. The European LT Registry did not report graft survival; however, since 2009, survival in 5061 patients was 85% at 5 years [20]. Survival outcomes reported are similar to these results with > 90% for both patient and graft survival at 1 year and 3 years, exemplifying SPLIT's mission to improve outcomes in children receiving LT.

During era 2 (2018–2023) of the SPLIT Registry, two key changes to the pediatric LT allocation system occurred to improve transplant equity and access. First, the implementation of the NLRB occurred in 2019 and may account for the change in distribution of PELD exception scores that was seen in era 2 [21]. The number of recipients with PELD exception scores > 40 decreased as compared to era 1; however, the number of recipients with PELD exception scores between 30 and 40 increased by nearly 20%, suggesting that the NLRB led to potentially more equitable distribution of exception scores across the country. Previously published studies have shown significant differences in exception scores across regions, and it is possible that NLRB implementation may have addressed some of these regional differences [22]. The second allocation change was the implementation of acuity circles in 2020, which were meant to distribute organs more efficiently to those with highest priority. Despite these changes, more than half of pediatric participants still required MELD/PELD exception scores at time of transplant (58% in era 2 vs. only 45% in era 1). The number of exception requests was rising prior to the implementation of acuity circles and has continued to increase [7]. This highlights the difficulty in prioritizing pediatric patients, suggesting that further policy changes need to be pursued. Changes in behaviors including organ acceptance rates, use of technical variants, and living donor grafts may have impacted observed trends in reaction to changes in organ allocation. In addition, changes to the organ allocation system may have increased competition from adult recipients, and these implications will need to be carefully considered as we move toward continuous distribution and future policy changes [23].

Many participants in the SPLIT Registry continued to receive deceased donor whole organ grafts. There was no increased use of living donor or split liver grafts despite studies showing equivalent to improved outcomes for both patient and graft survival in living donor LTs [5, 10, 24–27] and equivalent outcomes for deceased donor technical variant grafts [10, 25, 28, 29]. This may be secondary to a shortage of transplant surgeons in the U.S. with expertise to split a liver into two transplant variant grafts and with living donor procedures. Improvement of transplant surgical training with a focus on these techniques, or dual listing at centers with such expertise, could present an opportunity for equitable access to increased donor organs in the future. Perhaps this could mitigate the continued need for allocated exception points and higher scores to receive deceased donor grafts. National donor allocation policy changes to prioritize grafts that are split and shared by two recipients may also encourage increased use of technical variant grafts. During era 2, there was an increase in the use of ABO-I grafts with almost double the number of participants receiving an ABO-I graft, and with similar patient outcomes across eras, but slightly lower graft survival when compared to ABO-compatible. ABO-I are often reserved for young infants due to improved graft tolerance in the setting of a lack of a robust immune system or very sick children with high mortality risk. The increased use of ABO-I grafts, living donor, and technical variant grafts across the two eras with no significant increase in morbidity or mortality supports the strategy that these modalities may be a way to help decrease waitlist mortality without sacrificing patient survival. An investigation of donor characteristics associated with the best outcomes should be further studied.

The number of infants weighing < 10 kg undergoing LT increased by 2% in the second era. Historically, these infants have worse outcomes due to small size and medical complexity [29, 30]. Despite a shift toward transplanting smaller patients, both graft and patient outcomes remained consistent between eras, likely secondary to advancements in surgical techniques such as hyper-educed and nonanatomic reduced size grafts and post-operative management [31, 32]. It is possible that patient selection also played a role, as participants < 10 kg were mostly between 5 and 10 kg, with reduced infants < 5 kg decreasing in era 2. Extremely small infants carry the greatest risk of poor outcomes after LT and remain at the greatest risk of dying prior to LT [30, 33].

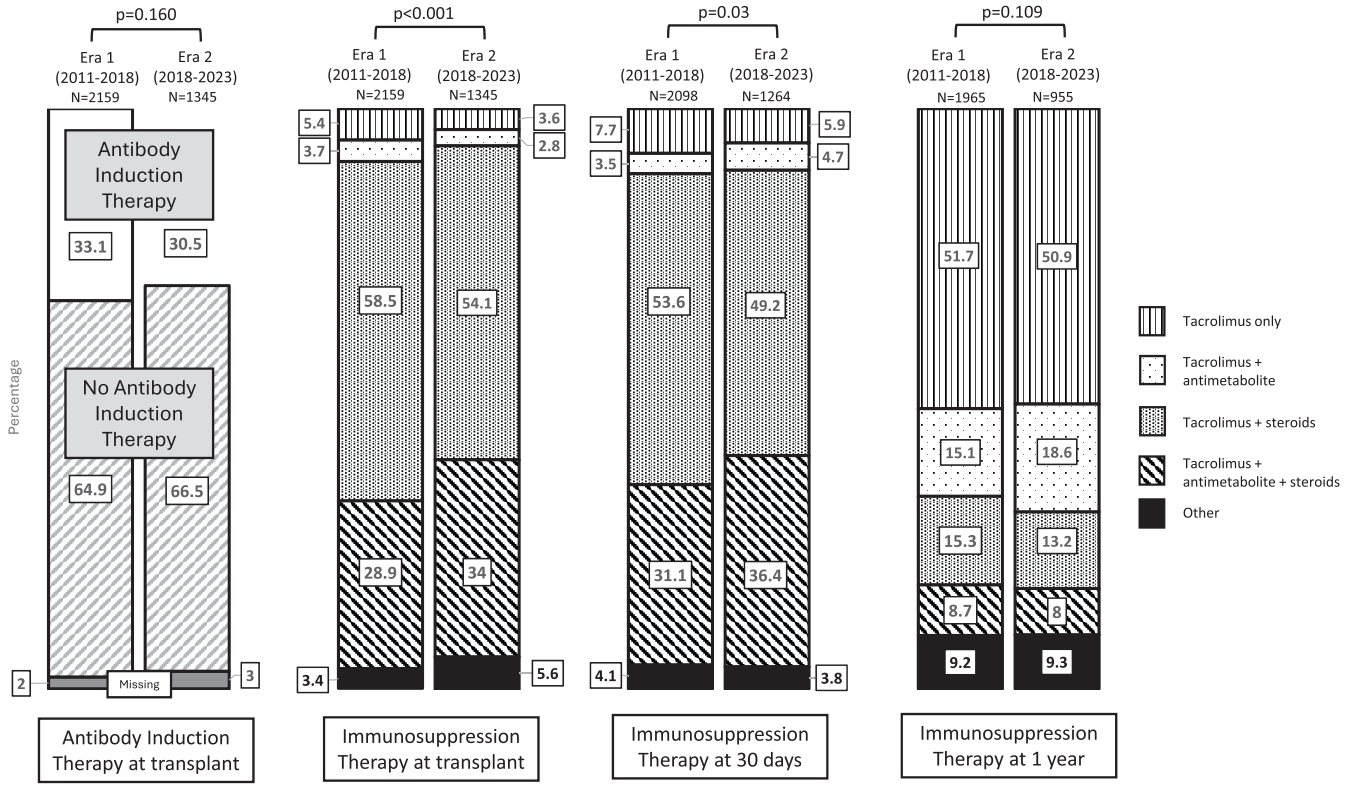


FIGURE 4 | Induction and maintenance immunosuppression after liver transplant.

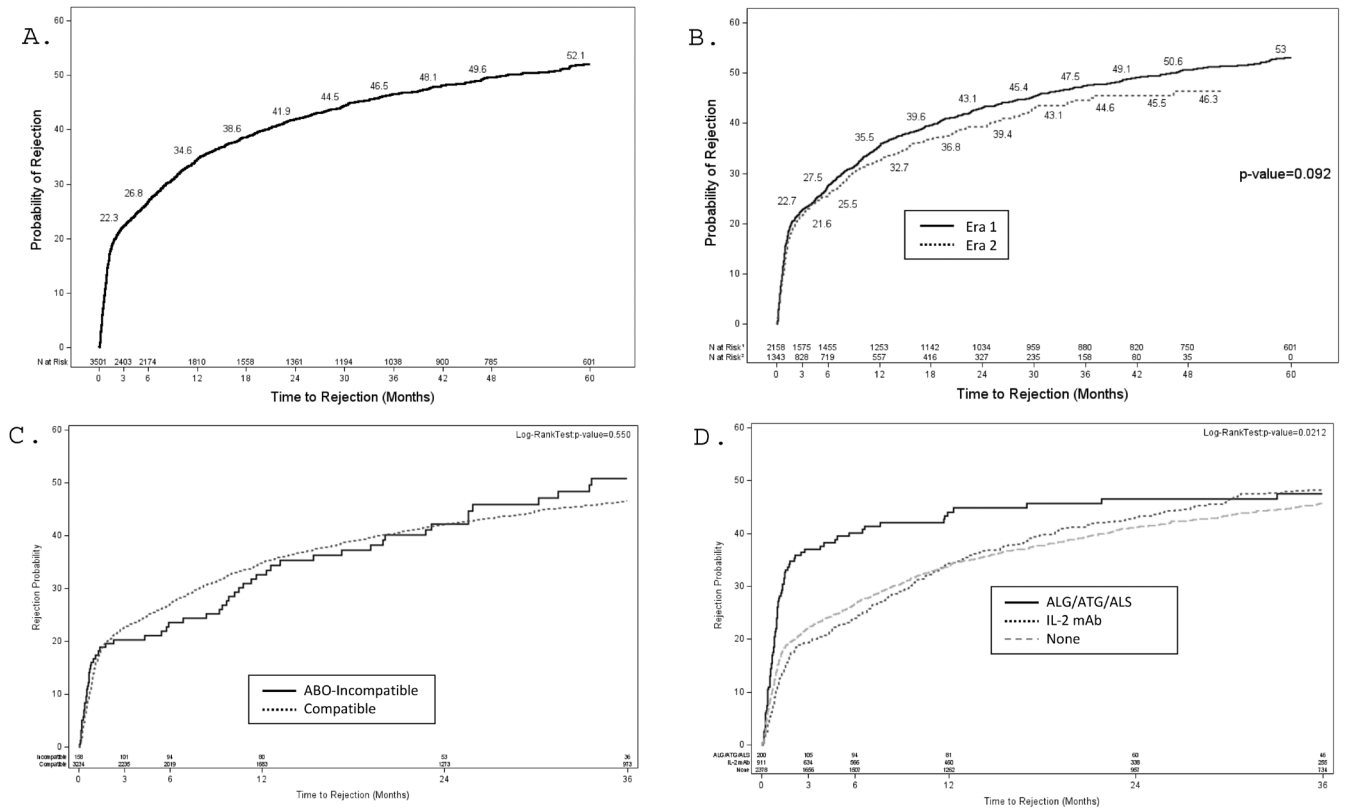


FIGURE 5 | Kaplan–Meier estimates for rejection. (A) Overall probability of rejection over time. (B) Overall probability of rejection separated by era. (C) Overall probability of rejection by ABO status. (D) Overall probability of rejection based on antibody induction type for patients who received antibody induction.

Vascular complications are a leading cause of retransplantation and morbidity in pediatric LT recipients [24, 27, 34]. Although HAT rates were lower in era 2 (only 4% vs. 7% in era 1), HAT remained the most common indication for retransplantation in era 2 and was less commonly associated with death. However, these data should be interpreted with caution as HAT can lead to sepsis and multiorgan system failure, with one of these associated causes being entered for cause of death or retransplantation. Hopefully, this trend indicates an improved ability to bridge patients to second transplant following HAT, or to potentially rescue the organ without retransplantation. Finally, it is interesting that there was a lower percentage of HAT in the second era, despite transplanting smaller children (< 10 kg) which is a known risk factor and may suggest improved surgical technique or other changes in management during the immediate post-op period contributing to this lower incidence. Notably, anticoagulation practices are not captured in the SPLIT database, and this requires further study.

There remains significant variability in induction and maintenance IS regimens across centers. Approximately 2/3 of SPLIT sites use one or more IS agents for induction, yet only about 30% of participants received induction therapy without any significant difference across eras. Immediately after LT, a significantly higher percentage of children received triple IS with tacrolimus, steroids, and antimetabolite in the second era (34%) as compared to the first (28.9%). As participants progressed post-transplant, participants in era 2 received more IS at 30 days and 1-year (Figure 4). Despite the additional IS agents in era 2, there was no decrease in rates of rejection or increase in participants achieving ideal graft outcome with single IS and normal graft function at 1–2 years post-transplant. It is possible that the practice of using multiple agents at lower doses to avoid toxicity with less agents at higher doses may explain this trend. This is supported by the observation that recipients did not experience high rates of infectious complications in era 2. Although other long-term complications and comorbidities were not assessed in this analysis, such as chronic kidney disease, the practice of using multiple agents to avoid individual agent toxicity may have other beneficial effects. Increased cumulative IS exposure may potentially explain the increased risk of development of PTLD seen in era 2. However, increased ability to detect PTLD with more sensitive testing may have impacted the incidence. Additional studies are needed to evaluate the cumulative effect of additional IS agents and whether the combined use of multiple agents can allow the safe targeting of lower tacrolimus troughs to reduce the rate of chronic kidney disease and other long-term complications. As significant IS variability exists across centers, we require comparative effectiveness trials using consensus treatment protocols to help inform and guide evidence-based IS approaches to achieve optimal graft outcome.

The SPLIT Registry is the largest database of pediatric LT recipients in North America that contains longitudinal granular detail about recipient characteristics, IS, and transplant complications. While this is a prospective dataset, some participants are enrolled retrospectively, leading to a lag in data entry. Although enrollment during the COVID-19 pandemic was robust, it is possible that data entry and enrollment lagged at certain centers or study participation was declined by participants/parents due to other factors that arose during the pandemic. Additionally, as SPLIT does not include all pediatric LT centers in North America, selection bias may play a role in the reported outcomes.

In summary, pediatric LT recipients within the SPLIT Registry have demonstrated similar utilization of deceased and living donor grafts over time, and lower rates of HAT despite transplanting smaller children < 10 kg. The underutilization of technical variant deceased and living donor grafts identifies an opportunity to impact the number of available organs for children and to reduce persistent waitlist mortality. Despite recent organ allocation policy changes, more children are requiring exception points at transplant to receive an organ, albeit at lower ranges. Transplant centers have been utilizing more IS agents at transplant and within the first year, but without any significant decrease in rates of rejection or increases in IS-related complications. The SPLIT Registry remains a unique and granular database of pediatric LT recipients that tracks trends leading to future studies, interventional trials, and practice changes. The registry will soon be merged with the UNOS database, allowing for more simplified data entry as well as expanding the research possibilities as well as opening potential collaborations with other networks and transplant registries. Additionally, as SPLIT has become an international society, incorporating data from pediatric transplant centers outside of North America will further strengthen research opportunities to improve LT outcomes across the world. As a society, we hope to continue to use insights gained from SPLIT studies to expand the research agenda, to positively impact evidence-based patient advocacy, to improve organ allocation policy, and to optimize pediatric outcomes and the patient experience.

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Conflicts of Interest

Pamela L. Valentino: Mirum Pharmaceuticals Speakers' Bureau and consulting for Grifols. Ajay K. Jain: Consultant and Advisory Role Mirum Pharmaceuticals, Camp 4; Advisory role for Gilead. Debra H. Pan: Medical advisory role for Mirum Pharmaceuticals. Amber Hildreth: Consulting for Mirum Pharmaceuticals and Ipsen. Nanda Kerkar: Advisory Board for Mirum and Ipsen; Royalties from Elsevier.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.