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Not everything that counts can be counted: Tracking long-term outcomes in pediatric liver transplant recipients

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Abstract

For pediatric liver transplant (LT) recipients, an ideal outcome is to survive and thrive into adulthood. However, outcomes reporting for all LT recipients typically rely on much shorter-term outcomes, 1–5 years post-LT. Using Organ Procurement and Transplantation Network (OPTN) registry data from 1990–2018, this analysis seeks to determine if long-term follow-up and outcomes data are complete for pediatric LT recipients age 0 to 12 years who survive at least 1 year post-LT without graft loss (n=9,309). Of the 7,948 pediatric transplant recipients who did not die or require re-LT, 1 in 6 was reported as lost to follow-up by their transplant center during long-term follow-up. Rates of lost to follow-up were highest in those transplanted between 1990 and 1999 and increased in early adulthood for all recipients. Almost 10% of pediatric LT recipients that remained in follow-up required relisting for LT. 8% of children remaining in follow-up had graft failure. Lost to follow-up may bias estimates of long-term outcomes, and risk factors for poor outcomes. For those remaining in follow-up, graft failure and death continue to occur in the decades after LT. Continued proactive monitoring, management, and innovations are needed to truly optimize post-LT survival for all children.

1 Introduction:

Liver transplant (LT) is life-saving for children with chronic liver disease, acute liver failure, in operable tumors, and many inherited disorders of metabolism. Limited data availability is a barrier to understanding long-term outcomes after pediatric LT. In a report on 10-year outcomes from the Society of Pediatric Liver Transplantation's registry (SPLIT), only 56% of enrolled recipients had available data at 10 years or more post-LT[1]. The OPTN registry

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collects follow-up data on all U.S. LT recipients, with the aim of continuing follow-up through the life of the graft and the patient. However, previous analyses have not clearly delineated the long-term status of *all* of these children—including those who are lost to follow-up with true outcomes thus unknown, those who remain in follow-up but have poor graft function, and those who have late graft loss or death. Missing or incomplete data could bias analyses of long-term outcomes in pediatric LT recipients, distorting our understanding of risks and their determinants for these children.

Our objective in this study was to provide a comprehensive picture of long-term outcomes in all pediatric LT recipients, highlighting insights from and gaps in available data. We investigated the prevalence of and risk factors for three outcomes: lost to follow-up, re-listing for LT as an indicator of poor graft function and impending graft failure, and graft loss. These have not been explored comprehensively in previous analyses of United Network for Organ Sharing (UNOS) data, despite their substantial impact on recipient health and survival. We also evaluated late mortality, focusing on causes of death and the potential contribution of liver allograft dysfunction and long-term complications of LT to death.

2 Methods:

2.1 Study design and definitions

We conducted a retrospective analysis of the UNOS Standard Transplant Analysis and Research (UNOS STAR) files, which houses information on all transplant recipients in the United States, updated through 12/31/2019. We included children who received an isolated LT at age 0 to 12 years, from 1/1/1990 through 12/31/2018, to allow for at least 1 year of post-LT follow-up. We excluded multiple listings and transplants that occurred at a center other than the listing center to ensure that each transplant was reflected only once in the data. (Figure 1)

The first LT during the study period with more than 1 year of graft survival was the index transplant; However, for children who lost their first LT within 1 year after transplant but were re-transplanted, their index LT for this analysis was the 2nd LT if they subsequently had more than 1 year of graft survival. Similarly, follow up and graft survival time started at the time of index LT for this analysis. This enabled us to minimize the number of excluded patients, to focus on grafts with more than 1 year survival, and to explore early re-transplant (less than 1 year) as a predictor of long-term outcomes.

Lost to follow-up: In the STAR files, patient and graft survival times are based on the last known follow-up date that included patient contact and does not include time passed between last known follow-up and the date that “lost to follow-up” status was actually determined (personal communication, D. Tripp, UNOS). Notably, UNOS does not have specific criteria that transplant centers must meet to declare a patient “lost to follow-up”; this designation is determined by individual transplant centers and indicates that they do not expect to see the patient again. Categorizing a patient as “lost to follow-up” on an annual follow-up form halts the generation of additional annual follow-up forms in the OPTN registry. In this analysis, transplant recipients who were recorded as lost to follow-up but had

a death date in the STAR files (n=42) were counted as deaths, with follow-up through the date of death, not as lost to follow-up.

Re-listing for LT: Re-listing was identified as a subsequent listing in UNOS under the same patient code, following the index transplant. Patients may have been re-listed for transplant within 1 year post-initial LT but, per our inclusion criteria, they would have needed at least 1 year graft survival for that index graft prior to undergoing re-LT.

Graft loss: We defined graft failure as re-LT or death with a primary or contributing cause of death listed as "graft failure."

Death: We tabulated primary cause of death based on categories provided in the STAR form. We also reviewed data from text fields provided by the center, if available, to most accurately categorize patients (e.g. infection, hemorrhage, etc.). Those categorized as "non-specific" cause of death were listed in the STAR files as having a cause of death that is "unknown" or "other specify" without sufficient additional detail for further classification.

STAR files list age at transplant as an integer and provide follow-up time in days post-LT. Thus "age at last follow-up" is an estimate generated by assuming that all patients were age (integer years) + 182.5 days (0.5 years) at transplant, since their true age may have varied from age + 1 day to age + 364 days within the integer age provided.

Center volumes reflect the average annual number of pediatric LT centers over the study period. Categorization of UNOS regions as high, medium, and low median Model for End-Stage Liver Disease (MELD) or Pediatric End-stage Liver Disease (PELD) at transplant was based on median allocation MELD/PELD for children and adults transplanted during the study period.[2]

2.2 Statistical analysis

Descriptive statistics utilized chi-squared testing for categorical variables and median and interquartile range (IQR) with Kruskal-Wallis testing for continuous variables given skewed distributions.

Risk factors for lost to follow-up were identified using competing risks regression, with observation time measured from the date of LT to death or re-LT (competing risk) or last visit date (outcome). Patients who died or were re-transplanted were censored at death/re-transplant date. Using the Fine and Gray method, we identified risk factors for loss to follow up.[3] Predictors with $p<0.1$ in univariate analysis were considered for inclusion in the multivariate model.

Predictors of re-listing and graft failure were evaluated using Cox proportional hazards regression. For relisting, time was measured from date of index LT to re-listing date. For graft survival, time was measured from date of LT to date of death, re-LT, or last follow-up, with maximum included follow-up time of 30 years (censored). Predictors with $p<0.1$ in univariate analysis were considered for inclusion in the multivariate model.

All multivariate models were generated using backward stepwise regression, with retention of variable with $p<0.05$, and adjusted for UNOS region (http://optn.transplant.hrsa.gov/members/regions), using Region 3 as the reference. All data analysis was completed using Stata/IC 16 (StataCorp, College Station, TX). The Institutional Review Board at the University of California, San Francisco approved this study.

3 Results:

From 1990 through 2018, 12,646 children aged 0–12 received an LT with 9,309 that met study criteria, with graft survival of more than 1 year. This includes 8,996 children who underwent 1 transplant during the study period, 305 with 2 transplants, and 8 with 3 transplants (FIGURE 1). 843 children had early graft failure that required re-transplant within 1 year. This group was included in the study cohort, with their second transplant considered the index LT for this analysis so that follow-up started at the same date for all post-transplant outcomes.

Median age at the index LT was 1.5 years (IQR 0.5–5.5 years) The most common etiology for index LT was biliary atresia (45.1%), followed by other cirrhotic (25.5%), and non-cirrhotic conditions (15.8%). (SUPPLEMENTAL TABLE 1).

Following LT, included children had a median of 16 follow-up visits (IQR 11–21); follow-ups are reported to UNOS at 6 months, 1 year, and then annually post-LT. The median (IQR) time between visits was 350 (231–385) days, with 9.4% of visits occurring more than 15 months after previous visit. Median (IQR) duration of post-LT follow-up after the index LT was 9.4 (4.7–15.8) years. Median (IQR) age at last follow-up through the end of the study period was 13.5 (7.6–19.5) years.

3.1 Lost to follow-up

During the study period, 1,302 children were reported as lost to follow-up by their transplant center (16.4%). The rate of lost to follow-up, and the percentage of total children reported lost at ≥5 years, dereased significantly over the last three decades (FIGURE 2). Among children transplanted 1990–99, 32.6% were reported as lost during follow-up, compared to 8.6% of those transplanted 2000–09 and 0.8% of those transplanted 2010–18. When considered by years since transplant, there appears to be a steady rate of follow-up loss throughout 25 years following pediatric LT (Figure 2A). However, when examined by estimated age at last follow-up, an increased rate of lost to follow-up is evident at approximately 18 years of age (FIGURE 2B). This inflection, with significantly higher rate of lost to follow-up in late adolescence and early adulthood, is most prominent for 1990–99 and 2000–09. However, the number of LT recipients in the 2010–18 cohort with ≥5 years of follow-up is small.

There was no significant difference in follow-up interval among those lost [median (IQR) 366 (343–392) days] and not lost to follow-up [median (IQR) 364 (339–386) days]. However, among those who were lost to follow-up, 11.9% had intervals greater than 15 months between at least 2 visits, compared to only 8.1% in the not lost to follow-up group. Prior to their status being changed to “lost”, 78.2% (n=1,034) had laboratory values or a

visit recorded 1 day prior, reflecting database convention to back-date the “lost” date to last known follow-up; the true date at which the transplant center reported the patient as “lost” is not available in STAR files.

In univariable analysis, risk of being lost to follow-up was increased for those aged 4–12 at LT compared to <4 years, with LT at a high-volume center (> 15 LT/year), and those transplanted in earlier, in 1990–2009 compared to 2010–2018. Patients with decreased risk of lost to follow-up were female, black or “other” race, transplanted for non-cirrhotic liver disease, split LT, active PELD/MELD exception at the time of transplant, and transplanted in regions with low median regional MELD score. (SUPPLEMENTAL TABLE 1).

In multivariable analysis, children transplanted in 1990–99 and in 2000–09 had more than 8-fold and 3-fold risk, respectively, of being lost to follow-up compared to those transplanted 2010–18. Additional independent risk factors were age 4–12 years at time of LT, and LT at either a low (<5 LT/year) or a high volume center. Factors that modestly decreased risk for lost to follow-up included female sex and LT due to acute liver failure. UNOS Region of transplant was also associated with risk of loss to follow-up, with increased risk in Regions 2, 4, and 5 and decreased risk in Regions 8, 10, and 11 relative to Region 3. (TABLE 1)

In multivariable analysis, a transplant indication of acute liver failure reduced the risk of being lost to long-term follow up, but being Status 1A at time of transplant did not. We further examined risk within the status 1A and acute liver failure groups given their substantial overlap. Among all children transplanted as status 1A (N=698), 71.6% (n=500) had a primary diagnosis of acute liver failure. The remainder qualified for 1A based on hepatic artery thrombosis(n=51), primary graft non-function (n=12), Wilson disease (n=10) or exception for other diagnosis, most commonly biliary atresia (n=28). The analysis thus suggests that being status 1A for an indication other than acute liver failure does not increase the risk of being lost to follow-up.

3.2 Re-listing for LT more than 1 year after index LT:

Re-listing for LT after more than1 year of initial graft survival was evaluated as an outcome indicative of late graft failure. After the index LT, 883 children (9.5% of the total cohort) required re-listing for another LT during the study period. Re-listing occurred at a median (IQR) 5.3 (1.8–12.0) years after index LT with median (IQR) age of 9 (4–16) years at time of relisting.

Re-listed children were listed for their index LT at median PELD of 14 (IQR 5–25) with median (IQR) bilirubin 8.7 (2.0–14.6) mg/dL, INR 1.4 (1.13–2.3) and albumin 3.1(2.6–3.6) g/dL. Labs at re-listing were similar, with median(IQR) PELD 15 (6–23), median (IQR) bilirubin 8.5 (1.9–19) mg/dL, INR 1.3 (1.1–1.6), and albumin 3.0 (2.5–3.6) g/dL.

Re-listing occurred steadily over time after index LT for recipients from all three decades (FIGURE 3). Of note, biliary atresia was listed as the diagnostic indication for re-listing in 22.1% of children (n=184). This is presumably a shortcoming of the STAR files, as biliary atresia is not a disease that recurs post-LT; likely other events led to graft failure and need for re-transplant but these either were not specified or not captured at time of re-listing.

In univariable analysis, risk factors for re-listing more than 1 year after index LT included age 4–12 years at time of first LT, public insurance, Black or Hispanic race/ethnicity, initial transplant due to acute liver failure, initial listing as status 1A, re-listing diagnosis of non-cirrhotic disease, index transplant 1990–2009 (vs 2010–18), and initial LT at a low or a high-volume center. Those with active PELD exceptions at initial listing, re-listing diagnosis of other cirrhotic conditions, initial transplant in a high median MELD region, UNOS region 1 or Region 5 were less likely to be relisted during long-term follow-up. (SUPPLEMENTAL TABLE 2)

In multivariable analysis, being Black, Hispanic, or listed as status 1A at initial transplant were associated with an increased likelihood of relisting more than1 year after index LT. Other patient and index LT characteristics, including transplant decade, whole vs. split LT, and transplant indication, were not associated with a higher risk of re-listing in multivariate analysis. (TABLE 2)

Among re-listed children, 12.1% (n=107) died awaiting re-transplantation, after a median (IQR) of 173 (41–460) days on the waitlist. (FIGURE 4) The median (IQR) age at death was 7.6(6.7–18.5) years. Of the 107 re-listed children who died on the waitlist, 36.5% were white, 31.8% black, 26.2% Hispanic. Graft failure was the primary cause of death in only 13.1%. After reviewing categorical and text variables that described contributing cause, no additional cases of graft failure were identified.

The relationship of graft failure to death after re-listing was otherwise difficult to determine, as the most commonly listed primary cause of death in this group was “non-specific” (28.0%), followed by multi-organ system failure (27.1%), infection (10.3%), and hemorrhage (7.5%). Causes of death for patients that had been re-listed but died on the waitlist are detailed in SUPPLEMENTAL TABLE 3. No relisted patients were reported to have died of trauma or suicide.

Among re-listed patients, those who died awaiting re-transplant had significantly higher bilirubin, creatine, and PELD/MELD score at the time of re-listing than those who received a second transplant (SUPPLEMENTAL TABLE 4). Even amongst those for whom graft failure was not listed as the primary cause of death, levels of median (IQR) levels for bilirubin were 13.5 (4.5–22.5) mg/dL, creatinine were 0.7 (0.43–1.16) mg/dL and laboratory PELD/MELD score were 16 (11–27) at re-listing, indicative of graft dysfunction.

Of re-listed pediatric LT recipients, 78.3% (n=691) underwent re-transplant prior to the end of 2018, including 8 that died during the re-transplant surgery. The median time between the two transplants was 5.7 years (IQR 2.5–11.9 years) and the median time from re-listing to re-transplant was 122 days (IQR 36–313 days). Thirty remained on the waitlist at last follow-up, and 19 were reported lost to follow-up despite re-listing.

3.3 Late graft loss, and death secondary to graft failure:

After index LT, 765 children lost their grafts during long-term follow-up (8.2% of the total cohort), including the 691 re-transplanted and 74 that died with graft failure as the reported primary cause of death. Among these 74 children, only 19% had been re-listed prior to

death. Centers are able to select multiple reasons for graft loss but the top reasons provided were chronic rejection (n=276), followed by unknown (n=199) and biliary tract complication (n=107) (SUPPLEMENTAL TABLE 5).

The median (IQR) time from index LT to graft loss for the 765 children was 5.9 (2.5–12.4) years; median (IQR) age at graft loss was 10.2 (4.9–17.2) years. Graft loss also occurred at a steady rate over time in the long-term, with a lower but still steady rate of graft failure over time in more recent decades (FIGURE 5).

In univariable analysis, risk of graft loss was increased in children who were 4–12 years at index LT, Black, had public insurance, listed as status 1A, or transplanted for acute liver failure, in earlier decades (1990–99 and 2000–09), or at low-volume pediatric LT centers. Graft loss was less likely to occur in those who were transplanted for non-cirrhotic disease, had an active exception case at time of index LT, or were transplanted in high median MELD/PELD regions. Risk of late graft loss differed by UNOS Region. (SUPPLEMENTAL TABLE 6)

In multivariable analysis, children of Black or Hispanic race/ethnicity and those listed as status 1A had a higher risk of late graft loss, after controlling for UNOS Region. Age, sex, insurance type, LT indication, donor type, transplant decade and having an active MELD/PELD exception were not significant predictors of late graft loss. (TABLE 3)

3.4 Death during follow-up

Among all pediatric LT recipients with more than1 year of graft survival, 736 children (7.9%) died more than 1 year after the index LT. Deaths occurred at a median (IQR) of 6.74 (2.37–13.22) years after transplant.

Graft failure was reported as the primary cause of death in 10.1% of all late deaths. Causes that might have been related to cumulative immunosuppression toxicity accounted for 26% of deaths, including infection (n=90), malignancy (n=95), and renal failure (n=5).

Lack of specificity in cause of death reporting hindered interpretation of the roles of either graft failure or immunosuppression in 24% of cases, as the most common causes of death reported were non-specific (n=177) and multiorgan failure (SUPPLEMENTAL TABLE 7). Only 7 children died from trauma/suicide, accounting for 0.9% of late post-transplant deaths. None who died had been classified as lost to follow-up.

4 Discussion:

Among children 0–12 year old who have undergone LT in the United States since 1990, 16% have unknown outcomes after being lost to long-term follow-up, and another 8% with graft loss, leaving nearly 25% of pediatric transplant recipients with unknown or poor outcomes. The 16% that are lost to follow-up highlights that literature reporting on the longest-term outcomes after pediatric LT—those that follow children into adulthood—exclude a significant percentage of the total pediatric LT population. The OPTN registry is more comprehensive than any other dataset available on U.S. LT recipients. But the significant portion of pediatric LT recipients lost to follow-up, even after being transplanted

at a young age and followed for several years before young adulthood hinders accurate delineation of long-term graft and patient outcomes.

This analysis expands our understanding of the impact of losses to follow-up in pediatric solid organ transplant recipients, by including the youngest LT recipients, extending the length of follow-up considered, and examining the implications of these “missing children” on our understanding of overall outcomes for this population. Significant loss to follow-up rates in all pediatric solid organ transplant recipients has been reported from the UNOS database, specifically inspiring recent guidance on successful transition for these children from pediatric to adult transplant care. This prior report focused on 10-years post-LT, and found similar rates of loss to follow-up among children < 12 (6.8% vs. 8.6% in our study for those transplanted between 2000–2009); we also included children < 6.[4] In our analysis, including a longer follow-up period highlights that the rate of loss to follow-up increased distinctly during early adulthood for children transplanted at any age, not just adolescents.

The transition from pediatric to adult care in late adolescence or early adulthood is an extremely vulnerable time for pediatric LT recipients for non-adherence, loss to follow-up, and graft loss or death. [5] In pediatric kidney transplant recipients, 40% had graft failure within 36 months of transfer from pediatric to adult care.[6] Recent single-center studies of pediatric LT recipients also reported alarmingly high death rates after transition, 28% of 32 young adults in New York, and 28% of 64 in Atlanta. [7, 8] In the latter group, 55% of deaths occurred within 5 years after transition of care. [8] Although our data confirms that young adulthood is a vulnerable time across transplant centers, the OPTN registry unfortunately does not include data on transition of care from the pediatric to an adult center, so we were not able to specifically evaluate the impact of this transition on lost to follow-up, graft dysfunction, or graft loss.

To more fully characterize long-term outcomes, we also explored re-listing for LT as a proxy for significant graft dysfunction. One in 10 pediatric LT recipients required re-listing during long-term follow-up. Although most of these children were re-transplanted, 12% died awaiting re-LT. Cholestasis and hypoalbuminemia in these re-listed children suggest that graft dysfunction was long-standing prior to re-listing. But diagnoses listed on re-listing were frequently the indication for initial LT which is likely inaccurate since pediatric liver diseases rarely recur. Among children with graft loss, 26% of children did not have a reported specific cause. Given that ideal outcomes for children include many decades of expected post-LT survival, standardized, pediatric-specific variables to record reasons for re-listing and graft loss should be strongly considered.

Our study also identified racial disparities in long-term outcomes; Black and Hispanic children were more likely to require re-listing and to lose their grafts, even after adjusting for LT indication, other patient characteristics, transplant characteristics, and LT center volume. One previous single-center study found that African Americans had higher rates of death after transition to adult transplant centers, with nearly 50% mortality at 20 years after initial LT.[8] This may be related to disparities such as lack of resources for these children overtime, leading to non-adherences overtime. Further prospective studies are necessary

in the future to better understand the impact of socioeconomic deprivation on impact of transplant outcomes.[9]

Limitations of our study relate to its dependence on retrospective data. Although the OPTN registry is more comprehensive than any other dataset available on LT recipients in the U.S. a significant proportion of pediatric LT recipients are lost to follow-up, hindering an accurate depiction of long-term graft dysfunction or loss and their risk factors. In addition, the UNOS STAR files report the date of loss to follow-up almost immediately following the last known visit for the vast majority of those lost. For most analyses, this convention prevents counting unknown time as reported follow-up; but for our analysis, this prevents a full depiction of the interval between the last recorded follow-up and the patient truly being "lost." This time period may be a critical window for intervention to maintain follow-up. A study in-depth using medical records may be informative as to issues and strategies.

Similarly, lack of specificity about causes of death makes it difficult to determine the impact of graft dysfunction and other co-morbidities survival after pediatric LT. In a previous analysis using SPLIT data, Soltys and colleagues found that late graft loss was caused by acute or chronic rejection in almost 50% of cases,[10] slightly higher than our cohort's reported prevalence of 41%. The frequent missingness of this critical data point is a limitation of our study, and poses a major barrier to accurately and comprehensively understanding long-term outcomes after pediatric LT. It and could be remedied by increased accountability and incentives for centers to track children in the longer-term, particularly as they transition to adults. This would necessarily apply to both the transplanting pediatric center and the adult centers to which these patients presumably transfer.

Current consensus guidelines from both American Association for the Study of Liver Diseases and European Society for Pediatric Gastroenterology, Hepatology and Nutrition encompass not only short-term but also long-term goals for children's health and well-being that extend beyond the survival of a graft. [11, 12] The OPTN registry provides critical infrastructure for collecting meaningful long-term data on pediatric LT recipients. But system improvements and transplant center incentives are needed to improve the quality and comprehensiveness of data for this important cohort. Clarifying the definition of when a patient is "lost to follow-up," and including detail about transfer of care to another center would help accurately reporting of patient status. Reporting long-term outcomes and losses to follow-up as a quality or performance metric could incentivize centers to improve long-term data collection. Providing internet or app-based opportunities for patients to self-report—with reminders by text or email—could help reduce missing data without increasing burden on transplant centers. Additional resources to help pediatric centers accurately report causes of and contributing factors to death, and potentially incorporation of variables specific to pediatric LT in the OPTN registry, would help us understand late mortality and other outcomes over decades.

Although reported outcomes over the medium and longer-term after pediatric LT are generally optimistic, our analysis highlights that most reports have not painted a complete picture of outcomes for all transplanted children. The assumption should not be that since these lost children are not reported as dead that they are actually healthy, well, or receiving

optimal support from our healthcare system. Within the current system, it is feasible – and should be more strongly incentivized or even required – to more accurately report on how transplanted children are doing. Our analysis also highlighted the problematic transition of care period, and the need for future observational and interventional work to improve care in the future. Comprehensive, accurate, and truly long-term data collection is essential to understanding the health of this vulnerable population and to accurately identify opportunities for care improvement for subset(s) of children who face the highest risk of poor outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement:

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

Abbreviations:

AASLD	American Association for the Study of Liver Diseases
CI	Confidence Interval
ESPGHAN	European Society for Pediatric Gastroenterology, Hepatology and Nutrition
IQR	Interquartile range
LT	Liver transplant
MELD	Model for End-Stage Liver Disease
OPTN	Organ Procurement and Transplantation Network
PELD	Pediatric end-stage Liver Disease
SHR	Subdistribution hazard ratio
SPLIT	Society of Pediatric Liver Transplantation’s registry
STAR	Standard Transplant Analysis and Research
UNOS	United Network for Organ Sharing

U.S. United States

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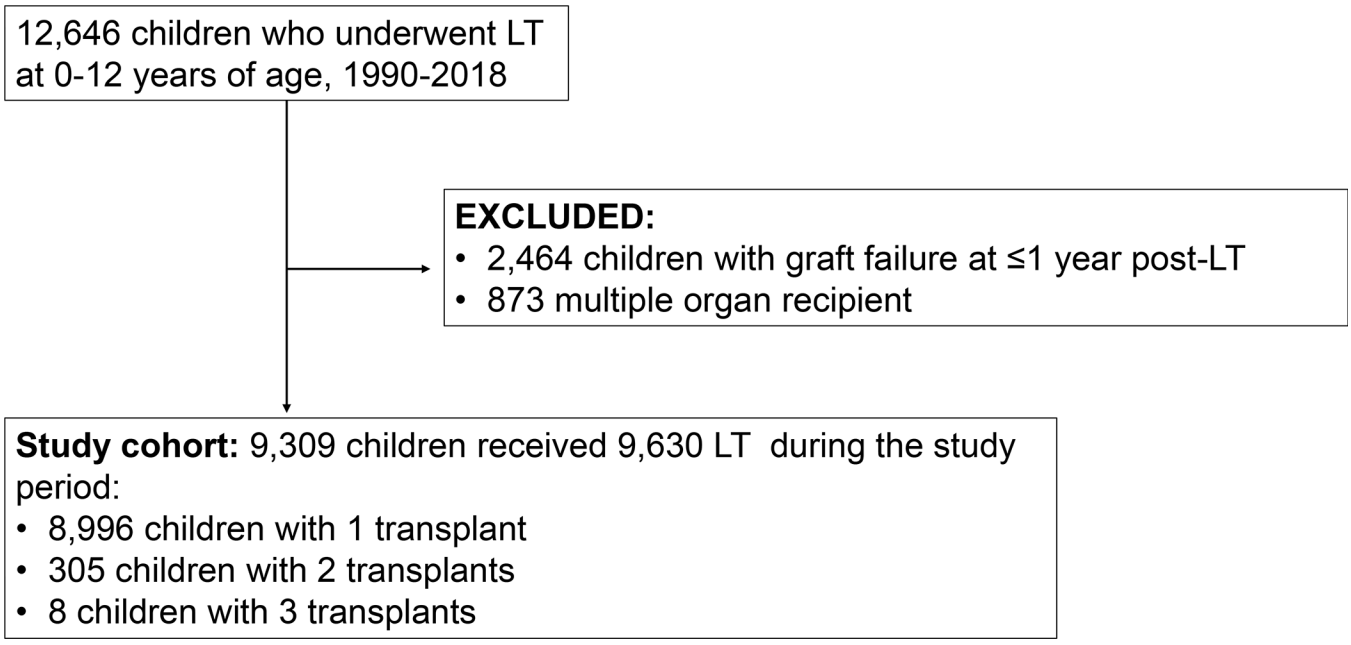


Figure 1:
Inclusion and exclusion criteria for the study cohort

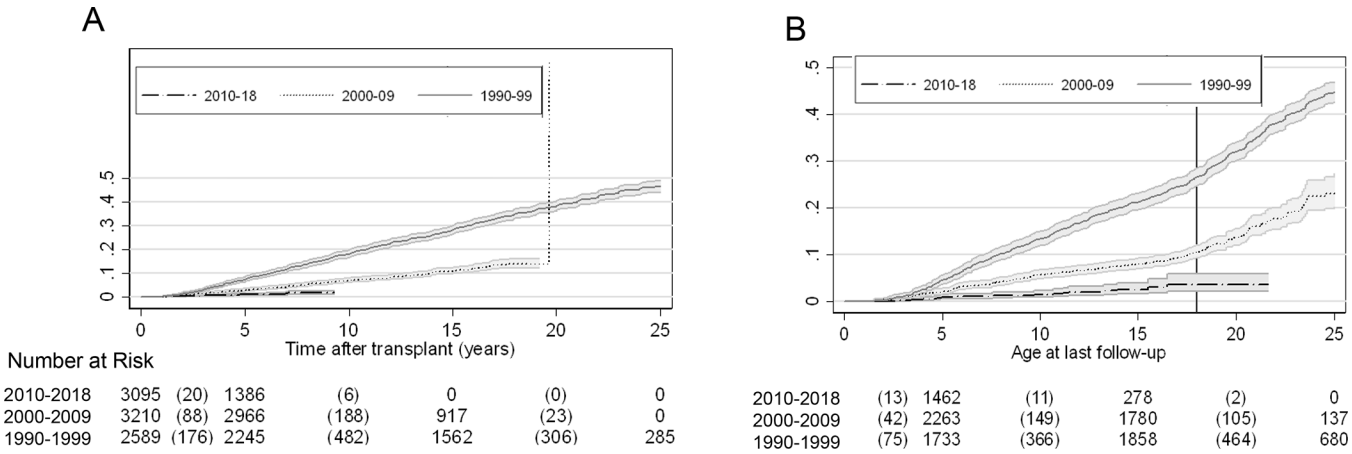
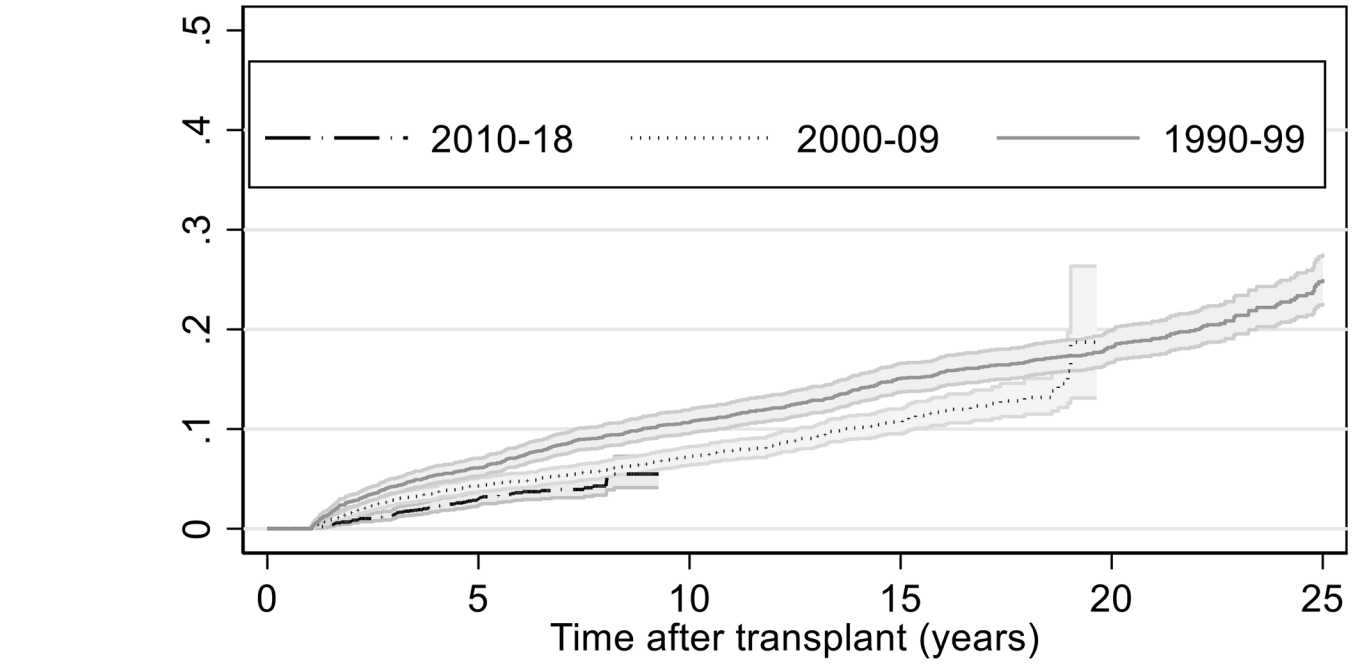


Figure 2:

Rates of lost to follow-up among pediatric LT recipient by decade of transplant (a) by years since transplant and (b) by age at last reported follow-up. At risk table includes number at risk at 0, 5, 15 and 25 years with numbers in ( ) representing number of lost to follow-up by that time period.



Number at Risk

2010-2018	3086	(65)	1366	(17)	0	(0)	0
2000-2009	3307	(138)	2963	(147)	895	(20)	0
1990-1999	2916	(170)	2439	(202)	1626	(101)	289

Figure 3:

Rate of re-listing for repeat LT after pediatric LT, by decade of index LT. At risk table includes number at risk at 0, 5, 15 and 25 years with numbers in ( ) representing number of re-listing by that time period.

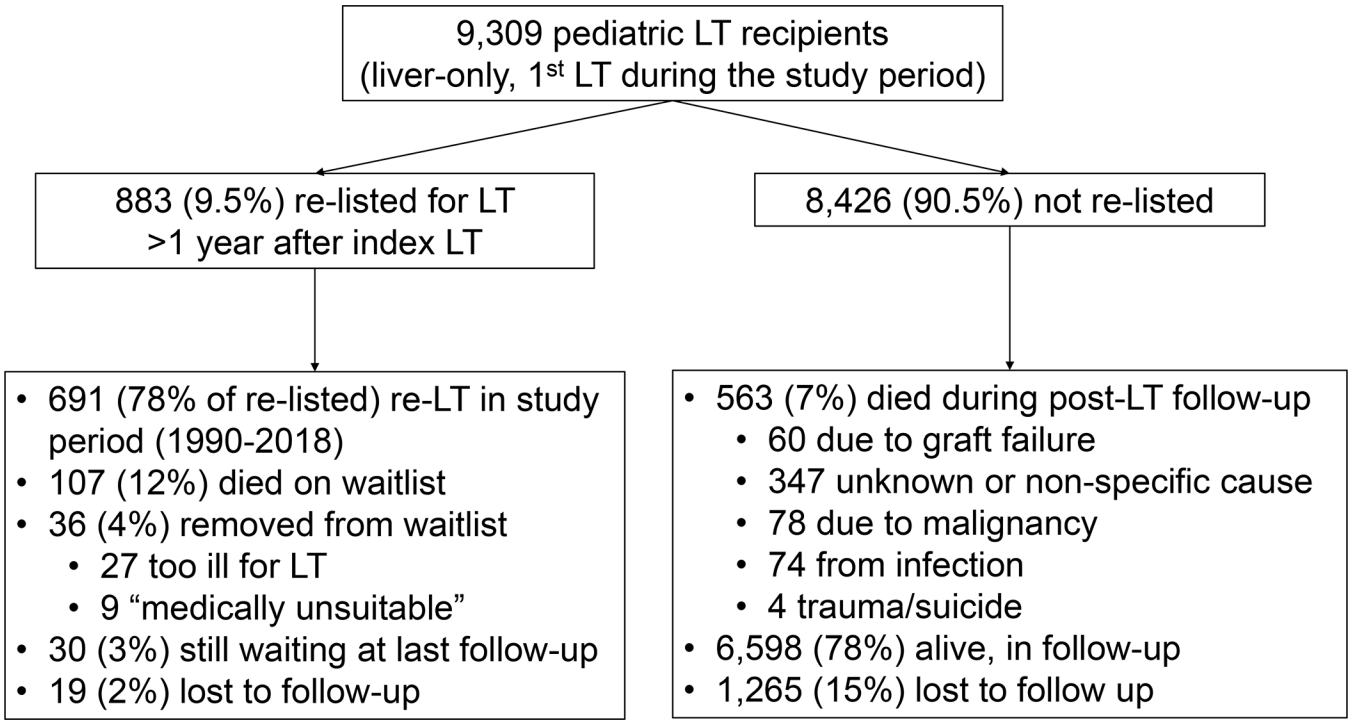
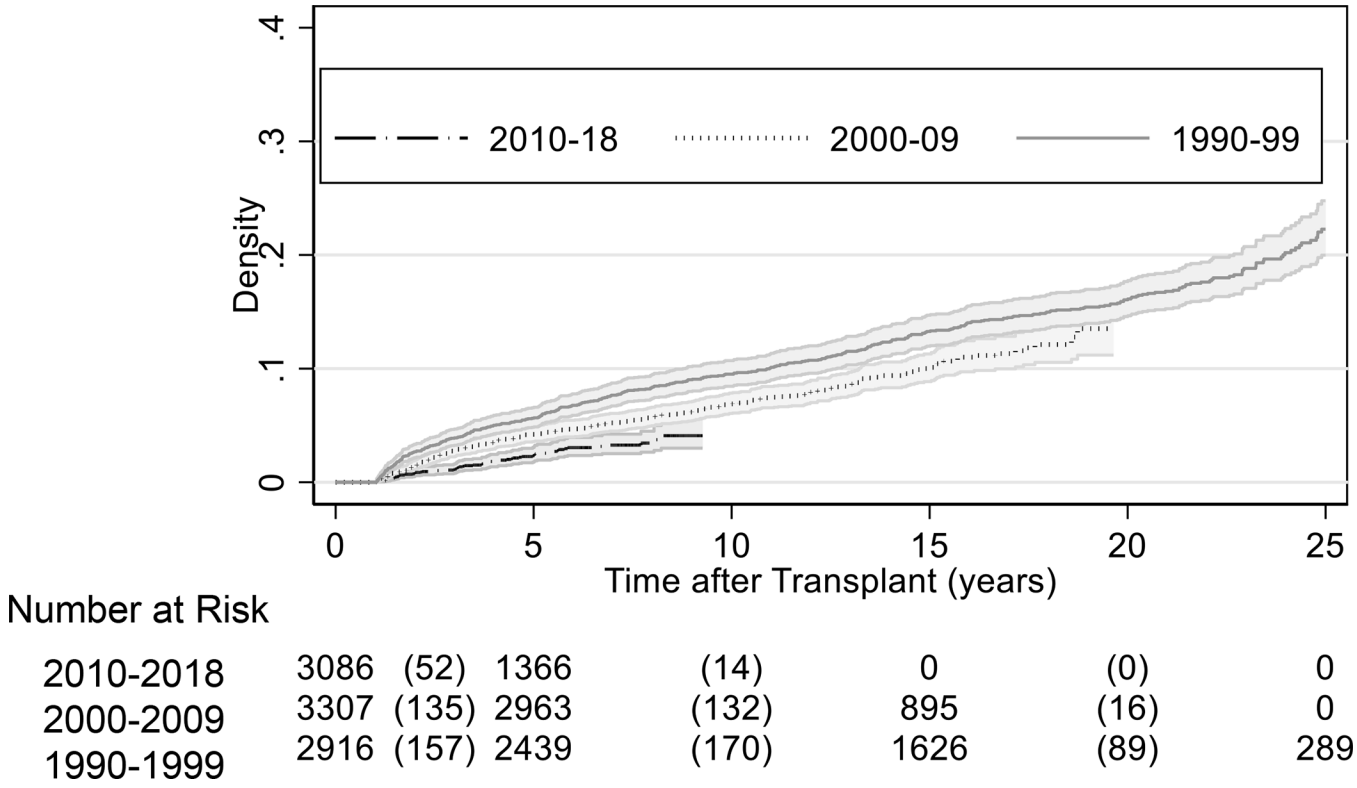


Figure 4:
Long-term outcomes for pediatric LT recipients



Number at Risk

2010-2018	3086	(52)	1366	(14)	0	(0)	0
2000-2009	3307	(135)	2963	(132)	895	(16)	0
1990-1999	2916	(157)	2439	(170)	1626	(89)	289

Figure 5:

Rates of late graft loss in pediatric LT recipients, by years post-LT and decade of index LT. At risk table includes number at risk at 0, 5, 15 and 25 years with numbers in ( ) representing number of late graft loss by that time period.

TABLE 1:

Multivariable analysis of risk factors for being lost to follow-up post-LT

	SHR	95% CI	P
Age at transplant			
<4 years	Ref		
4–12 years	1.40	1.24–1.58	<0.001
Female	0.86	0.77–0.96	0.007
Indications for transplant ‡			
Biliary atresia	Ref		
Other cirrhotic disease	0.88	0.76–1.01	0.060
Acute liver failure	0.80	0.67–0.96	0.018
Other non-cirrhotic disease	0.85	0.69–1.05	0.130
Unknown/not specified	1.06	0.64–1.74	0.828
Transplant year			
1990–99	8.40	5.66–12.45	<0.001
2000–09	3.18	2.13–4.76	<0.001
2010–18	Ref		
Pediatric transplant center volume, average annual 1990–2018			
0–5 per year	1.63	1.35–1.98	<0.001
6–15 per year	Ref		
>15 per year	1.14	1.01–1.28	0.038
UNOS region			
1 (CT, ME, MA, NH, RI, VT-East)	0.97	0.66–1.42	0.860
2 (DE, DC, MD, NJ, PA, WV, VA)	1.59	1.28–1.97	<0.001
3 (AL, AR, FL, GA, LA, MS, PR)	Ref		
4 (OK, TX)	1.89	1.48–2.41	<0.001
5 (AZ, CA, NV, NM, UT)	1.38	1.12–1.71	0.003
6 (AK, HI, ID, MT, OR, WA)	0.61	0.31–1.20	0.151
7 (IL, MN, ND, SD, WI)	1.21	0.95–1.54	0.115
8 (CO, IA, KS, MO, NB, WY)	0.64	0.49–0.85	0.002
9 (NY, VT-West)	1.09	0.79–1.49	0.592
10 (IN, MI, OH)	0.54	0.39–0.74	<0.001
11 (KY, NC, SC, TN, VA)	0.31	0.18–0.51	<0.001

‡**Other cirrhotic disease** includes: Alagille syndrome, alpha-1-antitrypsin deficiency, choledochal cyst, cystic fibrosis, glycogen storage disease, progressive intrahepatic cholestatic syndromes, total parenteral nutrition cholestasis, primary sclerosing cholangitis or primary biliary cirrhosis, idiopathic cholestasis, congenital hepatic fibrosis, autoimmune hepatitis cirrhosis, drug toxicity, hepatitis C cirrhosis, non-alcoholic steatohepatitis cirrhosis, unknown cirrhosis, chronic rejection/graft failure, inborn errors in bile acid metabolism, Wilson's disease.

Other non-cirrhotic disease includes: tumors without underlying cirrhosis, primary hyperoxaluria, maple syrup urine disease, trauma, urea cycle defects, mitochondrial disease/encephalopathy, ethylmalonic encephalopathy, Budd-Chiari, Crigler-Najjar, tyrosinemia, hyperlipidemia/homozygous hypercholesterolemia. **Acute liver failure** includes diagnoses coded or text-described as "acute liver failure", "fulminant liver failure", or "fulminant" without other specifying diagnosis.

TABLE 2:

Multivariable analysis of predictors of relisting for transplant, >1 year post-LT, in pediatric LT candidates (N=9,630)

	SHR	95% CI	P
Ethnicity ¶			
White	Ref		
Black	1.71	1.23–2.37	0.001
Hispanic	1.56	1.13–2.15	0.007
Other	1.02	0.62–1.68	0.925
Status at transplant			
Listed by MELD/PELD	Ref		
Status 1A	1.56	1.11–2.20	0.011
Status 1B	0.99	0.64–1.53	0.973
UNOS Region			
1 (CT, ME, MA, NH, RI, VT-East)	0.57	0.26–1.24	0.156
2 (DE, DC, MD, NJ, PA, WV, VA)	0.64	0.40–1.04	0.072
3 (AL, AR, FL, GA, LA, MS, PR)	Ref		
4 (OK, TX)	0.67	0.41–1.10	0.115
5 (AZ, CA, NV, NM, UT)	0.48	0.30–0.77	0.002
6 (AK, HI, ID, MT, OR, WA)	1.09	0.53–2.27	0.813
7 (IL, MN, ND, SD, WI)	0.81	0.49–1.34	0.414
8 (CO, IA, KS, MO, NB, WY)	0.91	0.55–1.50	0.722
9 (NY, VT-West)	0.65	0.36–1.16	0.148
10 (IN, MI, OH)	0.66	0.38–1.13	0.126
11 (KY, NC, SC, TN, VA)	1.07	0.62–1.84	0.807

¶ **Other race/ethnicity** includes Asian, Pacific Islander, Native American, Alaskan, Hawaiian, Multiracial

TABLE 3:

Multivariable analyses of predictors of late graft failure/loss in pediatric liver transplant candidates

	SHR	95% CI	P
Ethnicity ¶			
White	Ref		
Black	1.48	1.04–2.12	0.030
Hispanic	1.45	1.02–2.06	0.037
Other	0.96	0.56–1.64	0.883
Status at transplant			
Listed by MELD/PELD	Ref		
Status 1A	1.56	1.09–2.25	0.016
Status 1B	0.92	0.57–1.48	0.721
UNOS Region			
1 (CT, ME, MA, NH, RI, VT-East)	0.61	0.28–1.31	0.204
2 (DE, DC, MD, NJ, PA, WV, VA)	0.50	0.30–0.82	0.006
3 (AL, AR, FL, GA, LA, MS, PR)	Ref		
4 (OK, TX)	0.43	0.24–0.76	0.004
5 (AZ, CA, NV, NM, UT)	0.34	0.21–0.57	<0.001
6 (AK, HI, ID, MT, OR, WA)	0.76	0.34–1.70	0.501
7 (IL, MN, ND, SD, WI)	0.57	0.33–0.99	0.046
8 (CO, IA, KS, MO, NB, WY)	0.93	0.57–1.51	0.771
9 (NY, VT-West)	0.46	0.24–0.87	0.018
10 (IN, MI, OH)	0.57	0.33–0.99	0.047
11 (KY, NC, SC, TN, VA)	1.03	0.60–1.76	0.925

¶**Other race/ethnicity** includes Asian, Pacific Islander, Native American, Alaskan, Hawaiian, Multiracial