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Denise Lo Date

Waitlist Outcomes After Acuity Circle-Based Distribution in Pediatric Liver Transplantation

By

Denise Lo
Master of Public Health

Executive Master of Public Health

Katherine Ross-Driscoll
Committee Chair

Joseph Magliocca
Committee Member

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By

Denise Lo
BA, Northwestern University, 2002
MD, Northwestern University Feinberg School of Medicine, 2006

Thesis Committee Chair: Katherine Ross-Driscoll, PhD, MPH

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Abstract

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By Denise Lo

Pediatric liver transplant (LT) waitlist mortality has been stagnant for several years. In 2020, the Organ Procurement and Transplantation Network (OPTN) implemented acuity circles (AC)-based liver distribution and national pediatric prioritization of pediatric donor livers. Using OPTN data, waitlist outcomes for pediatric LT candidates listed between February 4, 2016 and February 3, 2024, were studied by age group and era relative to AC implementation. There were 5,605 pediatric waitlist registrations and 3,778 pediatric liver transplants during the study period. At 1 year, cumulative incidence of transplant was 77.8% pre-AC vs 79.9% post-AC, while cumulative incidence of mortality was 5.4% pre-AC vs 5.9% post-AC. Median allocation MELD/PELD at LT significantly decreased across all age groups post-AC ($p<0.001$). For candidates age 12-17 years, cumulative incidence of transplant increased (65.6% pre-AC to 79.5% post-AC at 1 year), median time to transplant decreased (66 days pre-AC to 37 days post-AC, $p<0.001$), and proportion of recipients receiving pediatric donor livers increased (37.9% pre-AC vs 66.2% post-AC, $p<0.001$). AC group was associated with increased likelihood of waitlist mortality for those age 1-5 years and increased likelihood of transplant for those age 12-17 years. LT candidates age 12-17 years derived the most benefit from AC-based liver distribution.

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Chapter 1

Background Literature Review

Liver transplantation (LT) is a life-saving therapy with restoration of quality of life for pediatric patients with severe liver disease. In 2023, 534 pediatric liver transplants were performed in the United States.[1] Annual data published by the Organ Procurement & Transplantation Network (OPTN) and Scientific Registry of Transplant Recipients (SRTR) showed that leading indications for pediatric LT in 2022 were biliary atresia (37.3%), other/unknown diagnosis (23.4%), metabolic disease (15.0%), and acute liver failure (9.5%).[2] Trends in both the volume and indications for pediatric LT have remained stable over time. Types of liver allograft used in pediatric LT include whole organs from deceased donors or technical variant (TV) liver allografts from deceased or living donors. TV liver allografts include deceased donor split liver grafts, deceased donor partial (reduced sized) grafts, or living donor partial grafts.[3,4] Trends in use of whole organ or technical variant grafts have remained stable from 2012-2022; in 2022, graft type in pediatric LT included 59.7% whole liver, 23.2% partial liver, and 17.1% split liver.[2]

Unfortunately, every year pediatric candidates die awaiting LT or are removed from the waitlist for being too sick to transplant. Pediatric liver waitlist mortality in 2022 was 6.0 deaths per 100 patient-years and has been remained unchanged since 2017.[2] Although the highest waitlist mortality was still found in candidates < 1 year of age, there was a substantial decrease in waitlist mortality in this age group in 2022 compared to 2021 (9.4 deaths vs 21.7 deaths per 100 patient-years).[2] High waitlist mortality in this youngest age group is likely due to a combination of factors, including lack of size-matched whole organ donors necessitating reliance on TV liver allografts that require more surgical expertise to recover and transplant.[5,6]

The pediatric liver transplant community has set a goal to eliminate pediatric waitlist mortality and strongly advocates for organ allocation policies that prioritize the pediatric population.[5] There are ethical justifications and international consensus statements that support giving additional priority to children in the allocation of resources. In 1924, the League of Nations adopted the Geneva Declaration of the Rights of the Child, which states that humanity “owes to the Child the best that it has to give.”[7] With similar

sentiment, the United Nations (UN) General Assembly adopted the Declaration of the Rights of the Child in 1959. This UN Declaration states that the child, "by reason of his physical and mental immaturity, needs special safeguards and care" and "shall enjoy special protection, and shall be given opportunities and facilities, by law and by other means, to enable him to develop physically, mentally, morally, spiritually and socially in a healthy and normal manner…"[8]

These declarations of the rights of children can be applied to the allocation of life-saving resources such as donor organs to children in need. The National Organ Transplant Act (NOTA) was passed in 1984 to address the nation's critical organ donation shortage.[9] NOTA established the OPTN as a private, non-profit entity to govern organ donation and transplantation. The mission of the OPTN is to promote "maximized organ supply, effective and safe care, and equitable organ allocation and access to transplantation."[10] NOTA also gave special acknowledgement to pediatric populations, mandating the OPTN to "recognize the differences in health and in organ transplantation issues between children and adults throughout the system and adopt criteria, policies, and procedures that address the unique health care needs of children."[9]

In 2014, the OPTN Pediatric and Ethics Committees jointly published a guidance document to address organ allocation policy for children with adherence to the NOTA mandate and ethical framework.[11] This guidance document cites four ethical principles supporting the need for pediatric prioritization in donor organ allocation and includes the Prudential Lifespan Account, the Fair Innings Argument, the "Maximin" Principle, and the concept of utility. The Prudential Lifespan Account asks that each individual account for how they would want resources allocated over their lifespan.[12] Understanding that age is a universal trait and that a child's cognitive and physical development are impaired from chronic disease,[13] the Prudential Lifespan Account supports the prioritization of children in donor organ allocation. The Fair Innings principle argues that everyone deserves the opportunity to live a full life and lifespan and that society should allocate resources so that all individuals have this opportunity.[14] This implies that pediatric

populations with end-stage organ failure should have every opportunity to receive the life-saving organ transplant that would allow them to enjoy a full lifespan. The "Maximin" Principle argues to *maxi*mize the *min*imum benefit to the least advantaged population or, in other words, give priority to the most disadvantaged populations.[15] Children are regarded as disadvantaged by their inherent vulnerability, the lack of size-matched donor organs, and the known deleterious effects of end-stage organ failure on development and growth in childhood.[13] Finally, the principle of utility argues that children are positioned to maximize life-years provided by each donor organ due to lack of other chronic comorbidities.[11] In total, there is substantial ethical justification to provide pediatric populations priority in donor organ allocation.

Donor liver allocation policy in the United States has undergone several major changes in the quest to maximize utilization and equitably allocate organs. Initially, candidates were allocated donor livers within their local organ procurement organization (OPO) donor service area (DSA) based on candidate severity of illness (classified by location at home, hospitalized, intensive care unit) and accrued time on the waitlist.[16] Since both factors were able to be manipulated independent of medical necessity, the allocation system needed more objective criteria. In 1997, the Child-Turcotte-Pugh score was adopted but still incorporated subjective components and was not validated for predicting waitlist mortality.[16] Finally, in 2002, the Model for End-Stage Liver Disease (MELD) score was adopted for liver allocation.[16] The MELD score was originally developed to estimate 90-day mortality after undergoing a transjugular intrahepatic portosystemic shunt (TIPS) procedure for portal hypertension and was found to be a good surrogate for estimated mortality while awaiting liver transplantation.[16,17] The MELD score was calculated using serum bilirubin, creatinine, and international normalized ratio (INR), and ultimately was used for liver allocation for adults and children aged 12 years and older.

The Pediatric Model for End-Stage Liver Disease (PELD) score was developed based on data from 884 patients enrolled in the Studies of Pediatric Liver Transplantation (SPLIT) registry and calculated using serum bilirubin, INR, albumin, age less than 1 year, and growth failure.[18] Adopted in 2002, and later

restricted to children less than 12 years old in 2005, the PELD allocation system introduced a much more objective national allocation scheme compared to prior iterations. The allocation policy also allowed transplant programs to apply for non-standard exception points on a case-by-case basis. Transplant programs would petition transplant regional review boards for a higher PELD score by providing a written narrative to illustrate their patient's increased medical necessity and justify higher priority in allocation.

Over the next few years after implementation, there was lingering concern that PELD did not accurately estimate mortality risk for pediatric populations based on the widespread use of non-standard exception scores. Shneider et al. found that 53% of transplants did not use actual calculated PELD scores to determine liver allocation. Instead, 24% of transplants occurred in patients granted PELD exception scores, and 29% of transplants occurred in high acuity (Status 1) candidates that did not have acute liver failure.[19] During a slightly earlier time period, Salvalaggio et al. found that 52% of all pediatric transplant recipients utilized actual calculated PELD score, 18% used non-standard PELD exception scores, and 30% were classified as status 1.[20] Both studies demonstrated wide regional variation in use of exception scores suggesting lack of standardization in listing practices and allocation.[19,20] Requests for non-standard exception points increased over 5-fold between 2002 and 2013,[21] and from 2009-2014, 41% of all pediatric transplant recipients achieved transplant with non-standard PELD exception scores.[22] In 2016, Chang et al. found concordance between actual calculated PELD scores and mortality, but that the estimated 90-day mortality using PELD score underestimated the actual pretransplant probability of death by up to 17%.[23] This study explained the prevalent use of non-standard PELD exception scores in pediatric LT and provided critical data to scrutinize a system that integrated adult and pediatric transplant candidates into a single allocation schema while simultaneously underestimating pediatric waitlist mortality. Together, these data created a compelling argument for additional pediatric candidate prioritization, both to ensure fair organ allocation to pediatric populations and to adhere to ethical mandates to protect children.

An important aspect in prioritizing liver allocation for children includes the prioritization of pediatric donor livers for pediatric transplant candidates, which has been woven into allocation policy over the past 2 decades.[24] An early study in the pre-MELD era found that pediatric graft survival was significantly superior when pediatric recipients received a pediatric graft compared to an adult graft.[25] Since that time, there has been a deliberate effort to prioritize pediatric candidates for pediatric liver grafts. In 2002, livers from pediatric donors were first allocated to pediatric candidates with a greater than 50% probability of death within 90 days as estimated by PELD.[16] Adults received 60% of pediatric donor livers in the pre-MELD/PELD era, and 54% after MELD/PELD implementation. Livers from pediatric donors age 9 or older were much more likely to be placed into adult recipients (83% pre-MELD/PELD vs 77% post-MELD/PELD).[16] Livers were geographically distributed based on local DSA and regional boundaries, suggesting that there may have been no eligible pediatric recipients in the local or regional area for those pediatric organs that were transplanted into adults. Since older pediatric donors more closely approximate adult size, adult allocation of pediatric livers was even more pronounced for older pediatric donors.

As pediatric waitlist mortality remained stagnant over the years, more data emerged citing the need for improved pediatric prioritization for pediatric organs. Ge et al analyzed nearly 3,500 pediatric donor offers from 2010 to 2014 and found that 45% of pediatric donor livers were transplanted into adult recipients.[26] Of those transplants, 390 adults were transplanted with a pediatric liver before any pediatric candidate had been offered that organ. Similarly, Hsu et al found that from 2007 to 2014, 143 children died or were delisted for being too sick to transplant without receiving a single liver offer.[27] Both these studies suggested that the DSA/regional system for distribution of pediatric livers did not provide enough access to donor livers for children awaiting transplant. Adults were still being prioritized ahead of children such that some children died or became too sick to transplant without ever receiving a single organ offer. Therefore, in February 2020, in conjunction with another major overhaul in geographic liver distribution, OPTN further increased prioritization of pediatric candidates for pediatric donor livers such

that livers from all pediatric donors less than 18 years old are allocated to national pediatric candidates and status 1A (acute liver failure) adults before all non-status 1A adults.[28] The effect of national pediatric organ prioritization on pediatric LT waitlist metrics has not been studied.

The recent major national policy change in liver distribution occurred on February 4, 2020, when OPTN eliminated liver distribution based on DSAs and regional boundaries (which were mostly drawn using state lines) in favor of distribution based on geographic distance from a deceased donor.[29] These concentric acuity circles (AC) were drawn at a radius of 150, 250, and 500 nautical miles around the donor hospital so that allocation was jointly tiered based on medical acuity (MELD/PELD) and geographic distance from the donor (concentric circles). The primary goal of AC-based distribution was to reduce the variability in median MELD at transplant that might reflect geographic disparities in access to transplantation.[29]

OPTN liver policy proposals are studied using the SRTR Liver Simulated Allocation Model (LSAM) during the policy evaluation period to examine the predicted effect of policy proposals. Although AC-based distribution was primarily intended to address geographic disparities in adult LT, LSAM projections for pediatric LT over a 3-year time period were that AC-based distribution would result in significantly less waitlist mortality, significantly more transplants, and significantly lower PELD/MELD at LT for infants, children, and teenagers. Additionally, AC-based distribution would result in allocation of 77% of pediatric donor livers to pediatric candidates compared to only 46% in DSA and region-based allocation.[30] Although these were encouraging findings, a study published in 2021, the year after AC implementation, found that the SRTR LSAM predicted accept/decline decisions much worse for pediatric candidates compared to adults, and predictive performance declined as pediatric populations got younger.[31] Since LSAM did not accurately account for pediatric-specific clinical decision making, there was potential for inaccurate prediction of the effect of ACs and all other allocation policies pertaining to pediatric LT where LSAM had been applied.

Since the implementation of AC-based distribution in 2020, there has been some published data on the effect of this allocation policy. OPTN released a review of key numerical findings in the 2-years post AC implementation.[32] They reported 716 more adult and 84 fewer pediatric deceased donor liver transplants, 207 fewer adult and 18 fewer pediatric candidate waitlist removals for death or too sick to transplant, and 1005 more adult and 69 fewer pediatric deceased donor livers recovered. Transplant rates were significantly increased for MELD/PELD 15 or lower, 29 or higher, and Status 1A/1B candidates. National mean transplant score decreased from 35 to 30 for pediatric transplant recipients. The effects of AC-based distribution appear to be heterogeneous, with disparate effects based on MELD score,[32,33] transplant center practices,[33,34] and graft type.[35]

In a rapidly changing policy landscape since AC-based distribution was implemented, other significant national policy changes have occurred. Centers for Medicare & Medicaid Services (CMS) adopted new OPO performance metrics designed to improve OPO performance and increase organ donation.[36,37] New versions of the MELD and PELD scores (MELD 3.0 and PELD-Cr, respectively) have been adopted to decrease disparities driven by older versions of MELD and PELD.[38] These concurrent policy changes may have obscured studying the effects of AC-based distribution in isolation and may have contributed to the paucity of research on the effect of AC-based distribution on pediatric LT.

Overall, national liver allocation policy has evolved in an effort to fulfill many competing, but not mutually exclusive, priorities. Children merit unique consideration in liver allocation to ensure equitable distribution of organs, minimize waitlist mortality, and protect a vulnerable population. In 2020, OPTN enacted AC-based distribution and national prioritization of pediatric livers to pediatric LT candidates. The purpose of this thesis is to understand the effect of these recent policy changes on important pediatric LT waitlist metrics, including waitlist mortality and time to transplant. Quantifying the effect of these policy changes will provide feedback to the liver transplant community and may inform policy decisions,

which occur in an iterative fashion. If the most recent policy changes produced a substantial decrease in pediatric liver waitlist mortality and time to transplant, this will affirm the current policy. If there was no impact or a negative impact on waitlist and transplant metrics for children, more work must be done to improve liver allocation. Future steps could include further pediatric prioritization for adult livers that may be split or size-reduced for children. The United States can also learn from the global transplant community and consider additional pediatric prioritization tactics that have been successful internationally.[39,40] Future decisions are contingent upon quantifying the effect of the most recent OPTN policy changes.

Student Contribution

Study design, data analysis, writing, figures and tables

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Chapter 2

Journal Article

Waitlist Outcomes After Acuity Circle-Based Distribution in Pediatric Liver Transplantation

Denise J. Lo[1], Joseph F. Magliocca[2], Katherine Ross-Driscoll[3,4,5]

1 Department of Surgery, Emory University School of Medicine, Atlanta, GA, USA
2 Department of Surgery, Vanderbilt University Medical Center, Nashville, TN, USA
3 Department of Surgery, Indiana University, Indianapolis, IN, USA
4 Regenstrief Institute, Indianapolis, IN, USA
5 Department of Epidemiology, Emory University Rollins School of Public Health, Atlanta, GA, USA

Corresponding Author:
Denise J. Lo, MD
Division of Transplantation
Emory University School of Medicine
1364 Clifton Road NE, B222
Atlanta, GA 30322, USA
Email: denise.lo@emory.edu

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Abstract

Pediatric liver transplant (LT) waitlist mortality has been stagnant for several years. In 2020, the Organ Procurement and Transplantation Network (OPTN) implemented acuity circles (AC)-based liver distribution and national pediatric prioritization of pediatric donor livers. Using OPTN data, waitlist outcomes for pediatric LT candidates listed between February 4, 2016 and February 3, 2024, were studied by age group and era relative to AC implementation. There were 5,605 pediatric waitlist registrations and 3,778 pediatric liver transplants during the study period. At 1 year, cumulative incidence of transplant was 77.8% pre-AC vs 79.9% post-AC, while cumulative incidence of mortality was 5.4% pre-AC vs 5.9% post-AC. Median allocation MELD/PELD at LT significantly decreased across all age groups post-AC ($p<0.001$). For candidates age 12-17 years, cumulative incidence of transplant increased (65.6% pre-AC to 79.5% post-AC at 1 year), median time to transplant decreased (66 days pre-AC to 37 days post-AC, $p<0.001$), and proportion of recipients receiving pediatric donor livers increased (37.9% pre-AC vs 66.2% post-AC, $p<0.001$). AC group was associated with increased likelihood of waitlist mortality for those age 1-5 years and increased likelihood of transplant for those age 12-17 years. LT candidates age 12-17 years derived the most benefit from AC-based liver distribution.

Introduction

Liver transplantation (LT) is a life-saving therapy with restoration of quality of life for pediatric patients with severe liver disease. Pediatric candidates for LT are prioritized for deceased donor organs according to their Pediatric End-Stage Liver Disease (PELD) (for ages less than 12 years) or Model for End-Stage Liver Disease (MELD) (age 12 years or older) score. Unfortunately, pediatric liver waitlist mortality was 6.0 deaths per 100 patient-years in 2022 and has remained stagnant since 2018.[2] The limited size-matched allograft options as well as complexities associated with technical variant graft use reduce access to LT for pediatric waitlist candidates.[41] Prior studies have suggested that the donor specific area (DSA) and region-based allocation system did not provide enough access to LT for pediatric candidates. Ge et al found 45% of pediatric donor livers were transplanted into adult recipients from 2010 to 2014.[26] Of those transplants, 390 adults were transplanted with a pediatric liver before any pediatric candidate had been offered that organ. Similarly, Hsu et al found that from 2007 to 2014, 143 children died or were delisted for being too sick to transplant without receiving a single liver offer.[27]

On February 4, 2020, OPTN changed distribution of deceased donor livers from DSA and region-based allocation to acuity circles (AC), a hybrid of clinical urgency, determined by MELD/PELD score, and geographic distance from the donor hospital.[29] Embedded within AC distribution, OPTN increased priority granted to pediatric candidates for pediatric donor livers such that livers from all donors less than 18 years old were allocated to national pediatric candidates and status 1A adults before all non-status 1A adults.[28] Although AC-based distribution was primarily intended to address geographic disparities in adult LT, the Scientific Registry for Transplant Recipients (SRTR) Liver Simulated Allocation Model (LSAM) projected that AC-based distribution would result in significantly lower pediatric waitlist mortality, more pediatric transplants, and lower PELD/MELD score at transplant for infants, children, and teenagers over a 3-year time period.[30] Additionally, AC-based distribution was projected to result in allocation of 77% of pediatric donor livers to pediatric candidates compared to only 46% in DSA and region-based allocation.[30]

Although these were encouraging projections, a study published in 2021, the year after AC implementation, found that the SRTR LSAM predicted accept/decline decisions less accurately for pediatric candidates compared to adults, and predictive performance declined as pediatric populations got younger.[31] Since LSAM might not accurately account for pediatric-specific clinical decision making, there was potential for LSAM to inaccurately predict the effect of AC policy on pediatric LT. Given the major shift in liver distribution, we sought to quantify the effect of AC policy and pediatric prioritization 4 years after policy implementation.

Materials and Methods

Study Population

This study used data from the Scientific Registry for Transplant Recipients (SRTR). The SRTR data system includes data on all donor, waitlisted candidates, and transplant recipients in the US, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration, US Department of Health and Human Services, provides oversight to the activities of the OPTN and SRTR contractors. This study was acknowledged by the Institutional Review Board at Emory University School of Medicine as being except from review.

The study cohort included patients less than 18 years old registered on the liver transplant waitlist from February 4, 2016 to February 3, 2024. Patients with simultaneous transplant waitlisting for organs other than kidney were excluded. On February 4, 2020, the acuity circles (AC) liver distribution policy went into effect. The cohort was divided into pre-AC (February 4, 2016 – February 3, 2020) and post-AC (February 4, 2020 – February 3, 2024) cohorts based on date of liver waitlist registration. Each registration was followed for the primary events of transplant or waitlist mortality, where waitlist mortality was defined as removal from waitlist for death or being too sick to transplant. Registrants that experienced neither primary event or were removed from the liver transplant waitlist for other reasons

were censored on date of waitlist removal or end of the cohort date, whichever was first. Deceased donors were considered pediatric if they were less than 18 years old at the time of organ donation.

Variables

Candidate demographic and clinical variables were included in the analysis if they were deemed to have plausible clinical relevance to likelihood of waitlist mortality or transplantation. These variables included age at time of waitlist registration, gender, race, blood type, history of previous liver transplant, indication for transplant, initial laboratory MELD/PELD score at listing, and urgency status as determined by allocation MELD/PELD score. Since pediatric patients vary tremendously in size, physiology, and development across a relatively small age range, age as a categorical variable was used throughout the analysis. Given the smaller group sizes after age stratification, race, blood type, and indication for transplant were transformed into dichotomous variables to ensure adequate sample sizes for analysis. MELD/PELD scores were also combined into wider, clinically relevant ranges to ensure adequate sample size.

The primary exposure was timing of waitlist registration relative to AC policy implementation. The primary outcome was cumulative incidence of waitlist mortality or transplant. Secondary outcomes included median time to transplant, allocation MELD/PELD score at transplant, and proportion of pediatric transplant recipients that received pediatric deceased donor livers.

Statistical Analysis

Descriptive statistics utilized counts and percentages to summarize categorical variables. Distribution summaries, including mean, median, and percentiles, were used for continuous variables. MELD/PELD scores below 0 defaulted to a value of 0 for numerical calculations. Median allocation MELD/PELD score was calculated after substituting a MELD/PELD score of 40 for all Status 1A and Status 1B listings. Chi-square testing was used to compare categorical variables, while a t-test was used to compare continuous

variables. A wilcoxon rank sum test was used to compare median values. Statistical tests were two-sided, and a p-value of <0.05 was used to determine statistical significance.

Cumulative incidence function was used to estimate probabilities of waitlist mortality or transplant. Total time to incident event was calculated from date of waitlist registration to date of primary event. Inactive days after waitlist registration were included in follow-up and counted in overall time to event.

Cause-specific hazard models were used to determine hazard ratios for the competing events of waitlist mortality or transplant. An age-stratified, multivariable cause-specific hazard model was used and included the transformed variables as described. Hazard ratios with 95% confidence intervals were reported. Data was analyzed using R version 4.3.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Characteristics of Waitlist Registrants and Transplant Recipients

There were 5,605 registrations added to the LT waitlist over the 8-year study period (Table 1). This ncluded 2,899 registrations pre-AC and 2,706 registrations post-AC. Among LT registrants, those in the pre-AC era were more likely to be younger (5.0 vs 5.4 years, p=0.01) and have a history of prior liver transplant (8.3% vs 6.7%, p=0.02). For both AC groups, the most common listing diagnosis was biliary atresia (30.7%). Most registrants (58.4%) were listed with a laboratory MELD/PELD score less than 15. Median initial allocation MELD/PELD score was 19 pre-AC and 17 post-AC (p=0.80), with a significant difference in the distribution (p<0.001). There were no differences in the median or distribution of laboratory MELD/PELD score. There were significant differences between pre-AC and post-AC groups in the distribution of race (p<0.001) and diagnosis at listing (p=0.04). Although the mean age between AC groups was significantly different, the age distribution was not.

Of the 5,605 waitlist registrations, there were 3,778 pediatric liver transplants during the 8-year study period: 1,949 transplants pre-AC and 1,829 transplants post-AC (Table 2). Eleven recipients with most recent listing status reported as "inactive" were excluded. Mean age at transplant was 4.8 years pre-AC and 5.4 years post-AC (p=0.002). There was a significant difference in age distribution (p = 0.003) with a higher proportion of those 12 years and older transplanted in the post-AC group (22.4% vs 17.4%). Between AC groups, there were significant differences in blood type (p=0.02) and indication for transplant (p=0.008). Among all recipients, the most common indication for transplant was biliary atresia (34.4%). Most transplant recipients (55.3%) had a laboratory MELD/PELD score of 14 or lower at time of transplant with no difference before or after AC policy. Median allocation MELD/PELD score at transplant was significantly decreased after AC policy implementation (MELD/PELD score 40 pre-AC vs 33 post-AC, p<0.001). There were more living donor liver transplants in the post-AC group (15.3% vs 13.1%, p=0.06).

Cumulative Incidence of Waitlist Mortality or Transplant

Overall, there was a higher cumulative incidence of transplant, especially in the first 180 days after listing, and no difference in waitlist mortality after AC implementation (Figure 1). After age stratification, the most striking change post-AC policy was in the 12-17 years group where there was a higher cumulative incidence of transplant (79.5% vs 65.6% at 365 days) and lower cumulative incidence of mortality (4.3% vs 6.0% at 365 days) throughout the first year on the waitlist (Table 3). Notably, the cumulative incidence of transplant in the 12-17 years group was lower than all other age groups at all timepoints pre-AC but became comparable to other age groups after AC implementation.

For candidates age < 1 year there was no difference in cumulative incidence of waitlist mortality or transplant between AC groups (Table 3). In the 1-5 years and 6-11 years groups, there was a lower cumulative incidence of transplant (77.8% vs 80.0%, 1-5 years; 76.9% to 78.6%, 6-11 years) and higher

cumulative incidence of mortality (5.5% vs 3.3%, 1-5 years; 4.1% to 2.8%, 6-11 years) at 365 days after AC implementation.

Multivariable Regression Analysis

Since AC policy had a differential impact on cumulative incidence of waitlist mortality and transplant across age groups, a multivariable cause-specific hazard model was developed after age stratification. In this model, there was increased risk of waitlist mortality in candidates aged 1-5 years after AC implementation (HR 1.79, 95% CI: 1.10, 2.89) (Table 4a). AC policy did not significantly change the risk of waitlist mortality in other age groups. Other variables that significantly increased risk of waitlist mortality included non-white race in the 1-5 years group and history of prior transplant in the 1-5 and 12-17 years groups. Allocation MELD/PELD score 25 and higher carried significant risk of waitlist mortality in the <1 year group. Allocation MELD/PELD score 35 and higher also increased waitlist mortality risk for age groups 1-5 years and 12-17 years. Status 1A or 1B listing significantly increased risk of waitlist mortality among all age groups. No factors were found to reduce risk of waitlist mortality in this model.

After AC implementation, the likelihood of transplant was significantly higher for candidates age 12-17 years (HR 1.46, 95% CI: 1.26, 1.68) and <1 year (HR 1.11, 95% CI: 1.00, 1.24) (Table 4b). The likelihood of transplant was not significantly affected by AC policy in other age groups. In candidates age 5 years or younger, transplant was more likely in non-O blood types and less likely to occur if there was a prior history of liver transplant. Similar to waitlist mortality, the likelihood of transplant was increased across all age groups when listed as Status 1A or 1B. Allocation MELD/PELD score 25-34 significantly increased the likelihood of transplant in age groups <1 year, 1-5 years, and 12-17 years. Allocation MELD score 35 or higher significantly increased likelihood of transplant in candidates ages 5 or younger. Non biliary atresia diagnosis significantly decreased the likelihood of transplant in those <1 year old.

Secondary Outcomes

The median time to transplant was significantly shorter after AC implementation (44 days vs 54 days, $p < 0.001$) (Table 5). After stratifying for age, only the 12-17 years age group experienced a statistically significant reduction in waiting time, with median time to transplant decreasing from 65.5 days to 37 days post-AC implementation ($p < 0.001$). Additionaly, median allocation MELD/PELD score was significantly decreased after AC implementation (MELD/PELD score 40 pre-AC vs 33 post-AC; $p < 0.001$) (Table 6). After age stratification, median allocation MELD/PELD score dropped significantly across all age groups with the largest numerical decrease in the age 12-17 years group (MELD/PELD score 37 pre-AC vs 23 post-AC ($p<0.001$).

Since pediatric prioritization for pediatric deceased donor livers changed with AC implementation, transplant with pediatric deceased donor livers among this cohort was analyzed before and after AC policy. Transplant recipients in the study cohort received livers from a total of 2,369 pediatric donors (73.0%) and 874 adult donors (27.0%) (Table 7). Recipients received 1,184 pediatric donor livers pre-AC and 1,185 pediatric donor livers post-AC (69.9% pre-AC vs 76.5% post-AC; $p < 0.001$). After stratifying transplant recipients based on their age at listing, there was no change in proportion of pediatric donors to candidates less than 12 years of age before and after AC policy. However, the proportion of pediatric deceased donor livers allocated to candidates age 12-17 years significantly increased after AC implementation (37.9% pre-AC vs 66.2% post-AC; $p < 0.001$).

Discussion

In this study the impact of AC policy on pediatric liver transplant waitlist registrants varied by age. Candidates age 12-17 years clearly derived the most benefit from AC policy, presumably because they received pediatric donor livers that previously were offered first to non-status 1A adult recipients in their UNOS region under DSA and region-based liver allocation. No other age group demonstrated a significant increase in transplants using pediatric deceased donor livers after AC implementation. Accordingly, median time to transplant decreased across all age groups, but most dramatically in the age

12-17 years group. Median MELD/PELD allocation score for transplant significantly decreased post-AC policy across all age groups, similar to the findings published by OPTN after 2 years of follow-up post-AC policy[32], but the largest numerical decrease in median allocation MELD/PELD score was in the age 12-17 years group.

Conversely, there was increased cumulative incidence of waitlist mortality and decreased cumulative incidence of transplant among pediatric candidates ages 1 to 11 years, and AC policy was associated with increased likelihood of waitlist mortality in the 1-5 years age group. The number of deceased adult donors, but not pediatric donors, increased dramatically in the post-AC period. OPTN reported 1005 more adult and 69 fewer pediatric deceased donor livers recovered in the 2 years post AC policy implementation.[32] Unfavorable outcomes in the age 1-5 years group could have been related to a natural declination in pediatric liver donors in the years after AC policy implementation. Additionally, it is possible that livers ideal for splitting were allocated to high MELD adults over a much larger geographic area under AC policy, thus limiting the opportunities for deceased donor split LT with left lobe or left lateral segment allografts in this younger age group. Risk of waitlist mortality and likelihood of transplant were not affected by AC policy in candidates <1 year old. This age group may have remained unaffected due to availability of living donor LT as well as ABO-incompatible transplantation for recipients with acceptable anti-ABO titers, neither of which should be affected by AC policy.

These study findings raise important questions regarding how to further increase access to liver transplantation for small pediatric candidates, especially those less than 5 years old, who have limited opportunities to receive size-matched organs. Previous studies have cited the low number of split liver transplants performed in the US compared to the number of splitable deceased donor livers available.[42] Several pediatric prioritization tactics designed to increase the number of pediatric liver transplants have been successful internationally.[39,40] Future policy considerations in the US should include primary allocation of ideal adult livers to pediatric candidates as a liver segment before whole organ offers to

adults below a pre-determined MELD threshold. Similar "intention to split" policies have been effective strategies in Italy and the United Kingdom to increase split LT and reduce pediatric waitlist mortality.[43,44] Any new allocation policy must improve access to transplant for pediatric candidates while maintaining access to LT for adult candidates. Policies that encourage split LT would increase the overall number of transplants performed and benefit both pediatric and adult populations.

Currently, there is wide variation in the proportion of technical variant (TV) graft use among pediatric LT programs in the US, with most TV LT performed at a small concentration of transplant programs.[6,45] High volume TV LT programs were shown to have equivalent outcomes between TV grafts and whole organs,[46] and transplant program TV graft use is associated with lower waitlist mortality.[6] Similarly, pediatric living donor LT programs are limited but are critical to ensure that our youngest candidates have appropriate access to LT.[47] Access to nearby transplant center with sufficient experience utilizing TV grafts must be more widely available to achieve high quality outcomes for all pediatric candidates. Opportunities exist to develop multi-institutional collaborations, regional partnerships, and formal training pathways to facilitate broader access to all types of LT.[5] Advances in machine perfusion technology may allow livers to be split while on a machine perfusion device or provide machine perfusion preservation of TV allografts after split,[48,49] mitigating some of the current surgical expertise, geographic, and time constraints associated with split LT.

This study analyzed a large population of pediatric LT waitlist registrants 4 years before and after AC policy implementation. However, there were significant national policies and events that may have affected the interpretation of these results. Policies introduced post-AC include new Centers for Medicare & Medicaid Services (CMS) organ performance organization (OPO) performance metrics designed to increase organ donation[36,37] and new versions of the MELD and PELD scores (MELD 3.0 and PELD-Cr, respectively).[38] Since many of the recent gains in organ donation include older, Hepatitis C-viremic, or donation after circulatory determination of death donors[50] that were unlikely to be accepted for pediatric

recipients,[2] recent increases in adult organ donation may not have directly impacted pediatric LT waitlist outcomes. Establishment of the National Liver Review Board in May 2019 could have impacted allocation MELD/PELD scores, which were lower across all age groups in the post-AC era. Lastly, the COVID-19 pandemic in early 2020 may have caused a limited period of alteration in clinical practice across transplant programs and OPOs that could have resulted in higher waitlist mortality, decreased likelihood of transplant, or delay in transplantation for pediatric LT candidates.

Overall, national liver allocation policy has evolved in an effort to fulfill many competing, but not mutually exclusive, priorities. Children merit unique consideration in liver allocation to equitably distribute organs, minimize waitlist mortality, and protect a vulnerable population. Although AC policy appears to have improved transplant access for older pediatric candidates, opportunities remain to increase access for the youngest liver transplant candidates.

Tables and Figures

Table 1. Characteristics of pediatric registrants on the liver transplant waitlist

	Pre-AC (n=2899) n (%)	Post-AC (n=2706) n (%)	p-value
Age, mean (years)	5.0	5.4	0.01
Age categories			0.07
Age < 0 years	966 (33.3)	891 (32.9)	
Age 1-5 years	896 (30.9)	791 (29.2)	
Age 6-11 years	451 (15.6)	400 (14.8)	
Age 12-17 years	586 (20.2)	624 (23.1)	
Gender			0.14
Male	1465 (50.5)	1313 (48.5)	
Female	1434 (49.5)	1393 (51.5)	
Race			<0.001
White	1427 (49.2)	1249 (46.2)	
Black	474 (16.4)	476 (17.6)	
Asian	213 (7.3)	167 (6.2)	
Hispanic	683 (23.6)	687 (25.4)	
Other	102 (3.5)	115 (4.2)	
Missing	0	12	
Blood type			0.07
O	1468 (50.6)	1369 (50.6)	
A	965 (33.3)	894 (33.0)	
B	390 (13.5)	340 (12.6)	
AB	76 (2.6)	103 (3.8)	
Previous Liver Transplant			0.02
Yes	242 (8.3)	181 (6.7)	
No	2657 (91.7)	2525 (93.3)	
Diagnosis at Listing			0.04
Acute liver failure	303 (10.5)	332 (12.3)	
Biliary atresia	908 (31.3)	815 (30.1)	
Other cholestatic disorders	322 (11.1)	286 (10.6)	
Malignancy	234 (8.1)	223 (8.2)	
Metabolic disorders	398 (13.7)	325 (12.0)	
Other	733 (25.3)	719 (26.6)	
Missing	1	6	
Lab MELD/PELD at listing			
MELD/PELD, median (IQR)	11 [0, 21]	12 [0, 22]	0.14
MELD/PELD 14 or lower	1706 (58.8)	1567 (57.9)	0.15
MELD/PELD 15-24	682 (23.5)	603 (22.3)	
MELD/PELD 25-34	344 (11.9)	339 (12.5)	
MELD/PELD 35-39	74 (2.6)	83 (3.1)	

MELD/PELD 40+	93 (3.2)	114 (4.2)	
Urgency Status at listing			
MELD/PELD, median (IQR)	19 [8, 35]	17 [8, 40]	0.80
MELD/PELD 14 or lower	1138 (39.3)	1094 (40.4)	<0.001
MELD/PELD 15-24	536 (18.5)	461 (17.0)	
MELD/PELD 25-34	398 (13.7)	193 (7.1)	
MELD/PELD 35-39	83 (2.9)	141 (5.2)	
MELD/PELD 40+	49 (1.7)	42 (1.6)	
Status 1A	402 (13.9)	426 (15.7)	
Status 1B	211 (7.3)	206 (7.6)	
Inactive	82 (2.8)	143 (5.3)	

Table 2. Characteristics of pediatric liver transplant recipients

	Pre-AC (n = 1949) n (%)	Post-AC (n = 1829) n (%)	p-value
Age, mean (years)	4.8	5.4	0.002
Age categories			0.003
Age < 0	569 (29.2)	528 (28.9)	
Age 1-5	725 (37.2)	621 (34.0)	
Age 6-11	315 (16.2)	271 (14.8)	
Age 12-17	320 (16.4)	380 (20.8)	
Age 18+	20 (1.0)	29 (1.6)	
Gender			0.12
Male	1003 (51.5)	894 (48.9)	
Female	946 (48.5)	935 (51.1)	
Race			0.08
White	967 (49.6)	881 (48.2)	
Black	316 (16.2)	318 (17.4)	
Asian	138 (7.1)	113 (6.2)	
Hispanic	470 (24.1)	442 (24.2)	
Other	58 (3.0)	70 (3.8)	
Missing	0	5 (0.3)	
Blood Type			0.02
O	959 (49.2)	886 (48.4)	
A	657 (33.7)	629 (34.4)	
B	278 (14.3)	230 (12.6)	
AB	55 (2.8)	84 (4.6)	
Previous Liver Transplant			0.07
Yes	124 (6.4)	90 (4.9)	
No	1825 (93.6)	1739 (95.1)	
Indication for transplant			0.008
Acute liver failure	203 (10.4)	185 (10.1)	
Biliary atresia	664 (34.1)	634 (34.7)	
Other cholestatic disorders	243 (12.5)	216 (11.8)	
Malignancy	202 (10.4)	187 (10.2)	
Metabolic disorders	347 (17.8)	270 (14.8)	
Other/unknown	290 (14.9)	332 (18.2)	
Missing	0	5 (0.3)	
Lab MELD/PELD at transplant			
MELD/PELD, median (IQR)	12 [0, 24]	13 [0, 23]	1.0
MELD/PELD 14 or lower	1074 (55.1)	1015 (55.5)	0.36
MELD/PELD 15-24	420 (21.5)	417 (22.8)	
MELD/PELD 25-34	291 (14.9)	240 (13.1)	
MELD/PELD 35-39	82 (4.2)	68 (3.7)	
MELD/PELD 40+	82 (4.2)	89 (4.9)	

Urgency Status at transplant			
MELD/PELD, median (IQR)	40 [30, 40]	33 [14, 40]	<0.001
MELD/PELD 14 or lower	176 (9.0)	481 (26.3)	<0.001
MELD/PELD 15-24	123 (6.3)	254 (13.9)	
MELD/PELD 25-34	296 (15.2)	197 (10.8)	
MELD/PELD 35-39	226 (11.6)	175 (9.6)	
MELD/PELD 40+	385 (19.8)	93 (5.1)	
Status 1A	277 (14.2)	241 (13.2)	
Status 1B	466 (23.9)	388 (21.2)	
Donor Type			0.06
Deceased	1694 (86.9)	1549 (84.7)	
Living	255 (13.1)	280 (15.3)	

Figure 1. Cumulative incidence of event for pediatric liver waitlist additions by era

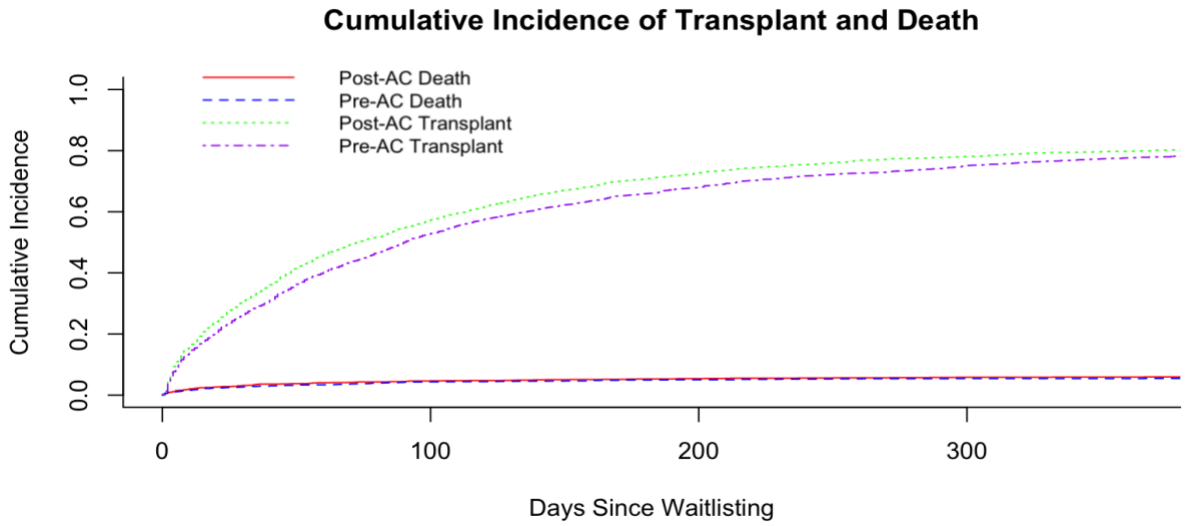

Table 3. Cumulative incidence of transplant or death for pediatric liver waitlist additions by AC and age group

Age Group	Outcome	90d		180d		365d	
		Pre-AC (%)	Post-AC (%)	Pre-AC (%)	Post-AC (%	Pre-AC (%)	Post-AC (%)
Overall	Transplant	50.0	54.8	65.9	70.7	77.8	79.9
	Death	4.2	4.4	4.9	5.3	5.4	5.9
<1 yr	Transplant	53.4	55.5	71.9	74.0	82.7	83.0
	Death	6.2	6.3	7.7	7.9	8.2	8.0
1-5 y	Transplant	53.3	54.2	67.9	68.7	80.0	77.8
	Death	2.9	4.7	3.2	4.9	3.3	5.5
6-11 y	Transplant	50.7	53.5	65.7	68.9	78.6	76.9
	Death	2.3	2.4	2.6	3.0	2.8	4.1
12-17 y	Transplant	38.6	55.2	52.6	68.9	65.6	79.5
	Death	4.3	2.5	4.9	3.2	6.0	4.3

Table 4a. Multivariable cause-specific hazard model for waitlist mortality stratified by age

	Age < 1 yr	Age 1-5 y	Age 6-11 y	Age 12-17 y
AC Group (Ref: pre-AC)	1.07 (0.76, 1.50)	1.79 (1.10, 2.89)	1.38 (0.64, 2.95)	0.65 (0.37, 1.11)
Race (Ref: White)				
Non-white	1.51 (1.07, 2.13)	2.00 (1.22, 3.29)	1.15 (0.53, 2.50)	1.29 (0.76, 2.17)
Blood group (Ref: O)				
Non-O	0.97 (0.70, 1.36)	1.38 (0.87, 2.21)	0.59 (0.27, 1.31)	0.74 (0.43, 1.27)
Previous Liver Transplant	0.56 (0.25, 1.25)	4.34 (2.58, 7.31)	1.59 (0.55, 4.66)	3.86 (2.11, 7.05)
Indication for transplant (Ref: biliary atresia)				
Non biliary atresia	1.13 (0.73, 1.74)	1.95 (0.85, 4.48)	1.89 (0.55, 6.51)	1.54 (0.53, 4.39)
Urgency Status at listing (Ref: MELD/PELD 24 or lower)				
MELD/PELD 25-34	2.34 (1.37, 4.02)	2.17 (0.85, 5.55)	0.44 (0.06, 3.32)	2.01 (0.92, 4.39)
MELD/PELD 35 or higher	2.84 (1.55, 5.21)	4.80 (2.04, 11.3)	0.68 (0.09, 5.18)	4.66 (1.72, 12.7)
Status 1A or 1B	7.55 (4.47, 12.7)	5.29 (2.93, 9.58)	3.19 (1.25, 8.16)	11.4 (5.93, 21.9)

Table 4b. Multivariable cause-specific hazard model for transplant stratified by age

	Age < 1 yr	Age 1-5 y	Age 6-11 y	Age 12-17 y
AC Group (Ref: pre-AC)	1.11 (1.00, 1.24)	1.04 (0.93, 1.17)	0.96 (0.82, 1.12)	1.46 (1.26, 1.68)
Race (Ref: White)				
Non-white	1.00 (0.90, 1.11)	0.97 (0.87, 1.09)	0.89 (0.76, 1.04)	0.91 (0.79, 1.05)
Blood group (Ref: O)				
Non-O	1.12 (1.00, 1.24)	1.34 (1.20, 1.50)	1.09 (0.93, 1.28)	1.12 (0.97, 1.29)
Previous Liver Transplant	0.40 (0.27, 0.58)	0.75 (0.60, 0.93)	0.84 (0.64, 1.10)	0.84 (0.65, 1.09)
Indication for transplant (Ref: biliary atresia)				
Non biliary atresia	0.75 (0.65, 0.86)	0.96 (0.82, 1.11)	0.95 (0.77, 1.17)	1.14 (0.90, 1.44)
Urgency Status at listing (Ref: MELD/PELD 24 or lower)				
MELD/PELD 25-34	1.94 (1.64, 2.28)	1.39 (1.14, 1.70)	0.97 (0.71, 1.32)	1.51 (1.23, 1.87)
MELD/PELD 35 or higher	1.73 (1.40, 2.15)	1.64 (1.29, 2.09)	1.35 (0.96, 1.89)	0.81 (0.50, 1.33)
Status 1A or 1B	2.92 (2.38, 3.59)	2.84 (2.46, 3.27)	3.06 (2.47, 3.78)	3.48 (2.85, 4.25)

Table 5. Median time to transplant for pediatric liver waitlist registrants

	Pre-AC n=1949 [IQR]	Post-AC n=1829 [IQR]	p-value
Overall	54 [17, 127]	44 [14, 111]	<0.001
< 1 years	58 [22, 114]	52 [20, 115]	0.30
1-5 years	49 [15, 124]	42 [12, 109]	0.06
6-11 years	53 [13, 130]	40 [12, 102]	0.05
12-17 years	65.5 [11, 175]	37 [7, 104]	<0.001

Table 6: Median allocation MELD/PELD at LT by age

	Pre-AC n=1949 [IQR]	Post-AC n=1829 [IQR]	p-value
Overall	40 [30, 40]	33 [14, 40]	<0.001
< 1 years	40 [35, 40]	35 [17, 40]	<0.001
1-5 years	40 [30, 40]	40 [12, 40]	<0.001
6-11 years	40 [28, 40]	32 [6, 40]	<0.001
12-17 years	37 [30, 40]	23 [12, 40]	<0.001

Table 7. Proportion of pediatric LT recipients receiving pediatric or adult deceased donor livers

	Era						
	Pre-AC (n=1694) (%)			Post-AC (n=1549) (%)			
Candidate Age	Total	Pediatric Donor	Adult Donor	Total	Pediatric Donor	Adult Donor	p-value
Total	1694	1184 (69.9)	510 (30.1)	1549	1185 (76.5)	364 (23.5)	<0.001
<1	575	453 (78.8)	122 (21.2)	507	418 (82.4)	89 (17.6)	0.15
1-5 years	531	409 (77.0)	122 (23.0)	407	313 (76.9)	94 (23.1)	1.0
6-11 years	282	206 (73.0)	76 (27.0)	250	199 (79.6)	51 (20.4)	0.10
12-17 years	306	116 (37.9)	190 (62.1)	385	255 (66.2)	130 (33.8)	<0.001

Chapter 3

Future Directions/Public Health Implications

This thesis examined the relationship between AC liver distribution policy and the outcome of pediatric waitlist registrants listed for LT. Although AC policy increased access to LT for older pediatric waitlist registrants, these results suggest that AC distribution and pediatric prioritization for pediatric donor livers still does not provide sufficient access to LT for all individuals on the pediatric waitlist. Additional strategies are necessary to further reduce — or eliminiate — waitlist mortality for all children awaiting LT. Two areas of opportunities to increase access to LT include expanding the donor pool and increasing pediatric priority in the overall deceased donor liver allocation system.

One method of increasing the donor liver pool includes increasing usage of technical variant (TV) grafts, or partial liver transplantation, in the form of living donor liver transplantation (LDLT) or split liver transplantation (SLT). Historically, TV grafts were associated with higher complications rates, but modern era data suggest equivalent results between TV grafts and whole liver grafts, especially when performed at high volume LT centers.[46] Living donation is also a source of additional donor livers.[51] Unfortunately, TV grafts are underutilized due to multiple factors, including increased surgical complexity, limited surgical expertise, and resource constraints.[45] Concerted efforts should be made by LT programs to train and hire a surgeon workforce that can utilize TV grafts sucessfully.[5]

Internationally, others have implemented deceased donor liver allocation strategies designed to increase the use of SLT. The Queen Elizabeth University Hospital, a combined pediatric and adult LT center in Birmingham, United Kingdom, established an “Intention to Split” policy and eliminated pediatric waitlist mortality at their center during the 4 years prior to study publication in 2017.[43] In Italy, a national mandatory split liver policy was enacted to allocate splittable livers to pediatric LT candidates as the primary recipient for a split liver graft as long as there were no adult candidates listed with MELD score 30 or higher.[44] After the national mandatory split liver policy went into effect in 2015, the SLT rate increased from 6% to 8.4%, median pediatric LT waitlist time dropped from 229 to 80 days, and post-transplant outcomes before and after the mandatory split liver policy were similar.

In these two international examples of successful split liver policies, success was predicated on clear definitions of splittable livers, defined allocation pathways, standardized operative protocols for anatomic division of the liver and vasculature, cooperation between adult and pediatric transplant programs, and availability of appropriately trained surgical expertise. In the United States, there is tremendous opportunity to refine national allocation policy and enhance surgical training and institutional collaboration, which may improve access to LT for pediatric transplant candidates and reduce pediatric waitlist mortality.

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