IMPROVING OUTCOMES FOR CHILDREN WITH END-STAGE LIVER DISEASE THROUGH GREATER USE OF TECHNICAL-VARIANT GRAFTS

by
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A dissertation submitted to Johns Hopkins University in conformity with the requirements for the degree of Doctor of Philosophy

Baltimore, Maryland
October 2018

ABSTRACT

Pediatric liver transplantation provides life-saving therapy to children with end-stage liver disease but more widespread use is greatly hindered by the availability of deceased donor organs. Newer surgical techniques that use partial grafts (i.e., “technical-variant transplantation), including living-donor liver transplantation (LDLT) and split liver transplantation (SLT), allow for opportunities to increase the supply of organs and reduce waitlist mortality and morbidity.

To understand the potential benefit of these technical-variants grafts, we first conducted an analysis of patient and graft survival using the Scientific Registry of Transplant Recipients (SRTR) to determine if there was a change in outcomes over time associated with use of these newer surgical procedures. We subsequently explored outcomes for children on the liver transplant waitlist using SRTR and determined how waitlist outcomes, including living donation, vary based on sociodemographic characteristics. In order to better understand why African Americans and individuals on public assistance use LDLT at lower rates, we conducted a survey of potential barriers for parents of children with ESLD or transplant recipients including an assessment of their understanding of LDLT, its process, risks and harms. Finally, we performed an analysis of effect modifiers for SLT using SRTR data to identify which candidates had worse relative outcomes with SLT compared to WLT, and which candidates had similar outcomes irrespective of graft type.

We determined that, for pediatric (<18 years) candidates from 2002-2009, post-transplant mortality for whole liver transplant (WLT, 95%) was similar to LDLT (96%; P = 0.2) but worse for SLT (92%; P = 0.002). Since 2010, mortality for WLT (95%) was

worse than LDLT (98%; *P* = 0.01) and similar to SLT (95%; *P* = 0.7). We also showed that individuals were half as likely to use LDLT if they were on public assistance (sHR: $_{0.43}0.52_{0.63}$) or African American (sHR: $_{0.41}0.56_{0.75}$). Our survey demonstrated that many individuals in the pediatric liver transplant community are not aware of the steps for LDLT evaluation (28% unaware), who to ask (10%), that the procedure is covered by insurance (31%), and what the impact might be on the donor's work (24%) or health (25%). These barriers were generally seen in higher frequencies for individuals that are often disadvantaged (e.g., beneficiaries of public insurance). Finally, we identified subgroups of individuals that experienced higher graft failure following SLT compared to WLT including individuals with non-BA congenital cholestasis (aHR: $_{1.10}2.09_{3.97}$) or metabolic disease (aHR: $_{1.06}1.57_{2.28}$), as well as children between 10-35 kg (aHR: $_{1.10}1.37_{1.70}$).

Collectively, this research provides updated information regarding outcomes for these procedures, identifies barriers towards their application, and suggests potential clinical or policy changes that could promote their greater use.

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ACKNOWLEDGEMENTS

This work was supported by a Patient-Centered Outcomes Research Mentored Clinical Investigator Award from the Agency for Healthcare Research and Quality (AHRQ; K08 HS02387604). The contents of this dissertation are solely the responsibility of the author and do not necessarily represent the official views of the Johns Hopkins Medical Institutions or the AHRQ.

My deepest thanks and gratitude to the following:

Dr. John Bridges-

Thank you for your mentorship, and friendship, in my pursuits within the walls of the Johns Hopkins institutions, and outside.

Dr. Dorry Segev

Thank you for being a "pusher," for guiding me through all stages of the scientific process, and for sharing with me the application of innovative approaches to clinical problems.

Dr. Kathy Schwarz-

I have said it many times but now it will be enshrined on a shelf in Welch Library: Only you could have convinced me to move from San Francisco to Baltimore, and it was the best professional decision I have ever made. You are a triple threat in medicine, research, and leadership and have more greatly impacted my professional life than any other single individual.

Dr. Andrew Cameron-

Thank you for being available in so many capacities – from this dissertation, to the many challenging patients we share. You are truly a mensch.

Dr. Jodi Segal-

For your added time and for your support in allowing me to have a flexible curriculum that matched my goals.

The Epidemiology Research Group in Organ Transplantation-

Thank you for being there to answer questions both big and small. This research could only have happened with your presence. Special shout-outs to Xun Luo and Mary Grace Bowring.

The faculty and staff of the Johns Hopkins University Bloomberg School of Public Health, and particularly the faculty and staff of the Graduate Training Program in Clinical Investigation-

It is an honor to have studied at the premier school of public health in the world and to be given the opportunity to acquire skills that have launched my career as a physician scientist. Thanks for creating the program!

My thesis committee-

Thank you for your time, effort, and dedication to the academic process. I know all too well how these activities don't fit neatly into our spreadsheets for full-time equivalents that explain our work.

The Division of Pediatric Gastroenterology in the Department of Pediatrics of the Johns Hopkins University School of Medicine-

Thank you for training me as a clinician and for giving me the time and opportunity to further my research career.

Ultimately, I dedicate this work to my family-

To my mother, Harriette Mogul, the first clinician-scientist I knew and the person who first demonstrated that this occupation is best-positioned to unlock the contributions of science for the benefit of humankind. You are my inspiration.

To my father, Malcolm Mogul, who has pursued with every ounce of his being his goal of creating opportunity for his children so that we can achieve our dreams. No father has been more successful in this pursuit.

To my wife, Alexis Mogul, best of wives and best of women: You have been repeatedly asked to make deep sacrifices so that I could obtain this doctoral degree and you have never hesitated in your support. Rather, you have faced each challenge with a smile so bright and with the levitating power to get me out of bed each day.

And to my children, Amelia and Jonah: I would likely have quit this endeavor many times if not for a desire to show you the importance of perseverance and the value in making the world a better place.

-DBM

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LIST OF ABBREVIATIONS

LDLT – Living-donor Liver Transplantation

WLT – Whole Liver Transplantation

DDLT – Deceased-donor Liver Transplantation

SLT – Split Liver Transplantation

aHR – Adjusted Hazard Ratio

sHR – sub Hazard Ratio

PELD – Pediatric End-stage Liver Disease score

MELD – Model for End-stage Liver Disease score

Chapter 1. Introduction

Pediatric end-stage liver disease (ESLD) results from multiple congenital and acquired diseases and is universally fatal without intervention. Children with ESLD invariably experience severe disability and profound impairments in nutrition, cognitive development, immunity, coagulation and quality of life.[1–3] Over the last 25 years, liver transplantation has been utilized as a life-saving treatment for over 15,000 children in the United States with ESLD, thereby providing these individuals with decades of high quality of life.[2,4] Outcomes are generally very good, with 5-year graft survival of 82% for recipients of deceased-donor grafts and 86% for recipients of living-donor grafts.[5]

Liver transplantation is greatly hindered by a scarcity of available organs.[5] Since 2002, the United States has allocated livers using a quantitative assessment of an individual's pre-transplant mortality risk derived from the Pediatric End-stage Liver Disease (PELD) score for individuals <12 years, and the Model for End-stage Liver Disease (MELD) score for individuals ≥12 years but this strategy means that most individuals are extremely sick before they receive a new liver, and in some instances they will die while waiting. [6–8] Children less than 1 year are especially vulnerable to organ shortages and have higher mortality on the waitlist compared to adults (12.4 vs 10.0 deaths per 100 waitlist years) given the rarity of suitable deceased donors (i.e., appropriately-sized individuals without medical comorbidities) for children. This imbalance between the supply of available livers and its demand means that as many as 10% of children on the waitlist die while waiting for an offer.

In addition to waitlist mortality, organ shortage prolongs the time that waitlist candidates experience substantial morbidity. Approximately 700 new pediatric candidates are added to the waitlist every year; the need for organs has been steadily increasing, while the number of transplants, 500-600 per year, has been relatively constant.[5] Over the last decade, adults and pediatric candidates waiting for organs have higher allocation scores, and, at least among adults, individuals with higher allocation scores have significantly increased morbidity.[6] This is likely to be so among children as well.

One exciting solution to organ shortage is the use of technical-variant grafts such as living-donor liver transplantation (LDLT), during which a friend or relative donate a portion of his/her liver.[9] Since this technique was first reported in 1989, a number of potential benefits have been noted.[10,11] LDLT provides the opportunity to transplant patients before they begin to experience substantial morbidity. Recipients of organs from biologically-related individuals may also have a higher likelihood of being able to discontinue immunosuppression and would be able to avoid or mitigate the complications of long-term immunosuppression such as chronic kidney disease and diabetes. Even though LDLT is a more complex surgery than whole liver transplantation (WLT), and may have higher rates of vascular thrombosis or biliary stricture, overall graft failure is similar, as was described in 2007 in a large registry study of pediatric recipients.[12]

Split-liver transplantation (SLT) is a second type of technical-variant surgery that involves transplanting a single *deceased*-donor liver into two recipients, with a larger portion going typically to an adult and a smaller portion going to a child. Given that nearly 5,000 adult deceased-donor livers are available for transplant into adult recipients every year, increasing use of SLT with these organs would have a dramatic impact on

organ shortage for the 700 children that are waiting for a liver transplant and would lead to substantial reductions in waitlist morbidity and mortality. Outcomes following SLT have been inferior to WLT for pediatric recipients due to higher rates of vascular thrombosis and biliary stricture as well as graft failure, although recent data are not available.[12] Despite the problem of waitlist mortality and morbidity that results from decreased organ availability, only 10% of pediatric transplant recipients are transplanted using a living-donor and 15% are transplanted with a split-liver.[5]

The overarching goal of this dissertation is to better understand how the principal outcomes in liver transplantation, patient and graft survival, are influenced by graft type and to learn more about outcomes with technical-variant graft surgery. In Chapter 2, we use data from the Scientific Registry for Transplant Recipients (SRTR) to evaluate 15-year trends in graft and patient survival for WLT, LDLT, and SLT. Our hypothesis is that outcomes for LDLT and SLT, while initially reported to be inferior to WLT, have improved. If so, greater use of technical-variant grafts will provide an opportunity to substantially increase the organ supply while decreasing waitlist morbidity and mortality.

Chapters 3 and 4 directly address barriers to access of LDLT. There is strong evidence of health disparities between individuals from different racial/ethnic groups awaiting transplantation, with use of living-donation being substantially lower among African-American and Hispanic adults.[13,13] First, we analyze SRTR to determine if waitlist outcomes (i.e., deceased-donation, living-donation, and death) for pediatric liver transplant candidates vary by race/ethnicity. Our hypothesis was that children from racial and ethnic minority groups on the waitlist for liver transplants are less likely to utilize LDLT, and that they may have higher rates of waitlist mortality.

Second, we developed a survey for parents of children that are waiting or who have received a liver transplant to further explore barriers to LDLT. Literature from adult kidney transplant patients has identified a number of important barriers to living-donation including inadequate patient information, poor provider communication, diminished social network, and mistrust of the medical community.[14–16] Evidence from studies of adult transplant candidates/recipients supports that these barriers are more frequent among individuals with specific sociodemographic characteristics including African Americans, and individuals with lower income and lower educational attainment. Our hypothesis was that these barriers exist in pediatric liver transplantation as well, and that these barriers are more frequent in groups that are underserved or with decreased resources.

In Chapter 5, we address the potential to expand the supply of organs through greater use of SLT by further exploring which patients are appropriate candidates SLT. Using the SRTR, we studied individuals that received either a WLT or SLT and explored whether the relationship between graft type and graft failure was modified by specific donor, recipient, or surgical characteristics. We hypothesized that the relationship between graft type and graft failure would vary depending on recipient characteristics and that there are subgroups of pediatric recipients having equivalent risk of graft failure irrespective of whether they receive an SLT or WLT. Individuals with these characteristics may be optimal candidates for SLT. This information will guide clinical decision-making, and may inform policy decisions surrounding liver allocation as well.

Chapter 2. Fifteen-year Trends in Pediatric Liver Transplants: Split, Whole Deceased, and Living Donor Grafts

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ABSTRACT

Background: To evaluate changes in patient and graft survival for pediatric liver transplant recipients since 2002, and to determine if these outcomes vary by graft type (whole liver transplant (WLT), split liver transplant (SLT), and living-donor liver transplant (LDLT)).

Methods: We evaluated patient and graft survival among pediatric liver-only transplant recipients the PELD/MELD system was implemented using the Scientific Registry of Transplant Recipients.

Results: From 2002-2009 to 2010-2015, survival for SLT improved at 30 days (94% vs 98%; *P*<0.001), and at 1 year improved for SLT (89% to 95%; *P*<0.001) and LDLT (93% to 98%; *P*=0.002); there was no change in survival for WLT at either 30 days (98% in both; *P*=0.7) or 1 year (94% vs 95%; *P*=0.2). Risk of early death with SLT was 2.14-fold higher in 2002-2009 (adjusted hazard ratio (aHR) vs WLT: $_{1.47}2.14_{3.12}$) but this risk disappeared in 2010-2015 (aHR: $_{0.65}1.13_{1.96}$), representing a significant improvement (*P*=0.04). Risk of late death following SLT was similar in both time periods (aHR 2002-2009: $_{0.87}1.14_{1.48}$; aHR 2010-2015: $_{0.56}0.88_{1.37}$). LDLT had similar risk of early death (aHR 2002-2009: $_{0.49}1.03_{2.14}$; aHR 2010-2015: $_{0.26}0.74_{2.10}$) and late death (aHR 2002-2009: $_{0.52}0.83_{1.32}$; aHR 2010-2015: $_{0.17}0.44_{1.11}$). Graft loss was similar for SLT (aHR: $_{0.93}1.09_{1.28}$) and was actually lower for LDLT (aHR: $_{0.53}0.71_{0.95}$).

Conclusion: In recent years, outcomes following use of technical-variant grafts are comparable to whole grafts, and may be even be superior for LDLT. Greater use of technical-variant grafts might provide an opportunity to increase organ supply without compromising post-transplant outcomes.

INTRODUCTION

Liver transplantation provides life-saving therapy for children with end-stage liver disease.[1,2] Unfortunately, successful pediatric transplantation is hindered by a scarcity of suitable livers.[18] Under the current PELD (Pediatric End-stage Liver Disease) and MELD (Model for End-stage Liver Disease) system, organs are allocated to patients based on their probability of death within 90 days while awaiting transplant. This strategy means: (1) the pre-transplant course for most individuals is associated with significant morbidity, hospitalization, and costs; (2) delays in transplantation exacerbate long-term impairments in cognition and growth; and (3) in some instances, children die on the waitlist.[1,2,6]

Use of technical-variant donation, including split liver transplantation (SLT) and living-donor liver transplantation (LDLT), represents a potential solution to the organ shortage.[7] Given that approximately 6,000 whole livers are used for adult recipients each year, SLT for children represents an exciting opportunity to improve organ supply, shorten waitlist times, and decrease pre-transplant morbidity and mortality. Evidence from studies of adult recipients suggest that outcomes following SLT have improved in recent years and may have achieved parity with WLT.[19] However, reports on outcomes for pediatric recipients following technical-variant donation, and in particular SLT, are conflicting.[12,20,21]

Given these inconsistent findings, the purpose of our analysis was to use a large national registry to better understand the impact of allograft type on patient and graft survival for pediatric liver transplant recipients in the most recent era. Furthermore, we sought to assess whether the association between allograft type and outcomes following transplantation have changed over time period and whether these effects vary by follow-

up time. Finally, we wanted to better understand which factors are associated with graft failure and whether the causes of graft failure have changed in recent years.

METHODS

Data Source

This study used data from the SRTR. The SRTR data system includes data on all donors, waitlisted candidates, and transplant recipients in the U.S., submitted by the members of the Organ Procurement and Transplantation Network (OPTN) and has been described elsewhere.[22] The Health Resources and Services Administration, U.S. Department of Health and Human Services, provides oversight to the activities of the OPTN and SRTR contractors. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of, or interpretation by, the SRTR or the U.S. Government.

Study Population

We identified 5715 pediatric (age < 18 years), liver-only, first transplant recipients who received an organ between March 1, 2002 (i.e., after implementation of the PELD/MELD system) and December 31, 2015. Additionally, people were excluded for the following reasons: listed as live donor whole liver (n = 10), missing weight (n = 1), missing cold ischemia time (n = 395; 6% of eligible individuals). No donor organs were obtained from executed prisoners or other institutionalized persons. Individuals were defined as having a split liver transplant (SLT) if they received a portion of a deceased donor graft, irrespective of whether the organ was used by one or two recipients as evidence from other studies suggest comparable graft and patient survival, and even potentially comparable biliary strictures and vascular thromboses.[12,19] We compared demographic (e.g. age, sex, race, and insurance status) and clinical (e.g., weight, PELD/MELD, and

diagnosis) characteristics between pediatric recipients of SLT, whole liver transplantation (WLT) and living donor liver transplantation (LDLT) using χ^2 tests for categorical variables and analysis of variance (ANOVA) for continuous variables.

Unadjusted Patient and Graft Survival

We calculated patient and graft survival at 30-days and 1-year following SLT, WLT, or LDLT, and compared survival between allograft types using Kaplan-Meier curves and log-rank tests. Patient death was identified using the SRTR, which is linked to the Social Security Master File and confirmed through clinician report. Graft failure was identified as any reported graft failure or death (i.e., "all cause graft loss"). Recipients were censored upon re-transplantation or multi-organ transplantation (e.g., liver-kidney).

Adjusted Patient and Graft Survival

We used Cox proportional hazards models to characterize the association between allograft type and graft and patient survival after adjustment for recipient weight at transplant, recipient age at transplant, gender, race/ethnicity, underlying disease, allocation PELD/MELD at transplant, status 1 designation, donor age, cold ischemia time (CIT), and insurance type; sensitivity analysis with laboratory PELD/MELD and exception status were also performed and did not influence findings. Additional sensitivity analysis with transplant region was assessed using shared frailty.[23] The decision to include these specific variables in the final model for multivariable regression was derived from associations between covariates with risk factors and the outcome in both the published literature as well as statistical tests (e.g., chi-square, ANOVA) within this cohort.

Trends Over Time

To characterize changes in unadjusted patient and graft survival over time, 30-day and 1-year survival between allograft types were further stratified by time period of transplantation (i.e., 2002-2009 vs 2010-2015). We used an interaction term analysis to determine whether the association between allograft type and adjusted patient and graft survival varied over time period.

Time-varying Hazard of Patient Survival

We tested whether the hazard associated with patient survival following SLT, LDLT, and WLT varied over follow-up time using a time-binned analysis and estimated the hazard associated with each allograft type within the first 30 days post-transplant (i.e., early) and after the first 30 days post-transplant (i.e., late).

Statistical Analysis

All statistical tests used a two-sided α of 0.05. Categorical variables were compared using a chi-square test and continuous variables were compared using ANOVA. Confidence intervals are reported using the method of Louis and Zeger, as previously reported.[24] All analyses were performed using STATA 14.0 (College Station, TX, USA). This study was approved by the Institutional Review Board of Johns Hopkins University School of Medicine.

RESULTS

Patient characteristics

Among the 5715 children who underwent liver transplantation, 3428 (60%) received a WLT, 1626 (28.5%) a SLT, and 661 (11.6%) a LDLT (Table 1 online). SLT and LDLT recipients were more likely to be under 2 years and 10 kg ($P < 0.001$ for both age and weight). African Americans were less likely than Caucasians to undergo LDLT, and more

likely to receive a whole graft ($P < 0.001$). LDLT recipients were more likely to have had biliary atresia ($P < 0.001$). The donor age for nearly all individuals receiving a living donor was 18-50 years of age, whereas WLT recipients were more likely to have donors age 0-17 years ($P < 0.001$). PELD/MELD score at transplant was lower in LDLT ($P < 0.001$), while SLT recipients were more likely to be status 1 than WLT and LDLT recipients ($P < 0.001$). The mean cold ischemia time (CIT) was shortest for LDLT ($P < 0.001$). LDLT recipients were more likely to have private insurance and SLT recipients were more likely to have public insurance ($P < 0.001$).

Trends in Allograft Volume

From 2002-2009 to 2010-2015, the frequency of transplants was similar for WLT (60% for both), SLT (29% and 28%) and LDLT (11% and 12%) ($P = 0.6$). Frequency of reduced SLT (i.e., “cut-down”), where only one portion was used, was the same for both periods (13.2% and 13.6%). Among 104 centers performing any type of liver transplant, 66 (63%) centers performed at least 1 SLT over the entire study period, and 8 (8%) performed at least 1 SLT each year. Fifty-seven (55%) centers performed at least 1 LDLT over the entire study period, and 4 (4%) centers performed at least 1 LDLT per year.

Short-term Patient Survival

Since the PELD/MELD system was implemented in 2002, the unadjusted 30-day patient survival across all allograft types was 97%, and was significantly lower in SLT compared to WLT (96% vs 98%; $P < 0.001$), while survival for LDLT and WLT was similar (98% for both; $P = 0.4$; Table 2). The relative impact of allograft type on short-term survival varied by time period (Figure 1). From 2002-2009, survival following SLT was worse than WLT (94% vs 98%; $P < 0.001$) whereas from 2010-2015, no significant difference was

observed (98% for both; *P* = 0.96). Outcomes following LDLT were similar to WLT in both 2002-2009 (97% vs 98% *P* = 0.96) and 2010-2015 (99% vs 98%; *P* = 0.2). Only SLT demonstrated an improvement in short-term survival (94% in 2002-2009 vs 98% in 2010-2015; *P* < 0.001). In an adjusted model, SLT was associated with a 2.14-fold higher risk of early death (i.e., within 30 days) from 2002-2009 (aHR: $_{1.47}2.14_{3.12}$; Table 3) while there was no increased risk of early death from 2010-2015 (aHR: $_{0.65}1.13_{1.96}$), representing a significant improvement (*P* for interaction = 0.04). Adjustment for transplant region did not change inferences. Short-term survival following LDLT was the same in both time periods (aHR vs WLT in 2002-2009: $_{0.49}1.03_{2.14}$; aHR vs WLT in 2010-2015: $_{0.26}0.74_{2.10}$).

Long-term Patient Survival

Patient survival at 1 year was 94% for all pediatric recipients over the study period and significantly lower for SLT compared to WLT (92% vs 95%; *P* = 0.002), but similar for LDLT and WLT (96% vs 95%; *P* = 0.2). The relative impact of allograft type on short-term survival varied by time period. From 2002-2009, survival following SLT was worse than WLT (89% vs 94%; *P* < 0.001), whereas no significant difference was observed from 2010-2015 (95% for both; *P* = 0.2). From 2002-2009, survival following LDLT was similar to WLT (93% vs 94%, *P* = 0.6), but from 2010-2015, survival was higher for LDLT (98% vs 95%; *P* = 0.01). Survival at 1 year improved for both SLT (89% in 2002-2009 and 95% in 2010-2015; *P* < 0.001) and LDLT (93% in 2002-2009 and 98% in 2010-2015; *P* = 0.002) but did not improve for WLT (94% in 2002-2009 and 95% in 2010-2015; *P* = 0.2). Compared to WLT, the long-term (i.e., after 30 days) risk of death was similar in both time periods for SLT (aHR in 2002-2009: $_{0.87}1.14_{1.48}$; aHR in 2010-2015: $_{0.56}0.88_{1.37}$) and LDLT (aHR in 2002-2009: $_{0.52}0.83_{1.32}$; aHR in 2010-2015: $_{0.17}0.44_{1.11}$).

Graft Survival

Overall unadjusted 30-day graft survival was 93% (Table 4 online; Figure 2 online). Only SLT showed significant improvement from 2002-2009 to 2010-2015 (90% vs 93%; *P* = 0.01) whereas no improvement was seen in WLT (92% vs 93%; *P* = 0.1) or LDLT (94% vs 95%; *P* = 0.6). Graft survival at 1 year improved for SLT (85% vs 90%; *P* = 0.002) and LDLT (89% vs 94%; *P* = 0.03) but not WLT 89% vs 90%; *P* = 0.14). In an adjusted model, the association between allograft type and graft survival did not vary by time period (*P* > 0.05 for interaction coefficients) and thus, overall estimates are reported instead. Additionally, the hazard of graft failure was proportionally constant throughout the follow-up period and therefore early and late graft failure were not evaluated separately. Compared to WLT, SLT was not associated with an increased risk of graft failure (aHR: $_{0.93}1.09_{1.28}$), while LDLT was associated with a lower risk of graft failure (aHR: $_{0.53}0.71_{0.95}$; Table 5). Overall graft survival improved from 2002-2009 to 2010-2015 (aHR: $_{0.65}0.74_{0.86}$).

Additional Risk Factors for Death and Graft Failure

In a multivariable model, several other characteristics were associated with both death and graft failure (Table 6 online). Acute hepatic necrosis, malignancy, and status 1 designation were associated with increased death and graft loss, as was public insurance and donor age >50 years. Recipient race/ethnicity, weight, and allocation score at transplant were not associated with death or graft failure. Although recipient age was not associated with death, children 2-12 years had lower graft loss than children <2 years. Years 2010-2015 was overall associated with lower death and graft loss.

Regional Variation

Transplant region was associated with allograft type in both 2002-2009 ($P < 0.001$) and 2010-2015 ($P < 0.001$). Inclusion of transplant region into the model did not affect inferences on patient. For example, similar to the model without region, the 30-day risk of death for SLT was increased in 2002-2009 (aHR: $_{1.48}2.16_{3.13}$) but not increased in 2010-2015 (aHR: $_{0.68}1.18_{2.04}$) representing a significant improvement ($P = 0.04$). Similarly, inclusion of region into the model did not influence risk of graft loss (aHR for SLT: $_{0.94}1.10_{1.29;}$ aHR for LDLT: $_{0.55}0.74_{1.00}$).

DISCUSSION

In this national study examining trends in pediatric liver transplantation since the implementation of the PELD/MELD system, several important findings were evident with respect to the relationship between allograft type and patient/graft survival. First, while overall outcomes have improved, these can be largely attributed to improvements in early outcomes following SLT, as well as to improvements in long-term outcomes following SLT and LDLT; outcomes following WLT have been largely unchanged since the current PELD/MELD system was implemented. Second, poor outcomes for SLT were initially due to increased early death but this problem is no longer evident such that risk of early death in SLT has decreased, and is similar to, WLT. Finally, graft survival for LDLT appears to be superior to WLT. Collectively, these findings suggest that the increasing experience with technical-variant grafts such as SLT and LDLT have coincided with improved patient and graft survival.

Our analysis also identifies several important risk factors for death and graft failure in this large cohort including notable findings that better outcomes may be seen in biliary atresia, as well as lower rates of graft failure in children between 2-12 years. Additionally, although all race/ethnic groups had comparable outcomes, higher rates of

death and graft loss were seen in individuals with public insurance. These findings are consistent with other challenges facing individuals in the pediatric liver transplant community with public insurance such as higher rates of waitlist mortality, and lower likelihood of obtaining exception points.[25,26]

Reports on the impact of allograft type in pediatric liver transplantation have been conflicting. The SPLIT consortium of 44 pediatric centers examined a range of outcomes on recipients from 1995-2006 and found increased graft failure in SLT, but not LDLT, when compared with WLT in an unadjusted model.[12] These authors also reported higher rates of complications requiring either surgical revision in both SLT and LDLT compared with WLT. A second study from the SPLIT consortium showed increased death and graft loss for both technical-variant grafts.[27] A large single-center study of recipients between 1993-2006 similarly found a higher risk of mortality and graft failure in SLT, but not LDLT.[20] Other studies derived from the UNOS and SRTR registries prior to the implementation of PELD/MELD have shown a general tendency for SLT to have worse patient and graft survival, whereas LDLT may have superior or equivalent outcomes compared with WLT.[28,29] At the same time, some studies have suggested that allograft type does not affect outcomes. Austin *et al.* looked at outcomes in UNOS from as early as 1987-2004 and showed no difference in patient and graft survival by allograft type, but this finding may be driven by relatively poor outcomes in this cohort from all transplants in the early years of the cohort. For example, the authors report an overall 1-year patient survival of 83% compared with 94% in our study.[10] Finally, in the most recent study from SRTR that evaluated patient and graft survival in a limited cohort of children under 12 years old from 2002-2004, there was no variability in outcomes by allograft type.[21]

Our finding that overall patient and graft survival following pediatric liver transplantation have improved over time is broadly consistent with other studies.[30,31] One large study derived from the United Network for Organ Sharing (UNOS) database from 1995-2010 of children showed that patient and graft survival improved from 1995-2000 to 2006-2010, but saw similar results between 2001-2005 and the end of the study period.[30] This study was limited to children under 2 years old that received a whole or deceased split graft, and because it spanned the implementation of PELD/MELD, it was not possible to adjust for the score or status 1 designation and authors used ICU and ventilator status instead. They also tested for interaction between eras and allograft status and showed a trend toward improved relative hazard following SLT compared with WLT, but the interaction between era and allograft type was not significant for patient or graft survival. Here, we demonstrated overall improvement since PELD/MELD was implemented and across all pediatric age groups. Furthermore, we showed significant improvement in the most recent transplant period (i.e., 2010-2015) such that outcomes following SLT are now similar to WLT.

An important consideration when discussing increased adoption of SLT is the impact on the adult recipient who might otherwise get a whole graft, especially as split liver transplantation has been seen as contributing to a donor risk index in some, but not all, adult studies.[32,33] A recent study of the UNOS database looking at adult SLT recipients reported similar findings that patient and graft survival have improved over time and are now similar to WLT.[19] At the same time, increased vascular and biliary complications continue to be reported in technical-variant donation relative to WLT and one important limitation of our study was that we were unable to explore these additional complications.[27,34,35] While use of these grafts will increase the organ supply, allow for earlier transplantation, and potentially decrease total costs, at the same time,

complications from these grafts are likely to be associated with longer length of stay and greater cost in the perioperative period.[6,35,36] Given the current need to optimize outcomes and reduce costs (i.e., increase value), the decision to use these organs by transplant teams, and to advocate for greater use through policy, will require a better understanding of the frequency of these complications and how these complications impact care from a number of perspectives.[37] Nonetheless, some centers have incorporated practices where SLT is prioritized, and have been able to achieve the competing goal of good long-term outcomes alongside the benefits of increased organ supply.[38]

Another limitation of our study was that it was derived from an observational cohort as opposed to an experimental study. While the finding that overall outcomes have improved over time should be expected, it is difficult to know whether the decision by the transplant team to perform a specific type of transplant is a reflection of their assessment of the patient's disease severity, surgical experience, or some other factor; if SLT was only performed when the patient was perceived to be relatively stable, this decision might influence the observed outcomes. One advantage of our study is that it is conducted exclusively in the PELD/MELD era, and we adjusted for the score at transplant as well as exception status, a well-validated tool for assessing medical severity. Consequently, the relative effects that were seen in the multivariable model that adjusted for score and exception status should account for the impact of disease severity. But while it is possible that the improvement seen in SLT can be attributed to unmeasured or residual confounding of disease severity that coincides with a shift in clinical practice and decision making, our evidence nonetheless suggests that a group of children can do well with SLT, and that more research should be performed to identify the specific patient, donor, and surgical characteristics that yield good outcomes.

Finally, it should be noted that there can be errors in reporting from studies derived from national registries, such as patients being incorrectly classified as dead or with graft failure. However, these errors should be minimal, if they exist at all, given that SRTR verifies death with the Social Security Master File and that graft failure must be accurately identified in the registry in order for a patient to receive a new liver.

Given shortages in organ supply, there is continued interest and effort in identifying additional opportunities to expand the supply, including use of extended criteria donors, donation after cardiac death, and technical-variant donation.[7,39–41] Children may be particularly vulnerable to decreased supply, with a recent report suggesting that nearly half of all children that died on the waitlist had not received a single offer of a liver, with a median offer number of one.[25] Size mismatch was identified in nearly one third of patients as a reasons offers were not accepted, though nearly half may have actually been an appropriate size, suggesting the potential for greater use of split transplantation in reducing waitlist mortality. Our national study of over 5000 pediatric liver transplant recipients provides strong evidence that allograft type no longer predicts patient and graft survival in this population. These findings have the potential to substantially influence policy for allocation of deceased organs to children in need. Given that children compose a relatively small percentage of people on the national waitlist, increased use of SLT might provide an optimal way to increase the supply for children, without placing them at risk for worse outcomes, so that pre-transplant mortality and morbidity can be minimized.

Table 1: Demographic and Clinical Characteristics by Transplant Type

Characteristic	WLT	SLT	LDLT	*P***
Total	3428 (60.0)	1626 (28.5)	661 (11.6)	
Recipient Age				
<2 years	1328 (38.7)	983 (60.5)	418 (63.2)	<0.001
2-5 years	592 (17.3)	355 (21.8)	95 (14.4)	
5-12 years	709 (20.7)	225 (13.8)	87 (13.2)	
12-18 years	799 (23.3)	63 (3.9)	61 (9.2)	
Recipient Weight				
<10 kg	1119 (32.6)	832 (51.2)	361 (54.6)	<0.001
10-35 kg	1296 (37.8)	691 (42.5)	218 (33.0)	
>35 kg	1013 (29.6)	103 (6.3)	82 (12.4)	
Female	1769 (51.6)	812 (49.9)	331 (50.1)	0.5
Race/ethnicity				
Caucasian, non-Hispanic	1793 (52.3)	796 (49.0)	389 (58.9)	<0.001
African American	594 (17.3)	243 (15.4)	74 (11.2)	
Hispanic	736 (21.5)	431 (26.5)	142 (21.5)	
Asian	193 (5.6)	99 (6.1)	43 (6.5)	
mixed/other	112 (3.3)	50 (3.1)	13 (2.0)	
Disease				
biliary atresia	1195 (34.9)	710 (43.7)	341 (51.6)	<0.001
metabolic disease	578 (16.9)	231 (14.2)	50 (7.6)	
acute hepatic necrosis	451 (13.2)	222 (13.7)	81 (12.3)	
tumor	314 (9.2)	159 (9.8)	31 (4.7)	
miscellaneous	890 (26.0)	304 (18.7)	158 (23.9)	
Donor Age				
0-17 years	2890 (84.3)	968 (59.5)	1 (0.2)	<0.001
18-50 years	468 (13.7)	628 (38.6)	642 (97.1)	
>50 years	70 (2.0)	30 (1.8)	18 (2.7)	
PELD/MELD at transplant*	23.6 (8.9)	24.9 (8.6)	21.0 (11.8)	<0.001
Status 1	1089 (31.8)	614 (37.8)	144 (21.8)	<0.001
Cold Ischemia Time* (hour)	7.3 (3.5)	7.3 (2.9)	2.8 (5.3)	<0.001
Insurance				
public	1697 (46.9)	898 (55.2)	217 (32.8)	<0.001
private	1608 (46.9)	685 (42.1)	413 (62.5)	

mixed/other	123 (3.6)	43 (2.6)	31 (4.7)	
Time Period				
2002-2009	1842 (53.7)	890 (54.7)	346 (52.3)	0.6
2010-2015	1586 (46.3)	736 (45.3)	315 (47.7)	

* mean (SD)

** P value from chi square test for categorical variables and ANOVA for continuous variables

Table 2: 30-day and 1-year Unadjusted Patient Survival

	Overall		2002-2009		2010-2015		
	Survival	***P***	**Survival**	***P***	**Survival**	***P***	***P****
30-day							
all allografts	0.97		0.96		0.98		0.004
WLT	0.98	--	0.98	--	0.98	--	0.7
SLT	0.96	<0.001	0.94	<0.001	0.98	0.96	<0.001
LDLT	0.98	0.4	0.97	0.96	0.99	0.2	0.2
1-year							
all allografts	0.94		0.93		0.96		<0.001
WLT	0.95	--	0.94	--	0.95	--	0.2
SLT	0.92	0.002	0.89	<0.001	0.95	0.7	<0.001
LDLT	0.96	0.2	0.93	0.6	0.98	0.01	0.002

WLT (whole liver transplantation); SLT (split liver transplantation); LDLT (living-donor liver transplantation)

*P** represents test of significance from log-rank tests for difference in survival for a specific allograft type from 2002-2009 to 2010-2015

Table 3: Adjusted Hazard Ratio (aHR) for Risk of Death

	2002-2009		2010-2015		
	aHR (95% CI)	***P***	**aHR (95% CI)**	***P***	***P****
Within 30 days					
WLT	--	--	--	--	--
SLT	$_{1.47}2.14_{3.12}$	<0.001	$_{0.65}1.13_{1.96}$	0.7	0.04
LDLT	$_{0.49}1.03_{2.14}$	0.9	$_{0.26}0.74_{2.10}$	0.65	0.6
After 30 days					
WLT	--	--	--	--	--
SLT	$_{0.87}1.14_{1.48}$	0.4	$_{0.56}0.88_{1.37}$	0.6	0.3
LDLT	$_{0.52}0.83_{1.32}$	0.4	$_{0.17}0.44_{1.11}$	0.08	0.2

CI (confidence interval); WLT (whole liver transplantation); SLT (split liver transplantation); LDLT (living-donor liver transplantation)

*P** tests whether the aHR for SLT and LDLT, each compared to WLT, varies by time period (i.e., interaction).

Table 4: 30-day and 1-year Unadjusted Graft Survival

	Overall		2002-2009		2010-2015		
	Survival	***P***	**Survival**	***P***	**Survival**	***P***	***P****
30-day							
all allografts	0.93		0.92		0.93		0.1
WLT	0.93	--	0.93	--	0.93	--	0.9
SLT	0.92	0.06	0.90	0.005	0.93	0.7	0.01
LDLT	0.94	0.2	0.94	0.6	0.95	0.2	0.6
1-year							
all allografts	0.89		0.87		0.91		<0.001
WLT	0.89	--	0.89	--	0.90	--	0.14
SLT	0.87	0.02	0.85	0.004	0.90	0.9	0.002
LDLT	0.91	0.2	0.89	0.9	0.94	0.05	0.03

WLT (whole liver transplantation); SLT (split liver transplantation); LDLT (living-donor liver transplantation)

*P** represents test of significance using log-rank test of difference in survival for a specific allograft type from 2002-2009 to 2010-2015

Table 5: Adjusted Hazard Ratio (aHR) for Graft Failure

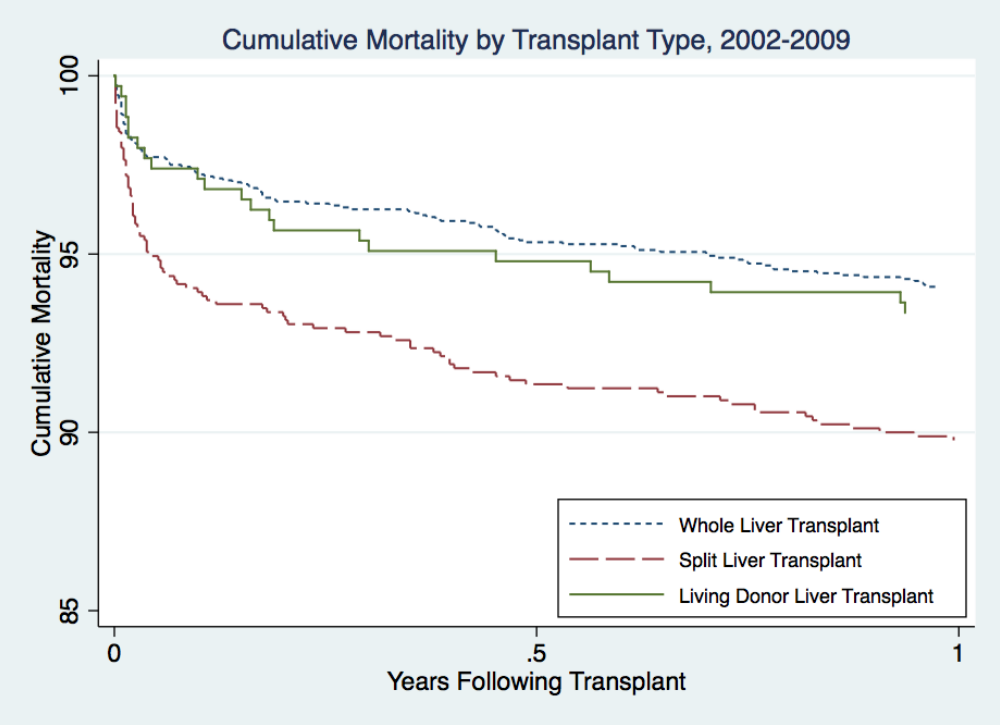
	Graft Failure	
Allograft	**aHR (95% CI)**	***P***
WLT	--	--
SLT	$_{0.93}1.09_{1.28}$	0.3
LDLT	$_{0.53}0.71_{0.95}$	0.02

CI (confidence interval); WLT (whole liver transplantation); SLT (split liver transplantation); LDLT (living-donor liver transplantation)

Table 6: Additional Risk Factors for Death and Graft Failure

	Death		Graft Failure	
Characteristic	**aHR**	***P***	**aHR**	***P***
Disease				
Biliary Atresia	--	--	--	--
Metabolic Disease	$_{0.85}1.17_{1.61}$	0.3	$_{0.89}1.12_{1.41}$	0.3
Acute Hepatic Necrosis	$_{1.20}1.67_{2.31}$	0.002	$_{1.18}1.51_{1.93}$	0.001
Malignancy	$_{2.20}2.97_{4.02}$	<0.001	$_{1.49}1.89_{2.41}$	<0.001
Other/unknown	$_{1.51}1.92_{2.45}$	<0.001	$_{1.30}1.56_{1.86}$	<0.001
Recipient race/ethnicity				
Caucasian, non-Hispanic	--	--	--	--
African American	$_{0.96}1.21_{1.52}$	0.1	$_{0.92}1.10_{1.30}$	0.3
Hispanic	$_{0.78}0.96_{1.20}$	0.7	$_{0.74}0.87_{1.03}$	0.1
Asian	$_{0.61}0.91_{1.35}$	0.6	$_{0.57}0.78_{1.06}$	0.1
Mixed/other	$_{0.58}0.95_{1.57}$	0.8	$_{0.61}0.89_{1.29}$	0.5
Recipient weight				
<10 kg	--	--	--	--
10-35 kg	$_{0.69}0.93_{1.26}$	0.7	$_{0.73}0.92_{1.15}$	0.5
>35 kg	$_{0.58}0.95_{1.57}$	0.8	$_{0.62}0.91_{1.33}$	0.6
Recipient age				
<2 years	--	--	--	--
2-5 years	$_{0.53}0.75_{1.04}$	0.09	$_{0.60}0.77_{0.99}$	0.04
5-12 years	$_{0.58}1.85_{1.23}$	0.4	$_{0.54}0.71_{0.95}$	0.02
12-18 years	$_{0.70}1.17_{1.95}$	0.5	$_{0.66}0.97_{1.44}$	0.9
Insurance				
Private	--	--	--	--
Public	$_{1.20}1.44_{1.72}$	<0.001	$_{1.08}1.24_{1.41}$	0.002
Other/missing	$_{0.54}0.94_{1.61}$	0.8	$_{0.52}0.79_{1.20}$	0.3
Allocation score at transplant	$_{0.99}1.00_{1.01}$	0.5	$_{0.99}1.00_{1.00}$	0.3
Status 1	$_{1.00}1.23_{1.51}$	0.05	$_{1.02}1.19_{1.61}$	0.03

Cold ischemia time (hour)	$_{0.99}1.01_{1.03}$	0.2	$_{1.00}1.01_{1.03}$	0.07
Donor age				
<18 years	--	--	--	--
18-50 years	$_{0.91}1.15_{1.44}$	0.2	$_{0.98}1.18_{1.41}$	0.07
>50 years	$_{1.17}1.79_{1.2.73}$	0.007	$_{1.74}2.38_{3.24}$	<0.001
Era (versus 2002-2009)	$_{0.58}0.74_{0.95}$	0.02	$_{0.65}0.74_{0.86}$	<0.001



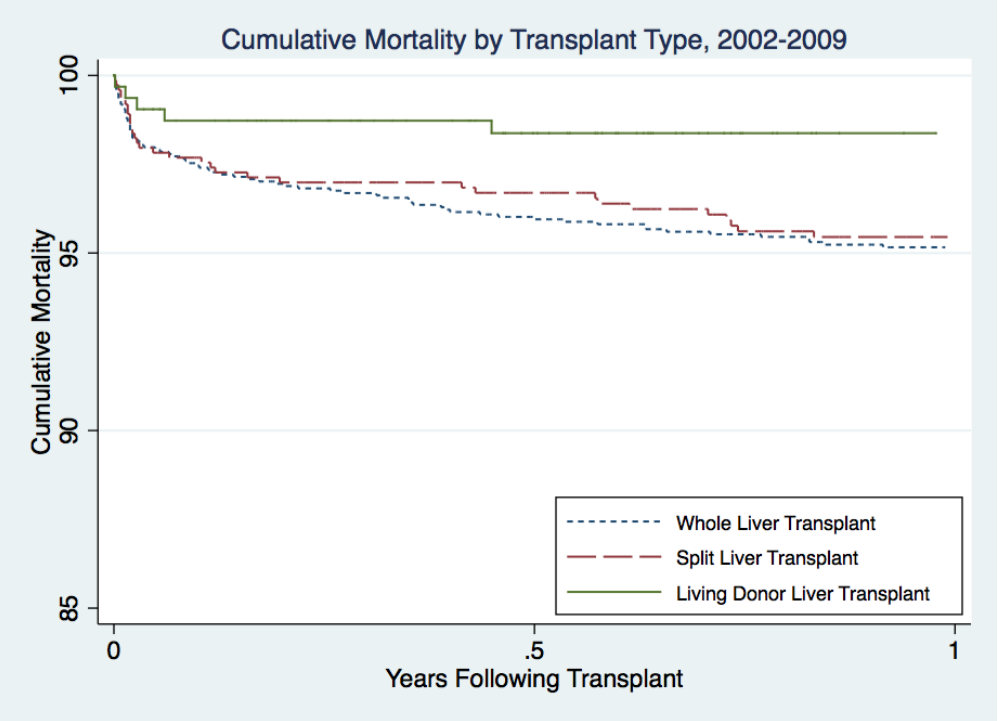
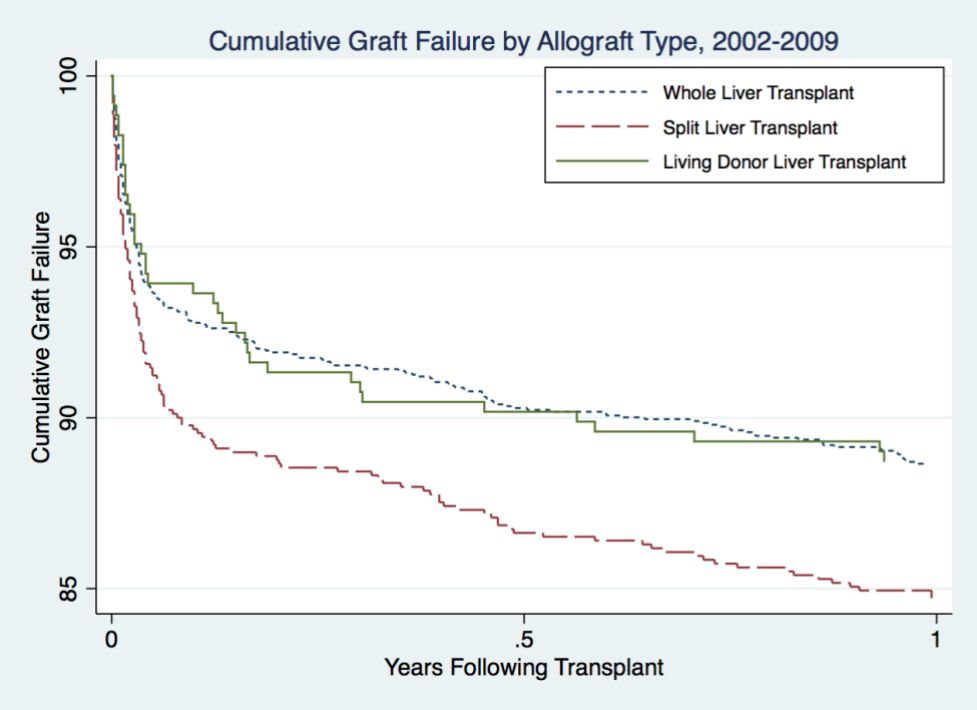


Figure 1: Kaplan-Meier curves of patient survival by allograft type in the first year after transplant from (A) 2002-2009; and (B) 2010-2015



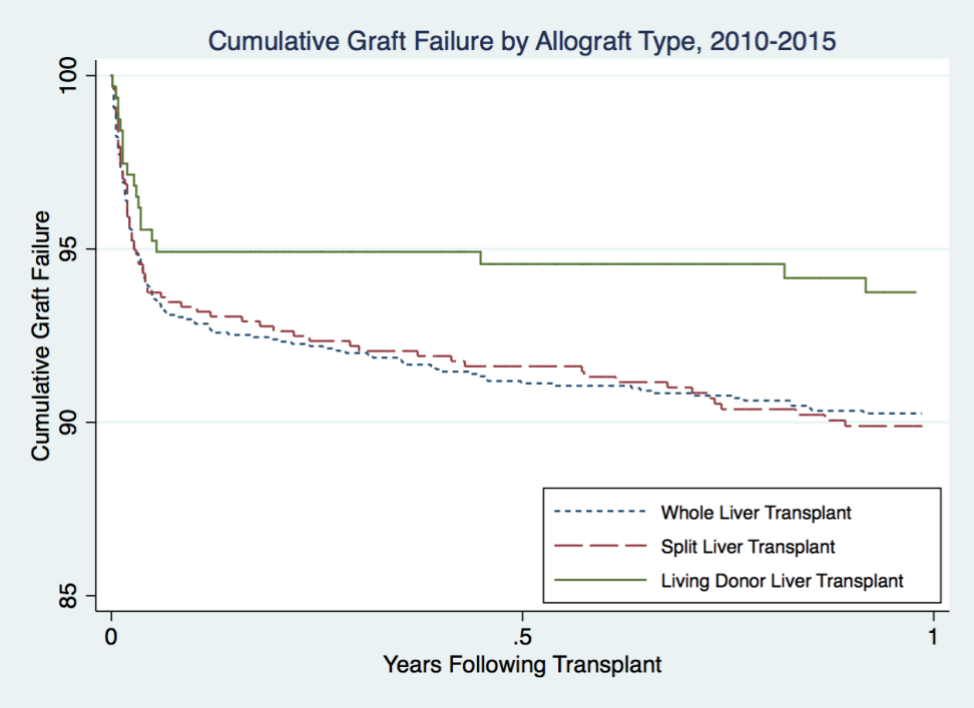


Figure 2: Kaplan-Meier curves of graft survival by allograft type in the first year after transplant from (A) 2002-2009; (B) 2010-2015

Chapter 3. Impact of Race and Ethnicity on Outcomes for Children Waitlisted for Pediatric Liver Transplantation

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ABSTRACT

Background: African Americans and other minorities are known to face barriers to health care influencing their access to organ transplantation but it is not known whether these barriers exist among pediatric liver transplant waitlist candidates. We sought to determine whether outcomes on the waitlist (i.e., mortality, deceased donor liver transplantation (DDLT), and living-donor liver transplantation (LDLT)) varied by race/ethnicity.

Methods: National registry data were studied to estimate the race/ethnicity-specific risk of waitlist mortality, DDLT and LDLT in children (<18 years) waitlisted between March, 2002 and March, 2015.

Results: There was no evidence of racial/ethnic disparities in waitlist mortality. Compared to Caucasians, LDLT varied by race/ethnicity, with only 6.7% African Americans and 10.3% Hispanic children receiving LDLT compared with 12.4% Caucasian, 13.3% Asian, and 9.4% mix/other children. In an adjusted Cox proportional hazards model, African Americans were half as likely as Caucasians to use LDLT (hazard ratio (HR): $_{0.41}0.55_{0.73}$) but had similar use of DDLT (HR: $_{0.98}1.06_{1.16}$). In a model that considered mortality, DDLT, and LDLT as competing risks, African Americans had significantly reduced incidence of LDLT (subhazard ratio (sHR): $_{0.41}0.56_{0.75}$) compared to Caucasians, but increased use of DDLT (sHR: $_{1.06}1.16_{1.26}$).

Conclusion: Compared to Caucasian children, African-American children are less likely to use LDLT but have higher rates of DDLT and similar survival on the waitlist. Additional research is necessary to understand the clinical and socioeconomic factors contributing to lower utilization of LDLT among African-American children awaiting transplantation.

INTRODUCTION

Since implementation of the Pediatric End-stage Liver Disease (PELD) and Model for End-stage Liver Disease (MELD) system in 2002, liver transplantation has provided life-saving therapy for over 5,000 children in the United States.[42] Outcomes after transplantation in children are excellent, with 1-year and 5-year survival reported to be 95% and 85%, respectively.[17] Furthermore, increasing experience with newer surgical techniques in recent years, such as living-donor liver transplantation (LDLT), may yield outcomes that are superior to whole liver transplantation while allowing for shorter waitlist periods and a reduction in associated pre-transplant morbidity.[21,43]

There is strong evidence that health disparities exist between individuals from different racial/ethnic groups that are waitlisted for organ donation, and these disparities are likely to apply to children with end-stage liver disease (ESLD) as well.[13,14] First, African-American adults with ESLD are less likely to be referred for liver transplantation and are more likely to die while awaiting transplantation.[13] Second, use of LDLT is significantly reduced in African-American adults.[44] Third, racial/ethnic disparities exist in access for children with end-stage kidney disease awaiting transplantation, as well as in their use of living donation.[45] Fourth, Hsu *et al.* report that nearly one third of children on the liver transplant waitlist are ultimately transplanted through use of exception points, for which use differs by race/ethnicity.[46,47]

Given the evidence that racial/ethnic disparities exist among adults awaiting organ donation and children awaiting kidney donation, we evaluated whether these disparities exist for children awaiting liver transplantation. Specifically, we hypothesize that African-American children have lower rates of living donation for liver transplantation and that the lower rate cannot be explained by geographic consolidation around centers that do

not offer LDLT. Furthermore, given the lower use of exception points for African Americans, the possibility exists that this group is disadvantaged with respect to waitlist mortality and access to deceased livers.

METHODS

Data Source

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donors, waitlisted candidates, and transplant recipients in the U.S., submitted by the members of the Organ Procurement and Transplantation Network (OPTN) and has been described elsewhere.[22] The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services, provides oversight to the activities of the OPTN and SRTR contractors. The interpretation and reporting of these data are the responsibility of the author(s) and in no way should be seen as an official policy of, or interpretation by, the SRTR or the U.S. Government.

Study Population

This study included pediatric (age less than 18 years), liver-only transplant candidates who were initially listed between March 1, 2002 (i.e., implementation of PELD/MELD), and October 31, 2014. Data were administratively censored on March 31, 2015. Candidates listed for re-transplantation or listed as Status 1A were excluded from analysis.

Candidate Race/Ethnicity

Candidate race/ethnicity was classified as Caucasian/White (i.e., Caucasian non-Hispanic), African American/Black, Hispanic/Latino (i.e., Caucasian Hispanic), Asian, and mixed/other.

Hazard of Waitlist Outcomes by Candidate Race/Ethnicity Group

Waitlisted candidates were followed until they received a DDLT (either a whole liver transplant or segmental graft from a deceased donor), LDLT, or died. Death was defined by the date that an individual was removed from the waitlist due to death, medical unsuitability or refusal to transplant for declining health, or deteriorating condition, regardless of whether the candidate was active or not on the waitlist. The hazards of DDLT, LDLT, and mortality while on the waitlist were examined individually using Cox proportional hazards regressions to model the cause-specific hazards in unadjusted and adjusted models. In Cox proportional hazard models, individuals are followed from time entry (i.e., listing) to the time that they have an event (e.g., transplant, death), are lost-to-follow-up, or are administratively censored. In considering one of the three specific events, candidates were censored when either of the other two outcomes occurred (for example, in considering mortality, candidates were censored once they received either a DDLT or LDLT). This method allowed us to identify candidate-specific risk factors, including race/ethnicity and other potential biologic associations with waitlist outcomes independent of the effects of organ allocation.

Subhazard of Waitlist Outcomes Accounting for Organ Allocation

In order to evaluate the association between race/ethnicity and outcomes due to the allocation system, DDLT, LDLT, and mortality were considered together in a competing risk regression.[48] In a competing risk regression, instead of censoring candidates when an alternate outcome occurs, the subhazards account for the fact that the candidate is at

risk of more than one outcome and that these outcomes compete with each other. For example, if a candidate receives a LDLT, they are no longer at risk of receiving a DDLT.

Sensitivity Analysis of Centers Performing LDLT

To verify that any reduced rate of LDLT among African Americans (or any race/ethnic group) was not due to geographic consolidation away from centers where LDLT was not available, a sensitivity analysis was performed on centers that had performed ≥1 LDLT per year during the study period on pediatric recipients.

Statistical Analysis

Categorical variables were compared using a chi-square test. Comparison of continuous variables was made using Wilcoxon rank-sum test. Cox proportional hazard models were used to compare the hazard ratio (HR) for each outcome, as well as the subhazard ratio (sHR) in a competing risk model. All analyses were adjusted for primary diagnosis (i.e., biliary atresia, inborn error of metabolism, tumor, and other), weight, ABO blood type, status 1B, insurance status, and year. Age was excluded from the multivariable analysis because there was evidence of collinearity with weight (variance inflation factor >2.5), which would lead to overfitting of the model. Analyses were also adjusted using a patient's calculated or laboratory PELD/MELD score; based on prior research, exception points were considered a mediator between race/ethnicity and outcomes and therefore should not be included from adjustment in a multivariable model [46]. PELD was used for children on the waitlist before they turned 12 years old, and MELD was used for children on the waitlist who were older than 12 years. Because an individual's weight and PELD/MELD score change over time, these variables were treated as time-varying variables, meaning that the specific time that an individual spent at each level contributed separately to the risk of a given outcome. The multivariable model also

analyzed the change in the allocation score for every 5 points. There were no missing data for any variables in the model. The proportional hazards assumption was checked using complementary log-log curves. Statistical significance was tested using a two-sided α of 0.05. Confidence intervals are reported using the method of Louis and Zeger, as previously reported.[24,49] All analyses were performed using STATA 14.0 (College Station, TX, USA). This study was approved by the Institutional Review Board of Johns Hopkins University School of Medicine.

RESULTS

Waitlist Registrants

We studied 7,355 children on the liver waitlist including 1,184 (16.1%) African American, 3,927 (53.4%) Caucasian, 1,629 (22.1%) Hispanic, 390 (5.3%) Asian, and 225 (3.1%) children of mixed/other race/ethnicity (Table 1). Biliary atresia (BA) was the indication for transplant in 2,398 (32.6%) registrants, whereas 3,869 (52.6%) were listed for reasons other than BA, metabolic disease, or malignancy. The median (interquartile range (IQR)) calculated PELD/MELD score at listing was 15 (6-27). Among waitlisted children, 4,532 (61.6%) ultimately received a DDLT and 558 (7.6%) received a LDLT, whereas 631 (8.6%) children died on the waitlist and 1,634 (22.2%) were still on the waitlist at the end of the study.

Characteristics by Race/Ethnicity

Compared to Caucasians, African Americans had lower median age at listing (14 vs. 20 months; pairwise $P = 0.002$) and at removal (22.2 vs. 31.2 months; $P = 0.01$; Table 2) alongside lower median weight at listing (8.7 vs. 10.9 kg; pairwise $P < 0.001$) and at removal (10.2 vs. 12.0 kg; $P < 0.001$). At the same time, the median allocation score was higher for African Americans compared to Caucasians at listing (15 vs.10; pairwise $P <$

0.001) and at removal (17 vs.14; $P < 0.001$). ABO blood type and disease category also varied across all races (groupwise $P < 0.001$). African Americans were less likely to be granted exception points compared to Caucasian (30.7% vs 41.3%; pairwise $P < 0.001$), Asian (40%; $P = 0.001$), or Hispanic (35.2%; $P = 0.017$) children on the waitlist. Among those who ultimately received a DDLT, there was no difference in the use of whole liver transplantation compared to split liver transplantation by African-American and Caucasian recipients (split: 75.2 vs. 74.3%; pairwise $P > 0.05$).

Predictors of Outcomes on Waitlist

Compared to Caucasians, African Americans had significantly higher 1-year unadjusted cumulative incidence of DDLT (65.3% vs. 63.8%; competing risk model $P = 0.04$), lower LDLT (4.9% vs. 8.8%; $P < 0.001$) and similar mortality (8.5% vs. 8.3%; $P > 0.05$; Table 3). Hispanics had higher mortality than Caucasian non-Hispanics (10.1% vs 8.3%; $P = 0.02$), lower use of LDLT (7.0 vs 8.8; $P = 0.047$) and similar use of DDLT (64.1% vs 63.8%; $P > 0.05$). In an adjusted Cox proportional hazard model, African Americans were half as likely as Caucasians to receive LDLT (HR: $_{0.41}0.55_{0.73}$) compared with Caucasians (Table 4a), while having similar rate of mortality (HR: $_{0.79}1.00_{1.26}$) and DDLT (HR: $_{0.98}1.06_{1.16}$). In an adjusted model that that considered the competing risk of DDLT, LDLT, and mortality, African Americans continued to show decreased use of LDLT (sHR: $_{0.41}0.56_{0.75}$) compared with Caucasians but had corresponding higher risk of DDLT (sHR: $_{1.06}1.16_{1.26}$; Table 4b). Subhazard of mortality in a competing risk did not vary by race/ethnicity. Analysis of data that excluded inactive person time did not change the findings.

In the competing risk model, for every 5 points higher in allocation score (e.g., 35 vs. 30, 15 vs. 10), there was greater risk of mortality (sHR: $_{1.94}2.03_{2.12}$), LDLT (sHR: $_{1.25}1.31_{1.38}$)

and DDLT (sHR: $_{1.23}1.26_{1.28}$). However, compared to an allocation score of 40, status 1B was associated with lower mortality (sHR: $_{0.27}0.35_{0.45}$) and lower use of LDLT (sHR: $_{0.20}0.33_{0.54}$) but greater use of DDLT (sHR: $_{1.33}1.53_{1.77}$). Children ≤10 kg also had higher likelihood of death (sHR: $_{1.72}$ 2.13 $_{2.64}$), DDLT (sHR: $_{1.05}$ 1.14 $_{1.22}$) and LDLT (sHR: $_{1.77}$ 2.23 $_{2.82}$) compared with children weighing 15 kg or more. Individuals with blood type A (sHR: $_{1.24}1.33_{1.42}$) and AB (sHR: $_{.52}1.74_{2.00}$) had greater use of DDLT compared to individuals with blood type O, but did not have higher rate of mortality. Individuals with public insurance had lower use of LDLT (sHR: $_{0.45}0.54_{0.65}$), higher use of DDLT (sHR: $_{1.02}1.08_{1.15}$) and higher mortality (sHR: $_{1.16}1.38_{1.54}$). The probability of dying on the waitlist decreased each year from 2002 onward (sHR: $_{0.94}0.96_{0.99}$), while the probability of getting transplanted using DDLT (sHR: $_{1.02}1.03_{1.04}$) or LDLT (sHR: $_{1.02}1.04_{1.07}$) increased.

Center Impact

Among the 106 centers that performed a pediatric liver transplant over the study period, 89 centers performed at least one LDLT (84%), and 29 (27%) performed ≥1 LDLT per year. For individuals transplanted at centers performing ≥1 LDLT per year, the likelihood of LDLT for African Americans was one quarter that of Caucasians (sHR $_{0.39}0.25_{0.61}$; Table 5).

DISCUSSION

To the best of our knowledge, our study is the first to look at potential disparities for all outcomes (i.e., DDLT, LDLT, and death) for children awaiting liver transplantation since the adoption of the PELD/MELD system, and we demonstrate that disparities do exist for waitlisted children. Specifically, African Americans are half as likely as Caucasians to use LDLT. Furthermore, this observation was independent of insurance status, a factor

that is well-known to correlate with, but not thoroughly account for, socioeconomic status (SES). Therefore, other aspects of an individual's SES may provide additional explanation for reduced use of LDLT in African Americans. Our findings also suggest that these variations are not due to consolidation of African Americans around centers that don't offer LDLT. These data also indicate that African Americans correspondingly receive DDLT at increased rates compared with Caucasians, an observation that could not be explained by a lack of availability of LDLT at those centers. Finally, Hispanic children had higher mortality compared to Caucasian non-Hispanic children in an unadjusted analysis, but risk of mortality between these groups was similar after adjustment in the multivariable model.

While the probability of waitlist mortality does not vary across race/ethnic groups, the use of exception points is associated with reduced risk of mortality, and their use has been shown to correlate with race/ethnicity.[47,50] Specifically, a recent publication by Hsu *et al.* noted that, while exception score request were made for 34% of waitlisted children and granted for 90% of these requests, the rate of requests for non-Caucasian children throughout their time on the waitlist was significantly lower than for Caucasian children.[46] Not surprisingly, these exception points were associated with increased likelihood of transplantation. However, the authors found a lower, but not statistically significant, rate of transplantation for non-Whites, whereas we demonstrate a higher rate of DDLT for African Americans. This discordance is likely to be explained in that our analysis separates out living and deceased donors and that the lower use of LDLT among African Americans correlates with the higher use of DDLT in this group. Additionally, the earlier study did not report on racial differences in mortality, whereas our study suggests that the overall mortality is the same between groups.

We found that African Americans, compared to Caucasians, have younger age and lower weights at listing and removal from the list (i.e., death or transplant) while simultaneously they have higher allocation scores at listing and removal. It is not clear if these observations are the consequence of some bias on the part of providers, if the natural history varies by race such that African American children progress more rapidly toward ESLD, or if race is correlated with other socioeconomic determinants of Presently, there is little evidence to suggest that the natural history of biliary atresia, the indication for nearly half of all liver transplants, varies by race/ethnicity.[51,52] Similarly, there is no evidence that age at Kasai, an important predictor of outcomes in biliary atresia, is associated with race. At the same time, listing individuals when they have more severe disease, as evidenced by higher PELD/MELD score and lower weight, may make LDLT less feasible and may be associated with worse outcomes after transplantation.

The evaluation of the association between race/ethnicity and outcomes for individuals awaiting liver transplantation has been inconclusive, and research has been largely limited to studies of adult candidates that vary from children with respect to their underlying disorders. Reid *et al.* looked at outcomes for adult waitlist candidates in the pre-MELD era and found higher rates of mortality and lower rates of transplantation in African-American candidates compared to Caucasians.[53] However, two studies from the post-MELD era found equivalent likelihood of death and transplantation for African Americans and Caucasians.[54,55] Finally, a study of children with BA, the most common pediatric cause of ESLD, did not identify race/ethnicity as a risk factor for waitlist mortality but also did not specifically look at rates of LDLT.[51]

Our finding that African-American children waitlisted for transplant are half as likely to use LDLT is new, but not surprising. Several investigators have identified a range of barriers to transplantation experienced by racial/ethnic minorities awaiting transplantation, and have suggested these barriers are multifactorial.[13,14] For example, a study of adult liver transplant patients that collected data on the evaluation of potential living donors noted that African-American patients had less inquiries per patient for LDLT than Caucasian patients.[44] Although this study of waitlisted adult patients did not have additional socioeconomic data of potential living donors or recipients, reports from the kidney transplant literature show a similar decrease in the rates of living donation among African Americans and these have been attributed to financial concerns, reluctance to ask family members, distrust of the medical community, and lack of health literacy or understanding of the process.[14,44,56,57] One limitation from our study is that the only socioeconomic status variable recorded in SRTR is insurance status, which does not fully represent a true surrogate. Consequently, we are not able to explain how varying rates of LDLT by race may be due in part to variations in socioeconomic status such as education and cultural literacy or frequency of single-income household.

Although pre-transplant mortality was comparable for African Americans and Caucasians, lower rates of LDLT in African Americans may have significant effects on both their pre-transplant morbidity as well as their post-transplant morbidity and mortality. Specifically, studies of adult candidates awaiting transplant have demonstrated that patients undergoing LDLT are transplanted at lower MELD scores and consequently have lower pre-transplant length of hospital stay, length of stay in the intensive care unit, and lower hospital costs.[6] Similar discrepancies in pre-transplant morbidity likely occurs among children awaiting transplantation. At the same time, living donation may be associated with improved patient and graft survival compared to deceased

donation.[21,43,58] Therefore, lower rates of LDLT among African-American children awaiting transplantation has implications that extend beyond access to treatment for ESLD, but to long-term morbidity and mortality as well.

It is clear that increasing the supply of available organs will positively affect quality of life for children awaiting transplantation, and earlier transplantation would likely have a positive impact on long-term outcomes following transplantation as well. Living donation is one important method of increasing this supply. While our study identifies African-American children as being listed at higher PELD/MELD scores and less likely to use a living donor, our study is limited in its ability to identify the root cause of these disparities. Do physicians advocate for this approach at different rates depending on race/ethnicity? Are the patients' families unaware LDLT is an option? Is the decision to pursue LDLT or DDLT influenced heavily by the family's available resources and ability to interrupt a source of income while care is being provided to both the sick child and the donor? Or do other variables such as health literacy or differences in culture account for reduced rates of living donation? Depending on the reason for decreased rates of LDLT in African-American children, there may be solutions that would yield higher rates of living donation to the benefit of African Americans and all waitlisted children.

Table 1: Characteristics of pediatric waitlist registrants

Characteristic	No. (%)
Age in months (median, IQR)	
at listing	16 (7-101)
at end of follow-up*	25.5 (10.3-114.6)
Weight in kg (median, IQR)	
at listing	9.7 (6.6-24.8)
at end of follow-up	11 (7.3-26.3)
Female	3,726 (50.7)
Race/ethnic group	
African American	1,184 (16.1)
Caucasian	3,927 (53.4)
Hispanic	1,629 (22.1)
Asian	390 (5.3)
mixed/other	225 (3.1)
Blood type	
O	3,648 (49.6)
A	2,467 (33.5)
B	952 (13)
AB	288 (3.9)
Disease	
biliary atresia	2,398 (32.6)
metabolic disease	211 (2.9)
malignancy	877 (11.9)
other	3,869 (52.6)
Outcome	
death	631 (8.6)
living-donor liver transplant	558 (7.6)
deceased donor liver transplant	4,532 (61.6)
whole liver transplant	3,304 (72.9)
split/partial	1,228 (27.1)
censored	1,634 (22.2)
PELD/MELD score (median, IQR)	
at listing	15 (6-27)

at end of follow-up	27 (15-40)
Status 1B	323 (4.4)
Private insurance	3,392 (46.1)

*end of follow-up occurs at transplantation, death, or administrative censoring

Table 2: Patient characteristics by race/ethnicity

	Caucasian	African American	Hispanic	Asian	mixed/other	*P**
Number	3,927	1,184	1,629	390	225	
Age in months (median, IQR)						
at listing	20 (7-121)	14 (7-102.5)	14 (6-70)	13 (7-74)	10 (6-30)	<0.001
at end of follow-up**	31.2 (10.7-131)	22.2 (10.9-113.2)	23 (9.9-87.6)	21.3 (9.5-88.7)	15.2 (8.0-39.1)	<0.001
Weight in kg (median, IQR)						
at listing	10.9 (6.7-20.6)	8.7 (6.3-25.5)	9.0 (6.6-19.0)	8.9 (6.8-18.6)	7.8 (6.2-12.5)	<0.001
at end of follow-up*	12.0 (7.4-30.3)	10.2 (7.2-27.0)	10.3 (7.4-21.0)	10.3 (7.4-19.6)	9.0 (6.9-13.7)	<0.001
Female (%)	49.6	52	53.3	47.4	48.9	>0.05
Blood type (%)						
O	46.3	47.8	60.4	40.8	53.8	<0.001
A	39.3	25	28.2	25.6	31.1	
B	10.4	21.8	8.8	29.7	11.5	
AB	4	5.4	2.6	3.9	3.6	
Years of follow-up (med, IQR)	0.5 (0.2-1.5)	0.5 (0.2-1.5)	0.4 (0.2-1.3)	0.5 (0.2-1.1)	0.4 (0.2-1.0)	>0.05
PELD/MELD (median IQR)						
at listing	10 (6-18)	15 (7-21)	11 (6-20)	12 (6-20)	15 (6-22)	<0.001
at end of follow-up	14 (6-22)	17 (9-23)	15 (6-23)	13 (6-21)	18 (8-27)	<0.001
Exception points (%)	41.3	30.7	35.2	40	28.9	<0.001
Status 1B (%)	4.3	4	4.8	3.6	6.7	>0.05
Disease (%)						
biliary atresia	29.7	36.5	32.3	46.7	40	<0.001
metabolic	3.6	1.3	3	1.8	0.9	
malignancy	12.8	7.5	12.8	13.1	11.5	
other	53.9	54.7	51.9	38.4	47.6	
Private insurance (%)	59.4	30.9	24.1	58.5	33.3	<0.001

*Groupwise *P* values

**End of follow-up occurs at transplantation, death, or administrative censoring.

Table 3: 1-year unadjusted cumulative incidence by race/ethnic group

	Mortality (%)	*P*	DDLT (%)	*P*	LDLT (%)	*P*
Caucasian non-Hispanic	8.3	--	63.8	--	8.8	--
African American	8.5	>0.05	65.3	0.04	4.9	<0.001
Hispanic	10.1	0.02	64.1	>0.05	7	0.047
Asian	7	>0.05	68	>0.05	10.1	>0.05
mixed/other	14.3	0.001	64.9	>0.05	5.7	>0.05

DDLT = decreased donor liver transplant; LDLT = living donor liver transplant
P value from coefficient in competing risk regression

Table 4: Estimates of Hazard Ratios (HR) by Outcome

	Mortality	DDLT	LDLT
Race/ethnic group			
Caucasian non-Hispanic	--	--	--
African American	0.79**1.00**1.26	0.98**1.06**1.16	**0.41****0.55****0.73**
Hispanic	0.94**1.14**1.39	0.92**0.99**1.08	0.73**0.92**1.15
Asian	0.71**1.06**1.59	0.93**1.06**1.21	0.67**0.94**1.33
mixed/other	0.97**1.41**2.06	0.79**0.94**1.11	0.41**0.70**1.20
Allocation score (per 5 points) increase)	**1.94****2.03****2.12**	**1.23****1.26****1.28**	**1.25****1.31****1.38**
Status 1B (to PELD/MELD 40)	**0.27****0.35****0.45**	**1.33****1.53****1.77**	**0.20****0.33****0.54**
Diagnosis			
biliary atresia	--	--	--
metabolic disease	0.26**0.70**1.92	1.00**1.18**1.39	0.34**0.62**1.15
malignancy	0.49**0.74**1.13	**1.04****1.16****1.30**	0.54**0.78**1.12
other	**1.75****2.16****2.66**	**0.64****0.69****0.74**	**0.35****0.43****0.52**
Weight			
≥15 kg	--	--	--
10-15 kg	**1.19****1.57****2.06**	0.85**0.93**1.02	**1.14****1.52****2.03**
≤10 kg	**1.72****2.13****2.64**	**1.05****1.14****1.22**	**1.77****2.23****2.82**
Blood type			
O	--	--	--
A	0.93**1.11**1.33	**1.24****1.33****1.42**	0.91**1.09**1.31
B	0.96**1.22**1.54	1.00**1.10**1.21	0.81**1.05**1.36
AB	0.39**0.70**1.25	**1.52****1.74****2.00**	0.38**0.69**1.22
Insurance			
private	--	--	--
public/other	**1.16****1.38****1.54**	**1.02****1.08****1.15**	**0.45****0.54****0.65**
Year (2002 reference)	**0.94****0.96****0.99**	**1.02****1.03****1.04**	**1.02****1.04****1.07**

DDLT = deceased donor liver transplant; LDLT = living donor liver transplant

Table 5: Estimates of Subhazard Ratios (sHR) by Outcome

	Mortality	DDLT	LDLT
Race/ethnic group			
Caucasian non-Hispanic	--	--	--
African American	0.74 0.94 1.19	**1.06 1.16 1.26**	**0.41 0.56 0.75**
Hispanic	0.89 1.10 1.36	0.91 0.99 1.07	0.71 0.90 1.13
Asian	0.57 0.87 1.34	0.90 1.04 1.20	0.65 0.91 1.28
mixed/other	0.92 1.37 2.06	0.77 0.93 1.13	0.39 0.66 1.14
Allocation score (per 5 point increase)	**1.60 1.69 1.77**	**1.06 1.08 1.11**	**1.07 1.13 1.19**
Status 1B (to PELD/MELD 40)	**0.23 0.32 0.44**	**1.80 2.12 2.50**	**0.21 0.34 0.54**
Diagnosis			
biliary atresia	--	--	--
metabolic disease	0.27 0.74 2.06	**1.03 1.18 1.36**	0.31 0.57 1.03
malignancy	0.50 0.81 1.33	**1.15 1.29 1.45**	**0.40 0.57 0.81**
other	**2.47 3.09 3.86**	**0.65 0.69 0.75**	**0.38 0.46 0.56**
Weight			
≥15 kg	--	--	--
10-15 kg	**1.09 1.44 1.89**	0.77 0.84 0.92	**1.15 1.52 2.01**
≤10 kg	**1.23 1.53 1.91**	**0.79 0.86 0.93**	**1.45 1.81 2.27**
Blood type			
O	--	--	--
A	0.77 0.93 1.12	**1.16 1.24 1.33**	0.76 0.92 1.11
B	0.91 1.17 1.49	0.94 1.04 1.15	0.73 0.95 1.24
AB	**0.25 0.45 0.82**	**1.57 1.83 2.14**	**0.27 0.48 0.85**
Insurance			
private	--	--	--
public/other	**1.10 1.33 1.53**	**1.04 1.11 1.19**	**0.43 0.52 0.63**
Year (2002 reference)	**0.91 0.93 0.95**	**1.03 1.04 1.05**	1.00 1.03 1.06

DDLT = deceased donor liver transplant; LDLT = living donor liver transplant

Table 6: Estimates of Subhazard Ratio (sHR) for Living Donor Liver Transplantation (LDLT) for Individuals Waitlisted at Centers Performing ≥3 LDLT

Race/ethnic group	LDLT
Caucasian non-Hispanic	--
African American	**$_{0.38}$0.53$_{0.72}$**
Hispanic	$_{0.72}$0.92$_{1.16}$
Asian	$_{0.70}$1.00$_{1.42}$
mixed/other	$_{0.43}$0.74$_{1.28}$

Chapter 4. Barriers to Access in Pediatric Living-donor Liver Transplantation

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ABSTRACT

Background: Children receiving a living-donor liver transplant (LDLT) have superior post-transplant outcomes but this procedure is only used for 10% of transplant recipients. Better understanding about barriers toward LDLT and the sociodemographic characteristics that influence these variables would help to inform strategies to increase its use.

Methods: Using a convenience sample, we conducted an online, anonymous survey of parents and caregivers for children who are awaiting, or have received, a liver transplant regarding their knowledge and attitudes about the procedure.

Results: The survey was completed by 217 respondents including 27 (12%) parents of children that are currently being evaluated/waitlisted and 190 (88%) parents of children that have been transplanted. We found that while 97% of respondents understood that an individual could donate a portion of their liver, only 72% knew the steps in the process, and 69% understood that the donor surgery was covered by the recipient's insurance. Individuals with public insurance were significantly less likely than those with private insurance to know the steps for living donor evaluation (44% vs 82%; $P < 0.001$). Only 38% of respondents correctly understood that outcomes following living donation are better than deceased donation, whereas 46% thought the outcomes were the same, 17% thought living donation was worse, and 9% of respondents had no opinion about relative outcomes for each surgery. Respondents with public insurance were less likely than those with private insurance to know someone who had been a living donor (44% vs 56%; $P = 0.005$) as were individuals without a college degree compared to those with a college degree (64% vs 85%; $P = 0.007$). Nearly all respondents generally trusted their healthcare team. Among respondents, 82% believed they were well-informed about

LDLT but individuals with public insurance were significantly less likely to feel well-informed about LDLT (67% vs 87%; *P* = 0.03) and to understand how the donor surgery might impact donor work/time-off (44% vs 81%; *P* = 0.001).

Conclusion: Substantial gaps exist in parental understanding about LDLT, including the process of living-donor evaluation, its potential benefits, and complications. Greater emphasis on addressing identified barriers to access of LDLT, especially communication to individuals with fewer resources, such as those receiving public insurance, will be helpful to expand the use of LDLT.

INTRODUCTION

Liver transplantation is the definitive cure for children with end-stage liver disease and has provided life-saving therapy to more than 5,000 children in the United States over the past decade.[42] Outcomes following transplant are excellent with an overall 1-year patient survival of 93% and 1-year graft survival of 89%.[59] Living-donor liver transplantation (LDLT), although more surgically complex than whole liver transplantation (WLT), has superior outcomes with a 96% 1-year patient survival and 94% 1-year graft survival. This finding is particularly exciting because LDLT provides an opportunity to transplant children before they develop substantial pre-transplant morbidity and to mitigate the risk of dying on the waitlist. Despite these benefits, only 10% of pediatric liver transplant candidates are transplanted using a living donor and its use has been stable over recent years.[5,59,60]

Purnell et al. created a framework that describe how access to care in living donation is influenced by patient/donor, provider, healthcare system, and community factors.[61] Much of what is known about barriers in access to living-donor transplantation has been observed within the context of adult kidney transplantation. First, studies of adult kidney transplant patients suggest that candidates may lack information about living donation including benefits to the recipient and the potential risk/safety for the donor.[14–16,62] Second, evidence exists from this population that some patients and potential donors may have general mistrust of the medical community and therefore seek to avoid an additional surgery.[63] Third, candidates and their families may have, or perceive they have, limited social networks or individuals that they feel comfortable approaching about living donation.[64–66] Fourth, there may be social or financial limitations on an individual's ability to pursue living donation.[67–70] And fifth, transplant teams may variably support the option of living donation for their patients, such that the option is not offered at their

center or even region. Socioeconomic characteristics have also been shown in liver transplantation to influence access of LDLT and further promote health disparities in both adult and pediatric candidates.[71–75] For example, children on public insurance are half as likely to use a living donor as children with private insurance, and African-American children are half as likely as Caucasian children to be transplanted with a living donor.

To better understand barriers toward access of LDLT for pediatric candidates, and to explore how these barriers may be influenced by sociodemographic characteristics, we surveyed online Facebook communities of parents and caregivers for children who are awaiting, or have received, a liver transplant. This information could then help to identify potential strategies to increase the use of LDLT for pediatric candidates awaiting transplantation.

METHODS

Study Population

The study population was a convenience sample of parents of children (<18 years) who are currently being evaluated for a liver transplant, waitlisted for transplant, or recipients of a liver transplant. Parents who were >18 years of age and able to speak English were eligible to participate.

Recruitment Strategy

Respondents were recruited over Facebook using several mechanisms from February to April, 2018. First, respondents were recruited through Liver Space “app,”, a Facebook-integrated app that is free and available on the Apple and Android stores and that has been described elsewhere.[76] Briefly, Liver Space provides users with several functions

such as the ability to receive the latest news of interest to the user, ask-an-expert questions, locate other members of the community to arrange meetups, and track laboratory results. At the beginning of the study period, Liver Space had 450 users including 38% parent/caregivers, 51% patients and 11% healthcare providers. Among users, 23% were listed as transplant recipients. Second, respondents were recruited through the Liver Space "page" on Facebook, which had 982 followers at the start of the recruitment period. Third, two paid Facebook campaigns directed toward adults with interest in liver issues were promoted in a campaign that had a combined reach of 2,099 people. And finally, Facebook posts were shared over five large groups, each with greater than 1,000 members and are focused on pediatric liver disease or liver transplantation. Respondents were informed that participation was voluntary, and they would not be reimbursed for completing the study. The anonymous study was exempted by the Institutional Review Board of the Johns Hopkins University School of Medicine.

Instrument

The survey was developed by study team members including individuals with expertise in transplant hepatology, clinical research, survey development, health services research, epidemiology, and health disparities research. The anonymous, quantitative survey consisted of 44 questions including 25 questions addressing knowledge and attitudes about transplantation that used a 5-point Likert scale (i.e., "strongly agree," "somewhat agree," "neutral," "somewhat disagree," and "strongly disagree"). Questions assessed the following potential barriers: (1) *knowledge about the living donor evaluation process,* including an understanding that a family member or friend can donate a part of their liver, the steps for evaluation, and that the cost of donor surgery and follow-up is covered by recipient's insurance; (2) *knowledge about outcomes following living donation* as compared to WLT; (3) size and nature of an individual's

social network, including whether they knew someone that been evaluated, or served, as a living donor; the number of people with whom they discuss health-related issues; and their perception of how it might affect relationships; (4) *trust in the medical community*, including whether they trust their doctor to do the right thing, typically agree with their doctor, and felt their questions were answered; and (5) their perception about *provider communication* as it relates to concerns about outcomes for the donor, outcomes for the recipient, and concerns about the burden associated with donation.

Respondents were also asked additional questions that further characterized their sociodemographic background including: (1) insurance status, i.e., public (exclusively Medicaid or public insurance connected to income) versus private or mixed public/private; (2) education level; (3) marital status, i.e., single versus married or living with partner; (4) employment status, i.e., fully employed, part-time employed, homemaker, other; (5) number of working adults in the house; and (6) race/ethnicity. Their technological "fluency" (i.e., frequency and use of digital devices) was also assessed. They survey was pilot tested for grammar and clarity by patients. The survey was created and distributed through Qualtrics (Provo, UT).

Missing Data

Among 217 eligible respondents, missingness from the survey occurred for the following demographic variables: sex (n = 56), race/ethnicity, marital status, employment, education, and number of working adults (n = 58). At least one missing demographic variable occurred in 85 (39%) respondents. A missing indicator variable was created in order to test whether missingness affected responses to a random selection of questions from the domains. In all instances, missingness was not associated with the response

and subsequent analyses were therefore made only for individuals that had complete data without imputation of missing data.

Statistical Analysis

Data were summarized using frequencies, percentages, medians, and interquartile ranges (IQR). Associations between categorical variables were tested using a Fisher's exact (when $n < 5$) or chi-squared tests, whereas associations between ordinal variables used a Wilcoxon rank sum test. Questions using a 5-point Likert scale were ultimately dichotomized to compare the two affirmative responses (i.e., “strongly agree” and “somewhat agree”) with the remaining three options (i.e., “strongly disagree,” “somewhat disagree,” and “neutral”). Statistical significance was assessed at the $\alpha = 0.05$ confidence level. All analyses were performed using Stata 14.0/MP for Apple (College Station, TX).

RESULTS

Study Population

A total of 217 eligible individuals completed the survey including 27 (12%) that were parents of children being evaluated or waitlisted for a liver transplant and 190 (88%) that were parents of children that had received a transplant; 34 individuals were excluded because their child was neither being evaluated or waitlisted for transplant, nor had they received a transplant. There was no difference in the demographic characteristics of respondents of children that were evaluated/waitlisted compared to children that had already been transplanted (Table 1). Respondents were mostly female (93%) with a median age of 38 (IQR: 34-45) years and the median age of the child was 5 (2-11) years. The insurance status of participants included 64% with only private insurance, 12% with only Medicaid, and 24% with a combination of public and private payers. The

majority of participants were married or living with a partner (86%). Half of respondents were fully employed and 61% were from families that had >1 working adult. A college degree was obtained by 77% of participants. Among respondents, 87% identified as white non-Hispanic, 4% Asian, 3% African American, 3% Hispanic, and 4% mixed/other. The respondents were technologically fluent, with 94% owning multiple digital devices (i.e., smartphones, tablets, computers) and 99% using these devices for at least 1 hour each day. Their health status was rated as at least "good" by 91% of respondents.

Knowledge of Living-Donor Evaluation

When asked about their understanding of living donation, 97% were aware that LDLT was an option and 90% knew who to ask about the process, but only 72% were knowledgeable about the actual steps and 69% were aware that costs were covered by the recipient's insurance (Table 2). Awareness that LDLT was an option was similar for parents of children that are currently being evaluated or waitlisted compared to transplant recipients (91% vs 98%; $P = 0.1$), but the former were less likely to know who to ask (65% vs 93%; $P < 0.001$), know the steps for evaluation (44% vs 77%; $P = 0.001$), or know that the cost of the procedure was covered by the recipient's insurance (43% vs 77%; $P = 0.004$).

Insurance status (exclusively public vs private/mixed) was not associated with general awareness that LDLT is an option (100% vs 98%; $P = 0.6$), knowledge about which provider to ask about the evaluation (89% vs 95%; $P = 0.3$), or knowledge that the donor surgery is covered by the recipient's insurance (61% vs 78%; $P = 0.1$), but respondents with public insurance were nearly half as likely to know the actual steps for LDLT evaluation (44% vs 82%; $P < 0.001$). Similarly, single parents were equally likely to be aware that LDLT is an option (96% vs 99%; $P = 0.3$) and which provider to ask about the

evaluation (92% vs 100%; *P* = 0.2), but significantly less likely to know the specific steps for the evaluation (57% vs 81%; *P* = 0.01) or that the cost of the donor surgery was covered by the recipient's insurance (52% vs 76%; *P* = 0.02). Employment status (i.e., full-time employment vs non-full-time employment), number of working adults in the house, education level, and race/ethnicity were not associated with knowledge about LDLT, which provider to ask about the evaluation, the steps for evaluation, or insurance coverage for the procedure.

Outcomes Following Living Donation

Only 38% of respondents correctly understood that outcomes following living donation are better than deceased donation, whereas 46% thought the outcomes were the same, 17% thought deceased donation was worse, and 9% of respondents had no opinion about relative outcomes for each surgery. Understanding about outcomes following LDLT was not associated with whether the respondent's child was currently being evaluated or waitlisted or had been transplanted (*P* = 0.3). Single parents were more likely than parents that were married or living with a partner to believe outcomes were worse following living donation (22% vs 4%; *P* = 0.03); otherwise, insurance, educational, employment, or race/ethnicity were not associated with knowledge about outcomes following LDLT compared to deceased donation.

Social Network

Over 90% of respondents indicated they had at least 2 individuals with whom they were comfortable asking to be a living donor. The number of people with whom respondents would be comfortable asking to consider living donation for their child was independent of a respondent's sociodemographic background. Likewise, whereas 26% of respondents believed that asking a friend or family member about potentially being a

donor may cause stress in the relationship, this belief was independent of sociodemographic variables. Respondents with public insurance were less likely than those with private insurance to actually know someone who had been a living donor (44% vs 56%; *P* = 0.005) as were individuals without a college degree compared to those with a college degree (64% vs 85%; *P* = 0.007). Employment status, number of working adults in household, or race/ethnicity were not associated with knowing someone who had been a living donor.

Trust in Medical Community

Although some respondents were told they were ineligible to donate (16%), among parents that perceived they could be considered potential LDLT donors (n = 157), 97% were comfortable with the idea. Over 90% of respondents indicated that they liked their doctor, trusted their doctor to do the right thing for their child, generally agreed with the treatment plan, and felt their doctor answered all their questions (Table 3). Respondents with public insurance were equally likely to trust their child's doctor, agree with the medical plan, and feel their questions were answered but were less likely to like their doctor than individuals with private insurance (83% vs 97%; *P* = 0.04). Neither parental education level nor marital status were associated with trust in the medical community. However, while having ≤1 working adult in the household was not associated with trust in the medical community, fully-employed parents were more likely to trust their doctor (99% vs 91%; *P* = 0.03) and feel their questions were answered (99% vs 89%; *P* = 0.02). Race/ethnicity was not associated with any aspect of trust in the medical community.

Provider Communication

Overall, 82% of respondents believed they were generally well-informed by their healthcare team about LDLT (Table 4). Parents of children who are currently undergoing evaluation or waitlisted were less likely than children who have been transplanted to feel well-informed (43% vs 87%; $P < 0.001$). Individuals with public insurance were less likely to feel well-informed about LDLT (67% vs 87%; $P = 0.03$) whereas this perception did not vary by marital status, education, employment, or race/ethnicity. Only 86% of respondents believed they were well-informed about complications to the recipient and 76% believed they were well-informed about potential complications to the donor, and this was independent of sociodemographic background.

With respect to feeling well-informed about the impact of living donation on the donor's work (i.e., time off), 75% felt they were adequately informed, but this was lower in individuals on public insurance (44% vs 81%; $P = 0.001$). Otherwise, education, employment, marital status or race were not associated with whether respondents considered themselves fully informed about the impact of LDLT on donor work.

DISCUSSION

There is tremendous need to better understand barriers toward access of LDLT for pediatric candidates given that outcomes following LDLT are better than deceased donation and that the procedure offers opportunities to reduce waitlist morbidity and mortality. Among our cohort of largely healthy parents, a number of important observations can be identified regarding barriers toward LDLT and factors that potentiate these barriers. First, while nearly all parents were broadly aware of living donation as an option, substantially fewer were knowledgeable about the process including which providers to ask, what are the steps, and that the procedure is covered by insurance. Parents with public insurance or from single-parent households were less likely to

understand the process. Second, 18% of parents felt they were generally poorly informed by their providers about LDLT and 24% felt they were specifically not well-informed about risk to the donor, or the impact on the donor's work. Third, only approximately one-third of parents correctly knew that outcomes following LDLT were actually better than deceased donation. Fourth, while many of the respondents were generally comfortable asking several people to be a living donor, one quarter believed this may cause stress in a relationship. And fifth, low use of living donation cannot be explained by a lack of trust in the medical community.

While most respondents were aware that living donation is an option, it is concerning that a large percentage of parents do not know basic aspects of the process such as which provider to ask, what are the relative outcomes compared to deceased donation, and what are complications for the donor and recipient. One explanation may be that many respondents are receiving care for their children at centers where LDLT is not performed and that less information may be provided to families at these centers. Presently, LDLT is only offered in approximately a quarter of all programs.[77] However, it is an ethical requirements for informed consent that people be well-informed about *all* options, and the Center for Medicare Services mandates that people undergoing evaluation for transplantation be presented with patient and graft survival for both deceased and living donation.[78] Therefore, a lack of availability of LDLT at a specific center is not a sufficient explanation to justify a lack of understanding about its outcomes, the process, and the specific risks and benefits of the procedure.

Several encouraging observations should be noted. First, individuals generally trusted their doctors and believed that their healthcare team would do the right thing for the

patient. Second, individuals generally reported strong social networks and willingness to discuss living donation with other people.

The association between specific sociodemographic characteristics and reduced use of LDLT have been reported elsewhere.[79] In a large registry study of children with biliary atresia, individuals with public insurance had significantly lower rates of LDLT, which is not surprising given that public insurance can serve as a proxy for lower income and fewer resources, alongside the observation that the procedure is associated with increased financial burden for donors.[67,71] Here, we explore in greater detail other potential mechanisms that may act as barriers, including that this population is less likely to know the steps for living donor evaluation, to feel generally well-informed about LDLT, to understand how LDLT may impact their work and other responsibilities, and to know someone that had gone through the process. Lack of adequate information is also evident with single parents and this finding has been reported from adult studies as well.[80]

Sociodemographic variables such as insurance status likely mediate the relationship between race/ethnicity and access to living donation, and substantial research exists in the adult liver and kidney literature as well as pediatric kidney literature that may help elucidate these barriers.[81] For example, studies have identified that African Americans are more likely to be concerned about the procedure's impact on personal relationships and concerns about finances, to have greater distrust of the medical community, and to have decreased medical literacy as it relates to LDLT.[14,45,56,57] Among African Americans, these barriers have been shown to lead to fewer inquiries by potential living donors per candidate.[82]

Unfortunately, one major limitation of our study was the low response rate of non-Caucasian individuals in our sample, making it impossible to understand any potential impact of race/ethnicity on the use of living donation in pediatric liver candidates; although Facebook is used by all racial/ethnic groups equally at around 75%, it has been reported that African Americans may be less willing to share health information online compared with other groups.[83–85] A second limitation of our study is that it was distributed over social media, allowing for the possibility that our sample is not broadly representative of the population of parents of children with end-stage liver disease. Rather, our cohort may represent a sample that is both more trusting of healthcare providers/scientists such that they are willing to complete a survey, and that they are more open to sharing their health experiences and struggles.

These findings highlight the need for programs to provide additional education to the community, through public forums, social media, and other mechanisms to provide comprehensive information to all individuals.[86] Although we didn't measure health literacy directly, education level has been shown to correlate with health literacy in the transplant population.[87,88] Navigating the transplant process, from referral through surgery, has been shown to depend heavily on education, and this need is especially true for living donor transplantation.[89,90] Fortunately, evidence exists from clinical trials of adult kidney transplant candidates that educational programs can lead to higher knowledge and fewer concerns with living donation as well as an increase the number of donor inquiries.[91] Application of education programs regarding LDLT to the pediatric liver community can therefore be reasonably expected to increase its use, further decrease waitlist morbidity and mortality, and lead to better long-term survival.

Table 1: Demographic characteristics of survey respondents

	All	Evaluated/ Waitlisted	Transplanted	*P*
Female, n (%)	149 (93)	14 (88)	135 (93)	0.3
Parent age (years), median (IQR)	38 (34-45)	36 (31-42)	38 (34-45)	0.2
Child age (years), median (IQR)	5 (2-11)	4 (1-6)	5 (2-11)	0.2
Insurance, n (%)				
public	18 (12)	3 (20)	15 (11)	0.1
private	93 (64)	6 (40)	87 (66)	
mixed	35 (24)	6 (40)	29 (22)	
Marital status, n (%)				
single	23 (14)	2 (13)	21 (15)	0.9
married/partner	136 (86)	14 (88)	122 (85)	
Employment, n (%)				
full-time	81 (51)	9 (56)	72 (50)	0.4
part-time	21 (13)	3 (19)	18 (13)	
homemaker	43 (27)	2 (13)	41 (29)	
other	14 (9)	2 (13)	12 (8)	
Number of working adults in house, n (%)				
≤1	62 (39)	5 (31)	57 (40)	0.5
>1	97 (61)	11 (69)	86 (60)	
Education, n (%)				
less than college degree	36 (23)	5 (31)	31 (22)	0.4
college degree	123 (77)	11 (69)	112 (78)	
Race/ethnicity, n (%)				
Caucasian non-Hispanic	138 (87)	13 (81)	125 (87)	0.4
other	21 (13)	3 (19)	18 (13)	
Device ownership, n (%)				
multiple	149 (94)	14 (88)	135 (94)	0.3
single (smartphone or computer)	10 (6)	2 (13)	8 (6)	
Access of internet >1 hour per day, n (%)	157 (99%)	16 (100)	141 (99)	0.9

Health status (of respondent), n (%)				
poor or fair	15 (9)	0 (0)	15 (11)	0.4
good, very good or excellent	143 (91)	16 (100)	127 (89)	

Table 2: Understanding about living donation and steps for evaluation

	Family/friend can donate		Which provider to ask about evaluation		Steps for evaluation		Costs covered by recipient insurance	
	%	*P*	%	*P*	%	*P*	%	*P*
Overall	97	--	90	--	72	--	69	--
Transplant status								
evaluated/waitlisted	91	0.1	65	<0.001	43	0.001	43	0.004
transplanted	98		93		77		73	
Insurance								
public	100	0.6	89	0.3	44	<0.001	61	0.1
mixed or private	98		95		82		78	
Marital status								
single	96	0.3	100	0.2	57	0.01	52	0.02
married/partner	99		92		81		76	
Employment								
full-time	99	0.9	96	0.1	77	0.8	73	0.9
other	99		90		78		73	
Number of working adults in house								
≤1	98	0.9	95	0.5	77	0.9	71	0.7
>1	99		92		77		74	
Education								
less than college degree	100	0.9	92	0.7	78	0.9	67	0.3
college degree	98		94		77		75	
Race/ethnicity								
Caucasian non-Hispanic	99	0.9	94	0.2	77	0.7	75	0.2
other	100		86		81		62	

Table 3: Trust in medical community

	Trust medical team		Agree with medical team		Like medical team		Team answered questions	
	%	*P*	%	*P*	%	*P*	%	*P*
Overall	94	--	93	--	93	--	94	--
Insurance								
public	94	0.9	89	0.3	83	0.04	94	0.5
mixed or private	95		95		97		96	
Marital status								
single	100	0.6	100	0.4	100	0.4	100	0.4
married/partner	94		92		93		94	
Employment								
full-time	99	0.03	96	0.1	95	0.5	99	0.02
other	91		90		92		89	
Number of working adults in house								
≤1	92	0.3	89	0.1	92	0.5	91	0.1
>1	97		96		95		97	
Education								
less than college degree	89	0.1	89	0.3	92	0.7	94	0.9
college degree	97		94		94		94	
Race/ethnicity								
Caucasian non-Hispanic	95	0.9	93	0.6	93	0.9	95	0.3
other	95		90		95		90	

Table 4: Provider communication about living-donor liver transplantation

	Well-informed		Complications to recipient		Complications to donor		Impact on donor work	
	%	*P*	%	*P*	%	*P*	%	*P*
Overall	82	--	86	--	76	--	75	--
Transplant status								
evaluated/ waitlisted	43	<0.001	75	0.3	75	0.9	69	0.5
transplanted	87		87		76		76	
Insurance								
public	67	0.03	72	0.05	61	0.1	44	0.001
mixed or private	87		89		79		81	
Marital status								
single	74	0.1	91	0.7	70	0.4	74	0.9
married/partner	86		84		77		75	
Employment								
full-time	85	0.7	89	0.2	79	0.4	78	0.4
other	83		82		72		71	
Number of working adults in house								
≤1	85	0.7	87	0.7	77	0.8	75	0.9
>1	84		85		75		74	
Education								
less than college degree	81	0.5	89	0.8	74	0.8	66	0.2
college degree	85		84		76		77	
Race/ethnicity								
Caucasian non-Hispanic	85	0.7	86	0.5	76	0.9	74	0.6
other	81		81		76		81	

CHAPTER 5. Expansion of the Liver Donor Supply Through Greater Use of Split Liver Transplantation: Identifying Optimal Recipients

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ABSTRACT

Background: The increased use of split liver transplantation (SLT) represents one strategy to increase the supply of organs. Although outcomes after SLT and whole liver transplantation (WLT) are similar on average among pediatric recipients, we hypothesized that the relationship between graft type and outcomes may vary depending on patient, donor, and surgical characteristics.

Methods: We evaluated graft survival among pediatric (<18 years), deceased-donor, liver-only transplant recipients from March, 2002, until December, 2015, using data from the Scientific Registry of Transplant Recipients. Graft survival was assessed in a Cox proportional hazards model, with and without effect modification between graft type and donor, recipient, and surgical characteristics, to identify conditions where the risk of graft loss for SLT and WLT were similar.

Results: In a traditional multivariable model, characteristics associated with graft loss included donor age >50 years, recipient weight <10 kg, acute hepatic necrosis, autoimmune diseases, tumor, public insurance, and cold ischemia time (CIT) >8 hours. In an analysis that explored whether these characteristics modified the relationship between graft type and graft loss, many characteristics associated with loss actually had similar outcomes irrespective of graft type including weight <10 kg, acute hepatic necrosis, autoimmune diseases, and tumor. In contrast, several subgroups had worse outcomes when SLT was used, including recipient weight 10−35 kg, non-BA cholestasis, and metabolic disease. Allocation score, share type, or CIT did not modify risk of graft type and graft failure.

Conclusion: Although one might anticipate that individuals with higher rates of graft loss would be worse candidates for SLT, data suggest that these patients actually have similar rates of graft loss. These findings can guide surgical decision-making and may support policy changes that promote the increased use of SLT for specific pediatric recipients.

INTRODUCTION

Pediatric liver transplantation provides life-saving therapy for children with end-stage liver disease and other metabolic conditions but continues to be hindered by a scarcity of available organs.[5] Waitlisted children typically receive fewer offers for deceased donor organs than adults, suggesting that they are especially vulnerable to an imbalance in need and availability.[25] Consequently, neonates have the highest rate of waitlist mortality for any age group, with nearly one-third of waitlisted neonates dying before receiving a suitable offer.[7]

The use of split liver transplantation (SLT) represents one opportunity to increase the supply of organs and has the potential to shorten waitlist times and decrease pre-transplant morbidity and mortality, particularly for children. Recent evidence suggests that outcomes following SLT are now likely comparable to whole liver transplantation (WLT) for both pediatric and adult recipients.[19,59,92] At the same time, the benefit of SLT may vary among patients with different donor, recipient, or surgical characteristics. For example, a study of adult transplant recipients concluded that graft failure following SLT and WLT was equivalent on average, but that status 1 recipients had poorer outcomes when receiving SLT compared to WLT.[19] Analysis of recipient, donor, and surgical characteristics can serve to identify optimal individuals for higher-risk organs that are not at increased risk of graft loss as well as suboptimal recipients for whom whole livers would yield better outcomes.[93]

In pediatric liver transplantation, several donor, recipient, and surgical characteristics have been shown to influence outcomes, such as donor age, cause of death, fulminant disease in the recipient, and prolonged cold ischemia time (CIT).[27,32] As with adults, these characteristics may yield subgroups of pediatric candidates whose outcomes are

worse when receiving SLT, and other groups for whom outcomes are not affected by graft type. Better understanding of which characteristics are modified by graft type would serve to better inform surgical decision-making about which recipients are appropriate for SLT and could potentially inform policy to promote SLT. In this study, we used a large national registry to explore which characteristics modify the association between graft type and graft failure among pediatric deceased organ recipients in order to better understand the opportunities to expand the organ supply through further use of SLT.

METHODS

Data Source

This study used data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donors, wait-listed candidates, and transplant recipients in the U.S., submitted by the members of the Organ Procurement and Transplantation Network (OPTN), and has been described elsewhere.[22] The Health Resources and Services Administration (HRSA), U.S. Department of Health and Human Services, provides oversight to the activities of the OPTN and SRTR contractors.

Study Population

We identified 5,345 pediatric liver-only, first-time transplant recipients of a deceased WLT or SLT who received an organ between March 1, 2002 (i.e., after implementation of the PELD/MELD system), and December 31, 2015; patients with missing weight (n = 1) or missing CIT (n = 284) were excluded. We compared donor, recipient, and surgical characteristics between recipients of WLT and SLT using χ^2 tests.

Graft Type

All individuals were defined as having an SLT if they received a portion of a deceased donor graft. Sensitivity analyses exploring the impact of organs used by one recipient (i.e., “cut down”) versus two recipients, and in vivo versus ex vivo splits showed no difference in graft failure, a finding consistent with other studies demonstrating similar occurrence of graft failure, biliary strictures, and vascular thromboses.[12,19]

Graft Survival

Graft failure was identified as any reported graft failure or death (i.e., “all cause graft loss”). This means that: (1) all deaths are attributed to a graft failure, but not all graft failure leads to death; and (2) risk of graft failure is always greater than risk of death. The functional form for recipient, donor, and surgical characteristics were explored using Kaplan-Meier curves and log-rank tests. We used Cox proportional hazards models to characterize the association between allograft type and graft survival after adjustment for the following variables: donor age and race, cause of death, recipient weight at transplant, recipient sex, recipient race/ethnicity, underlying disease, laboratory PELD/MELD at transplant, status 1 designation, insurance type, CIT, and share type (i.e., local, regional or national). The decision to include these specific variables in the final model for multivariable regression was derived from associations between covariates with risk factors and the outcome in both the published literature as well as statistical tests within this cohort. Recipients were censored upon re-transplantation or multi-organ transplantation (e.g., liver-kidney).

Effect Modification

To identify specific recipient, donor, and surgical characteristics that modify the effect of allograft type on graft survival, we performed Cox regression analysis with effect modification between allograft type with additional covariates for which an *a priori*

hypothesis existed that the association between the covariate and graft failure may vary by allograft type. Test for effect modification was assessed in an unadjusted analysis as well as a parsimonious model that adjusted for donor cause of death, recipient weight, recipient diagnosis, allocation score, share type, and CIT as previously described.[93] Donor age was excluded from effect modification analysis given the small number of individuals receiving a split from a donor >50 years (n < 100). Donor race, recipient race, and recipient insurance were excluded due to there being no *a priori* reason to consider that the association between allograft type and graft failure would vary by these characteristics. From this model, the relative impact of SLT *versus* WLT could be evaluated, with factors that exacerbated the impact of SLT versus WLT being defined as "optimal," whereas those that had no impact (or attenuated the impact) on SLT versus WLT were defined as "suboptimal."

Potential for Increased SLT

In order to further quantify opportunities to increase the use of SLT among pediatric liver transplant candidates, we identified the number of waitlisted individuals who died, or were delisted due to medical unsuitability or declining health, having been on the waitlist for at least 7 days in the period from March 1, 2002 to December 31, 2016 (n = 1,160); since it can be reasonably assumed that individuals would only be listed if they were appropriate candidates for transplant, individuals delisted 7 days later due to death or medical unsuitability represent instances where an offer through SLT would have benefited the candidates. The number of individuals with optimal characteristics that had been listed but then delisted served to provide an estimate of the potential reduction in waitlist mortality that may have occurred if greater use of SLT had occurred.

Statistical Analysis

All statistical tests used a two-sided α of 0.05. Confidence intervals are reported using the method of Louis and Zeger, as previously reported.[24] All analyses were performed using STATA 14.0 (College Station, TX, USA). This study was approved by the Institutional Review Board of Johns Hopkins University School of Medicine. No organs were used from executed prisoners.

RESULTS

Patient Characteristics

Among 5,345 pediatric recipients in our study, 1,694 (31.7%) received an SLT and 3,651 (68.3%) received a WLT (Table 1). SLT recipients were less likely than WLT recipients to have a donor that was <18 years (59.4% for SLT and 84.3% for WLT) and more likely to have a donor between 18 and 50 years (38.7% vs 13.6%; $P < 0.001$). SLT recipients were less likely to have a donor with anoxia (19.5% vs 35.1%) and more likely that the donor had head trauma (63.1% vs 49.8%; $P < 0.001$). A larger percentage of SLT recipients were <10 kg (51.7% vs 32.9%; $P < 0.001$), had biliary atresia (BA) (44.2% vs 36.0%; $P < 0.001$), and were status 1 (37.7% vs 31.2%; $P < 0.001$). SLT recipients were less likely to receive the organ from a national share (4.7% vs 23.5%; $P < 0.001$), but CIT did not vary between the two graft types.

Graft Failure

Although SLT was associated with increased graft failure in an unadjusted model (HR: $_{1.03}1.17_{1.32}$), there was no evidence of increased risk after adjustment for confounding donor, recipient, and surgical characteristics, on average among the entire study population (aHR: $_{0.91}1.07_{1.24}$; Table 2). Characteristics associated with graft failure in a traditional multivariable model included donor age 18−50 years (aHR: $_{1.05}1.25_{1.48}$) and ≥50 years (aHR: $_{1.92}2.66_{3.68}$), recipient weight <10 kg (aHR: $_{1.24}1.44_{1.69}$), recipients with

acute hepatic necrosis (aHR: $_{1.23}1.57_{1.99}$), autoimmune diseases (aHR: $_{1.55}2.05_{2.71}$), tumor (aHR: $_{1.57}1.97_{2.47}$), and other diseases (aHR: $_{1.19}1.45_{1.76}$), but status 1 was not associated with greater graft failure (aHR: $_{0.75}0.89_{1.06}$). CIT was also associated with graft failure at 8−12 hours (aHR: $_{1.06}1.22_{1.39}$) and ≥12 hours (aHR: $_{1.20}1.45_{1.74}$). Increased graft failure was also seen in unadjusted model for stroke (HR: $_{1.22}1.48_{1.80}$), recipient weight ≥35 kg (HR: $_{1.18}1.39_{1.62}$), and an allocation score ≥30 or status 1 (HR $_{1.21}1.38_{1.58}$), but these were not independently significant after adjusting for other confounders.

Effect Modification

To determine if specific characteristics modified the effect between graft type and graft failure, several variables were tested in unadjusted and adjusted models. In these models, a coefficient of 1 (or a non-significant coefficient at the 95% confidence level) indicates that, for individuals within that subcohort, the risk of graft failure did not vary between individuals receiving an SLT or WLT (Figure). Alternatively, a coefficient of 1.4 means that, among individuals with that specific characteristic (e.g., a specific weight category), individuals who received a SLT had 1.4 times the risk of graft failure than individuals with a WLT. In general, subcohorts with the highest overall graft failure were not further negatively impacted by having an SLT vs WLT, and therefore would be optimal candidates for SLT, whereas recipients with overall favorable outcomes had higher rates of graft failure with SLT compared to WLT, and would be suboptimal candidates. For example, recipient weight <10 kg was associated with increased graft failure in general (Table 2, aHR: $_{1.24}1.44_{1.69}$), but this risk was the same irrespective of graft type (Figure, aHR: $_{0.82}1.00_{1.22}$) suggesting this is an optimal characteristic for SLT. In contrast, recipients with weight between 10 and 35 kg had overall lower risk of graft failure but actually had 1.46 times higher rate of graft failure following SLT compared to WLT (aHR: $_{1.10}1.37_{1.70}$). A similar pattern was evident when considering indication for

transplant, where an equivalent risk of graft failure in SLT and WLT existed for recipients that had the highest overall risk—acute hepatic necrosis (aHR for SLT vs WLT: $_{0.80}1.11_{1.53}$), autoimmune disease (aHR SLT vs WLT: $_{0.92}1.71_{3.17}$), and tumor (aHR SLT vs WLT: $_{0.72}1.03_{1.48}$)—whereas SLT was associated with higher graft failure, and suboptimal, for individuals that generally had favorable overall risk such as non-BA congenital cholestasis (aHR for SLT vs WLT: $_{1.13}2.14_{4.07}$) and metabolic disorders (aHR SLT vs WLT: $_{1.08}1.57_{2.28}$). Notably, BA had generally low risk of graft failure, and was not adversely impacted by use of SLT (aHR SLT vs WLT: $_{0.88}1.09_{1.36}$). Graft type did not modify the association between allocation score and graft failure, with similar risk for SLT versus WLT in individuals with PELD/MELD <30 (aHR: $_{0.95}1.18_{1.47}$), ≥30 without status 1 (aHR: $_{0.98}1.30_{1.72}$), and ≥30 with status 1 (aHR: $_{0.94}1.15_{1.41}$).

Although higher risk of graft failure was seen with CIT >8 hours, this association was not modified by graft type in recipients with CIT 8-12 hrs (aHR SLT vs WLT: $_{0.85}1.07_{1.34}$) or CIT ≥12 hrs (aHR SLT vs WLT: $_{0.97}1.36_{1.92}$). Among individuals with CIT <8 hours, there was a trend toward increased graft failure in individuals when receiving SLT compared to WLT (aHR SLT vs WLT: $_{1.00}1.20_{1.43}$). Graft type did not modify risk of graft failure in individuals who received a local share (aHR SLT vs WLT: $_{0.96}1.18_{1.46}$) or regional/national share (aHR SLT vs WLT: $_{0.98}1.16_{1.38}$). While donor stroke was not generally associated with graft failure, recipients of SLT from donors with stroke had increased graft failure compared to WLT from donor with stroke (aHR SLT vs WLT: $_{1.05}1.46_{2.02}$).

Potential for Increased SLT

For those characteristics in which some subcohorts were optimal (i.e., weight <10 kg; all recipient diagnoses except non-BA cholestasis and metabolic disorder), we identified the number of recipients that were waitlisted for at least 7 days but ultimately died or were

delisted due to medical unsuitability while waiting for an offer over the study period (i.e., 178 months; n = 1,160). Among waitlist deaths, 451 pediatric candidates were <10 kg and 348 (78%) were on the waitlist for at least 7 days before death or delisting due to poor health indicating that as many as approximately 23 candidates per year may likely have benefitted from increased availability of SLT. Furthermore, within this group of 348 pediatric candidates, 320 (92%) had optimal underlying conditions and 28 had suboptimal conditions (i.e., 13 with non-BA neonatal cholestasis and 15 with metabolic disorders) indicating that as many as 22 children per year with optimal weight and underlying disease died after waiting at least 7 days for an organ and would likely have benefited from increased use of SLT.

DISCUSSION

Increasing evidence suggests that outcomes following SLT and WLT are similar.[19,21,59,92] However, this assessment should not be taken to indicate that risk of graft failure is equivalent for all subgroups of patients. While there may be a tendency by healthcare providers to anticipate that the sickest children with the highest rates of pre-transplant mortality (e.g., PELD/MELD ≥30, or status 1) would be relatively poorer candidates for SLT and have worse outcomes, our findings from this national study of 5,345 pediatric recipients indicate that the opposite is true. Specifically, characteristics associated with overall higher rates of graft failure (e.g., recipient weight <10 kg; recipient diagnosis of acute hepatic necrosis, autoimmune disorders, or tumor; and CIT ≥ 8 hours) had equivalent risk of graft failure among SLT recipients when compared to WLT. At the same time, pediatric recipients with the lowest overall risk of graft failure (e.g., recipient weight 10-35 kg; non-BA congenital cholestasis, metabolic disorders; CIT <8 hours) fared worse when they received a SLT compared to WLT. These findings were independent of pre-transplant mortality risk as determined by PELD/MELD.

Our findings that graft failure among children less than 10 kg and those with status 1 are not adversely impacted by the type of deceased donor allograft type dovetails with the fact that patients with these characteristics are also recipients with highest rates of death while awaiting liver transplantation.[5,94] Consequently, our findings strengthen the argument that there should be broader use of SLT for these fragile subgroups of children and that such a practice, and policy, would likely translate to important reductions in waitlist death, the stated goal of our current allocation system.[95] Notably, broader geographic sharing, including national sharing, was not associated with worse outcomes for children. Our analysis also attempted to quantify the degree to which increased use of SLT could potentially reduce waitlist mortality and determined that most children that die on the waitlist were waiting for at least a week, and approximately half these children meet criteria for being an optimal recipient for SLT, with a predicted graft survival that would be similar for SLT and WLT. These findings should be considered in the context of work by Hsu *et a*l. that showed nearly half of the children who died on the waitlist never received a single offer of a liver.[25] Furthermore, recent research by Perito *et al*. showed that approximately half of the most "split-able" livers, by strict criteria, were not utilized for SLT.[96]

While our findings show the potential for a modest, but meaningful, opportunity to reduce waitlist mortality following greater use of SLT for children in select groups (e.g., recipient weight <10 kg), there are likely several other downstream benefits as well. First, broader use of SLT would likely mean that many children could be transplanted at lower allocation scores, corresponding both to lower pre-transplant morbidity and cost. Second, broader use of SLT for select groups of children would then allow for greater number of whole organs to be available for other groups such as slightly larger children.

At the same time, one limitation of our study is that we did not formally incorporate an analysis that combined pre-transplant and post-transplant mortality (i.e., survival benefit). However, given that we analyzed all cause graft loss and there was no increase in graft failure for select recipients, it can be inferred that there is no increase in post-transplant mortality as well.

One important limitation of our study is that, through SRTR, we do not have information about other meaningful outcomes such as biliary strictures and vascular thromboses. Similarly, we do not have specific information as to why some subgroups had higher rates of graft failure. The SPLIT (Studies in Pediatric Liver Transplantation) Consortium published outcomes from 1995-2006 and identified both higher rates of graft failure as well as biliary strictures and vascular complications in children receiving technical-variant grafts.[12] However, it is not clear if these complications currently exist at higher rates in SLT, especially given more recent reports that graft failure in SLT, both immediate and long-term, is currently equivalent to WLT.[59] Reports from adult literature have been conflicting with some studies showing similar rates of biliary stricture and vascular thromboses, whereas other studies still showing higher rates of these surgical complications. Nonetheless, one likely explanation for higher rates of graft failure among certain groups is that they have higher rates of these well-established complications leading to graft failure.

A second limitation of our study is that it is derived from observational, as opposed to experimental, data; randomized trials would be impractical so observational studies represent the best opportunity to identify the benefit of different types of allografts. In this instance, it is possible that favorable outcomes seen in SLT are due to careful candidate selection on the part of healthcare teams. However, this potential for bias is not likely to

impact our analysis since we have adjusted for many known characteristics associated with disease severity including both PELD/MELD, and therefore are making comparisons among people with similar health status. Nonetheless, residual confounding of disease severity may occur. A final limitation is that the sample size was very small for certain subcohorts (e.g., weight >35 kg) making it hard to obtain a precise estimate for the relative impact of SLT versus WLT in these groups.

Although many considerations go into the decision to use SLT for a specific patient, there is clear agreement in the transplant community that demand for organs exceed the supply, and that minimization of pre-transplant mortality risk should be the highest priority. In the context of demonstrably equivalent outcomes for adult recipients of SLT, our findings further support that greater use of SLT in the majority of recipients can address the problem of organ scarcity such that fewer children would die while awaiting an offer and still have acceptable outcomes after transplantation.

Table 1: Characteristics of 5,345 pediatric deceased donor liver transplants performed in the United States in the PELD/MELD era by graft type

Characteristic	WLT	SLT	*P*
Total (N, %)	3,651 (68.3)	1,694 (31.7)	
Donor			
Age (years)			
<18	3,079 (84.3)	1,008 (59.5)	<0.001
18-50	497 (13.6)	656 (38.7)	
≥50	75 (2.1)	30 (1.8)	
Female	1,553 (42.5)	644 (38.0)	0.002
Ethnicity/race			
Caucasian, non-Hispanic	2,015 (55.2)	1,050 (62.0)	<0.001
African American	765 (21.0)	260 (15.4)	
Hispanic	736 (20.2)	331 (19.5)	
Asian	72 (2.0)	25 (1.5)	
Mixed/other	63 (1.7)	28 (1.7)	
Cause of death			
Anoxia	1,281 (35.1)	331 (19.5)	<0.001
Stroke	382 (10.5)	225 (13.3)	
Head trauma	1,816 (49.8)	1,069 (63.1)	
unknown/other	172 (4.7)	69 (4.1)	
Recipient			
Weight (kg)			
<10	1,201 (32.9)	875 (51.7)	<0.001
10-35	1,367 (37.4)	710 (41.9)	
≥35	1,083 (29.7)	109 (6.4)	
Female	1,887 (51.7)	847 (50.0)	
Ethnicity/race			
Caucasian, non-Hispanic	1,919 (52.6)	820 (48.4)	<0.001
African American	639 (17.5)	270 (15.9)	
Hispanic	772 (21.2)	450 (26.6)	
Asian	199 (5.5)	102 (6.0)	
Mixed/other	122 (3.3)	52 (3.1)	
Diagnosis			
Biliary atresia (BA)	1,315 (36.0)	748 (44.2)	<0.001
Acute hepatic necrosis	471 (12.9)	222 (13.1)	

Autoimmune	229 (6.3)	28 (1.7)	
Congenital cholestasis (non-BA)	148 (4.1)	91 (5.4)	
Metabolic	561 (15.4)	219 (12.9)	
Tumor	346 (9.5)	170 (10.0)	
Other	581 (15.9)	216 (12.8)	
Allocation score at transplant			
aPELD/MELD <30, non-status 1	1,657 (45.4)	618 (36.5)	<0.001
aPELD/MELD ≥30, non-status 1	854 (23.4)	438 (25.9)	
aPELD/MELD ≥30, status 1	1,140 (31.2)	638 (37.7)	
Insurance			
Private	1,731 (47.4)	715 (42.2)	<0.001
Public	1,791 (49.1)	935 (55.2)	
Other/missing	129 (3.5)	44 (2.6)	
Surgery			
Share type			
Local	1,285 (35.2)	744 (43.9)	<0.001
Regional	1,509 (41.3)	871 (51.4)	
National	856 (23.5)	79 (4.7)	
Cold ischemia time (hours)			
<8	2,190 (60.0)	1,009 (59.6)	0.09
8-12	1,054 (28.9)	525 (31.0)	
≥12	406 (11.1)	160 (9.5)	

WLT = whole liver transplant; SLT = split liver transplant

Table 2: Characteristics associated with graft failure in pediatric recipients

Characteristic	Unadjusted		Multivariable	
	HR	*P*	aHR	*P*
Split liver transplant	$_{1.03}1.17_{1.33}$	0.02	$_{0.91}1.07_{1.24}$	0.4
Donor				
Age (years)				
<18	--	--	--	--
18-50	$_{1.22}1.40_{1.61}$	<0.001	$_{1.05}1.24_{1.48}$	0.01
≥50	$_{2.45}3.23_{4.26}$	<0.001	$_{1.91}2.64_{3.65}$	<0.001
Race/ethnicity				
Caucasian	--	--	--	--
African American	$_{0.93}1.09_{1.28}$	0.3	$_{0.99}1.16_{1.36}$	0.1
Hispanic	$_{0.80}0.94_{1.10}$	0.4	$_{0.83}0.97_{1.14}$	0.7
Asian	$_{0.72}1.12_{1.73}$	0.6	$_{0.62}0.97_{1.50}$	0.9
Mixed/other	$_{0.58}0.94_{1.52}$	0.8	$_{0.61}0.99_{1.61}$	1.0
Cause of death				
Anoxia	--	--	--	--
Stroke	$_{1.22}1.48_{1.80}$	<0.001	$_{0.89}1.10_{1.37}$	0.4
Head Trauma	$_{0.96}1.11_{1.28}$	0.2	$_{0.90}1.04_{1.21}$	0.6
Other/unknown	$_{0.72}0.99_{1.36}$	0.9	$_{0.68}0.94_{1.29}$	0.7
Recipient				
Weight (kg)				
<10	$_{1.07}1.24_{1.42}$	0.003	$_{1.24}1.44_{1.69}$	<0.001
10-35	--	--	--	--
≥35	$_{1.18}1.39_{1.62}$	<0.001	$_{0.90}1.09_{1.32}$	0.4
Female	$_{0.93}1.05_{1.18}$	0.5	$_{0.95}1.07_{1.21}$	0.3
Race/ethnicity				
Caucasian	--	--	--	--
African American	$_{1.05}1.23_{1.44}$	0.01	$_{0.95}1.11_{1.32}$	0.2
Hispanic	$_{0.90}1.05_{1.22}$	0.5	$_{0.80}0.95_{1.11}$	0.5
Asian	$_{0.55}0.75_{1.02}$	0.1	$_{0.58}0.79_{1.07}$	0.1
Mixed/other	$_{0.76}1.07_{1.51}$	0.7	$_{0.68}0.96_{1.37}$	0.8
Diagnosis				
Biliary atresia	--	--	--	--
Acute hepatic necrosis	$_{1.35}1.62_{1.94}$	<0.001	$_{1.24}1.58_{2.02}$	<0.001
Autoimmune	$_{1.41}1.81_{2.31}$	<0.001	$_{1.55}2.06_{2.72}$	<0.001

Congenital cholestasis*	$_{0.71}0.99_{1.39}$	0.9	$_{0.77}1.07_{1.51}$	0.7
Metabolic	$_{0.79}0.98_{1.20}$	0.8	$_{0.91}1.14_{1.44}$	0.3
Tumor	$_{1.45}1.77_{2.16}$	<0.001	$_{1.58}1.99_{2.50}$	<0.001
Other	$_{1.15}1.38_{1.65}$	<0.001	$_{1.19}1.46_{1.78}$	<0.001
Allocation PELD/MELD				
<30	--	--	--	--
≥30, non-status 1	$_{0.81}0.95_{1.12}$	0.6	$_{0.75}0.89_{1.06}$	0.2
≥30 and status 1	$_{1.20}1.38_{1.58}$	<0.001	$_{0.89}1.07_{1.28}$	0.5
Insurance status				
Private	--	--	--	--
Public	$_{1.04}1.17_{1.33}$	0.01	$_{1.06}1.21_{1.38}$	0.006
Other/missing	$_{0.44}0.68_{1.04}$	0.1	$_{0.48}0.74_{1.15}$	0.2
Surgery				
Share				
Local	--	--	--	--
Regional	$_{0.83}0.94_{1.07}$	0.4	$_{0.83}0.95_{1.09}$	0.4
National	$_{0.71}0.85_{1.01}$	0.1	$_{0.70}0.86_{1.06}$	0.1
Cold ischemia time (hours)				
<8	--	--	--	--
8-12	$_{1.03}1.18_{1.35}$	0.02	$_{1.06}1.21_{1.39}$	0.005
≥12	$_{1.15}1.38_{1.65}$	<0.001	$_{1.20}1.45_{1.74}$	<0.001

*non-biliary atresia congenital cholestasis (e.g., Alagille syndrome)

Table 3: Analysis of effect measure modification of graft type on donor, recipient and surgical characteristics with graft failure

Characteristic	Unadjusted SLT vs WLT*		Adjusted SLT vs WLT	
	HR	*P*	aHR	*P*
Donor cause of death				
non-Stroke	$_{0.97}1.12_{1.25}$	0.1	$_{0.98}1.13_{1.31}$	0.1
Stroke	$_{1.03}1.40_{1.92}$	0.03	$_{1.05}1.46_{2.02}$	0.02
Recipient weight (kg)				
<10	$_{0.85}1.03_{1.25}$	0.8	$_{0.82}1.00_{1.22}$	0.8
10-35	$_{1.23}1.52_{1.88}$	<0.001	$_{1.10}1.37_{1.70}$	0.004
≥35	$_{0.93}1.34_{1.94}$	0.1	$_{0.92}1.34_{1.90}$	0.1
Diagnosis				
Biliary atresia (BA)	$_{0.92}1.15_{1.43}$	0.2	$_{0.86}1.08_{1.34}$	0.5
Acute hepatic necrosis	$_{0.78}1.07_{1.45}$	0.7	$_{0.78}1.09_{1.50}$	0.6
Autoimmune disease	$_{0.89}1.65_{3.05}$	0.1	$_{0.92}1.70_{3.15}$	0.1
Congenital cholestasis	$_{1.18}2.24_{4.25}$	0.01	$_{1.10}2.09_{3.97}$	0.02
Metabolic	$_{1.10}1.60_{2.32}$	0.01	$_{1.06}1.57_{2.28}$	0.02
Tumor	$_{0.71}1.02_{1.46}$	0.9	$_{0.70}1.01_{1.45}$	1.0
Other	$_{0.88}1.20_{1.65}$	0.3	$_{0.81}1.12_{1.56}$	0.5
Allocation PELD/MELD				
<30	$_{0.88}1.08_{1.34}$	0.5	$_{0.94}1.17_{1.46}$	0.2
≥30, non-status 1	$_{0.96}1.26_{1.66}$	0.1	$_{0.96}1.27_{1.69}$	0.1
≥30 and status 1	$_{0.94}1.14_{1.38}$	0.2	$_{0.92}1.13_{1.38}$	0.3
Share				
Local	$_{0.96}1.16_{1.41}$	0.1	$_{0.96}1.18_{1.46}$	0.1
Regional/national	$_{0.98}1.16_{1.37}$	0.1	$_{0.98}1.16_{1.38}$	0.1
Cold ischemia time (hours)				
<8	$_{0.98}1.17_{1.39}$	0.1	$_{1.00}1.20_{1.43}$	0.05
8-12	$_{0.88}1.10_{1.37}$	0.4	$_{0.85}1.07_{1.34}$	0.6
≥12	$_{1.00}1.41_{1.97}$	0.05	$_{0.97}1.36_{1.92}$	0.1

SLT = Split liver transplant; WLT = Whole liver transplant

Chapter 6. Conclusion

Our research demonstrates that outcomes for pediatric liver transplant recipients following technical-variant donation, including both living-donor liver transplantation (LDLT) and split liver transplantation (SLT), are now at least equivalent to whole liver transplantation (WLT). Given that LDLT and SLT are each used in only approximately 10-15% of children who receive a transplant, our findings suggest tremendous opportunity for greater use of these newer surgeries as well as the potential to mitigate the consequences of organ scarcity: increased waitlist morbidity and mortality.

Our research on national trends in outcomes for pediatric liver transplant recipients identified that the early experience (i.e., 2002-2009) of SLT, a more complex surgery, showed inferior patient and graft survival. Complications in this period could be traced largely to inferior outcomes in the immediate post-operative period. As transplant programs gained more experience, risk of graft failure or death in the immediate post-operative abated such that outcomes following SLT and WLT have more recently been comparable. Outcomes following LDLT were initially similar to WLT but again, with more experience, are now superior to WLT.

Even though our findings suggest that risk of graft failure is now similar for SLT and WLT, some subgroups of children may be better candidates for SLT than others. Our analysis of donor, recipient and surgical characteristics identified that the relationship between graft type and graft failure was modified by the underlying disease, with higher graft failure only in SLT recipients that had non-BA congenital cholestasis and metabolic disorders as their underlying disorder compared to other disorders such as biliary atresia and acute liver failure. Similarly, recipient weight modified the relationship between graft

type and graft failure, with higher risk of graft failure only in those SLT recipients that were between 10-35 kg. These subgroups of disease and weight category were actually the individuals that had the lowest rates of graft failure overall but were negatively impacted by getting a split liver. At the same time, individuals that had higher rates of graft failure overall (e.g., acute liver failure, recipient weight <10 kg) had similar outcomes irrespective of which graft type they received.

LDLT provides an opportunity to be transplanted before individuals becomes extremely sick and assures they will not die while waiting for an offer. But despite these benefits, living donation is infrequently used for pediatric liver candidates. Using the Scientific Registry of Transplant Recipients, we identified African-American race and use of public insurance as sociodemographic characteristics associated with reduced likelihood of LDLT and sought to further understand barriers in these groups through our survey.

Our survey to parents of children awaiting a liver transplant or recipients of a liver transplant identifies specific barriers towards living donation. Parental understanding about the evaluation process was largely insufficient, with only 72% of respondents knowing the steps and 69% knowing that the cost was covered by the recipient's insurance. One quarter of respondents were not informed about potential complications to the donor or how the surgery might impact the donor's need for time off from work. In general, individuals with fewer resources such as those individuals with public insurance or from single-family homes were less likely to feel well-informed about the process.

This an exciting for liver transplantation. The last major change in allocation occurred in 2002 with the implementation of PELD/MELD but there is increasing understanding about disparities that exist in the system, and how it fails to adhere to federally-

mandated guidance about fairness in the distribution of a scarce resource for adults and pediatric candidates.[97] At the same time, these newer technical-variant surgeries are increasingly understood to provide an appropriate solution to organ scarcity. We believe this research provides valuable insight into how these surgeries ought to be promoted in the next wave of discussions about living-donor awareness and organ allocation in the United States.

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Appendix A

Living-donor Liver Transplantation Survey for Parents

Start of Block: Choice tasks

Q1 **Living-Donor Liver Transplantation Survey**

Thank you for taking the time to complete our survey. Your answers are very important to us. This survey is for research purposes only. The answers are anonymous and will be kept strictly confidential. Your participation is completely voluntary and will not influence your treatment. You can stop at any time if you no longer want to participate in this research study.

THIS BRIEF SURVEY SHOULD ONLY BE COMPLETED BY PARENTS OF CHILDREN WITH LIVER DISEASE ESTIMATED TIME REQUIRED: 5-10 MINUTES This is a survey about Living-donor Liver Transplantation, the process by which a part of a healthy liver is transplanted from a living person into another person with advanced liver disease. We are interested in understanding what you know and think about living-donor liver transplantation. While you can discuss this survey with other people, it is important that you give us your opinion and not someone else's opinion.

PLEASE ONLY COMPLETE THIS SURVEY ONE TIME This study is being conducted by Dr. Douglas Mogul, Assistant Professor of Pediatric Gastroenterology and Hepatology at Johns Hopkins University and was approved by the Institutional Review Board at Johns Hopkins University (protocol #00096438).

Page Break

Q2 **Has your child had a liver transplant?**

- ○ Yes, my child **has had** a liver transplant (1)
- ○ No, but my child is currently **on the waitlist** for a liver transplant (2)
- ○ No, but my child is currently **being evaluated** for a liver transplant (5)
- ○ No, and my child is **not currently being evaluated** (considered) for a liver transplant (3)
- ○ No, and I am not sure whether my child is currently on the waitlist for a liver transplant (4)
- ○ Other (6)

Skip To: Q4 If Has your child had a liver transplant? = Yes, my child has had a liver transplant

Skip To: Q4 If Has your child had a liver transplant? = No, but my child is currently on the waitlist for a liver transplant

Skip To: Q4 If Has your child had a liver transplant? = No, but my child is currently being evaluated for a liver transplant

Q3 Thank you for your consideration. There is no need to answer any additional questions.

Skip To: End of Survey If Thank you for your consideration. There is no need to answer any additional questions. () Is Displayed

Page Break

Q30 My child's transplant center performs living-donor liver transplantation for children

- ○ Yes (1)
- ○ No (2)
- ○ Not sure (3)

Q4 **These questions ask about your knowledge of living-donor liver transplantation. Please indicate whether you: strongly agree; agree; neither agree nor disagree (neutral); disagree; or strongly disagree**

	Strongly agree (1)	Agree (2)	Neutral (3)	Disagree (4)	Strongly disagree (5)
A family member or friend can donate a part of their liver to a patient with liver disease. (1)	○	○	○	○	○
I know someone who is going through, or has gone through, the living-donor liver transplantation process. (2)	○	○	○	○	○
The cost of healthcare for the living donor including the evaluation, surgery, and follow-up care, are covered by the recipient's health insurance. (3)	○	○	○	○	○
I know what all the necessary next steps are for evaluation of a living-donor liver transplantation. (4)	○	○	○	○	○

I know who to ask if I have questions about living-donor liver transplantation. (5)	○	○	○	○	○
Based on discussions with my child's doctor, I feel well-informed about living donation (6)	○	○	○	○	○

Q5 Based on discussion with my child's doctor/surgeon, including options such as living donation and deceased donation, I felt that:

- ○ living donation is a better option compared to deceased donation (1)
- ○ living donation and deceased donation are equally good options (4)
- ○ living donation is a worse option compared to deceased donation (2)
- ○ I have/had no opinion about which option is better (3)

Page Break

Q6 **How comfortable are you (or were you) with the idea of trying to donate a part of your liver to your child?**

- ○ Very comfortable (1)
- ○ Somewhat comfortable (2)
- ○ Neutral (3)
- ○ Somewhat uncomfortable (4)
- ○ Very uncomfortable (6)
- ○ I have been told by a doctor that I am not eligible to donate (7)

Page Break

Q7

Thinking about your social circle, how many people do you know that you would (or did) feel comfortable asking to be a living donor for your child?

- ○ 0 (1)
- ○ 1 (2)
- ○ 2 (3)
- ○ 3 (4)
- ○ 4 or more (5)

Q8 Please rate the following question: If I ask a friend or family member to consider being a living donor, it may cause problems or stress in our relationship.

- ○ Strongly disagree (25)
- ○ Somewhat disagree (26)
- ○ Neither agree nor disagree (27)
- ○ Somewhat agree (28)
- ○ Strongly agree (29)

Q9 **Looking back over the last year, how many people did you talk to about important health-related things in your life, such as important health concerns, achieving an important milestone, or health problems you or your family are having?**

- ○ 0 (1)
- ○ 1 (2)
- ○ 2 (3)
- ○ 3 (4)
- ○ 4 or more (5)

Page Break

Q10 **These questions ask about your relationship with your child's liver doctor. Please indicate whether you: strongly agree; agree; neither agree nor disagree (neutral); disagree; or strongly disagree with the following statements.**

	Strongly Agree (1)	Agree (2)	Neutral (3)	Disagree (4)	Strongly Disagree (5)
My child's doctor likes me. (1)	○	○	○	○	○
I like my child's doctor. (2)	○	○	○	○	○
I trust my child's doctor to do the right things for my child and my child. (3)	○	○	○	○	○
My doctor and I generally agree about the best treatment plan for my child. (4)	○	○	○	○	○
My child's doctor has (had) adequately answered all of my questions about the transplant process. (5)	○	○	○	○	○

Page Break

Q11 **Some parents may have concerns about how a living-donor liver transplant will affect their <u>child and family</u>.**

With respect to living-donor liver transplantation, rate the extent to which you feel concerns about the RECIPIENT AND FAMILY have been answered for you

	Very well addressed (1)	Moderately addressed (2)	Somewhat addressed (3)	Not addressed (4)	I don't know (5)
Chance of health complications for the recipient (your child). (1)	○	○	○	○	○
Chance of good emotional outcome for recipient (your child). (2)	○	○	○	○	○
Impact of transplant on parental work and amount of time off required to take care of the recipient (your child). (3)	○	○	○	○	○
Impact of transplant on work and ability to take care of your family. (4)	○	○	○	○	○

Q12 **Some parents may have concerns about how a living-donor liver donation will affect the donor. With respect to living-donor liver transplantation, rate the extent to which you feel concerns about the DONOR have been answered for you**

	Very well addressed (1)	Moderately addressed (2)	Somewhat addressed (3)	Not addressed (4)	I don't know (5)
Chance of health complications for the donor. (1)	○	○	○	○	○
Chance of good emotional outcome for the donor. (2)	○	○	○	○	○
Impact of transplant on donor's work and amount of time off required. (3)	○	○	○	○	○
Impact of transplant on donor's ability to take care of family. (4)	○	○	○	○	○

Page Break

End of Block: Choice tasks

Start of Block: Background information

Q13 **Background Information About You**

What is your age in years?

_____

Q14 **What is your child's age?**

_____

Q15 **What is your (i.e., the parent) gender?**

- ○ Female (1)
- ○ Male (2)
- ○ Transgender (3)

Q32 Is your child's transplant center in the United States

- ○ Yes (1)
- ○ No (2)

Skip To: Q16 If Is your child's transplant center in the United States = No

Q31 In which state is your child's transplant center

▼ Alabama (4) ... Other US territories (55)

Q16 **What race/ethnic groups best describes you?** ***(Please check all that apply)***

- ☐ White (1)
- ☐ Black or African-American (2)
- ☐ American Indian or Alaskan Native (3)
- ☐ Asian or Pacific Islander (4)
- ☐ Hispanic (5)
- ☐ Other (6) _____

Q17 **Which of the following devices do you currently own?** ***(Please check all that apply)***

- ☐ Desktop computer (1)
- ☐ Laptop computer (2)
- ☐ Tablet device (such as iPad, Kindle Fire, Samsung Galaxy Note, etc.) (3)
- ☐ Cell phone WITH internet capabilities (such as iPhone, Samsung Galaxy, Android, etc.) (4)

Q18 **How often do you use your computer, tablet, or cellphone to access the internet?**

- ○ Less than 60 minutes a day (1)
- ○ 1-4 hours a day (2)
- ○ 5-8 hours a day (3)
- ○ Almost constantly (4)

Q19 **What is your marital status?**

- ○ Married/living with a partner (1)
- ○ Widowed (2)
- ○ Divorced (3)
- ○ Separated (4)
- ○ Never married (5)

Q20 **What is your current employment status?**

- ○ Employed full-time (1)
- ○ Employed part-time (2)
- ○ Retired (3)
- ○ Disabled (4)
- ○ Homemaker (5)
- ○ Student (6)
- ○ Unemployed (7)
- ○ Other (Specify) (8) _____

Q21 **Are you the primary breadwinner for your household?**

- ○ Yes (1)
- ○ No (2)
- ○ No clear primary breadwinner (3)

Q22 **Including yourself, how many working adults are in your household?**

- ○ 0 (1)
- ○ 1 (2)
- ○ 2 (3)
- ○ 3 or more (4)

Q23 **What is the highest level of school you (the parent) have completed or the highest degree you have received?**

- ○ Less than high school degree (1)
- ○ High school degree or equivalent (e.g. GED) (2)
- ○ Some college or vocational/technical degree (3)
- ○ College or vocational/technical degree (4)
- ○ Graduate or professional degree (e.g. Master's, MD, JD) (5)

Q24 **Are you CURRENTLY covered by any of the following types of health insurance or health coverage plans? (Mark 'yes' or 'no' for EACH type of coverage listed below)**

	Yes (1)	No (2)	Don't Know (3)
Private insurance (1)	○	○	○
Medicaid (i.e., state medical assistance) (2)	○	○	○
Medicare (for people over 65 years) (3)	○	○	○
Other type of health insurance (e.g. Indian Health Service, TRICARE, VA, or other military health care) (4)	○	○	○

Q25 **In general, how would you (the parent) rate your overall health?**

- ○ Poor (1)
- ○ Fair (2)
- ○ Good (3)
- ○ Very good (4)
- ○ Excellent (5)

Q26 **Please select the severity level that best describes your child's liver disease.**

- ○ Mild: my child can perform most routine daily activities (e.g., school or daycare), and his or her life is not disrupted by the liver disease (1)
- ○ Moderate: my child can perform most daily activities, but he or she is not able to do everything because of the liver disease (2)
- ○ Severe: my child is not able to perform most activities that other children are able to, although they are rarely in the hospital (3)
- ○ Life-threatening: my child is often in the hospital as a result of the liver disease. (4)

Page Break

Q27 **Thank you very much for your time!**

End of Block: Background information

Curriculum Vitae

CURRICULUM VITAE FOR ACADEMIC PROMOTION

The Johns Hopkins University School of Medicine

(Signature) Douglas Mogul 5/1/18
(Date of this version)

DEMOGRAPHIC AND PERSONAL INFORMATION

Douglas B. Mogul, MD MPH
Assistant Professor of Pediatrics
Division of Pediatric Gastroenterology, Hepatology, and Nutrition
Johns Hopkins Hospital
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Baltimore, MD 21287
Tel: (410) 955 8769
Fax: (41) 955 1464
Email: dmogul1@jhmi.edu

Education and Training

Date	Degree/ Certificate	Institution	Discipline
1994-1998	BA	Bowdoin College, Brunswick, ME	History, Biochemistry
1998-2000	MPH	University of California, Berkeley	Epidemiology
2001-2006	MD	Albert Einstein College of Med., Bronx, NY	Medicine
2004-2005	CRTP	National Institute of Health, Bethesda, MD	
2006-2007	Internship	Packard Children's Hospital, Palo Alto, CA	Pediatrics
2007-2009	Residency	Packard Children's Hospital, Palo Alto, CA	Pediatrics
2009-2012	Fellowship	Johns Hopkins University, Baltimore, MD	Pediatric GI
2015-	PhD	Johns Hopkins University, Baltimore, MD	Clinical Investigation

Professional Experience

Date	Position	Institution
2012-	Assistant Professor, Department of Pediatrics	Johns Hopkins University
2017-	Medical Director, Pediatric Liver Transplantation	Johns Hopkins University

RESEARCH ACTIVITIES

Peer-reviewed Publications

1. Nitahara JA, Cheng WL, Li B, Leri A, Li P, **Mogul DB,** Gambert SR, Kajstura J, Anversa P. Intracellular calcium, DNase activity and myocyte apoptosis in aging Fischer 344 rats. *Journal of Molecular and Cellular Cardiology*, v.30, n.3, March, 1998:519-535. PMID 9515029
2. Quist RG, Callen PW, **Mogul DB**, Bass NM. Renal hemodynamics assessed with spectral and power Doppler ultrasound in cirrhosis: Correspondence with severity of liver disease. *Hepatology*, v.30, n.4 PART 2, Oct., 1999.:293A.
3. Soroudi N, Wylie-Rosett J, **Mogul DB.** Quick WAVE screener: a tool to address weight, activity, variety, and excess. *Diabetes Educator*, v.30, n.4, Jul.-Aug., 2004: 618-22. PMID 15669779
4. Bulua A, **Mogul D**, Aksentijevich I, Singh H, Dean J, He D, Muenz L, Ward M, Yarboro C, Kastner D, Siegel R, Hull K. Efficacy of Etanercept in the Tumor Necrosis Factor Receptor–Associated Periodic Syndrome (TRAPS). *Arthritis and Rheumatism*. Mar 2012;64(3):908-13.
5. **Mogul D**, Zhou M, Intihar P, Schwarz K, Frick K. Cost-effective analysis of screening for biliary atresia with the stool color card. *J Pediar Gastroenterol Nutr*. 2015 Jan;60(1):91-87.
6. Franciscovich A, Vaidya D, Doyle J, Bolinger J, Capdevilla M, Rice M, Hancock L, Mahr T, **Mogul D**. PoopMD, a mobile health application, accurately identifies infant acholic stools. *Plos ONE*. 2015 Jul 29;10(7):e0132270
7. Schwarz KB, Molleston JP, Jonas MM, Wen J, Murray KF, Rosenthal P, Gonzalez-Peralta RP, Lobritto SJ, **Mogul D**, Pavlovic V, Warne C, Wat C, Thompson B. Durability of Response in Children Treated with Pegylated Interferon alfa-2a +/- Ribavirin for Chronic Hepatitis C. *J Pediatr Gastroenterol Nutr*. 2015 Aug 12.
8. Schwarz KB, Cloonan YK, Ling SC, et al. Children with Chronic Hepatitis B in the United States and Canada. *J Pediatr*. 2015 Dec; 167(6); 1287-1294.
9. Wang KS, Section on Surgery for the Committee in Fetus and Newborn. Newborn Screening for Biliary Atresia. *Pediatrics*. 2015 Dec; 136(6):e1663-9.
10. Schwarz KB, Cloonan YK, Ling SC, et al. Children with Chronic Hepatitis B in the United States and Canada. *J Pediatr Gastroenterol Nutr*. 2016 Jan;62(1):93-6
11. Wang KS, Tiao G, Bass LM, Hertel PM, **Mogul D**, et al. Analysis of surgical interruption of the enterohepatic circulation as a treatment for pediatric cholestasis. *Hepatology*. 2016 May;65(5):1645-165.
12. **Mogul D**, Nakamura Y, Seo J, Blauvelt B, Bridges JF. The Unknown Burden and Cost of Celiac Disease in the U.S. *Expert Rev Pharmacoecon Outcomes Res.* 2017 Apr;17(2):181-188.
13. **Mogul D**, Nagy P, Bridges JFP. Building Stronger Online Communities Through the Creation of Facebook-integrated Health Applications. *JAMA Pediatrics*. 2017, August 28.
14. **Mogul D**, Luo X, Chow E, Massie A, et al. Impact of Race and Ethnicity on Outcomes for Children Waitlisted for Pediatric Liver Transplantation. *J Pediatr Gastoenterol Nutr*. Epub Nov, 2017.

15. **Mogul D**, Henderson M, Bridges JFP. Expanding the Facebook Platform to Engage and Educate Online Communities. *Am. J Gastroenterol*. 2018 Apr; 113(4): 457-8.
16. **Mogul D**, Luo X, Bowring MG, Chow EK, Massie AB, Schwarz KB, Cameron AM, Bridges JFP, Segev DL. Fifteen-year Trends In Pediatric Liver Transplants: Split, Whole Deceased, and Living Donor Grafts. *J Pediatr*. 2018 May; 196:148-153.

Inventions, Patents, Copyrights (pending, awarded)

Date	**Title**
2013	PoopMD: mobile app to evaluate acholic stools and gastrointestinal bleeding for Apple, Android and web-based platforms
2014	Liver Space: mobile app to educate and increase social engagement among individuals with pediatric liver disease; and to facilitate patient-centered research

Extramural Funding (current, pending, previous)

Date	**Title**
Current	
2015-	Improving pediatric liver transplant allocation. NIH/AHRQ. 1K08HS023876-01. $729,875. PI: Douglas Mogul. 75% effort.
2017	Immunologic and virologic correlates of the age-related decrease in HBV DNA in Children. NIDDK. 5U01DK082916-10. PI: Kathleen Schwarz. 5% effort.
Previous	
2015-2017	Development of Liver Space, an app for individuals with pediatric liver disease. Gilead Foundation. $100,000. PI: Douglas Mogul.
2015-2017	Integration of Apple ResearchKit and a content management system for PoopMD. Pershing Square Foundation. $41,000 PI: Douglas Mogul.
2010-2015	Effect of HBA DNA Methylation and the Mutant 1762T / 1764A on Viral Load & HCC HBV Clinical Research Network. NIDDK. U01DK 082916-01 $2,520,427 PI: Kathleen Schwarz, MD; Co-Investigator 6% effort
2011-2013	Epigenetic Regulation of Hepatitis B Virus, American College of Gastroenterology Clinical Research Award, $30,250 (research only); PI: Douglas Mogul, MD MPH
2011-2012	T32 National Research Service Award, NIIH. $47,000; PI: George Dover, MD JHU Dept of Pediatrics; Trainee recipient – 80% effort

Intramural Funding (current, pending, previous)

Date	Title
2018	Developing a digital tool to improve transition readiness for pediatric liver transplant recipients: a multi-stakeholder approach. Department of Pediatrics Innovation Award. PI: Douglas Mogul. $40,000. 5% effort.

Contracts

Date	Title
2013-2015	HCB Health, Austin, TX: Health marketing firm to develop mobile app to evaluate acholic stools and gastrointestinal bleeding for Apple, Android and web-based platforms; update stool color information on CMSC website.
2013-	Procter & Gamble, Cincinnati, OH: Manufacturer of Pampers™, which is distributed to ~95% of nurseries in the U.S. Company, will distribute stool color card to nurseries and direct patients to CMSC website for more information. Company will provide link to CMSC website to 3 million subscribers of their digital content, and to PoopMD in the Apple and Android store.
2014-2015	iHealthVentures, New Jersey: Developer of mobile health apps. Will develop Liver Space, mobile app to educate and socially engage children with liver disease, and provide a means to conduct survey research in these diseases.
2015-2016	Beneufit, San Francisco, CA: Developer of mobile health applications and expert in Apple ResearchKit. Company will update PoopMD including integration of Apple ResearchKit for future research.

EDUCATIONAL ACTIVITIES

Educational Publications

Invited Review Articles

1. **Mogul D,** Torbenson M, Schwarz. Epigenetic Regulation of Hepatitis B Virus. *Current Hepatitis Reports.* Sep 2011; 10:277-84.

2. **Mogul D**, Schwarz K. Managing HCV-infected children. *Clinical Liver Diseases.* Sep 2012; 1(3): 77-80.

3. Mogul D, Ng K. Pediatric Liver Tumors. *Clinics in Liver Disease*. In press.

Book Chapters

1. **Mogul D**, Sibley E. Congenital Disorders of Digestion and Absorption, In: *Diarrhea: Diagnostic and Therapeutic Advances*. Guandalini S, Vaziri H, Eds. New York: Springer. pp. 159-176. 2010.

2. **Mogul D**, Schwarz K. What is the correct management and follow up for infants whose mothers are infected with Hepatitis B? In: Bousvaros A, Rosh J. Curbside Consultation in Pediatric GI. SLACK Inc. 2013.
3. Laroche G, **Mogul D**. Biliary atresia. 5 minute Pediatric Consult, 7th ed. Wolters Kluwer. New York. 2015.
4. Ogholikhan S, **Mogul D**. Biliary atresia. 5 minute Pediatric Consult, 8th ed. Wolters Kluwer. New York. In press.

Other Media

1. Videotaped for Fox45 News segment on PoopMD. June 29, 2014.
2. Webinar for Johns Hopkins Community Physicians on neonatal cholestasis. March 6, 2018.

Teaching

Date	Title
11/3/17	"Meet the professors breakfast" on Using social media for research, North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition annual meeting, Las Vegas, NV.
10/23/2017	"Meet the professors breakfast" on Neonatal cholestasis, American Association of the Study of Liver Diseases annual meeting, Washington, DC.
10/10/2015	"Meet the professors breakfast" on Hepatitis B virus, North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition, annual meeting, Washington, DC.
7/30/2014	Lectures on acute liver failure and gastrointestinal bleeding to PICU fellows. Bloomberg Children's Center.
8/1/2013	Lectures on acute liver failure and gastrointestinal bleeding to PICU fellows. Bloomberg Children's Center.
4/13/2013	Lecture on gallstone and cholecystitis as part of Pediatric Trends. Turner Auditorium.
2/27/2013	Lecture on gastrointestinal reflux to medical students. Bloomberg Children's Center.
8/7/2012	Lectures on acute liver failure and gastrointestinal bleeding to PICU fellows. Bloomberg Children's Center.

Mentoring

Date	Responsibility	Current Position
2013	Grace Felix, pediatric resident, for project on biliary atresia stool card.	Senior fellow

2013	Stephanie Honigbaum, fellow in pediatric gastroenterology, for project on biliary atresia stool card.	Private practice
2013	Anna Schuettge, nurse practitioner student, for project on biliary atresia stool card.	NP in private practice
2014-2016	Amy Franciscovich, pediatric resident, for research on PoopMD, an app to screen infants with biliary atresia. Publication and Johns Hopkins pediatric research prize.	Private practice
2015-2017	Sina Ogholikhan, pediatric GI fellow, multiple projects related to biliary atresia.	Private practice
2017-	Karina Covarrubias, medical student, project on length of stay in pediatric liver transplantation	Medical student

CLINICAL ACTIVITIES

Certification

Date	**Title**
2009	Board Certified in General Pediatrics, American Board of Pediatrics
2013	Board Certified in Pediatric Gastroenterology, American Board of Pediatrics

Licensure

Date	**State**
2008	California Medical Board
2012	Maryland Medical Board

Position

Date	**Title**
2012-	Attending, Pediatric Gastroenterology, Nutrition and Hepatology Division, the Johns Hopkins University School of Medicine, Baltimore, MD. Floor rounds, outpatient clinics, multidisciplinary conferences, didactic rounds, procedures. Perform and train post-doctoral fellows in pediatric gastroenterology procedures.
2017-	Medical Director, Pediatric Liver Transplantation. Floor rounds and outpatient clinics, multidisciplinary conferences, didactic rounds and procedures. Also oversee pediatric liver and liver transplantation rounds

with liver and liver transplant nurse practitioners, post-doctoral fellows on the liver and liver transplant elective.

ORGANIZATIONAL ACTIVITIES

Societies, Committees

Date	State
2009	North American Society of Pediatric Gastroenterology, Hepatology and Nutrition Inflammatory Bowel Disease Committee, North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition
2011	American Association for the Study of Liver Diseases
2014-2017	Technology Committee, North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition
2014-2015	Clinical and Public Policy Committee, American Association for the Study of Liver Diseases
2016-	Communications and Technology Committee, American Association for the Study of Liver Diseases

RECOGNITION

Honors

Date	Title
2007	Teaching and Tomorrow Program, North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition, Salt Lake City, UT.
2009	Resident Teacher Award, Lucile Packard Children's Hospital of Stanford University, Palo Alto, CA.
2014	Young Faculty Clinical Research Award, North American Society of Pediatric Gastroenterology, Hepatology, and Nutrition, Atlanta, GA
2017	Nomination for Excellence in Service and Professionalism Award, Johns Hopkins School of Medicine

Invited Talks/Panels

Date	Title
May, 2015	PoopMD: A mobile health application, accurately identifies perinatal alcoholic stools. Pediatric Grand Rounds, Johns Hopkins University.

Feb, 2017 Liver Space: A Facebook Health Application to Strengthen Online Communities. Bioinformatics Grand Rounds, Johns Hopkins University.

May, 2017 Using social media to improve outcomes in pediatric liver disease. American Association for Study of Liver Diseases annual meeting, Washington, DC.

Biosketch

Dr. Douglas Mogul was born on August 30, 1976 at New York Hospital and lived throughout his childhood in Chappaqua, NY. After graduating from Horace Greely High School in 1994, he studied biochemistry and modern European history at Bowdoin College in Brunswick, ME where he graduated *magna cum laude* in 1998. After college, he earned a Masters in Public Health at the University of California, Berkeley where he concentrated his studies in the epidemiology of infectious disease including tropical medicine and hepatitis C virus. After graduate school, he lived in Salvador de Bahia, Brazil, where he researched schistosomiasis in a rural community. He attended the Albert Einstein College of Medicine at Yeshiva University. After completing his pre-clinical third year, he was accepted into the Clinical Research Training Program of the National Institutes of Health, where he worked for one year under Dr. Daniel Kastner studying periodic fever syndromes. Dr. Mogul graduated from medical school in 2006 and completed internship and residency at the Lucile Packard Children's Hospital of Stanford University. He completed his clinical training as a fellow in pediatric gastroenterology, hepatology and nutrition at the Johns Hopkins University School of Medicine in 2009. Since that time, he has been an Assistant Professor of Pediatrics at Johns Hopkins.

Dr. Mogul's research is focused on three main areas. First, he was awarded an NIH training grant to study ways to improve outcomes for children with end-stage liver disease under the mentorship of Dr. Dorry Segev and Dr. John Bridges. This

research has been presented at national meetings including as a plenary and has yielded several publications. He has also received grants from the Gilead Foundation as well as a Johns Hopkins Innovation award to create digital tools that help patients and families with liver disease. One tool, PoopMD, has been chosen as a top app for parents of newborn babies by several organizations including YahooHealth News and Huffington Post. Finally, he is a member of the NIH Hepatitis B Research network through which he conducts studies of children with hepatitis B, and he participates in clinical trials of viral hepatitis.