UCSF
UC San Francisco Previously Published Works

Title
Receipt of a pediatric liver offer as the first offer reduces waitlist mortality for adult women

Permalink
https://escholarship.org/uc/item/3sg5t37r

Journal
Hepatology, 68(3)

ISSN
0270-9139

Authors
Ge, Jin
Gilroy, Richard
Lai, Jennifer C

Publication Date
2018-09-01

DOI
10.1002/hep.29906

Peer reviewed

eScholarship.org
Powered by the California Digital Library
University of California

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access
Author manuscript
Hepatology. Author manuscript; available in PMC 2019 April 02.

Published in final edited form as:
Hepatology. 2018 September ; 68(3): 1101–1110. doi:10.1002/hep.29906.

Receipt of a Pediatric Liver Offer as the First Offer Reduces Waitlist Mortality for Adult Women

Jin Ge[1], **Richard Gilroy**[2], and **Jennifer C. Lai**[1,3]

[1]Department of Medicine, University of California – San Francisco, San Francisco, CA

[2]Liver Transplant Program, Intermountain Medical Center, Murray, UT

[3]Division of Gastroenterology and Hepatology, Department of Medicine, University of California – San Francisco, San Francisco, CA.

Abstract

In liver transplantation, adults with small stature have a greater susceptibility to waitlist mortality. This may explain the persistent waitlist mortality disparity that exists for women. We hypothesized that women who receive early offers of pediatric donor livers have improved waitlist survival, and that preferentially offering these organs to women mitigates this sex-based disparity. We analyzed donor liver offers from 2010 to 2014. Adult candidates who received a first offer that ranked within the first three match run positions from the donors' perspective were classified based on gender and whether they received a pediatric versus adult offer. We used competing risks regression to associate first offer type and waitlist mortality. A total of 8,101 waitlist candidates received a first offer that was ranked within the first three match run positions: 5.6% (293/5,202) men and 6.2% (179/2,899) women received a pediatric donor liver as their first offer. In multivariable analyses, compared with adult-first men, adult-first women (subhazard ratio [sHR] 1.33, 95% confidence interval 1.17–1.51, $P < 0.01$) had an increased pretransplant mortality risk while pediatric-first men and pediatric-first women had noninferior risks of morality. Pediatric-to-adult and adult-to-adult recipients had similar risks of graft failure and posttransplant mortality. *Conclusion:* Our study examines allograft selection by donor age, recipient sex, and in effect size as a means to address disparities in waitlist mortality. We found that women who received a pediatric donor liver as the first offer had a lower risk of waitlist mortality compared with those who receive adult offers. Our data provides a simple approach to mitigating the increased waitlist mortality experienced by women by incorporating donor and recipient size as variables into organ allocation. (HEPATOLOGY 2018; 68:1101–1110).

Although incorporation of the Model for End-Stage Liver Disease (MELD) score into the liver allocation system ameliorated disparities in transplantation with respect to race and ethnicity, the sex disparity has persisted.[1,2] In liver transplantation in the United States, women continue to be significantly more likely than men to die or to be removed from the waitlist without transplantation.[1–3] Many factors contribute to this sex disparity, but

ADDRESS CORRESPONDENCE AND REPRINT REQUESTS TO: Jennifer C. Lai, M.D., M.B.A., 513 Parnassus Avenue, UCSF Box 0538, San Francisco, CA 94143, jennifer.lai@ucsf.edu, Tel.: 415-476-6422.

Potential conflict of interest: Dr. Gilroy is on the speakers' bureau for Gilead.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

conventional wisdom attributes the majority of this inequity to reduced access to size-appropriate livers for adults with short stature.[3–5] Previous research has demonstrated that although liver volumes among women are substantially smaller than those among men, organs offered to both women and men were similar in size.[6] Moreover, this size-mismatch that effected candidates of short stature disproportionately disadvantaged women, as they were 4 times more likely than men to see organ offers declined.[7]

Livers from pediatric donors, which may be better matched in size to adults of small stature, may offer a solution. Retrospective studies have demonstrated that adult recipients of pediatric grafts are more likely to be women and have a lower body mass index (BMI).[8] In addition, adult recipients of pediatric grafts have equivalent outcomes in terms of both recipient and graft survival when compared with adult recipients of adult grafts.[8–10] Under current policies, pediatric donor livers are prioritized for regional pediatric candidates prior to being available for local and regional adult candidates. National pediatric candidates, however, are generally considered after local or regional adult candidates in the current system with few exceptions.[11] This implies that policy changes effecting pediatric to adult allocation may impact prioritization to pediatric candidates currently seeing national pediatric donor organ offers. Any modifications to policies that influence pediatric to adult organ utilization, therefore, must be considered for the impact upon national allocation to pediatric recipients. These impacts must be addressed before changes to adult allocation policies occur.

With these considerations in mind, we hypothesized that preferentially allocating offers from pediatric liver donors to adults with small stature on the liver transplant waitlist after all viable (local, regional, and national) pediatric candidates are exhausted may help mitigate the persistent sex-based disparity in waitlist mortality. Using national registry data of all liver transplant candidates in the United States, we tested this hypothesis.

Patients and Methods

SUBJECTS

Data on liver transplant waitlist candidates, deceased liver donors, and match-run information were obtained from the United Network for Organ Sharing (UNOS)/Organ Procurement and Transplantation Network (OPTN) Standard Transplant Analysis and Research (STAR) and Potential Transplant Recipient (PTR) files as of March 31, 2016.[12] The study population included all adult (age ≥18 years) non-Status 1 candidates on the liver transplantation waitlist from January 1, 2010 through December 31, 2014. Candidates who were <18 years old or those listed at Status 1 (i.e., with fulminant hepatic failure or acute hepatic necrosis) were excluded. Pediatric donors were defined as donors <18 years old and adult donors were defined as those aged ≥18 years. This delineation was used as UNOS allocation rules governing donors diverge at age 18.[11] Donor and waitlist candidate UNOS regions were categorized based on the median allocation MELD score at transplantation during the study period: "low" for regions with MELD <27, "medium" for regions with MELD ≥27 and <30, and "high" for regions with MELD ≥30 similar to the categorization used in a previous analysis.[13]

Author Manuscript
Author Manuscript
Author Manuscript
Author Manuscript

DECEASED DONOR CHARACTERISTICS

Donors were characterized by factors included in the donor risk index (DRI),[14] including age, sex, race/ethnicity, height, HCV antibody status, Centers for Disease Control (CDC) high risk for disease transmission status, cause of death, and donation after cardiac death. Split liver allocations were considered the same as whole liver allocations in our analyses. Characteristics of each donor liver were available only at transplant; therefore, we obtained these data by matching the donor identification number at offer with that at transplantation.

WAITLIST CANDIDATE CHARACTERISTICS

Demographic data on waitlist candidates included age, sex, race/ethnicity, height, weight, and calculated BMI at the time of listing. Clinical variables included recipient ABO blood type, etiology of liver disease, exception points granted, allocation MELD score at first offer, death date, date of removal from the waiting list, reason for removal, transplant date, type of transplant, and UNOS region of listing. Race/ethnicity was classified into the following categories: Non-Hispanic white, Hispanic, black, Asian, or Other/Multiracial. Etiologies of liver disease were grouped as follows: hepatitis C, alcoholic, nonalcoholic fatty liver disease, cholestatic, hepatitis B, and other. Candidates were classified as “small stature” defined as those with heights less than twenty-fifth percentile across the entire waitlist candidate pool.

We divided waitlist candidates into four cohorts based on sex and the first liver offer the waitlist candidate received in the match sequence. Each time a donor organ becomes available, candidates are ranked with the first match run position from the donor organ perspective, guaranteed to be offered the organ. Organs that are declined are then offered to the candidate in the next match run position. We limited waitlist candidates to those whose first liver offer occurred in the setting in which the candidate ranked in match run positions one, two, or three among non-Status 1 adult candidates (Status 1 and pediatric candidates matches excluded) from the donors’ perspective. We adopted this previously published[7] methodology in order to isolate this analysis to those who were deemed most medically urgent and to control for liver quality (assuming that livers offered to candidates in the first three match run positions are of higher quality and therefore more “acceptable” than livers that are offered to candidates further down the match-run list). Of note, approximately 53% of all donor livers were accepted in the top three match positions during the study period of January 1, 2010 through December 31, 2014. The four cohorts were defined as follows:

1. “Pedi-first men” – Male waitlist candidates who received a pediatric donor liver as their first waitlist offer with the candidate ranking in positions one, two, or three for that pediatric donor organ.

2. “Adult-first men” – Male waitlist candidates who received an adult donor liver as their first waitlist offer with the candidate ranking in positions one, two, or three for that adult donor organ.

3. “Pedi-first women” – Female waitlist candidates who received a pediatric donor liver as their first waitlist offer with the candidate ranking in positions one, two, or three for that pediatric donor organ.

4. "Adult-first women" – Female waitlist candidates who received an adult donor liver as their first waitlist offer with the candidate ranking in positions one, two, or three for that adult donor organ.

STATISTICAL ANALYSES

Clinical characteristics and laboratory data were summarized by medians and interquartile ranges (IQR) for continuous variables or numbers and percentages (%) for categorical variables. Comparisons between groups were performed using chi-square and Kruskal-Wallis tests. Rationale for declining first offers were tabulated based on refusal codes for the four cohorts. To evaluate donor-recipient size matching for the subjects and their respective first donor offers, we utilized estimated liver volumes (eLV) equations previously validated for adult and pediatric donor populations.[6,15]

The primary predictors were sex and the first liver offer (pediatric donor liver versus adult donor liver) the candidate received, provided he or she ranked within the top three positions in the match sequence. The primary outcome was pretransplantation waitlist mortality, defined as death on the waitlist or delisting due to illness. Patients who remained on the waitlist after December 31, 2014, received a living donor liver transplant, or were removed from the waiting list for nonmedical reasons (defined as "condition improved," "other," "refused transplant," "transferred to another center," and "unable to contact candidate") were censored from the analysis.

We used competing risk regressions, of the Fine-Gray method, to evaluate the risks of pretransplant waitlist mortality with deceased donor transplantation treated as a competing event.[16] Covariables included recipient age, race/ethnicity, BMI, recipient ABO status, allocation MELD at first offer, and region. Covariables were selected using backwards deletion to reduce residual confounding and avoid model overfitting. Posttransplant outcomes included patient mortality and graft failure. We used Cox proportional hazards regression models to estimate graft failure and survival rates for transplant recipients. Covariables evaluated in the posttransplant mortality and graft function Cox models included recipient age, race/ethnicity, BMI, recipient ABO status, allocation MELD at first offer, and UNOS region.

We then explored the potential impact of prioritizing national pediatric candidates in the allocation of pediatric donor organs on the number of pediatric-to-adult transplants and donor quality. We calculated a ceiling acceptance value by using the pediatric candidates' acceptance rate of pediatric donor livers prior to their being offered to adults during the study period and an addressable population of pediatric candidates that was not transplanted during the study period. In addition, we calculated the modified DRI of pediatric organs transplanted into national non-Status 1 adult candidates to be used as a ceiling value to estimate any possible degradation in organ quality.

Two-sided *P* values <0.05 were considered statistically significant in all analyses. Analyses were performed using STATA statistical software, version 13.0 (StataCorp, College Station, TX, USA). The Institutional Review Board at the University of California, San Francisco approved this study.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Author Manuscript
Author Manuscript
Author Manuscript
Author Manuscript

Results

A total of 1,569 pediatric donor livers (80% from donors above the age of 11-years-old; median donor age 15-years-old) and 26,054 adult donor livers (median donor age 44-years-old) were offered to 39,349 adult men and 21,150 adult women on the waitlist between January 1, 2010 and December 31, 2014.

DECEASED DONOR CHARACTERISTICS

Pediatric donors and adult donors differed significantly in baseline characteristics (Table 1). Pediatric donors were more likely to be male (66% versus 58%), African-American (22% versus 18%), have B blood type (15% versus 13%), and originate in a "low" MELD region (52% versus 47%). Pediatric donors were more likely to have died from trauma (54% versus 32%) and less likely from cerebrovascular accident (6.1% versus 38%[$P < 0.01$ for all]). They were less likely to be categorized as CDC high risk (7.2% versus 14%) or have positive HCV antibody (0.6% versus 4.2% [$P < 0.01$ for all]). Pediatric donors had a median (IQR) height of 167 cm (154–179): lower than that of adult donors with a median (IQR) height of 173 cm (165–180 [$P < 0.01$]). The median (IQR) DRI (where lower values indicate higher-quality livers) was lower for pediatric donors at 1.27 (1.11–1.64) versus 1.46 (1.20–1.76) for adult donors [$P < 0.01$]. Overall acceptance rates for pediatric donor livers offered to women and those offered to men were both 63%. Overall acceptance rates for adult donor livers offered to women was 48% and those offered to men was 80%.

WAITLIST CANDIDATE CHARACTERISTICS

Baseline characteristics of the four candidate cohorts are shown in Table 2. Among the 8,101 adult waitlist candidates that who had a first offer that was in the first three match run positions, 5.6% (293/5,202) of men and 6.2% (179/2,899) of women received a pediatric donor liver offer as their first offer. Forty-four percent (3,573/8,101) of all candidates who received a first offer and ranked within first three match run positions accepted their first offer, and 66% (5,306/8,101) of all candidates accepted an offer within the first three offers they received.

Baseline Characteristics of the Male Candidate Groups—There were no significant differences between adult-first men and pedi-first men with regards to age (median 56 years for both groups), race/ethnicity (68% versus 70% non-Hispanic white), height (median 178cm for both groups), weight (median 90kg versus 89kg), BMI (median 28.6 versus 28.4), ABO status (33% versus 40% blood group O), etiology of liver disease (43% versus 42% Hepatitis C), and listing UNOS region (59% versus 53% in "low" MELD region) between pedi-first men and adult-first men, respectively. Compared to adult-first men, pedi-first men were more likely to be listed with hepatocellular carcinoma (HCC) exception points (19% versus 13%, $P < 0.01$) and also had a lower median (IQR) MELD score of 28 (22–36) at first offer compared with adult-first men at 31 (23–39) [$P < 0.01$]. Compared to adult-first men, pedi-first men had similar number of offers (two versus two, $P = 0.84$) and waited longer for their first offer (10 versus 7 days, $P = 0.02$). Pedi-first men were more likely to be offered a split liver (4.4% versus 0.9%, $P < 0.01$).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Baseline Characteristics of the Female Candidate Groups—There were no significant differences between adult-first women and pedi-first women with regards to age (57 versus 55 years), race/ethnicity (69% versus 66% non-Hispanic white), weight (median 72 versus 76kg), BMI (median 27.9 versus 28.7), etiology of liver disease (32% versus 29% Hepatitis C), HCC exception points (9% versus 7%), time to first waitlist offer (8 versus 6.5 days), and listing UNOS region (53% versus 52% in “low” MELD region) between pedi-first women and adult-first women, respectively. Compared to adult-first women, pedi-first women were more likely to be shorter in height (median 160cm versus 163cm, $P = 0.02$), to have blood type O (43% versus 39%, $P < 0.01$), and also had a lower median (IQR) MELD score of 29 (22–39) at first offer compared with adult-first women at 32 (25–40) [$P = 0.04$]. Compared to adult-first women, pedi-first women had a fewer number of offers, median (IQR) 2 (1–3), versus adult-first women, median (IQR) 2 (1–4) [$P < 0.01$]. Pedi-first women were also more likely to be offered a split liver (6.1% versus 1.0%, $P < 0.01$).

REASONS FOR DECLINING FIRST OFFERS

Refusal codes for candidates who declined their first offers differed significantly between the four cohorts and are presented in Table 3. Donor age or quality was the most common refusal rationale for adult-first men and women at 45% and 39%, respectively. For pedi-first men and women, donor age or quality was a less common rationale, at 12% and 28%, respectively. Pedi-first men were more likely to refuse their first offers due to donor size/weight at 55% versus 37% for pedi-first women, whereas adult-first women were more likely to refuse their first offers due to donor size/weight at 21% versus 11% for adult-first men.

DONOR-RECIPIENT SIZE MATCHING

Next, we evaluated size mismatch between the donor and the recipient using eLV equations previously validated for adult and pediatric donor populations.[6,15] In these results, a ratio greater than 1 indicated that the donor had a greater eLV than the waitlist candidate while a ratio less than 1 indicated that the donor had a smaller eLV compared with the candidate. As expected, there were substantial differences in the eLV ratios between the four groups (Fig. 1). Both adult-first and pedi-first men at their first offer received donor offers that had eLV ratios less than 1: 0.9 and 0.7 for adult-first men and pedi-first men, respectively. At first offer acceptance, the eLV ratios approached but remained less than 1, indicating that recipients received donor livers that were slightly smaller than their estimated liver size.

Among women, adult-first women at their first offer received donor offers who had eLV ratios above 1 at 1.08. This indicated that adult-first women typically received organ offers from donors with livers larger than their own. This difference persisted at first offer acceptance with adult-first women accepting organs with an eLV ratio of 1.04. Pedi-first women, however, were offered smaller organs with median eLV ratio of 0.89. For the pedi-first women who accepted their first offers, the median eLV ratio remained at 0.89.

PRE-TRANSPLANT WAITLIST MORTALITY

Results from univariable and multivariable competing risks analyses of pretransplant waitlist mortality among the four cohorts are described in Fig. 2. Using the adult-first men as a reference group in our univariable model, adult-first women had a higher risk of pretransplant waitlist mortality (sHR 1.40, 95% CI 1.24–1.58, $P < 0.01$). In contrast, pediatric-first men (sHR 0.76, 95% CI 0.52–1.11, $P = 0.16$) and pediatric-first women (sHR 1.00, 95% CI 0.66–1.52, $P = 0.99$) had noninferior risks of pretransplant waitlist mortality in univariable analysis.

In our multivariable model, once again using adult-first men as a reference group, adult-first women had an increased waitlist mortality risk (sHR 1.33, 95% CI 1.17–1.51, $P < 0.01$). Pediatric-first men (sHR 0.94, 95% CI 0.64–1.37, P 5 0.73) and pediatric-first women (sHR 1.06, 95% CI 0.70–1.61, $P = 0.79$) had noninferior risks of pretransplant waitlist mortality as well in adjusted multivariable analysis.

GRAFT AND POST-TRANSPLANT OUTCOMES

Of the 5,202 male and 2,899 female waitlist candidates included in this study, 4,368 (84%) men and 2,257 (78%) women ultimately underwent deceased donor liver transplantation. These figures include split liver transplants. Of the 4,368 men, 6.1% (266/4,368) underwent pediatric-to-adult transplantation. Of the 2,257 women, 7.0% (159/2,257) underwent pediatric-to-adult transplantation.

Median follow-up posttransplant was 1,054 days (IQR 481–1,477) across the four groups. Among men, recipients of pediatric livers had noninferior risks of graft failure when compared with recipients of adult livers in both univariable (hazard ratio [HR] 0.67, 95% CI 0.37–1.23, $P = 0.19$) and multivariable analyses (HR 0.64, 95% CI 0.35–1.18, $P = 0.16$). Male recipients of pediatric livers also had noninferior rates of posttransplant mortality rates when compared with recipients of adult livers in both univariable analysis (HR 0.98, 95% CI 0.73–1.32, $P = 0.90$) and multivariable analyses (HR 0.96, 95% CI 0.72–1.29, $P = 0.80$).

Among women, recipients of pediatric livers have noninferior risks of graft failure as recipients of adult livers in both univariable (HR 1.21, 95% CI 0.67–2.19, $P = 0.53$) and multivariable modeling (HR 1.121, 95% CI 0.67–2.20, $P = 0.63$). With respect to posttransplant mortality, compared with female recipients of adult livers, female recipients of pediatric livers had noninferior risks of posttransplant mortality in both univariable analysis (HR 0.82, 95% CI 0.56–1.22, $P = 0.33$) and multivariable analysis (HR 0.81, 95% CI 0.54–1.19, $P = 0.28$).

IMPACT OF PRIORITIZING NATIONAL PEDIATRIC CANDIDATES

During the study period, 50,524 offers of pediatric livers were made, of which 60.4% (30,500/50,524) were to adult recipients. Of the 16,544 pediatric donor livers that were offered to pediatric candidates prior to offers to adult candidates, the offer acceptance rate by pediatric candidates was 10.3% (1,710/16,544). Of the 3,480 pediatric donor offers to pediatric candidates that took place after offers to adult candidates, the offer acceptance rate by pediatric candidates was 5.8% (203/3,277). There were 7,899 national pediatric donor offers to pediatric candidates, of which 6.9% (543/7,356) were accepted by a national pediatric candidate. Of note, of the 4,298 pediatric candidates on the waitlist during the study period, 70% (3,014/4,298) underwent either deceased or living donor liver

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

transplantation and 30% (1,284/4,298) remained on the list or were removed from the list due to death, illness, or for other reasons.

The median modified DRI, which does not take into account cold ischemic time or sharing type, for pediatric donor livers accepted by all adults was 1.12 (IQR 1.09–1.53) while that for pediatric donor livers accepted by all pediatric candidates was 1.29 (IQR 1.09–1.53). For nationally placed pediatric donor livers, those accepted by non-Status 1 pediatric candidates had a median modified DRI of 1.61 (IQR 1.43–1.75). The modified DRI for nationally placed pediatric donor livers accepted by non-Status 1 adult candidates (currently prioritized after national non-Status 1 pediatric candidates) was 1.46 (1.15–1.92). In comparison, the median modified DRI for adult livers accepted by non-Status 1 adults in the same period was 1.33 (1.10–1.62) and that for adult livers accepted by non-Status 1 adult women was 1.33 (1.10–1.62).

Discussion

Our study examines the possible impact of pediatric-to-adult liver transplant policy upon the sex disparity in waitlist mortality. Previous studies have demonstrated that the sex disparity in waitlist mortality is partially driven by body size [(7)]; our data confirmed that women are especially disadvantaged in this situation. We found that women who received a pediatric donor liver offer as the first offer were more likely to accept this offer versus men who were in the same position. More importantly, we found that women who received a pediatric donor liver as their first offer had a lower risk of pretransplant mortality compared with women who received an adult donor liver as their first offer. When compared with men, women who received a pediatric donor liver as their first offer had a noninferior risk of pretransplant mortality. This demonstrates the potential of utilizing pediatric donor liver offers as a means to mitigate the sex-based disparity in pretransplant waitlist mortality that has been well-documented.[(1,2)] In addition, we confirmed that pediatric-to-adult transplants have similar graft failure and posttransplant mortality rates compared with adult-to-adult transplants.

We offer several explanations for these findings. First, livers from pediatric donors were, in general, associated with more favorable donor risk profiles, as evidenced by the significantly lower DRI (where lower values indicate higher quality livers).[(14)] Second, pediatric donor livers represented an opportunity for candidates to access an organ more quickly: for both men and women, pedi-first candidates received these offers at lower MELD scores compared with adult-first candidates – 28 versus 31 for men and 29 versus 32 for women. In addition, for the pedi-first candidates of both genders, their pediatric donor first offer came 9 days (for men) and 8 days (for women) earlier than a subsequent adult donor offer (for those who did not accept their pediatric first offer).

Third, and perhaps most importantly, women who were offered pediatric first offers had improved access to organs that matched their body size (Fig. 1). Women who were initially offered livers from adults had donors with eLVs that were median 8% larger than their eLVs. Women who were initially offered livers from pediatric donors had donors with eLVs that were median 11% smaller than their eLVs – a value that is more consistent with men. In

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

support of this finding, we found that height/size was a more commonly cited factor for rejection by men who received a pediatric offer as their first offer compared with women who received pediatric donor offers as their first offer.

Our analyses revealed several other interesting observations. First, the vast majority (80%) of pediatric donors were older than 11-years-old. Despite being younger in age, pediatric donors were taller (at 167 cm) than adult female recipients (at 163cm and 160cm for the two female cohorts). Pediatric donors whose livers were offered to adults were more likely to have died of trauma, more likely to be black, and more likely to have blood type B. This implies that candidates with favorable ABO blood types, such as B or AB, may disproportionately benefit from pediatric donor livers allocated to adults.[(17)]

We acknowledge several limitations to our analyses. First, this study relied upon UNOS registry data, which could be subject to entry error or inconsistencies with respect to subjective errors. Second, we restricted our analysis to only those candidates who had their first offer from the first three match-run positions. Although this only reflects 13% of the total waitlist population, this methodology isolates the analysis to those candidates deemed most medically urgent and to livers that are of higher quality (and therefore more "acceptable"). Third, this study only demonstrates noninferiority for women who receive a pediatric donor liver offer versus men. We do, however, demonstrate superiority to receiving a pediatric donor liver versus receiving an adult donor liver as the first offer for female waitlist candidates.

Fourth, the current pediatric donor liver allocation algorithms allocate livers to local and regional adults before allocation to national pediatric candidates. Given that many pediatric patients die on the waiting list and many declined offers before their death,[(18)] we should consider national allocation of pediatric donor livers to pediatric candidates before local and regional allocation to adults. In prioritizing national pediatric candidates over local and regional adults, we estimate such a change would have only a modest (although still important) impact upon organs available to adult women.

During the study period, all pediatric candidates accepted pediatric liver offers (prior to these offers becoming available to adults) at a rate of 10.3%. In contrast, national pediatric candidates accepted nationally placed pediatric liver offers at a rate of 6.9%. Using the ceiling acceptance rate of 10.3% and assuming that all 1,284 pediatric candidates over the 5-year study period who were not transplanted all become national candidates, we estimated that there would only be a net reduction of ~26 out of the 314 pediatric livers available to adults – this would have a modest impact upon the benefits seen by adult women and the small number of men with very short stature who might petition access to policy, of female before male allocation of pediatric offers, via a guidance document and pathway created within the newly established National Review Board.

Our calculations of modified DRIs, which does not take into account cold ischemic time or sharing type, provides an estimate of the impact of prioritizing national pediatric candidates on the quality of livers made available for adults. Under the current allocation algorithm, national non-Status 1 adult candidates are prioritized after national pediatric candidates. The median modified DRI of pediatric livers allocated to national non-Status 1 adult candidates is 1.46. In comparison, the median modified DRI of adult livers allocated to any non-Status 1 adult candidates is 1.33. While there may be a reduction in the quality of livers made available for adults should national pediatric candidates become prioritized, this impact may not be clinically significant. This speaks to the fact that pediatric donor livers, as a group, are generally of higher quality when compared with adult donor livers.[(14)] While these retrospective estimates serve as an initial guidance to the impact of proposed policy changes, prospective stimulations must also be conducted and analyzed prior to any policies being implemented.

Lastly, this study only assessed patients who were ultimately listed for liver transplantation and donors whose organs were not discarded prior to being offered to candidates. These analyses did not allow for any definitive conclusions surrounding patients who were not listed for liver transplantation or surrounding donors whose organs were not utilized.

Despite these limitations, our results open a line of inquiry to optimize the judicious use of pediatric donor livers that have been selected for adult allocation under current OPTN policy. Based on these results, we urge the transplant community to explore the following changes to the current liver allocation system: that offers of pediatric donor liver be prioritized to women, who are generally of shorter stature, once allocation to the entire (local, regional, and national) pediatric waitlist pool has occurred. This policy modification would provide additional offers to adult women on the waitlist and should thereby reduce the established disparity in waitlist mortality for women, while not impacting pediatric candidates. Our data, however, have the limitations outlined above and these limitations provide compelling evidence to conduct further prospective simulations and modeling with a view to confirm and optimize our proposal’s design.

Acknowledgments

Supported by grants from Paul B. Beeson Career Development Award in Aging Research (K23AG048337) and UCSF Liver Center (P30 DK026743). These funding agencies played no role in the analysis of the data or the preparation of this manuscript.

Abbreviations:

BMI	body mass index
CDC	Centers for Disease Control
DRI	donor risk index
eLV	estimated liver volume
HCC	hepatocellular carcinoma
HR	hazard ratio
IQR	interquartile ranges
MELD	Model for End-Stage Liver Disease

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

OPTN	Organ Procurement and Transplantation Network
sHR	subhazard ratio
UNOS	United Network for Organ Sharing

REFERENCES

1). Moylan CA, Brady CW, Johnson JL, Smith AD, Tuttle-Newhall JE, Muir AJ. Disparities in liver transplantation before and after introduction of the MELD score. JAMA 2008;300: 2371–2378. [PubMed: 19033587]

2). Mathur AK, Schaubel DE, Gong Q, Guidinger MK, Merion RM. Sex-based disparities in liver transplant rates in the United States. Am J Transplant 2011;11:1435–1443. [PubMed: 21718440]

3). Lai JC, Terrault NA, Vittinghoff E, Biggins SW. Height contributes to the gender difference in wait-list mortality under the MELD-based liver allocation system. Am J Transplant 2010;10: 2658–2664. [PubMed: 21087414]

4). Mindikoglu AL, Emre SH, Magder LS. Impact of estimated liver volume and liver weight on gender disparity in liver transplantation. Liver Transpl 2013;19:89–95. [PubMed: 23008117]

5). Sarkar M, Watt KD, Terrault N, Berenguer M. Outcomes in liver transplantation: Does sex matter? J Hepatol 2015;62:946–955. [PubMed: 25433162]

6). Bowring MG, Ruck JM, Haugen CE, Massie AB, Segev DL, Gentry SE. Deceased-donor liver size and the sex-based disparity in liver transplantation. Transplantation 2017;101:e329. [PubMed: 28737603]

7). Nephew LD, Goldberg DS, Lewis JD, Abt P, Bryan M, Forde KA. Exception points and body size contribute to gender disparity in liver transplantation. Clin Gastroenterol Hepatol 2017;15: 1293e2.

8). Croome KP, Lee DD, Burns JM, Saucedo-Crespo H, Perry DK, Nguyen JH, et al. Outcomes of liver transplantation with liver grafts from pediatric donors used in adult recipients. Liver Transpl 2016;22:1099–1106. [PubMed: 27145067]

9). Emre S, Soejima Y, Altaca G, Facciuto M, Fishbein TM, Sheiner PA, et al. Safety and risk of using pediatric donor livers in adult liver transplantation. Liver Transpl 2001;7:41–47. [PubMed: 11150421]

10). Hu L, Liu X, Zhang X, Yu L, Sha H, Zhou Y, et al. Child-to-adult liver transplantation with donation after cardiac death donors: Three case reports. Medicine (Baltimore) 2016;95:e2834. [PubMed: 26886643]

11). Organ Procurement and Transplantation Network. OPTN Policies 2016 https://optn.transplant.hrsa.gov/media/1200/optn_policies.pdf. Accessed June 27, 2017.

12). Preface. OPTN/SRTR 2013 Annual Data Report. Am J Transplant 2015;15 Suppl 2:4–7. [PubMed: 25626349]

13). Ge J, Roberts JP, Lai JC. Race/ethnicity is associated with ABO-nonidentical liver transplantation in the United States. Clin Transplant 2017;31. doi: 10.1111/ctr.13011. Epub 2017 Jun 19.

14). Feng S, Goodrich NP, Bragg-Gresham JL, Dykstra DM, Punch JD, DebRoy MA, et al. Characteristics associated with liver graft failure: The concept of a donor risk index. Am J Transplant 2006;6:783–790. [PubMed: 16539636]

15). Johnson TN, Tucker GT, Tanner MS, Rostami-Hodjegan A. Changes in liver volume from birth to adulthood: A meta-analysis. Liver Transpl 2005;11:1481–1493. [PubMed: 16315293]

16). Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. Journal of the American Statistical Association 1999;94:496–509.

17). Lai JC, Roberts JP. ABO-nonidentical liver transplantation in the United States. Am J Transplant 2016;16:2430–2436. [PubMed: 26932134]

18). Hsu EK, Shaffer ML, Gao L, Sonnenday C, Volk ML, Bucuvalas J, et al. Analysis of liver offers to pediatric candidates on the transplant wait list. Gastroenterology 2017;153:988–995. [PubMed: 28711630]

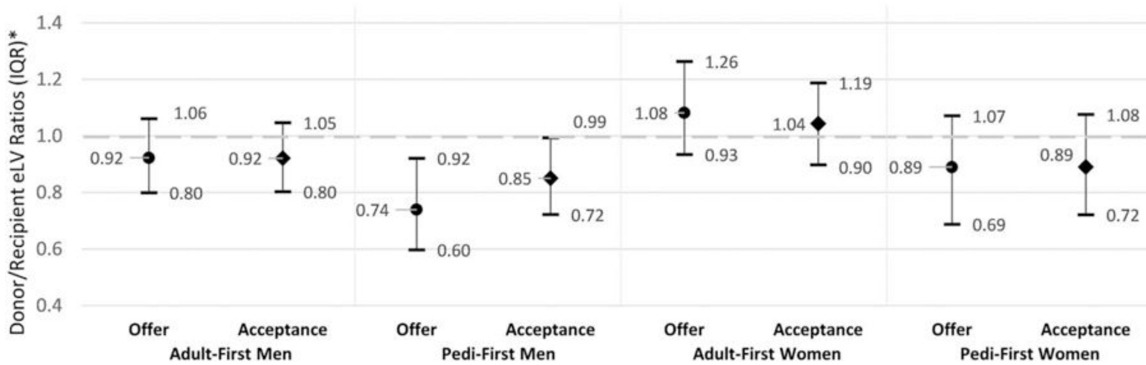

FIG. 1.

Differences in eLV ratios between donors and recipients at first offer and offer acceptance. *Bars represent twenty-fifth and seventy-fifth percentile values, circles represent median eLV ratio at first offer, and diamonds represent median eLV at first offer acceptance. Greater than 1 indicates donor liver volume was estimated to be larger than recipient; less than 1 indicates vice-versa.

Author Manuscript
Author Manuscript
Author Manuscript
Author Manuscript

Author Manuscript
Author Manuscript
Author Manuscript
Author Manuscript

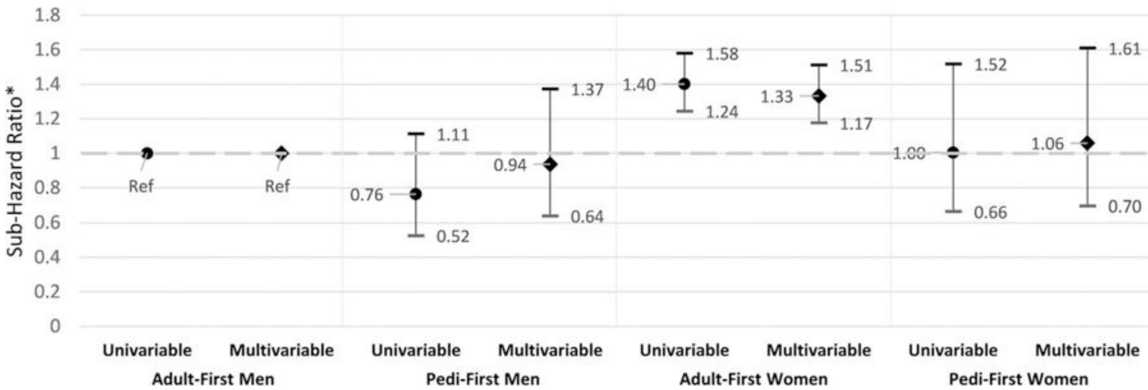

FIG. 2.

Waitlist mortality subhazard ratios among adult-first and pedi-first cohorts. Adult-first women have higher risks of pretransplant mortality compared with adult-first men, while pedi-first women do not. *Bars represent 95% CI, circles represent subhazard ratios for univariable analyses, diamonds represent subhazard ratios for multivariable analyses.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

TABLE 1.

Baseline Characteristics of Deceased Donors Whose Livers Were Offered to Adult Waitlist Candidates in the United States from January 1, 2010 Through December 31, 2014.

	Pediatric Donors (n = 1,569)	Adult Donors (n = 26,054)	P-Value
Male sex, number (%)	1,034 (66)	15,122 (58)	<0.01
Median age at donation, year (IQR)	15 (12–16)	43 (29–55)	<0.01
Black race, number (%)	341 (22)	4,607 (18)	<0.01
Median height, cm (IQR)	167 (154–179)	173 (165–180)	<0.01
Positive HCV antibody, number (%)	9 (0.6)	1,102 (4.2)	<0.01
CDC High Risk, number (%)	113 (7.2)	3,750 (14)	<0.01
ABO, number (%)			0.01
O	675 (43)	12,173 (47)	
A	604 (39)	9,775 (38)	
B	228 (15)	3,230 (12)	
AB	62 (4.0)	876 (3.4)	
Cause of death, number (%)			<0.01
Anoxia	550 (35)	6,836 (26)	
Cerebrovascular accident	95 (6.1)	9,925 (38)	
Trauma	850 (54)	8,322 (32)	
Other	59 (3.8)	624 (2.4)	
Total number of offers received	30,041	532,247	
Acceptance rates, %	93.9%	99.6%	
Median MELD at acceptance (IQR)	25 (22–31)	28 (22–34)	<0.01
Region of origin, categorized by median MELD at transplantation, number (%)			
Low (MELD <27: 3, 8, 10, 11)	809 (52)	12,288 (47)	<0.01
Medium (MELD 27–30: 2, 4, 6)	382 (24)	6,142 (24)	
High (MELD >30: 1, 5, 7, 9)	378 (24)	7,624 (29)	
Donation after cardiac death, number (%)	143 (9.1)	1,280 (4.9)	<0.01
Median cold ischemia time, hours (IQR)	6.2 (4.6–8.0)	6.1 (4.8–7.8)	0.32
Split liver status, number (%)	134 (8.5)	214 (0.8)	<0.01
Donor risk index (IQR)	1.27 (1.11–1.64)	1.46 (1.20–1.76)	<0.01

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

	Pediatric Donors (n = 1,569)	Adult Donors (n = 26,054)	P-Value
Median Distance between donor/recipient, miles (IQR)	59 (4–169)	59 (8–167)	0.03

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

TABLE 2.

Baseline Characteristics of Waitlist Candidates Who Received Either a Pediatric Donor Liver or Adult Donor Liver as Their First Offer and Ranked Within Top Three Match Run Positions From January 1, 2010 Through December 31, 2014

	Men			Women		
	Adult-First (n = 4,909)	**Pedi-First (n = 293)**	***P* Value**	**Adult-First (n = 2,720)**	**Pedi-First (n = 179)**	***P* Value**
Median age at listing, year (IQR)	56 (49–61)	56 (50–61)	0.97	55 (47–61)	57 (49–61)	0.01
Race/ethnicity, number (%)			0.92			0.40
White	3,440 (70)	200 (68)		1,803 (66)	124 (69)	
Black	550 (11)	35 (12)		400 (15)	28 (16)	
Hispanic	669 (14)	44 (15)		374 (14)	16 (8.9)	
Asian	182 (3.7)	11 (3.8)		103 (3.8)	9 (5.0)	
Other	68 (1.4)	3 (1.0)		40 (1.5)	2 (1.1)	
Height, cm (IQR)	178 (172–183)	178 (172–183)	0.89	163 (157–168)	160 (157–168)	0.02
Small stature, number (%)*	263 (5.4)	18 (6.1)	0.57	1,675 (62)	121 (68)	0.11
Median weight, kg (IQR)	89 (77–102)	90 (77–104)	0.73	76 (64–90)	72 (61–88)	0.09
Median BMI, kg/m^2 (IQR)	28.4 (25.0–32.5)	28.6 (25.1–32.6)	0.83	28.7 (24.4–33.8)	27.9 (23.7–34.4)	0.52
ABO, number (%)			0.12			0.04
O	1,953 (40)	96 (33)		1,068 (39)	76 (43)	
A	1,728 (35)	115 (39)		970 (36)	46 (26)	
B	914 (19)	60 (21)		525 (19)	45 (25)	
AB	314 (6.4)	22 (7.5)		157 (5.8)	12 (6.7)	
Etiology of Liver Disease, number (%)			0.78			0.48
Hepatitis C	2,058 (42)	126 (43)		785 (29)	57 (32)	
Alcoholic	1,024 (21)	55 (19)		339 (13)	21 (12)	
Nonalcoholic fatty	334 (6.8)	21 (7.2)		509 (19)	24 (13)	
Cholestatic	450 (9.2)	33 (11)		419 (15)	31 (17)	
Hepatitis B	187 (3.8)	9 (3.1)		48 (1.8)	5 (2.8)	
Other etiologies	856 (17)	49 (17)		620 (23)	41 (23)	
HCC exception points, number (%)	617 (13)	55 (19)	<0.01	194 (7.1)	16 (8.9)	0.37
Median MELD at first offer (IQR)	31 (23–39)	28 (22–36)	<0.01	32 (25–40)	29 (22–39)	0.03
Median offers/candidate, number (IQR)	2 (1–4)	2 (1–4)	0.84	2 (1–4)	2 (1–3)	<0.01

	Men			Women		
	Adult-First (n = 4,909)	Pedi-First (n = 293)	*P* Value	Adult-First (n = 2,720)	Pedi-First (n = 179)	*P* Value
Split liver offers, number (%)	45 (0.9)	13 (4.4)	<0.01	26 (1.0)	11 (6.1)	<0.01
Median time on waitlist, day (IQR)						
Median time to first offer	7 (2–25)	10 (3–34)	0.02	6.5 (2–26)	8 (3–24)	0.33
Median time to first pediatic	38 (14–101)	10 (3–34)	<0.01	13 (39–140)	8 (3–24)	<0.01
Median time to first adult	7 (2–25)	19 (6–58)	<0.01	6.5 (2–26)	16 (6–33)	<0.01
Median days on waitlist	17 (6–58)	19 (6–82)	0.11	17 (6–67.5)	15 (5–49)	0.30
Listing region, categorized by median MELD at transplantation, number (%)			0.12			0.46
Low (<27: 3, 8, 10, 11)	2,591 (53)	172 (59)		1,406 (52)	95 (53)	
Medium (27–30: 2, 4, 6)	1,103 (23)	54 (18)		615 (23)	45 (25)	
High (>30: 1, 5, 7, 9)	1,215 (25)	67 (23)		699 (26)	39 (22)	
Waitlist Outcome (%)			0.51			0.05
Death or too sick	627 (13)	29 (9.9)		472 (17)	23 (13)	
DDLT	4,075 (83)	253 (86)		2,110 (78)	147 (82)	
Other removal	90 (1.8)	5 (1.7)		67 (2.5)	8 (4.5)	
Censored	117 (2.4)	6 (2.0)		71 (2.6)	1 (0.6)	

[*] ”Small Stature” was defined as candidates with heights less than 25th percentile across the entire waitlist candidate pool (<165cm)

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

TABLE 3.

Donor Age Was the Most Common Rationale for Refusing Adult Donor Livers While Donor Size/Weight Was the Most Common Rationale for Refusing Pediatric Donor Livers

#	Total Number of First Offer Refusals	Adult-First Men (n = 2,631)	Pedi-First Men (n = 162)	Adult-First Women (n = 1,645)	Pedi-First Women (n = 90)
830	Donor age or quality, number (%)	1,185 (45)	19 (12)	638 (39)	25 (28)
801	Recipient ill, unavailable, refused or temporarily unsuitable, number (%)	577 (22)	24 (15)	369 (22)	13 (14)
831	Donor size/weight, number (%)	290 (11)	89 (55)	344 (21)	34 (38)
802	Multiple organ transplant or different laterality required, number (%)	124 (4.7)	9 (5.6)	73 (4.4)	4 (4.4)
837	Organ-specific donor issue, number (%)	97 (3.7)	8 (4.9)	39 (2.4)	3 (3.3)
Other	All other codes, number (%)	358 (14)	13 (8.0)	182 (11)	11 (12)