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Influence of Graft Type on Outcomes After Pediatric Liver Transplantation

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We sought to determine which type of donor graft provides children and young adults with the best outcomes following liver transplantation. Using the US Scientific Registry of Transplant Recipients database, we identified 6467 recipients of first liver transplants during 1989–2000 aged < 30 years. We used Cox models to examine adjusted patient and graft outcomes by age (< 2, 2–10, 11–16, 17–29) and donor graft type (deceased donor full size (DD-F), split (DD-S), living donor (LD)].

For patients aged < 2, LD grafts had a significantly lower risk of graft failure than DD-S (RR = 0.49, p < 0.0001) and DD-F (RR = 0.70, p = 0.02) and lower mortality risk than DD-S (RR = 0.71, p = 0.08) during the first year post-transplant. In contrast, older children exhibited a higher risk of graft loss and a trend toward higher mortality associated with LD transplants. In young adults, DD-S transplants were associated with poor outcomes. Three-year follow up yielded similar graft survival results but no significant differences in mortality risk by graft type within age group.

For recipients aged < 2, LD transplants provide superior graft survival than DD-F or DD-S and trend toward better patient survival than DD-S. Living donor is the preferred donor source in the most common pediatric age group (< 2 years) undergoing liver transplantation.

Key words: Deceased donor, graft survival, liver transplantation, living donor, patient survival, pediatric transplantation, split liver, SRTR

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Introduction

The development of transplantation of partial liver grafts in children has been an important advance in pediatric transplantation. The use of partial grafts has overcome the shortage of full-size grafts from pediatric donors. These grafts can come from either living donors or deceased (cadaveric) donors. In the latter, the liver is split between an adult and child, or a portion of a deceased donor liver is used after size reduction (1). The use of these techniques has been reported to reduce waiting list mortality for pediatric patients (2,3). Despite the use of these techniques, the waiting list mortality rate for the youngest pediatric patients (less than 5 years of age) remains several times higher than the adult waiting list mortality rate (4).

For the youngest patients, the left lateral segment from an adult liver provides adequate mass to allow survival following transplantation. Because of the two sources for the lateral segment, living donors and deceased donors, and the availability of whole donor organs from pediatric donors, there is controversy over which source provides the best patient and graft survival (5–7).

Living donor transplantation offers the advantage of transplantation at an earlier stage in the course of pediatric liver disease because children then do not have to compete in the deceased donor organ allocation system, which prioritizes the sickest patients first and gives some priority for pediatric candidates. Because there appear to be advantages of early transplantation in this population, the operation can be timed for optimum results (8). On the other hand, the donor operation exposes the living donor to risks of mortality and morbidity that would best be avoided if there is no demonstrable recipient outcome advantage in using this donor source.

There have been advances in the recovery of the left lateral segment from deceased donor donors, such as *in-situ* removal, which may improve the outcome from deceased donor transplantation with these segments. Good results have been reported after split liver transplantation, but some studies report higher risks of graft loss when compared with whole organ deceased donor transplantation (9,10).

Because of controversy regarding the use of living donor transplantation and the importance of comparing outcomes of the different possible procedures, we examined national data for pediatric first liver transplants from living donors and the two major types of deceased donor liver transplantation: whole organ or partial (split or reduced size).

Methods

This study used national transplant data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR database includes data collected by the Organ Procurement and Transplantation Network (OPTN) and is supplemented by the Social Security Death Master File (SSDMF) for extra mortality ascertainment.

The study included all primary liver transplants performed between 1989 and 2000 for recipients less than 30 years of age. Recipients of heterotopic, multiorgan, and domino transplants were excluded. All statistical analyses were performed using SAS 8.0 [Cary, NC: SAS Institute Inc., 1999].

One-year graft and patient survivals were analyzed using Cox regression models. Graft failure was defined by a record of graft failure, repeat transplant, or death. Patient death was ascertained by a death record in either the OPTN or SSDMF data, with OPTN data taking priority in cases of conflicting death dates.

For the patient survival analyses, recipients were followed until death, with follow-up time censored at 1 year after transplant. Recipients with no record of a death in either source were classified as alive as of the end of the 1-year follow up. For the graft survival analyses, recipients were followed until graft failure (including death), with follow up censored at the earliest of last known OPTN follow up, SSDMF death date, or 1 year after transplant. Sensitivity analyses were carried out by following patients for up to 3 years after transplant. Additional sensitivity analyses were carried out to consider interaction effects between center and graft type for patients less than 2 years of age.

We compared outcomes by graft source for pediatric and young adult age groups (< 30 years) using Cox regression models fitted for 6467 recipients of first single-organ liver transplants during 1989–2000 (5142 full deceased donor [DD-F], 746 split or reduced deceased donor [DD-S], and 579 living donor [LD]). Relative risks of mortality and graft failure were assessed by age group (< 2, 2–10, 11–16, 17–29) and organ type (DD-F, DD-S, LD), adjusted for recipient race, ethnicity, sex, diagnosis, life support, medical urgency status at transplant, ABO compatibility, year of transplant, and transplant center (adjustments for the 63 centers that had performed at least 20 transplants of a graft type during 1989–2000).

Results

The distribution of liver transplants by age group and donor source is shown in Table 1. Recipients in the 0–2-year age group accounted for 35% of all pediatric and young adult transplants (or 50% among ages 0–16). The most common transplant across all young age groups used a deceased full liver (80%). Split/partial deceased donor organs were used primarily in the youngest age groups, as were living donor transplants.

Table 1: First liver transplants 1989–2000 by age group (years)

Graft type	< 2	2–10	11–16	17–29	All
Full deceased donor	1438	1182	705	1817	5142
Split or reduced deceased donor	454	218	57	17	746
Living donor	385	134	22	38	579
All transplants	2277	1534	784	1872	6467

Patient and graft survival results during the first year after transplant for each donor graft type varied dramatically depending on the age group of the recipient (Figures 1 and 2). For patients 0–2 years of age, living donor grafts had a 51% lower relative risk (RR) of graft failure than DD-S (RR = 0.49 [= 1.18/2.39], $p < 0.0001$) and 30% lower risk of graft failure when compared with DD-F (RR = 0.70, $p = 0.02$) (Figures 1 and 3). Differences in mortality risk among the donor graft types in the 0–2 age group favored recipients of LD grafts over DD-S (RR = 0.71, $p = 0.08$), while there was no significant difference between LD and DD-F recipient death mortality risk (RR = 0.92; $p = 0.66$) (Figures 2 and 4). Recipients in the 0–2 age group had higher risk of mortality and graft failure with DD-S livers than DD-F livers (RR = 1.31, $p = 0.04$ for mortality; RR = 1.42, $p < 0.001$ for graft failure).

For patients aged 2–10 years, the relative risks of mortality and graft loss were higher after LD than after DD-F (RR = 1.78, $p = 0.02$ for mortality; RR = 1.53, $p = 0.02$ for

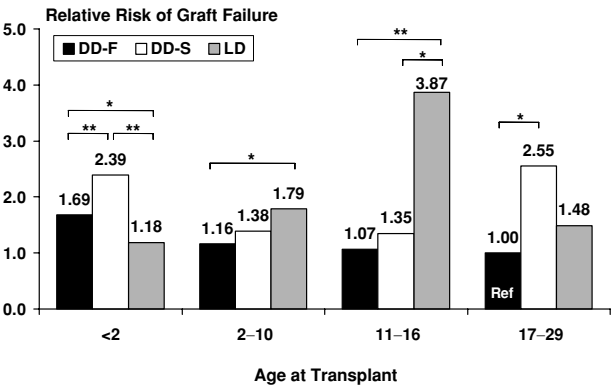

Figure 1: Relative risk of graft failure in first year by age group and graft type. Reference group is recipients of full deceased donor liver aged 17–29 years. Adjustments include recipient race, ethnicity, sex, diagnosis, life support, medical urgency status at transplant, ABO compatibility, year of transplant, and transplant center. Within each age group, all statistically significant differences in outcomes between graft types are indicated with brackets. *$p < 0.05$ for the comparison indicated; **$p < 0.001$ for the comparison indicated.

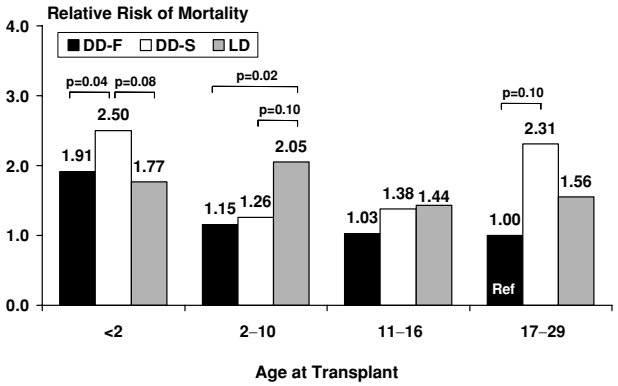

Figure 2: Relative risk of mortality in first year by age group and graft type. Reference and adjustments as in Figure 1. Within each age group, all statistically significant differences in outcomes between graft types are indicated by brackets.

graft loss). Living donor transplants also tended to have higher mortality risk than DD-S in this age group, in terms of mortality (RR = 1.63, p = 0.10), but there was no significant difference in the risk of graft loss (RR = 1.29, p = 0.26). In the 11–16 age group, a significantly higher relative risk of graft failure was observed after LD than after DD-F transplant (RR = 3.63, p = 0.0001) or DD-S transplant (RR = 2.87, p = 0.02), although mortality risks were similar for the three donor graft types. Among patients aged 17–29 years, the relative risk of graft failure was significantly higher for DD-S than for DD-F livers (RR = 2.55, p = 0.02), while the mortality risks were higher but did not reach statistical significance (RR = 2.31, p = 0.10).

Sensitivity analyses

Similar analyses following patients for up to 3 years after transplant supported the results found for the first year after transplant. The results are shown in Figures 5 and 6.

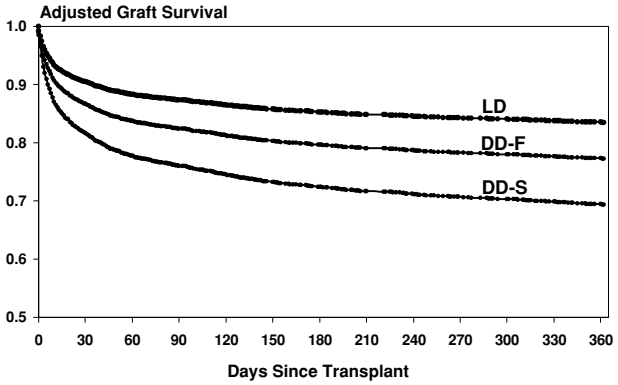

Figure 3: Adjusted graft survival for recipients < 2 years by graft type. Shown for the average patient aged < 2 years in the population.

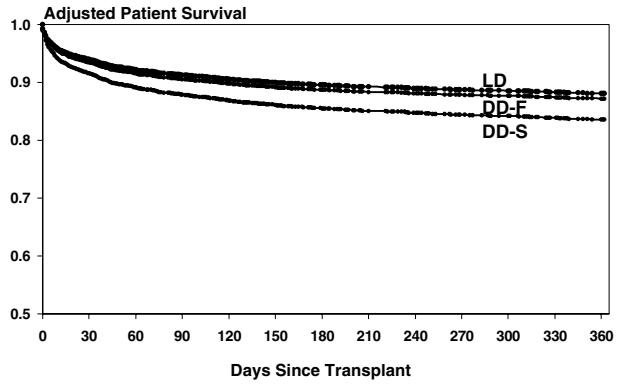

Figure 4 : Adjusted patient survival for recipients < 2 years by graft type. Shown for the average patient aged < 2 years in the population.

The graft survival results were qualitatively similar, although some differences no longer reached statistical significance. Within age groups, there were no longer any statistically significant differences in mortality by graft type, although the patterns remained similar to the first-year results.

One concern with our analysis is whether there might be a group of experienced centers whose outcomes for split and living donor transplants differ from those of all other US centers. To answer this question, center by graft type interactions were evaluated separately for the 2277 patients less than 2 years of age. Interaction terms were included for five centers that had performed at least 20 split transplants and five that had performed at least 20 living transplants for patients aged less than 2 years during the time period. As a group, the relative mortality or graft

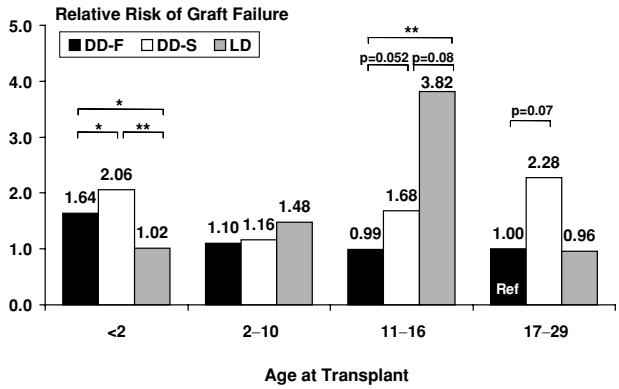

Figure 5: Relative risk of graft failure by age group and graft type with patients followed for up to 3 years. Reference group and adjustments as in Figure 1. Within each age group, all statistically significant differences in outcomes between graft types are indicated by brackets. *p < 0.05 for the comparison indicated; **p < 0.001 for the comparison indicated.

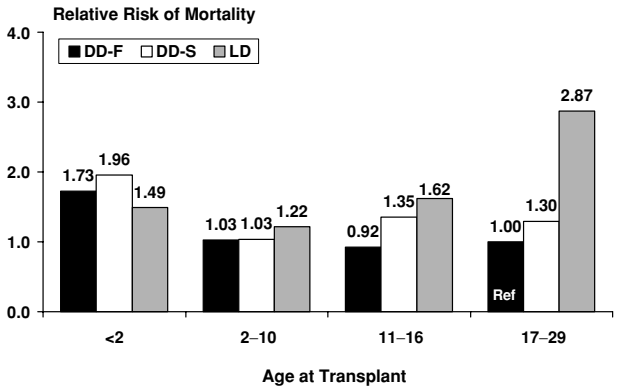

Figure 6: Relative risk of mortality by age group and graft type with patients followed for up to 3 years. Reference group and adjustments as in Figure 1. There were no statistically significant differences in outcomes between graft types within age groups.

failure outcomes of the different graft types did not differ significantly from the relative outcomes observed for the remaining centers for split livers, for living livers, or overall ($p > 0.35$ for all).

Discussion

There is an ongoing concern about the risk of mortality of pediatric patients while awaiting liver transplantation. The parents of children and the physicians caring for younger patients are frequently challenged by the competing risks of waiting list mortality, mortality after transplantation, and the risk to a living donor from operation. The results of this study should help to elucidate a strategy for this population.

For the youngest age group, the data suggest that split liver transplantation from deceased donors should be viewed as the least attractive option. These grafts have a higher risk of graft loss than the two other types of grafts and are associated with an increased risk of post-transplant death. Transplantation with the other two graft types offers better outcomes.

These findings extend those previously reported from single centers. Three authors have examined outcomes for living vs. cadaveric transplantation in the pediatric population (5–7). In each of these studies, living donor transplantation was shown to have superior results to cadaveric transplantation, though in each study the difference did not reach statistical significance. In our analysis, we did not find there to be a group of experienced centers that appeared to have a different relative outcome in terms of graft types. While there may be individual centers that have significantly different results, this does not appear to be common. If there are centers whose survivals differ from those in this analysis, communication with the patients' families of the relative outcomes of the different graft types would be important.

There are potential limitations to this registry analysis in that there maybe variables that influence graft choice and outcome that are not included in these models. These variables could include issues related to the ability to undergo live donor transplantation that may also decrease survival after DD transplantation.

Living donor transplantation provides superior graft survival over DD-F grafts for patients younger than 2 years old. As the current organ allocation system uses the Pediatric End-stage Liver Disease (11) scoring system to prioritize children for deceased donor transplantation, DD-F grafts are more likely to be offered earlier to sicker children, and the additional benefit of early transplantation before marked clinical deterioration may not be available. Living donor and to some extent split transplantation may provide access to early transplantation. Given the relative scarcity of suitably sized DD-F grafts for children and the better outcomes associated with LD grafts, parents should be informed of the results of LD grafts to allow a decision regarding the risk-to-benefit ratio of living donation compared with transplantation using organs from deceased donors.

For older children, LD transplantation does not seem to offer any benefit, as it is accompanied by a higher risk of graft loss and a trend toward higher mortality. The reason for this finding is not clear, though it may represent the use of left lateral segment grafts in larger children where the graft may be too small and the retransplant rate is higher (12,13). In this older pediatric population, there appears to be roughly equivalent graft survival for DD-S and DD-F grafts. In the young adult population, transplants using DD-S appear to do poorly.

The results observed with follow up beyond the first year after transplantation were less significant, although in the same direction as the findings for the first year. These additional analyses suggest that the choice of donor organ has a great effect during the first year and that the subsequent course is affected more by factors other than the type of organ (DD-S, DD-F, or LD).

In summary, LD grafts in the 0–2-year age group appear to offer the lowest risk of post-transplant graft failure and mortality, particularly during the first year. Combined with the expected advantages associated with earlier transplantation in children and the risk of death associated with waiting for transplantation, living donor transplantation should be explored with the families of transplant candidates who are younger than 2 years old.

Acknowledgments

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