Deceased-Donor Split-Liver Transplantation in Adult Recipients: Is the Learning Curve Over?

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BACKGROUND: Infants have the highest wait-list mortality of all liver transplantation candidates. Deceased-donor split-liver transplantation, a technique that provides both an adult and pediatric graft, might be the best way to decrease this disproportionate mortality. Yet concern for an increased risk to adult split recipients has discouraged its widespread adoption. We aimed to determine the current risk of graft failure in adult recipients after split-liver transplantation.

STUDY DESIGN: United Network for Organ Sharing data from 62,190 first-time adult recipients of deceased-donor liver transplants (1995−2010) were analyzed (889 split grafts). Bivariate risk factors ($p < 0.2$) were included in Cox proportional hazards models of the effect of transplant type on graft failure.

RESULTS: Split-liver recipients had an overall hazard ratio of graft failure of 1.26 ($p < 0.001$) compared with whole-liver recipients. The split-liver hazard ratio was 1.45 ($p < 0.001$) in the pre−Model for End-Stage Liver Disease era (1995−2002) and 1.10 ($p = 0.28$) in the Model for End-Stage Liver Disease era (2002−2010). Interaction analyses suggested an increased risk of split-graft failure in status 1 recipients and those given an exception for hepatocellular carcinoma. Excluding higher-risk recipients, split and whole grafts had similar outcomes (hazard ratio = 0.94; $p = 0.59$).

CONCLUSIONS: The risk of graft failure is now similar between split and whole-liver recipients in the vast majority of cases, which demonstrates that the expansion of split-liver allocation might be possible without increasing the overall risk of long-term graft failure in adult recipients. Additional prospective analysis should examine if selection bias might account for the possible increase in risk for recipients with hepatocellular carcinoma or designated status 1. (J Am Coll Surg 2013;217:672−684. © 2013 by the American College of Surgeons)

Infants awaiting liver transplantation have the highest mortality rate of all liver transplantation candidates[1-3] and might be at the greatest risk for long-term morbidities.[4-6] Facing a severe shortage of size-matched pediatric whole organs, living-donor (LD) and deceased-donor (DD) partial liver grafts have been used increasingly as a means to expand the pediatric donor pool.[2,5] Split-liver transplantation, in which a single DD liver is shared between 2 recipients, has been demonstrated to be a safe alternative for small children when a whole or LD liver is unavailable.[2,7-10] An increase in the splitting of adult donor organs would potentially shorten pediatric wait-list times and could decrease the disproportionately high wait-list morbidity and mortality in this age group.[11]

Despite an increase in the number of DD adult livers that were split in the past decade, the current liver allocation system is not designed to optimize the use of this valuable resource; <10% of donors that met criteria between 1996 and 2006, including age 40 years or younger and a body mass index ≤28, were actually made available for splitting.[8] Efforts to change liver-allocation policy to increase the number of split-liver transplants have been hampered by past analyses showing an increased risk for split-graft failure in adult recipients.

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Abbreviations and Acronyms
DD = deceased donor
HCC = hepatocellular carcinoma
LD = living donor
MELD = Model for End-Stage Liver Disease
UNOS = United Network for Organ Sharing

Studies have estimated that the adjusted risk of graft failure in adult split-liver recipients might be up to 1.51 to 2.55 times that experienced by whole-liver recipients.[7,12,13] In addition, it has been suggested that some high-risk individuals, such as those with a higher Model for End-Stage Liver Disease (MELD) score or a status 1A designation, might be at disproportionately increased risk when accepting split grafts.[8,14] Other studies have suggested that the diagnosis of hepatocellular carcinoma (HCC) can be also associated with poorer outcomes when accepting LD partial grafts,[15-17] an association that has never been investigated in DD split grafts. Although more recent studies have shown improved outcomes in split-liver transplantation,[8,10,13,14,18,19] there has been no significant increase in its use during the past decade.[1,20]

The aims of this study were to estimate the current risk of graft failure in adult recipients of split-liver grafts relative to whole-liver grafts, to identify the effects of other known risk factors on the risk of split-liver graft failure; and to explore if recipient selection can be optimized to mitigate any possible adverse effects on adult recipients of split grafts.

METHODS

Data

All DD liver transplants reported in the United Network for Organ Sharing (UNOS) Standard Transplant Analysis and Research Files were considered for analysis. Institutional Review Board approval was obtained from Boston Children's Hospital.

All DD transplants in adults (18 years or older) from 1995−2010 were analyzed. We excluded recipients of LD transplants, multi-organ transplants, re-transplants, and transplants using organs procured after circulatory death of the donor. The follow-up period extended from January 1, 1995 to August 31, 2011. Overall median follow-up time was 1,289 days (95% CI, 374−2,546), and did not differ by graft type. Adult candidates with fulminant hepatic failure judged to have a life expectancy <7 days were designated status 1A, the highest priority on the liver transplantation wait list.[21] Non-status 1A candidates were listed on the wait list according to the MELD score in descending order. The MELD score (introduced March 1, 2002), based on common laboratory values (ie, bilirubin, creatinine, international normalized ratio), predicts the probability of pretransplantation death, with higher scores signifying higher risk.[21] The MELD era includes all transplantations performed after February 28, 2002. The "HCC exception," introduced in 2002, provides additional status points for candidates suspected to have HCC based on clinical and radiologic findings.[21,22] Laboratory MELD score was calculated purely by laboratory values and was not point adjusted for exceptions.

All variables considered to be possible risk factors for graft failure in previous analyses were considered for investigation.[8,12,23] Split livers were first subdivided by split type and side, including in situ (split in vivo, before cross clamp of the aorta) and ex vivo (split on bench) and right and left-sided grafts. As all split grafts had comparable outcomes on bivariate analysis, type and side of split graft were not specified in the adjusted models. Missing values of included variables were categorized as "missing." All variables included in the analysis had <20% missing data. The primary outcomes variable of interest was time to graft loss as defined by retransplantation or death determined by the Social Security Master Death File, which was available for all recipients in the study. Patients were followed until they were lost to follow-up, the date of graft loss, or the end of the study follow-up period. As the stated reason for graft failure was often left incomplete, these data were not included in the analysis, in accordance with previous studies.[8,12]

Analysis

Recipient and donor demographic and clinical characteristics were compared between the whole and split-liver groups using chi-square tests for categorical variables. Normally distributed data were compared with Student's *t*-tests, and skewed continuous variables (eg, MELD score, wait list, and cold ischemia time) were compared with Wilcoxon rank-sum tests.

Kaplan-Meier survival curves and log-rank tests were used to examine the unadjusted association of each variable with graft failure. Due to the differential in median donor age by transplant type, we used donor-age−restricted subsets (40 years and younger) to reveal the unadjusted effects of previously suggested risk factors of split-graft outcomes. The proportion of functioning grafts at 3 months, 1 year, and 3 years was estimated from the survival curve analysis and compared using Fisher's exact test, as in previous studies of the UNOS database.[12]

Factors suggestive of an association with graft failure on bivariate analysis ($p < 0.2$) were included in the multivariate analysis. A Cox proportional hazards model was used