ORIGINAL ARTICLE

Outcomes of domino liver transplantation compared to deceased donor liver transplantation: a propensity-matching approach

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SUMMARY

Domino liver transplantation (DLT) utilizes the explanted liver of one liver transplant recipient as a donor graft in another patient. While there may be unique risks associated with DLT, it is unclear if DLT has less favorable long-term outcomes than deceased donor liver transplantation (DDLT). We used a propensity score matching approach to compare the outcomes of DLT recipients to DDLT recipients. The United Network for Organ Sharing (UNOS) registry was queried for patients undergoing DLT or DDLT in 2002–2016. Each DLT recipient was matched to a unique DDLT recipient to compare mortality and graft failure. There were 126 DLT and 62 835 DDLT recipients meeting inclusion criteria. After propensity score matching on recipient pre-transplant characteristics, 123 DLT cases were matched to DDLT controls from the same UNOS region. On stratified Cox proportional hazards regression, DLT incurred no increase in the hazard of mortality [hazard ratio (HR) = 1.4; 95% confidence interval (CI): 0.8, 2.7; $P = 0.265$] or graft failure (HR = 1.2; 95% CI: 0.7, 2.1; $P = 0.556$) compared to DDLT. Using a large national registry, a propensity-matched analysis found no increased risk of mortality or graft failure associated with DLT compared to DDLT.

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Key words
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Introduction

Domino liver transplantation (DLT) is performed using the explanted liver of a liver transplant (LT) recipient as the donor graft in another patient [1–3]. This procedure is feasible when LT is performed in the initial recipient due to a hereditary metabolic disease (e.g., familial amyloid polyneuropathy; FAP) that does not compromise the structure and function of the explanted liver [1]. For the second recipient involved in DLT, transplantation of a whole liver from a living donor offers a substitute for deceased donor liver transplantation (DDLT), but with some risks that are unique to DLT. Most importantly, the genetic disorder present in the DLT

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donor may secondarily impact the DLT explant recipient, leading to mortality or the need for re-transplantation [3]. According to the Domino Liver Transplant Registry (DLTR), the most common indication for DLT is primary hepatic malignancy and the most common cause of death following DLT is tumor recurrence [4]. In a large retrospective study of patients undergoing LT for hepatocellular carcinoma (HCC), the incidence of major complications was higher among patients receiving DLT explants than among patients receiving DDLT, although patient survival was similar between the two groups [5]. Another single-center analysis and several case reports have reported successful outcomes of patients receiving a DLT explant for a wide range of patient demographics and indications for LT [6–10].

While the safety of DLT has been established for the initial LT recipient (who receives DDLT and donates their explanted liver), outcomes for recipients of DLT explants are unclear for several reasons [1–3]. First, DLT is a rare procedure, limiting the feasibility of comparing outcomes to DDLT in single-center report [8]. Second, an existing international DLT registry does not facilitate comparisons between DLT explant recipients and potential DLT explant candidates who received DDLT instead [11]. Finally, DLT explant recipients are a nonrepresentative subgroup of candidates for LT, as patients tend to be considered for DLT when they are poor candidates for DDLT or have a low priority for DDLT [3]. These limitations may bias comparisons of DLT recipients to broadly defined cohorts of patients receiving DDLT. To determine whether patient and graft survival are equivalent between DLT and DDLT recipients, propensity score matching analysis was performed using a national registry.

Materials and methods

The study was deemed exempt from review by the Institutional Review Board at Nationwide Children's Hospital due to de-identified patient data from a publicly available registry. The United Network for Organ Sharing (UNOS) registry was queried for first-time isolated LT performed since February 2002, when the model for end-stage liver disease (MELD) score was introduced for donor liver allocation, until December 2016 [12]. DLT explant recipients were identified if the living donor type was coded as "domino" in a forced-choice field, or if DLT was noted in a free-text field. In the comparison group of DDLT recipients, we excluded LT involving split grafts and donation after cardiac death (DCD), to eliminate the possibility of confounding due to these factors. In both the DLT and DDLT groups, the following were excluded: patients who were too young to be assigned a MELD score (age <12 years at LT); patients listed as Status 1 (urgent priority for LT); and patients with missing data on recipient characteristics, described below.

The primary outcome in the study was a composite of mortality and graft failure, while these endpoints were examined separately in secondary analyses. Survival with a functioning graft was described using Kaplan–Meier curves, with a log-rank test comparing DLT to DDLT recipients. For descriptive analysis of recipient and donor characteristics, continuous variables were summarized as means with standard deviations and compared using unpaired *t*-tests, while categorical variables were summarized as counts with percentages and compared using chi-square tests. Recipient characteristics included age, gender, race, body mass index (BMI), indication for LT, time on the LT wait list, final laboratory MELD score, medical condition at the time of LT (hospitalized versus outpatient), history of diabetes, and year of transplant. Donor characteristics in both DLT and DDLT groups included age, gender, race, BMI, and graft ischemia time.

The primary analysis used propensity score matching to identify similar DDLT recipients for each DLT recipient in the study sample. The propensity model was a logistic regression of transplant type (DLT versus DDLT), including all recipient characteristics as independent variables, and the propensity score was the linear prediction from this model [13]. To improve covariate balance between DLT and DDLT recipients in the matched sample, the propensity model included interactions between each categorical variable and the continuous variables of patient age, MELD score, days on the waitlist, and year of transplant [14]. This model did not account for donor characteristics because donors involved in DLT and DDLT were inherently different from one another, and donor characteristics did not causally influence the decision to consider the recipient for DLT as opposed to DDLT.

To obtain the most similar unique DDLT control for each DLT case, we used one-to-one nearest neighbor matching without replacement. A caliper equal to 0.2 standard deviations of the propensity score was used to ensure similarity between DLT cases and matched DDLT controls [15]. Furthermore, as centers' use of DLT may be dependent on regional availability of deceased donor organs, each DLT case was specifically matched to the most similar DDLT control in the same UNOS region. DLT cases that could not be matched to

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Table 1. Characteristics of domino liver transplants and deceased donor liver transplants in the United Network for Organ Sharing registry (N = 62 961).

	Domino liver transplant (N = 126) N (%) or mean (SD)	Deceased donor liver transplant (N = 62 835) N (%) or mean (SD)	P value
Male recipient	81 (64%)	43 348 (69%)	0.254
Recipient age (years)	57 (14)	54 (10)	0.011
Recipient race			
White	103 (82%)	45 519 (72%)	0.065
African American	7 (6%)	5557 (9%)	
Other	16 (13%)	11 759 (19%)	
Recipient BMI (kg/m^2)	27 (5)	28 (6)	0.001
Laboratory MELD score	15 (5)	21 (10)	<0.001
Etiology of liver disease			
Viral	25 (20%)	16 245 (26%)	0.001
Cryptogenic	12 (10%)	3481 (6%)	
Autoimmune	23 (18%)	6379 (10%)	
NASH	8 (6%)	4303 (7%)	
Alcoholic	18 (14%)	11 357 (18%)	
HCC	18 (14%)	14 348 (23%)	
Other	22 (17%)	6722 (11%)	
Recipient history of diabetes	32 (25%)	15 275 (24%)	0.776
Recipient hospitalized prior to transplant	7 (6%)	16 961 (27%)	<0.001
Year of transplant	2009 (4)	2009 (4)	0.731
Days on wait list	584 (830)	272 (490)	<0.001
Male donor	86 (68%)	37 105 (59%)	0.036
Donor age (years)*	46 (17)	43 (17)	0.029
Donor race			
White	89 (71%)	41 664 (66%)	0.113
African American	13 (10%)	10 827 (17%)	
Other	24 (19%)	10 344 (16%)	
Donor BMI (kg/m^2)†	26 (5)	27 (6)	0.001
Allograft cold ischemia time (h)‡	4.5 (3.9)	6.9 (3.1)	<0.001

BMI, body mass index; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; NASH, nonalcoholic steatohepatitis; SD, standard deviation.

*Data missing in three cases.

†Data missing in 87 cases.

‡Data missing in 2622 cases.

any sufficiently similar DDLT controls in the same region, and DDLT controls not matched to a DLT case, were excluded from further analysis. The balance of recipient characteristics between DLT and DDLT recipients in the matched sample was checked using standardized differences, where a standardized difference <0.1 was considered to indicate adequate balance [16]. The outcomes were evaluated in the matched sample using Cox proportional hazards regression, with the baseline hazard stratified on the matched DLT-DDLT pairs [13]. Data analysis was performed in STATA/IC 13.1 (College Station, TX, USA: StataCorp LP), and $P < 0.05$ was considered statistically significant.

Results

We evaluated 76 667 isolated first-time LT performed during the study period for inclusion in the analysis. Cases were excluded if they involved split grafts (n = 2014), DCD (n = 3689), recipients age <12 years (n = 3999), or Status 1 candidates (n = 2807). A further 1038 cases were excluded for missing data on recipient characteristics, leaving a final sample of 126 DLT and 62 835 DDLT recipients. Recipient and donor characteristics are compared between the DLT and DDLT groups in Table 1. DLT recipients tended to have lower MELD scores (15 ± 5 vs. 21 ± 10 in the DDLT group)

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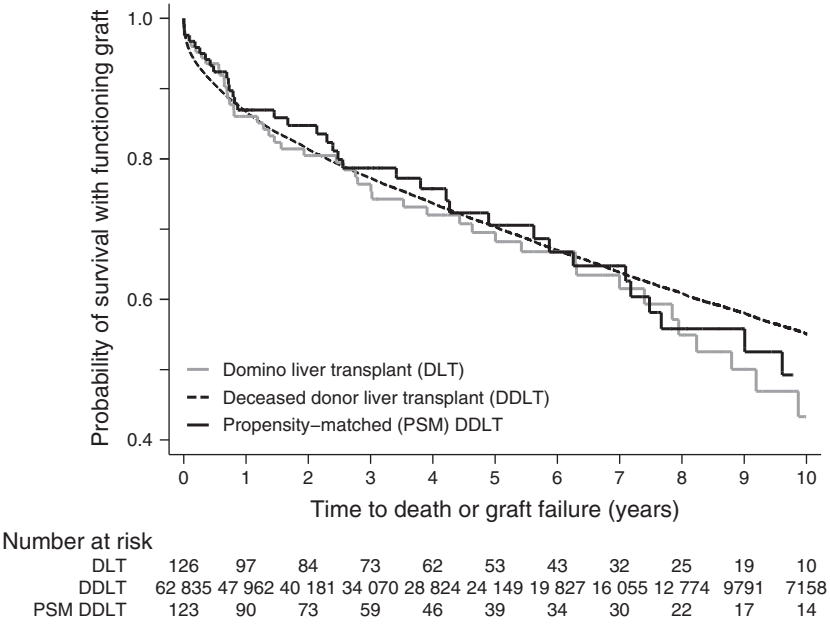

Figure 1 Kaplan–Meier curve of survival with a functioning graft after domino liver transplantation and deceased donor liver transplantation.

and longer wait times (584 ± 830 vs. 272 ± 490 days), indicating lower priority for transplantation compared to the DDLT cohort. In the DLT group, 37% patients died or experienced graft failure during follow-up, compared to 32% in the DDLT group. However, a log-rank test comparing this outcome in univariate survival analysis found no statistically significant difference between the DLT and DDLT groups (Fig. 1; $P = 0.273$).

After propensity score matching, 123 DLT cases were identified that could be matched to sufficiently similar DDLT controls from the same UNOS region. The comparison of recipient characteristics between DLT cases and one-to-one-matched DDLT controls is illustrated in Table 2. Covariates were generally well balanced between the cases and controls, as compared to the large and statistically significant differences in DLT and DDLT recipient characteristics seen before propensity score matching. In pair-stratified Cox proportional hazards regression on the matched sample, there was no difference in the hazard of the composite study outcome when receiving DLT as compared to DDLT [hazard ratio (HR) = 1.1; 95% CI: 0.6, 1.9; $P = 0.773$). Likewise, DLT incurred no increase in the hazard of mortality (HR = 1.4; 95% CI: 0.8, 2.7; $P = 0.265$) or graft failure (HR = 1.2; 95% CI: 0.7, 2.1; $P = 0.556$), compared to DDLT, when these outcomes were examined separately.

Discussion

The population of patients in need of LT continues to increase, but access to this procedure is constrained by a limited supply of donor organs [1]. The shortage of available donor organs has given rise to innovations in expanding the donor pool, such as the use of DLT explants. When a patient receives a LT due to a hereditary metabolic disease that leaves the structure and function of the explanted liver intact, there is potential for that recipient to become a donor via DLT. While DLT is relatively uncommon, it offers the possibility of a second recipient receiving a whole liver from a living donor as a substitute for a DDLT. Several unique risks exist for DLT, but a growing body of literature, including case reports, illustrates successful DLT. Upon successfully receiving LT's, the livers of patients with various genetic and metabolic disorders including maple syrup urine disease (MSUD) and protein C (PC) deficiency have been safely used as domino grafts in non-MSUD and non-PC deficient recipients, respectively [8,9,17]. Such a procedure is feasible as the enzyme, although deficient in the liver to be transplanted, is not deficient in other organs and tissues of the recipient and hence the transplanted liver, although enzyme deficient, functions adequately in other regards. Furthermore, in these patients, the other tissues and organs provide the deficient enzyme.

Domino liver transplantation is a more commonly utilized option in patients who receive a DDLT for FAP. Upon receiving a liver transplant, FAP patients become DLT donors, and institutions have reported success in both the FAP patients and the explanted liver recipients [7]. This anecdotal work has demonstrated that patients with hereditary metabolic diseases that receive LT's can

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Table 2. Characteristics of domino liver transplant and propensity-matched deceased donor liver transplant recipients in the United Network for Organ Sharing registry ($N = 246$).

	Domino liver transplant ($N = 123$)* N (%) or mean (SD)	Deceased donor liver transplant ($N = 123$) N (%) or mean (SD)	Standardized difference†
Male recipient	80 (65%)	80 (65%)	0.00
Recipient age (years)	57 (14)	56 (14)	0.02
Recipient race			
White	101 (82%)	100 (81%)	0.02
African American	7 (6%)	9 (7%)	0.07
Other	15 (12%)	14 (11%)	0.03
Recipient BMI (kg/m^2)	27 (5)	27 (5)	0.01
Laboratory MELD score	15 (5)	15 (7)	0.05
Etiology of liver disease			
Viral	25 (20%)	36 (29%)	0.21
Cryptogenic	12 (10%)	8 (7%)	0.12
Autoimmune	21 (17%)	12 (10%)	0.22
NASH	8 (7%)	9 (7%)	0.03
Alcoholic	17 (14%)	16 (13%)	0.02
HCC	18 (15%)	19 (15%)	0.02
Other	22 (18%)	23 (19%)	0.02
Recipient history of diabetes	30 (24%)	31 (25%)	0.02
Recipient hospitalized prior to transplant	7 (6%)	5 (4%)	0.08
Year of transplant	2009 (4)	2010 (4)	0.12
Days on wait list	529 (732)	518 (767)	0.01

BMI, body mass index; HCC, hepatocellular carcinoma; MELD, model for end-stage liver disease; NASH, nonalcoholic steatohepatitis; SD, standard deviation; UNOS, United Network for Organ Sharing.

*Three domino liver transplant cases did not have suitable deceased donor liver transplant controls in the same UNOS region.

†Standardized difference <0.1 indicates good covariate balance.

be DLT donors, providing a viable alternative to DDLT. The current study, using a propensity-matching approach in a large registry data set, demonstrates that outcomes of patients receiving a DLT explant are comparable to outcomes of DDLT, providing further evidence for the safety of the former technique.

Unique risks exist regarding the use of a DLT explant. As a group, DLT recipients are typically older, have more comorbid conditions, and may have more advanced malignant disease, sometimes not even qualifying as candidates for the conventional DDLT [1]. However, single-center reviews of DLT outcomes have been inconclusive due to small sample sizes. In the DLTR, 1-, 5-, and 8-year graft survival after receiving a DLT explant has been estimated as 79.9%, 65.3%, and 61.6%, respectively [18]. The DLTR data supports DLT as a valuable liver donor resource to certain patients, but unique risks of DLT allografts must be evaluated as they pertain to clinical outcomes of DLT explant recipients [4]. While the risks of DLT are unique, our data suggest that they do not contribute to an elevated hazard of graft failure or mortality, as compared to receiving organs from deceased donors.

Before propensity matching, DLT recipients were distinguished by lower average MELD scores compared to DDLT recipients (15 vs. 21), signifying less severe disease, in contrast to a previous report [1]. DLT recipients also had a higher average number of days on the wait list (584 days) compared to DDLT recipients (272 days). Furthermore, only 6% of DLT recipients were hospitalized prior to transplant compared to 26% of DDLT. These differences may confound comparisons of outcomes to DDLT recipients; however, after propensity matching was performed to balance these characteristics between DLT and DDLT recipients, DLT did not increase the hazard of mortality or likelihood of graft failure when compared to DDLT. One possible explanation for this finding is that in the propensity-matched DDLT cohort, long-term outcomes may have been compromised by the use of low-quality donors secondary to candidates' low priority on the DDLT waiting list. Nevertheless, our results indicate that, although rare, DLT is a feasible and

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evidently safe option for extending donor organ access for patients with low priority and long time on the DDLT wait list.

Several limitations apply to the conclusions of this analysis. First, we performed a retrospective analysis of data collected across multiple centers, with potential inconsistency or error in data entry. Second, we matched DLT and DDLT patients on recipient characteristics, but not on donor characteristics due to inherent differences between donors in each case. Nevertheless, this approach achieved good balance of recipient characteristics in the propensity-matched DLT and DDLT groups. We have also elected to compare DLT recipients to DDLT recipients, but not to living donor transplant recipients, although living donation may have been a more feasible alternative to DLT for some candidates with very low priority on the DDLT waiting list. Lastly, there were limited data on morbidity and specific causes of death in DLT recipients. For example, DLT explant recipients may be at risk due to the metabolic disease present in the DLT explant donor [3]. If the systematic enzyme disorder persists, it can lead to mortality or the need for re-transplantation, so both the DLT donor and recipient must undergo screening to avoid these consequences. Although the outcomes in this study included mortality and graft failure, less severe morbidity associated with transmission of metabolic disease may not have been captured by this approach. Most importantly, complications unique to DLT such as conferring the metabolic disease to the recipient may emerge late in the post-transplant course (e.g., 7–9 years post-transplant, as reported by Barreiros *et al.* [19]) and should be closely monitored during patient follow-up.

In summary, DLT has emerged as an effective option for specific types of hereditary metabolic disease that do not compromise the structure and function of the explanted liver. Our propensity-matched analysis of the UNOS registry demonstrates similar outcomes of patient and graft survival when comparing receipt of a DLT explant with the more common DDLT procedures. While there are unique risks for the second recipient involved in DLT, these risks do not appear to exceed the risks associated with DDLT, at least in the short- and medium-term after transplantation. In the long-term, complications associated with *de novo* metabolic disease in DLT recipients have been reported. Nevertheless, given the high demand for LT and shortage of available deceased donor organs, DLT appears to be a safe and reasonable option to consider for suitable patients who have low priority for DDLT according to the allocation system based on the MELD score.

Authorship

EDG: performed interpretation of results, drafting of manuscript. CB: performed interpretation of results, and critical revision of manuscript. DT: involved in study design, data analysis, interpretation of results, and drafting of manuscript. DH: involved in study design, data acquisition, interpretation of results, and critical revision of manuscript. SMB: performed interpretation of results and critical revision of manuscript. KW: performed interpretation of results and critical revision of manuscript. JDT: involved in study design, interpretation of results, and critical revision of manuscript.

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Conflicts of interest

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