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Outcomes in living donor compared to deceased donor primary liver transplant in lower acuity patients with MELD score < 30

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Footnote Page

List of Abbreviations:

Adult-to-Adult Living Donor Liver Transplantation Cohort Study, A2ALL; CI, confidence interval; DBD, donors after brain death; DCD, donation after circulatory death; DDLT, deceased donor liver transplantation; HCC, hepatocellular carcinoma; HR, hazard ratio; LDLT, living donor liver transplant; LT, liver transplantation; MELD, Model for End-stage Liver Disease; PHT, portal hypertension; SFSS, small-for-size syndrome; STAR, Standard Transplant Analysis and Research; UNOS, United Network for Organ Sharing

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Abstract

While recent studies have reported favorable outcomes in living donor liver transplantation (LDLT), it remains unclear which populations benefit most from LDLT. The aim of this study is to evaluate post-transplant outcomes in LDLT compared to deceased donor liver transplant (DDLT) according to Model for End-Stage Liver Disease (MELD) score categories. Using data from the OPTN/UNOS registry, outcomes were compared between 1,486 LDLT, 13,568 donation after brain death (DBD) DDLT, and 1,171 donation after circulatory death (DCD) DDLT transplanted between 2009 and 2018. Because LDLT for patients with MELD score >30 was rare (1.8% of all LDLT), all patients with scores > 30 were excluded to equalize LDLT and DDLT cohorts. Risk factors for one-year graft loss were determined in LDLT and DDLT, separately. Compared with LDLT, DBD-DDLT had significantly lower risk of 30-day (aHR 0.60, P<0.001) and one-year graft loss (aHR 0.57, P<0.001). The significantly lower risk of graft loss was more prominent in the mid-MELD score category (score 15-29). DCD-DDLT, compared to LDLT, had significantly lower risk of 30-day graft loss, but comparable risk of one-year graft loss regardless of MELD score category. In LDLT, significant ascites was an independent risk factor for graft loss in patients with mid-MELD scores (aHR 1.68, P=0.02), but not in the lower-MELD score group. Risk of one-year graft loss in LDLT patients with ascites who received left liver was significantly higher than either those who received right liver or those without ascites who received left liver.

Conclusion: In LDLT, combinations of MELD score of 15-29, moderate/severe ascites and use of left liver, are associated with worse outcomes. These findings help calibrate appropriate patient and graft selection in LDLT.

Introduction

Living donor liver transplantation (LDLT) in adults emerged in the United States in 1998(1), increased rapidly for three years and then declined after 2001 coinciding with introduction of Model for End-stage Liver Disease (MELD) allocation and a peri-operative donor death. The number of LDLT has increased in recent years (2) but remains a small percentage of total LT (<5%). Although early studies reported inferior outcomes with LDLT compared to deceased donor LT (DDLT) (3, 4), LDLT outcomes have improved over time. The Adult-to-Adult Living Donor Liver Transplantation Cohort Study (A2ALL) and several reports from large single centers have demonstrated excellent post-transplant outcomes associated with increasing numbers and experience and relatively low MELD scores in the LDLT population(5-8). The A2ALL consortium includes nine experienced LDLT centers in the US, and it is unclear whether their excellent results have been reproduced nationwide.

While recent studies have reported comparable outcomes between LDLT and DDLT, it is not clear if this is dependent on careful selection of LDLT patients. Studies comparing outcomes in LDLT vs. DDLT uniformly find LDLT patients are younger, have lower MELD scores and are more likely to be at home (3, 7, 9, 10). While a recent report suggests a successful role for LDLT in patients with higher MELD scores(7), few large studies have looked at LDLT outcomes as a function of MELD scores. It remains unclear which succinct patient and donor characteristics should be considered in determining the role of LDLT in more ill and complex patients. In addition, assessing LDLT outcomes compared to LT using donation after circulatory death (DCD) grafts in each MELD score category may also help to determine appropriate donor selection. We

hypothesized that determining differences in post-transplant outcomes based on liver disease severity at LT could help determine optimal indications for LDLT. In this study, we focused on the patients with MELD score < 30 at the time of LT because of the small percentage of LDLT in those with MELD scores \geq 30. The aim of this study is to compare early post-transplant outcomes between LDLT, DCD-DDLT, and LT from donation after brain death (DBD-DDLT) using the (OPTN/UNOS) registry and to define factors that influence outcomes in recipients with MELD score < 30.

Methods

Patient cohort

This study uses data from the OPTN/UNOS contained in the Standard Transplant Analysis and Research file, which includes data for all patients listed for and who received LT in the United States. Adult patients (\geq 18 years old) who received LT between January 1, 2009 and June 30, 2018 were evaluated. First, patients who received LDLT at centers that performed 15 or less LDLT before the study period were excluded to minimize the learning-curve effect.(10) Using uncensored cohort, post-transplant outcomes were compared between LDLT and DDLT. To compare outcomes in more homogeneous cohorts according to MELD score at the time of transplant, the following patients were excluded; patients with status 1A, re-transplantation, exception scores, and LT combined with other organs (**Figure 1A**). Those who received DCD grafts were included. Because only 1.8% of LDLT patients had a MELD score 30 or higher, patients with MELD scores \geq 30 were excluded (**Figure 1B**). The study period includes patients in

both the MELD and MELD-Na score eras. The “MELD score” is used in this study.

Patients with HCC were analyzed separately. Patients with a primary or secondary diagnosis of HCC who received LDLT, DBD-DDLT, and DCD-DDLT with approved MELD exception scores were compared in this separate analysis.

Comparison of post-transplant outcomes between LDLT, DBD-DDLT, and DCD-DDLT according to MELD score categories: Non-HCC population

In the non-HCC population, LDLT, DBD-DDLT, and DCD-DDLT recipients were categorized into two groups according to laboratory MELD score at LT; lower-MELD score group of 6-14 and mid-MELD score group of 15-29. 30-day and one-year graft survival were compared between the three groups by MELD score category. Hazards of 30-day and one-year graft loss in DBD-DDLT and DCD-DDLT compared to LDLT were assessed based on MELD score category adjusted by recipient and donor variables. Recipient variables included age, race, body mass index, gender, history of diabetes, Karnofsky score, use of life support, use of dialysis, MELD score at LT, serum sodium, and presence of ascites or hepatic encephalopathy. Donor variables included age, gender, and race. Risk factors for one-year graft loss were determined for LDLT and DDLT (including both DBD-DDLT and DCD-DDLT), separately. Risks were adjusted for recipient and donor characteristics and year of LT (2009-2012, 2013-2015 or 2016-2018).

To consider center experience of LDLT, LDLT centers were classified into two groups; more-experienced center group and less-experienced center group. The more-experienced group included six centers that performed more than 100 LDLT during the 10-year study period while

the less-experienced group performed 100 or less. LDLT outcomes in each group were compared with DDLT.

Comparison of post-transplant outcomes according to the presence of moderate/severe ascites and graft type

In the non-HCC population, the prognostic effects of ascites at the time of LT in LDLT and DDLT were assessed separately. In the UNOS registry, the amount of ascites is categorized as ‘absent’, ‘slight’, ‘moderate’, ‘unknown’ and ‘not reported’. We considered “moderate” to mean the presence of significant or moderate/severe ascites. Hazards of one-year graft loss in patients with significant ascites were assessed after the adjustment for recipient and donor variables in each LDLT and DDLT group, separately. In the DDLT group, adjustment variables were same as used in the risk factor analysis. In the LDLT group, variables identified significant in the risk factor analysis were used for risk adjustment in each lower-MELD and mid-MELD category because of the limited number of patients who lost graft within one-year in each subgroup. In addition, one-year graft survival in LDLT was compared according to graft type (right liver [RL] and left liver [LL]) and the presence of moderate ascites. Hazards of one-year graft loss were adjusted for the same donor and recipient variables identified in the risk factor analysis in the LDLT group.

Statistical analysis

Data were summarized using median with interquartile range for continuous variables and percentage for discrete variables. Comparisons of continuous and discrete variables were

performed using the Kruskal-Wallis test and chi-square test. Risk factors for post-transplant mortality and hazard risks were analyzed using Cox proportional hazards models. P <0.05 was considered statistically significant. All statistical analyses were completed by using SPSS version 25 (IBM, Chicago, USA).

Results

Uncensored cohort

A total of 56,370 patients underwent LT during the study period. 244 patients who received LDLT at centers who performed ≤ 15 LDLT before the study period were excluded (**Figure 1A**). First, post-transplant outcomes were compared between LDLT and DDLT in uncensored cohort. In this cohort, the LDLT group (n=1,789) had significantly better 1-year and 5-year patient survival than the DDLT group (n=54,337) whereas 30-day patient survival was similar (LDLT group vs. DDLT group: 30-day 97.6% vs 97.0%, P=0.13; 1-year 92.4% vs 90.5%, P=0.009; 5-year 82.3% vs 76.7%, P<0.001). In contrast, the LDLT group had significantly worse 30-day graft survival but similar 1-year and 5-year graft survival (LDLT group vs. DDLT group: 30-day 94.4% vs 95.8%, P=0.003; 1-year 87.3% vs 88.5%, P=0.107; 5-year 76.6% vs 74.6%, P=0.56).

Non-HCC cohort

Next, the exclusion criteria were applied and post-transplant outcomes in non-HCC cohort were compared between LDLT and DDLT. The following populations were excluded from this analysis; 1,704 with status 1A, 20,760 with DDLT with approved MELD exceptions, 5,214 with

LT combined with other organs, 3,045 with re-transplant and 10,707 patients with MELD score 30 or higher. 15,244 patients who had HCC as their primary or secondary diagnosis or who had HCC exception scores were not included in this analysis. The remaining 1,486 LDLT and 14,739 DDLT patients were evaluated. DDLT patients included both 13,568 DBD-DDLT and 1,171 DCD-DDLT patients (**Figure 1A, B**).

In this cohort, 30-day and 1-year patient survival was similar between 2 groups (LDLT group vs. DDLT group: 30-day 98.0% vs 97.9%, P=0.794; 1-year 92.9% vs 92.7%, P=0.71). In contrast, the LDLT group had significantly worse 30-day and 1-year graft survival (LDLT group vs. DDLT group: 30-day 94.7% vs 96.8%, P<0.001; 1-year 87.6% vs 90.5%, P<0.001). In the LDLT group, of the 174 patients who lost their graft within a year, 80 patients (46.0%) received a second transplant.

Comparison of post-transplant outcomes between LDLT, DBD-DDLT and DCD-DDLT according to MELD score categories

Post-transplant outcomes were compared between 14,739 DBD-DDLT, 1,171 DCD-DDLT, and 1,486 LDLT. Patient characteristics are shown in **Table 1**. The DBD-DDLT group (90.7%) had significantly higher one-year graft survival rate than the DCD-DDLT (88.1%; P=0.006) and LDLT groups (87.6%; P<0.001) whereas the DCD-DDLT and LDLT groups had comparable graft survival (P=0.61). When comparing outcomes according to the MELD score categories, one-year graft survival rates were comparable between three groups in the lower-MELD score group (DBD-DDLT 90.3%, DCD-DDLT 90.9%, LDLT 88.5%, P=0.55) whereas the DBD-DDLT group

(90.7%) had significantly higher one-year graft survival rate than the DCD-DDLT (87.9%; P=0.003) and LDLT groups (86.9%; P<0.001) in the mid-MELD score group (**Figure 2**).

After the adjustment for recipient and donor variables, compared to the LDLT group, the DBD-DDLT group had a significantly lower adjusted risk of 30-day (aHR 0.60, 95% CI 0.46-0.80, P<0.001) and one-year graft loss (aHR 0.57, 95% CI 0.48-0.69, P<0.001). When assessing hazards of graft loss by MELD score category, the significantly lower adjusted risk of graft loss in DBD-DDLT was more prominent in the mid-MELD score group (30-day: aHR 0.52, 95% CI 0.38-0.71; P<0.001, 1-year: aHR 0.54, 95% CI 0.44-0.67; P<0.001). Compared to the LDLT group, the DCD-DDLT group showed a significantly lower adjusted risk of 30-day graft loss overall (aHR 0.60, 95% CI 0.39-0.91; P=0.02) and in the mid-MELD score groups (aHR 0.55, 95% CI 0.35-0.87; P=0.009) whereas the risk of 30-day graft loss in the lower-MELD category was similar (aHR 0.20, 95% CI 0.03-1.54, P=0.12). Adjusted risks of one-year graft loss were comparable between the LDLT and DCD-DDLT groups regardless of MELD score category (overall: aHR 0.89 95% CI 0.70-1.14, P=0.36; lower-MELD: aHR 0.73, 95% CI 0.34-1.56, P=0.42; mid-MELD: aHR 0.88, 95% CI 0.67-1.15, P=0.33) (**Figure 3**). The adjusted hazards of all variables included in this model was shown in **Supplemental Table 1**.

In evaluating cause of graft loss, the incidence of vascular thrombosis (30-day: LDLT 1.3% vs DCD-DDLT 0% vs DBD-DDLT 0.3%, P<0.001; 1-year: LDLT 1.6% vs DCD-DDLT 0.3% vs DBD-DDLT 0.6%, P<0.001) and hepatic artery thrombosis (HAT) (30-day: LDLT 1.0% vs DCD-DDLT 0.2% vs DBD-DDLT 0.3%, P<0.001; 1-year: LDLT 1.3% vs DCD-DDLT 0.5% vs DBD-DDLT 0.5%, P<0.001) was significantly higher in the LDLT group than in the DCD-DDLT

and DBD-DDLT groups. The incidence of biliary complication was significantly higher in the LDLT group than in the DBD-DDLT group (30-day: LDLT 0.3% vs DBD-DDLT 0%, P=0.01; 1-year: LDLT 0.7% vs DBD-DDLT 0.3%, P=0.02) whereas there was no statistical difference between the LDLT and DCD-DDLT groups (30-day: LDLT 0.3% vs DCD-DDLT 0.1%, P=0.39; 1-year: LDLT 0.7% vs DCD-DDLT 0.8%, P=1.00, **Supplemental Table 2**).

LDLT center experience and post-transplant outcomes

LDLT outcomes were assessed in six more-experienced centers and 37 less-experienced centers (**Supplemental Figure 1**). The characteristics in the two groups are shown in **Supplemental Table 3**. LDLT and DDLT outcomes were compared in each group. In the less-experienced group, risks of 30-day graft loss (aHR 1.89, 95% CI 1.35-2.64; P<0.001) and 1-year graft loss (aHR 1.82, 95% CI 1.45-2.27; P<0.001) were significantly higher in LDLT than DDLT. In the more-experienced group, risk of 30-day graft loss was comparable between LDLT and DDLT, but risk of one-year graft loss was significantly higher in LDLT (aHR 1.46, 95% CI 1.14-1.87; P=0.003) (**Supplemental Figure 2**). The higher risk of graft loss in LDLT was more prominent in patients with a higher-MELD score, which was observed in both groups.

Risk factors for one-year graft loss in LDLT and DDLT

In the LDLT group, multivariable Cox regression analysis revealed that significant ascites (aHR 1.52, 95% CI 1.05-2.20; P=0.03 [ref. none or mild]), life-support requirement (aHR 3.80, 95% CI 1.19-12.20; P=0.03), lower Karnofsky score (10-30%; aHR 1.75, 95% CI 1.08-2.85; P=0.02 [ref.

40-100%]), earlier transplant era (2009-2012; aHR 1.57, 95% CI 1.05-2.36; P=0.03 [ref. 2016-2018]), donor age 40-59 (aHR 1.77, 95% CI 1.28-2.45; P=0.001 [ref. age <40]) and the use of left liver graft (aHR 1.91, 95% CI 1.29-2.84; P=0.001 [ref. RL graft]) were independent risk factors for one-year graft loss.

In the DDLT group, recipient age \geq 60 (aHR 1.65, 95% CI 1.28-2.11; P<0.001, [ref. <40]), black race (aHR 1.22, 95% CI 1.01-1.47; P=0.04 [ref. white]), life-support (aHR 1.97, 95% CI 1.52-2.56; P<0.001), lower Karnofsky score (10-30%; aHR 1.46, 95% CI 1.26-1.69; P<0.001), hypernatremia (>145mmol/L, aHR 1.62, 95% CI 1.20-2.20; P=0.002, [ref. normonatremia 135-145mmol/L]), earlier transplant era (2009-2012, aHR 1.24, 95% CI 1.09-1.42; P=0.001, [ref. 2016-2018]), donor age (40-59; aHR 1.24, 95% CI 1.09-1.41; P=0.001, \geq 60; aHR 1.54, 95% CI 1.32-1.80; P<0.001, [ref. <40]), split liver graft (aHR 1.64, 95% CI 1.04-2.58; P=0.03, [ref. whole liver graft]) and DCD donor (aHR 1.58, 95% CI 1.31-1.92; P<0.001, [ref. DBD donor]) were independent risk factors for one-year graft loss. (**Table 2**)

Comparison of hazards of one-year graft loss in recipients with significant ascites according to MELD category and graft type

Significant ascites was an independent risk factor for graft loss only in LDLT (**Table 2**). LDLT patients without significant ascites who received RL showed significantly better graft survival than those who received a RL with ascites and those who received a LL without significant ascites (**Supplemental Figure 3**). 30-day and one-year graft survival was 80.6% and 69.3% in those with significant ascites who received a LL, which was significantly worse than other groups (P<0.001).

The adverse impact of significant ascites was assessed according to MELD category and graft type by adjusting for recipient and donor variables (**Figure 4**). In mid-MELD score groups, LDLT patients with significant ascites had higher adjusted risk of graft loss than LDLT patients without significant ascites (aHR 1.68, 95% CI 1.10-2.55; P=0.02) and DDLT patients with significant ascites (aHR 2.05, 95% CI 1.47-2.86; P<0.001). Ascites did not increase the risk of graft loss in LDLT patients with a lower-MELD score or in DDLT patients with any MELD score (**Figure 4A**).

In LDLT, compared to patients with significant ascites who received LL, adjusted hazards of 1-year graft loss were significantly lower in those without significant ascites who received RL (aHR 0.26, 95% CI 0.13-0.49, P<0.001), those without significant ascites who received LL (aHR 0.37, 95% CI 0.18-0.75, P=0.006), and those with significant ascites who received RL (aHR 0.36, 95% CI 0.18-0.72, P=0.004) (**Figure 4B**).

HCC cohort: Post-transplant outcomes in patients with HCC

239 LDLT, 13,873 DBD-DDLT, and 1,132 DCD-DDLT patients with HCC were evaluated separately. Of the 239 LDLT patients, 158 (66.1%) received an HCC MELD exception score. All DDLT patients included had HCC MELD exception scores. Days on waitlist was significantly shorter in the LDLT group than the DCD-DDLT or DBD-DDLT group (134 days vs. 193 days vs. 210 days; P<0.001), (**Supplemental Table 4**). One-year graft survival was compared between LDLT, DBD-DDLT, and DCD-DDLT groups. The DBD-DDLT group (91.0%) had significantly better graft survival than the DCD-DDLT group (87.5%; P<0.001) whereas the DCD-DDLT and

LDLT groups had comparable graft survival ($P=0.95$). Adjusted hazards of graft loss were significantly lower in the DBD-DDLT group than the LDLT group (30-day: aHR 0.39, 95% CI 0.23-0.64; $P<0.001$, 1-year: aHR 0.64, 95% CI 0.44-0.94; $P=0.02$) whereas the DCD-DDLT group had comparable risks to the LDLT group (**Supplemental Figure 4**). The incidence of graft loss due to vascular thrombosis and HAT was significantly higher in the LDLT group than the DBD-DDLT and DCD-DDLT group. The incidence of biliary complication within one-year was significantly higher in the DCD-DDLT group than in the DBD-DDLT group (DCD-DDLT 0.8% vs DBD-DDLT 0.2%, $P=0.001$) whereas there was no statistical difference between the LDLT group and DCD-DDLT group (LDLT 0% vs DCD-DDLT 0.8%, $P=0.37$, **Supplemental Table 5**).

Discussion

This study demonstrated that patients receiving primary LDLT had significantly higher risk of 30-day and one-year graft loss, compared to those receiving primary DBD-DDLT. The higher risk of graft loss in the LDLT group was more prominent in patients with a mid-MELD score (score of 15-29). Furthermore, the presence of significant ascites was associated with worse outcomes in the LDLT group but not in the DDLT group. Importantly, the negative effect of ascites in LDLT was not seen in the lower-MELD score group and was more prominent in patients who received LL graft than those who received RL graft. These results suggest that patient and graft selection in LDLT are important to secure optimal outcomes. It should be emphasized that this study excluded patients with MELD scores ≥ 30 at LT, because only 1.8% of LDLT patients had a MELD score ≥ 30 (**Figure 1**). It would be meaningful to evaluate post-transplant outcomes between the LDLT

and DDLT groups after excluding this population. Of note, in the LDLT group, 80 out of 174 patients who lost their liver grafts within a year received a second transplant, which might contribute to comparable patient survival between the LDLT and DDLT groups.

In LDLT, an association between increasing portal hypertension (PHT) and worse post-transplant outcomes is recognized (11, 12). The inferior outcomes in LDLT patients with significant ascites are confined to those with mid-MELD scores and in those receiving LL grafts. The findings are consistent with less tolerance of PHT in these LDLT recipients. These results emphasize the importance of careful recipient and donor selection to secure successful LDLT outcomes. LL grafts would be used with caution in patients with ascites and especially in those with mid-MELD scores (7). In patients with ascites and mid to higher-MELD scores receiving LL grafts, attention would be paid to an optimal graft to donor weight ratios, appropriate portal vein inflow modulation and hepatic vein reconstruction. The UNOS registry does not include data on graft size or weight, small-for-size graft syndrome (SFSS) or techniques to optimize vascular flow. However, when determining the role of LDLT, MELD score, presence of significant ascites and liver graft size would all be critical considerations that would allow for the anticipation and execution of techniques to optimize portal flow and hepatic vein reconstruction in patients with marked PHT (11).

In this study, 30-day graft loss associated with vascular thrombosis and HAT was significantly higher in LDLT than DCD-DDLT or DBD-DDLT. LDLT had significantly higher incidence of graft loss due to biliary complications than DBD-DDLT and similar incidence to DCD-DDLT. The A2ALL consortium reported a significantly higher incidence of HAT (6% vs.

4%) and bile leak (31.8% vs. 10.2%) in LDLT patients (9, 13). Vascular and biliary reconstructions in LDLT are technically more demanding than in DDLT (14). Although we acknowledge that the UNOS registry may not capture biliary and vascular complications accurately since the incidence of these complications was lower than that in previous A2ALL studies (13), inferior graft survival in the early period after LDLT might be partially attributable to technical difficulties. Graft loss associated with biliary complications was higher in DCD-DDLT than in DBD-DDLT, which was consistent with previous studies (15). The higher incidence in DCD-DDLT might be due to ischemic cholangiopathy, but detailed information about biliary complications is not available in the UNOS registry. Of note, in the analysis of HCC patients, the higher incidence of vascular complications leading to 30-day graft loss was also seen in LDLT.

This was the case even though, in the HCC population, LDLT and DDLT patients are more closely aligned by laboratory MELD score and rate of ascites. Continued refinement of surgical strategies and techniques in LDLT will be crucial to expanding LDLT to more ill and complex patients.(10) The inferior outcomes in LDLT were observed regardless of center experience, especially in the mid-MELD score group. LDLT requires medical and surgical expertise and center experience is important to secure successful outcomes. However, it should be noted that recipient and donor selection remain critical even at experienced centers.

The risk of graft loss in LDLT and DCD-DDLT in lower-MELD score patients (MELD score 6-14) was comparable. This result appears contradictory to a previous study which used the UNOS/OPTN registry to evaluate LT recipients between 2003 and 2016 (16). That study demonstrated that 10-year graft survival was significantly better in LDLT than in DCD-DDLT

recipients with low-MELD score (≤ 20) ($P<0.0001$). Although one-year survival was not specifically reported, LDLT had better one-year graft survival based on a Kaplan-Meier curve shown in their study. This discrepancy could be explained by the recent improvements in post-transplant outcomes in DCD-DDLT (17). Recent changes in the LT allocation in the United States may enhance broad sharing of donated liver grafts for patients with a higher MELD scores and some LT candidates with lower to mid MELD scores may not easily secure a DBD graft. Because post-transplant outcomes in LDLT and DCD-DDLT are comparable, either of these donor types would be an acceptable option for patients with relatively lower MELD scores, especially in those suffering from severe and uncaptured morbidity from their liver disease.

Similarly, compared to LDLT and DCD-DDLT, DBD-DDLT also shows the best early post-transplant outcome in HCC patients, and LDLT and DCD-DDLT had comparable outcomes. Previously, HCC patients who received a MELD exception would have scores ranging from 28 to 34. However, with recent revisions in liver exception (18) and allocation policies (19), the HCC exception score is fixed at the regional median MELD at transplant score minus 3. Here as well, LT candidates with HCC exception may not easily secure a DBD graft.

When considering indications of LDLT, both post-transplant and waitlist outcomes need to be taken into account. This study did not assess waitlist outcomes or intention-to-treat survival between LDLT and DDLT, because of lack of data regarding availability of living donor candidates or initiation of living donor evaluation in the OPTN/UNOS registry. However, we should acknowledge possible benefits of LDLT over DDLT. Berg et al. demonstrated a significant decrease in mortality from the time of initial donor evaluation in LDLT patients compared to

patients who did not undergo LDLT (18). In addition, increasing the number of LDLT may expand the donor pool, which could lead to improved waitlist outcomes in all LT candidates (10). Although this study indicated that LDLT might be associated with worse one-year graft survival than DBD-DDLT, the benefit of an assured transplant with LDLT might be weighed against the higher risk of graft loss, especially in those with lower-MELD scores and/or HCC.

While there are many studies investigating post-transplant outcomes between LDLT and DDLT, the present study provides new insights. Prior studies have focused more on overall comparisons of LDLT and DDLT outcomes, whereas we excluded patients with MELD scores 30 or higher and evaluated outcomes in those with MELD score 6-14 and 15-29, separately to determine appropriate donor and recipient selection. Few large studies comment on the role of MELD in survival after LDLT (3, 9, 10, 19) though, per A2ALL, increasing MELD score was associated with graft but not patient loss (8). In that analysis, the type of graft did not have an effect. In a single center report from Pittsburgh (7), 17 LDLT patients with a MELD score > 25 had one-year survival of 80%. While this was comparable to DDLT with MELD > 25 (88%), the figure was not compared to LDLT patients with lower scores. In addition, the current study identifies the significant impact of ascites on LDLT outcomes according to the liver graft type. Even fewer studies have looked at the role of ascites. Goldberg et al.(10), in developing a living donor risk index using the OPTN/UNOS registry, evaluated but did not include MELD score or ascites in the final formula.

Limitations of this study include its retrospective nature and the use of the OPTN/UNOS registry which lacks some detailed clinical data. First, we could not evaluate the exact effect of

PHT, graft size, or detailed surgical techniques on post-transplant outcomes. Although it would be important to evaluate the occurrence of hepatic venous outflow obstruction and liver graft congestion, especially in the LDLT group, these complications may well be underreported and surgical techniques for hepatic vein reconstruction in LDLT are not recorded in the UNOS registry. Although several technical innovations in the hepatic venous reconstruction might have contributed to the recent improvement in post-LDLT outcomes (20-22), these efforts cannot be assessed in this study. Second, intention-to-treat survival in the LDLT group is difficult to evaluate, because of lack of data in the OPTN/UNOS registry. Third, this study evaluated patients with MELD score < 30 at LT. Therefore, we should acknowledge that data in our study are not applicable to patients with MELD score ≥ 30. Fourth, although the graft selection between DBD-DDLT, DCD-DDLT, and LDLT might be influenced by inherent factors such as the presence of an appropriate living donor candidate, donor and recipient anatomy or the patient status which may need urgent LT, this possible selection bias cannot be captured in the OPTN/UNOS registry. Indications of LDLT may need to be altered depending on the availability of donated livers from DBD and DCD donors. Although we assessed center experience of LDLT based on the case numbers during whole study period in the OPTN/UNOS registry, this methodology might not reflect actual experience in each transplant center. Center experience might be multifactorial which should be considered based on year of surgeons' experience or transition of activities over time for LDLT or DCD-DDLT at each center which were not captured in this study. Multicenter studies would be necessary to address the effect of individual centers on post-transplant outcomes between different donor types.

In conclusion, this study demonstrates that LDLT is associated with a higher risk of early graft loss compared to DBD-DDLT and DCD-DDLT especially in patients with MELD score 15-29. The risk in LDLT patients with MELD score 15-29 is most pronounced in patients with ascites and/or who receive a LL graft. Decreased LDLT outcomes may be associated with early surgical complications. Recipient and donor selection are critical to successful outcomes in LDLT with consideration of MELD score, presence of significant ascites, and size match between graft and recipient. These findings help calibrate risk in LDLT.

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Figure Legends

Figure 1. Study cohort. **A.** Flow chart of patient selection. **B.** Distribution of patients according to laboratory MELD score at LT.

Figure 2. Graft survival between DBD-DDLT, DCD-DDLT, and LDLT according to MELD score category. **A.** Lower-MELD (6-14) group. **B.** Mid-MELD (15-29) group.

Figure 3. Adjusted hazards of 30-day and 1-year graft loss according to MELD categories in DBD-DDLT and DCD-DDLT (ref: LDLT). Hazards were adjusted by recipient and donor variables. Recipient variables included age, race, body mass index, gender, history of diabetes, Karnofsky score, use of life support, use of dialysis, MELD score at LT, serum sodium, and

presence of ascites or hepatic encephalopathy. Donor variables included age, gender, and race.

Figure 4. Adjusted hazards of 1-year graft loss according to significant ascites in LDLT. **A.** MELD categories (ref. without significant ascites). Hazards were adjusted by same recipient and donor variables as used in the risk factor analysis in the DDLT group. Six variables identified as independent risk factors for one-year graft loss (recipient age, transplant year, Karnofsky score, use of life support, donor age, and graft type) were used for risk adjustment in the LDLT group (Table 2). **B.** Graft type (ref: LL with significant ascites). Similarly, hazards were adjusted by the six independent risk factors for one-year graft loss in the LDLT group.

Supplemental Figure 1. Center experience in LDLT.

Supplemental Figure 2. Adjusted hazards of 30-day and 1-year graft loss according to center experience in LDLT (ref: DDLT). Hazards were adjusted by same recipient and donor variables as used in the risk factor analysis. **A.** 30-day graft survival. **B.** 1-year graft survival.

Supplemental Figure 3. Comparison of graft survival according to graft type and significant ascites in LDLT.

Supplemental Figure 4. Post-transplant outcomes in patients with HCC. **A.** Graft survival. **B.** Adjusted hazards of graft loss in DBD-DDLT and DCD-DDLT (ref: LDLT). Hazards were adjusted by same recipient and donor variables as used in the risk factor analysis.

Table 1 Recipient and donor characteristics.

	LDLT (n=1486)	DCD-DDLT (n=1171)	DBD-DDLT (n=13568)	P	
Recipient characteristics					
Age (years)	55.5 [45.0, 62.0]	57.0 [51.0, 62.0]	56.0 [50.0, 62.0]	<0.001	
Male (%)	831 (55.9)	798 (68.1)	8913 (65.7)	<0.001	
BMI (kg/m ²)	26.2 [23.3, 30.0]	28.4 [25.1, 32.6]	28.7 [25.1, 32.9]	<0.001	
Ethnicity (%)				<0.001	
White	1243 (83.7)	947 (80.9)	10445 (77.0)		
Black	48 (3.2)	75 (6.4)	1160 (8.5)		
Hispanic	149 (10.0)	109 (9.3)	1488 (11.0)		
Asian	31 (2.1)	26 (2.2)	278 (2.0)		
Others	15 (1.0)	14 (1.2)	197 (1.5)		
Significant ascites (%)				<0.001	
Yes	317 (21.3)	402 (34.3)	4717 (34.8)		
No	1169 (78.7)	769 (65.7)	8850 (65.2)		
Missing*	0 (0)	0 (0)	1 (0)		
Diabetes (%)				0.01	
Yes	334 (22.5)	305 (26.0)	3504 (25.8)		
No	1148 (77.3)	865 (73.9)	10001 (73.7)		
Missing*	4 (0.2)	1 (0.1)	63 (0.5)		
Dialysis (%)				<0.001	
Yes	3 (0.2)	5 (0.4)	186 (1.4)		
No	1483 (99.8)	1165 (99.6)	13376 (98.6)		
Encephalopathy (%)				<0.001	
Grade 3-4	63 (4.2)	116 (9.9)	1320 (9.7)		
Grade 1-2	1423 (95.8)	1055 (90.1)	12247 (90.3)		
Missing*	0 (0)	0 (0)	1 (0)		
Karnofsky score (%)	10-30%	107 (7.3)	135 (11.5)	2540 (18.7)	<0.001

	40-100%	1353 (91.0)	1026 (87.6)	10887 (80.2)	
	Missing*	26 (1.7)	10 (0.9)	141 (1.1)	
Life support (%)	Yes	6 (0.4)	17 (1.5)	324 (2.4)	<0.001
	No	1480 (99.6)	1154 (98.5)	13244 (97.6)	
Laboratory MELD score at LT		16.0 [12.0, 20.0]	20.0 [17.0, 24.0]	22.0 [18.0, 25.0]	<0.001
Days on waitlist		148 [76, 298]	75 [26, 226]	66 [19, 199]	<0.001
Previous abdominal surgery (%)	Yes	747 (50.3)	557 (47.6)	6284 (46.3)	0.01
	No	739 (49.7)	614 (52.4)	7284 (53.7)	
PVT at transplant (%)	Yes	186 (12.5)	155 (13.2)	1879 (13.8)	0.33
	No	1300 (87.5)	1016 (86.8)	11689 (86.2)	
TIPS (%)	Yes	129 (8.7)	167 (14.3)	1722 (12.7)	<0.001
	No	1357 (91.3)	1004 (85.7)	11846 (87.3)	
Follow-up (year)		2.1 [0.9, 4.9]	1.9 [0.6, 4.0]	2.7 [1.0, 5.1]	
Donor characteristics					
Age (years)		35.0 [28.0, 44.0]	35.0 [25.0, 48.0]	45.0 [29.0, 57.0]	<0.001
Male (%)		715 (48.1)	788 (67.3)	7983 (58.8)	<0.001
BMI (kg/m ²)		25.9 [23.3, 28.5]	26.2 [22.8, 30.7]	27.3 [23.7, 32.0]	<0.001
Graft type in LD: Right/Left		1202 (80.9)/218 (14.7)	-	-	

Bold type indicates statistically significant differences.

BMI, Body mass index; DBD, donors after brain death; DCD, donation after cardiac death; LD, living

donor; MELD, Model for End-stage Liver Disease; PVT, Portal venous thrombosis; TIPS, Transjugular intrahepatic portosystemic shunt

*"Unknown" and "Not reported" in the UNOS registry was labeled as "Missing" in Table 1.

Table 2. Multivariable risk factor analysis for 1-year graft loss in LDLT and DDLT group

		LDLT		DDLT	
		aHR (95% CI)	P	aHR (95% CI)	P
Age group (ref. <40)	40-59	0.63 (0.40-0.99)	0.046	1.21 (0.95-1.55)	0.12
	≥ 60	0.80 (0.50-1.28)	0.36	1.65 (1.28-2.11)	<0.001
Gender (ref. female)	Male	0.98 (0.71-1.36)	0.92	1.07 (0.95-1.20)	0.28
BMI group (ref. 18.5-25)	< 18.5	0.93 (0.22-3.87)	0.92	1.33 (0.80-2.20)	0.28
	25-30	0.85 (0.59-1.23)	0.38	0.94 (0.82-1.09)	0.44
	≥ 30	0.75 (0.47-1.18)	0.21	0.89 (0.77-1.03)	0.10
Race (ref. white)	Black	2.02 (0.56-7.27)	0.28	1.22 (1.01-1.47)	0.04
	Hispanic	0.87 (0.38-2.01)	0.75	0.91 (0.75-1.10)	0.32
	Asian	2.30 (0.85-6.26)	0.10	1.23 (0.86-1.75)	0.26
	Others	2.64 (0.79-8.76)	0.11	0.68 (0.38-1.19)	0.18
Diabetes	Yes	1.16 (0.79-1.70)	0.45	1.10 (0.97-1.24)	0.14
Ascites (ref. absent/slight)	Mod/severe	1.52 (1.05-2.20)	0.03	1.11 (0.99-1.25)	0.08
Dialysis	Yes	4.22	0.22	1.25 (0.86-1.81)	0.25

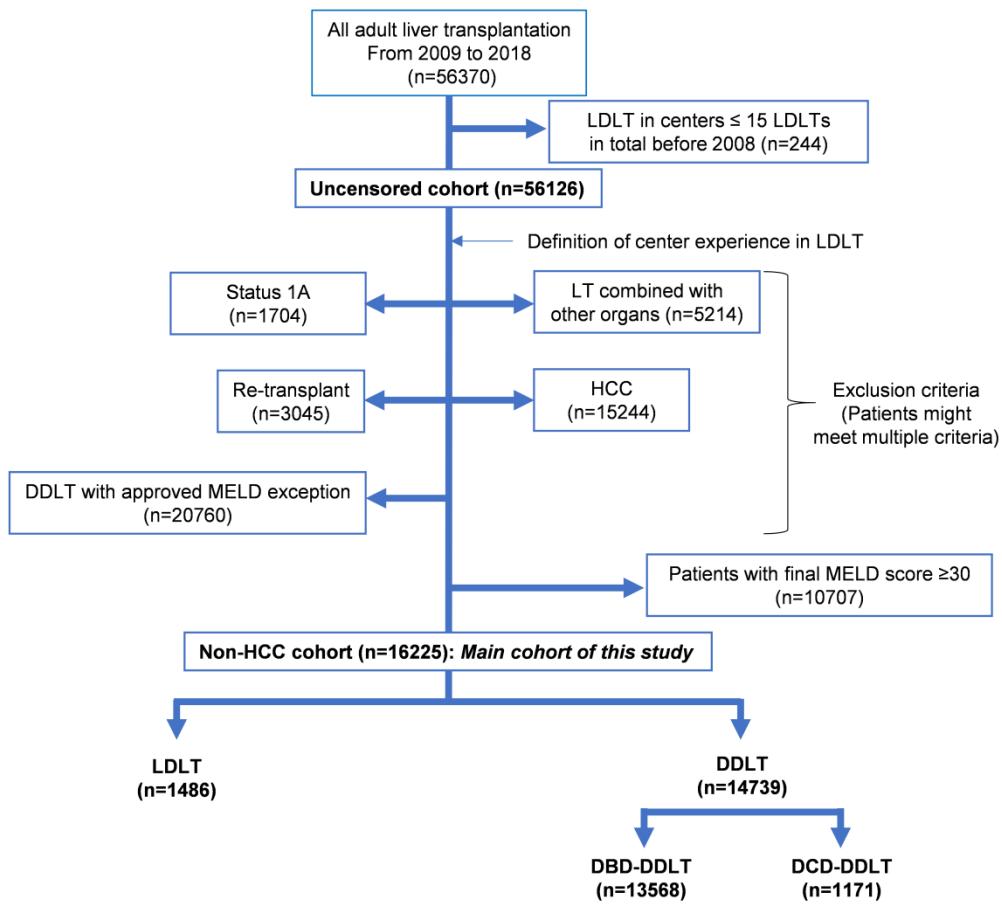
			(0.42-42.06)			
Encephalopathy	G3,4		1.74 (0.96-3.15)	0.07	1.16 (0.98-1.38)	0.08
Life support	Yes		3.80	0.03	1.97 (1.52-2.56)	<0.00
Karnofsky score	(ref. 10-30% 40-100%)		1.75 (1.08-2.85)	0.02	1.46 (1.26-1.69)	<0.00
Laboratory MELD score at LT			1.00 (0.97-1.04)	0.81	1.00 (0.99-1.01)	0.95
Serum sodium (ref. 135-145)	<130		0.85 (0.47-1.57)	0.61	1.03 (0.91-1.17)	0.66
	130-134		1.38 (0.96-1.98)	0.08	1.02 (0.86-1.20)	0.86
	>145		2.66 (0.92-7.68)	0.07	1.62 (1.20-2.20)	0.002
Transplant era	2009-2012		1.57 (1.05-2.36)	0.03	1.24 (1.09-1.42)	0.001
	(ref. 2016-2018)					
	2013-2015		1.18 (0.78-1.80)	0.43	0.94 (0.81-1.10)	0.94
Region (ref. low-MELD)	Mid-MELD		1.20 (0.71-2.03)	0.49	1.04 (0.91-1.18)	0.57
	High-MELD		1.08 (0.63-1.85)	0.78	0.92 (0.79-1.07)	0.28
Donor age (ref. <40)	40-59		1.77 (1.28-2.45)	0.001	1.24 (1.09-1.41)	0.001
	≥ 60		1.43	0.76	1.54 (1.32-1.80)	<0.00
			(0.15-13.88)			1
Donor gender	Male		0.73 (0.52-1.02)	0.06	0.99 (0.88-1.11)	0.87
Donor race (ref. white)	Black		0.58 (0.15-2.32)	0.44	1.08 (0.94-1.25)	0.27
	Others		0.99 (0.47-2.09)	0.98	1.26 (1.08-1.48)	0.004
Graft type (ref. right liver)	Left liver		1.91 (1.29-2.84)	0.001	-	-
Graft type (ref. whole)	Split		-	-	1.64 (1.04-2.58)	0.03
Donor type (ref. DBD)	DCD		-	-	1.58 (1.31-1.92)	<0.00

Bold type indicates statistically significant differences.

BMI, Body mass index; DBD, donors after brain death; DCD, donation after cardiac death; MELD, Model for End-stage Liver Disease

Figure 1. Study cohort

A. Flow chart of patient selection



B. Distribution of patients according to laboratory MELD score at LT

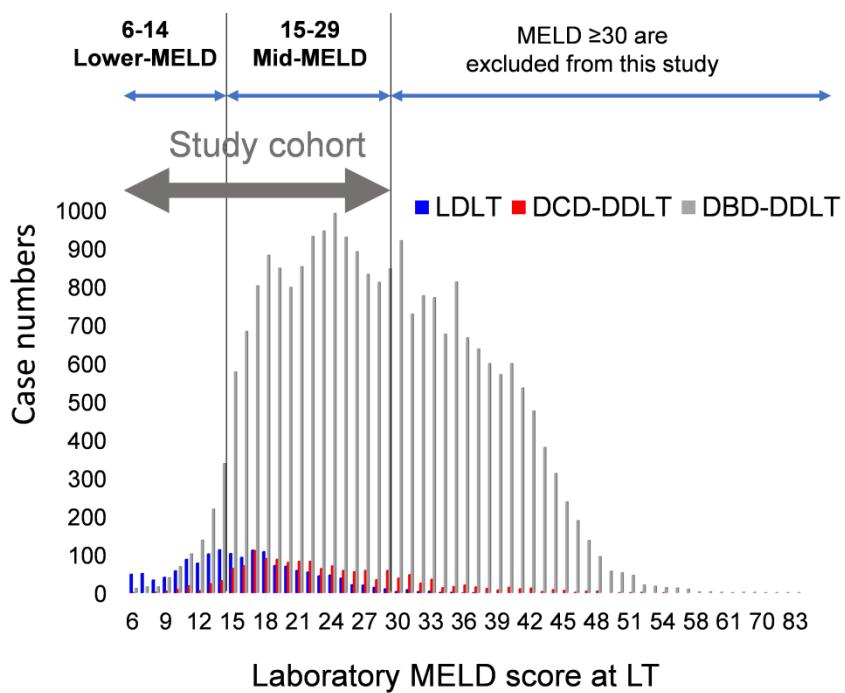
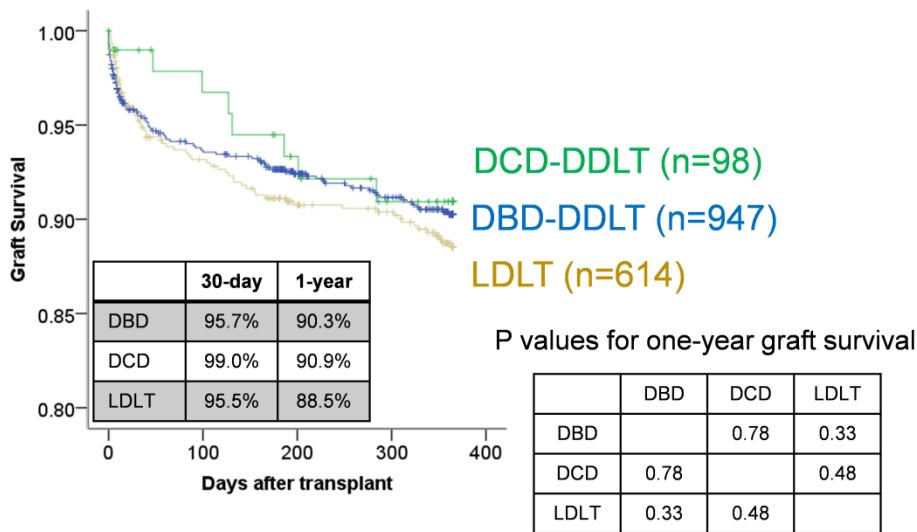


Figure 2. Comparisons of graft survival between DBD-DDLT, DCD-DDLT and LDLT according to MELD score categories

A. Lower-MELD (6-14) group



B. Mid-MELD (15-29) group

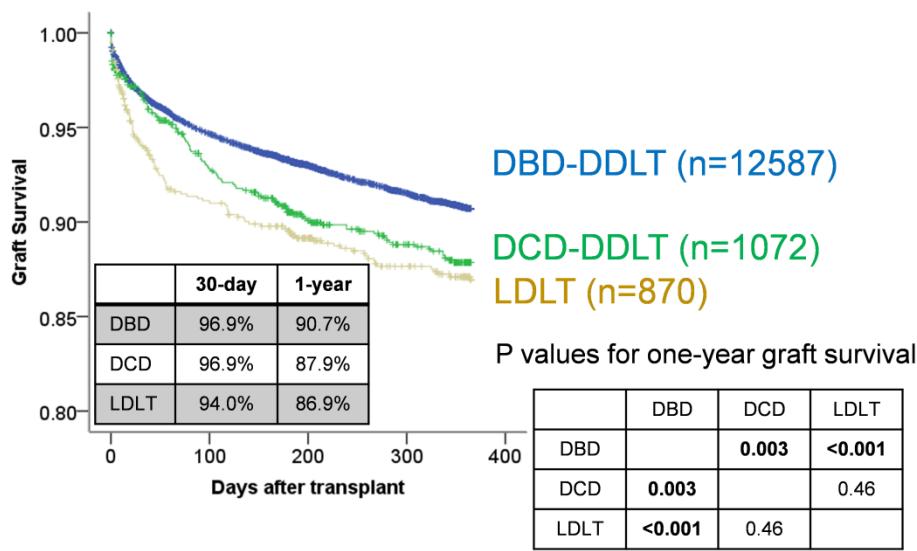
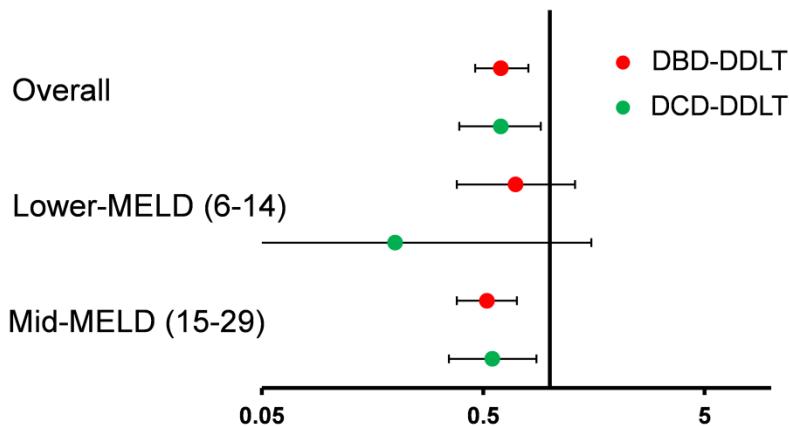


Figure 3. Adjusted hazards of 30-day and 1-year graft loss according to MELD categories in DBD-DDLT and DCD-DDLT (ref: LDLT)

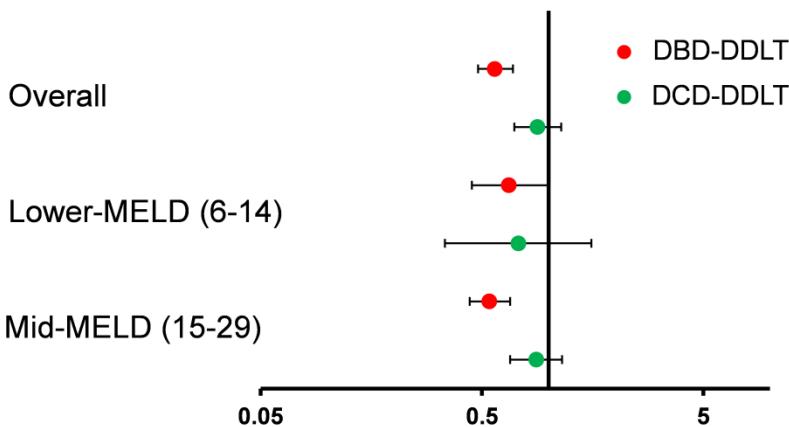
A. 30-day graft survival



Hazard Ratio

		aHR	lower	upper	P values
Overall	DBD	0.60	0.46	0.80	<0.001
	DCD	0.60	0.39	0.91	0.02
Lower-MELD	DBD	0.70	0.38	1.30	0.26
	DCD	0.20	0.03	1.54	0.12
Mid-MELD	DBD	0.52	0.38	0.71	<0.001
	DCD	0.55	0.35	0.87	0.009

B. 1-year graft survival

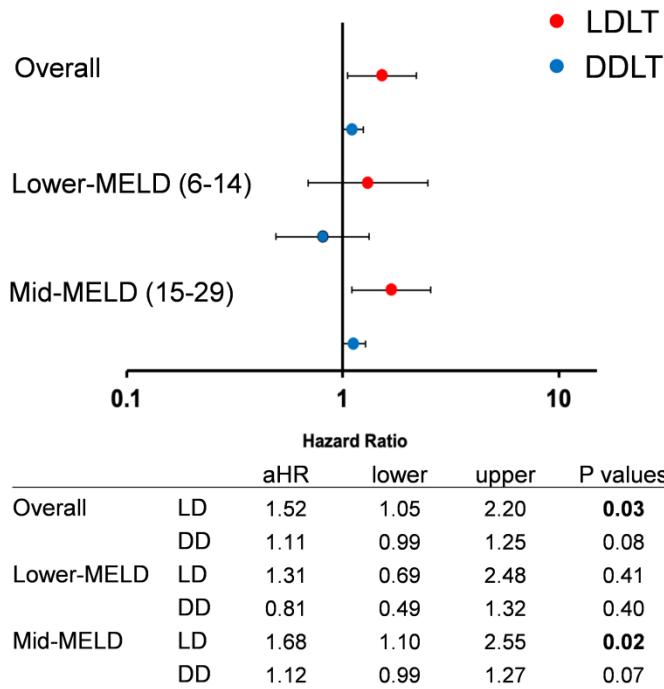


Hazard Ratio

		aHR	lower	upper	P values
Overall	DBD	0.57	0.48	0.69	<0.001
	DCD	0.89	0.70	1.14	0.36
Lower-MELD	DBD	0.66	0.45	0.99	0.04
	DCD	0.73	0.34	1.56	0.42
Mid-MELD	DBD	0.54	0.44	0.67	<0.001
	DCD	0.88	0.67	1.15	0.33

Figure 4. Adjusted hazards of 1-year graft loss for significant ascites in LDLT and DDLT

A. MELD categories (ref: without significant ascites)



B. Graft type (ref: LL with significant ascites)

