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# National experience with living donor liver transplantation for hepatocellular carcinoma

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## Abstract

Living donor liver transplantation (LDLT) is an attractive option to decrease waitlist dropout, particularly for patients with hepatocellular carcinoma (HCC) who face lengthening waiting times. Using the United Network for Organ Sharing (UNOS) national database, trends in LDLT utilization for patients with HCC were evaluated, and post-LT outcomes for LDLT versus deceased donor liver transplantation (DDLT) were compared. From 1998 to 2018, LT was performed in 20,161 patients with HCC including 726 (3.6%) who received LDLT. The highest LDLT utilization was prior to the 2002 HCC Model for End-Stage Liver Disease (MELD) exception policy (17.5%) and dropped thereafter (3.1%) with a slight increase following the 6-month wait policy in 2015 (3.8%). LDLT was more common in patients from long-wait UNOS regions with blood type O, in those with larger total tumor diameter (2.3 vs. 2.1 cm, $p = 0.02$), and higher alpha-fetoprotein at LT (11.5 vs. 9.0 ng/ml, $p = 0.04$). The 5-year post-LT survival (LDLT 77% vs. DDLT 75%), graft survival (72% vs. 72%), and HCC recurrence (11% vs. 13%) were similar between groups (all $p > 0.20$). In conclusion, LDLT utilization for HCC has remained low since 2002 with only a slight increase after the 6-month wait policy introduction in 2015. Given the excellent post-LT survival, LDLT appears to be an underutilized but valuable option for patients with HCC, especially those at high risk for waitlist dropout.

## INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most commonly diagnosed cancer and the fourth highest cause of cancer mortality worldwide.[1] Liver transplantation (LT) remains the treatment with the highest probability of cure.[2,3] Because of organ shortages, LT candidates

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CONFLICT OF INTEREST

Nothing to report.

within conventional transplantation criteria often have long waiting times and risk waitlist dropout while waiting for a deceased donor liver transplantation (DDLT).[4–6] In addition, the allocation system for deceased donors is largely limited to patients with HCC within Milan criteria and patients with even a modest expansion of tumor size are not eligible for Model for End-Stage Liver Disease (MELD) exception in the United States.[7] Living donor liver transplantation (LDLT) has been performed for patients with HCC to decrease waitlist dropout especially in long-wait regions (LWRs) as well as for patients beyond Milan criteria, adhering to the principle that the risk to the donor is justified by the expectation of an acceptable outcome for the recipient (double equipoise).[8]

The landscape of LT for HCC has changed dramatically after the introduction of the MELD priority exception system for HCC in 2002. The policy has increased access to LT for patients with HCC compared with patients with non-HCC.[9] However, even after implementation, there are still many patients who risk waitlist dropout. One study estimated that even after this policy, in formerly LWRs up to 30% of patients drop out, with about an 11% worse overall mortality for patients listed in LWR.[10] LDLT as an alternative to DDLT could play an especially important role for patients at high risk of dropout; however, no study to date has investigated LDLT utilization pattern differences by waiting time. The largest study that looked at utilization of LDLT for patients with HCC accounted for nine centers from 1998 to 2003, which captured utilization mostly prior to the MELD exception policy enacted in 2002.[11,12]

Two additional policy changes in October 2015, namely, a 6-month delay in awarding exception points and MELD exception cap at 34 points, dramatically changed the landscape for patients with HCC awaiting LT. These policies decreased access to DDLT for patients with HCC, especially in the first 6 months after listing with MELD exception.[13–16] In addition, the new policy as of May 19, 2019 aimed to decrease these geographic disparities by awarding median MELD at Transplant (MMAT) minus 3 points,[17] which assigns more HCC exception points to patients in centers with higher median MELD scores (typically LWRs). This could increase the use of LDLT for patients in all regions. Therefore, it seems as though LDLT may play an even more significant role for patients with HCC after the 2015 and 2019 policy changes.

This study aimed to use the national United Network for Organ Sharing (UNOS) database to assess temporal and regional utilization of LDLT for patients with HCC across the United States. Our secondary aim was to report the impact of LDLT versus DDLT on post-LT patient and graft survival as well as HCC recurrence.

## PATIENTS AND METHODS

### Study design and patient selection

In this retrospective cohort study, the UNOS national database was used to form two distinct cohorts (Figure 1). Cohort 1 (named the temporal trends cohort) included 20,161 adult patients with HCC who underwent LT between January 1, 1998, and December 31, 2018, at centers performing at least one LDLT during the study period. These patients were identified by having an HCC diagnosis and/or HCC exception and the only exclusion was patients

who received retransplantation. The primary objective for this larger cohort was to capture temporal and regional trends in LDLT.

Cohort 2 (named the posttransplantation outcomes cohort) was created primarily to assess relevant transplantation-related outcomes, including post-LT survival. This smaller subset included 9349 adult patients with HCC who underwent LT with MELD exception between January 1, 2005, and December 31, 2017. This group was restricted to a shorter time frame as this population had more sufficient data on tumor characteristics as well as at least 1 year of follow-up data. Exclusion criteria for this subset included retransplantations, patients with no recorded evidence of HCC (no tumor size at first, original, and last exception application), missing alpha-fetoprotein (AFP) data, patients with cholangiocarcinoma as a misdiagnosis of HCC ($n = 95$), and LT recipients from centers that never performed an LDLT ($n = 10,846$).

Further, the LDLT patients from Cohort 2 were compared with a cohort of patients listed for transplantation with HCC that either received DDLT or did not receive a transplantation ($n = 13,780$), including those that dropped off the waiting list due to tumor progression or liver-related death, to perform an intention-to-treat analysis. A sensitivity analysis of this cohort was conducted to account for the potential immortal time bias. The landmark analysis was conducted and the landmark time was set to 7.2 months, reflecting the median wait-list time for DDLT recipients.[18] Losses to follow-up and deaths prior to the landmark time were excluded from the computations, while patients remaining alive were classified based on their status at the landmark time. Therefore, patients receiving LDLT before the landmark time were assigned to the LDLT group and those receiving LDLT after the landmark time were assigned to the DDLT group because they were presumably still eligible for DDLT at that point. The DDLT group also included those receiving DDLT, dying after the landmark time without LT, and still waiting for LT. Second, a proportional hazards model with LDLT as a time-varying covariate was conducted to avoid selecting a landmark time and related misclassification errors. In this case, patients are included in the DDLT group until receipt of LDLT at which time they switch groups.

### National and regional trends

To understand LDLT trends from 1999 to 2018, the temporal trends cohort was stratified by wait time region and year, with the year examined individually and then grouped by era. The first era was chosen from 1999 to 2001, which started from the first year of more than one LDLT for patients with HCC and ended prior to the 2002 MELD exception rule. The second era was 2002–2014, which ended before the 2015 policy change requiring 6-month waiting time for awarding MELD exception points. Finally, the third era was 2015–2018 to capture trends following the 6-month wait policy. The UNOS regions were categorized into SWRs (regions 3, 10, and 11), medium-wait regions (MWRs; 2, 4, 6, 7, and 8) and LWRs (1, 5, and 9) based on previously used definitions.[10] Descriptive statistics were used to analyze trends over time.

### Study variables

For the 2005–2017 posttransplantation outcomes cohort, study variables collected from the UNOS database included age, sex, race/ethnicity, etiology of liver disease, blood type, and wait region. AFP and the size and number of HCC lesions at inclusion were determined at the time of initial MELD exception application. The percentage of patients who underwent local regional therapy while on the waiting list, time from initial listing to LT, the time from MELD exception to LT, MELD score at LT, and Child–Pugh at LT were also collected. AFP and radiographic tumor burden closest to the date of LT (within 90 days of LT) were obtained. Donor characteristics collected included donor age and donor ethnicity and for DDLT recipients, donor cause of death, share type, donation after circulatory death (DCD) donors, and cold ischemia time. Clinical and tumor characteristics were summarized using medians and interquartile ranges (IQRs) for continuous variables and proportions for categorical variables.

### HCC recurrence

To identify patients with post-LT HCC recurrence, liver malignancy follow-up data and cause of death variables underwent physician review (N.M.). Records indicating posttransplantation recurrence of pretransplantation malignancy or a cause of death indicating HCC or metastatic malignancy were classified as having HCC recurrence.

### Post-LT survival and recurrence statistical analysis

To determine post-LT patient survival, post-LT HCC recurrence, and graft survival (defined as patient death or retransplantation), outcomes were assessed for the overall cohort and stratified by type of donor (LDLT vs. DDLT). Observed post-LT patient and graft survival and HCC recurrence probabilities and 95% confidence intervals (CIs) were estimated at 1, 3, and 5 years using the Kaplan-Meier method and compared by type of donor using the log-rank test. For post-LT survival, follow-up was measured from the date of LT to the first of retransplantation, death, or last follow-up with survival censored at retransplantation (patient survival only) or last follow-up. For post-LT HCC recurrence, patient follow-up was measured from the date of LT to HCC recurrence or HCC-related death with patients censored at the date of non-HCC death or last follow-up. The association of post-LT outcomes with explanatory variables was explored using univariate and multivariable hazard ratios (HRs) and 95% CIs estimated by Cox proportional hazards regression for post-LT survival and HCC recurrence. Variables with a univariate $p$ value <0.1 were included in the multivariable analysis with the final models selected by backward elimination ($p$ for removal >0.05).

## RESULTS

### LDLT national and temporal trends

A summary of LDLT utilization by era using the temporal trends cohort is provided in Table 1. In Era 1 (1999–2001), 48 centers performed LDLT with LDLT accounting for 17.7% of total transplantations for patients with HCC. In Era 2 (2002–2014), 55 centers performed LDLT, which accounted for 3.0% of total LTs for patients with HCC. Most recently, in

Era 3 (2015–2018), 53 centers performed LDLT, with LDLT remaining fairly uncommon in patients with HCC at 3.8% of total LTs performed. In 2000, the largest proportion of total LTs for patients with HCC was LDLTs at 21%, and since 2002 LDLTs have been less than 5% of the total LT (Figure 2A). Similar trends were seen when accounting for all transplantation centers, not just the centers utilizing LDLTs (Figure 2B). The total number of LDLTs has slowly risen over time, peaking in 2016 and 2018 at 56 LDLTs for HCC performed in a single year (Figure 2C).

## Patient characteristics

Recipient and donor characteristics are summarized for the posttransplantation outcomes cohort (Cohort 2) in Table 2. Compared with recipients of DDLT, LDLT recipients were more often female (28.2% vs. 22.5%, $p = 0.03$), more often White (70.1% vs. 63.5%, $p = 0.01$), less often African American (5.3% vs. 10.9%, $p = 0.01$), more often type O blood group (47.2% vs. 44.8%, $p = 0.03$), had larger median total tumor diameter at LT of 2.3 cm (IQR 0.0–3.7) versus 2.1 cm (0.0–3.2; $p = 0.02$), and higher median AFP at LT of 11.5 ng/ml (5–38) versus 9.0 ng/ml (4–29; $p = 0.04$). Waiting time was shorter for LDLT at 4.2 months (2.6–6.7) versus 5.6 months (2.2–10.3, $p < 0.001$) with 53.5% of LDLT recipients being from LWRs compared with 39.4% of DDLT recipients ($p < 0.001$). LDLT donors were younger (35 vs. 44 years), more often White (68.7% vs. 65.6%), African American (18.0% vs. 13.4%), and Asian (6.0% vs. 2.7%), but less often Hispanic (5.6% vs. 17.3%; $p < 0.001$). There was no difference in age, etiology of liver disease, MELD, or Child-Pugh scores for DDLT versus LDLT.

## Post-LT overall patient survival

The posttransplantation outcomes cohort (Cohort 2) was used for all survival and recurrence analyses. The median post-LT follow-up was 4.0 years (3.1 years for LDLT recipients and 4.0 years for DDLT recipients). The LDLT group had 3- and 5-year post-LT patient survival of 84.1% (95% CI 78.8–88.2) and 76.6% (95% CI 70.0–82.0), respectively. Compared with LDLT recipients, DDLT recipients had no significant difference in post-LT patient survival with 5-year survival of 74.9% (95% CI 73.9–75.9; $p = 0.53$; Figure 3). Post-LT survival at 5 years was also similar when only including patients with HCC within Milan criteria (LDLT 77.8% vs. DDLT 75.7%; $p = 0.51$). Only seven LDLT recipients had tumor burden reported outside Milan criteria at LT. For these patients, 5-year post-LT survival was 48.9%, which was not statistically different than for DDLT patients beyond Milan at LT (61.7%; $p = 0.88$).

## Post-LT patient survival by era

For survival analysis, the posttransplantation outcomes cohort (Cohort 2) was divided into two eras, 2014–2017 and 2005–2013, to capture changes in outcomes over time (Figure 4). From 2014 to 2017, LDLT recipients had a post-LT 3-year survival of 87.7% (95% CI 78.1–93.2), while DDLT recipients in this period had a 3-year survival of 85.2% (95% CI 83.7–86.6). From 2005 to 2013, LDLT recipients had a 3-year survival of 81.5% (95% CI 74.4–86.9) while DDLT recipients had 80.8% (95% CI 79.8–81.8).

### Post-LT patient survival by AFP

LDLT recipients with AFP <100 ng/ml at LT had a 3-year post-LT survival of 84.3% (95% CI 78.6–88.6) and at 5 years of 76.7% (95% CI 69.4–82.5), which was not significantly different from those of DDLT recipients (3 years: 83.8% CI 82.9–84.6; 5 years: 76.9% CI 75.8–77.9; $p = 0.96$). There were 33 LDLT recipients with AFP ≥100 ng/ml; the 3-year survival rate was 83.3% (95% CI 64.4–92.7; $n = 21$) and the 5-year survival rate was 75.4% (95% CI 54.9–87.5; $n = 15$). For DDLT recipients with AFP ≥100, the 3-year survival rate was 71.1% (95% CI 68.1–73.8) and the 5-year survival rate was 61.8% (95% CI 58.5–64.9; $p = 0.15$).

### Post-LT graft survival and post-LT recurrence rates

LDLT graft survival at 3 years was 80.5% (95% CI 75.0–84.9) and at 5 years was 72.1% (95% CI 65.3–77.7). This was not significantly different from DDLT graft survival (3 years: 79.6%, 95% CI 78.7–80.5; 5 years: 72.1%, 95% CI 71.1–73.1; $p = 0.93$). HCC recurrence rate at 5 years was 12.9% (95% CI 8.8–18.5) for LDLT and was not significantly different from DDLT (10.8%, 95% CI 10.1–11.6; $p = 0.24$).

### Intention-to-treat survival analysis

The LDLT patients from Cohort 2 were compared with a cohort of patients listed for transplantation with HCC that either received DDLT or did not receive a transplantation ($n = 13,780$) to perform an intention-to-treat analysis. In this analysis, 3-year survival from the date of listing for the LDLT cohort was 87.2% (95% CI 82.4–90.8) compared with listed patients that either received a DDLT or did not receive a transplantation including due to waitlist dropout as a result of tumor progression or liver-related death had a 3-year intention to treat survival of 70.4% (95% CI 69.6–71.2; $p < 0.001$; Figure 5).

In the landmark sensitivity analysis to account for immortal time bias, the 3-year survival rate for the LDLT group was 88.3% (95% CI 82.0–92.5) and 75.7% (95% CI 74.8–76.5) for the DDLT group ($p < 0.001$). Furthermore, when modeling LDLT as a time-varying covariate, the HR for risk of death from the time of listing was 0.67 (95% CI 0.52–0.86; $p < 0.001$) for LDLT compared with the DDLT group.

### Predictors of post-LT survival and recurrence

Predictors of post-LT patient survival from Cox proportional hazards univariate and multivariable analyses are summarized in Table 3. On univariate analysis, receiving an LDLT was not a significant predictor of post-LT death (HR 0.91, 95% CI 0.69–1.21; $p = 0.53$). Older recipient age at listing, African American recipient, larger tumor burden prior to transplantation, higher AFP at transplantation, increasing Child-Pugh score and MELD score, outside Milan criteria, older donor age, and increased cold ischemia time were associated with worst post-LT mortality. Asian recipient, Hepatitis B as etiology of liver disease, and anoxia and head trauma as cause of donor death were associated with improved post-LT survival. In multivariate analysis, LDLT was again not a significant predictor of post-LT death (HR 0.98, 95% CI 0.74–1.30; $p = 0.88$). Age at listing, donor age, increasing last tumor diameter prior to LT, increasing AFP at LT, MELD score, and cold ischemia time remained associated with worse post-LT patient survival. LDLT was also not a significant

predictor of post-LT HCC recurrence (HR 1.25, 95% CI 0.85–1.84; $p = 0.25$) or graft survival (HR 0.99, 95% CI 0.77–1.27; $p = 0.94$).

### LDLT utilization by wait region

A secondary analysis of LDLT utilization by era and wait region was also performed on Cohort 1. Across all eras, LWR performed the most LDLTs and LDLTs accounted for a higher percentage of total transplantations for patients with HCC. Short-wait regions (SWRs) utilized LDLT the least across all years. LWR utilized LDLT the most across almost every year by absolute number, with the highest number in 2001 ($n = 34$ LDLT), compared with MWRs ($n = 5$) and SWRs ($n = 2$; Figure 6A,B).

## DISCUSSION

To date, this is the largest cohort study analyzing epidemiological trends and outcomes of patients with HCC who received LDLT in the United States. The UNOS database was used to evaluate all LDLT recipients, which included 20 years of LT data (1998–2018) beginning with the first LDLT ever performed for HCC in the United States. Overall, this study showed that LDLT has been most often utilized when patients with HCC have had less access to DDLT off the waiting list. The highest utilization of LDLT for HCC was prior to 2002, during which patients with HCC did not receive MELD exception points to increase access to DDLT.[16] The Adult-to-Adult Living Donor Liver Transplantation Cohort (A2ALL) study showed similarly high utilization prior to 2002.[11] After the 2002 MELD exception policy was implemented, which gave patients with HCC a large advantage for DDLT off the waiting list,[9] this study showed LDLT utilization for patients with HCC who were dropped. In 2013, the “Share 35” policy was implemented with a goal of increasing the proportion of patients with a MELD score >35 to undergo LT. The current study indicated that the Share 35 rule did not impact LDLT utilization along with previous studies that showed the policy did not impact the proportion of DDLTs going to patients with HCC or overall waiting time.[16,19] After the 2015 policy change, which required patients with HCC wait 6 months to receive exception points and capping at 34 points, the rate of DDLT for patients with HCC started to decline.[16] The results of this study indicate that there has been a corresponding rise in the number of LDLTs for patients with HCC over the same period, from 32 LDLTs per year prior to 2015 to greater than 50 per year after.

Across the United States, there are geographic disparities in access to DDLT, which also impact LDLT utilization differences across the nation. The geographic disparities have been historically divided into wait regions based on time from listing with MELD exception to DDLT, with LWR having the highest rate of dropout and lowest rate of LT compared with both MWR and SWR.[10,14] Accordingly, the current study showed the highest rate of LDLT utilization in LWR and lowest in SWR reflecting the trend that regions with more difficult access to DDLT utilize LDLT more frequently. A new policy in May 2019 aimed to decrease these geographic disparities by awarding median MELD at Transplant (MMAT) minus 3 points,[17] which assigns more HCC exception points to patients in centers with higher median MELD scores (typically LWR). Over time this is expected to geographically equalize waiting times for patients with HCC. Therefore, LDLT utilization for patients with

HCC can be reasonably expected to equalize across all regions and play a larger role to decrease waitlist dropout.

Although there has been a rise in LDLT utilization since 2015, the rate is slower than expected. The percentage of total LTs for patients with HCC dropped from 19.6% to 16.9% from 2008 to 2018.[20] Over a similar period, the number of patients with HCC listed with MELD exception increased by approximately 400 per year.[20] In addition, many patients have dropped off the waiting list with disproportionate amounts in MWRs and LWRs.[10] The decrease in LT for HCC coupled with the increase in waitlist dropouts reflects a large and growing gap between the lack of available transplantations and the number of patients with HCC who need one. LDLT is one possible way to close this gap, but the results of this study make it clear that LDLT is not currently meeting these needs. In addition to LDLT, DCD and other extended criteria donor organs can help close this gap as studies have shown favorable outcomes for these marginal deceased livers.[21,22] In addition, for patients who do not have a suitable living donor, especially as recipient age and national obesity increases, these alternative deceased liver options are also valuable.

Another goal of the study was to evaluate posttransplantation outcomes for patients with HCC receiving LDLT. Patients that received LDLT had factors that indicate a higher risk of waitlist dropout compared with DDLT recipients. LDLT recipients were more often in LWRs, with higher AFP, larger tumor burden, and more patients with blood types that are harder to find a match (A and O).[10] Even with this higher risk profile, LDLT recipients in this study had equivalent survival, recurrence, and graft survival rates to DDLT recipients using Kaplan–Meier, univariate, and multivariate regression analyses. Other studies have shown similar survival results, especially for patients with HCC with MELD ≥15.[23] Additionally, there was substantial survival benefit due to lack of waitlist dropout and decreased waiting time.[24–26] A 2011 analysis of A2ALL and several additional studies have demonstrated equivalent HCC recurrence rates, and increased recurrence in patients who receive LDLT is primarily due to more advanced HCC, not the graft itself.[11,27–30] In contrast to a recent study showing higher rates of graft loss for LDLT recipients 1 year after transplantation,[31] the present study showed equal graft survival for patients with HCC receiving LDLT and DDLT. Overall, LDLT appears to result in equivalent posttransplantation outcomes compared with DDLT for patients with HCC, with the benefit of decreasing waitlist dropout.

Incorporating the present data can better inform clinicians which patients with HCC should be considered candidates for LDLT. The appropriate use of LDLT not only takes into account the outcomes of the recipients but also the risks and benefits to the donor, a concept known as double equipoise where the risk to the donor can be justified by an acceptable outcome for the recipient.[8] At one extreme, patients with well-compensated disease and a single, small, well-treated tumor (about 20% of listed patients with HCC[32]) most likely derive less benefit from receiving an LDLT because that population can either wait for a DDLT or perhaps avoid LT altogether (until tumor recurrence).[33] In these cases, the risk to the donor is likely not justified. At the other extreme, patients who have higher risk characteristics may have outcomes that for the most part cannot justify the risk to the donor. The 2010 Consensus Conference on LT for HCC recommends LDLT for patients with

expected 5-year survival comparable to that of patients receiving DDLT, which has been estimated around 60%.[34–36] A recent study by Bhangui et al. suggested for patients without metastatic tumors or vascular invasion, a combination of AFP ≥100, positron emission tomography (PET) avidity, and University of California, San Francisco (UCSF) criteria can be used to risk stratify patients and therefore increase the number of patients who could receive LDLT with reasonable outcomes.[37] Similarly, another study by Kim et al. used a score that incorporated tumor size and number, AFP, vitamin K absence-II, and PET avidity to prognosticate LDLT for patients with HCC.[38] With careful consideration of the proper candidates for LDLT, many more patients with HCC can benefit from the use of LDLT either through existing LDLT centers expanding their volume or with new LDLT programs being created.

There are several limitations of this study. Although this is the largest reported sample of patients with HCC who received LDLT, there was a smaller number of LDLT recipients ($n$ = 284) compared with DDLT ($n$ = 6996). To this end, comparisons of post-LT survival and HCC recurrence by donor type, Milan criteria, AFP cut-offs, and era included relatively small numbers in the highest risk categories, limiting our ability to detect statistically significant differences, especially prior to 2013. In addition, most of these patients did not have explant data, so there is some uncertainty as to which patients were outside Milan criteria, limiting conclusions about safely expanding LDLT to patients outside Milan. While 60% of the current cohort had HCV, the use of direct-acting antiviral therapy has decreased this population of patients with HCC and decreases the generalizability of the current results.[39] Moreover, no mandate requires transplantation centers to report HCC recurrence, which could result in underestimating post-LT recurrence. This study did not take into account MMAT-3 or the impact of the COVID-19 pandemic which could both significantly impact LDLT utilizaton. In addition, graft survival was captured but the UNOS database does not report on the donor survival and thus we were unable to further study this secondary outcome, which is an important outcome that this study lacks.

## CONCLUSION

In the United States, LDLT is a small but important source of grafts for patients with HCC. Intuitively, more LDLTs are used when patients with HCC have less access to DDLT off the waiting list. Since the 2015 policy change, LDLT utilization has slightly increased, but still leaves a large and growing gap in the amount of available livers and patients with HCC in need. Patients with HCC in LWRs, with higher AFP and tumor burden, have historically received the most LDLTs, likely because these patients are at the highest risk for dropout. However, as newer policy changes try to equalize waiting times across all regions, LDLT will likely benefit traditionally SWRs as well. The overall survival and recurrence rates for LDLT recipients were equivalent to DDLT recipients, with a clear trend toward better overall survival especially in recent years. With appropriate use of the double equipoise principle, transplantation centers may use this information to advocate for pursuit of a higher volume of LDLTs for patients with HCC. With continued vigilance for donor safety and recipient outcomes, this study can help improve the growth of LDLT in the United States.

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## Abbreviations:

| | |
|---|---|
| **AFP** | alpha-fetoprotein |
| **A2ALL** | Adult-to-Adult Living Donor Liver Transplantation Cohort Study |
| **CI** | confidence interva |
| **CNS** | central nervous system |
| **CP** | Child-Pugh |
| **DBD** | donation after brain death |
| **DCD** | donation after circulatory death |
| **DDLT** | deceased donor liver transplantation |
| **HCC** | hepatocellular carcinoma |
| **HCV** | hepatitis C virus |
| **HR** | hazard ratio |
| **IQR** | interquartile range |
| **LDLT** | living donor liver transplantation |
| **LRT** | local regional therapy |
| **LT** | liver transplantation |
| **LWR** | long-wait region |
| **MELD** | Model for End-Stage Liver Disease |
| **MMAT** | Median MELD at Transplant |
| **MWR** | medium-wait region |
| **NAFLD** | nonalcoholic fatty liver disease |
| **PET** | positron emission tomography |
| **SWR** | short-wait region |
| **UNOS** | United Network for Organ Sharing |

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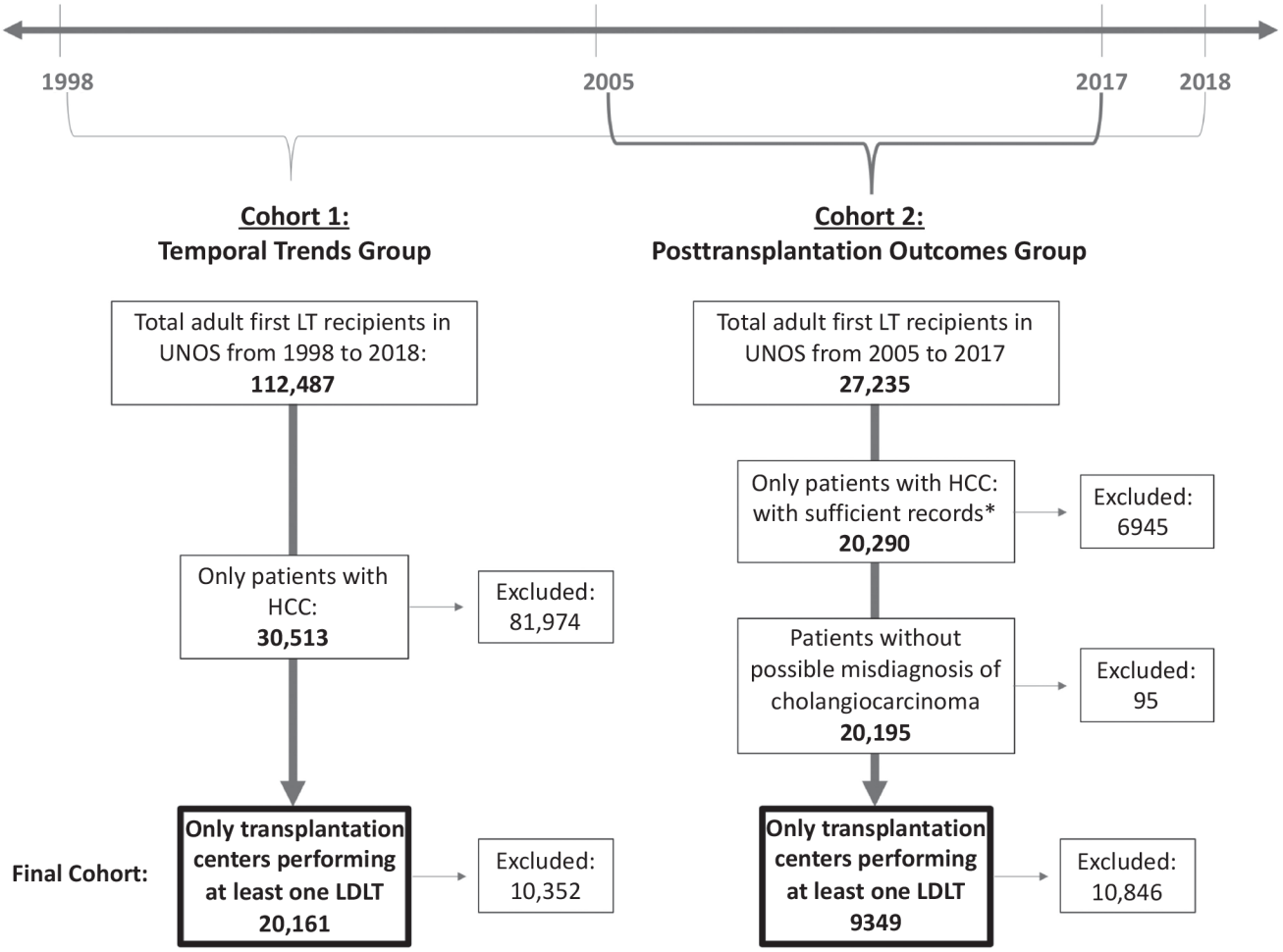
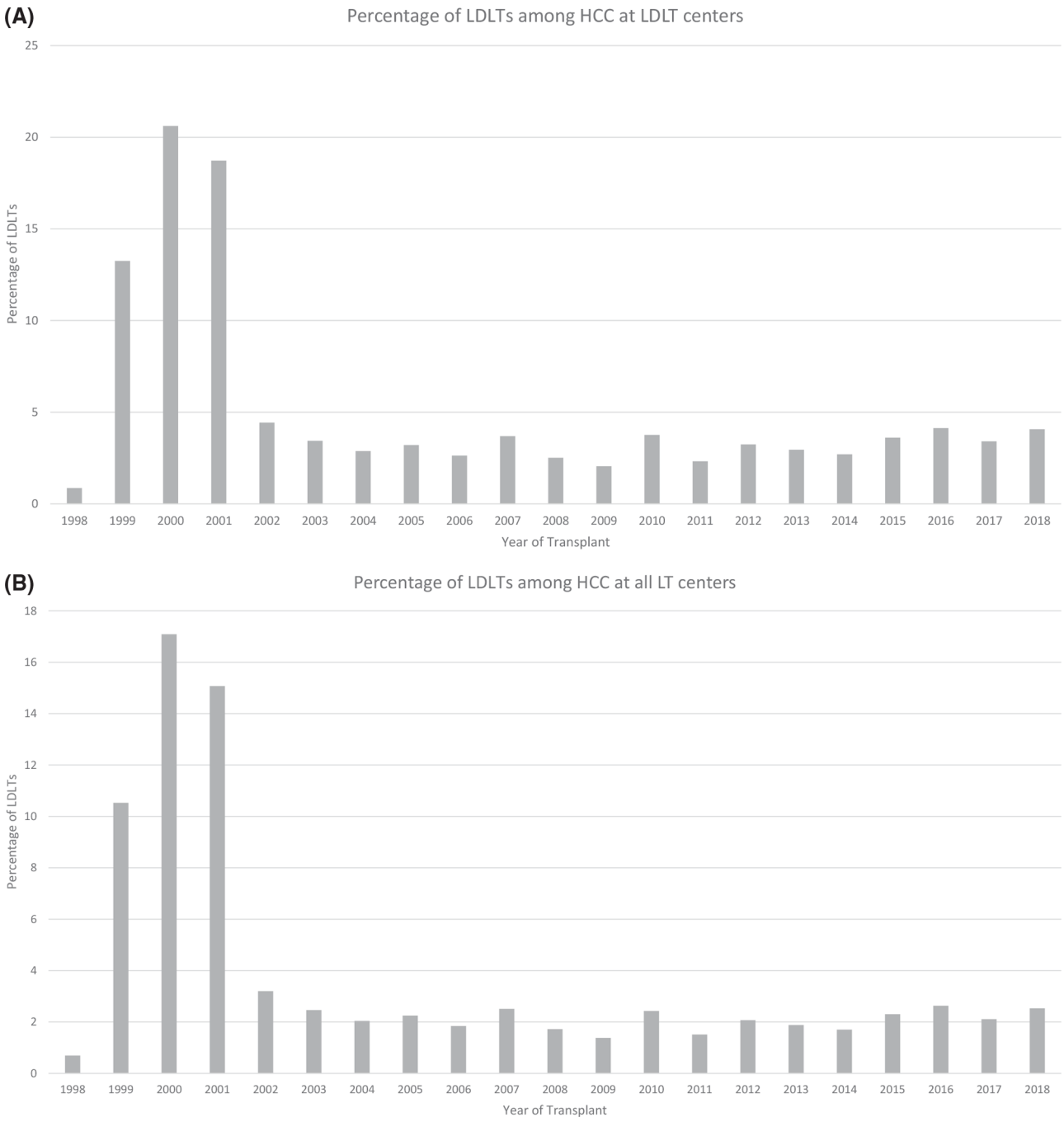



**FIGURE 1.**

Breakdown of inclusion criteria for the study by cohorts. Cohort 1: Temporal trends group, Cohort 2: Posttransplantation outcomes group



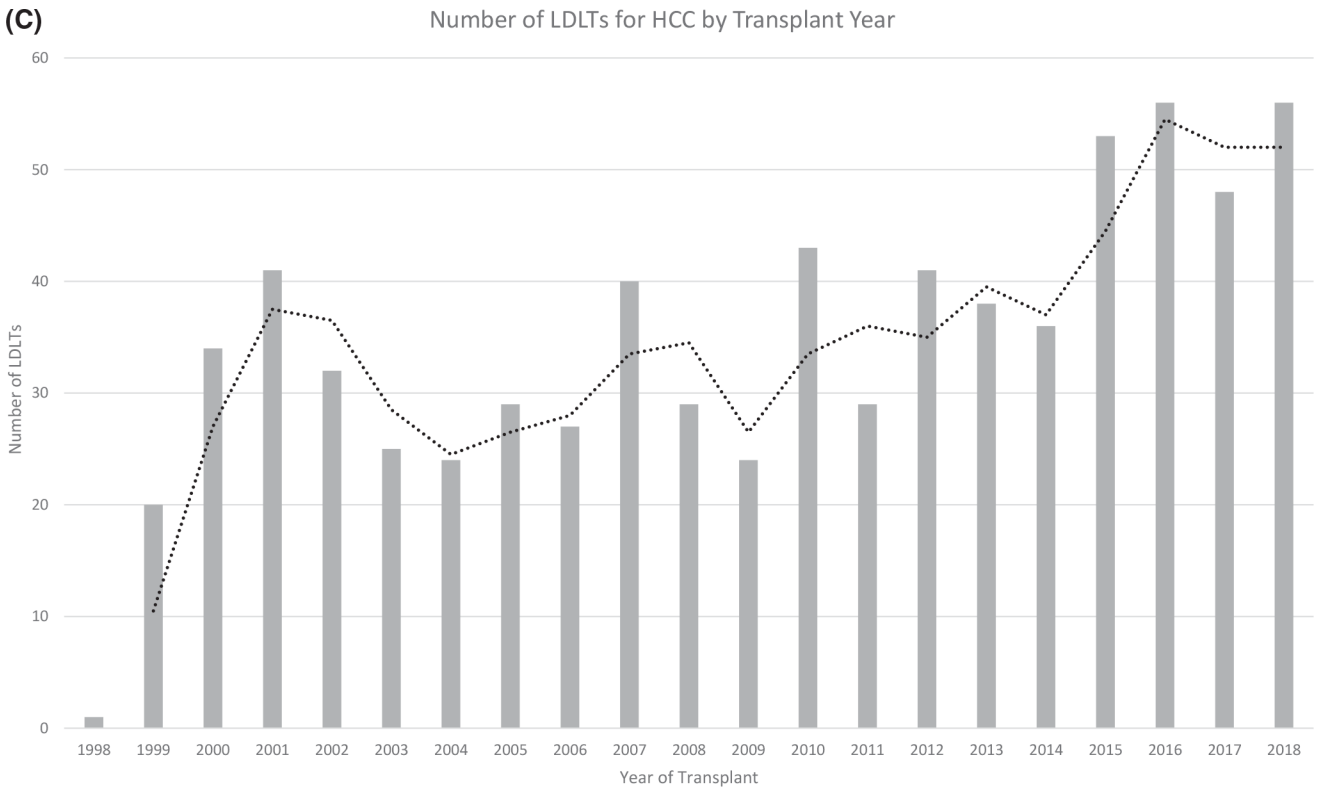



**FIGURE 2.**

(A) Percentage of LDLTs out of total LTs for patients with HCC at centers with at least 1 LDLT. (B) Percentage of LDLTs out of total LTs for patients with HCC at all transplantation centers. (C) Number of LDLTs per year with average trend line overlayed

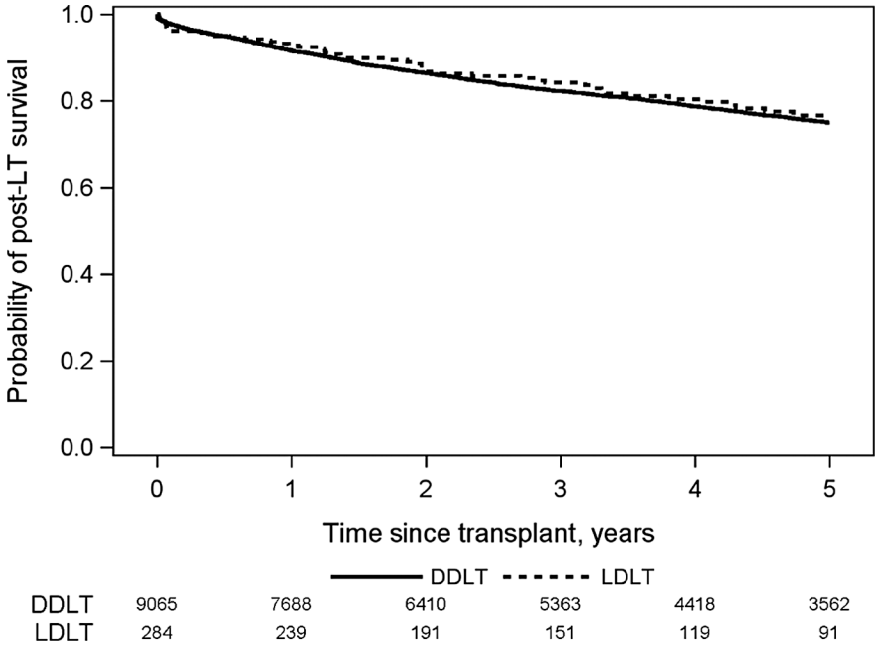



**FIGURE 3.**
Overall post-LT survival of patients with HCC by donor type, LDLT versus DDLT

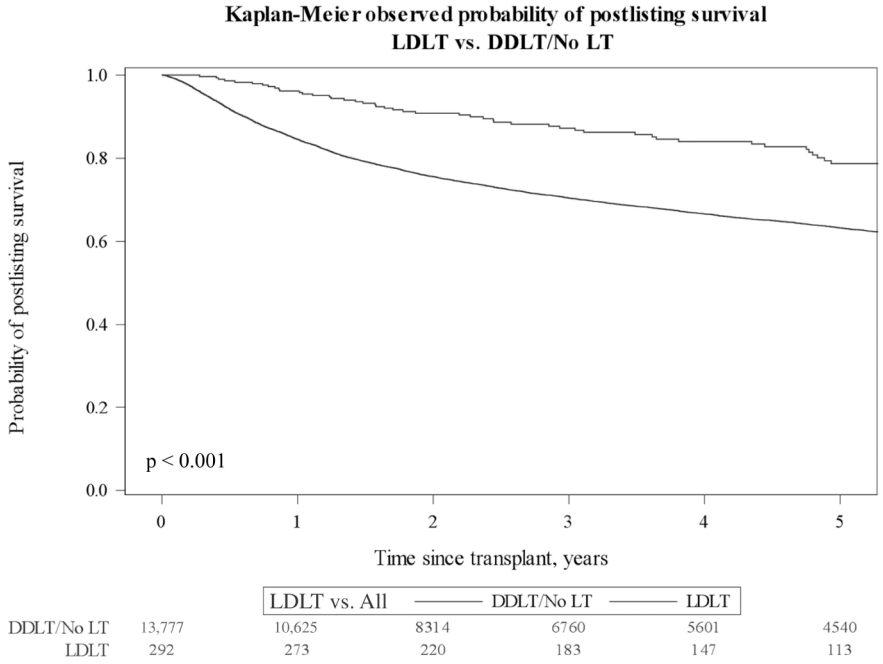



**FIGURE 4.**

Overall post-LT survival by era, 2005–2013 versus 2014–2017, and by donor type, LDLT versus DDLT

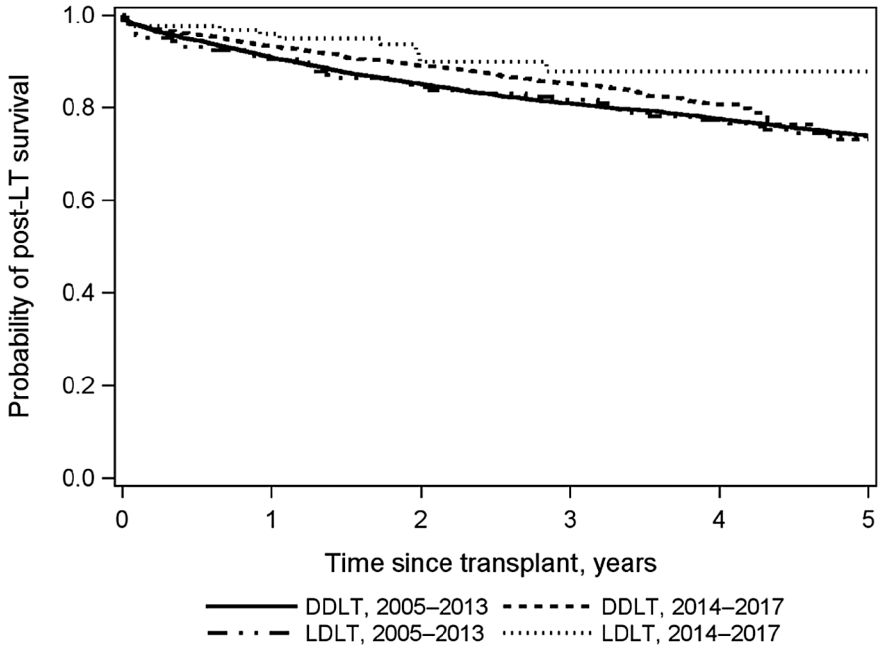



**FIGURE 5.**

Overall postlisting survival for LDLT patients versus patients listed for a DDLT that received a DDLT or did not receive a DDLT

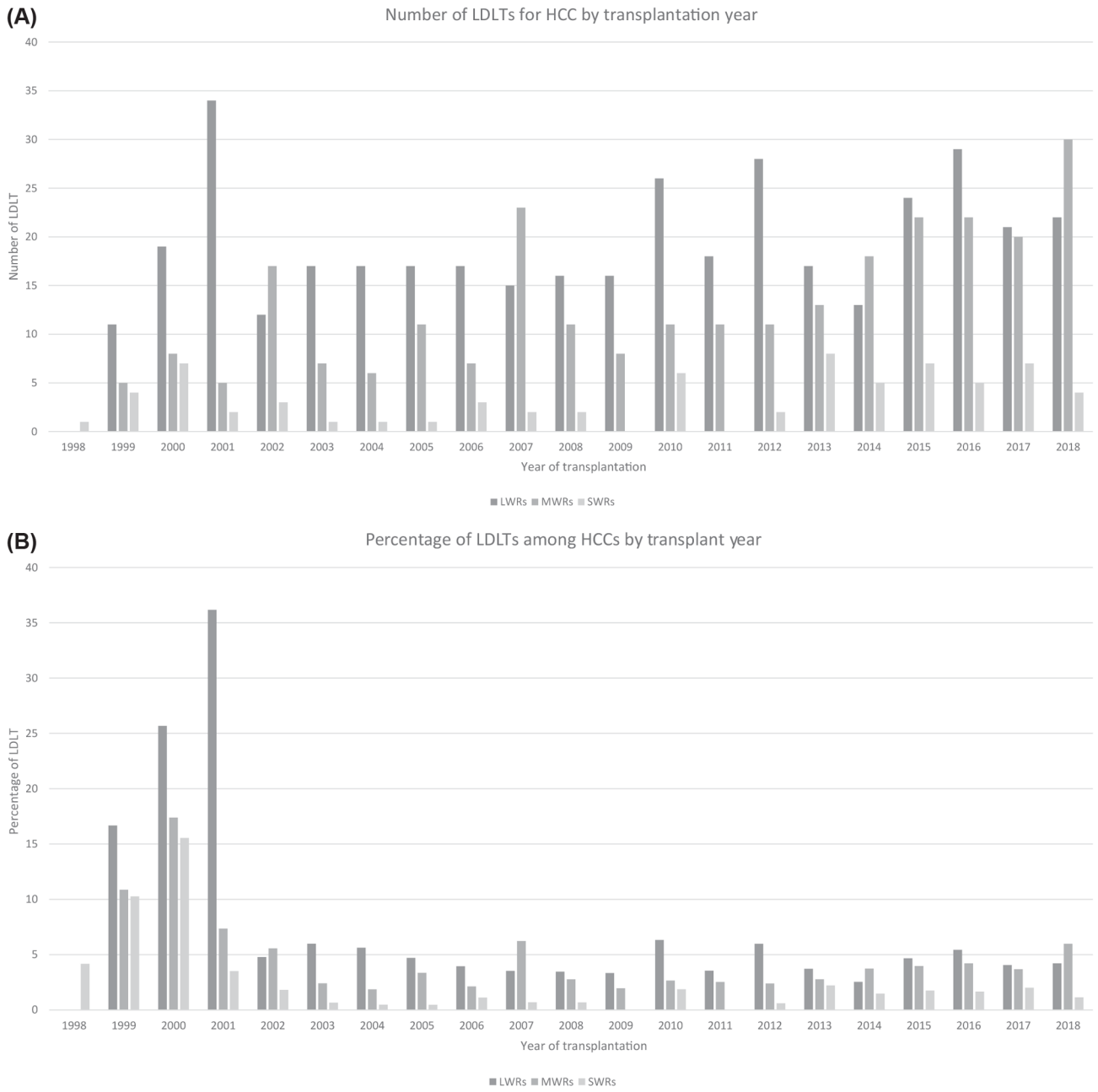



**FIGURE 6.**

(A) Number of LDLT for patients with HCC per year by wait time region. (B) Percentage of LDLT out of total LT for patients with HCC, at LDLT centers stratified by wait region

## TABLE 1

National trends by era

| LDLT national trends | Era 1: 1999–2001 | Era 2: 2002–2014 | Era 3: 2015–2018 |
|---|---|---|---|
| Transplantation centers performing LDLT, n | 48 | 55 | 53 |
| Total percentage of LDLT[a] | 17.7 | 3.0 | 3.8 |
| Average LDLT/year,[b] n | 31.7 | 32.1 | 53.3 |

Abbreviation: LDLT, living donor liver transplantation.

[a]Percentage of LDLT refers to the number of LDLTs out of the total number of LTs during that period.

[b]Total number of LDLT divided by number of years in the corresponding era.

**TABLE 2**

Baseline, waitlist, and donor characteristics of the study cohort stratified by donor type (DDLT vs. LDLT)

| Demographic/clinical characteristics | Overall (*n* = 9349) | DDLT (*n* = 9065) | LDLT (*n* = 284) | *p* value |
|---|---|---|---|---|
| Age at listing, years (IQR) | 61 (57–65) | 61 (57–65) | 61 (57–65) | 0.89 |
| Male | 7229 (77.3) | 7025 (77.5) | 204 (71.8) | 0.03 |
| Race/ethnicity | | | | |
| White | 5958 (63.7) | 5759 (63.5) | 199 (70.1) | 0.01 |
| Hispanic | 1447 (15.5) | 1400 (15.4) | 47 (16.5) | |
| African American | 1006 (10.8) | 991 (10.9) | 15 (5.3) | |
| Asian | 823 (8.8) | 803 (8.9) | 20 (7.0) | |
| Other | 115 (1.2) | 112 (1.2) | 3 (1.1) | |
| Etiology of liver disease | | | | |
| Hepatitis C | 5639 (60.3) | 5465 (60.3) | 174 (61.3) | 0.83 |
| Alcohol | 792 (8.5) | 774 (8.5) | 18 (6.3) | |
| NAFLD | 637 (6.8) | 615 (6.8) | 22 (7.7) | |
| Hepatitis B | 632 (6.8) | 614 (6.8) | 18 (6.3) | |
| Autoimmune[a] | 253 (2.7) | 245 (2.7) | 8 (2.8) | |
| Other | 1396 (14.9) | 1352 (14.9) | 44 (15.5) | |
| Recipient blood type | | | | |
| A | 3438 (36.8) | 3323 (36.7) | 115 (40.5) | 0.03 |
| AB | 401 (4.3) | 396 (4.4) | 5 (1.8) | |
| B | 1313 (14.0) | 1283 (14.2) | 30 (10.6) | |
| O | 4197 (44.9) | 4063 (44.8) | 134 (47.2) | |
| Listing tumor burden | | | | |
| 1 lesion ≤3 cm | 5388 (57.6) | 5234 (57.7) | 154 (54.2) | 0.66 |
| 1 lesion 3.1–5 cm | 1732 (18.5) | 1672 (18.4) | 60 (21.1) | |
| 2 lesions | 1507 (16.1) | 1460 (16.1) | 47 (16.5) | |
| 3 lesions | 413 (4.4) | 398 (4.4) | 15 (5.3) | |
| Initial AFP, ng/ml | 11.0 (5–37) | 11.0 (5–37) | 12.5 (5–38) | 0.24 |
| AFP at LT, ng/ml | | | | |
| Median | 9 (4–30) | 9 (4–29) | 12 (5–38) | 0.05 |

| Demographic/clinical characteristics | Overall ($n$ = 9349) | DDLT ($n$ = 9065) | LDLT ($n$ = 284) | $p$ value |
|---|---|---|---|---|
| AFP at LT <20 | 6362 (68.1) | 6187 (68.3) | 175 (61.6) | 0.05 |
| AFP at LT 20–99 | 1883 (20.1) | 1807 (19.9) | 76 (26.8) | |
| AFP at LT 100–999 | 970 (10.4) | 941 (10.4) | 29 (10.2) | |
| AFP at LT >1000 | 132 (1.4) | 128 (1.4) | 4 (1.4) | |
| MELD at LT | 12 (9–16) | 12 (9–16) | 12 (8–16) | 0.56 |
| Outside Milan at LT | 278 (3.0) | 271 (3.0) | 7 (2.5) | 0.61 |
| Child-Pugh at LT | | | | |
| A | 336 (35.7) | 3242 (35.8) | 94 (33.1) | 0.46 |
| B | 3990 (42.7) | 3869 (42.7) | 121 (42.6) | |
| C | 2017 (21.6) | 1948 (21.5) | 69 (24.3) | |
| Last total tumor diameter prior to LT, cm | 2.10 (0.00–3.30) | 2.10 (0.00–3.20) | 2.30 (0.00–3.70) | 0.02 |
| Tumor burden prior to LT | | | | |
| 0 lesions | 2144 (22.9) | 2080 (22.9) | 64 (22.5) | 0.01 |
| 1 lesion ≤3 cm | 4301 (46.0) | 4193 (46.3) | 108 (38.0) | |
| 1 lesion 3.1–5 cm | 1098 (11.7) | 1057 (11.7) | 41 (14.4) | |
| 2 lesions | 1168 (12.5) | 1123 (12.4) | 45 (15.8) | |
| 3 lesions | 360 (3.9) | 341 (3.8) | 19 (6.7) | |
| Beyond Milan | 278 (3.0) | 271 (3.0) | 7 (2.5) | |
| Received LRT | 7078 (75.7) | 6872 (75.8) | 206 (72.5) | 0.21 |
| Wait region | | | | |
| Short wait | 1700 (18.2) | 1669 (18.4) | 31 (10.9) | <0.001 |
| Medium wait | 3929 (42.0) | 3828 (42.2) | 101 (35.6) | |
| Long wait | 3720 (39.8) | 3568 (39.4) | 152 (53.5) | |
| Time from listing to LT, months | 7.07 (3.03–13.70) | 7.13 (3.03–13.83) | 5.30 (3.20–8.38) | <0.001 |
| Donor age, years | 44 (29–56) | 44 (29–56) | 35 (28–46) | <0.001 |
| Donor race/ethnicity | | | | |
| White | 6141 (65.7) | 5946 (65.6) | 195 (68.7) | <0.001 |
| Hispanic | 1584 (16.9) | 1568 (17.3) | 16 (5.6) | |
| African American | 1270 (13.6) | 1219 (13.4) | 51 (18.0) | |
| Asian | 263 (2.8) | 246 (2.7) | 17 (6.0) | |
| Other | 91 (1.0) | 86 (0.9) | 5 (1.8) | |

| Demographic/clinical characteristics | Overall (*n* = 9349) | DDLT (*n* = 9065) | LDLT (*n* = 284) | *p* value |
|---|---|---|---|---|
| Donor cause of death | | | N/A | N/A |
| Cardiovascular/stroke | 3365 (37.1) | 3365 (37.1) | | |
| Anoxia | 2837 (31.3) | 2837 (31.3) | | |
| Head trauma | 2620 (28.9) | 2620 (28.9) | | |
| CNS tumor | 49 (0.5) | 49 (0.5) | | |
| DCD donor | 754 (8.1) | 754 (8.3) | N/A | N/A |
| Share type | | | N/A | N/A |
| Local | 6953 (74.4) | 6669 (73.6) | | |
| Regional | 1841 (19.7) | 1841 (20.3) | | |
| National | 555 (5.9) | 555 (6.1) | | |

*Note:* Data are presented as median (IQR) or *n* (%). All missing data represents less than 1% of each variable.

Abbreviations: AFP, alpha-femiddlerotein; CNS, central nervous system; DCD, donation after circulatory death; DDLT, deceased donor liver transplantation; IQR, interquartile range; LDLT, living donor liver transplantation; LRT, local regional therapy; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; NAFLD, nonalcoholic fatty liver disease.

[a]Includes autoimmune hepatitis, primary biliary cholangitis, and primary sclerosing cholangitis.

## TABLE 3

Univariate and multivariable analyses of predictors of post-LT death using Cox proportional hazards regression among patients with HCC ($n$ = 7563)

| Predictor | HR (95% CI) | *p* value |
|---|---|---|
| *Univariate analysis* | | |
| Age at listing (per year) | 1.02 (1.01–1.03) | <0.001 |
| Etiology of liver disease (reference HCV) | | |
| NAFLD | 0.79 (0.65–0.97) | 0.02 |
| Alcohol | 0.97 (0.82–1.14) | 0.74 |
| Hepatitis B | 0.68 (0.55–0.84) | <0.001 |
| Autoimmune[a] | 0.89 (0.67–1.18) | 0.42 |
| Ethnicity recipient (reference White) | | |
| African American | 1.29 (1.13–1.48) | <0.001 |
| Asian | 0.68 (0.57–0.82) | <0.001 |
| Hispanic | 0.90 (0.79–1.02) | 0.11 |
| Received local-regional | 0.95 (0.86–1.05) | 0.29 |
| Therapy prior to transplantation | | |
| Last imaging prior to LT (reference 0 lesions) | | |
| 1 lesion ≤3 cm | 1.18 (1.04–1.34) | 0.01 |
| 1 lesion 3.1–5 cm | 1.50 (1.27–1.76) | <0.001 |
| 2 lesions | 1.33 (1.13–1.57) | <0.001 |
| 3 lesions | 1.66 (1.33–2.07) | <0.001 |
| Maximum total tumor diameter (per cm) | 1.08 (1.07–1.10) | <0.001 |
| Months from initial listing to LT | 0.99 (0.99–1.00) | 0.075 |
| Number of lesions + largest lesion diameter | 1.08 (1.07–1.11) | <0.001 |
| AFP at LT (reference <20 ng/ml) | | |
| 20–99 | 1.45 (1.30–1.62) | <0.001 |
| 100–999 | 1.84 (1.61–2.09) | <0.001 |
| >1000 | 3.21 (2.50–4.12) | <0.001 |
| CP Score (reference A) | | |
| B | 1.13 (1.02–1.25) | 0.02 |
| C | 1.17 (1.04–1.32) | 0.01 |
| Outside Milan ever | 1.72 (1.46–2.03) | <0.001 |
| Initial MELD score (per point) | 1.01 (1.00–1.02) | 0.04 |
| Donor factors | | |
| LDLT donor (reference DDLT) | 0.91 (0.69–1.21) | 0.53 |
| Donor age (per year) | 1.01 (1.01–1.01) | <0.001 |
| DCD donor (reference DBD) | 1.07 (0.90–1.26) | 0.45 |
| Cold ischemia time, h | 1.02 (1.00–1.04) | 0.02 |
| Donor cause of death (reference Cardiovascular/stroke) | | |
| Anoxia | 0.82 (0.73–0.91) | <0.001 |
| Head trauma | 0.82 (0.74–0.92) | 0.001 |

| Predictor | HR (95% CI) | *p* value |
|---|---|---|
| CNS tumor | 0.76 (0.40–1.47) | 0.42 |
| Share type (reference local) | | |
| Regional | 1.07 (0.96–1.20) | 0.23 |
| National | 1.27 (1.06–1.51) | 0.01 |
| *Multivariable analysis* | | |
| Age at listing (per year) | 1.02 (1.02–1.03) | <0.001 |
| Recipient Ethnicity (reference White) | | |
| African American | 1.17 (1.02–1.35) | 0.02 |
| Asian | 0.74 (0.60–0.92) | 0.01 |
| Hispanic | 0.89 (0.78–1.01) | 0.07 |
| Donor age (per year) | 1.01 (1.01–1.01) | <0.001 |
| LDLT donor (vs. DDLT) | 0.98 (0.74–1.30) | 0.88 |
| Etiology of liver disease (reference HCV) | | |
| NAFLD | 0.76 (0.62–0.94) | 0.01 |
| Alcohol | 0.94 (0.80–1.12) | 0.51 |
| Hepatitis B | 0.82 (0.64–1.03) | 0.09 |
| Autoimmune[a] | 0.82 (0.61–1.09) | 0.16 |
| Months for initial listing to LT | 1.00 (0.99–1.00) | 0.96 |
| Last tumor diameter (per cm) | 1.07 (1.05–1.11) | <0.001 |
| AFP at LT (reference <20 ng/ml) | | |
| 20–99 | 1.39 (1.24–1.55) | <0.001 |
| 100–999 | 1.75 (1.53–1.99) | <0.001 |
| >1000 | 3.15 (2.45–4.05) | <0.001 |
| MELD score (per point) | 1.01 (1.01–1.02) | 0.001 |
| Child-Pugh at LT (reference A) | | |
| B | 1.04 (0.93–1.16) | 0.54 |
| C | 0.96 (0.81–1.13) | 0.63 |
| Cold ischemia time | 1.03 (1.01–1.05) | 0.003 |

Abbreviations: AFP, alpha-femiddlerotein; CNS, central nervous system; CP, Child-Pugh; DBD, donation after brain death; DCD, donation after circulatory death; DDLT, deceased donor liver transplantation; HCV, hepatitis C virus; HR, hazard ratio; LDLT, living donor liver transplantation; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; NAFLD, nonalcoholic fatty liver disease.

[a]Includes autoimmune hepatitis, primary biliary cholangitis, and primary sclerosing cholangitis.