

Evaluation of the Intention-to-Treat Benefit of Living Donation in Patients With Hepatocellular Carcinoma Awaiting a Liver Transplant

Quirino Lai, MD, PhD; Gonzalo Sapisochin, MD, PhD; Andre Gorgen, MD; Alessandro Vitale, MD, PhD; Karim J. Halazun, MD, PhD; Samuele Iesari, MD; Benedikt Schaefer, MD; Prashant Bhangui, MD; Gianluca Mennini, MD, PhD; Tiffany C.L. Wong, MD; Shinji Uemoto, MD, PhD; Chih-Che Lin, MD, PhD; Jens Mittler, MD; Toru Ikegami, MD; Zhe Yang, MD; Anna Chiara Frigo, PhD; Shu-Sen Zheng, MD, PhD; Yuji Soejima, MD, PhD; Maria Hoppe-Lotichius, MD; Chao-Long Chen, MD, PhD; Toshimi Kaido, MD, PhD; Chung Mau Lo, MD; Massimo Rossi, MD; Arvinder Singh Soin, MD; Armin Finkenstedt, MD; Jean C. Emond, MD; Umberto Cillo, MD; Jan Paul Lerut, MD, PhD

IMPORTANCE Living-donor liver transplant (LDLT) offers advantages over deceased-donor liver transplant (DDLT) of improved intention-to-treat outcomes and management of the shortage of deceased-donor allografts. However, conflicting data still exist on the outcomes of LDLT in patients with hepatocellular carcinoma (HCC).

OBJECTIVE To investigate the potential survival benefit of an LDLT in patients with HCC from the time of waiting list inscription.

DESIGN, SETTING, AND PARTICIPANTS This multicenter cohort study with an intention-to-treat design analyzed the data of patients aged 18 years or older who had an HCC diagnosis and were on a waiting list for a first transplant. Patients from 12 collaborative centers in Europe, Asia, and the US who were on a transplant waiting list between January 1, 2000, and December 31, 2017, composed the international cohort. The Toronto cohort comprised patients from 1 transplant center in Toronto, Ontario, Canada who were on a waiting list between January 1, 2000, and December 31, 2015. The international cohort centers performed either an LDLT or a DDLT, whereas the Toronto cohort center was selected for its capability to perform both LDLT and DDLT. The benefit of LDLT was tested in the 2 cohorts before and after undergoing an inverse probability of treatment weighting (IPTW) analysis. Data were analyzed from February 1 to May 31, 2020.

MAIN OUTCOMES AND MEASURES Intention-to-treat death was defined as a patient death that occurred for any reason and was calculated from the time of waiting list inscription for liver transplant to the last follow-up date (December 31, 2019). Four multivariable Cox proportional hazards regression models for intention-to-treat death were created.

RESULTS A total of 3052 patients were analyzed in the international cohort, of whom 2447 were men (80.2%) and the median (IQR) age at first referral was 58 (53-63) years. The Toronto cohort comprised 906 patients, of whom 743 were men (82.0%) and the median (IQR) age at first referral was 59 (53-63) years. In all the settings, LDLT was an independent protective factor, reducing the risk of overall death by 49% in the pre-IPTW analysis for the international cohort (HR, 0.51; 95% CI, 0.36-0.71; $P < .001$), 33% in the post-IPTW analysis for the international cohort (HR, 0.67; 95% CI, 0.53-0.85; $P = .001$), 43% in the pre-IPTW analysis for the Toronto cohort (HR, 0.57; 95% CI, 0.45-0.73; $P < .001$), and 48% in the post-IPTW analysis for the Toronto cohort (HR, 0.52; 95% CI, 0.42 to 0.65; $P < .001$). The discriminatory ability of the mathematical models further improved in all of the cases in which LDLT was incorporated.

CONCLUSIONS AND RELEVANCE This study suggests that having a potential live donor could decrease the intention-to-treat risk of death in patients with HCC who are on a waiting list for a liver transplant. This benefit is associated with the elimination of the dropout risk and has been reported in centers in which both LDLT and DDLT options are equally available.

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 [Invited Commentary](#)

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Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Quirino Lai, MD, PhD, General Surgery and Organ Transplantation Unit, Department of General 3 Surgery and Organ Transplantation, Sapienza University of Rome, Viale del Policlinico 155, 00161 Rome, Italy (lai.quirino@libero.it).

Living-donor liver transplant (LDLT) offers advantages over deceased-donor liver transplant (DDLT) of improving intention-to-treat outcomes and managing the shortage of deceased-donor allografts.^{1,2} Nevertheless, the debate continues regarding the oncological benefit of an LDLT compared with a DDLT in patients with hepatocellular carcinoma (HCC).

Initial experiences have revealed higher recurrence rates in patients who underwent an LDLT compared with those who underwent a DDLT.³⁻⁶ Several reasons for these differences have been put forward. First, the fast-track approach should limit a suitable evaluation of the biological qualities of the tumor. Second, the parenchymal regeneration of the partial graft should favor tumor growth and spread. Third, the residual tumor should be present because of inferior vena cava preservation.⁷⁻⁹

However, later case series from Eastern and Western experiences have shown similar, or even better, results after an LDLT.¹⁰⁻¹³ Given these findings, one could hypothesize that patients with HCC who are on a waiting list are likely to obtain an intention-to-treat benefit from an LDLT.

This cohort study aimed to investigate the potential survival benefit of an LDLT in patients with HCC from the time of waiting list inscription. The benefit of live donation was tested in an international cohort; in a single-center cohort in Toronto, Canada; and in the same 2 populations after an inverse probability of treatment weighting (IPTW) analysis.

Methods

The present study was approved by the local ethics board of Sapienza University of Rome, Italy. Informed consent for the management of personal data was obtained for all patients at the time of the transplant; however, no consent was obtained for this study because of its retrospective nature. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Study Design, Setting, and Population

In this multicenter, retrospective cohort study with an intention-to-treat design, we investigated the data of adult patients (aged ≥ 18 years) with an HCC diagnosis who were on a waiting list for a first transplant. The potential survival benefit of an LDLT, calculated from the time of waiting list inscription, was explored in 4 different settings: (1) an international cohort representing 12 collaborative transplant centers in Europe, Asia, and the US; (2) the same international cohort but recalibrated after an IPTW analysis; (3) a Toronto cohort representing 1 transplant center; and (4) the same Toronto cohort but recalibrated after an IPTW analysis.

All participating centers in both cohorts were involved in the transplantation and transplant oncology fields and were part of The West-East Collaborative Liver Transplant Study Group. Specifically, the 12 centers that made up the international cohort were located in Europe (Université Catholique de Louvain, Brussels, Belgium; Sapienza University of Rome, Rome, Italy; University of Padua, Padua, Italy; University of

Key Points

Question Can the intention-to-treat survival benefit of a potential live donor be evaluated in a patient with hepatocellular carcinoma (HCC) who is on the waiting list for a liver transplant?

Findings In this cohort study of nearly 4000 patients with HCC who were on a waiting list at transplant centers in Europe, Asia, the US, and Canada, living-donor liver transplant (LDLT) was an independent protective factor, reducing the risk of intention-to-treat death in 4 different settings. When LDLT was incorporated in the mathematical models, their discriminatory ability further improved.

Meaning Findings from this study suggest that LDLT could potentially decrease the risk of death, by 33% to 49%, for patients with HCC awaiting a liver transplant.

Innsbruck, Innsbruck, Austria; and Universitätsmedizin Mainz, Mainz, Germany), Asia (Medanta-The Medicity, Delhi, India; University of Hong Kong, Hong Kong, China; Kyoto University, Kyoto, Japan; Chang Gung Memorial Hospital, Kaohsiung City, Taiwan; Kyushu University, Fukuoka, Japan; and Shulan Health Zhejiang University Hospital, Hangzhou, China), or the US (Columbia University, New York, New York). These 12 centers were dedicated to performing either an LDLT or a DDLT (eFigure in the Supplement).

The 1 center in the Toronto cohort was the University of Toronto in Toronto, Ontario, Canada. This center was selected as a separate cohort because of its capability to perform both complementary LDLT and DDLT. The international cohort was composed of 3052 patients with HCC who were on a waiting list for a first transplant between January 1, 2000, and December 31, 2017. The Toronto cohort included patients with HCC who were on a waiting list for a first transplant between January 1, 2000, and December 31, 2015. Excluded patients were those undergoing a retransplant and those with a graft treated with machine perfusion, with a donor after cardiac death, with mixed hepatocellular-cholangiocellular cancer, and with cholangiocellular cancer misdiagnosed as HCC.

Outcomes, Data Collection, and Definitions

The main outcome of the study was patient death that occurred for any reason from the time of waiting list inscription to the last follow-up. The last follow-up date was December 31, 2019.

Data were retrospectively retrieved from databases that are prospectively maintained by the transplant centers composing The West-East Collaborative Liver Transplant Study Group. One of us served as the guarantor of the data quality (Q.L., the data manager of the study group). Data errors and missingness across the databases were identified and solved, when possible, with specific queries to the centers. The missing data present in the evaluated databases are reported in eTable 1 in the Supplement.

All patients with a potential live donor during the waiting list period were included in the LDLT group. A potential live donor was defined as an individual who was suitable for donation after the screening phase and was enrolled for an

imaging assessment.¹³ To preserve the intention-to-treat design of the study, we considered including in the LDLT group those patients with a suitable live donor and who eventually had a DDLT. In the LDLT category, we included (1) patients with a deceased donor available before the scheduled live donation date and (2) expected insufficient liver volume after the imaging assessment. In the DDLT category, we included patients with potential live donors who were considered unsuitable for donation before an imaging assessment.

The tumor upper limit for waiting list inscription differed among the participating centers. From 2000 onward, the initially applied restrictive Milan criteria were progressively abandoned. Overall, a more conservative approach was reported in DDLT, for which the University of California San Francisco and the Up-to-Seven restriction criteria were primarily used for listing and staying on the list. Often, in LDLT, no morphological limitations were adopted, except for the presence of major vascular invasion and extrahepatic disease localization (eTable 2 in the [Supplement](#)). In accordance with previous studies, we defined a high-volume center as one with a cutoff of 70 liver transplants per year.¹⁴

Statistical Analysis

Continuous variables were reported as medians (interquartile ranges [IQRs]), and categorical variables were described as numbers (percentages). Comparisons between groups were made using the Fisher exact test or χ^2 test for categorical variables, as appropriate. The Mann-Whitney test was used for continuous variables. Missing data on study covariates (eTable 1 in the [Supplement](#)) always involved less than 10% of patients. In all cases, missing data were handled with a single imputation method. Specifically, a median of nearby points imputation was adopted. The median, instead of the mean, was adopted because of the skewed distribution of the managed variables.¹⁵

To compensate for the nonrandomized design of this study, we balanced (or corrected for potential confounders) the populations of the international cohort and Toronto cohort using the IPTW analysis. To compare the LDLT group with the DDLT group, we expressed continuous data as means (SDs) and based categorical data on the frequency distribution. The IPTW values were calculated using generalized boosted models as described by McCaffrey et al.¹⁶ This method is a machine learning technique that uses flexible estimation to adjust for a large number of covariates. Thirteen potential confounders were included in the boosted models: center case volume greater than 70 liver transplants per year, transplant year (before 2010), age, male sex, hepatitis C virus positive test result, hepatitis B virus positive test result, alcohol-related cirrhosis, waiting time duration, model for end-stage liver disease (MELD) score, diameter of the major lesion, number of HCC lesions, $\log_{10}$ α -fetoprotein level, and type of locoregional therapy.

To reduce the artificial increase of the sample size, and therefore the type I error rate (ie, increased number of false-positives) associated with the inflated sample size in the pseudo data, we used stabilized weights (SW) according to the following formula:

$$SW = p/PS \text{ for the Study Group, and } SW = (1 - p)/(1 - PS) \text{ for the Control Group,}$$

where p is the probability of cause without considering covariates, and PS is the propensity score.

Because P values can be biased from population size, results from the comparisons between covariate subgroups were reported as effect size (Cohen d value). The Cohen d values that were lower than 0.1 indicated very small differences between means, values between 0.1 and 0.3 indicated small differences, values between 0.3 and 0.5 indicated moderate differences, and values greater than 0.5 indicated large differences.¹⁷

Multivariable Cox proportional hazards regression models were run for the international cohort and Toronto cohort before and after the IPTW analysis to identify the risk factors for death evaluated from waiting list inscription. According to previous research on the same argument,¹³ the investigated variables were selected using a full model approach. In the pre-IPTW and post-IPTW analyses for the international cohorts, given the risk of data separation within the 12 liver transplant centers, a Cox proportional hazards regression model with mixed effects was created, in which the center was incorporated in the model as a cluster-specific random-effect variable.¹⁸ Hazard ratios (HRs) and 95% CIs were reported for significant variables.

The Akaike information criteria (AIC) value was calculated for the different regression models. The lowest AIC value was associated with the best discriminatory ability for the given model.¹⁹ Survival analyses were performed using the Kaplan-Meier method, and the log-rank test was adopted to compare the obtained survivals.

Variables with a 2-sided $P < .05$ were considered to be statistically significant. Statistical analyses were performed with SPSS, version 24.0 (IBM); Stata, version 14.0 (StataCorp LLC); and R.app 4.0.0 GUI 1.71 (R Foundation for Statistical Computing). Data were analyzed from February 1 to May 31, 2020.

Results

International Cohort Characteristics

Patient- and tumor-related characteristics of the international cohort population are summarized in [Table 1](#). The median (IQR) follow-up for the entire series was 3.3 (1.5-6.6) years.

Among the 3052 patients in the international cohort, 1011 (33.1%) had a potential LDLT and 2041 (66.9%) had a potential DDLT. The median (IQR) age at first referral was 58 (53-63) years, and the group was composed of 2447 men (80.2%) and 605 women (19.8%). Exclusive DDLT or LDLT activity was reported in 4 centers, and mixed activity was observed in 4 other centers. However, the DDLT activity was prominent (>90%) in 3 centers, whereas the Hong Kong center was the only 1 with a real mixed LDLT and DDLT activity (54.5% vs 45.5%) (eFigure in the [Supplement](#)).

Several differences existed between the LDLT and DDLT groups, such as transplant candidate features, underlying liver pathology, tumor characteristics, and management during the waiting period. At first referral, patients in both the DDLT and

Table 1. Characteristics of Patients in the International and Toronto Cohorts

Variable	No. (%)					
	International cohort			Toronto cohort		
	Total	DDLT	LDLT	Total	DDLT	LDLT
No. (%)	3052 (100.0)	2041 (66.9)	1011 (33.1)	906 (100.0)	661 (73.0)	245 (27.0)
Center volume >70 LT cases/y	2227 (73.0)	1587 (77.8)	640 (63.3)	NA	NA	NA
LT performed before 2010	1458 (47.8)	1102 (54.0)	356 (35.2)	487 (53.8)	366 (55.4)	121 (49.4)
Age at first referral, median (IQR), y	58 (53-63)	59 (54-63)	57 (52-62)	59 (53-63)	59 (53-63)	59 (54-63)
Male sex	2447 (80.2)	1707 (83.6)	740 (73.2)	743 (82.0)	544 (82.3)	199 (81.2)
Female sex	605 (19.8)	334 (16.4)	271 (26.8)	163 (18.0)	117 (17.7)	46 (18.8)
Underlying liver disease						
HCV	1383 (45.3)	889 (43.6)	494 (48.9)	471 (52.0)	335 (50.7)	136 (55.5)
HBV	880 (28.8)	493 (24.2)	387 (38.3)	194 (21.4)	169 (25.6)	25 (10.2)
Alcohol-related cirrhosis	630 (20.6)	539 (26.4)	91 (9.0)	121 (13.4)	85 (12.9)	36 (14.7)
NASH	204 (6.7)	140 (6.9)	64 (6.3)	78 (8.6)	49 (7.4)	29 (11.8)
Other	156 (5.1)	129 (6.3)	27 (2.7)	45 (5.0)	26 (3.9)	19 (7.8)
Waiting time duration, median (IQR), mo	4 (1-10)	6 (3-13)	1 (0-2)	6 (3-11)	6 (3-12)	5 (3-8)
MELD score at first referral, median (IQR)	12 (9-16)	12 (9-16)	12 (9-15)	10 (8-14)	10 (8-14)	11 (8-14)
Tumor characteristics at first referral						
Diameter of the major lesion, median (IQR), cm	2.5 (1.8-3.7)	2.5 (1.8-3.8)	2.5 (1.7-3.6)	2.7 (1.9-3.9)	2.7 (1.9-3.7)	2.9 (1.7-4.4)
No. of lesions, median (IQR)	2 (1-3)	1 (1-3)	2 (1-3)	1 (1-2)	1 (1-2)	1 (1-2)
Outside of MC	959 (31.4)	601 (29.4)	358 (35.4)	267 (29.5)	185 (28.9)	82 (33.5)
Tumor characteristics at LT or dropout						
Diameter of the major lesion, median (IQR), cm	2.2 (1.4-3.3)	2.1 (1.2-3.0)	2.5 (1.7-3.5)	2.0 (0.0-3.6)	2.0 (0.0-3.5)	2.2 (0.0-3.9)
No. of lesions, median (IQR)	2 (1-3)	2 (1-3)	2 (1-3)	1 (0-3)	1 (0-3)	1 (0-2)
Outside of MC	912 (29.9)	553 (27.1)	359 (35.5)	269 (29.7)	201 (30.4)	68 (27.8)
AFP level, median (IQR), ng/mL						
At first referral	14 (5-60)	11 (5-43)	22 (7-114)	11 (5-42)	12 (5-43)	10 (5-41)
At LT or dropout	11 (4-56)	10 (4-47)	14 (4-77)	11 (5-62)	12 (5-62)	10 (5-60)
LRT	2369 (77.6)	1819 (89.1)	550 (54.4)	623 (68.8)	474 (71.7)	149 (60.8)
Type of LRT						
TACE	1857 (60.8)	1451 (71.1)	406 (40.2)	146 (16.1)	104 (15.7)	42 (17.1)
PEI	486 (15.9)	402 (19.7)	84 (8.3)	22 (2.4)	18 (2.7)	4 (1.6)
RFA	743 (24.3)	506 (24.8)	237 (23.4)	423 (46.7)	329 (49.8)	94 (38.4)
Hepatic resection	266 (8.7)	218 (10.7)	48 (4.7)	14 (1.5)	14 (2.1)	0
Other	251 (8.2)	229 (11.2)	22 (2.2)	25 (2.8)	14 (2.1)	11 (4.5)
Dropout	295 (7.8)	295 (14.5)	0	247 (27.3)	213 (32.2)	34 (13.9)
Death during waiting time	159 (5.2)	159 (7.8)	0	70 (7.7)	59 (8.9)	11 (4.5)
Tumor progression	80 (2.6)	80 (3.9)	0	129 (14.3)	109 (16.5)	20 (8.2)
Posttransplant recurrence	360 (11.8)	223 (12.9)	137 (13.6)	116 (17.6)	88 (19.7)	28 (13.3)

Abbreviations: AFP, α -fetoprotein; DDLT, deceased-donor liver transplant; HBV, hepatitis B virus; HCV, hepatitis C virus; IQR, interquartile range; LDLT, living-donor liver transplant; LRT, locoregional therapy; LT, liver transplant; MC, Milan criteria; MELD, model for end-stage liver disease;

NA, not applicable; NASH, nonalcoholic steatohepatitis; PEI, percutaneous ethanol injection; RFA, radiofrequency ablation; TACE, transarterial chemoembolization.

LDLT groups were outside of the Milan criteria (601 [29.4%] vs 358 [35.4%]; $P < .001$). As expected, the median (IQR) waiting time was shorter in the LDLT vs DDLT group (1 [0-2] vs 6 [3-13] months; $P < .001$).

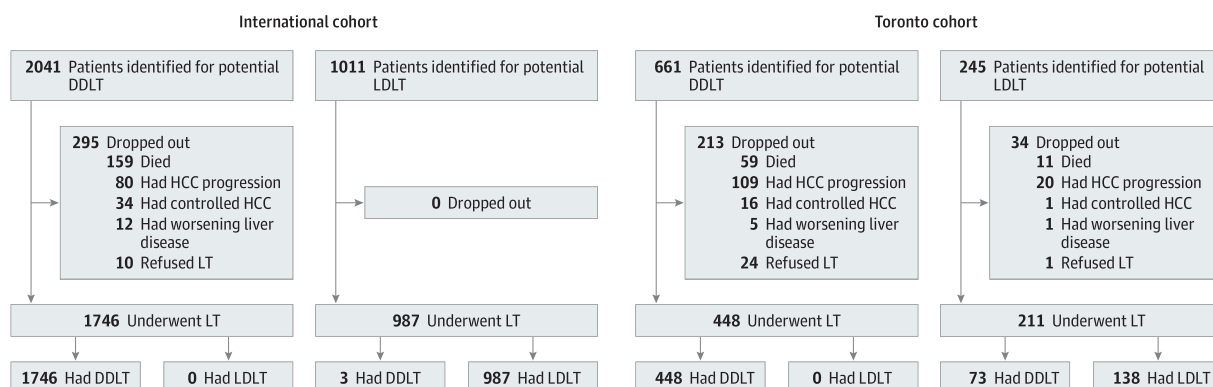
The number of dropouts was markedly superior in the DDLT group vs the LDLT group (295 vs 0 patients; $P < .001$). Figure 1 displays the reasons for the dropouts. A total of 295 patients (14.5%) dropped out from the DDLT group as a result of death while waiting for a transplant (159 [53.9%]), tumor progression (80 [27.1%]), or other factors (56 [19.0%]). Interestingly, no patients dropped out because of tumor progression or death

while on the waiting list in the LDLT group. Twenty-seven candidates for LDLT (2.7%) moved to the DDLT waiting list because of the availability of a deceased donor (3 [0.3%]) or the impossibility of receiving a live donation because of insufficient liver volume (24 [2.4%]).

Toronto Cohort Characteristics

Patient- and tumor-related characteristics of the Toronto cohort population are summarized in Table 1. The median (IQR) follow-up for the entire series was 3.2 (1.4-7.5) years.

Figure 1. Flowchart of Patients in the International and Toronto Cohorts



DDLT indicates deceased-donor liver transplant; HCC, hepatocellular carcinoma; LDLT, living-donor liver transplant; LT, liver transplant.

Among the 906 patients considered in the Toronto cohort, 245 (27.0%) had a potential LDLT and 661 (73.0%) had a potential DDLT. The median (IQR) age at first referral was 59 (53-63) years, and the group was composed of 743 men (82.0%) and 163 women (18.0%). Several differences existed between the 2 groups. The median (IQR) waiting time was shorter in the LDLT than in the DDLT group (5 [3-8] vs 6 [3-12] months; $P = .006$). The percentage of dropouts was superior in the DDLT group vs the LDLT group (32.2% vs 13.9%; $P < .001$). In Figure 1, the reasons for the dropouts are detailed.

In the DDLT group of the Toronto cohort, 213 patients (32.2%) dropped out as a result of death while waiting for a transplant (59 [27.7%]), tumor progression (109 [51.2%]), or other factors (45 [21.1%]). In the LDLT group, 34 patients (13.9%) dropped out as a result of tumor progression (20 [58.8%]), death while waiting for a transplant (11 [32.4%]), or other factors (3 [8.8%]). Seventy-three LDLT candidates (8.1%) moved to the DDLT program because of the availability of a deceased donor before the scheduled date of LDLT.

IPTW Analysis

To minimize the selection biases caused by the nonrandomized design of this cohort study, the international and Toronto cohorts were artificially balanced using the IPTW method. As reported in Table 2, both of the cohorts were balanced. Specifically, all the variables tested in the post-IPTW analysis of the international cohort showed only small differences, with 7 variables showing very small differences. In the post-IPTW analysis of the Toronto cohort, all the variables except for 1 showed very small differences.

LDLT and Multivariable Models

Four multivariable Cox proportional hazards regression models for the risk of intention-to-treat death were constructed using the pre-IPTW and post-IPTW analyses for the international cohort and the Toronto cohort (Table 3). In the pre-IPTW international cohort, a live donor availability was a protective factor for intention-to-treat death (HR, 0.51; 95% CI, 0.36-0.71; $P < .001$). Similar results were reported after the

IPTW analysis, with the confirmed protective factor of LDLT (HR, 0.67; 95% CI, 0.53-0.85; $P = .001$). When the Toronto cohort data were analyzed, the protective factor of live donor availability was confirmed again (pre-IPTW: HR, 0.57; [95% CI, 0.45-0.73; $P < .001$]; post-IPTW: HR, 0.52 [95% CI, 0.42 to 0.65; $P < .001$]).

According to the HRs observed in all 4 models, a living donation was associated with a 33% to 49% reduction of the intention-to-treat death risk. When the AIC value was calculated for each model, the introduction of the variable live donation always decreased the AIC value in the pre-IPTW analysis (13 204.6 without LDLT to 13 124.8 with LDLT) and post-IPTW analysis (13 262.7 without LDLT to 13 202.7 with LDLT) for the international cohort as well as the pre-IPTW (5579.5 without LDLT to 5490.3 with LDLT) and post-IPTW analyses (6299.2 without LDLT to 6259.9 with LDLT) for the Toronto cohort. These AIC values show an increase in the discriminative ability of the models.

Intention-to-Treat Survival Rates

During the follow-up period, 938 of 3052 patients (30.7%) in the international cohort and 447 of 906 patients (49.3%) in the Toronto cohort died. Specifically, 246 patients in the international cohort died during the waiting period or after dropout (184 HCC-related vs 62 nontumor-related deaths), and 692 died after transplant (242 HCC-related vs 450 nontumor-related deaths). In the Toronto cohort, 241 patients died during the waiting period or after dropout (129 HCC-related vs 112 nontumor-related deaths), and 206 died after transplant (96 HCC-related vs 110 nontumor-related deaths).

In the pre-IPTW analysis for the international cohort, the 5-year intention-to-treat survival rate was 79% and the 10-year rate was 65% for the LDLT group ($P < .001$), whereas the 5-year rate was 70% and the 10-year rate was 52% for the DDLT group ($P < .001$) (Figure 2). When the survival rates were recalculated in the post-IPTW population, only limited changes were observed. In the post-IPTW international cohort population, the 5-year intention-to-treat survival rate was 79% and the 10-year rate was 64% for the LDLT group ($P < .001$), whereas

Table 2. Association of Inverse Probability of Treatment Weighting (IPTW) With the Variables Used for Balancing the International and Toronto Cohorts

Variable	Pre-IPTW, No. (%)			Post-IPTW, No. (%)		
	DDLT	LDLT	Cohen <i>d</i> ^a	DDLT	LDLT	Cohen <i>d</i> ^a
International cohort						
No. of patients	2041	1011	NA	1748	741	NA
Center volume >70 LT/y	1587 (77.8)	640 (63.3)	-0.33	1329 (76.0)	543 (73.3)	-0.06
LT before 2010	1102 (54.0)	356 (35.2)	-0.38	877 (50.2)	344 (46.4)	-0.08
Age, mean (SD), y ^b	58 (8)	56 (8)	-0.25	57 (8)	57 (7)	-0.07
Male sex	1707 (83.6)	740 (73.2)	-0.26	1458 (83.4)	576 (77.7)	-0.15
Female sex	334 (16.4)	271 (26.8)	-0.26	290 (16.6)	165 (22.3)	-0.15
HCV	889 (43.6)	494 (48.9)	-0.11	760 (43.5)	400 (54.0)	0.21
HBV	493 (24.2)	387 (38.3)	0.31	475 (27.2)	223 (30.1)	0.07
Alcohol-related cirrhosis	539 (26.4)	91 (9.0)	-0.43	406 (23.2)	111 (15.0)	-0.21
Waiting time duration, mean (SD), mo	13 (23)	2 (5)	-0.53	11 (21)	6 (10)	-0.26
MELD score, mean (SD) ^b	13 (7)	13 (5)	-0.10	13 (6)	13 (5)	-0.03
Diameter of major lesion, mean (SD), cm ^b	3.1 (2.1)	3.1 (2.3)	0.01	3.0 (2.0)	2.9 (2.1)	-0.04
No. of lesions, mean (SD) ^b	2 (5)	3 (7)	0.09	2 (5)	2 (5)	0.00
AFP level, mean (SD), ng/mL ^b	354 (4850)	828 (7445)	0.39	384 (5267)	474 (5463)	0.20
LRT	1819 (89.1)	550 (54.4)	-0.83	1477 (84.5)	541 (72.9)	-0.27
Toronto cohort						
No. of patients	661	245	NA	690	317	NA
Center volume >70 LT/y	NA	NA	NA	NA	NA	NA
LT before 2010	366 (55.4)	121 (49.4)	-0.12	361 (52.3)	179 (56.3)	-0.03
Age, mean (SD), y ^b	58 (8)	58 (8)	-0.25	58 (8)	57 (8)	0.02
Male sex	544 (82.3)	199 (81.2)	-0.03	567 (82.2)	261 (82.3)	-0.01
Female sex	117 (17.7)	46 (18.8)	-0.03	123 (17.8)	56 (17.7)	-0.01
HCV	335 (50.7)	136 (55.5)	0.10	348 (50.4)	175 (55.0)	0.07
HBV	169 (25.6)	25 (10.2)	-0.37	177 (25.7)	29 (9.1)	-0.21
Alcohol-related cirrhosis	85 (12.9)	36 (14.7)	0.05	91 (13.2)	51 (16.1)	-0.01
Waiting time duration, mean (SD), mo	8 (7)	7 (6)	-0.53	8 (7)	7 (7)	-0.01
MELD score, mean (SD) ^b	11 (5)	12 (5)	-0.10	11 (5)	12 (5)	0.04
Diameter major lesion, mean (SD), cm ^b	3.0 (1.8)	3.5 (2.6)	0.01	3.0 (1.8)	3.6 (2.7)	0.06
No. of lesions, mean (SD) ^b	2 (1)	2 (2)	0.09	2 (1)	2 (2)	-0.01
AFP level, mean (SD), ng/mL ^b	386 (6097)	222 (940)	0.39	385 (6137)	232 (1002)	-0.05
LRT	474 (71.7)	149 (60.8)	-0.24	502 (72.6)	184 (57.9)	-0.10

Abbreviations: AFP, α-fetoprotein; HCV, hepatitis C virus; HBV, hepatitis B virus; LRT, locoregional therapy; LT, liver transplant; MELD, model for end-stage liver disease; NA, not applicable.

^a Cohen *d* values that were lower than 0.1 indicated very small differences

between means; between [0.1] and [0.3], small differences; between 0.3 and 0.5, moderate differences; and greater than 0.5, large differences.

^b At first referral.

the 5-year rate was 72% and the 10-year rate was 49% for the DDLT group ($P < .001$).

In the pre-IPTW analysis for the Toronto cohort, the 5-year intention-to-treat survival rate was 62% and the 10-year rate was 54% for the LDLT group ($P = .04$), whereas the 5-year rate was 55% and the 10-year rate was 42% for the DDLT group ($P = .04$) (Figure 2). In the post-IPTW population, the 5-year intention-to-treat survival rate was 66% and the 10-year rate was 52% for the LDLT group ($P < .001$), whereas the 5-year rate was 57% and the 10-year rate was 41% for the DDLT group ($P < .001$).

When only the 959 patients initially outside of the Milan criteria were considered in the international cohort, the 5-year intention-to-treat survival rate was 71% and the 10-year rate

was 62% for the LDLT group ($P < .001$), whereas the 5-year rate was 65% and the 10-year rate was 49% in the DDLT group ($P < .001$). In the 267 patients outside of the Milan criteria in the Toronto cohort, the 5-year intention-to-treat survival rate was 61% and the 10-year rate was 57% for the LDLT group ($P = .44$), whereas the 5-year rate was 48% and the 10-year rate was 40% for the DDLT group ($P = .44$).

Posttransplant Recurrence Rates

During the posttransplant follow-up period, 360 of 2733 patients (13.2%) in the international cohort and 116 of 659 patients (17.6%) in the Toronto cohort experienced HCC recurrence. In the pre-IPTW analysis for the international cohort, the 5-year recurrence rate was 16% and the 10-year rate was

Table 3. Multivariable Models for the Risk of Patient Death From the Time of Waiting List Inscription

Variable	Pre-IPTW International cohort ^a		Post-IPTW International cohort ^a		Pre-IPTW Toronto cohort		Post-IPTW Toronto cohort	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
LDLT	0.51 (0.36 to 0.71)	<.001	0.67 (0.53 to 0.85)	.001	0.57 (0.45 to 0.73)	<.001	0.52 (0.42 to 0.65)	<.001
Diameter of major lesion, cm	1.07 (1.03 to 1.12)	<.001	1.03 (0.99 to 1.07)	.20	1.08 (1.03 to 1.12)	.001	1.07 (1.03 to 1.11)	.001
Log ₁₀ AFP level	1.21 (1.13 to 1.28)	<.001	1.21 (1.11 to 1.33)	<.001	1.33 (1.18 to 1.49)	<.001	1.31 (1.18 to 1.46)	<.001
MELD score	1.02 (1.00 to 1.03)	.02	1.03 (1.02 to 1.04)	<.001	1.03 (1.01 to 1.05)	.01	1.03 (1.00 to 1.05)	.02
Patient age, y	1.01 (1.00 to 1.03)	.02	1.01 (1.00 to 1.02)	.03	1.02 (1.01 to 1.03)	.003	1.02 (1.01 to 1.03)	.002
Waiting time duration, mo	0.99 (0.99 to 1.00)	.05	1.11 (1.08 to 1.14)	<.001	0.99 (0.98 to 1.01)	.21	0.99 (0.98 to 1.00)	.21
No. of lesions	1.00 (.999 to 1.01)	.07	1.00 (0.99 to 1.02)	.91	0.96 (0.90 to 1.03)	.23	0.96 (0.90 to 1.02)	.16
HBV-related cirrhosis	0.82 (0.64 to 1.06)	.14	0.87 (0.70 to 1.08)	.21	0.69 (0.49 to 0.99)	.04	0.67 (0.48 to 0.94)	.02
HCV-related cirrhosis	1.15 (0.93 to 1.42)	.19	0.91 (0.75 to 1.10)	.34	1.17 (0.87 to 1.59)	.30	1.15 (0.86 to 1.53)	.34
Male sex	0.95 (0.84 to 1.08)	.45	1.07 (0.89 to 1.27)	.49	0.91 (0.72 to 1.16)	.46	0.92 (0.73 to 1.15)	.45
Female sex	1.05 (0.93 to 1.19)	.45	0.93 (0.79 to 1.12)	.49	1.10 (0.86 to 1.39)	.46	1.09 (0.87 to 1.37)	.45
Alcohol-related cirrhosis	1.13 (0.80 to 1.58)	.49	1.02 (0.84 to 1.25)	.83	1.00 (0.68 to 1.46)	.99	0.91 (0.64 to 1.31)	.62
Period of LT before 2010	0.92 (0.69 to 1.21)	.54	0.89 (0.76 to 1.03)	.11	1.05 (0.85 to 1.30)	.65	1.07 (0.87 to 1.31)	.54
LRT	1.09 (0.81 to 1.48)	.55	1.00 (0.81 to 1.22)	.96	0.79 (0.64 to 0.97)	.03	0.80 (0.66 to 0.98)	.03
Center volume >70 LT/y	1.10 (0.77 to 1.56)	.61	1.00 (0.85 to 1.18)	.99	NA	NA	NA	NA

Abbreviations: AFP, α-fetoprotein; HBV, hepatitis B virus; HR, hazard ratio; IPTW, inverse probability of treatment weighting; LDLT, living-donor liver transplant; LRT, locoregional therapy; LT, liver transplant; MELD, model for end-stage liver disease; NA, not applicable; NASH, nonalcoholic steatohepatitis.

^a Cox proportional hazards regression model with mixed effects (cluster-specific random-effects variable = LT center) was used.

17% for the LDLT group ($P = .57$), whereas the 5-year rate was 17% and the 10-year rate was 21% for the DDLT group ($P = .57$). In the post-IPTW population, the 5-year recurrence rate was 13% and the 10-year rate was 18% for the LDLT group ($P = .07$), whereas the 5-year rate was 16% and the 10-year rate was 22% for the DDLT group ($P = .07$).

In the pre-IPTW analysis for the Toronto cohort, the 5-year recurrence rate was 13% and the 10-year rate was 21% for the LDLT group ($P = .14$), whereas the 5-year rate was 20% and the 10-year rate was 23% for the DDLT group ($P = .14$). In the post-IPTW analysis for the Toronto cohort, the 5-year recurrence rate was 13% and the 10-year rate was 22% for the LDLT group ($P = .048$), whereas the 5-year rate was 18% and the 10-year rate was 23% for the LDLT group ($P = .048$).

When only the 890 patients initially outside of the Milan criteria who underwent a transplant were considered in the international cohort, the 5-year recurrence rate was 27% and the 10-year rate was 26% for the LDLT group ($P = .50$), whereas the 5-year rate was 30% and the 10-year rate was 28% for the DDLT group ($P = .50$). In the 204 patients outside of the Milan criteria in the Toronto cohort, the 5-year recurrence rate was 23% and the 10-year rate was 32% for the LDLT group ($P = .36$), whereas the 5-year rate was 23% and the 10-year rate was 35% for the DDLT group ($P = .36$).

Discussion

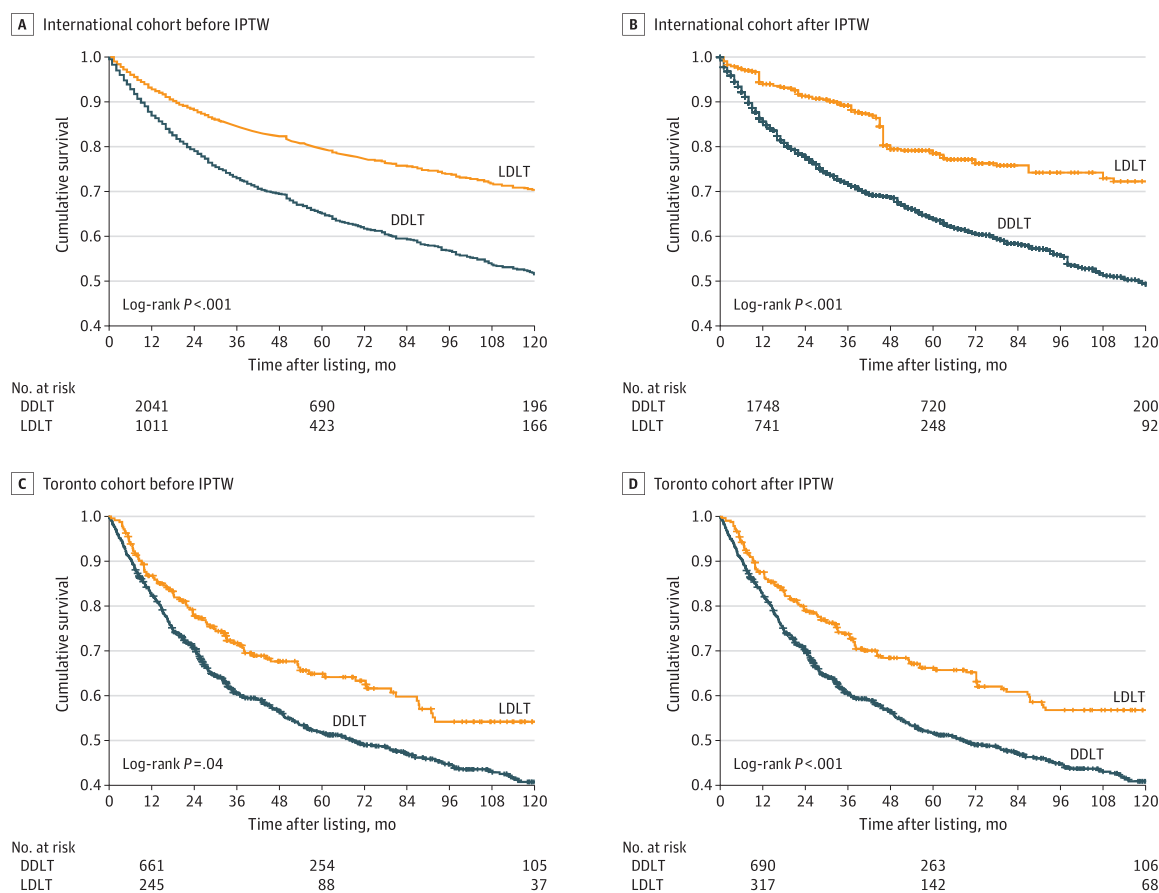
In the present study, a potential living donation was beneficial to the intention-to-treat survival of candidates for liver transplant. Analyzing a large international population com-

posed of centers in Europe, Asia, and the US revealed a 49% reduction in death risk from the time of waiting list inscription. After balancing the model for potential confounders using the IPTW method, the risk reduction remained high (ie, 33%). The 12 centers of the international cohort performed either a DDLT or an LDLT exclusively. When the protective factor of an LDLT was tested in the Toronto cohort, the risk reduction was 43% in the pre-IPTW population and 48% in the post-IPTW population. The Toronto center was chosen as a separate cohort because of its capability in performing both LDLT and DDLT as complementary approaches.

When the first living-donation case series were reported (mainly in the Eastern countries) 2 aspects of the procedure immediately emerged: the shorter, or even absent, waiting time and the concomitant decreased dropout risk of the transplant candidates.²⁰ Patients with a living donor were not affected by graft scarcity and did not add any competitive harm to the list of patients who were waiting for a DDLT.²¹ One could even argue that a living donor gives 2 organs back to the organ pool. However, living donation also presented risks to patients in need of a transplant with poorly investigated biological qualities of the tumor (fast-track approach).^{9,22} Consequently, poor results were initially reported in LDLT in HCC case series. For example, the Adult-to-Adult Living Donor Liver Transplantation Cohort Study (with 58 LDLTs vs 34 DDLTs) showed a higher 5-year recurrence rate in an LDLT compared with a DDLT (29% vs 0%).³ A meta-analysis (with 633 LDLTs vs 1232 DDLTs) also showed an increased risk for HCC recurrence after an LDLT (HR, 1.59; 95% CI, 1.02-2.49).⁵

A study from Hong Kong (with 43 LDLTs vs 17 DDLTs) also reported disappointing results after live donation (3-year

Figure 2. Intention-to-Treat Patient Survival Rates Before and After Inverse Probability of Treatment Weighting (IPTW) in the International Cohort (A and B) and Toronto Cohort (C and D)



DDLTL indicates deceased-donor liver transplant; LDLTL, living-donor liver transplant.

recurrence rates, 29% vs 0%).⁶ In this study, salvage transplant was a significant risk factor in recurrence.⁶ Another study that compared the Hong Kong with the Italian case series again found the unfavorable outcomes of salvage for HCC recurrence in LDLTL.²³

However, all of these results were potentially biased by the small number of cases and by more advanced tumors typically being transplanted in LDLTL case series.⁴

Recent studies of more homogeneous LDLTL and DDLTL populations showed the benefit of live donation.¹⁰⁻¹³ A French multicenter study (with 79 LDLTLs vs 782 DDLTLs) showed no dropouts (0% vs 20.7%; $P < .001$), better intention-to-treat overall survival rates, and no added recurrence risk in patients who underwent LDLTL.¹⁰ Another French study (with 36 LDLTLs vs 147 DDLTLs) found fewer dropouts and shorter median waiting times in patients who underwent LDLTL.¹¹ Using a propensity score match, a Hong Kong group reported similar recurrence-free survival rates, although more advanced tumors were transplanted in the LDLTL group.¹² The Toronto study (with 219 LDLTLs vs 632 DDLTLs) reported that having a potential live donor was protective for the risk of intention-to-treat death (HR, 0.67; 95% CI, 0.53-0.86).¹³

An international study based on 4089 patients recalibrating the Hazard Associated with Liver Transplantation for Hepatocellular Carcinoma database showed that undergoing a transplant in Asia reduced the risk of intention-to-treat death by 43%.²⁴ All of the Asian patients in the report had an LDLTL.²⁴ A recent meta-analysis (with 5376 patients) found that LDLTL was associated with better 5-year intention-to-treat patient survival rates (relative risk, 1.11; 95% CI, 1.01-1.22; $P = .04$), whereas the 5-year recurrence rates were similar (relative risk, 0.85; 95% CI, 0.56-1.31; $P = .47$).²⁵

Results of the present study were consistent with all of these previous findings, reporting the beneficial outcome of having a potential live donor for transplant candidates with HCC. Compared with previous studies, all of which were based on relatively small case series, the present study examined the data of almost 4000 patients who were on a waiting list for a transplant; therefore, this study may be the largest cohort study on this topic.

This analysis was supported by the IPTW approach, which balanced the potential biases in the international cohort and Toronto cohort. The reason for such an outcome was associated with the absence of dropouts in the LDLTL group. The

number of patients who switched to the DDLT group was minimal. The centers of the international cohort were almost exclusively LDLT or DDLT centers. Therefore, only by merging the data were we able to evaluate the outcome of living donation in the setting of HCC.

The combination of different experiences, management, and patient- and tumor-related characteristics may compel one to question the validity of the observed results. To minimize these potential limitations, we created Cox proportional hazards regression models with mixed effects, in which the transplant center was incorporated in the model as a cluster-specific random-effect variable.

Moreover, live donation was further evaluated in a single center that performed both live- and deceased-donor procedures without a particular attitude about or preference for one over another procedure. An LDLT was associated with a marked reduction in the risk of intention-to-treat death (pre-IPTW: 43%; post-IPTW: 48%) in the Toronto cohort.

Divergent experiences all converged to a similar 40% to 50% reduction in intention-to-treat death risk. This result was also observed in areas in which live donation is less commonly performed, such as the Toronto cohort. Therefore, the benefits of LDLT should motivate the implementation of live donations in Asia.²⁶⁻²⁸

Another critical aspect reported in this study is that patients who had an LDLT did not show an increased recurrence risk. An LDLT did not have unfavorable intent-to-treat survival and recurrence rates for the subgroup of patients who were initially outside of the Milan criteria.

All of these data are relevant, given that several centers adopted more liberal criteria (ie, more advanced tumors) in the case of live donation availability. Such consideration further underlines the importance of a live donor program in transplant centers that manage a high volume of patients with a tumor.

An LDLT program must have high standards of safety for the donor to minimize any potential risk of morbidity.²⁹ Therefore, the performance of an LDLT should be restricted to larger hepatopancreatobiliary and transplant programs, which have high transplant and hepatic surgery expertise.³⁰ Opportuni-

ties for training liver surgeons to master both liver resection and transplant must be made available.

Limitations

This study has some limitations. First, the retrospective study design and the potential initial selection biases could result in missing confounding factors, potentially favoring the outcomes in patients undergoing LDLT. The IPTW method and the evaluation of survival benefits of LDLT in a single-center cohort, in which both LDLT and DDLT are equally performed, were used to minimize these potential adverse effects. Second, the real number of patients who died or experienced tumor progression before listing could not be ascertained because of the absence of an available live donor. This limitation was particularly true in centers that performed LDLT exclusively. Therefore, a certain underestimation of the intention-to-treat mortality should be contemplated in the LDLT group.

Third, several differences were observed between patients in Eastern and Western countries, including HCC pretransplant treatments, genetics, and underlying liver disease.³¹ To minimize a potential geographical outcome, we constructed a Cox proportional hazards regression model with mixed effects in which the population was hierarchically clustered according to the center in which the transplant was performed. Moreover, the benefit of the live donation was investigated in a homogeneous single center in which both the LDLT and DDLT options were available.

Conclusions

This cohort study showed that a potential live donor availability decreased the risk of intention-to-treat death by as much as 49% in patients with HCC who were on a waiting list for a liver transplant. This benefit was associated with the reduction or even elimination of dropout rates. These results were supported by an IPTW analysis and were reported in centers in which both LDLT and DDLT options were equally available. Transplant programs worldwide should be encouraged to expand their live donor programs to manage patients with HCC.

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Author Affiliations: Institut de Recherche Clinique, Université Catholique de Louvain, Brussels, Belgium (Lai, Iesari, Lerut); General Surgery and Organ Transplantation Unit, Department of General 3 Surgery and Organ Transplantation, Sapienza University of Rome, Rome, Italy (Lai, Mennini, Rossi); Abdominal Transplant and HPB Surgical Oncology, Toronto General Hospital, University of Toronto, Toronto, Ontario, Canada (Sapisochin, Gorgen); Liver Transplantation and Hepatobiliary Surgery, Padua University Hospital, University of Padua, Padua, Italy (Vitale, Cillo); Center for Liver Disease and Transplantation, Columbia University Medical Center, New York Presbyterian Hospital, New York (Halazun, Emond); Division of Liver

Transplantation and Hepatobiliary Surgery, Department of Surgery, Weill Cornell Medicine, New York, New York (Halazun, Emond); Department of Medicine I, Medical University of Innsbruck, Innsbruck, Austria (Schaefer, Finkenstedt); Institute of Liver Transplantation and Regenerative Medicine, Medanta-The Medicity, Gurugram, Delhi, India (Bhangui, Soin); Department of Surgery, The University of Hong Kong, Hong Kong, China (Wong, Lo); Division of Hepato-Biliary-Pancreatic and Transplant Surgery, Department of Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan (Uemoto, Kaido); Liver Transplantation Center and Department of Surgery, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan (Lin, Chen); Klinik für Allgemein-, Viszeral- und Transplantationschirurgie Universitätsmedizin Mainz, Mainz, Germany (Mittler, Hoppe-Lotichius);

Department of Surgery and Science, Kyushu University, Fukuoka, Japan (Ikegami, Soejima); Department of Hepatobiliary and Pancreatic Surgery Shulan Hospital, Shulan Health Zhejiang University Hospital, Hangzhou, China (Yang, Zheng); Biostatistics Unit, University of Padua, Padua, Italy (Frigo).

Author Contributions: Dr Lai had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Lai and Sapisochin share co-first authorship.

Concept and design: Lai, Gorgen, Bhangui, Chen, Kaido, Soin, Lerut.

Acquisition, analysis, or interpretation of data: Lai, Sapisochin, Gorgen, Vitale, Halazun, Iesari, Schaefer, Bhangui, Mennini, Wong, Uemoto, Lin, Mittler, Ikegami, Yang, Frigo, Zheng, Soejima, Hoppe-Lotichius, Chen, Kaido, Lo, Rossi, Finkenstedt, Emond, Cillo, Lerut.

Drafting of the manuscript: Lai, Gorgen, Bhangu, Soin, Lerut.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Lai, Gorgen, Vitale, Wong, Ikegami, Frigo, Lerut.

Administrative, technical, or material support: Gorgen, Iesari, Bhangu, Wong, Ikegami, Yang, Lo, Soin.

Supervision: Sapisochin, Vitale, Bhangu, Mennini, Uemoto, Mittler, Zheng, Hoppe-Lotichius, Chen, Kaido, Lo, Rossi, Soin, Finkenstedt, Cillo, Lerut.

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