#### **REVIEW ARTICLE**



## Can living donor liver transplantation provide similar outcomes to deceased-donor liver transplantation for hepatocellular carcinoma? A systematic review and meta-analysis

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## Abstract

**Background and Aim** A potential solution to the deceased organ shortage is to include live organ donations and to identify patients with lower rates of HCC recurrence to fairly allocate liver grafts. Our aims were to detect the long-term outcomes of LDLT versus DDLT for HCC and predictors of recurrence after transplantation.

**Methods** PubMed, Scopus, Web of Science, Cochrane library were searched for eligible studies from inception to July 2021 and a systematic review and meta-analysis were done.

**Results** 35 studies with a total of 7822 patients were included. The 1-, 3-, 4 year-OS showed trivial improvement for LDLT recipients. However, the two modalities had similar 5-, 6- and 10-year OS. A significant improvement in the ITT-OS was observed for LDLT recipients. Regarding the DFS and recurrence after transplantation, no significant difference was observed between LDLT and DDLT. In addition to that, the pooled hazard ratio of the included studies showed that Milan criteria, level of AFP, presence of vascular invasion, tumor differentiation were significant predictors of recurrence.

**Conclusion** The cancer biology (not the graft type) is the most important determinant of recurrence and survival after LT. However, LDLT provided much better survival benefits to HCC patients especially in regions that suffer from low deceased organ availability.

**Keywords** Liver transplantation  $\cdot$  Living donor  $\cdot$  Living donor liver transplantation  $\cdot$  Deceased donor  $\cdot$  Deceased donor liver transplantation  $\cdot$  Hepatocellular carcinoma  $\cdot$  Cancer liver  $\cdot$  Liver tumor  $\cdot$  LT  $\cdot$  Hepatobiliary surgery

## Abbreviations

American association of study of liver disease
Alfa fetoprotein
Deceased donor liver transplant
Disease free survival
Hepatitis B virus
Hepatocellular carcinoma
Hepatitis C virus

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Hepatitis D virus
Intention to treat overall survival
Living donor liver transplant
Liver transplant
Milan criteria
Not applicable or not available
Overall survival
Vascular invasion
Microvascular invasion

## Introduction

Liver cancer remains a global health problem and its incidence is rising worldwide [1, 2]. It is estimated that, by 2025, > 1 million people will be diagnosed with liver cancer annually [3]. Hepatocellular carcinoma (HCC) is the most common form of primary liver cancer and accounts for ~90% of cases [4].

Therapeutic treatment options are available for patients with the local disease and include ablation, resection, and liver transplantation (LT) [5]. LT is a recognized treatment choice for patients with cirrhosis of the liver and HCC [6].

The greatest obstacle in liver transplant is the shortage of donors which has contributed to a remarkable increase in the waiting lists. Therefore, there is an increase in the time from the decision of transplantation to the LT itself. During this period, the HCC may progress and drop out from the waiting list [7–9].

Several strategies have been evaluated to reduce this risk: increasing the pool of donors by including live donors, treatment of HCC upon enlistment, and priority policies by identifying patients with lower rates of HCC recurrence and higher rates of survival to fairly allocate liver grafts. However, the long-term outcomes of LDLT versus DDLT for HCC are still controversial. Several studies demonstrate that LDLT was associated with better intention to treat overall survival (ITT-OS) when compared to DDLT [10, 11]. While some studies illustrated that HCC patients undergoing LDLT would result in worse DFS and recurrence rate [12, 13], other studies reported equal recurrence rate for the two modalities [14]. Moreover, some studies showed equal overall survival and DFS between the two modalities [10]. In addition to that, there are many predictors of recurrence other than the type of the graft such as level of AFP, vascular invasion and tumor grade that could be used to fairly allocate graft to those with lower incidence of recurrence [15-17].

## **Patients and methods**

#### Search strategy

The protocol for this meta-analysis was registered to PROS-PERO (CRD42021281670). The search was directed through PubMed, Scopus, Web of science, and the Cochrane Library for information from May 1963 to July 1, 2021 with a combination of the following terms: liver donor liver transplant, hepatocellular carcinoma, LDLT and HCC. More searches by Google Scholar have been used to supplement the search with the sites mentioned above. All studies were reviewed and evaluated by two authors (Elkomos, B. E.& Abdelaal, A.) according to the eligibility process. Abstract-based eligibility studies were obtained, and the manuscripts were fully reviewed.

#### Inclusion and exclusion criteria

The eligible studies included the following: (1) randomized controlled trials and prospective or retrospective cohort studies; (2) target population were patients diagnosed with HCC; (3) studies designating a comparison of LDLT and DDLT as

a primary aim; and (4) the primary outcomes were overall survival (OS), intention-to-treat overall survival (ITT-OS), disease-free survival (DFS) or recurrence of HCC for both LDLT and DDLT patients. Exclusion criteria: (1) reviews, case reports and case series; (2) studies designed to analyses information from the United Network for Organ Sharing database or the Scientific Registry of Transplant Recipients database; (3) studies missing a comparison group (DDLT recipients).

#### **Outcomes of interest**

We assessed 4 primary outcomes of LDLT and DDLT for HCC patients in this meta-analysis, including patient longterm overall survival from the time of transplant (1-, 2-, 3-, 4-,5-, 6- and 10-year OS), patient long-term overall survival from the time of listing to transplantation (1-, 2-, 3-, 4-,5-, 6- and 10-year ITT-OS), disease-free survival (1-, 2-, 3-, 4-,5-, 6- and 10-year DFS) and recurrence rate. In addition to that, our secondary outcomes were to detect the effect of age of recipient, sex of recipient, level of AFP and tumor biology (presence of vascular invasion and tumor grade) on the survival and recurrence of HCC after transplantation.

#### Quality assessment and data extraction

A modification of the Newcastle–Ottawa scale was used to assess the quality of all cohort studies included in this metaanalysis [18]. Only studies with seven or more stares were included (Table 2).

We extracted data on study characteristics (author, year of publication, country of transplant, number of institutes included in the study, the follow-up of the patients), patient characteristics (type of graft, sample size, age, gender ratio, wait-time on the listing to transplantation, number of tumor nodules, size of the largest one, Child score, tumor differentiation, vascular invasion, pre-transplant treatment), study primary outcomes and study secondary outcomes. The data were extracted by 2 investigators (Elkomos, B. E.& Abdelaal, A.) independently.

#### **Statistical analysis**

The meta-analysis was performed according to Cochrane Handbook for Systematic Reviews of Interventions [19], which is recommended by the Cochrane Collaboration. Regarding the primary outcomes (OS, DFS, ITT-OS, recurrence of HCC), the pooled risk ratios (RRs) and their corresponding 95% confidence intervals (CIs) were calculated with fixed effects models. However, if there was moderate or considerable heterogeneity ( $I^2 > 40$ ), random effects models were used to solve the heterogeneity between studies. Nevertheless, pooled hazard ratio were calculated for secondary

outcomes (predictors of recurrence and prognostic facts after transplantation). All calculations for the current meta-analysis were performed with Review Manager 5.4 for Windows (Cochrane Collaboration, Oxford, United Kingdom).

#### Assessment of publication bias and heterogeneity

Funnel plots were generated so that we could visually inspect for publication bias. Statistical heterogeneity was assessed with forest plots and the inconsistency statistic ( $I^2$ ). An  $I^2$  value of 40% or less corresponded to low heterogeneity. Statistical significance was considered at p < 0.05.

## Results

# Characteristics and quality assessment of eligible studies

As shown in the flow diagram (Fig. 1), 1584 articles were revealed using the following search string: living donor liver transplantation or LDLT and hepatocellular carcinoma or HCC. After careful selection according to our eligibility criteria, 35 controlled clinical trials with 7822 participants were included in the meta-analysis. These trials included 34 retrospective cohort studies and 1 prospective study. However, none of the included studies were randomized studies.

Recipients baseline data [including number, age, sex and waiting time], follow-up time and the tumor-related baseline variables [including percentage of patients beyond the Milan or UCSF criteria, number of tumors, tumor differentiation, the size of largest tumor, vascular invasion, MELD score, Child-Pugh class, and treatment before LT] were comparable between groups in all studies (Table 1). The quality assessment was conducted according to a modification of the Newcastle–Ottawa scale (Table 2). Most of the cohort studies included in this analysis demonstrated sufficient quality with reasonable selection criteria, comparable patient characteristics, and adequate follow-up of the subjects.

#### **Primary outcome**

#### **Overall survival**

21 studies (6045 participants) assessed 1-year OS, 19 studies (5859) reported 3-year OS and 12 studies (3817) calculated 4 year-OS. The pooled results from these studies showed possible improvement for LDLT recipients as follows (1-year OS, RR = 1.04, 95% CI 1.01–1.07, p = 0.01;  $I^2$  = 46%) and (3-year OS, RR = 1.07, 95% CI 1.01–1.13,



Fig. 1 PRISMA flow diagram

<b>Table 1</b> Basi	c data of t	he inclu	ded studi	es														
Studies: author, year, country	Study design	Study period	No. of centers	Arm	Sample size $(n)$	Age (years)	Gender: male/ female (n)	Waiting time (days)	Follow- up period (years)	Serology: HBV/HCV/ both/none ( <i>n</i> )	Child–Pugh class: A/B/C(n)	Within/ beyond Milan criteria (n)	Within/ beyond UCSF criteria (n)	No/ micro/ macro vascular invasion (n)	No. of tumor nodules $(1/2/3 \text{ or } n)$ more) $(n)$	Size of the largest nodule (cm)	Differentiation: well/moderate/ poor ( <i>n</i> )	Pretreat- ment: yes/none (n)
Gondolesi GE (2004) USA	Retrospec- tive	1998– 2002	-	LDLT	36	$56.17 \pm 7.56^{a}$	29/7	62	$1.25 \pm 0.84^{a}$	9/24/0/3	12/16/8	N/A	N/A	15/15/6	15/8/12	N/A	15/15/6	13/23
[20]	cohort	1992– 2002		DDLT	165	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Roayaie S	Retrospec-	1988-	1	LDLT	36	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
(2004) USA [ <mark>21</mark> ]	tive cohort	2002		DDLT	275	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Hwang S (2005)	Retrospec- tive	1992– 2002	4	LDLT	237	$50\pm 8^{a}$	196/41	N/A	3.75 (0.3–8.4) <sup>b</sup>	215/13/8/1	29/70/138	173/64	N/A	N/A	N/A	N/A	N/A	N/A
Korea [22]	cohort			DDLT	75	$49\pm7^{a}$	60/15	N/A	2.2 (0.3–6.7) <sup>b</sup>	68/6/0/1	4/13/55	53/22	N/A	N/A	N/A	N/A	N/A	N/A
Karakayali	Retrospec-	2004-	1	LDLT	11	$31.8 \pm 24.9^{a}$	N/A	N/A	N/A	2/4/0/5	N/A	N/A	N/A	N/A	N/A	N/A	N/A	9/2
H (2006) Turkey [23]	tive cohort	2005		DDLT	9	$55 \pm 4.7^{a}$	N/A	N/A	N/A	5/0/0/1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	3/3
Sotiropoulos	Retrospec-	1998 -	1	LDLT	45	$55.0\pm10.1^{a}$	33/12	N/A	N/A	12/18/2/13	10/24/11	23/22	25/20	N/A	20/8/1/16	N/A	N/A	N/A
GC (2007) Germany [24]	tive cohort	2006		DDLT	55	$53.4 \pm 9.1^{a}$	42/13	N/A	N/A	15/27/0/13	19/23/13	25/30	2728	N/A	26/9/2/18	N/A	N/A	N/A
Fisher RA	Retrospec-	1998 -	6	LDLT	58	$54.6 \pm 9^{a}$	45/13	95	4	N/A	N/A	21/37	28/28	43/9/3	N/A	N/A	N/A	26/32
(2007) USA [ <mark>25</mark> ]	tive cohort	2003		DDLT	34	$52.1 \pm 10^{a}$	25/9	353	3.4	N/A	N/A	20/14	24/10	27/3/0	N/A	N/A	N/A	14/20
Terrault NA	Retrospec-	1998–	6	LDLT	36	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
(2007) USA [26]	tive cohort	2003		DDLT	27	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Allam N	Retrospec-	2001 -	1	LDLT	8	$55.14 \pm 8.1^{a}$	6/3	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
(2008) KSA [ <mark>27</mark> ]	tive cohort	2007		DDLT	15	$48.78 \pm 17.5^{a}$	10/4	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Di Sandro S (2009) Italy	Retrospec- tive	2000- 2007	1	LDLT	25	N/A	N/A	107 (11–385) <sup>b</sup>	N/A	N/A	N/A	15/10	N/A	N/A	N/A	N/A	N/A	21/4
[28]	cohort			DDLT	154	N/A	N/A	404 (3–1704) <sup>b</sup>	N/A	N/A	N/A	106/48	N/A	N/A	N/A	N/A	N/A	107/47
Vakili K (2009) USA	Retrospec- tive	1999– 2007	1	LDLT	28	56 (47–67) <sup>b</sup>	21/7	N/A	3.4 (0.25– 8.7) <sup>b</sup>	15/2/0/11	N/A	21/7	26/2	N/A	18/7/2/1	$3.4 \pm 1.0^{a}$	6/19/3	5/23
[29]	cohort			DDLT	74	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Giacomoni A	Retrospec-	2000-	1	LDLT	25	57	N/A	264	N/A	N/A	N/A	15/10	N/A	N/A	N/A	N/A	N/A	21//4
(2009) Italy [ <b>30</b> ]	tive cohort	2007		DDLT	154	54	N/A	404	N/A	N/A	N/A	107/47	N/A	N/A	N/A	N/A	N/A	107/47
Hsieh TH	Retrospec-	1999–	1	LDLT	15	56	N/A	N/A	N/A	N/A	N/A	11//4	N/A	N/A	N/A	N/A	N/A	4/11
(2010) USA [31]	tive cohoi	1 2008		DDLT	121	56	N/A	N/A	N/A	N/A	N/A	90/31	N/A	N/A	N/A	N/A	N/A	88/33
Sharr WW	Retrospec-	1995–	1	LDLT	90	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0/06	N/A	N/A	N/A	N/A	N/A
(2011) China [ <b>32</b> ]	tive cohort	2005		DDLT	34	N/A	N/A	N/A	N/A	N/A	N/A	N/A	34/0	N/A	N/A	N/A	N/A	N/A

Table 1 (con	ttinued)																	
Studies: author, year, country	Study design	Study period	No. of centers	Arm	Sample size ( <i>n</i> )	Age (years)	Gender: male/ female ( <i>n</i> )	Waiting time (days)	Follow- up period (years)	Serology: HBV/HCV/ both/none (n)	Child–Pugh class: A/B/C(n)	Within/ beyond Milan criteria (n)	Within/ beyond UCSF criteria (n)	No/ micro/ macro vascular invasion (n)	No. of tumor nodules $(1/2/3 \text{ or } m)$ more) $(n)$	Size of the largest nodule (cm)	Differentiation: well/moderate/ poor ( <i>n</i> )	Pretreat- ment: yes/none ( <i>n</i> )
Kornberg A (2011) Ger-	Retrospec- tive	N/A	1	LDLT DDLT	12 78	N/A N/A	N/A N/A	120 365	N/A N/A	N/A N/A	N/A N/A	6/6 51/27	N/A N/A	N/A N/A	N/A N/A	N/A N/A	N/A N/A	N/A N/A
many [33]	cohort																	
Berg CL	Retrospec-	2002 -	6	LDLT	49	N/A	N/A	50.08	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
(2011) USA [34]	tive cohort	2009		DDLT	65	N/A	N/A	72.65	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Bhangui	Retrospec-	2000-	1	LDLT	36	$54 \pm 7^{a}$	32/4	$78 \pm 72^{a}$	$4.8 \pm 3^{a}$	N/A	N/A	26/10	31/5	N/A	N/A	$2.9 \pm 1.1^{a}$	N/A	12/24
P (2011) France [ <b>35</b> ]	tive cohort	2009		DDLT	120	$56\pm 8^{a}$	100/20	$237 \pm 270^{a}$	$4.2 \pm 2.6^{a}$	N/A	N/A	94/26	104/16	N/A	N/A	3±2.3 <sup>a</sup>	N/A	45/75
Azzam AZ	Retrospec-	2001 -	1	LDLT	18	N/A	N/A	N/A	N/A	N/A	N/A	18/0	N/A	N/A	N/A	N/A	N/A	N/A
(2011) KSA [36]	tive cohort	2011		DDLT	34	N/A	N/A	N/A	N/A	N/A	N/A	34/0	N/A	N/A	N/A	N/A	N/A	N/A
Kulik LM	Retrospec-	1998-	6	LDLT	100	$55.2\pm8^{a}$	75/25	$77.7 \pm 106^{a}$	5.9	78 (HCV)	N/A	41/59	65/35	N/A	$2.4 \pm 1.8^{a}$	$4.3 \pm 2.5^{a}$	N/A	59/41
(2012) USA [37]	tive cohort	2009		DDLT	76	53.9±8.5 <sup>a</sup>	76/21	$180.5 \pm 258^{a}$	4.3	78 (HCV)	N/A	71/26	83/14	N/A	$2.1 \pm 1.7^{a}$	$3.5 \pm 1.9^{a}$	N/A	73/24
Sandhu L (2012)	Retrospec- tive	1996– 2009	1	LDLT	58	$54.5\pm8.8^{a}$	46/12	93 (6–753) <sup>b</sup>	2.5 (0.2–7.3) <sup>b</sup>	8/38/0/12	N/A	42/16	N/A	N/A	1 (0–11)	3.9 (0.5– 22) <sup>b</sup>	49 W&M/3 p	29/29
Canada [38]	cohort			DDLT	287	$55.8 \pm 7.1^{a}$	246/41	159 (0–1071) <sup>b</sup>	3.2 (0–13.4) <sup>b</sup>	81/137/0/69	N/A	189/91	N/A	N/A	1 (0–12)	3.8 (0.5– 15.4) <sup>b</sup>	199 W&M/33 p	159/128
Li C (2013)	Retrospec-	2004-	1	LDLT	60	$45.23\pm8.18^{a}$	54/6	N/A	N/A	N/A	N/A	N/A	N/A	35/25/0	N/A	N/A	7/41/12	N/A
China [39]	tive cohort	2012		DDLT	156	$47.99 \pm 9.60^{a}$	138/18	N/A	N/A	N/A	N/A	N/A	N/A	111/45/0	N/A	N/A	25/106/25	N/A
Lei J (2013)	Retrospec-	2002 -	1	LDLT	31	$44.4 \pm 9.7^{a}$	18/13	N/A	N/A	26/1/1/3	15/3/3	N/A	N/A	N/A	14/8/9	N/A	10/15/8	31/0
China [40]	tive cohort	2009		DDLT	52	$44.0\pm 8.21^{a}$	31/21	N/A	N/A	39/3/3/7	14/6/3	N/A	N/A	N/A	22/16/14	N/A	20/20/12	52/0
Xiao GQ	Retrospec-	1999 -	1	LDLT	84	44.3	6/78	27	N/A	N/A	43/34/7	22/58	28//52	N/A	44.3	N/A	N/A	17/69
(2014) China [ <b>41</b> ]	tive cohort	2012		DDLT	276	47.3	29/247	48	N/A	N/A	137/119/20	66/169	84/184	N/A	47.3	N/A	N/A	101/175
Chen J (2014)	Retrospec-	2007-	1	LDLT	47	N/A	44/3	22	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	30 W&M/17 p	N/A
China [42]	tive cohort	2010		DDLT	94	N/A	88/6	91	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	55 W&M/39 p	N/A
Park MS	Retrospec-	N/A	1	LDLT	166	$52.5 \pm 7.7^{a}$	131/35	N/A	N/A	146/12/0/8	N/A	N/A	N/A	N/A	$1.4\pm0.6^{a}$	N/A	N/A	0L/96
(2014) Korea [12]	tive coho	e		DDLT	50	$54.3 \pm 9.6^{a}$	29/21	N/A	N/A	39/6/0/5	N/A	N/A	N/A	N/A	$1.5 \pm 0.7^{a}$	N/A	N/A	33/17
Wan P (2014) China [43]	Retrospec- tive cohoi	2007- t 2010	1	LDLT	40	$48.6 \pm 9.7^{a}$	N/A	N/A	1.75 (0.08– 6.25) <sup>b</sup>	40/0/0/0	12/18/10	24/16	N/A	N/A	$48.6 \pm 9.7^{a}$	N/A	N/A	12/28
				DDLT	80	$49.5 \pm 8.9^{a}$	N/A	N/A	24 (0.08–6.3) <sup>t</sup>	76/0/0/4	25/38/17	48/32	N/A	N/A	$49.5\pm8.9^{a}$	N/A	N/A	29/51
Bonadio I	Retrospec-	2000-	1	LDLT	28	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
(2014) Bel- gium [44]	tive cohort	2007		DDLT	48	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

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Table 1

Studies: author, year, country	Study design	Study period	No. of centers	Arm	Sample size (n)	Age (years)	Gender: male/ female ( <i>n</i> )	Waiting time (days)	Follow- up period (years)	Serology: HBV/HCV/ both/none (n)	Child–Pugh class: A/B/C(n)	Within/ Within/ beyond 1 Milan 1 criteria 6 (n) (n)	Within/ beyond UCSF criteria (n)	No/ micro/ macro vascular invasion (n)	No. of tumor nodules (1/2/3 or more) (n)	Size of the largest nodule (cm)	Differentiation: well/moderate/ poor ( <i>n</i> )	Pretreat- ment: yes/none ( <i>n</i> )
Ninomiya M	Retrospec-	2002-	2	LDLT	133	$57.6 \pm 7.1^{a}$	78/55	44 (4–236) <sup>b</sup>	6.3	21/100/12	N/A	N/A	N/A	N/A	$4.8 \pm 7.9^{a}$	$2.4 \pm 1.1^{a}$	7.5%/63.9%/28.6%	N/A
(2015) Japan USA [14]	/ tive cohor	t 2010		DDLT	362	$58.3 \pm 7.4^{a}$	285/77	196 (0–3996) <sup>b</sup>	5.6	51/212/99	N/A	N/A	N/A	N/A	$2.6 \pm 2.2^{a}$	$2.8 \pm 1.8^{a}$	40.8%/49.7%/9.7%	N/A
Chen LP	Retrospec-	2005-	1	LDLT	99	$45.82 \pm 7.72^{a}$	9//09	$23.37 \pm 16.32$	N/A	N/A	N/A	34/32	42/24	N/A	N/A	$5.22 \pm 2.31^{8}$	13/45/8	N/A
(2015) China [45]	tive cohort	2013		DDLT	163	$47.93 \pm 9.51^{a}$	144/19	$46.88 \pm 32.12^{a}$	N/A	N/A	N/A	12/91	95/68	N/A	N/A	5.24±2.24 <sup>8</sup>	'27/110/26	N/A
Tomiyama K (2016)	Retrospec- tive	2000– 2004	1	LDLT	106	N/A	N/A	264 (189– 450) <sup>b</sup>	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Canada [46]	cohort			DDLT	434	N/A	N/A	465 (210– 891) <sup>b</sup>	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Fonseca E	Retrospec-	2000-	1	LDLT	43	N/A	N/A	N/A	N/A	N/A	N/A	I N/A	N/A	N/A	N/A	N/A	N/A	N/A
(2016) Brazil [47]	tive cohort	2009		DDLT	23	N/A	N/A	N/A	N/A	N/A	N/A	I V/A	N/A	N/A	N/A	N/A	N/A	N/A
Azoulay D (2017)	Retrospec- tive	2000– 2009	5	LDLT	75	$54.2\pm7.6^{a}$	62/13	$78 \pm 69^{a}$	$8.5 \pm 1.9^{a}$	N/A	46 A&B/ 28 C	44/31	N/A	N/A	N/A	N/A	N/A	53/22
France [48]	cohort			DDLT	576	$56.3 \pm 7.4^{a}$	499/77	$183 \pm 219^{a}$	$5.6 \pm 13.4^{a}$	N/A	441/76	333/243	N/A	N/A	N/A	N/A	N/A	366/205
Goldaracena N (2019)	Retrospec- tive	2000– 2015	1	LDLT	118	N/A	N/A	108 (75–195) <sup>b</sup>	4 (1.7–8.2) <sup>b</sup>	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	64/54
Canada [11]	cohort			DDLT	527	N/A	N/A	189 (96–336) <sup>b</sup>	4.3 (2–9) <sup>b</sup>	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	380/147
Wong TCL (2019) China [10]	Retrospec- tive cohort	1995– 2014	1	LDLT	161	55 (30–73) <sup>b</sup>	129/32	N/A	N/A	125 (HBV) 28 (HCV)	81/48/32	113/48	141/20	N/A	85/47/20	2.9 (0.90– 8.80) <sup>b</sup>	45/91/10	N/A
				DDLT	85	57 (41–68) <sup>b</sup>	72/13	N/A	N/A	76 (HBV) 6 : (HCV)	32/31/22	72/13	85/0	N/A	57/17/11	2.4 (0.70– 0.60) <sup>b</sup>	16/46/6	N/A
Lee S (2020) Korea [49]	Retrospec- tive cohor	2005- t 2015	-	LDLT	829	$53.7 \pm 6.2^{a}$	709/120	N/A	N/A	728 (HBV) 45 (HCV)	346/319/164	N/A	N/A	N/A	N/A	$1.5 \pm 1.6^{a}$	N/A	635/194
				DDLT	67	$54.7 \pm 7.7^{a}$	51/16	N/A	N/A	58 (HBV) 4 (HCV)	8/20/39	N/A	N/A	N/A	N/A	$1.7 \pm 2.0^{a}$	N/A	53/14
Rahatli S	Retrospec-	1988–	1	LDLT	29	N/A	N/A	N/A	N/A	N/A	N/A	I N/A	N/A	N/A	N/A	N/A	N/A	N/A
(2020) Tur- key [ <b>50</b> ]	tive cohort	2018		DDLT	20	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
<sup>a</sup> The results	are present	ed as me	eans and	standard	deviatio	u												

<sup>b</sup>The results are presented as median and range

p=0.02;  $l^2=63\%$ ) However, this meta-analysis showed that LDLT recipients and DDLT recipients had similar 5-, 6and 10-year OS (5-year OS, RR = 0.99, 95% CI 0.92–1.08, p=0.89;  $l^2=75\%$ ) and (10-year OS, RR = 1.24, 95% CI 0.92–1.67, p=0.16;  $l^2=90\%$ ) as shown in 21 studies (6080) for 5-year OS, 5 studies (2002) for 6-year OS and 2 studies (1391) for 10-year OS (Fig. 2).

## RFS

14 studies (3978 participants) reported 1-year RFS, 6 studies (1282 participants) assessed 2-year DFS, 12 studies (3599 participants) reported 3-year RFS, 5 studies (1081 participants) calculated 4-year DFS, 15 studies (4133 participants) assessed 5-year DFS, 4 studies (1525 participants) reported 6-year DFS and only one study assessed 10-year DFS (896 participants). The pooled results from these studies showed no significant difference between LDLT and DDLT (Fig. 3).

## ITT-OS

While 1-, 3- and 5-year ITT-OS were reported in 5 studies (2934 participants) and 2-, 4-year ITT-OS were assessed in 3 studies (1419), no study calculated the 6-, 10-year ITT-OS. Significant improvement was observed for LDLT recipients especially for 5-year ITT-OS. (1-year, RR = 1.14, 95% CI 1.01–1.28, P = 0.03;  $I^2 = 88\%$ ), (2-year, RR = 1.23, 95% CI 1.00–1.50, P = 0.05;  $I^2 = 85\%$ ), (3-year, RR = 1.26, 95% CI 1.08–1.47, P = 0.004;  $I^2 = 84\%$ ), (4-year, RR = 1.46, 95% CI 1.07–1.99, P = 0.02;  $I^2 = 87\%$ ) and (5-year, RR = 1.37, 95% CI 1.09–1.72, P = 0.006;  $I^2 = 89\%$ ) (Fig. 4).

#### **Recurrence** rates

The number of HCC recurrence was pooled from 16 studies (3617 participants) and showed comparable recurrence between recipients after LDLT and DDLT (RR = 1.07, 95% CI 0.77-1.48, P = 0.70;  $l^2 = 62\%$ ) (Fig. 5).

#### Subgroup analysis

To investigate the source of heterogeneity among studies, a subgroup analysis was carried out by stratifying the analysis according to Milan criteria and region of transplant.

#### Milan criteria

We performed an additional comparative analysis of LDLT and DDLT in patients with HCC meeting or exceeding the Milan criteria regarding 0S and DFS (Table 3). For those meeting the Milan criteria, no significant difference in OS and DFS could be detected between LDLT and DDLT recipients. On the other hand, OS for those exceeding Milan criteria was better after LDLT. However, there were insufficient data to detect DFS for patients beyond Milan criteria. Notably, the outcome for those exceeding Milan criteria should be carefully interpreted because of the limited data (Tables 3, 4).

#### Region (Asia, America and Europe)

Another comparison was done to detect the OS and DFS between LDLT and DDLT recipients according to the region of transplant (Asia, America and Europe). No remarkable difference in OS between LDLT and DDLT could be detected according to the region (Tables 5, 6).

#### Secondary outcome

A secondary outcome was to detect the prognostic valves and predictors of recurrence after liver transplantation for HCC patients other than the type of graft.

#### Prognostic factors and predictor values of recurrence

The age and the sex of the recipient could not be used as a prognostic factor or as a predictive value of recurrence after liver transplantation. On the other hand, a remarkable decrease in survival and increase in the recurrence rate are associated with tumors which are beyond Milan criteria, number, size of the tumor, high levels of AFP (> 400 ng), the presence of vascular invasion and the poorly differentiated tumors (Tables 7, 8).

#### **Publication bias assessment**

No evidence of publication bias could be detected. The funnel plot analysis showed a symmetrical appearance.

## Discussion

Regarding the overall survival after liver transplantation, while some studies reported equal OS after LDLT and DDLT, some papers reported better survival after LDLT. In our study, pooled patient OS showed trivial improvement in LDLT recipients especially the 3-year OS. However, the long-term OS (5- and 10-year OS) did not show any significant difference between the two types of transplant. In addition to that, according to the pooled results of five studies, our subgroup analysis showed equal long-term OS between LDLT and DDLT for those who are within MC. Nevertheless, beyond Milan criteria, there was a better prognosis, could be detected for the patients who underwent LDLT but this data should be treated cautiously due to the small sample size.

## Table 2 Newcastle–Ottawa scale for included studies

Study	Representa- tiveness of expose of cohort	Selection of the non- exposed cohort	Ascertain- ment of exposure	Demonstra- tion that outcome of interest was not present at start of study	Comparability	Assessment of outcome	Adequate follow-up length	Adequacy of fol- lowup	Score
Gondolesi GE (2004) USA	*	*	*	*	**	*	*	*	9
Roayaie S (2004) USA	*	*	*	*		*	*	*	7
Hwang S (2005) Korea	*	*	*	*	**	*	*	*	9
Karakayali H (2006) Turkey	*	*	*	*	**	*			7
Sotiropoulos GC (2007) Germany	*	*	*	*	**	*	*	*	9
Fisher RA (2007) USA	*	*	*	*	**	*	*	*	9
Terrault NA (2007) USA	*	*	*	*	**	*			7
Allam N (2008) KSA	*	*	*	*	*	*	*	*	8
Di Sandro S (2009) Italy	*	*	*	*	*	*	*	*	9
Vakili K (2009) USA	*	*	*	*		*	*	*	7
Berg CL (2011) USA	*	*	*	*	*	*	*	*	8
Bhangui P (2011) France	*	*	*	*	**	*	*	*	9
Azzam AZ (2011) KSA	*	*	*	*	*	*	*		7
Kulik LM (2012) USA	*	*	*	*	**	*	*	*	9
Sandhu L (2012) Canada	*	*	*	*	**	*	*	*	9
Li C (2013) China	*	*	*	*	**	*	*	*	9
Lei J (2013) China	*	*	*	*	**	*	*	*	9
Xiao GQ (2014) China	*	*	*	*	*	*	*		7
Chen J (2014) China	*	*	*	*	*	*	*		7
Park MS (2014) Korea	*	*	*	*	**	*	*	*	9
Wan P (2014) China	*	*	*	*	**	*	*	*	9
Bonadio I (2014) Belgium	*	*	*	*	*	*	*		7

Table 2 (continued)

Study	Representa- tiveness of expose of cohort	Selection of the non- exposed cohort	Ascertain- ment of exposure	Demonstra- tion that outcome of interest was not present at start of study	Comparability	Assessment of outcome	Adequate follow-up length	Adequacy of fol- lowup	Score
Ninomiya M (2015) Japan USA	*	*	*	*	*	*	*	*	8
Chen LP (2015) China	*	*	*	*	**	*	*		8
Azoulay D (2017) France	*	*	*	*	**	*	*	*	9
Goldaracena N (2019) Canada	*	*	*	*	*	*	*	*	8
Wong TCL (2019) China	*	*	*	*	**	*	*	*	9
Lee S (2020) Korea	*	*	*	*	**	*	*	*	9
Rahatli S (2020) Turkey	*	*	*	*		*	*	*	7

\* stands for one point

\*\* stands for two points

On the other hand, according to a French study, the OS from the time of listing was similar for both LDLT and DDLT. However, this has been explained by a Canadian study by the small sample size that failed to address the better outcome after LDLT. This meta-analysis illustrated that the patients listed for LDLT showed a dramatic increase in the OS (ITT-OS) than those listed for DDLT. This could be attributed to the short waiting time and the low dropout rate. Thus it can be said that if dropout was taken into consideration, LDLT provided much better survival benefits to HCC patients especially in regions that suffer from low deceased organ availability as it provides an endless source of donors and eliminate the probability of progression while waiting [10].

Whether HCC recurrence is more frequent in LDLT remains controversial. Some studies attributed the high levels of recurrence after LDLT in their studies to the growth factors that are released during the natural course of liver regeneration of a partial liver graft [29] and according to Fisher et al. [25], the technique of living donor transplant is the determent factor for recurrence due to greater manipulation of the native liver and preservation of the native vena cava, as well as more hepatic artery and bile duct length that results in leaving residual tumor or violating tumor capsule and tumor embolization through the hepatic veins. However, in our study, no remarkable difference could be detected between LDLT and DDLT recipients in the DFS. Moreover, our subgroup analysis showed equal DFS between the two groups for those who are within MC. In addition to that no difference in the recurrence rate could be detected between LDLT and DDLT receipts and according to Bhangui et al. [35], there was no difference in the severity of recurrence at presentation in the two groups.

Moreover, the high incidence of recurrence in LDLT recipients that was mentioned in some studies could be explained by two reasons; first, the fast tracking to LDLT may not allow sufficient time for evaluation of the biological aggressiveness of tumors [29, 37]. Secondly, the presence of other factors related to the biology of the tumor, not the graft type. For instance, in the Fisher et al. [25] study, while 15% of the patients in the LDLT group had poorly differentiated tumors, only 3% of DDLT had poorly differentiated tumors and in the study by Vakili et al. [29] 46% of the tumors in the LDLT group had microvascular invasion. In other words, Macrovascular invasion, preoperative serum alpha-fetoprotein (AFP) level, tumor size, histopathologic grading were significant factors for survival and tumor-free survival by univariate analysis [28, 38].

Our secondary outcome was to detect these factors that affect the survival and recurrence after liver transplantation

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	LDL	г	DDL	т		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
Jondolesi GE (2004) USA	27	36	134	165	1.9%	0.92 [0.75, 1.13]	2004	
Iwang S (2005) Korea	195	237	54	75	2.9%	1.14 [0.98, 1.33]	2005	
Sotiropoulos GC (2007) Germany	31	45	46	55	1.5%	0.82 [0.66, 1.04]	2007	
isher RA (2007) USA	50	58	26	34	1.7%	1.13 [0.91, 1.39]	2007	
Mam N (2008) KSA	7	8	14	15	1.0%	0.94 [0.70, 1.26]	2008	
/akili K (2009) USA	27	28	63	74	4.2%	1.13 [1.01, 1.28]	2009	
3hangui P (2011) France	31	36	108	120	3.2%	0.96 [0.83, 1.11]	2011	
Sharr WW (2011) China	87	90	33	34	7.4%	1.00 [0.93, 1.07]	2011	
Sandhu L (2012) Canada	53	58	260	287	6.0%	1.01 [0.92, 1.10]	2012	<b>_</b>
(ulik LM (2012) USA	89	100	87	97	5.4%	0.99 [0.90, 1.09]	2012	
.i C (2013) China	49	60	137	156	3.6%	0.93 [0.81, 1.06]	2013	
ei J (2013) China	28	31	47	52	3.2%	1.00 [0.86, 1.16]	2013	
(iao GQ (2014) China	69	84	191	276	3.8%	1.19 [1.05, 1.35]	2014	· · · · · · · · · · · · · · · · · · ·
Van P (2014) China	36	40	68	80	3.4%	1.06 [0.92, 1.22]	2014	•
Chen J (2014) China	41	47	73	94	2.9%	1.12 [0.96, 1.31]	2014	+
Vinomiya M (2015) Japan USA	124	133	301	362	7.8%	1.12 [1.05, 1.20]	2015	_ <b>_</b>
Tomiyama K (2016) Canada	100	106	395	434	8.7%	1.04 [0.98, 1.10]	2016	+
zoulay D (2017) France	68	75	507	576	6.7%	1.03 [0.95, 1.11]	2017	_ <b>_</b>
Vong TCL (2019) China	154	161	79	85	7.6%	1.03 [0.96, 1.10]	2019	_ <b>+-</b> _
Foldaracena N (2019) Canada	107	118	427	527	7.3%	1.12 [1.04, 1.20]	2019	<b>_</b>
.ee S (2020) Korea	797	829	65	67	9.8%	0.99 [0.95, 1.04]	2020	
otal (95% CI)		2380		3665	100.0%	1.04 [1.01, 1.07]		•
Total events	2170		3115					
Heterogeneity: Tau <sup>2</sup> = 0.00; Chi <sup>2</sup> = 3	7.04. df=	20 (P =	: 0.01): P	= 46%				
East for everall effects $7 - 2.45$ /D - 1	0.041		2.01/11					0.7 0.85 1 1.2

## 2-year OS

	LDL	т	DDL	т		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
Gondolesi GE (2004) USA	22	36	116	165	5.0%	0.87 [0.66, 1.15]	2004	
Hwang S (2005) Korea	180	237	48	75	7.0%	1.19 [0.99, 1.43]	2005	
Sotiropoulos GC (2007) Germany	29	45	39	55	5.1%	0.91 [0.69, 1.20]	2007	
Fisher RA (2007) USA	44	58	25	34	5.6%	1.03 [0.80, 1.32]	2007	
Vakili K (2009) USA	27	28	58	74	8.1%	1.23 [1.07, 1.41]	2009	
Bhangui P (2011) France	21	36	105	120	4.9%	0.67 [0.50, 0.89]	2011	
Kulik LM (2012) USA	80	100	85	97	8.5%	0.91 [0.81, 1.03]	2012	
Sandhu L (2012) Canada	49	58	241	287	8.5%	1.01 [0.89, 1.14]	2012	<b>_</b>
Lei J (2013) China	26	31	44	52	6.8%	0.99 [0.82, 1.20]	2013	
Wan P (2014) China	32	40	60	80	6.7%	1.07 [0.87, 1.30]	2014	
Xiao GQ (2014) China	49	84	141	276	6.3%	1.14 [0.92, 1.41]	2014	
Ninomiya M (2015) Japan USA	121	133	238	362	9.2%	1.38 [1.26, 1.52]	2015	
Azoulay D (2017) France	66	75	473	576	9.2%	1.07 [0.98, 1.17]	2017	+
Lee S (2020) Korea	746	829	58	67	9.1%	1.04 [0.94, 1.15]	2020	
Total (95% CI)		1790		2320	100.0%	1.04 [0.96, 1.14]		•
Total events	1492		1731					
Heterogeneity: Tau² = 0.02; Chi² = 5	8.28, df=	13 (P •	0.00001	); l <sup>2</sup> = 7	'8%			
Test for overall effect: Z = 0.97 (P = 0	0.33)							Eavours [DDLT] Eavours [LDLT]
	,							Favours (DDLI) Favours (LDLI)

## 3-year OS

	LDL	т	DDL	т		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
Hwang S (2005) Korea	160	237	43	75	4.7%	1.18 [0.95, 1.46]	2005	
Sotiropoulos GC (2007) Germany	26	45	34	55	3.3%	0.93 [0.68, 1.29]	2007	
Allam N (2008) KSA	7	8	11	15	2.6%	1.19 [0.80, 1.78]	2008	
Vakili K (2009) USA	23	28	43	74	4.1%	1.41 [1.09, 1.83]	2009	
Di Sandro S (2009) Italy	17	25	118	154	3.8%	0.89 [0.67, 1.18]	2009	
Giacomoni A (2009)	15	25	119	124	3.4%	0.63 [0.45, 0.86]	2009	
Sharr WW (2011) China	73	90	30	34	5.6%	0.92 [0.78, 1.08]	2011	
Bhangui P (2011) France	27	36	99	120	4.9%	0.91 [0.74, 1.12]	2011	
Kulik LM (2012) USA	66	100	73	97	5.2%	0.88 [0.73, 1.05]	2012	
Sandhu L (2012) Canada	44	58	214	287	5.6%	1.02 [0.87, 1.19]	2012	<b>_</b>
Lei J (2013) China	22	31	35	52	3.7%	1.05 [0.79, 1.42]	2013	
Li C (2013) China	41	60	108	156	4.9%	0.99 [0.81, 1.21]	2013	
Chen J (2014) China	30	47	47	94	3.7%	1.28 [0.95, 1.72]	2014	+
Wan P (2014) China	30	40	53	80	4.4%	1.13 [0.89, 1.44]	2014	
Xiao GQ (2014) China	36	84	106	276	3.7%	1.12 [0.84, 1.49]	2014	
Ninomiya M (2015) Japan USA	105	133	230	362	6.2%	1.24 [1.10, 1.40]	2015	
Tomiyama K (2016) Canada	72	106	326	434	5.8%	0.90 [0.78, 1.04]	2016	
Azoulay D (2017) France	55	75	421	576	5.8%	1.00 [0.87, 1.16]	2017	<del></del>
Goldaracena N (2019) Canada	96	118	401	527	6.4%	1.07 [0.97, 1.18]	2019	+
Wong TCL (2019) China	129	161	72	85	6.2%	0.95 [0.84, 1.07]	2019	
Lee S (2020) Korea	465	829	55	67	6.0%	0.68 [0.60, 0.78]	2020	_ <b>-</b>
Total (95% CI)		2336		3744	100.0%	0.99 [0.92, 1.08]		◆
Total events	1539		2638					
Heterogeneity: Tau <sup>2</sup> = 0.02; Chi <sup>2</sup> = 7	9.26. df=	20 (P =	0.00001	); $ ^2 = 7$	5%			
Test for overall effect: Z = 0.14 (P = 0	0.89)	0						0.5 0.7 1 1.5 2
	,							Favours [DDL1] Favours [LDL1]

## Fig. 2 OS for LDLT and DDLT recipients

4-year OS
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	LDL	.т	DDL	Т		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
Hwang S (2005) Korea	160	237	43	75	7.1%	1.18 [0.95, 1.46]	2005	
Sotiropoulos GC (2007) Germany	28	45	37	55	4.5%	0.92 [0.69, 1.24]	2007	
Vakili K (2009) USA	23	28	44	74	5.5%	1.38 [1.07, 1.78]	2009	
Bhangui P (2011) France	27	36	99	120	7.5%	0.91 [0.74, 1.12]	2011	
Kulik LM (2012) USA	59	100	55	97	6.1%	1.04 [0.82, 1.32]	2012	
Sandhu L (2012) Canada	44	58	216	287	10.3%	1.01 [0.86, 1.18]	2012	
Lei J (2013) China	23	31	38	52	5.2%	1.02 [0.78, 1.32]	2013	
Xiao GQ (2014) China	36	84	107	276	4.6%	1.11 [0.83, 1.47]	2014	
Wan P (2014) China	31	40	53	80	6.5%	1.17 [0.93, 1.47]	2014	
Ninomiya M (2015) Japan USA	115	133	250	362	15.8%	1.25 [1.14, 1.38]	2015	
Azoulay D (2017) France	59	75	437	576	12.9%	1.04 [0.91, 1.18]	2017	
Lee S (2020) Korea	713	829	55	67	13.9%	1.05 [0.93, 1.18]	2020	
Total (95% CI)		1696		2121	<b>100.0</b> %	1.09 [1.02, 1.17]		◆
Total events	1318		1434					
Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup> =	18.54, df=	: 11 (P =	= 0.07); I <sup>z</sup>	= 41%				
Test for overall effect: Z = 2.40 (P =	0.02)							0.7 0.85 1 1.2 1.5 Favours (DDLT) Favours (LDLT)
5-year OS								
•	LDL1		DDLT			Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
Hwang S (2005) Korea	160	237	43	75	4.7%	1.18 [0.95, 1.46]	2005	+
Sotiropoulos GC (2007) Germany	26	45	34	55	3.3%	0.93 [0.68, 1.29]	2007	
Allam N (2008) KSA	7	8	11	15	2.6%	1.19 [0.80, 1.78]	2008	
Vakili K (2009) USA	23	28	43	74	4.1%	1.41 [1.09, 1.83]	2009	· · · · · · · · · · · · · · · · · · ·

Allam N (2008) KSA	7	8	11	15	2.6%	1.19 [0.80, 1.78]	2008	
Vakili K (2009) USA	23	28	43	74	4.1%	1.41 [1.09, 1.83]	2009	
Di Sandro S (2009) Italy	17	25	118	154	3.8%	0.89 [0.67, 1.18]	2009	
Giacomoni A (2009)	15	25	119	124	3.4%	0.63 [0.45, 0.86]	2009	
Sharr WW (2011) China	73	90	30	34	5.6%	0.92 [0.78, 1.08]	2011	
Bhangui P (2011) France	27	36	99	120	4.9%	0.91 [0.74, 1.12]	2011	
Kulik LM (2012) USA	66	100	73	97	5.2%	0.88 [0.73, 1.05]	2012	
Sandhu L (2012) Canada	44	58	214	287	5.6%	1.02 [0.87, 1.19]	2012	_ <b>-</b> _
Lei J (2013) China	22	31	35	52	3.7%	1.05 [0.79, 1.42]	2013	<del></del>
Li C (2013) China	41	60	108	156	4.9%	0.99 [0.81, 1.21]	2013	
Chen J (2014) China	30	47	47	94	3.7%	1.28 [0.95, 1.72]	2014	+
Wan P (2014) China	30	40	53	80	4.4%	1.13 [0.89, 1.44]	2014	
Xiao GQ (2014) China	36	84	106	276	3.7%	1.12 [0.84, 1.49]	2014	
Ninomiya M (2015) Japan USA	105	133	230	362	6.2%	1.24 [1.10, 1.40]	2015	
Tomiyama K (2016) Canada	72	106	326	434	5.8%	0.90 [0.78, 1.04]	2016	
Azoulay D (2017) France	55	75	421	576	5.8%	1.00 [0.87, 1.16]	2017	<del></del>
Goldaracena N (2019) Canada	96	118	401	527	6.4%	1.07 [0.97, 1.18]	2019	+
Wong TCL (2019) China	129	161	72	85	6.2%	0.95 [0.84, 1.07]	2019	
Lee S (2020) Korea	465	829	55	67	6.0%	0.68 [0.60, 0.78]	2020	
Total (95% CI)		2336		3744	100.0%	0.99 [0.92, 1.08]		
Total events	1539		2638					
Heterogeneity: Tau <sup>2</sup> = 0.02; Chi <sup>2</sup> = 7	9.26, df =	20 (P ≺ I	0.00001	); l <sup>z</sup> = 7	5%			
Test for overall effect: Z = 0.14 (P = 0	).89)	-						U.S U.7 I 1.S Z
•								Favours (DDET) Favours (EDET)

## 6-year OS

	LDLT DDLT				Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
Hwang S (2005) Korea	130	237	38	75	17.5%	1.08 [0.84, 1.39]	2005	
Vakili K (2009) USA	23	28	37	74	16.0%	1.64 [1.23, 2.19]	2009	<b>_</b>
Kulik LM (2012) USA	63	100	72	97	20.2%	0.85 [0.70, 1.03]	2012	
Ninomiya M (2015) Japan USA	106	133	219	362	23.1%	1.32 [1.17, 1.48]	2015	_ <b></b>
Lee S (2020) Korea	701	829	54	67	23.1%	1.05 [0.93, 1.18]	2020	
Total (95% CI)		1327		675	100.0%	1.14 [0.95, 1.38]		
Total events	1023		420					
Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup>	= 23.08, c	if = 4 (P	P = 0.0001	l); l² = 8	33%		_	
Test for overall effect: Z = 1.41 (P	= 0.16)							Favours [DDLT] Favours [LDLT]

## 10-year OS

	LDL	Т	DDL	Т		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
Ninomiya M (2015) Japan USA	101	133	190	362	49.8%	1.45 [1.26, 1.66]	2015	<b>_</b>
Lee S (2020) Korea	686	829	52	67	50.2%	1.07 [0.93, 1.22]	2020	-+=
Total (95% CI)		962		429	100.0%	1.24 [0.92, 1.67]		
Total events	787		242					
Heterogeneity: Tau <sup>2</sup> = 0.04; Chi <sup>2</sup> :	= 9.87, df	_						
Test for overall effect: Z = 1.42 (P	= 0.16)		Favours [DDLT] Favours [LDLT]					

Fig. 2 (continued)

#### 1-year DFS

	Experin	Experimental Control			Risk Ratio		Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
Gondolesi GE (2004) USA	29	36	149	165	5.6%	0.89 [0.75, 1.06]	2004	
Hwang S (2005) Korea	202	237	68	75	9.0%	0.94 [0.86, 1.03]	2005	
Fisher RA (2007) USA	42	58	26	34	3.5%	0.95 [0.74, 1.21]	2007	
Sharr WW (2011) China	82	90	32	34	8.2%	0.97 [0.87, 1.08]	2011	
Kulik LM (2012) USA	80	100	87	97	7.6%	0.89 [0.79, 1.00]	2012	
Sandhu L (2012) Canada	51	58	246	287	8.2%	1.03 [0.92, 1.14]	2012	_ <b>-</b>
Lei J (2013) China	24	31	42	52	3.8%	0.96 [0.76, 1.21]	2013	
Xiao GQ (2014) China	72	84	202	276	7.9%	1.17 [1.05, 1.31]	2014	— <b>—</b>
Chen J (2014) China	40	47	57	94	4.5%	1.40 [1.15, 1.72]	2014	· · · · · · · · · · · · · · · · · · ·
Park MS (2014) Korea	147	166	48	50	9.5%	0.92 [0.85, 1.00]	2014	
Wan P (2014) China	33	40	65	80	5.3%	1.02 (0.85, 1.21)	2014	
Goldaracena N (2019) Canada	101	118	401	527	9.1%	1.12 (1.03, 1.23)	2019	
Wong TCL (2019) China	141	161	71	85	8.0%	1.05 (0.94, 1.17)	2019	<b>_</b>
Lee S (2020) Korea	743	829	62	67	9.9%	0.97 [0.90, 1.04]	2020	
Total (95% CI)		2055		1923	100.0%	1.01 [0.95, 1.06]		•
Total events	1787		1556					
Heterogeneity: Tauf = 0.01; Chif =	= 38.76, df	°= 13 (P	= 0.0002	);	16%			0.7 0.85 1 1.2 1.5
Test for overall effect: $Z = 0.27$ (P	= 0.79)							Favours (DDLT) Favours (LDLT)
2-vear DFS								
	IDIT		DDI T			Risk Ratio		Risk Ratio
Study or Subgroup Ev	ents To	tal Eve	ents Tot	al We	eiaht IV.	Random, 95% Cl Ye	ar	IV. Random, 95% Cl
Gondolesi GE (2004) LISA	27	36	137 10	5 1/	5 7 %	0 90 10 74 1 101 20	0.4	
Hwang S (2005) Korea	101 2	37	66 7	75 7	2.6%	0.30 [0.74, 1.10] 20	05	<b>_</b> _
Fichor DA (2003) Notea	20	50 50	26 2	0 2. 01 11	0.070 1004		03	
KUBEL M (2007) COA	39 74 4	00	20 0	04 II 07 40	J.970 D.007	0.01 [0.70, 1.20] 20	40	
Kulik Livi (2012) USA	74 1	40	62 8	97 IS 20 4	9.970 • 007	0.88 [0.76, 1.01] 20	12	
Wan P (2014) China	31	40	5/ 10 50 011	50 14 20 44	4.0%	1.09 [0.88, 1.35] 20	14	
Xiao GQ (2014) China	57	84	149 27	0 10	0.5%	1.26[1.05, 1.51] 20	14	
Total (95% CI)	5	55	72	27 10	0.0%	0.98 [0.87, 1.09]		-
Total events	419		516					
Heterogeneity: Tau <sup>2</sup> = 0.01; Chi <sup>2</sup>	= 12.43. (	df = 5 (F	P = 0.03);	I² = 60	%		_	
Test for overall effect: Z = 0.40 (F	, e = 0.69)							U.7 U.85 1 1.2 1.5
3-year DFS								
	LDL	T	DDLT			Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
Hwang S (2005) Korea	198	237	63	75	10.1%	0.99 [0.89, 1.11]	2005	
Fisher RA (2007) USA	34	58	21	34	4.1%	0.95 [0.67, 1.34]	2007	
Di Sandro S (2009) Italy	24	25	140	154	10.7%	1.06 [0.96, 1.16]	2009	- <b>+</b>
Sharr WW (2011) China	75	90	31	34	9.3%	0.91 [0.79, 1.05]	2011	
Sandhu L (2012) Canada	44	58	216	287	8.6%	1.01 [0.86, 1.18]	2012	
Kulik LM (2012) USA	66	100	78	97	8.2%	0.82 [0.69, 0.97]	2012	
Lei J (2013) China	22	31	36	52	5.1%	1.03 [0.77, 1.37]	2013	
Xiao GQ (2014) China	47	84	136	276	6.6%	1.14 [0.91, 1.42]	2014	
Wan P (2014) China	29	40	57	80	6.3%	1.02 [0.80, 1.29]	2014	
Wong TCL (2019) China	146	161	62	85	9.3%	1.24 [1.08, 1.43]	2019	
Goldaracena N (2019) Canada	104	118	411	527	11.1%	1.13 [1.04, 1.22]	2019	— <b>•</b> —
Lee S (2020) Korea	589	829	59	67	10.6%	0.81 [0.73, 0.89]	2020	<b>_</b>
Total (95% CI)		1831		1769	100.0%	1 00 [0 02 1 00]		
Total avente	1270	1051	1210	1700	100.0%	1.00 [0.52, 1.09]		
Heterogeneity: Tau? = 0.02: Chi?	13/5 - NS Q1 - NS Q1 - NS Q1	f - 11 / P	1310 2 < N N N N S	11\·I₹–	76%			
Test for overall effect: 7 = 0.02, OII	= +3.31, u = 1 0.91	. – (r	- 0.0000		10.0			0.7 0.85 1 1.2 1.5
. 191101 010101 01001 <u>2</u> = 0.00 (I	0.007							Favours (DDL1) Favours (LDLT)

#### Fig. 3 DFS for LDLT and DDLT recipients

for HCC. To begin with, according to four of the included studies, the age and the sex of the receipt is not considered prognostic factor after transplantation.

Nevertheless, the MC have been well adopted worldwide as a set of guidelines for listing patients for LT [5]. However, these criteria are criticized for being too stringent, since many patients beyond the criteria could still have reasonable post-LT survival [51–53]. Nevertheless, according to the pooled hazard ratio, a significant increase in the recurrence of HCC could be detected for those who were beyond Milan criteria. In addition to that the biological markers could be used as a predictive value after liver transplantation. In other words, a high AFP level has been shown to be associated with poorer outcomes but the exact consensual cut-off value remains undefined [12, 38]. According to some recent studies, an AFP level of 54 ng/mL was associated with disease recurrence, and AFP level of 105 ng/mL was found to decrease overall survival [15]. In addition to that, using an AFP level > 1000 ng/mL as an exclusion criterion for LT within the MC may further improve posttransplant outcomes [54, 55]. In this meta-analysis, the pooled results from three

1.5

## 4-year DFS

	LDL	Г	DDL	Т		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
Hwang S (2005) Korea	196	237	61	75	28.2%	1.02 [0.90, 1.15]	2005	<b>#</b>
Fisher RA (2007) USA	28	58	22	34	11.8%	0.75 [0.52, 1.07]	2007	
Kulik LM (2012) USA	59	100	74	97	22.0%	0.77 [0.63, 0.94]	2012	
Wan P (2014) China	29	40	57	80	19.1%	1.02 [0.80, 1.29]	2014	<b>_</b>
Xiao GQ (2014) China	45	84	125	276	19.0%	1.18 [0.93, 1.50]	2014	
Total (95% CI)		519		562	100.0%	0.95 [0.81, 1.11]		-
Total events	357		339					
Heterogeneity: Tau <sup>2</sup> = 0.0	2; Chi <b>=</b> =	10.45, i	df = 4 (P :	= 0.03);	l² = 62%			
Test for overall effect: Z =	0.65 (P =	0.52)						Favours [DDLT] Favours [LDLT]

#### 5-year DFS

-	LDLT		DDLT		Risk Ratio			Risk Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Fixed, 95% Cl	Year	IV, Fixed, 95% Cl		
Hwang S (2005) Korea	196	237	57	75	8.6%	1.09 [0.95, 1.25]	2005	+		
Di Sandro S (2009) Italy	24	25	138	154	18.1%	1.07 [0.97, 1.18]	2009			
Giacomoni A (2009)	22	25	137	154	7.0%	0.99 [0.85, 1.16]	2009	<b>_</b> _		
Kornberg A (2011) Germany	10	12	56	78	2.0%	1.16 [0.87, 1.55]	2011			
Sharr WW (2011) China	70	90	31	34	7.3%	0.85 [0.73, 0.99]	2011			
Kulik LM (2012) USA	56	100	70	97	3.7%	0.78 [0.63, 0.96]	2012			
Sandhu L (2012) Canada	41	58	201	287	5.1%	1.01 [0.84, 1.21]	2012			
Lei J (2013) China	20	31	32	52	1.5%	1.05 [0.75, 1.47]	2013			
Wan P (2014) China	29	40	57	80	3.0%	1.02 [0.80, 1.29]	2014			
Xiao GQ (2014) China	45	84	125	276	3.0%	1.18 [0.93, 1.50]	2014			
Chen J (2014) China	28	47	43	94	1.6%	1.30 [0.94, 1.80]	2014			
Park MS (2014) Korea	39	166	18	50	0.8%	0.65 [0.41, 1.03]	2014			
Goldaracena N (2019) Canada	95	118	380	527	15.7%	1.12 [1.01, 1.24]	2019			
Wong TCL (2019) China	124	161	70	85	10.0%	0.94 [0.82, 1.06]	2019			
Lee S (2020) Korea	683	829	55	67	12.5%	1.00 [0.89, 1.13]	2020	-		
Total (95% CI)		2023		2110	100.0%	1.02 [0.98, 1.06]		•		
Total events	1482		1470							
Heterogeneity: Chi <sup>2</sup> = 26.44, df =	14 (P = 0.	02); I <sup>2</sup> =	: 47%							
Test for overall effect: Z = 0.94 (P	= 0.35)							Favours (DDLT) Favours (LDLT)		
6-year DFS										
L	DLT	D	DLT			Risk Ratio		Risk Ratio		

	LDL	LDLT		LDLT DDLT				Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl		
Hwang S (2005) Korea	196	237	57	75	29.9%	1.09 [0.95, 1.25]	2005			
Kulik LM (2012) USA	55	100	68	97	18.7%	0.78 [0.63, 0.98]	2012			
Wan P (2014) China	29	40	57	80	17.0%	1.02 [0.80, 1.29]	2014	<b>-</b>		
Lee S (2020) Korea	684	829	55	67	34.3%	1.01 [0.89, 1.13]	2020	<b>+</b>		
Total (95% CI)		1206		319	100.0%	0.98 [0.87, 1.11]		-		
Total events	964		237							
Heterogeneity: Tau <sup>2</sup> = 0.0	1; Chi <sup>2</sup> =	6.11, di	f= 3 (P =	0.11);1	²= 51%					
Test for overall effect: Z =	0.25 (P =	0.80)						Favours (DDLT) Favours (LDLT)		

#### 10-year DFS

	LDL	Т	DDLT		Risk Ratio			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
Hwang S (2005) Korea	196	237	57	75	29.9%	1.09 [0.95, 1.25]	2005	
Kulik LM (2012) USA	55	100	68	97	18.7%	0.78 [0.63, 0.98]	2012	<b>_</b>
Wan P (2014) China	29	40	57	80	17.0%	1.02 [0.80, 1.29]	2014	
Lee S (2020) Korea	684	829	55	67	34.3%	1.01 [0.89, 1.13]	2020	<b>+</b>
Total (95% CI)		1206		319	100.0%	0.98 [0.87, 1.11]		-
Total events	964		237					
Heterogeneity: Tau² = 0.0	1; Chi <sup>z</sup> =	6.11, d	f = 3 (P =	0.11);1	l² = 51%			
Test for overall effect: Z =	0.25 (P =	0.80)						Favours (DDLT) Favours (LDLT)

Fig. 3 (continued)

studies showed that an AFP level > 400 IU/mL at the time of transplantation was associated with a significant increase in the recurrence rate [12, 36, 38].

Additionally, this study illustrates that the presence of MVI increases the recurrence and mortality rate after transplantation. In addition to that, according to Lim et al. [16], HCC patients exceeding the MC without MVI could achieve comparable overall survival rates after surgical resection, relative to patients within Milan. In other words, to improve survival and decrease recurrence after

## 1-year ITT-OS

	LDL	т	DDL	т		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
Bhangui P (2011) France	31	36	130	147	17.3%	0.97 [0.84, 1.12]	2011	
Tomiyama K (2016) Canada	103	119	458	545	21.0%	1.03 [0.95, 1.12]	2016	
Azoulay D (2017) France	68	79	601	782	20.1%	1.12 [1.02, 1.23]	2017	
Goldaracena N (2019) Canada	189	219	398	632	21.0%	1.37 [1.27, 1.48]	2019	<b>_</b>
Wong TCL (2019) China	177	188	145	187	20.7%	1.21 [1.12, 1.32]	2019	<b>_</b>
Total (95% CI)		641		2293	100.0%	1.14 [1.01, 1.28]		
Total events	568		1732					
Heterogeneity: Tau <sup>2</sup> = 0.02; Chi <sup>2</sup> =	= 32.64, d	f=4 (P	< 0.0000	)1); I <sup>2</sup> =	88%		_	
Test for overall effect: Z = 2.16 (P	= 0.03)							Favours [DDLT] Favours [LDLT]

## 2-year ITT-OS

	LDL	Т	DDL	Т		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
Bhangui P (2011) France	29	36	122	147	30.5%	0.97 [0.81, 1.16]	2011	
Azoulay D (2017) France	66	79	518	782	35.4%	1.26 [1.13, 1.41]	2017	<b></b>
Wong TCL (2019) China	165	188	112	187	34.1%	1.47 [1.29, 1.67]	2019	<b>_</b>
Total (95% CI)		303		1116	<b>100.0</b> %	1.23 [1.00, 1.50]		
Total events	260		752					
Heterogeneity: Tau² = 0.03;	Chi <sup>2</sup> = 13	.67, df	= 2 (P = 0	0.001);	I² = 85%			
Test for overall effect: Z = 1.	94 (P = 0.	05)						0.7 0.85 T T.2 T.5 Favours (DDLT) Favours (LDLT)

## 3-year ITT-OS

	LDL	Т	DDL	Т		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
Bhangui P (2011) France	29	36	113	147	18.0%	1.05 [0.87, 1.26]	2011	
Tomiyama K (2016) Canada	88	119	365	545	21.0%	1.10 [0.98, 1.25]	2016	
Azoulay D (2017) France	60	79	419	782	20.1%	1.42 [1.23, 1.63]	2017	
Goldaracena N (2019) Canada	159	219	398	632	21.9%	1.15 [1.04, 1.28]	2019	_ <b></b>
Wong TCL (2019) China	153	188	91	187	19.0%	1.67 [1.42, 1.97]	2019	
Total (95% CI)		641		2293	100.0%	1.26 [1.08, 1.47]		-
Total events	489		1386					
Heterogeneity: Tau <sup>2</sup> = 0.03; Chi <sup>2</sup> :	= 25.22, d	f=4 (P	< 0.0001	l); I² = 8	34%		_	
Test for overall effect: Z = 2.91 (P	= 0.004)							Favours (DDLT) Favours (LDLT)

## 4-year ITT-OS

	LDL	LDLT		DDLT		Risk Ratio		Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% Cl	Year	IV, Random, 95% Cl
Bhangui P (2011) France	27	36	106	147	32.3%	1.04 [0.84, 1.29]	2011	— <b>—</b> —
Azoulay D (2017) France	55	79	327	782	34.4%	1.66 [1.41, 1.97]	2017	
Wong TCL (2019) China	138	188	77	187	33.3%	1.78 [1.47, 2.16]	2019	_ <b>_</b>
Total (95% CI)		303		1116	100.0%	1.46 [1.07, 1.99]		
Total events	220		510					
Heterogeneity: Tau <sup>2</sup> = 0.07;	Chi <sup>2</sup> = 15	.87, df	= 2 (P = 0	).0004)	; I² = 87%	•		
Test for overall effect: Z = 2.	41 (P = 0.	02)						Favours [DDLT] Favours [LDLT]

## 5-year ITT-OS

	LDL	LDLT DDLT		Т	Risk Ratio			Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	Year	M-H, Random, 95% Cl
Bhangui P (2011) France	26	36	105	147	18.7%	1.01 [0.81, 1.27]	2011	<b>+</b>
Tomiyama K (2016) Canada	81	119	322	545	21.1%	1.15 [1.00, 1.33]	2016	
Azoulay D (2017) France	49	79	259	782	19.5%	1.87 [1.53, 2.29]	2017	
Goldaracena N (2019) Canada	149	219	360	632	21.7%	1.19 [1.07, 1.34]	2019	
Wong TCL (2019) China	127	188	66	187	19.0%	1.91 [1.54, 2.38]	2019	<b>_</b>
Total (95% CI)		641		2293	100.0%	1.37 [1.09, 1.72]		-
Total events	432		1112					
Heterogeneity: Tau <sup>2</sup> = 0.06; Chi <sup>2</sup> =	= 35.47, d	f= 4 (P	< 0.0000	01); I² =	89%		_	
Test for overall effect: Z = 2.74 (P	= 0.006)							Favours (DDLT) Favours (LDLT)

## Fig. 4 ITT-OS for LDLT and DDLT recipients

	LDLT		DDL	Т	Risk Ratio			Risk Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% Cl	Year	r IV, Random, 95% Cl	
Roayaie S (2004) USA	7	36	50	275	7.7%	1.07 [0.53, 2.18]	2004	4 —	
Hwang S (2005) Korea	33	273	11	75	8.3%	0.82 [0.44, 1.55]	2005	5	
Fisher RA (2007) USA	17	58	0	34	1.3%	20.76 [1.29, 334.62]	2007	7	-
Allam N (2008) KSA	1	8	2	15	1.8%	0.94 [0.10, 8.82]	2008	в	
Di Sandro S (2009) Italy	1	25	16	154	2.2%	0.39 [0.05, 2.78]	2009	3	
Vakili K (2009) USA	8	28	7	74	6.2%	3.02 [1.21, 7.55]	2009	9	
Azzam AZ (2011) KSA	2	18	5	34	3.3%	0.76 [0.16, 3.51]	2011	1	
Bhangui P (2011) France	4	31	14	110	5.5%	1.01 [0.36, 2.86]	2011	1	
Kulik LM (2012) USA	28	100	8	97	7.5%	3.40 [1.63, 7.08]	2012	2	
Lei J (2013) China	7	31	13	52	7.0%	0.90 [0.40, 2.02]	2013	3	
Li C (2013) China	18	160	43	156	9.3%	0.41 [0.25, 0.68]	2013	3	
Chen J (2014) China	19	47	49	94	10.2%	0.78 [0.52, 1.15]	2014	4	
Wan P (2014) China	10	40	22	80	8.2%	0.91 [0.48, 1.73]	2014	4 -	
Park MS (2014) Korea	29	166	3	50	4.9%	2.91 [0.93, 9.16]	2014	4	
Azoulay D (2017) France	7	75	51	576	7.3%	1.05 [0.50, 2.24]	2017	7 +	
Goldaracena N (2019) Canada	17	118	97	527	9.5%	0.78 [0.49, 1.26]	2019	9	
Total (95% CI)		1214		2403	100.0%	1.07 [0.77, 1.48]		. ◆	
Total events	208		391						
Heterogeneity: Tau <sup>2</sup> = 0.24; Chi <sup>2</sup> =	: 39.72, d	f= 15 (	P = 0.000	l5); l² =	62%				_
Test for overall effect: Z = 0.38 (P	= 0.70)							Favours (LDLT) Favours (DDLT)	J

#### Fig. 5 Recurrence for LDLT and DDLT recipients

Table 3 OS for LDLT and DDLT within and be	eyond	Milan	criteria
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Subgroup	Outcome	Studies (n)	Patient ( <i>n</i> )	Effect estimate [RR (95% CI)]	Heterogeneity	Test for overall effect	Favour group
Within Milan	1 year OS	5	1593	1.04 [0.96, 1.12]	$I^2 = 72\% \ (p = 0.006)$	Z=1.02 (p=0.31)	None
	2 year OS	4	1502	1.06 [0.97, 1.16]	$I^2 = 70\% \ (p = 0.02)$	$Z = 1.23 \ (p = 0.22)$	None
	3 year OS	5	1580	1.01 [0.88, 1.16]	$I^2 = 81\% (p = 0.0002)$	Z = 0.15 (p = 0.88)	None
	4 year OS	4	1502	1.07 [0.92, 1.25]	$I^2 = 83\% \ (p = 0.0005)$	Z = 0.85 (p = 0.39)	None
	5 year OS	5	1593	1.10 [0.93, 1.29]	$I^2 = 83\% (p = 0.0001)$	Z = 1.10 (p = 0.27)	None
	6 year OS	3	1271	1.22 [0.97, 1.52]	$I^2 = 88\% \ (p = 0.0002)$	$Z = 1.70 \ (p = 0.09)$	None
	10 year OS	2	1078	1.23 [0.83, 1.84]	$I^2 = 96\% \ (p < 0.00001)$	$Z = 1.04 \ (p = 0.30)$	None
Beyond Milan	1 year OS	4	501	1.02 [0.94, 1.10]	$I^2 = 0\% (p = 0.73)$	Z = 0.50 (p = 0.62)	None
	2 year OS	4	501	1.06 [0.95, 1.18]	$I^2 = 0\% \ (p = 0.83)$	Z = 0.98 (p = 0.33)	None
	3 year OS	4	501	1.16 [1.01, 1.32]	$I^2 = 0\% \ (p = 0.60)$	Z = 2.16 (p = 0.03)	LDLT
	4 year OS	4	501	1.20 [1.04, 1.38]	$I^2 = 32\% \ (p = 0.22)$	$Z = 2.44 \ (p = 0.01)$	LDLT
	5 year OS	3	420	1.32 [1.13, 1.54]	$I^2 = 0\% (p = 0.79)$	$Z = 3.44 \ (p = 0.0006)$	LDLT
	6 year OS	2	313	1.30 [1.03, 1.64]	$I^2 = 0\% (p = 0.75)$	Z = 2.25 (p = 0.02)	LDLT
	10 year OS	2	313	1.42 [1.07, 1.87]	$I^2 = 34\% \ (p = 0.22)$	Z = 2.47 (p = 0.01)	LDLT

transplantation, radiological tools are needed to predict the presence of MVI before liver transplantation [56, 57]. Moreover, macrovascular invasion of hepatic or portal veins has been documented in up to one-third of patients with hepatocellular carcinoma (HCC) [58]. According to AASLD Guidelines it is considered a contraindication to liver transplantation [59]. In our study, the presence of macrovascular invasion is associated with a dramatic increase in the recurrence rate and a significant decrease in survival. Thus it can be said that those patients could benefit from down staging [60].

Moreover, tumor grade of differentiation had a statistically significant effect on the long-term prognosis of HCC after LT. This is explained by Pawlik et al. that the grade was the most powerful predictor of occult vascular invasion [17]. Therefore, the role of percutaneous biopsy for grading prior to transplantation requires study as a way to improve outcomes.

Subgroup	Outcome	Studies (n)	Patient (n)	Effect estimate [RR (95% CI)]	Heterogeneity	Test for overall effect	Favour group
Within Milan	1 year DFS	2	853	0.99 [0.89, 1.10]	$I^2 = 64\% \ (p = 0.10)$	Z = 0.18 (p = 0.86)	None
	2 year DFS	1	762	N/A	N/A	N/A	N/A
	3 year DFS	2	853	0.93 [0.89, 0.97]	$I^2 = 6\% \ (p = 0.30)$	$Z = 3.42 \ (p = 0.0006)$	DDLT
	4 year DFS	1	762	N/A	N/A	N/A	N/A
	5 year DFS	2	853	0.96 [0.83, 1.11]	$I^2 = 47\% (p = 0.17)$	$Z = 0.61 \ (p = 0.54)$	None
	6 year DFS	1	762	N/A	N/A	N/A	N/A
	10 year DFS	1	762	N/A	N/A	N/A	N/A
Beyond Milan	1 year DFS	1	134	N/A	N/A	N/A	N/A
	2 year DFS	1	134	N/A	N/A	N/A	N/A
	3 year DFS	1	134	N/A	N/A	N/A	N/A
	4 year DFS	1	134	N/A	N/A	N/A	N/A
	5 year DFS	1	134	N/A	N/A	N/A	N/A
	6 year DFS	1	134	N/A	N/A	N/A	N/A
	10 year DFS	1	134	N/A	N/A	N/A	N/A

Table 4 DFS for LDLT and DDLT within and beyond Milan criteria

 Table 5
 OS for LDLT and DDLT according to the region of transplantation

Subgroup	Outcome	Studies (n)	Patient (n)	Effect estimate [RR (95% CI)]	Heterogeneity	Test for overall effect	Favour group
Asia	1 year OS	11	2722	1.03 [0.98, 1.07]	$I^2 = 44\% \ (p = 0.06)$	Z=1.14 (p=0.25)	None
	2 year OS	5	1771	1.07 [1.00, 1.14]	$I^2 = 0\% \ (p = 0.56)$	Z = 1.82 (p = 0.07)	None
	3 year OS	8	2357	1.09 [0.98, 1.21]	$I^2 = 68\% (p = 0.003)$	$Z = 1.64 \ (p = 0.10)$	None
	4 year OS	5	1771	1.08 [1.00, 1.18]	$I^2 = 0\% (p = 0.81)$	Z = 1.89 (p = 0.06)	None
	5 year OS	9	1625	1.03 [0.95, 1.12]	$I^2 = 22\% \ (p = 0.25)$	Z = 0.82 (p = 0.41)	None
	6 year OS	2	1208	1.06 [0.95, 1.18]	$I^2 = 0\% \ (p = 0.83)$	Z=0.97 (p=0.33)	None
	10 year OS	1	896	N/A	N/A	N/A	N/A
America	1 year OS	8	2434	1.06 [1.02, 1.10]	$I^2 = 31\% \ (p = 0.18)$	Z = 3.08 (p = 0.002)	LDLT
	2 year OS	5	937	1.01 [0.89, 1.15]	$I^2 = 67\% \ (p = 0.02)$	$Z = 0.21 \ (p = 0.83)$	None
	3 year OS	6	1921	1.05 [0.93, 1.18]	$I^2 = 77\% \ (p = 0.0005)$	Z=0.75 (p=0.45)	None
	4 year OS	3	644	1.11 [0.93, 1.34]	$I^2 = 54\% \ (p = 0.11)$	Z = 1.13 (p = 0.26)	None
	5 year OS	5	1829	1.02 [0.90, 1.16]	$I^2 = 68\% (p = 0.01)$	$Z = 0.31 \ (p = 0.76)$	None
	6 year OS	2	299	1.17 [0.61, 2.23]	$I^2 = 93\% \ (p = 0.0002)$	Z = 0.48 (p = 0.63)	None
	10 year OS	0	0	N/A	N/A	N/A	N/A
Europe	1 year OS	5	1420	0.99 [0.91, 1.09]	$I^2 = 44\% \ (p = 0.13)$	Z=0.13 (p=0.90)	None
	2 year OS	3	907	0.88 [0.64, 1.22]	$I^2 = 85\% (p = 0.001)$	Z = 0.77 (p = 0.44)	None
	3 year OS	4	1086	1.03 [0.95, 1.13]	$I^2 = 0\% (p = 0.72)$	Z = 0.75 (p = 0.46)	None
	4 year OS	3	907	0.99 [0.90, 1.10]	$I^2 = 0\% (p = 0.50)$	Z = 0.18 (p = 0.86)	None
	5 year OS	4	1079	0.87 [0.71, 1.06]	$I^2 = 58\% (p = 0.07)$	Z = 1.35 (p = 0.18)	None
	6 year OS	1	197	N/A	N/A	N/A	N/A
	10 year OS	0	0	N/A	N/A	N/A	N/A

To our knowledge, it is the first time for 2-, 4-, 6-, 10-year outcomes and predictors of recurrence after liver transplantation to be included in a meta-analysis. In addition to that, all studies designed to compare the outcome between LDLT and DDLT for HCC patients were included to increase the statistical power of the results.

However, we have to acknowledge some limitations in our study. First, all the studies included were cohort

Subgroup	Outcome	Studies (n)	Patient (n)	Effect estimate [RR (95% CI)]	Heterogeneity	Test for overall effect	Favour group
Asia	1 year DFS	9	2498	1.02 [0.95, 1.09]	$I^2 = 69\% \ (p = 0.001)$	Z=0.52 (p=0.60)	None
	2 year DFS	3	792	1.07 [0.87, 1.31]	$I^2 = 78\% \ (p = 0.010)$	Z = 0.61 (p = 0.54)	None
	3 year DFS	7	2141	1.00 [0.88, 1.14]	$I^2 = 79\% \ (p < 0.0001)$	Z = 0.03 (p = 0.98)	None
	4 year DFS	3	792	1.04 [0.95, 1.15]	$I^2 = 0\% (p = 0.53)$	Z = 0.85 (p = 0.39)	None
	5 year DFS	10	2843	1.00 [0.93, 1.08]	$I^2 = 38\% \ (p = 0.11)$	$Z = 0.00 \ (p = 1.00)$	None
	6 year DFS	3	1328	1.04 [0.95, 1.13]	$I^2 = 0\% (p = 0.68)$	Z = 0.82 (p = 0.41)	None
	10 year DFS	1	896	N/A	N/A	N/A	N/A
America	1 year DFS	5	1480	0.99 [0.89, 1.09]	$I^2 = 68\% (p = 0.01)$	Z = 0.28 (p = 0.78)	None
	2 year DFS	3	490	0.89 [0.80, 0.99]	$I^2 = 0\% (p = 0.95)$	Z=2.14 (p=0.03)	DDLT
	3 year DFS	4	1279	0.99 [0.84, 1.16]	$I^2 = 74\% \ (p = 0.008)$	Z = 0.18 (p = 0.85)	None
	4 year DFS	2	289	0.77 [0.64, 0.91]	$I^2 = 0\% (p = 0.86)$	Z=2.99 (p=0.003)	DDLT
	5 year DFS	3	1187	0.97 [0.79, 1.19]	$I^2 = 78\% \ (p = 0.01)$	Z=0.27 (p=0.78)	None
	6 year DFS	1	197	N/A	N/A	N/A	N/A
	10 year DFS	0	0	N/A	N/A	N/A	N/A
Europe	1 year DFS	0	0	N/A	N/A	N/A	N/A
	2 year DFS	0	0	N/A	N/A	N/A	N/A
	3 year DFS	1	179	N/A	N/A	N/A	N/A
	4 year DFS	0	0	N/A	N/A	N/A	N/A
	5 year DFS	3	448	1.06 [0.98, 1.14]	$I^2 = 0\% (p = 0.55)$	Z = 1.35 (p = 0.18)	None
	6 year DFS	0	0	N/A	N/A	N/A	N/A
	10 year DFS	0	0	N/A	N/A	N/A	N/A

 Table 6
 DFS for LDLT and DDLT according to the region of transplantation

 Table 7
 Prognostic factors after liver transplantation

Variable	Studies (n)	Effect estimate [HR (95% CI)]	Heterogeneity	Test for overall effect	Reference
Recipient male sex	2	0.97 [0.74, 1.27]	$I^2 = 38\% (p = 0.20)$	Z=0.21 (p=0.83)	Female sex
Recipient age, years	2	1.01 [0.99, 1.03]	$I^2 = 24\% (p = 0.27)$	Z=1.17 (p=0.24)	Per 1 year increase
Beyond Milan criteria	2	1.89 [1.19, 3.00]	$I^2 = 71\% (p = 0.03)$	Z=2.69 (p=0.007)	Within Milan
AFP>400	0	N/A	N/A	N/A	N/A
No. of tumor nodules	2	1.04 [1.01, 1.07]	$I^2 = 70\% (p = 0.03)$	$Z = 2.40 \ (p = 0.02)$	Per 1 nodule increase
Largest tumor diameter, cm	2	1.09 [1.05, 1.12]	$I^2 = 33\% (p = 0.22)$	$Z = 4.91 \ (p < 0.00001)$	Per 1 cm increase
Microscopic vascular invasion	2	1.89 [1.52, 2.36]	$I^2 = 0\% (p = 0.44)$	$Z = 5.64 \ (p < 0.00001)$	No
Macroscopic vascular invasion	1	N/A	N/A	N/A	N/A
Poor differentiation	2	1.65 [1.21, 2.25]	$I^2 = 0\% (p = 0.69)$	Z = 3.16 (p = 0.002)	Well/mod differentiated

studies because no randomized controlled trials could be found. Second, the existence of significant heterogeneity in several outcomes could not be explained well enough by subgroup analysis. Third, included studies were conducted in different regions where policies and ethics about LT were different, and this might cause potential bias.

## Conclusion

This study is in consonance with the view that cancer biology (not the graft type) is the most important determinant of recurrence and survival after LT. However, LDLT provided much better survival benefits to HCC patients especially in regions that suffer from low deceased organ availability.

Table 8 Predictor values of recurrence after liver transplantation

Variable	Studies (n)	Effect estimate [HR (95% CI)]	Heterogeneity	Test for overall effect	Reference
Recipient male sex	3	1.02 [0.70, 1.48]	$I^2 = 0\% \ (p = 0.83)$	Z=0.09 (p=0.93)	Female sex
Recipient age, years	4	0.99 [0.97, 1.01]	$I^2 = 0\% (p = 0.57)$	Z = 1.12 (p = 0.26)	Per 1 year increase
Beyond Milan criteria	4	2.81 [1.69, 4.69]	$I^2 = 73\% \ (p = 0.005)$	Z = 3.98 (p < 0.0001)	Within Milan
AFP > 400	3	3.70 [2.11, 6.47]	$I^2 = 33\% (p = 0.22)$	$Z = 4.58 \ (p < 0.00001)$	AF <i>P</i> < 400
No. of tumor nodules	4	1.14 [1.08, 1.20]	$I^2 = 46\% \ (p = 0.12)$	$Z = 4.83 \ (p < 0.00001)$	Per 1 nodule increase
Largest tumor diameter, cm	4	1.19 [1.06, 1.32]	$I^2 = 86\% \ (p < 0.00001)$	Z = 3.04 (p = 0.002)	Per 1 cm increase
Microscopic vascular invasion	4	3.73 [2.78, 5.01]	$I^2 = 26\% (p = 0.25)$	$Z = 8.77 \ (p < 0.00001)$	No
Macroscopic vascular invasion	3	3.88 [2.64, 5.70]	$I^2 = 53\% (p = 0.12)$	$Z = 6.91 \ (p < 0.00001)$	No
Poor differentiation	2	2.69 [1.29, 5.61]	$I^2 = 62\% \ (p = 0.07)$	$Z = 2.63 \ (p = 0.008)$	Well/mod differentiated

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#### Declarations

**Conflict of interest** Beshoy Effat Elkomos, Mostafa Abdo, Remon Mamdouh and Amr Abdelaal declare no competing interest.

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