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META-ANALYSIS

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Salvage Liver Transplant versus Primary Liver Transplant for Patients with Hepatocellular Carcinoma

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Background: The strategy of salvage liver transplantation (SLT) originated for initially resectable and transplantable hepatocellular carcinoma (HCC) to preclude upfront transplantation, with SLT in the case of recurrence. However, SLT remains a controversial approach in comparison to primary liver transplant (PLT). The aim of our study was to conduct a systemic review and meta-analysis to assess the short-term outcomes, overall survival (OS), and disease-free survival (DFS) between SLT and PLT for patients with HCC, stratifying results according to the Milan criteria and donor types.

Material/Methods: A search of PubMed, EMBASE, and the Cochrane Library was conducted to identify studies comparing SLT and PLT. A fixed effects model and a random effects model meta-analysis were conducted to assess the short-term outcomes, OS, and DFS based on the evaluation of heterogeneity.

Results: SLT had superior 1-year, 3-year, and 5-year OS and DFS compared with that of PLT. After classifying data according to donor type and Milan criteria, our meta-analysis revealed: that for deceased-donor liver transplantation (DDLT) recipients, there were no significant differences in 1-year and 3-year OS rate between the SLT group and the PLT group. However, the 5-year OS rate was superior in the SLT group compared to the PLT group. Similarly, SLT had superior 1-year, 3-year, and 5-year OS rate compared to PLT in living-donor liver transplantation (LDLT) recipients. Moreover, 1-year, 3-year, and 5-year DFS were also superior in SLT compared to PLT in both the DDLT and LDLT recipients. In patients within Milan criteria there were no statistically significant differences in 1-year, 3-year, and 5-year OS and DFS between the SLT group and the PLT group. Similarly, in patients beyond Milan criteria, both SLT and PLT showed no significant difference for 1-year, 3-year, and 5-year OS rate.

Conclusions: Our meta-analysis included the largest number of studies comparing SLT and PLT, and SLT was found to have significantly better OS and DFS. Moreover, this meta-analysis suggests that SLT has comparable postoperative complications to that of PLT, and thus, SLT may be a better treatment strategy for recurrent HCC patients and patients with compensated liver, whenever feasible, considering the severe organ limitation and the safety of SLT. However, PLT can be referred as a treatment strategy for HCC patients with cirrhotic and decompensated liver.

MeSH Keywords: Carcinoma, Hepatocellular • Hepatectomy • Liver Transplantation

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Background

Hepatocellular carcinoma (HCC) is the most common liver cancer [1,2], and it is the third highest cause of cancer-associated deaths worldwide [3]. HCC has become a considerable global health issue. Currently, liver transplantation (LT) is an ideal treatment for early stage HCC patients [4,5]. LT treats both the tumor and concealed liver disease, and it has the highest cure rate among treatments [5,6]. In recent years, transplant centers have experienced a consistent growth in the number of patients with HCC who are contenders for LT. LT for HCC constitutes 15–50% of all LTs performed in most transplant centers [7,8]. Even though LT is an exceptional treatment option for HCC patients, the number of patients waiting for an LT surpasses the number of available donors [9,10]. Thus, not all patients with HCC are a considered for primary liver transplantation (PLT).

The shortage of donors compared with the number of patients in need of a transplant is a serious and a persisting problem worldwide. To overcome long waiting lists, disease progression, and the dropout rate for LT, different "bridging" therapies, such as liver resection (LR) [11], radioembolization [12], radiofrequency ablation [13], and transarterial chemoembolization [14], have been used if waiting time for LT is more than 6 months. Majno et al. was the first to suggest salvage liver transplantation (SLT), which refers to an LT done after LR for HCC or crumbling of liver function after LR [15]. Since then, several studies have shown SLT is an effective approach for patients with recurrent HCC or crumbling of liver function after LR [11,16]. However, some studies have shown negative results for SLT compared to PLT [17,18], mainly related to surgical difficulties due to adhesions, increased rate of post-transplant complications, and poor long-term outcomes. Thus, SLT remains a controversial approach for many surgeons.

To our knowledge, only a few systematic evaluations of the short-term and long-term outcomes between SLT and PLT have been performed, and these evaluations have included only a few studies and a small total number of patients. Therefore, the main aim of this meta-analysis was to include more studies and a larger sample size in the comparison of SLT and PLT for short-term and long-term outcomes. Our study results may help physicians select which approach would likely have a major survival benefit for HCC patients and allow physicians to efficiently utilize a limited source of liver donors.

Material and Methods

Search strategy

Eligible studies for this systematic review and meta-analyses were identified by 2 authors (DY and WC) independently, following an a priori established protocol using the PubMed/MEDLINE, Embase, and Cochrane Library databases, and combining Medical Subject Headings (MeSH) and non-MeSH terms: liver transplantation, salvage liver transplantation, salvage transplantation, liver resection, PLT, SLT, hepatic resection, hepatectomy, hepatocellular carcinoma, tumor recurrence, primary liver carcinoma, and HCC. In addition, relevant bibliographical lists of reviews were searched to identify other relevant studies. After an initial screening, abstracts, duplicate articles, or unpublished studies were excluded. The meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [19].

Study selection

Considering that this systematic review investigated data with respect to outcomes, both retrospective and prospective studies were considered eligible. The goal was to guarantee the quality of the systematic review by only considering complete articles and not abstracts. We established a priori defined eligibility criteria for selection of studies. The inclusion criteria included: 1) study had a definition of SLT and PLT with SLT referred to as an LT done after LR for HCC or crumbling of liver function after LR, and PLT characterized as an LT done for HCC without any prior LR. 2) Study that had patients with HCC and compared short-term and long-term results between SLT and PLT. 3) Study had sufficient data to conduct a meta-analysis.

The exclusion criteria included: 1) study without human subjects. 2) Study containing advance disease stage or extrahepatic metastases. 3) Study with no comparison between SLT and PLT. 4) Study with a multi-organ transplant. 5) Study with patients older than 70 years. 6) Study with duplicate data from the same institution. 7) Publication such as review article, editorial, case report, conference report, or letter.

Data extraction

All data were extracted according to the study selection criteria in a systematize data abstraction form in Microsoft Excel 2007 (Microsoft Corp.). The extracted data included the name of the first author, study characteristics (publication year, country, and study design), participant characteristics (average age of the recipients, sample size of SLT and PLT within and beyond Milan criteria, and sample size of SLT and PLT according to donor types), pre-transplant Model for End-Stage Liver Disease (MELD) score, pre-transplant alpha-fetoprotein (AFP) level,

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pre-transplant tumor status, pre-transplant "bridging" therapies, the duration of follow-up, and outcomes (biliary complications, sepsis, postoperative bleeding, vascular complications, perioperative mortality, OS, and DFS). Moreover, in case of insufficient data, investigators were approached to collect more relevant results. Conflicts in data extraction were resolved by discussion or consensus with a third reviewer.

Quality assessment

The quality of included studies was evaluated with the Newcastle-Ottawa scale (NOS) [20]. The scale is comprised of 3 assessment factors: 1) assessment of a selection of the study groups; 2) comparability of 2 groups; and 3) outcome assessment. The NOS ranges from 0 to 9. Studies with scores 7 were thought to be high quality, 4-6 moderate quality, and less than 4 low quality **(**Table 1).

Statistical analysis

All results are accounted for as in the original articles and were double-checked. A meta-analysis was carried out with RevMan Version 5.3 (Review Manager, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Outcomes are calculated as pooled odds ratios (ORs) and standard mean difference (SMD) with corresponding 95% confidence intervals (CIs). Fixed-effect or random-effect models were utilized to compute summary estimates based on the evaluation of heterogeneity. Overall effects were evaluated using the Z-test; heterogeneity was tested using Cochran's χ^2 test. The I^2 statistic was used to evaluate heterogeneity, which was characterized as low, moderate, or high (>25%, >50%, and >75% respectively) [21]. Two-sided *P*-values less than 0.05 were considered significant.

Outcome measures

Pre-transplant parameters examined were: MELD score, AFP level, bridging therapies, and tumor status. Postoperative outcome parameters examined were: biliary complications (includes biliary strictures or fistulas), sepsis, postoperative bleeding, vascular complications, and operative mortality. Long-term outcomes were: 1-year, 3-year, and 5-year OS and DFS rates for patients within and beyond Milan criteria, and donor types along with follow-up period.

Results

Study search and included studies

The database search identified 3714 references for assessment (Figure 1) of which 154 full-text articles were assessed for eligibility; of these, 134 articles were excluded (121 did not meet inclusion criteria and 13 had insufficient data). The remaining 20 retrospective studies between 2003 and 2017 were eligible according to our inclusion criteria and were included in this meta-analysis [11,16–18,22–37], with a total of 9879 patients included (SLT=1306 patients and PLT=8573 patients) (Table 2).

Meta-analysis

Pre-transplant MELD score between SLT and PLT

To assess the outcome measurement of MELD scores, a total of 1308 patients were included from 7 studies [16,23,26–28,31,32]. The χ^2 test revealed *P*=0.07 and I^2=48%; meta-analysis using a fixed effect model revealed that SLT had significantly lower MELD score than that of PLT (SMD: –0.22, 95% CI: –0.37 to –0.07, *P*=0.004) (Figure 2A).

Pre-transplant AFP level between SLT and PLT

To assess the outcome measurement of AFP level, a total of 8382 patients were included from 7 studies [17,18,26,27,30,32,37]. The χ^2 test revealed *P*=0.002 and I^2=71%; meta-analysis using a random effect model revealed that SLT had a significantly lower AFP level than that of PLT (SMD: –0.27, 95% CI: –0.51 to –0.04, *P*=0.02) (Figure 2B).

Pre-transplant tumor status between SLT and PLT

Our meta-analysis found that the maximum tumor diameter and the number of tumors >3 cm was significantly higher in PLT patients than in SLT patients: (SMD: –0.51, 95% CI: –0.95 to –0.08, *P*=0.02, Figure 3A) [17,22,26,30,32,35,37], and (OR: 0.59, 95% CI: 0.41 to 0.86, *P*=0.006, Figure 3B) [17,26,27,33,34] respectively. However, SLT patients had significantly higher numbers of nodules than PLT patients (SMD: 0.57, 95% CI: 0.17 to 0.97, *P*=0.005, Figure 3C) [17,22,26,30,32,35,37]. But, the meta-analysis of >3 nodules was not significantly different between the 2 groups (OR: 2.36, 95% CI: 0.86 to 6.46, *P*=0.09, Figure 3D) [16,17,33,34].

Pre-transplant therapy between SLT and PLT

While looking at pre-transplant therapy between SLT patients and PLT patients in the included studies, we found no significant difference between the 2 groups (OR: 1.78, 95% CI: 0.87 to 3.62, *P*=0.11, Figure 4A) [16,17,26,28,30,33,34].

Follow-up period between SLT patients and PLT patients

While looking at the follow-up period between SLT patients and PLT patients in the included studies we found that there was no significant difference between the 2 groups (SMD: –0.25, 95% CI: –0.56 to 0.05, *P*=0.10, Figure 4B) [16–18,22–24,26–31,34–37].

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Table 1. Newcastle-Ottawa Quality Assessment Scale.

Study	Selection				Comparability	Outcome			Overall
	Representativeness of exposed cohort	Selection of non exposed	Ascertainment of exposure	Outcome Not Present at Start Of study	Comparability of cohorts	Assessment of Outcome	Adequate Follow-Up Length	Adequacy of Follow-Up	
Adam 2003 [17]	1	1	1	1	2	1	1	0	8
Belghiti 2003 [22]	1	1	1	1	2	0	1	0	7
Hwang 2007 [23]	1	1	1	1	2	0	0	0	6
Scatton 2008 [24]	1	1	1	1	1	0	1	0	6
Margarit 2005 [25]	1	1	1	1	1	0	1	0	6
Del Gaudio 2008 [26]	1	1	1	1	2	0	1	1	8
Wang 2016 [27]	1	1	1	1	2	0	0	1	7
Liu 2012 [28]	1	1	1	1	1	1	0	1	7
Facciuto 2008 [29]	1	1	1	1	1	0	0	1	6
Hu 2012 [30]	1	1	1	1	2	0	1	0	7
Cherqui 2009 [11]	1	1	1	1	2	0	1	0	7
Kim 2008 [31]	1	1	1	1	2	0	0	1	8
Vasavada 2015 [32]	1	1	1	1	2	0	1	1	8
Wu 2012 [16]	1	1	1	1	2	0	1	1	8
Bhangui 2016 [33]	1	1	1	1	2	0	1	1	8
Moon 2012 [34]	1	1	1	1	2	0	1	1	8
Sapisochin 2010 [35]	1	1	1	1	2	0	0	1	7
Shan 2017 [18]	1	1	1	1	2	0	0	1	6
Vennarecci 2007 [36]	1	1	1	1	2	1	0	0	7
Shao 2008 [37]	1	1	1	1	2	0	0	0	6

OS outcomes between SLT and PLT

To assess the outcome measurement of 1-year OS, a total of 9725 patients were included from 19 studies [16–18,22–37]. The χ^2 test revealed P=0.48 and I^2=0%; meta-analysis using a fixed effect model revealed that the SLT group (74.30%) had superior 1-year OS rate compared to the PLT group (77.01%), which was statistically significant (OR: 0.86, 95% CI: 0.75 to 0.98, P=0.03) Figure 5A.

To assess the outcome measurement of the 3-year OS rate, a total of 9649 patients were included from 18 studies [16–18, 22–30,32–37]. The χ^2 test revealed P=0.48 and I^2=0%; meta-analysis using a fixed effect model revealed that the SLT group

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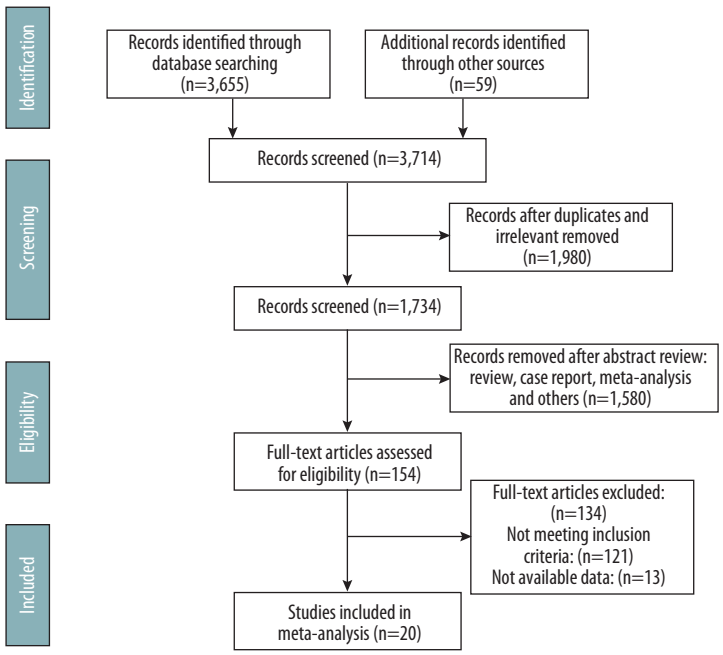

Figure 1. Database search.

(55.69%) had a superior 3-year OS rate compared to the PLT group (59.07%), which was statistically significant (OR: 0.85, 95% CI: 0.76 to 0.96, *P*=0.01) Figure 5B.

To assess the outcome measurement of the 5-year OS rate, a total of 9756 patients were included from 18 studies [11,16–18,22–30,32–36]. The χ^2 test revealed *P*=0.37 and I^2=7%; meta-analysis using a fixed effect model revealed that the SLT group (48.67%) had a superior 5-year OS rate compared to the PLT group (52.32%), which was statistically significant (OR: 0.85, 95% CI: 0.76 to 0.96, *P*=0.009) Figure 5C.

Data was classified according to donor type: DDLT and LDLT. In DDLT recipients, there was no significant difference in 1-year OS rate (OR: 0.93, 95% CI: 0.80 to 1.09, *P*=0.40, Figure 6A) [16,17,22,24–27,29,30,33,35–37] and 3-year OS rate (OR: 0.89, 95% CI: 0.78 to 1.02, *P*=0.08, Figure 6B) [16–18, 22,24–27,29,30,33,35–37] between the SLT group and the PLT group. However, 5-year OS rate was superior in the SLT group compared to the PLT group (OR: 0.81, 95% CI: 0.71 to 0.92, *P*=0.001, Figure 6C) [16,17,22,24–27,29,30,33,35,36]. In LDLT recipients, SLT had superior 1-year, 3-year, and 5-year OS rates compared to PLT: (OR: 0.49, 95% CI: 0.26 to 0.95, *P*=0.03, Figure 7A) [23,30,32,34], (OR: 0.47, 95% CI: 0.28 to 0.79, *P*=0.004, Figure 7B) [23,30,32,34], and (OR: 0.43, 95% CI: 0.26 to 0.71, *P*=0.0009, Figure 7C) [23,30,32,34], respectively.

Additionally, data were classified according to Milan criteria: within Milan criteria and beyond Milan criteria. In patients within Milan criteria, the meta-analysis revealed no statistically significant difference for 1-year, 3-year, and 5-year OS rates between the SLT group and the PLT group: (OR: 0.68, 95% CI: 0.44 to 1.04, *P*=0.08, Figure 8A) [16,18,22,23,25–27,31,33,33,36], (OR: 0.78, 95% CI: 0.55 to 1.11, *P*=0.17, Figure 8B) [16,18,22,23, 25–27,33,35,36], and (OR: 0.75, 95% CI: 0.40 to 1.42, *P*=0.38, Figure 8C) [11,16,18,22,23,25–27,33,35,36], respectively. Similarly, in patients beyond the Milan criteria, both SLT and PLT showed no significant difference for 1-year, 3-year, and 5-year OS rates: (OR: 0.68, 95% CI: 0.19 to 2.48, *P*=0.56, Figure 9A) [18,29,31,37], (OR: 2.07, 95% CI: 0.92 to 4.66, *P*=0.08, Figure 9B) [18,29,37], and (OR: 2.01, 95% CI: 0.75 to 5.40, *P*=0.17, Figure 9C) [18,29], respectively.

DFS outcomes between SLT patients and PLT patients

To assess the outcome measurement of 1-year DFS a total of 8868 patients were included from 13 studies [16–18, 26,28–30,32–37]. The χ^2 test revealed *P*=0.08 and I^2=38%; meta-analysis using a fixed effect model revealed that the SLT group (67.69%) had superior 1-year DFS rate compared to the PLT group (70.03%), which was statistically significant (OR: 0.86, 95% CI: 0.75 to 0.99, *P*=0.03) Figure 10A.

To assess the outcome measurement of 3-year DFS, a total of 6910 patients were included from 14 studies [16–18, 22,26,28–30,32–37]. The χ^2 test revealed *P*=0.02 and I^2=50%; meta-analysis using a random-effect model revealed that the SLT group (57.02%) had superior 3-year DFS rate compared to the PLT group (74.08%), which was statistically significant (OR: 0.56, 95% CI: 0.39 to 0.81, *P*=0.002) Figure 10B.

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Table 2. Study characteristics included in meta-analysis.

Study code	Study	Year	Country	Study type	Total N	Follow-up (mo)	Arms	n	Age (yrs)
1	Adam et al. [17]	2003	France	Case-control	212	49±50	SLT	17	55.1±9.2
						51±46	PLT	195	53.3±8.1
2	Belghiti et al. [22]	2003	France	Case-control	88	50.5±33	SLT	18	55±10
						50.5±33	PLT	70	53±7
3	Hwang et al. [23]	2007	Korea	Case-control	217	30.7±26.8	SLT	17	49.3±8.6
						40.1±22.4	PLT	200	51.2±7.0
4	Scatton et al. [24]	2008	France	Retrospective cohort	93	45.6±52.8	SLT	20	53.5±8
						32.4±54	PLT	73	<70
5	Margarit et al. [25]	2005	Spain	Retrospective cohort	42	50	SLT	6	62±6
						44	PLT	36	59.9±7.6
6	Del Gaudio et al. [26]	2008	Italy	Retrospective cohort	163	26.2±26.3	SLT	16	54±8
						36±32	PLT	147	55±7
7	Wang et al. [27]	2016	China	Retrospective cohort	371	19.5±24.4	SLT	76	48.5±8.6
						19.5±24.4	PLT	295	48.3±8.5
8	Liu et al. [28]	2012	China	Retrospective cohort	219	30±20.25	SLT	39	44
						33±22	PLT	180	47
9	Facciuto et al. [29]	2008	USA	Retrospective cohort	37	27.75±18.77	SLT	5	<70
						35±33	PLT	32	<70
10	Hu et al. [30]	2012	China	Retrospective cohort	6975	12.2±4.4	SLT	888	50.0±9.28
						12.4±4.2	PLT	6087	49.7±9.67
11	Cherqui et al. [11]	2009	France	Retrospective cohort	154	>5 years	SLT	18	<70
						>5 years	PLT	136	<70
12	Kim et al. [31]	2008	South Korea	Retrospective cohort	46	18.3±8	SLT	15	48.1±7
						18.7±7.2	PLT	31	51.2±6.2
13	Vasavada et al. [32]	2015	India	Retrospective cohort	109	31	SLT	18	56±5
						31	PLT	91	56±6
14	Wu et al. [16]	2012	China	Retrospective cohort	183	58.7±20.7	SLT	36	49.46±7.1
						64.2±18.1	PLT	147	47.66±5.8
15	Bhangui et al. [33]	2016	France	Retrospective cohort	371	>5 years	SLT	31	<65
						>5 years	PLT	340	<65
16	Moon et al. [34]	2012	Korea	Retrospective cohort	186	27.2±21.7	SLT	17	51
						39±18.8	PLT	169	52
17	Sapisochin et al. [35]	2010	Spain	Case-control	51	88.9±47.5	SLT	17	59
						88.9±47.5	PLT	34	62
18	Shan et al. [18]	2017	China	Retrospective cohort	239	35±10.2	SLT	28	47.79±.64
						35±6.8	PLT	211	50.45±9.24
19	Vennarecci et al. [36]	2007	Italy	Retrospective cohort	46	28.5±17.1	SLT	9	<70
						26.3±14.8	PLT	37	<70
20	Shao et al. [37]	2008	China	Retrospective cohort	77	18±3.4	SLT	15	<60
						21±4.5	PLT	62	<60

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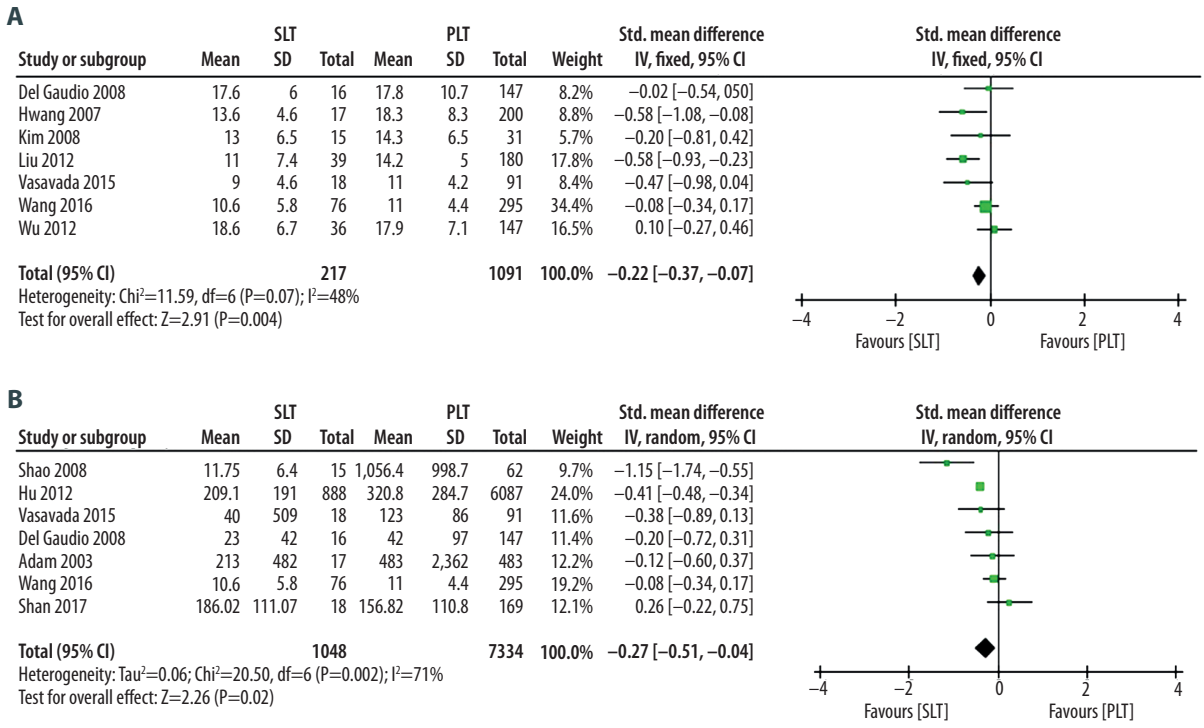

Figure 2. (**A**) Pre-operative MELD scores between SLT and PLT; (**B**) pre-transplant AFP levels between SLT and PLT.

To assess the outcome measurement of 5-year DFS, a total of 8842 patients were included from 12 studies [16–18,22,26, 28,30,32–36]. The χ^2 test revealed *P*=0.18 and I^2=27%; meta-analysis using a fixed effect model revealed that the SLT group (41.27%) had superior 5-year DFS rate compared to the PLT group (47.09%), which was statistically significant (OR: 0.75, 95% CI: 0.66 to 0.86, *P*<0.0001) Figure 10C.

Data was classified according to donor type: DDLT and LDLT. SLT had superior 1-year, 3-year, and 5-year DFS rates compared to PLT in DDLT recipients: (OR: 0.77, 95% CI: 0.67 to 0.90, *P*=0.0006, Figure 11A) [16–18,26,29,30,33,35–37], (OR: 0.71, 95% CI: 0.62 to 0.81, *P*<0.00001, Figure 11B) [16–18,22,26,29,30,33,35–37], and (OR: 0.60, 95% CI: 0.53 to 0.69, *P*<0.00001, Figure 11C) [16–18,22,26,30,32,33,35], respectively. Similarly, SLT had better 1-year, 3-year, and 5-year DFS rates compared to PLT in LDLT recipients: (OR: 0.40, 95% CI: 0.21 to 0.77, *P*=0.006, Figure 12A) [30,32,34] (OR: 0.52, 95% CI: 0.30 to 0.90, *P*=0.02, Figure 12B) [30,32,34], and (OR: 0.55, 95% CI: 0.32 to 0.94, *P*=0.03, Figure 12C) [30,32,34], respectively.

We further classified data according to Milan criteria: within Milan criteria and beyond Milan criteria. In patients within Milan criteria, there was no statistically significant difference for 1-year, 3-year, and 5-year DFS rates between SLT and PLT groups: (OR: 0.62, 95% CI: 0.22 to 1.78, *P*=0.37, Figure 13A) [16,18,26,27,33,35,36], (OR: 0.60, 95% CI: 0.29 to 1.22, *P*=0.16, Figure 13B) [16,18,22,26,27,33,35,36], and (OR: 0.61, 95% CI: 0.32 to 1.19, *P*=0.15, Figure 13C) [16,18,22,26,27,33,35,36], respectively. There was not enough data to do meta-analysis of DFS for patients beyond the Milan criteria.

Postoperative outcomes

Biliary complication between SLT and PLT

To assess the outcome measurement of biliary complication, a total of 8172 patients were included from 9 studies [16,17,22,23,28,30,31,34,36]. The χ^2 test revealed *P*=0.62 and I^2=0%; meta-analysis using a fixed effect model revealed no statistically significant difference between SLT and PLT (OR: 1.14, 95% CI: 0.94 to 1.40, *P*=0.19) Figure 14A.

Sepsis between SLT and PLT

To assess the outcome measurement of sepsis, a total of 782 patients were included from 5 studies [17,22,23,28,36]. The χ^2 test revealed *P*=0.99 and I^2=0%; meta-analysis using a fixed effect model revealed no statistically significant difference between SLT and PLT (OR: 1.14, 95% CI: 0.63 to 2.06, *P*=0.68) Figure 14B.

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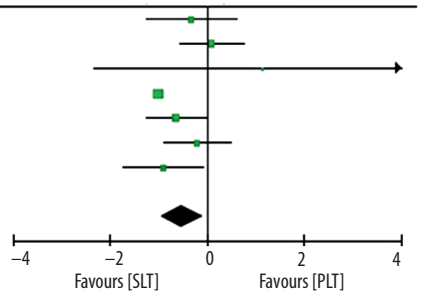
A

Study or subgroup	SLT Mean	SLT SD	SLT Total	PLT Mean	PLT SD	PLT Total	Weight	Mean difference IV, random, 95% CI
Adam 2003	3.35	1.88	17	3.67	2.11	195	11.6%	−0.32 [−1.26, 0.62]
Belghiti 2003	2.3	1.4	18	2.2	0.7	70	15.9%	0.10 [−0.57, 0.77]
Del Gaudio 2008	2.43	7.1	16	1.27	1.34	147	1.5%	1.16 [−2.33, 4.65]
Hu 2012	3	0.5	888	4	0.75	6087	25.4%	−1.00 [−1.04, −0.96]
Sapisochin 2010	2.37	0.87	17	3	1.37	34	16.8%	−0.63 [−1.25, −0.01]
Shao 2008	3.4	1.3	15	3.6	0.87	62	15.5%	−0.20 [−0.89, 0.49]
Vasavada 2015	2.1	1.6	18	3	1.8	91	13.3%	−0.90 [−1.73, −0.07]
Total (95% CI)			**989**			**6686**	**100%**	**−0.51 [−0.95, −0.08]**

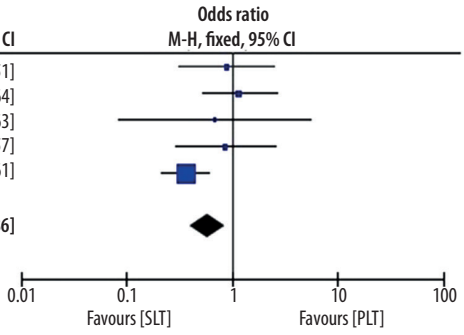
Heterogeneity: Tau²=0.19; Chi²=20.27, df=6 (P=0.002); I²=70%
Test for overall effect: Z=2.31 (P=0.02)



B

Study or subgroup	SLT Events	SLT Total	PLT Events	PLT Total	Weight	Odds ratio M-H, fixed, 95% CI
Adam 2003	6	17	74	195	10.3%	0.89 [032, 2.51]
Bhangui 2016	9	31	88	340	14.0%	1.17 [0.52, 2.64]
Del Gaudio 2008	1	16	13	147	3.2%	0.69 [0.08, 5.63]
Moon 2012	5	17	55	169	9.5%	0.86 [0.29, 2.57]
Wang 2016	30	76	189	295	62.9%	0.37 [0.22, 0.61]
Total (95% CI)		**157**		**1146**	**100.0%**	**0.59 [0.41, 0.86]**
Total events	51		419			

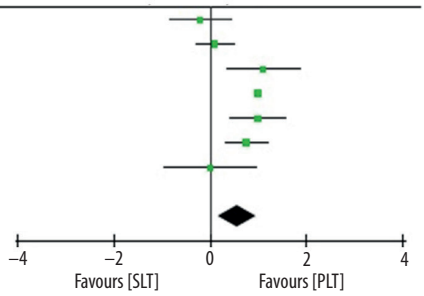
Heterogeneity: Chi²=7.11, df=4 (P=0.13); I²=44%
Test for overall effect: Z=2.76 (P=0.006)



C

Study or subgroup	SLT Mean	SLT SD	SLT Total	PLT Mean	PLT SD	PLT Total	Weight	Mean difference IV, random, 95% CI
Adam 2003	1.7	1.3	17	1.9	1.1	195	13.2%	−20 [−0.84, 0.44]
Belghiti 2003	1.7	0.8	18	1.6	0.7	70	16.4%	0.10 [−0.30, 0.50]
Del Gaudio 2008	2.8	1.5	16	1.7	1.2	147	11.6%	1.10 [0.34, 1.86]
Hu 2012	2	0.5	888	1	0.16	6087	19.6%	1.00 [0.97, 1.03]
Sapisochin 2010	2	1	17	1	1	34	13.9%	1.00 [0.42, 1.58]
Shao 2008	1.75	0.87	15	1	0.25	62	15.9%	0.75 [0.31, 1.19]
Vasavada 2015	1	2	18	1	1	91	9.4%	0.00 [−0.95, 0.95]
Total (95% CI)			**989**			**6686**	**100.0%**	**0.57 [0.17, 0.97]**

Heterogeneity: Tau²=0.22; Chi²=37.77, df=6 (P<0.00001); I²=84%
Test for overall effect: Z=2.78 (P=0.005)



D

Study or subgroup	SLT Events	SLT Total	PLT Events	PLT Total	Weight	Odds ratio M-H, random, 95% CI
Adam 2003	1	17	27	195	16.6%	0.39 [0.05, 3.05]
Bhangui 2016	10	31	41	340	40.2%	3.47 [1.53, 7.89]
Moon 2012	6	17	36	169	34.1%	2.02 [070, 5.82]
Wu 2012	2	36	0	147	9.0%	21.38 [1.00, 455.42]
Total (95% CI)		**101**		**851**	**100.0%**	**2.36 [0.86, 6.46]**
Total events	19		104			

Heterogeneity: Tau²=0.48; Chi²=5.93, df=3 (P=0.12); I²=49%
Test for overall effect: Z=1.67 (P=0.09)

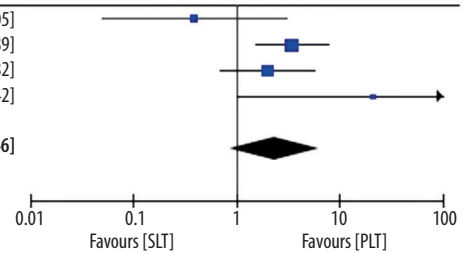


Figure 3. Pre-transplant tumor status between SLT and PLT: (**A**) maximum tumor diameter, (**B**) number of tumors >3 cm, (**C**) number of nodules, (**D**) >3 nodules.

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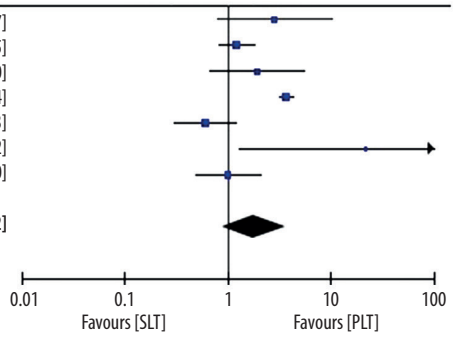
A

Study or subgroup	SLT Events	SLT Total	PLT Events	PLT Total	Weight	Odds ratio M-H, random, 95% CI
Adam 2003	14	17	121	195	11.9%	2.85 [0.79, 10.27]
Bhangui 2016	78	130	187	340	18.2%	1.23 [0.81, 1.85]
Del Gaudio 2008	10	16	68	147	13.5%	1.94 [0.67, 5.60]
Hu 2012	548	888	1829	6087	19.2%	3.75 [3.24, 4.34]
Liu 2012	18	39	105	180	16.3%	0.61 [0.31, 1.23]
Moon 2012	17	17	104	169	4.8%	21.94 [1.30, 371.02]
Wu 2012	18	36	73	147	16.1%	1.01 [0.49, 2.10]
Total (95% CI)		**1143**		**7265**	**100.0%**	**1.78 [0.87, 3.62]**
Total events	703		2487			

Heterogeneity: Tau²=0.68; Chi²=58.33, df=6 (P<0.00001); I²=90%
Test for overall effect: Z=1.58 (P=0.11)



B

Study or subgroup	SLT Mean	SLT SD	SLT Total	PLT Mean	PLT SD	PLT Total	Weight	Mean difference IV, fixed, 95% CI
Adam 2003	49	50	17	51	46	195	0.0%	−2.00 [−26.63, 22.63]
Belghiti 2003	50.5	33	18	50.5	33	70	0.0%	0.00 [−17.09, 17.09]
Del Gaudio 2008	26.2	26.3	16	36	32	147	0.0%	−9.80 [−23.69, 4.09]
Faciutto 2008	27.75	18.77	5	35	33	32	0.0%	−7.25 [−27.29, 12.79]
Hu 2012	12.24	4.48	888	12.4	4.24	6087	95.8%	−0.16 [−0.47, 0.15]
Hwang 2007	30.7	26.8	17	40.1	22.4	200	0.1%	−9.40 [−22.51, 3.71]
Kim 2008	18.3	8	15	18.7	7.2	31	0.4%	−0.40 [−5.18, 4.38]
Liu 2012	30	20.25	39	33	22	180	0.2%	−3.00 [−10.12, 4.12]
Moon 2012	27.25	21.75	17	39	18.83	169	0.1%	−11.75 [−22.47, −1.03]
Sapisochin 2010	88.92	47.57	17	88.92	47.57	34	0.0%	0.00 [−27.70, 27.70]
Scatton 2008	45.6	52.8	20	32.4	54	73	0.0%	13.20 [−13.05, 39.45]
Shan 2017	35	10.25	28	35	6.83	211	0.6%	0.00 [−3.91, 3.91]
Shao 2008	18	3.46	15	21	4.5	62	2.2%	−3.00 [−5.08, −0.92]
Vennarecci 2007	28.52	17.18	9	26.3	14.87	37	0.1%	2.22 [−9.98, 14.42]
Wang 2006	19.53	24.42	79	19.53	24.42	295	0.2%	0.00 [−6.16, 6.16]
Wu 0212	58.7	20.7	36	64.2	18.1	147	0.2%	−5.50 [−12.87, 1.87]
Total (95% CI)			**1233**			**7970**	**100.0%**	**−0.25 [−0.56, 0.05]**

Heterogeneity: Chi²=19.35, df=15 (P=0.20); I²=22%
Test for overall effect: Z=1.62 (P=0.10)

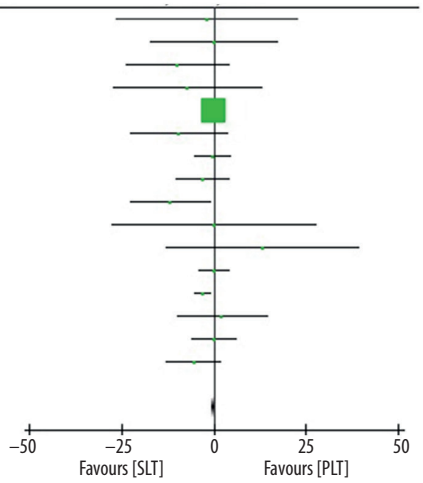


Figure 4. (**A**) Pre-transplant therapy between SLT and PLT; (**B**) follow-up period.

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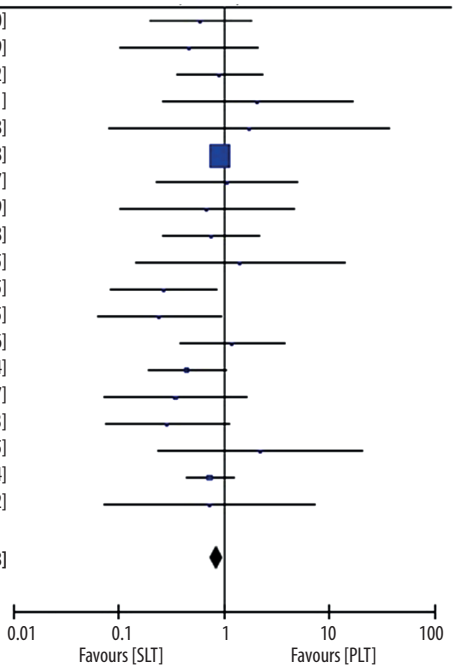
A

Study or subgroup	SLT Events	SLT Total	PLT Events	PLT Total	Weight	Odds ratio M-H, fixed, 95% CI
Adam 2003	12	17	156	195	1.7%	0.60 [0.20, 1.80]
Belghiti 2003	15	18	64	70	1.0%	0.47 [0.11, 2.09]
Bhangui 2016	25	31	279	340	2.1%	0.91 [0.36, 2.32]
Del Gaudio 2008	15	16	129	147	0.4%	2.09 [0.26, 16.81]
Faciutto 2008	5	5	28	32	0.2%	1.74 [0.08, 37.08]
Hu 2012	648	888	4534	6087	72.4%	0.92 [0.79, 1.08]
Hwang 2007	15	17	175	200	0.7%	1.07 [0.23, 4.97]
Kim 2008	13	15	28	31	0.6%	0.70 [0.10, 4.69]
Liu 2012	34	39	162	180	1.7%	0.76 [0.26, 2.18]
Margarit 2005	5	6	28	36	0.3%	1.43 [0.15, 14.05]
Moon 2012	12	17	152	169	1.9%	0.27 [0.08, 0.85]
Sapisochin 2010	10	17	29	34	1.8%	0.25 [0.06, 0.95]
Scatton 2008	15	20	52	73	1.3%	1.21 [0.39, 3.76]
Shan 2017	18	28	169	211	3.3%	0.45 [0.19, 1.04]
Shao 2008	12	15	57	62	1.0%	0.35 [0.07, 1.67]
Vasavada 2015	14	18	84	91	1.4%	0.29 [0.08, 1.13]
Vennarecci 2007	8	9	29	37	0.3%	2.21 [0.24, 20.35]
Wang 2016	46	76	199	295	7.5%	0.74 [0.44, 1.24]
Wu 2012	35	36	144	147	0.4%	0.73 [0.07, 7.22]
Total (95% CI)		**1288**		**8437**	**100.0%**	**0.86 [0.75, 0.98]**
Total events	957		6498			

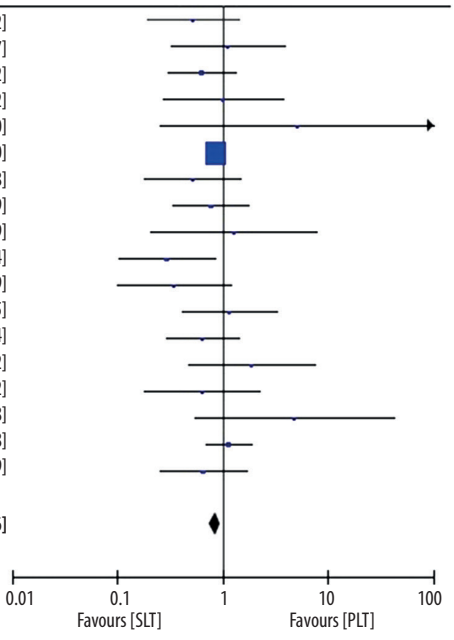
Heterogeneity: Chi^2=17.68, df=18 (P=0.48); I^2=0%
Test for overall effect: Z=2.23 (P=0.03)



B

Study or subgroup	SLT Events	SLT Total	PLT Events	PLT Total	Weight	Odds ratio M-H, fixed, 95% CI
Adam 2003	9	17	133	195	1.8%	0.52 [0.19, 1.42]
Belghiti 2003	14	18	53	70	0.9%	1.12 [0.33, 3.87]
Bhangui 2016	13	31	182	340	3.1%	0.63 [0.30, 1.32]
Del Gaudio 2008	13	16	119	147	0.8%	1.02 [0.27, 3.82]
Faciutto 2008	5	5	22	32	0.1%	5.13 [0.26, 101.70]
Hu 2012	460	888	3354	6057	73.6%	0.87 [0.75, 1.00]
Hwang 2007	11	17	156	200	1.5%	0.52 [0.18, 1.48]
Liu 2012	30	39	146	180	2.1%	0.78 [0.34, 1.79]
Margarit 2005	4	6	22	36	0.4%	1.27 [0.21, 7.89]
Moon 2012	10	17	140	169	1.9%	0.30 [0.10, 0.84]
Sapisochin 2010	9	17	26	34	1.5%	0.35 [0.10, 1.19]
Scatton 2008	13	20	45	73	1.2%	0.16 [0.41, 3.25]
Shan 2017	15	28	135	211	2.6%	0.65 [0.19, 1.44]
Shao 2008	12	15	42	62	0.6%	1.90 [0.48, 7.52]
Vasavada 2015	14	18	77	91	1.0%	0.64 [0.18, 2.22]
Vennarecci 2007	8	9	23	37	0.2%	4.87 [0.55, 43.18]
Wang 2016	40	76	146	295	5.0%	1.13 [0.68, 1.88]
Wu 2012	29	36	127	147	1.7%	0.65 [0.25, 1.69]
Total (95% CI)		**1273**		**8376**	**100.0%**	**0.85 [0.76, 0.96]**
Total events	709		4948			

Heterogeneity: Chi^2=16.64, df=17 (P=0.48); I^2=0%
Test for overall effect: Z=2.54 (P=0.01)



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C

Study or subgroup	SLT Events	SLT Total	PLT Events	PLT Total	Weight	Odds ratio M-H, fixed, 95% CI
Adam 2003	7	17	119	195	1.9%	0.45 [0.16, 1.22]
Belghiti 2003	10	18	37	70	1.2%	1.11 [0.39, 3.16]
Bhangui 2016	10	31	135	340	2.6%	0.72 [0.33, 1.58]
Cherqui 2009	13	18	101	136	1.1%	0.90 [0.30, 2.71]
Del Gaudio 2008	10	16	107	147	1.4%	0.62 [0.21, 1.83]
Faciutto 2008	5	5	19	32	0.1%	7.62 [0.39, 149.49]
Hu 2012	407	888	2971	6087	70.7%	0.89 [0.77, 1.02]
Hwang 2007	9	17	144	200	1.8%	0.44 [0.16, 1.19]
Liu 2012	24	39	130	180	3.1%	0.62 [0.30, 1.27]
Margarit 2005	2	6	11	36	0.4%	1.14 [0.18, 7.15]
Moon 2012	10	17	134	169	1.7%	0.37 [0.13, 1.05]
Sapisochin 2010	9	17	22	34	1.2%	0.61 [0.19, 2.00]
Scatton 2008	13	20	40	73	1.0%	1.53 [0.55, 4.28]
Shan 2017	12	28	125	211	2.9%	0.52 [0.23, 1.15]
Vasavada 2015	12	18	77	91	1.5%	0.36 [0.12, 1.13]
Vennarecci 2007	8	9	23	37	0.2%	4.87 [0.55, 43.18]
Wang 2006	35	76	131	295	5.0%	1.07 [0.64, 1.77]
Wu 2012	25	36	111	147	2.3%	0.74 [0.33, 1.64]
Total (95% CI)		**1276**		**8480**	**100.0%**	**0.85 [0.76, 0.96]**
Total events	621		4437			

Heterogeneity: Chi^2=18.33, df=17 (P=0.37); I^2=7%
Test for overall effect: Z=2.61 (P=0.009)

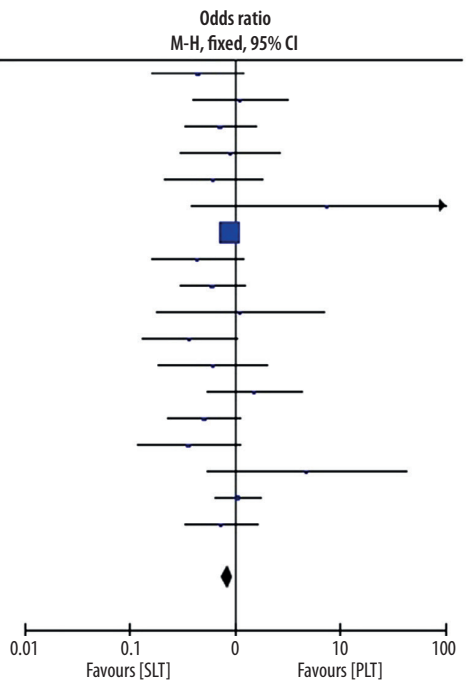
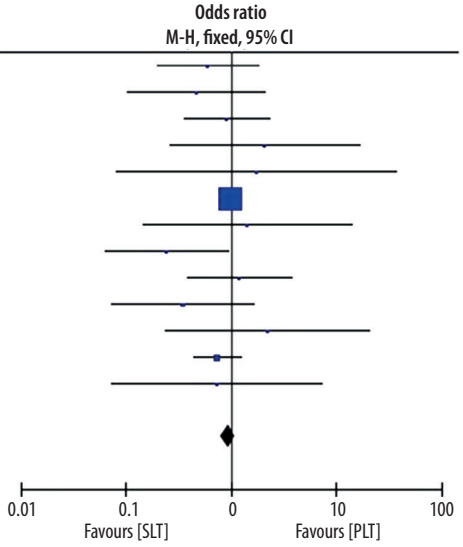


Figure 5. Overall survival outcomes between SLT group and PLT group: (**A**) 1-year, (**B**) 3-year, (**C**) 5-year.

A

Study or subgroup	SLT Events	SLT Total	PLT Events	PLT Total	Weight	Odds ratio M-H, fixed, 95% CI
Adam 2003	12	17	156	195	2.3%	0.60 [0.20, 1.80]
Belghiti 2003	15	18	64	70	1.4%	0.47 [0.11, 2.09]
Bhangui 2016	25	331	279	340	2.9%	0.91 [0.36, 2.32]
Del Gaudio 2008	15	16	129	147	0.5%	2.09 [0.26, 16.81]
Faciutto 2008	5	5	28	32	0.2%	1.74 [0.08, 37.08]
Hu 2012	688	859	4596	5727	75.5%	0.99 [0.83, 1.18]
Margarit 2005	5	6	28	36	0.4%	1.43 [0.15, 14.05]
Sapisochin 2010	10	17	29	34	2.5%	0.25 [0.06, 0.95]
Scatton 2008	15	20	52	73	1.8%	1.21 [0.39, 3.76]
Shao 2008	12	15	57	62	1.4%	0.35 [0.07, 1.67]
Vennarecci 2007	8	9	29	37	0.4%	2.21 [0.24, 20.35]
Wang 2006	46	76	199	295	10.2%	0.74 [0.44, 1.24]
Wu 2012	35	36	144	147	0.5%	0.73 [0.07, 7.22]
Total (95% CI)		**1125**		**7195**	**100.0%**	**0.93 [0.80, 1.09]**
Total events	621		5790			

Heterogeneity: Chi^2=9.54, df=12 (P=0.66); I^2=0%
Test for overall effect: Z=0.84 (P=0.40)



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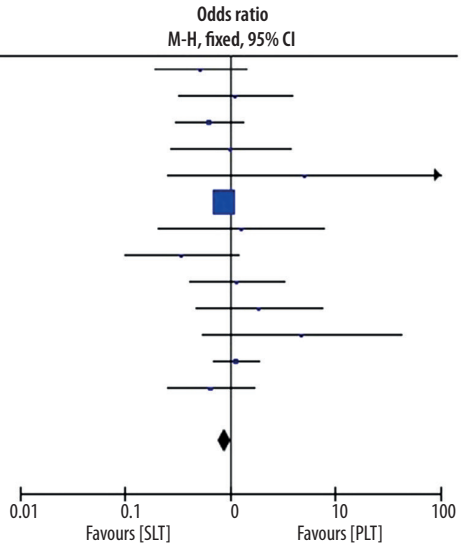
B

Study or subgroup	SLT Events	SLT Total	PLT Events	PLT Total	Weight	Odds ratio M-H, fixed, 95% CI
Adam 2003	9	17	133	195	2.2%	0.52 [0.19, 1.42]
Belghiti 2003	14	18	53	70	1.0%	1.12 [0.33, 3.87]
Bhangui 2016	13	31	182	340	3.8%	0.63 [0.30, 1.32]
Del Gaudio 2008	13	16	119	147	0.9%	1.02 [0.27, 3.82]
Faciutto 2008	5	5	22	32	0.1%	5.13 [0.26, 101.70]
Hu 2012	533	859	3731	5727	79.2%	0.87 [0.75, 1.01]
Margarit 2005	4	6	22	36	0.4%	1.27 [0.21, 7.89]
Sapisochin 2010	9	17	26	34	1.7%	0.35 [0.10, 1.19]
Scatton 2008	13	20	45	73	1.5%	1.16 [0.41, 3.25]
Shao 2008	12	15	42	62	0.7%	1.90 [0.48, 7.52]
Vennarecci 2007	8	9	23	37	0.2%	4.87 [0.55, 43.18]
Wang 2006	40	76	146	295	6.1%	1.13 [0.68, 1.88]
Wu 2012	29	36	127	147	2.1%	0.65 [0.25, 1.69]
Total (95% CI)		**1125**		**7195**	**100.0%**	**0.89 [0.78, 1.02]**
Total events	702		4671			

Heterogeneity: Chi²=10.91, df=12 (P=0.54); I²=0%
Test for overall effect: Z=1.73 (P=0.08)



C

Study or subgroup	SLT Events	SLT Total	PLT Events	PLT Total	Weight	Odds ratio M-H, fixed, 95% CI
Adam 2003	7	17	119	195	2.2%	0.45 [0.16, 1.22]
Belghiti 2003	10	18	37	70	1.3%	1.11 [0.39, 3.16]
Bhangui 2016	10	31	135	340	3.0%	0.72 [0.33, 1.58]
Del Gaudio 2008	10	16	107	147	1.5%	0.62 [0.21, 1.83]
Faciutto 2008	5	5	19	32	0.1%	7.62 [0.39, 149.49]
Hu 2012	465	859	3454	5727	80.5%	0.78 [0.67, 0.90]
Margarit 2005	2	6	11	36	0.4%	1.14 [0.18, 7.15]
Sapisochin 2010	9	17	22	34	1.3%	0.61 [0.19, 2.00]
Scatton 2008	13	20	40	73	1.2%	1.53 [0.55, 4.28]
Vennarecci 2007	8	9	23	37	0.2%	4.87 [0.55, 43.18]
Wang 2006	35	76	131	295	5.6%	1.07 [0.64, 1.77]
Wu 2012	25	36	111	147	2.6%	0.74 [0.33, 1.64]
Total (95% CI)		**1110**		**7133**	**100.0%**	**0.81 [0.71, 0.92]**
Total events	599		4209			

Heterogeneity: Chi²=10.12, df=11 (P=0.52); I²=0%
Test for overall effect: Z=3.25 (P=0.001)

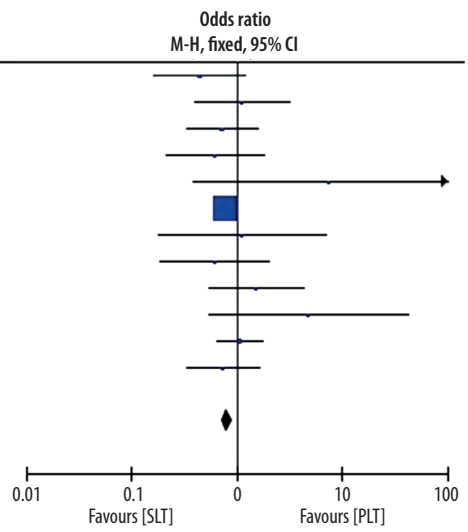


Figure 6. Overall survival outcomes for DDLT between SLT group and PLT group: (**A**) 1-year, (**B**) 3-year, and (**C**) 5-year.

Postoperative bleeding between SLT and PLT

To assess the outcome measurement of postoperative bleeding, a total of 8172 patients were included from 9 studies [16,17,22,23,28,30,31,34,36]. The χ^2 test revealed P=0.25 and I^2=21%; meta-analysis using a fixed effect model revealed SLT had higher rates of postoperative bleeding than that of PLT (OR: 1.32, 95% CI: 1.03 to 1.71, P=0.03) Figure 14C.

Vascular complications between SLT and PLT

To assess the outcome measurement of vascular complications, a total of 8172 patients were included from 9 studies [16,17,22,23,28,30,31,34,36]. The χ^2 test revealed P=0.96 and I^2=0%; meta-analysis using a fixed effect model revealed no statistically significant difference between SLT and PLT (OR: 1.35, 95% CI: 0.98 to 1.85, P=0.07) Figure 14D.

Operative mortality between SLT and PLT

To assess the outcome measurement of operative mortality, a total of 1738 patients were included from 12 studies [16,17,22,23,25,27,28,31,34–37]. The χ^2 test revealed P=0.52 and I^2=0%; meta-analysis using a fixed effect model revealed SLT had higher rates of operative mortality than that of PLT (OR: 2, 95% CI: 1.21 to 3.31, P=0.007) Figure 14E.

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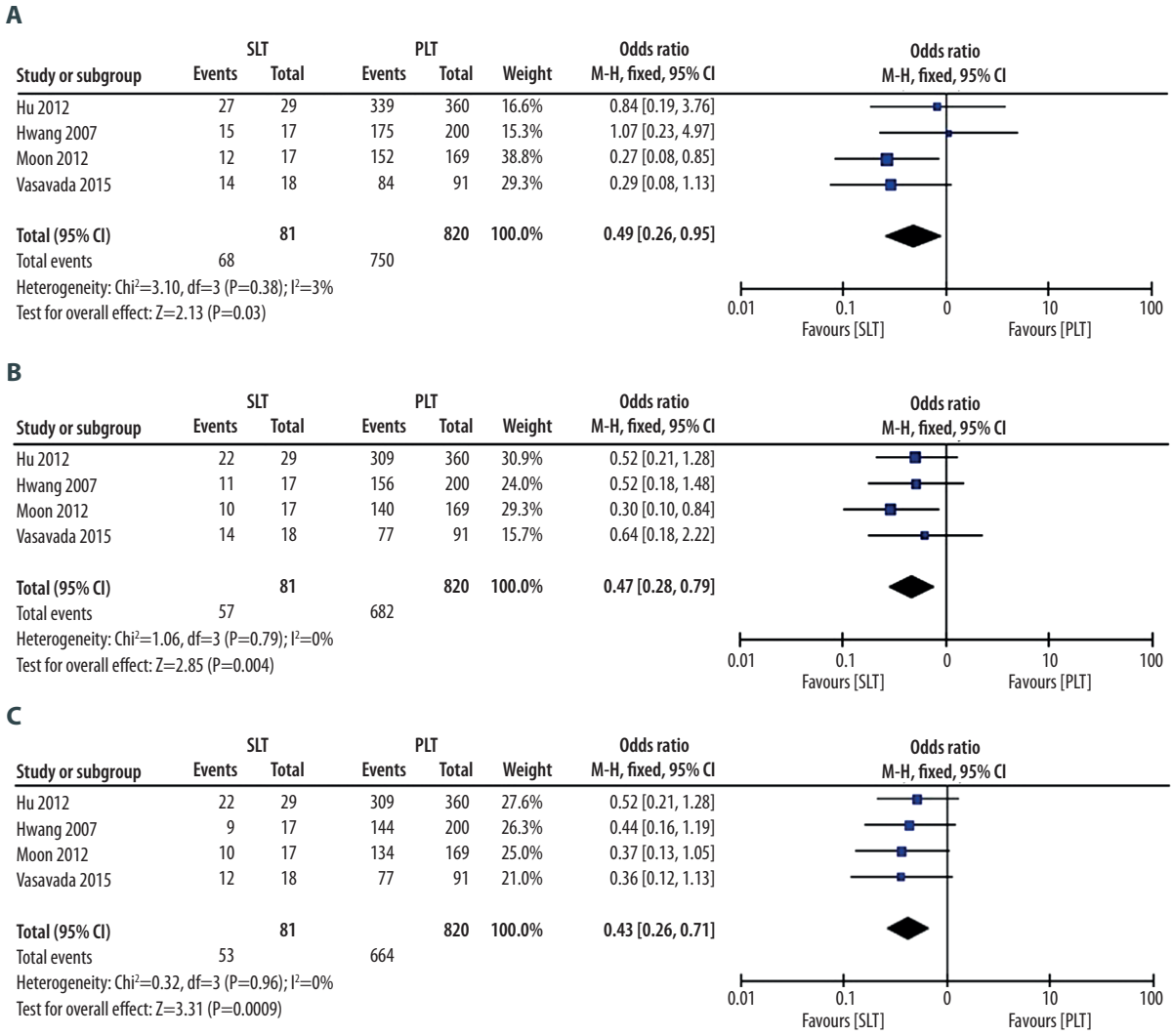

Figure 7. Overall survival outcomes for LDLT between SLT group and PLT group: (**A**) 1-year, (**B**) 3-year, (**C**) 5-year.

Discussion

PLT is a well-accepted ideal treatment strategy for patients with early stage HCC, but the lack of available organ donors requires the use of restrictive criteria to assure the optimal use of the available grafts. On the other hand, LR remains a valuable curative option for non-transplantable HCC patients or for those waiting for LT. However, the tumor recurrence rate is higher after LR within 5 years [38]. Thus, SLT after primary LR remains the ideal treatment for recurrent HCC and decompensated liver after primary LR [11,15,16]. Notwithstanding, the intensity of surgical difficulty during SLT and the potential for reduced OS is a concern for a large portion of experts. Substantial adhesions and portal collateral circulations are frequently experienced after earlier LR [16]. Likewise, because of adhesion, heedless dissection of adhesions around the liver may bring heavy bleeding at the dissection area. Moreover, because of adhesions, it's also hard to separate a hepatic vein and the inferior vena cava. However, some studies have demonstrated that SLT has similar perioperative and postoperative complications as that of the PLT [22,23,31]. Furthermore, reports suggest that meticulous sharp dissection with a sufficient dissection plan can resolve the problem of excessive bleeding in cases of excessive adhesions [23,31]. Nevertheless, there are serious concerns among experts about the outcomes of SLT in comparison with the PLT, since most of the studies have reported conflicting results. However, there is still a need for a large multi-center study to compare the advantages and disadvantages of SLT and PLT.

Until now, few systematic reviews and meta-analysis have been conducted comprehensively to analyze the short-term

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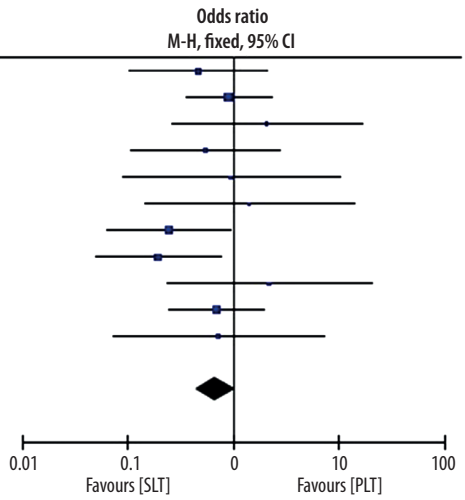
A

Study or subgroup	SLT Events	SLT Total	PLT Events	PLT Total	Weight	Odds ratio M-H, fixed, 95% CI
Belghiti 2003	15	18	64	70	9.4%	0.47 [0.11, 2.09]
Bhangui 2016	25	31	279	340	19.5%	0.91 [0.36, 2.32]
Del Gaudio 2008	15	16	129	147	3.4%	2.09 [0.26, 16.81]
Hwang 2007	8	10	139	158	7.2%	0.55 [0.11, 2.77]
Kim 2008	9	10	28	31	3.0%	0.96 [0.09, 10.47]
Margarit 2005	5	6	28	36	2.9%	1.43 [0.15, 14.05]
Sapisochin 2010	10	17	29	34	17.2%	0.25 [0.06, 0.95]
Shan 2017	9	13	104	113	14.3%	0.19 [0.05, 0.76]
Vennarecci 2007	8	9	29	37	2.7%	2.21 [0.24, 20.35]
Wang 2016	24	30	86	101	17.0%	0.70 [0.24, 1.99]
Wu 2012	35	36	144	147	3.4%	0.73 [0.07, 7.22]
Total (95% CI)		**196**		**1214**	**100.0%**	**0.68 [0.44, 1.04]**
Total events	163		1059			

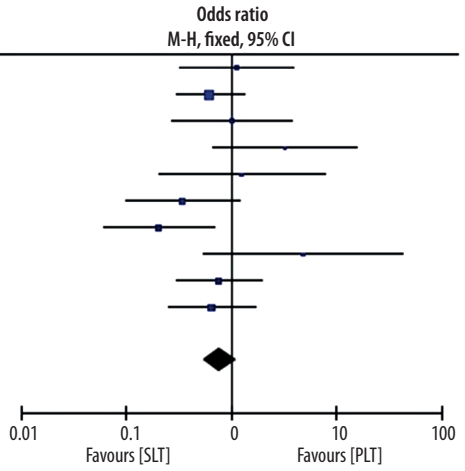
Heterogeneity: Chi²=8.77, df=10 (P=0.55); I²=0%
Test for overall effect: Z=1.78 (P=0.08)



B

Study or subgroup	SLT Events	SLT Total	PLT Events	PLT Total	Weight	Odds ratio M-H, fixed, 95% CI
Belghiti 2003	14	18	53	70	7.0%	1.12 [0.33, 3.87]
Bhangui 2016	13	31	182	340	25.7%	0.63 [0.30, 1.32]
Del Gaudio 2008	13	16	119	147	6.4%	1.02 [0.27, 3.82]
Hwang 2007	8	10	87	158	3.0%	3.26 [0.67, 15.86]
Margarit 2005	4	6	22	36	3.1%	1.27 [0.21, 7.89]
Sapisochin 2010	9	17	26	34	11.9%	0.35 [0.10, 1.19]
Shan 2017	7	13	96	113	13.3%	0.21 [0.06, 0.69]
Vennarecci 2007	8	9	23	37	1.5%	4.87 [0.55, 43.18]
Wang 2016	22	30	79	101	14.0%	0.77 [0.30, 1.95]
Wu 2012	29	36	127	147	14.1%	0.65 [0.25, 1.69]
Total (95% CI)		**186**		**1183**	**100.0%**	**0.78 [0.55, 1.11]**
Total events	127		814			

Heterogeneity: Chi²=13.41, df=9 (P=0.14); I²=33%
Test for overall effect: Z=1.38 (P=0.17)



C

Study or subgroup	SLT Events	SLT Total	PLT Events	PLT Total	Weight	Odds ratio M-H, random, 95% CI
Belghiti 2003	10	18	37	70	10.6%	1.11 [0.39, 3.16]
Bhangui 2016	1	31	135	340	6.0%	0.05 [0.01, 0.38]
Cherqui 2009	13	18	101	136	10.2%	0.90 [0.30, 2.71]
Del Gaudio 2008	10	16	107	147	10.4%	0.62 [0.21, 1.83]
Hwang 2007	8	10	39	158	7.7%	12.21 [2.49, 59.92]
Margarit 2005	2	6	11	36	6.6%	1.14 [0.18, 7.15]
Sapisochin 2010	9	17	22	34	9.8%	0.61 [0.19, 2.00]
Shan 2017	6	13	93	113	9.7%	0.18 [0.06, 0.61]
Vennarecci 2007	8	9	23	37	5.4%	4.87 [0.55, 43.18]
Wang 2016	17	30	75	101	11.7%	0.45 [0.19, 1.06]
Wu 2012	25	36	111	147	12.0%	0.74 [0.33, 1.64]
Total (95% CI)		**204**		**1319**	**100.0%**	**0.75 [0.40, 1.42]**
Total events	109		754			

Heterogeneity: Tau²=0.70; Chi²=29.32, df=10 (P=0.001); I²=66%
Test for overall effect: Z=0.87 (P=0.38)

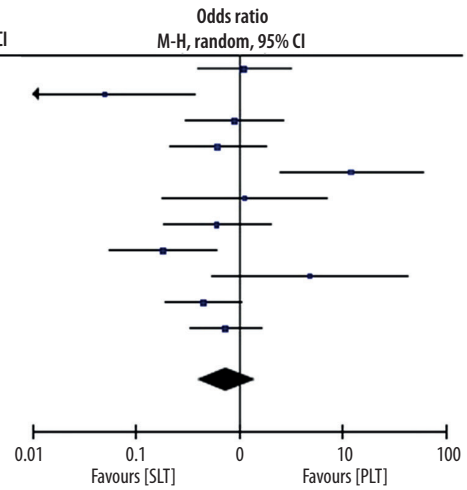


Figure 8. Overall survival outcomes for patients within Milan criteria between SLT group and PLT group: (**A**) 1-year, (**B**) 3-year, (**C**) 5-year.

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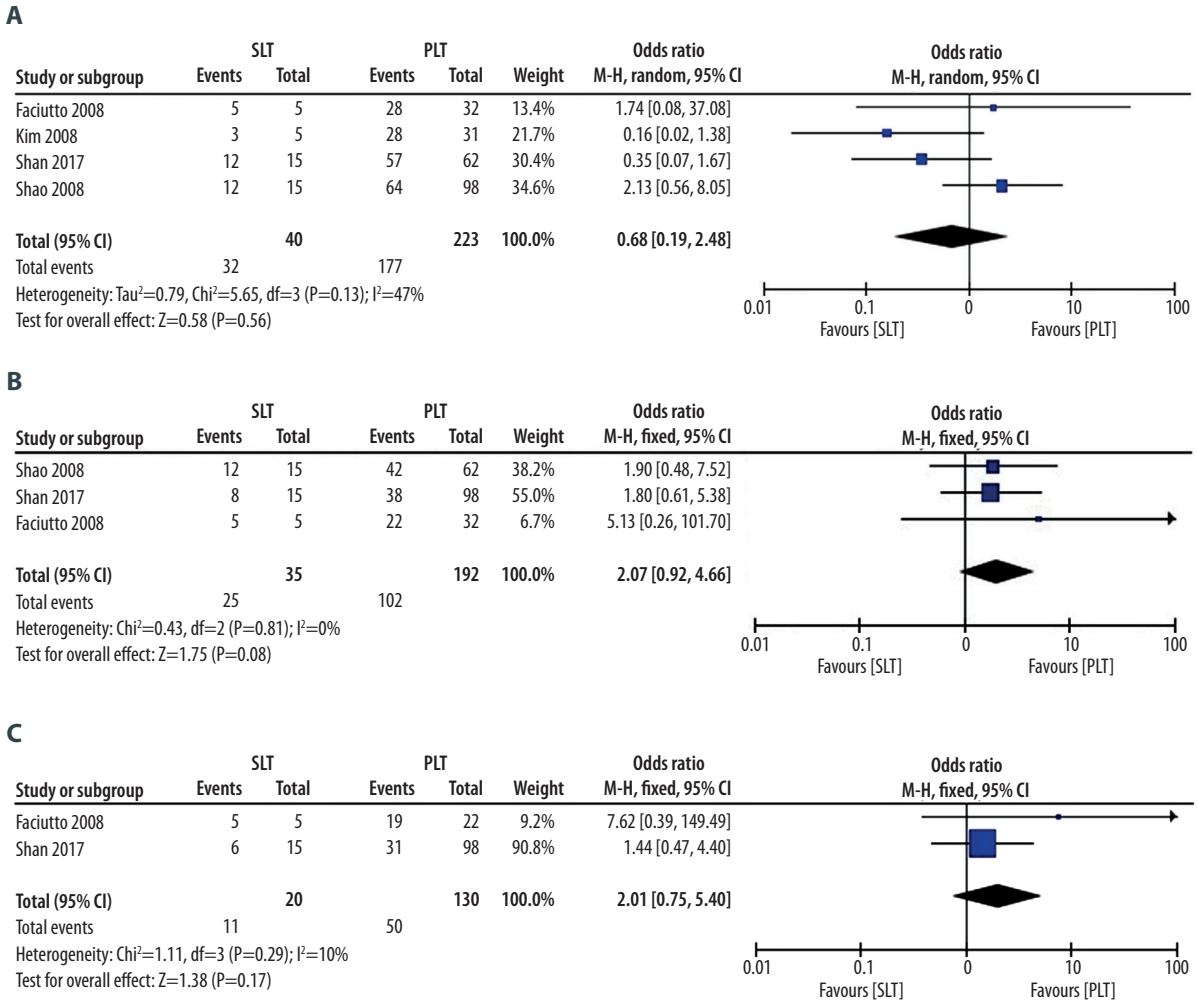

Figure 9. Overall survival outcomes for patients beyond Milan criteria between SLT group and PLT group: (**A**) 1-year, (**B**) 3-year, (**C**) 5-year.

and long-term outcomes of SLT and PLT. However, an earlier meta-analysis was reported but had only a few studies and had small total number of patients. Our meta-analysis includes 20 relatively high-quality studies conducted from 2003 to 2017, with a total 9879 patients (SLT=1306 and PLT=8573), thus we believe it is the first study of its type. In our meta-analysis, we found that SLT was superior and feasible in terms of OS and DFS compared to PLT, and we found that the incidence of postoperative complications, such as biliary complications, sepsis, and vascular complications of SLT were similar to that of PLT; however, there was a significantly higher rate of post-operative bleeding and operative mortality with the SLT group than the PLT group.

In the scenario of conflicting results from different studies, the most important finding regarding SLT was its post-transplant survival rate and DFS rate compared to PLT. Adam et al. [17] found that SLT was related to a higher risk of recurrence and a poorer outcome compared to PLT. Nonetheless, a study carried out in the same year by Belghiti et al. [22] found contrasting results and concluded that SLT and PLT were similar in term of OS rates. Moreover, a study by Scatton et al. [24] showed that careful consideration of histological features of resected tumor specimens may be used as selection criteria for SLT, with similar survival and recurrence result as PLT. As reported earlier by Adam et al. [17], the poor results after SLT were basically because of increased operative mortality and excess bleeding at the time of surgery, because of surgical difficulties during dissecting the substantial adhesions and portal collateral circulations during LT. However, the other studies have suggested that meticulous sharp dissection with a sufficient dissection plan can resolve the problem of excessive bleeding [23,31].

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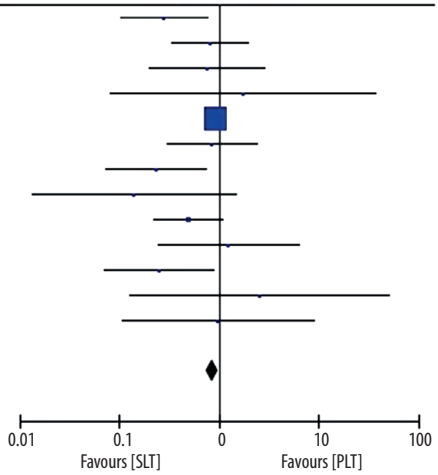
A

Study or subgroup	SLT Events	SLT Total	PLT Events	PLT Total	Weight	Odds ratio M-H, fixed, 95% CI
Adam 2003	8	17	148	195	2.9%	0.28 [0.10, 0.77]
Bhangui 2016	24	31	274	340	2.4%	0.83 [0.34, 2.00]
Del Gaudio 2008	13	16	125	147	1.0%	0.76 [0.20, 2.90]
Faciuto 2008	5	5	28	32	0.2%	1.74 [0.08, 37.08]
Hu 2012	575	888	4041	6087	82.5%	0.93 [0.80, 1.08]
Liu 2012	34	39	160	180	1.7%	0.85 [0.30, 2.42]
Moon 2012	12	17	154	169	1.9%	0.23 [0.07, 0.75]
Sapisochin 2010	14	17	33	34	0.9%	0.14 [0.01, 1.48]
Shan 2017	14	28	141	211	3.8%	0.50 [0.22, 1.10]
Shao 2008	13	15	52	62	0.6%	1.25 [0.24, 6.41]
Vasavada 2015	13	18	83	91	1.7%	0.25 [0.07, 0.88]
Vennarecci 2007	9	9	33	37	0.2%	2.55 [0.13, 51.74]
Wu 2012	35	36	143	147	0.4%	0.98 [0.11, 9.03]
Total (95% CI)		**1136**		**7732**	**100.0%**	**0.86 [0.75, 0.99]**
Total events	769		5415			

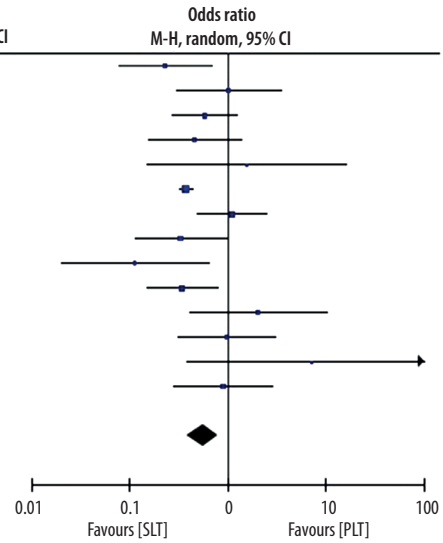
Heterogeneity: Chi^2=19.29, df=12 (P=0.08); I^2=38%
Test for overall effect: Z=2.11 (P=0.03)



B

Study or subgroup	SLT Events	SLT Total	PLT Events	PLT Total	Weight	Odds ratio M-H, random, 95% CI
Adam 2003	5	17	125	195	7.1%	0.23 [0.08, 0.69]
Belghiti 2003	14	18	54	70	5.9%	1.04 [0.30, 3.60]
Bhangui 2016	12	31	176	340	10.5%	0.59 [0.28, 1.25]
Del Gaudio 2008	10	16	115	147	7.1%	0.46 [0.16, 1.37]
Faciuto 2008	4	5	23	32	2.2%	1.57 [0.15, 15.97]
Hu 2012	485	888	3067	4041	18.4%	0.38 [0.33, 0.44]
Liu 2012	30	39	135	180	9.7%	1.11 [0.49, 2.52]
Moon 2012	11	17	143	169	7.2%	0.33 [0.11, 0.98]
Sapisochin 2010	11	17	32	34	3.6%	0.11 [0.02, 0.65]
Shan 2017	9	28	122	211	9.5%	0.35 [0.15, 0.80]
Shao 2008	13	15	47	62	4.1%	2.07 [0.42, 10.26]
Vasavada 2015	13	18	66	91	6.7%	0.98 [0.32, 3.05]
Vennarecci 2007	9	9	27	37	1.4%	7.25 [0.39, 136.04]
Wu 2012	32	36	132	147	6.5%	0.91 [0.28, 2.92]
Total (95% CI)		**1154**		**5756**	**100.0%**	**0.56 [0.39, 0.81]**
Total events	658		4264			

Heterogeneity: Tau^2=0.18, Chi^2=26.08, df=13 (P=0.02); I^2=50%
Test for overall effect: Z=3.08 (P=0.002)



C

Study or subgroup	SLT Events	SLT Total	PLT Events	PLT Total	Weight	Odds ratio M-H, fixed, 95% CI
Adam 2003	5	17	113	195	2.4%	0.30 [0.10, 0.89]
Belghiti 2003	10	18	39	70	1.3%	0.99 [0.35, 2.82]
Bhangui 2016	9	31	129	340	2.9%	0.67 [0.30, 1.50]
Del Gaudio 2008	8	16	104	147	1.9%	0.41 [0.15, 1.17]
Hu 2012	336	888	2648	6087	78.4%	0.79 [0.68, 0.91]
Liu 2012	26	39	124	180	2.8%	0.90 [0.43, 1.89]
Moon 2012	11	17	140	169	1.7%	0.38 [0.13, 1.11]
Sapisochin 2010	10	17	30	34	1.5%	0.19 [0.05, 0.79]
Shan 2017	9	28	116	211	3.4%	0.39 [0.17, 0.90]
Vasavada 2015	8	18	42	91	1.4%	0.93 [0.34, 2.58]
Vennarecci 2007	9	9	27	37	0.1%	7.25 [0.39, 136.04]
Wu 2012	27	36	118	147	2.2%	0.74 [0.31, 1.74]
Total (95% CI)		**1134**		**7708**	**100.0%**	**0.75 [0.66, 0.86]**
Total events	468		3630			

Heterogeneity: Chi^2=15.05, df=11 (P=0.18); I^2=27%
Test for overall effect: Z=4.31 (P<0.0001)

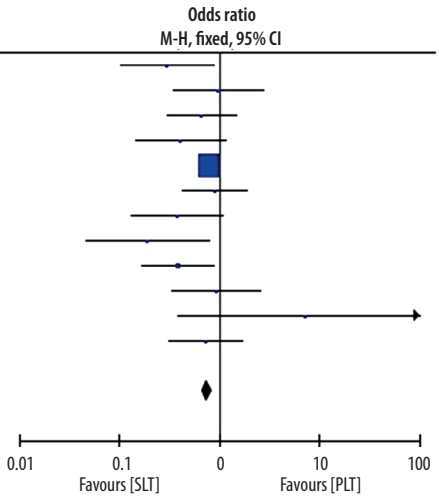


Figure 10. Disease-free survival outcomes between SLT group and PLT group: (**A**) 1-year, (**B**) 3-year, (**C**) 5-year.

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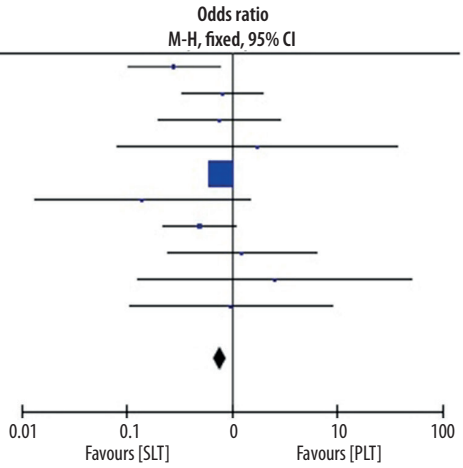
A

Study or subgroup	SLT Events	SLT Total	PLT Events	PLT Total	Weight	Odds ratio M-H, fixed, 95% CI
Adam 2003	8	17	148	195	3.3%	0.28 [0.10, 0.77]
Bhangui 2016	24	31	274	340	2.7%	0.83 [0.34, 2.00]
Del Gaudio 2008	13	16	125	147	1.2%	0.76 [0.20, 2.90]
Faciuto 2008	5	5	28	32	0.2%	1.74 [0.08, 37.08]
Hu 2012	606	859	4292	5727	86.0%	0.80 [0.68, 0.94]
Sapisochin 2010	14	17	33	34	1.0%	0.14 [0.01, 1.48]
Shan 2017	14	28	141	211	4.3%	0.50 [0.22, 1.10]
Shao 2008	13	15	52	62	0.7%	1.25 [0.24, 6.41]
Vennarecci 2007	9	9	33	37	0.2%	2.55 [0.13, 51.74]
Wu 2012	35	36	143	147	0.4%	0.98 [0.11, 9.03]
Total (95% CI)		**1033**		**6932**	**100.0%**	**0.77 [0.67, 0.90]**
Total events	741		5269			

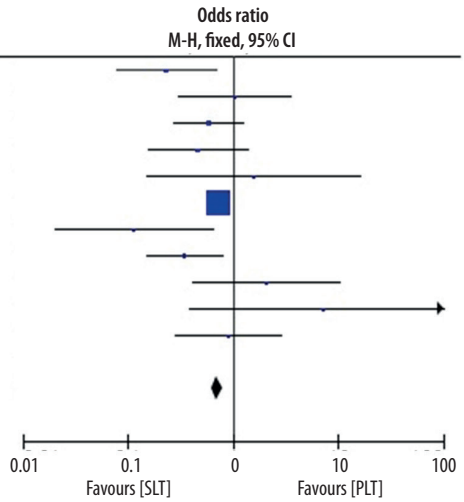
Heterogeneity: Chi²=8.51, df=9 (P=0.48); I²=0%
Test for overall effect: Z=3.41 (P=0.0006)



B

Study or subgroup	SLT Events	SLT Total	PLT Events	PLT Total	Weight	Odds ratio M-H, fixed, 95% CI
Adam 2003	5	17	125	195	2.8%	0.23 [0.08, 0.69]
Belghiti 2003	14	18	54	70	1.0%	1.04 [0.30, 3.60]
Bhangui 2016	12	31	176	340	3.6%	0.59 [0.28, 1.25]
Del Gaudio 2008	10	16	115	147	1.7%	0.46 [0.16, 1.37]
Faciuto 2008	4	5	23	32	0.2%	1.57 [0.15, 15.97]
Hu 2012	463	859	3520	5727	83.7%	0.73 [0.63, 0.85]
Sapisochin 2010	11	17	32	34	1.5%	0.11 [0.02, 0.65]
Shan 2017	9	28	122	211	3.8%	0.35 [0.15, 0.80]
Shao 2008	13	15	47	62	0.5%	2.07 [0.42, 10.26]
Vennarecci 2007	9	9	27	37	0.1%	7.25 [0.39, 136.04]
Wu 2012	32	36	132	147	1.1%	0.91 [0.28, 2.92]
Total (95% CI)		**1051**		**7002**	**100.0%**	**0.71 [0.62, 0.81]**
Total events	582		4373			

Heterogeneity: Chi²=17.22, df=10 (P=0.07); I²=42%
Test for overall effect: Z=5.12 (P<0.00001)



C

Study or subgroup	SLT Events	SLT Total	PLT Events	PLT Total	Weight	Odds ratio M-H, fixed, 95% CI
Adam 2003	5	17	113	195	2.3%	0.30 [0.10, 0.89]
Belghiti 2003	10	18	39	70	1.3%	0.99 [0.35, 2.82]
Bhangui 2016	9	31	129	340	2.8%	0.67 [0.30, 1.50]
Del Gaudio 2008	8	16	104	147	1.8%	0.41 [0.15, 1.17]
Hu 2012	374	859	3191	5727	84.8%	0.61 [0.53, 0.71]
Sapisochin 2010	10	17	30	34	1.5%	0.19 [0.05, 0.79]
Shan 2017	9	28	116	211	3.3%	0.39 [0.17, 0.90]
Vennarecci 2007	9	9	27	37	0.1%	7.25 [0.39, 136.04]
Wu 2012	27	36	118	147	2.1%	0.74 [0.31, 1.74]
Total (95% CI)		**1031**		**6908**	**100.0%**	**0.60 [0.53, 0.69]**
Total events	461		3867			

Heterogeneity: Chi²=9.63, df=8 (P=0.29); I²=17%
Test for overall effect: Z=7.39 (P<0.00001)

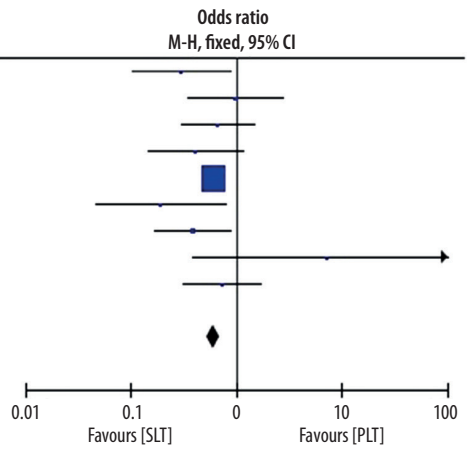


Figure 11. Disease-free survival outcomes for DDLT between SLT group and PLT group: (**A**) 1-year, (**B**) 3-year, (**C**) 5-year.

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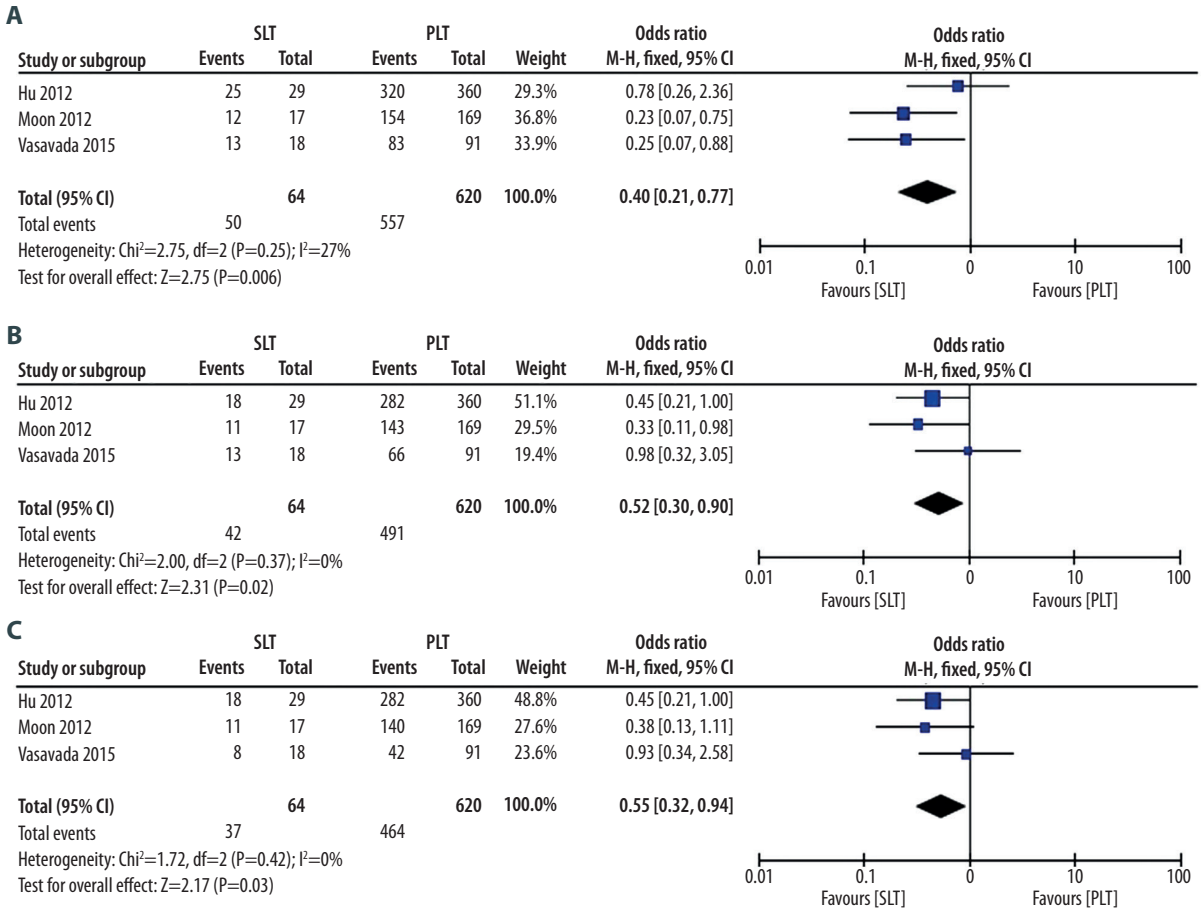

Figure 12. Disease-free survival Outcomes for LDLT between SLT group and PLT group: (**A**) 1-year, (**B**) 3-year, (**C**) 5-year.

As observed from pooled estimates of our meta-analysis, SLT showed superior 1-year, 3-year, and 5-year OS and DFS rates in comparison with PLT. After classifying data according to donor type, we found DDLT recipients showed no significant difference in 1-year and 3-year OS rates between the SLT and PLT groups. However, 5-year OS rates for DDLT recipients was superior in the SLT group compared to the PLT group. In LDLT recipients, SLT had superior 1-year, 3-year, and 5-year OS rates compared to PLT. Moreover, 1-year, 3-year, and 5-year DFS rates were also superior in SLT compared to PLT in both the DDLT and LDLT recipients. In addition, classifying data according to Milan criteria, our meta-analysis didn't find any difference for OS and DFS rates between the SLT and PLT groups for patients within the Milan criteria. The meta-analysis for OS beyond the Milan criteria was also not significant between SLT and PLT groups. SLT after LR has the advantage that surgeons are aware of the histological status of the tumor, which allows surgeons to choose appropriate patients for SLT. Currently, there are no definitive answers as to why the OS and DFS rates of SLT patients surpassed those of PLT patients. One possible explanation is that after primary liver resection, there is downstaging of the tumor, and the patients presenting for SLT are mostly patients with Child A, lower MELD score, lower AFP level, and fewer nodules compared to PLT patients [25,26,39–41]. Interestingly, when we compared MELD score and pre-transplant AFP levels between SLT and PLT groups, we found both MELD score and pre-transplant AFP levels were significantly lower in SLT patients than in PLT patients. Thus, the meta-analysis of MELD score and pre-transplant AFP levels seems to justify our findings, that SLT is superior to PLT in terms of OS and DFS. However, our meta-analysis showed the SLT group had a higher number of nodules, but smaller size of tumors compared to the PLT group. The reason for a higher number of nodules can be explained in 2 ways: 1) local recurrence and 2) de nova HCC, as LR is associated with high tumor recurrence because it leaves diseased liver in a place where local recurrence might be from insufficient R1 resection or micro-vascular invasion from segmental portal circulation. Furthermore, de nova HCC is still present in the diseased liver after LR, leading to distant recurrence from the resection area [42]. These 2 phenomena might be responsible for a higher number of nodules in the SLT group. However, regular monitoring of HCC

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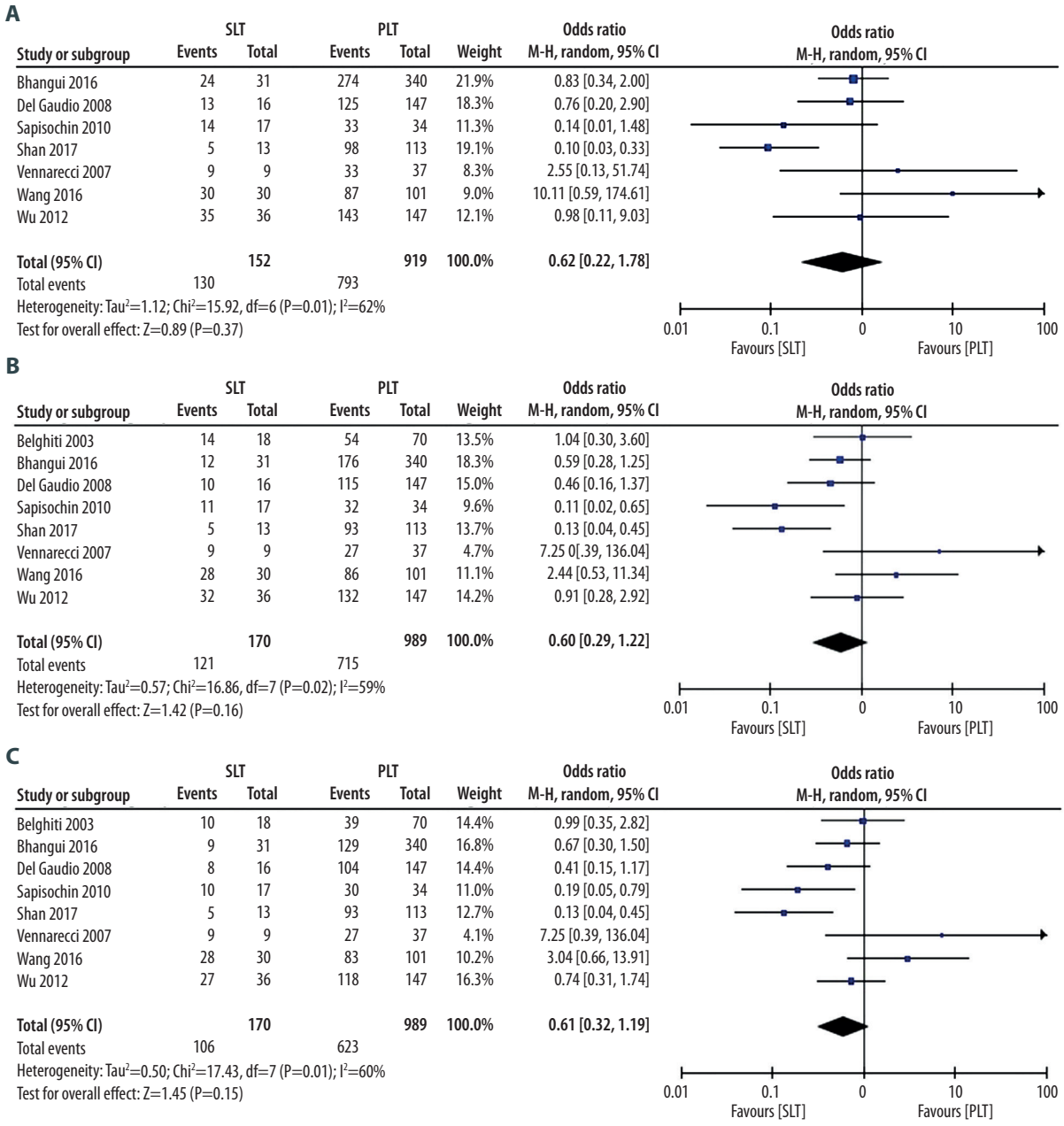

Figure 13. Disease-free survival outcomes for patients within Milan criteria between SLT group and PLT group: (**A**) 1-year, (**B**) 3-year, (**C**) 5-year.

patients after LR might be the result of smaller tumors in the SLT group compared to the PLT group. These results should be reevaluated according to the recent transplant selection requirements. Additionally, these findings also showed that the patient selection standard for SLT demands careful consideration and redefinition. Moreover, our review of studies suggested that along with tumor size and numbers of tumors, the liver transplantation could be implemented for less aggressive and pathological well differentiated tumors. This meta-analysis also showed that SLT is similar to PLT for patients within and beyond Milan criteria, and can be performed safely after LR.

Moreover, concern regarding postoperative outcomes between SLT and PLT results showed that the rate of postoperative complications like biliary, sepsis, and vascular complications, were similar among SLT and PLT patients; however, postoperative bleeding and operative mortality was significantly high in the SLT group compare to the PLT group. The possible causes of

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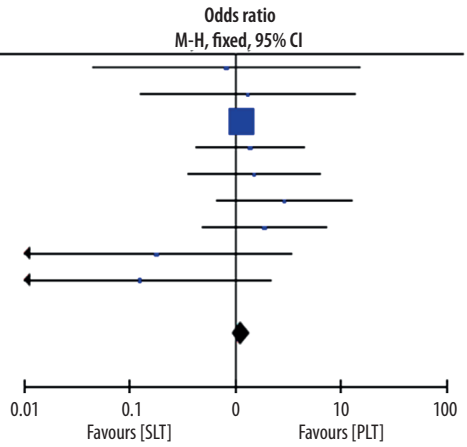
A

Study or subgroup	SLT Events	SLT Total	PLT Events	PLT Total	Weight	Odds ratio M-H, fixed, 95% CI
Adam 2003	0	17	6	195	0.6%	0.83 [0.05, 15.41]
Belghiti 2003	1	18	3	70	0.7%	1.31 [0.13, 13.43]
Hu 2012	113	888	681	6087	87.0%	1.16 [0.94, 1.43]
Hwang 2007	4	17	36	200	2.5%	1.40 [0.43, 4.55]
Kim 2008	4	15	6	31	1.6%	1.52 [0.36, 6.46]
Liu 2012	3	39	5	180	0.9%	2.92 [0.67, 12.76]
Moon 2012	3	17	17	169	1.5%	1.92 [0.50, 7.35]
Vennarecci 2007	0	9	8	37	1.9%	0.18 [0.01, 3.47]
Wu 2012	0	36	14	147	3.3%	0.13 [0.01, 2.16]
Total (95% CI)		**1056**		**7116**	**100.0%**	**1.14 [0.94, 1.40]**
Total events	128		776			

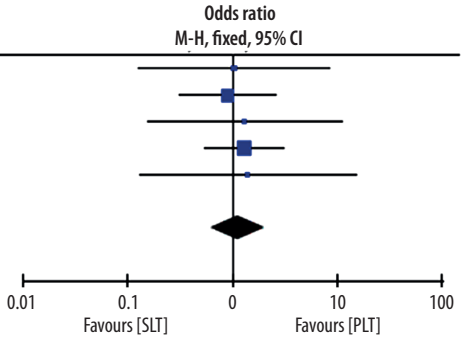
Heterogeneity: Chi²=6.25, df=8 (P=0.62); I²=0%
Test for overall effect: Z=1.31 (P=0.19)



B

Study or subgroup	SLT Events	SLT Total	PLT Events	PLT Total	Weight	Odds ratio M-H, fixed, 95% CI
Adam 2003	1	17	11	195	8.4%	1.05 [0.13, 8.62]
Belghiti 2003	7	18	29	70	36.7%	0.90 [0.31, 2.60]
Hwang 2007	1	17	9	200	6.7%	1.33 [0.16, 11.14]
Liu 2012	8	39	30	180	43.0%	1.29 [0.54, 3.08]
Vennarecci 2007	1	9	3	37	5.3%	1.42 [0.13, 15.47]
Total (95% CI)		**100**		**682**	**100.0%**	**1.14 [0.63, 2.06]**
Total events	18		82			

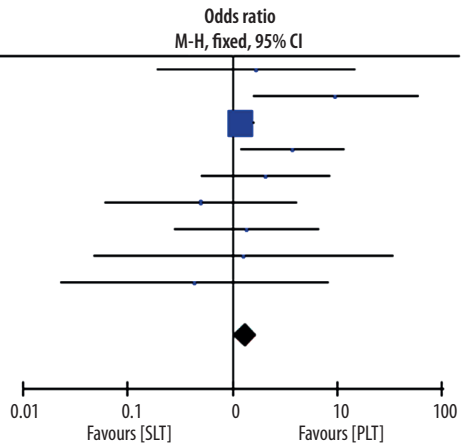
Heterogeneity: Chi²=0.33, df=4 (P=0.99); I²=0%
Test for overall effect: Z=0.42 (P=0.68)



C

Study or subgroup	SLT Events	SLT Total	PLT Events	PLT Total	Weight	Odds ratio M-H, fixed, 95% CI
Adam 2003	1	17	7	195	1.1%	1.68 [0.19, 14.51]
Belghiti 2003	4	18	2	70	0.7%	9.71 [1.62, 58.31]
Hu 2012	59	888	338	6087	84.8%	1.21 [0.91, 1.61]
Hwang 2007	5	17	20	200	2.3%	3.75 [1.20, 11.74]
Kim 2008	5	15	6	31	2.8%	2.08 [0.52, 8.41]
Liu 2012	1	39	9	180	3.3%	0.50 [0.06, 4.07]
Moon 2012	2	17	15	169	2.6%	1.37 [0.29, 6.57]
Vennarecci 2007	0	9	1	37	0.6%	1.28 [0.05, 34.01]
Wu 2012	0	36	4	147	1.9%	0.44 [0.02, 8.30]
Total (95% CI)		**1056**		**7116**	**100.0%**	**1.32 [1.03, 1.71]**
Total events	77		402			

Heterogeneity: Chi²=10.16, df=8 (P=0.25); I²=21%
Test for overall effect: Z=2.15 (P=0.03)



postoperative bleeding and operative mortality in SLT patients has already been discussed earlier in this article. Additionally, despite surgical difficulties in SLT, primary laparoscopic resection of the liver and postsurgical intra-abdominal anti-adhesive products are found to be effective in reducing adhesions and thereby minimizing the risks of complications in SLT [43,44].

Despite the high quality of the papers included in this meta-analysis, there are various shortcomings concerning our meta-analysis. First, there is a potential publication bias, because studies are less likely to outline negative findings and there are limited resources available to identify unpublished trials. Second, only English-language studies were included. Thus, the quality of outcomes was compromised to some extent, which is a typical reason for publication bias. In the future, high quality randomized controlled trials with large sample size should be performed. However, this meta-analysis is still of great significance for comparing different outcomes between SLT and PLT and may prove beneficial for clinicians in choosing the appropriate treatment option.

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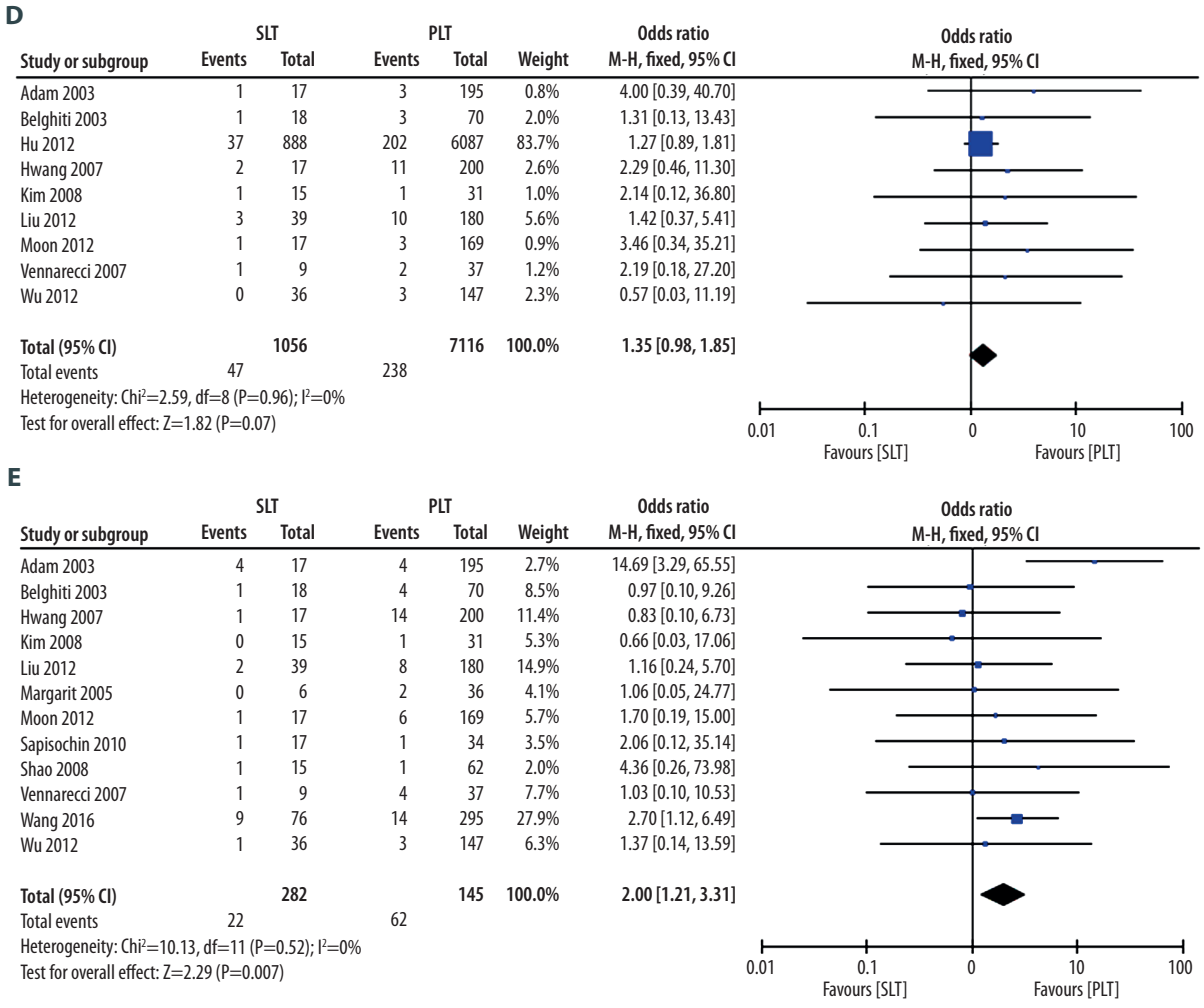

Figure 14. Postoperative complications between SLT and PLT: (**A**) biliary complication, (**B**) sepsis, (**C**) postoperative bleeding, (**D**) vascular complication, (**E**) operative mortality.

Conclusions

Compared with PLT, SLT had more postoperative bleeding and increased operative mortality. However, SLT was shown to have better 1-year, 3-year, and 5-year OS and DFS rates compared to PLT. As shown in the results of this meta-analysis of 9879 patients, SLT may be a better treatment strategy for recurrent HCC and for patients with compensated liver, whenever feasible, considering the severe organ limitation and the safety of SLT. However, PLT can be referred as a treatment strategy for HCC patients with cirrhotic and decompensated liver.

Conflict of interests

None.

Abbreviations

SLT – salvage liver transplantation; **PLT** – primary liver transplantation; **HCC** – hepatocellular carcinoma; **OR** – odds ratio; **CI** – confidence interval; **OS** – overall survival; **DFS** – disease free survival; **PRISMA** – preferred reporting items for systematic reviews and meta-analysis; **SMD** – standard mean difference.

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