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REVIEW ARTICLE

Open versus laparoscopic hepatic resection for hepatocellular carcinoma: a systematic review and meta-analysis

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Abstract

Background Several studies have been conducted comparing laparoscopic liver resection (LLR) versus open liver resection (OLR) for hepatocellular carcinoma (HCC), however, the optimal therapeutic approach has not been established. Therefore, we conducted a systematic review and meta-analysis of studies comparing LLR versus OLR for HCC.

Methods MEDLINE and Cochrane Central Register of Controlled Trials database were systematically searched for relevant studies.

Results Fifty-one studies were identified including a total of 6812 patients (2786 patients underwent LLR and 4026 patients were subjected to OLR). Blood transfusion rate, hospital stay in days, 30-days mortality rate and morbidity were significantly lower in LLR comparing with OLR (odds ratio (OR) 0.45; 95% confidence interval (CI) 0.30–0.69; $P=0.001$; $I^2=55.83\%$), (MD −3.87; 95% CI −4.86 to −2.89; $P=0.001$; $I^2=87.35\%$), (OR 0.32; 95% CI 0.16–0.66; $P=0.001$; $I^2=0\%$), and (OR 0.42; 95% CI 0.34–0.52; $P=0.001$; $I^2=39.64$), respectively. There was no significant difference between LLR and OLR regarding the operative time in minutes, resection margin in centimeter and R0 resection (MD 18.29; 95% CI −1.58 to 38.15; $p=0.07$; $I^2=91.73\%$), (MD 0.04; 95% CI −0.06 to 0.14; $P=0.41$; $I^2=48.03\%$) and (OR 1.31; 95% CI 0.98–1.76; $P=0.07$; $I^2=0\%$), respectively. The 1-year overall survival (1-OS) and 5-OS rates were significantly higher in LLR comparing with OLR (OR 1.45; 95% CI 1.06–1.99; $P=0.02$; $I^2=25.59\%$) and (OR 1.36; 95% CI 1.07–1.72; $P=0.01$; $I^2=14.88\%$), respectively.

Conclusion LLR is superior to OLR regarding intraoperative blood loss, blood transfusion rate, hospital stay in days, 30-days mortality and morbidity, however, randomized controlled trials are needed to identify the superiority of either strategy.

Keywords Carcinoma · Hepatocellular · Laparoscopy · Hepatectomy · Liver neoplasms

Hepatocellular carcinoma is the third most common causes of cancer-related death in the world [1]. Liver resection is considered the most widely used treatment for patients with hepatocellular carcinoma (HCC) [2]. Laparoscopic liver resection (LLR) has increasingly been adopted since it was first introduced in 1991 [3]. There has been a growing body of evidence that LLR is associated with lower mortality and morbidity rates in comparison with open liver resection (OLR) [4]. However, LLR is still a challenging approach for patients as well as surgeons since most HCC are developed on top of cirrhotic liver or chronic hepatitis [5–7]. Furthermore, LLR is associated with technical difficulties, relatively longer operative time and bleeding risk in parenchymal resection [8, 9]. Although many studies have been conducted comparing LLR versus OLR for HCC, data are still relatively controversial, given the recent advancements in laparoscopic devices and techniques over the last few years and the increase in surgeons' experience [10–16]. The recently published meta-analysis comparing between LLR and OLR did not differentiate between propensity score-matched studies and unmatched studies, therefore, its results might have an inherent risk of confounding bias limiting the causal relationship between both interventions and the observed clinical outcomes [17, 18]. Moreover, several studies have reported favorable clinical outcomes associated

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with LLR for right HCC, however, the efficacy of LLR in right hepatectomy has not been well established [19, 20]. Therefore, we sought to conduct a systematic review and meta-analysis of studies comparing LLR versus OLR in patients with right and left HCC and reported clinical outcomes in propensity-score matched and unmatched cohorts, to mitigate the potential risk of confounding bias, to identify the safety and efficacy of LLR in terms of surgical and oncological outcomes.

Methods

This systematic review and meta-analysis is reported according to the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) [21]. MEDLINE and Cochrane Central Register of Controlled Trials database were systematically searched through July 2018 using the following search terms: (1) hepatocellular carcinoma, liver neoplasms, liver cirrhosis/complications, malignant liver tumor; (2) hepatectomy, open liver resection, open hepatectomy (3) laparoscopy, laparoscopic hepatectomy. We had no restrictions on studies' design. We included prospective and retrospective observational studies and randomized controlled trials (RCTs). Studies had to fulfill the following prespecified criteria to be considered qualified for inclusion in our meta-analysis; (1) comparing in a head to head fashion between LLR and OLR in patients with right or left HCC; (2) reported oncological and surgical outcomes, as mentioned below, in both treatment groups; (3) included patients with primary HCC. In case of duplicate publications reflecting the same population, we included the report with the longer follow-up duration. Our outcomes of interest were operative time in minutes (min), amount of blood loss in milliliter (ml), rate of blood transfusion, length of hospital stay in days, 30-days mortality, morbidity, recurrence rate, resection margin in centimeter (cm), R0 resection, 1-year over-all survival (1-OS), 3-years overall survival (3-OS), 5-years overall survival (5-OS), 1-year disease-free survival (1-DFS), 3-years disease-free survival (3-DFS), and 5-years disease-free survival (5-DFS) rates.

Two reviewers (Meng and Xu) independently screened databases for relevant studies based on the abovementioned criteria. After title and abstract screening, the full text of the selected articles was evaluated for eligibility. The two reviewers independently extracted the relevant data in a standardized extraction form, and third reviewer's opinion was sought in case of disagreements (Duan). We performed a subgroup analysis restricted to studies reported clinical outcomes in propensity-score matched cohorts to mitigate the potential risk of confounding bias in data gleaned from observational studies. We conducted a subgroup analysis focused on studies exclusively recruited patients with right HCC to investigate the role of LLR in comparison with OLR in right HCC.

This meta-analysis is exempt from the need for IRB approval.

Statistical analysis

For categorical variables, summary estimates were expressed as odds ratio (OR) with corresponding 95% confidence interval (CI), and for continuous variables, summary estimates were expressed as mean difference (MD) with corresponding CI. The OR of our outcomes of interest was calculated according to the DerSimonian-Laird random effects model [22]. Heterogeneity across studies was assessed using Q-statistic and I^2 –statistic [23]. The I^2 statistic describes the percentage of total variation across studies that is due to heterogeneity. Sensitivity analyses were performed using the one-study-removed method to show how the summary estimate changes if the study that has the largest effect size is removed. Egger's regression test and visual inspection of funnel plots were used to assess for potential publication bias since studies with statistically significant results are more likely to be published than studies with non-significant findings [24]. The statistical level of significance was 2-tailed $P < 0.05$. All Analyses were performed using random-effects model. All analyses were performed using Comprehensive Meta-analysis version 3.0 software (Biostat, Inc., New Jersey, USA).

Results

All studies meta-analysis

The process of studies selection is displayed in Fig. 1. Out of 1004 studies screened, the full text of 72 articles was reviewed. Fifty-one studies were identified including a total of 6812 patients, 2786 patients underwent LLR and 4026 patients were subjected to OLR. Studies' characteristics are shown in Table 1. Patients' characteristics are shown in Table 2. The recruitment periods of the included studies was between 1990 and 2017. The follow-up duration of the included studies ranged from 3 to 78.5 months.

The mean of operative time in minutes was reported in 26 studies including 3664 patients. There was no significant difference between LLR and OLR regarding the operative time in min (MD 18.29; 95% CI − 1.58 to 38.15; $P = 0.07$; $I^2 = 91.73\%$), Fig. 2. The operative blood loss in ml was reported in 19 studies including 2112 patients. Operative blood loss was significantly lower in LLR in comparison with OLR (MD − 124.09; 95% CI − 188.21 to − 59.97; $P = 0.001$; $I^2 = 94.09\%$). The incidence of blood transfusion

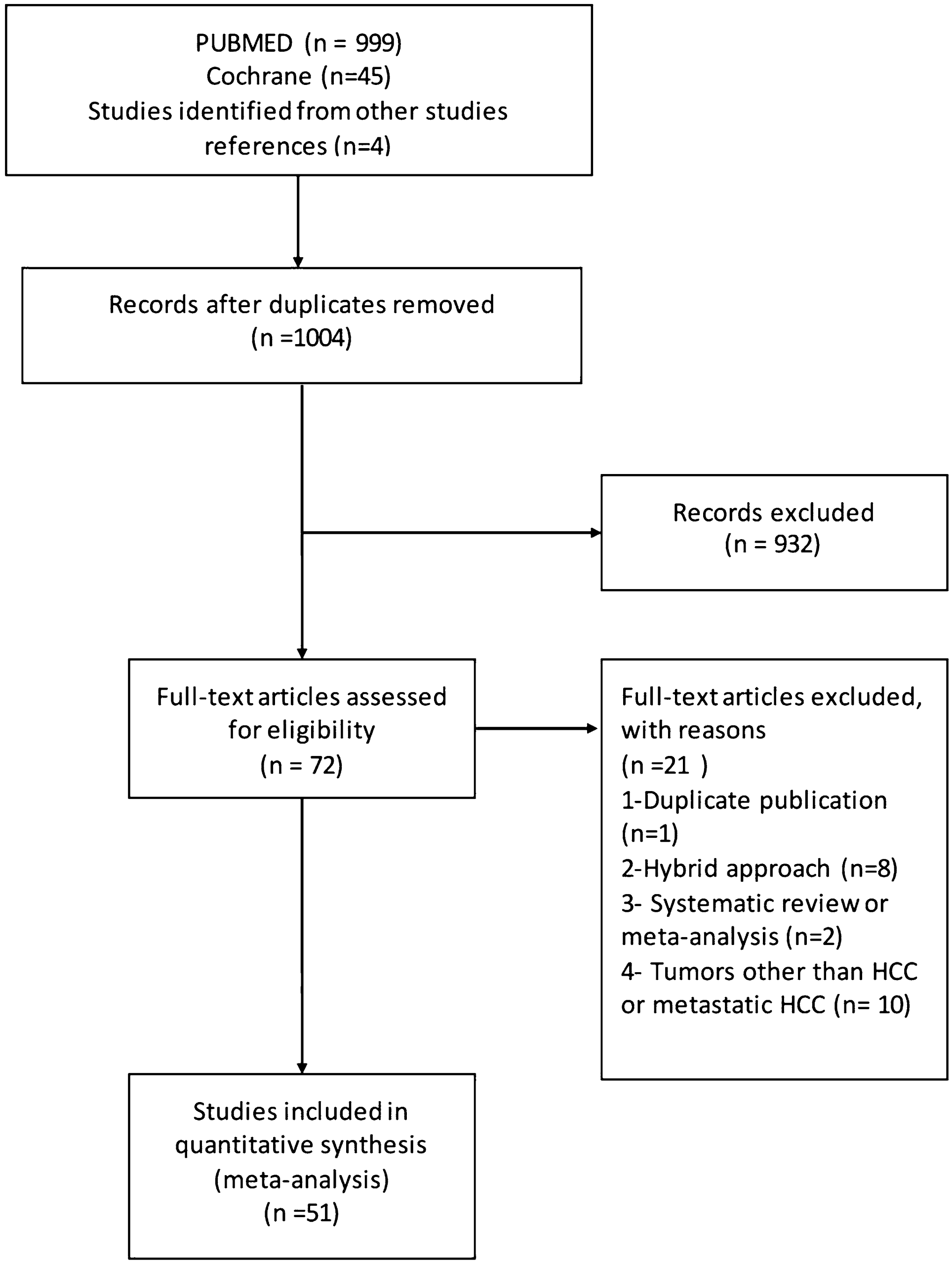


Fig. 1 Flow chart showing the process of studies screening and selection

was significantly lower in LLR comparing with OLR (OR 0.45; 95% CI 0.30–0.69; $P=0.001$; $I^2=55.83\%$).

The mean of hospital stay in days, 30-days mortality rate and morbidity were significantly lower in LLR comparing with OLR (MD − 3.87; 95% CI − 4.86 to − 2.89; $P=0.001$; $I^2=87.35\%$), (OR 0.32; 95% CI 0.16–0.66; $P=0.001$; $I^2=0\%$), and (OR 0.42; 95% CI 0.34–0.52; $P=0.001$; $I^2=39.64$), respectively, Fig. 3.

Resection margin in centimeter (cm) and R0 resection were not significantly different between LLR and OLR groups (MD 0.04; 95% CI − 0.06 to 0.14; $P=0.41$; $I^2=48.03\%$) and (OR 1.31; 95% CI 0.98 —1.76; $P=0.07$; $I^2=0\%$), respectively. The recurrence rate was significantly higher in the OLR group than LLR group (OR 0.83; 95% CI 0.71–0.98; $P=0.03$; $I^2=0\%$), Fig. 4.

The 1-OS and 5-OS were significantly higher in LLR comparing with OLR group (OR 1.45; 95% CI 1.06–1.99; $P=0.02$; $I^2=25.59\%$) and (OR 1.36; 95% CI 1.07–1.72; $P=0.01$; $I^2=14.88\%$), respectively, Fig. 5. 3-OS was not significantly different between both groups (OR 1.07; 95% CI 0.70–1.63; $P=0.77$; $I^2=56.6$). 1-DFS was significantly higher in LLR group comparing with OLR group (OR 1.42; 95% CI 1.032–1.972; $P=0.032$; $I^2=55.57\%$), however, 3-DFS and 5-DFS did not differ significantly between both approaches (OR 1.349; 95% CI 1.349; 0.939–1.938;

Table 1 Characteristics of the included studies

Study name	Publication year	Study country	Study period	Design
Cheung [39]	2016	China (Hong Kong	2004–2014	Retrospective with propensity score matching 1:3
Ahn [29]	2016	Korea	2000–2013	Retrospective not matched
Xiang [14]	2016	China	2012–2015	Retrospective not matched
Lai [30]	2016	China	2005–2010	Retrospective not matched
Tanaka [16]	2015	Japan	2007–2014	Retrospective with propensity score matching 1:1
Jiang [40]	2015	China	2010–2014	Prospective patients randomly divided
Luo [41]	2015	China	2008–2015	Retrospective matched study 1:1
Takahara [38]	2015	Japan	2000–2010	Retrospective matched study 1:1
Han [42]	2015	Korea	2004–2013	Retrospective propensity score matched 1:1
Komatsu [43]	2015	France	2006–2014	Retrospective matched-pair analysis 1:1
Xiao [44]	2015	China	2010–2012	Retrospective not matched
Cho [45]	2015	Korea	2003–2012	Retrospective not matched
Leee [46]	2015	Canada	2006–2013	Retrospective 1:2 matchedpair analysis
Yoon [47]	2014	Korea	2007–2011	Retrospective 1:3 matched
Siniscalchi [48]	2014	Italy	2005–2010	Retrospective not matched
Yamashita [31]	2014	Japan	2000–2013	Retrospective not matched
Ahn [49]	2014	Korea	2005–2013	Retrospective matched 1:1
Memeo [50]	2014	France	1990–2009	Retrospective case–control study 1:1
Kim [51]	2014	Korea	2004–2012	Retrospective score matched 1:1
Cheung [52]	2013	China	2002–2009	Retrospective matched 1:2
Ai [53]	2013	China	2007–2011	Retrospective not matched
Kobayashi [54, 55]	2013	Japan	1997–2011	Prospective not matched Retrospective matched
HU [54, 55]	2011	China	2006–2011	Prospective matched analysis
Lee [56]	2011	Hong Kong	2004–2010	Prospective matched analysis
Ker [28]	2011	Taiwan	1998–2006	Prospective not matched
Kim [57]	2011	Korea	2005–2009	Prospective for LLRRetrospective for OLR case matched analysis 1:1
Truant [58]	2011	France	2002–2009	Retrospective matched
Aldrighetti [59]	2010	Italy	NA	prospective case matched analysis
Tranchart [60]	2011	France		Retrospective case–control 1:1
Alemi [61]	2010	USA		Retrospective, NA about matching
Sarpel [62]	2009	USA		Prospective matched analysis
Lai [63]	2009	Hong Kong		Retrospective matched study
Cai [64]	2008	China		A pair-matched retrospective analysis
Laurent [65]	2003	France	1998–2000	Matched prospective analysis
Shimada [66]	2001	Japan	NA- 2000	Retrospective not matched
Chen [13]	2017	China	2015–2016	Retrospective analysis not matched
Jun-hua [53]	2013	China	2007–2011	Retrospective not matched
Amato [10]	2017	Italy	2010–2014	retrospective analysis not matchd
Wenda [12]	2016	China	2005–2010	Retrospective not matched
Cheung [67]	2018	Hong Kong	2015–2016	Prospective matched
Xu [68]	2017	China	2011–2016	Retrospective not matched
Tarantino [20]	2017	Italy	2000–2016	Retrospective not matched
Yoon [19]	2017	Korea	2008–2015	Retrospective matched 1;1
Xu 2018 [69]	2018	China	2015–2017	Retrospective with propensity score matching 1:1
Tomoki [70]	2017	Japan	2008–2014.	Retrospective not matched
Li [12]	2017	china	2005 to July 2010	Retrospective not matched
Zhang [71]	2016	China	2010–2015	Retrospective not matched
Zhang [72]	2016	China	2012–2014	Retrospective not matched

Table 1 (continued)

Study name	Publication year	Study country	Study period	Design
Sposito [73]	2016	Italy	2006 to 2013	Retrospective with propensity score matching 1:1
Sotiropoulos [74]	2016	Greece	2011–2016	Retrospective not matched
Jiang [75]	2016	China	NA	Retrospective score matched 1:1
Study name	**LLR (n)**	**OLR**	**Total *n***	**Resected lobe**
Cheung [39]	110	330	440	Left lobe
Ahn [29]	32	93	125	Left lobe
Xiang [14]	128	207	335	Both
Lai [30]	28	33	61	Both
Tanaka [16]	20	20	40	Both
Jiang [40]	50	50	100	Both
Luo [41]	53	53	106	Both
Takahara [38]	387	387	774	Both
Han [42]	88	88	176	Both
Komatsu [43]	38	38	76	Both
Xiao [44]	41	86	127	Both
Cho [45]	24	19	43	Right lobe
Leee [46]	43	86	129	Both
Yoon 2014 [47]	58	174	232	Both
Siniscalchi [48]	23	133	156	Both
Yamashita [31]	63	99	162	Both
Ahn [49]	51	51	102	Both
Memeo [50]	45	45	90	Both
Kim [51]	70	76	146	Both
Cheung [52]	32	64	96	Both
Ai [53]	97	178	275	Both
Kobayashi [54, 55]	21	27	48	Both Both
HU [54, 55]	30	30	60	Both
Lee [56]	33	50	83	Both
Ker [28]	116	208	324	Both
Kim [57]	26	29	55	Both
Truant [58]	36	53	89	Both
Aldrighetti [59]	16	16	32	Both
Tranchart [60]	42	42	84	Both
Alemi [61]	28	25	53	Both
Sarpel [62]	20	56	76	Both
Lai [63]	25	33	58	Both
Cai [64]	31	31	62	Both
Laurent [65]	13	14	27	Both
Shimada [66]	17	38	55	Both
Chen [13]	126	133	259	Both
Jun-hua [53]	97	178	275	Both
Amato [10]	11	18	29	Both
Wenda [12]	133	87	220	Both
Cheung [67]	20	120	140	Both
Xu [68]	50	59	109	Both
Tarantino [20]	13	51	64	Right lobe
Yoon [19]	33	33	66	Right lobe
Xu [69]	32	32	64	Both

Table 1 (continued)

Study name	LLR (n)	OLR	Total *n*	Resected lobe
Tomoki [70]	40	30	70	Both
Li [12]	133	87	220	Both
Zhang [71]	35	42	77	Right lobe
Zhang [72]	20	25	45	Left lobe
Sposito [73]	43	43	86	Both
Sotiropoulos [74]	11	21	32	Both
Jiang [75]	59	59	118	Both

LLR Laparoscopic liver resection, *OLR* open liver resection

$P=0.105$; $I^2=78.66\%$) and (OR 0.79; 95% CI 0.48–1.31; $P=0.36$; $I^2=81.49\%$), respectively, Fig. 6.

Propensity score-matched studies subgroup analysis

Our subgroup analysis restricted to propensity score-matched studies did not show significant difference between both methods in terms of operative time in min (MD 11.64; 95% CI −20.02 to 43.33; $P=0.47$; I2 = 87.53%), blood loos in ml (MD −95.62; 95% CI −206.17 to 14.93; $P=0.09$; $I^2=82.32$), but significantly reduced blood transfusion rate with LLR than with OLR (OR 0.54; 95% CI 0.38–0.78; $P=0.001$; $I^2=0\%$), Fig. 7.

The mean of hospital stay in days, 30-days mortality, and morbidity were significantly lower in LLR in comparison with OLR (MD −4.306; 95% CI −5.79 to −2.81; $P=0.001$; $I^2=62.68\%$), (OR 0.31; 95% CI 0.11–0.84; $P=0.02$; $I^2=0\%$), and (OR 0.51; 95% CI 0.39–0.67; $P=0.001$; $I^2=33.98\%$), respectively, Fig. 8. Resection margin in cm and R0 resection did not differ from all-studies analysis, Fig. 9. However, recurrence rate showed non-significant difference between both approaches when the analysis was limited to propensity-score matched studies (OR 0.93; 95% CI 0.74–1.16; $P=0.50$; $I^2=13.86\%$).

1-OS showed a trend favoring LLR over OLR (OR 1.53; 95% CI 0.94–2.47; $P=0.09$; $I^2=39.4\%$). 3-OS and 5-OS did not differ from all-studies analysis, Fig. 10. 1-DFS and 3-DFS showed a trend favoring LLR over OLR (OR 1.527; 95% CI 0.99–2.34; $P=0.05$; $I^2=68.13\%$) and (OR 1.24; 95% CI 1.01–1.53; $P=0.04$; $I^2=18.18\%$), Fig. 11. 5-DFS did not differ from all-studies analysis.

Right hepatectomy subgroup analysis

When the analysis was restricted to studies of right hepatectomy, operative time was significantly lower in the OLR group than LLR group (MD 135.05; 95% CI 47.83–222.27; $P=0.001$; $I^2=70.57\%$). Blood loss showed a trend of reduced blood loss amount with LLR than with OLR group (MD 43.88; 95% CI − 162.54 to 9.48; $P=0.08$; $I^2=45.05\%$). Hospital stay in days and morbidity were significantly lower in LLR comparing with OLR (MD -3.96; 95% CI − 6.19 to − 1.743; $P=0.001$; $I I^2=83.04\%$) and (OR 0.16; 95% CI 0.06–0.43; $P=0.001$; $I I^2=0\%$), respectively, Fig. 12. Resection margin did not significantly differ between both approaches (MD 0.03; 95% CI − 0.20 to 0.25; $P=0.82$; $I^2=60.00\%$).

Our sensitivity analysis using one-study-removal approach did not show any change in any outcomes of our interest, Supplemental Figs. 1, 2, and 3. Funnel plots of publication bias didn't show any risk of publication bias with our outcomes of interest, Supplemental Fig. 4. Egger's test showed a significant risk of publication bias with morbidity (Egger's regression intercept − 1.37; 95% CI − 2.06 to − 0.68; $P=0.001$), R0 resection (Egger's regression intercept 0.88; 95% CI 0.18 –.57; $P=0.015$) and 5-years DFS (Egger's regression intercept 5.56; 95% CI 3.38–7.74; $P=0.001$), Table 3. Egger's test did not show any significant risk of publication bias with any other outcome.

Discussion

Our meta-analysis showed that blood loss, blood transfusion rate, 30-days mortality, hospital stay in days and recurrence rate were significantly lower in the LLR group in comparison with OLR group. 1-OS, 5-OS and 1-DFS rates showed a significantly favorable outcome associated with LLR in comparison with OLR. There was no significant difference between both groups regarding operative time in min, 3-OS, 3-DFS and 5-DFS. In a subgroup analysis restricted to right hepatectomy, our meta-analysis did not find any significant difference between both groups in terms of operative time in min and resection margin in cm. There was a strong trend, albeit non-significant, favoring LLR over OLR regarding blood loss. Hospital stay in days and morbidity were significantly lower in LLR comparing with OLR. Our subgroup analysis restricted to studies reported clinical outcomes in propensity-score matched populations showed

Table 2 Patients' baseline characteristics of the included studies

Study name	Age		M/F		Tumor size (cm)		Child–pugh A/B	
	OLR	LLR	OLR	LLR	OLR	LLR	OLR	LLR
Cheung [39]	61 (25–89)	60 (32–84)	258/72	80/30	2.85 (0.8–10)	2.6 (0.6–10)	330/0	110/0
Ahn [29]	56.9 ± 9.6	55.6 ± 11.5	80/13	26/6	3.02 ± 2.3	3.1 ± 1.9	83/9	28/2
Xiang [14]	50.5	50.9	171/36	109/19	6.9 (1.5)	6.7 (1.5)	183/24	108/20
Lai [30]	52.8 ± 11.8	56.5 ± 12.6	28/33	24/28	3.3 ± 1.1	3.0 ± 1.1	31/33	28/28
Tanaka [16]	71 (67–75)	70 (66–73)	14/6	17/3	2.3 (1.9–2.8)	2.3 (2.0–2.7)	20/0	20/0
Jiang [40]	56.55 ± 1.87	55.40 ± 2.62	37/13	35/15	3.22 ± 0.31	3.18 ± 0.29	NA	NA
Luo [41]	51 (38–68)	49 (36–72)	35/18	38/15	3 (1–6)	3 (2–5)	53/0	53/0
Takahara [38]	66.19 ± 9.96	66.42 ± 9.84	261/126	262/125	28.8 ± 15.0	28.8 ± 15.1	311/70	312/65
Han [42]	59.5 (20–85)	60 (26–81)	74/14	72/16	3 (1.5–15)	3 (1–12)	77/9	79/6
Komatsu [43]	61.7 (16.1)	61.5 (12.2)	33/5	34/4	85.0 (20–180)	47.5 (23–180	38/0	38/0
Xiao [44]	50.28 ± 11.89	52.07 ± 11.62	77/9	34/7	4.30 ± 1.49	4.22 ± 2.05	83/3	39/2
Cho [45]	60.0 ± 8.9	53.9 ± 12.6	16/3	17/7	4.8 ± 2.5	3.7 ± 1.8	NA	NA
Leee [46]	63.0 (34–84)	62.0 (30–86)	69/17	29/14	4.4 (2–14)	5.4 (2–16)	81/2	41/1
Yoon [47]	55.0 (49–61)	54.3 (49–63)	130/44	45/13	3.04 (0.20–4.9)	2.87 (0.70–4.9)	158/16	53/5
Siniscalchi [48]	63.26 (41–77)	57.91 (30–73)	104/29	15/8	NA	NA	NA	NA
Yamashita [31]	65.2 (10.1)	67.5 (9.5)	74/25	48/15	2.6 (1.1)	2.5 (1.0)	96/3	59/4
Ahn [49]	57.1 ± 10.6	58.2 ± 10.4	40/11	36/15	2.8 ± 1.2	2.6 ± 1.5	51/0	51/0
Memeo [50]	60 (43–80)	62 (34–75)	37/8	35/10	3.7 (0.1–15)	3.2 (0.9–11)	43/2	44/1
Kim [51]	57.41 ± 8.64	59.30 ± 9.43	58/18	58/12	2.45 ± 1.27	2.58 ± 1.44	NA	NA
Cheung [52]	61 (29–82)	59.5 (39–79)	50/14	22/10	3 (1–10)	2.5 (1–10)	60/4	32/0
Ai [53]	52.36	51.64	137/41	75/22	7.64 ± 2.36	7.85 ± 2.15	104/74	59/38
Kobayashi [54, 55]	66 (44–81)	67 (48–86)	19/8	15/9	22 (10–30)	20 (10–54)	20/4	25/4
HU [54, 55]	48 ± 15	46 ± 12	19/11	20/10	8.7 ± 2.3	6.7 ± 3.1	24/6	29/1
Lee [56]	58.5 (32–81)	59 (36–85)	40/10	24/9	2.9 (1.2–9)	2.5 (1.5–9)	50/0	33/0
Ker [28]	57.9 ± 11.2	58.31 ± 12.7	156/52	92/24	5.4 ± 3.5	2.5 ± 1.2	197/10	98/17
Kim [57]	57.08 ± 9.78	57.84 ± 9.66	20/9	18/8	3.6 (1–19)	3.15 (1–8)	NA	NA
Truant [58]	63.3 ± 7.6	60.6 ± 10.2	47/6	31/5	3.1 ± 1.2	2.9 ± 1.2	53/0	36/0
Aldrighetti [59]	71 ± 6	65 ± 10	12/4	11/5	4.6 ± 2.5	4 ± 2.2	9/16	9/16
Tranchart [60]	65.7 ± 7.1	63.7 ± 13.1	28/14	27/15	36.8 ± 20.9	35.8 ± 17.5	33/1	30/1
Alemi [61]	65.1 (49–88)	61.4 (37–81)	24/1	27/1	5.2	4	NA	NA
Sarpel [62]	58.3 ± 11.0	63.8 ± 10.3	45/11	15/5	4.3 ± 2.2	4.3 ± 2.1	56/0	20/0
Lai [63]	59 (38–77)	59 (35–79)	21/12	18/7	2.6 (1–8)	2.5 (1–7)	31 (class A)	23 (Class A
Truant [58]	51.7 (38–71)	54.2 (23–81)	26/5	24/7	3.62 (1.8–8.9)	3.99 (1.5–9)	14/4	13/3
Laurent [65]	65.9 ± 5.5	62.6 ± 9.5	10/4	10/3	34.3 ± 10.5	33.5 ± 8.9	14 (100%)	13 (100%)
Shimada [66]	63 ± 79	62 ± 9	24/14	15/2	2.5 ± 1.0	2.6 ± 0.9	NA	NA
Chen [13]	51 (12–74)	51 (21–76)	108/25	93/33	6.7 (1.6–24.0)	6.4 (1.4–13.0)	127/6	124/2
Jun-hua [53]	52.36	51.64	137/41	75/22	7.64 ± 2.36	7.85 ± 2.15	104/74	59/38
Amato [10]	78 ± 1.9	77 ± 1.6	6/12	4/7	39.83 ± 6.8	35.45 ± 5.27	NA	NA
Wenda [12]	63(40–77)	61(33–73)	71/16	112/21	2.3 ± 0.5	2.0 ± 0.5	62/25	101/32
Cheung [67]	61.5 (25.0–86.0)	60.5 (47.0–73.0)	99/21	15/5	3.45 (1–9.5)	2.75 (1.2–6.5)	120/0	20/0
Xu [68]	55.39 ± 9.2	55.18 ± 10.9	46/13	35/15	4.03 ± 2.67	3.38 ± 1.99	53/6	44/6
Tarantino [20]								
Yoon [19]	65.5 ± 9	65 ± 13	37/14	7/6	26.5 ± 9.5	36.78 ± 23.4	9/4	46/5
Xu [69]	57.33	56.03	26/7	23/10	2.96 (1.5)	3.31 (1.65)	33/0	33/0
Tomoki [70]	52.0	53.5	28/4	28/4	6.2 (1.5–10.0)	4.0 (1.0–10.0)	NA	NA
Cheung [67]	70 (40–82)	69 (33–86)	23/7	31/9	4.9 (1.0–14.5)	3.9 (1.1–17.0)	30/0	40/0
Li [12]	63(40–77)	61(33–73)	71/16	112/21	2.3 ± 0.5	2.0 ± 0.5	62/25	101/32
Zhang [71]	63 ± 10.5	58 ± 9.5	26/16	25/10	5.91 ± 3.01	6.68 ± 4.15	NA	NA

Table 2 (continued)

Study name	Age		M/F		Tumor size (cm)		Child–pugh A/B	
	OLR	LLR	OLR	LLR	OLR	LLR	OLR	LLR
Zhang [72]	52 ± 10.5	47 ± 8.5	15/10	12/8	NA	NA	25/0	20/0
Sposito [73]	68 (49–83)	66 (40–85)	35/8	28/15	2·2 (1·0–8·5)	2·6 (1·0–6·5)	41/2	42/1
Sotiropoulos [74]	70 (40–89)	65 (54–81)	20/1	9/2	6.1 (2.5–22)	4.7 (1.8–9.7)	30/2	
Jiang [75]	51 (36–68)	50 (38–70)	42/17	38/21	3 (2–5)	3 (1–6)	NA	NA

Study name	Conversion to labarotomy		HBV n (%)		HCV n (%)		Cirrhosis	
	OLR	LLR	OLR	LLR	OLR	LLR	OLR	LLR
Cheung [39]	NA	NA	285 (86.4%)	88 (80%)	23 (7%)	7 (6.4%)	NA	NA
Ahn [29]	NA	NA	61 (65.5%)	17 (53.1%)	NA	NA	62 (66.6%)	24 (75%)
Xiang [14]	NA	2	172 (83.1%)	172 (83.1%)	NA	NA	167 (80.7%)	104 (80.7%)
Lai [30]	0	0	29 (88%)	23 (82%)	0 (0%)	1 (4%)	22 (67%)	18 (64%)
Tanaka [16]	0	0	2 (10%)	4 (20%)	15 (75%)	12 (60%)	20 (100%)	20 (100%)
Jiang [40]	NA	NA	NA	NA	NA	NA	36 (72%)	40 (80%)
Luo [41]	0	0	38 (71%)	41 (77.4%)	8 (15.1%)	8 (15.1%)	53 (100%)	53 (100%)
Takahara [38]	0	18	100 (25.84%)	1 (23.51%)	198 (51.16%)	195 (50.39%)	NA	NA
Han [42]	0	8	65	61	4	6	52 (40.9%)	55 (37.5%)
Komatsu [43]	0	13	9 (23.7%)	10 (26.3%)	6 (15.8%)	7 (18.4%)	38 (100%)	38 (100%)
Xiao [44]	0	3	81 (94%)	37 (90.2%)	NA	NA	72 (83.7%)	33 (80.4%)
Cho [45]	0	3	NA	NA	NA	3.7 ± 1.8	10 (23.5%)	
Lee [46]	0	6	52 (60.5%)	19 (44.2%)	18 (20.9%)	13 (30.2%)	33 (38.4%)	18 (41.8%)
Yoon [47]	0	0	165 (94.8%)	54 (93.1%)	6 (3.5%)	3 (5.2%)	NA	NA
Siniscalchi [48]	NA	NA	35 (26.5%)	6 (26.1%)	88 (67.6%)	17 (73.9%)	133 (100%)	23 (100%0
Yamashita [31]	NA	NA	17 (17%)	10 (16%)	68 (68%)	40 (63%)	99 (100%)	63 (100%)
Ahn [49]	NA	NA	37 (72.5%)	40 (78.4%)	5 (9.8%)	1 (2.0%)	34 (66.75%)	35 (68.6%)
Memeo [50]	NA	NA	13 (29%)	16 (35%)	17 (38%)	18 (40%)	45 (100%)	45 (100%)
Kim [51]	0	6	54 (71.05%)	46 (65.71%)	2 (2.63%)	1 (1.43%)	NA	NA
Cheung [52]	NA	NA	49 (76.6%)	26 (81.3%)	7 (10.9%)	2 (6.3%)	64 (100%)	32 (100%)
Ai [53]	0	9	136	75	NA	NA	143	78
Kobayashi [54, 55]	NA	NA	12 (44.4%)	9 (37.5%)	15 (55.6%)	12 (50.0%)	NA	NA
HU [54, 55]	NA	NA	NA	24 (80%)	NA	3 (10%)	NA	25 (83%)
Lee [56]	0	6	43 (86%)	22 (72.7%)	6 (12%)	8(24.2%)	32 (64%)	28 (84.8%)
Ker [28]	0	6	124 (59.6%)	74 (63.8%)	78 (37.5%)	41 (35.3%)	NA	NA
Kim [57]	0	3	20 (69.0%)	16 (61.5%)	1 (3.4%)	2 (7.7%)	25 (86.2%)	24 (92.3%)
Truant [58]	0	7	4 (7.6%)	3 (8.3%)	6 (11.3%)	4 (11.1%)	53 (100%)	36 (100%)
Aldrighetti [59]	0	1	NA	NA	NA	NA	16 (100%)	16(100%)
Tranchart [60]	0	2	NA	NA	NA	NA	34 (81)	31 (73.8)
Alemi [61]	NA	NA	0	0	25 (100%)	28 (100%)	25 (100%)	28 (100%)
Sarpel [62]	0	4	NA	NA	NA	NA	27 (48%)	9 (45%)
Lai [63]	0	1	NA	23 (92%)	NA	1 (4%)	33 (100%)	25 (100%)
Cai [64]	NA	NA	18 (58%)	18 (60%)	NA	NA	18 (58.1%)	16 (51.6%)
Laurent [65]	0	2	6 (42.8%)	4 (30.7%)	5 (35.7%)	5 (38.4%)	14 (100%)	13 (100%)
Shimada [66]	NA	NA	18.40%	11.80%	63.20%	70.60%	73.70%	76.50%
Chen [13]	0	3	104 (78.2%)	95 (75.4%)	2 (1.5%)	2 (1.6%)	NA	NA
Jun-hua [53]	0	9	136	75	NA	NA	143	78
Amato [10]	NA	NA	NA	NA	NA	NA	NA	NA
Wenda [12]	NA	NA	NA	NA	NA	NA	NA	NA

Table 2 (continued)

Study name	Conversion to labarotomy		HBV n (%)		HCV n (%)		Cirrhosis	
	OLR	LLR	OLR	LLR	OLR	LLR	OLR	LLR
Cheung [67]	NA	NA	104 (86.7%)	18 (90.0%)	5 (4.2%)	1 (5.0%)	120 (100%)	20 (100%)
Xu [68]	NA	NA	NA	NA	NA	NA	84.7%	86%
Tarantino [20]	0	3	8 (15.6%)	3 (23%)	41 (80%)	7 (53.8%)	49 (96%)	13 (100%)
Yoon [19]	0	0	28 (80.7%)	29 (87.88%)	2 (6.06%)	1 (3.03%)	33 (100%)	33 (100%)
Xu [69]	NA	NA	15 (46.9%)	18 (56.3%)	NA	NA	NA	NA
Tomoki [70]	NA	NA	6 (20%)	5 (12%)	11 (37%)	20 (50%)	13 (43%)	12 (40%)
Li [12]	NA	NA	NA	NA	NA	NA	NA	NA
Zhang [71]	NA	NA	NA	NA	NA	NA	NA	NA
Zhang [72]	0	0	NA	NA	NA	NA	NA	NA
Sposito [73]	0	2	10 (23%)	6 (14%)	23 (53%)	28 (65%)	43 (100%)	43 (100%)
Sotiropoulos [74]	0	0	10 (47.6%)	7 (63.6%)	2 (6.2%)		12 (37.5%)	
Jiang [75]	0	3	35	32	5	3	NA	NA

a non-significant difference regarding blood loss and recurrence rate between both approaches, however LLR was associated with a significantly reduced blood transfusion rate.

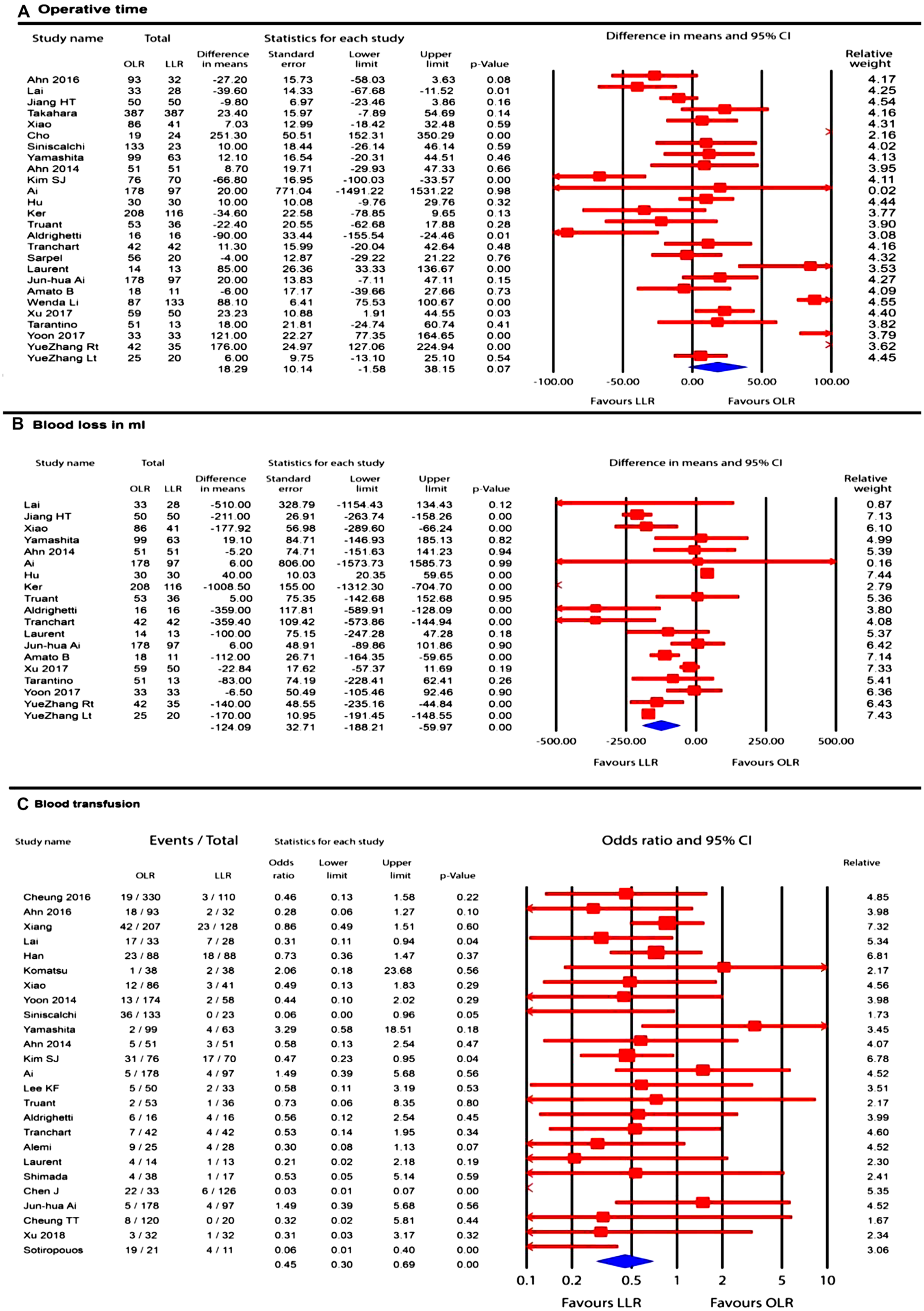
In consistent with previous studies, we found favorable outcomes associated with LLR regarding operative blood loss and blood transfusion [18, 25]. The reduction in bleeding with LLR may be explained by the less risk of hepatic vein or vena cava injury because of the meticulous parenchymal dissection provided by the laparoscopy modality and the hemostatic effect of pneumoperitoneum which might have controlled bleeding from hepatic vein branches [26]. Furthermore, the magnification provided by laparoscopy allows better identification of small blood vessels which might have reduced the risk of blood loss and subsequently the blood transfusion rate.

In line with previous meta-analyses, LLR was significantly associated with lower postoperative 30-days mortality and shorter hospital stay in days comparing with OLR group [18, 25]. This might be explained by the less manipulation of abdominal organs, smaller incision, decreased rate of complications, less severe pain, lower need for narcotic pain medications, and early ambulation in the LLR group in comparison with OLR group.

In contradiction with previous studies, our all-studies meta-analysis showed that LLR was significantly associated with decreased recurrence rate comparing with OLR [25], which came as no surprise because of the decreased operative blood loss in the LLR group. Katz et al. concluded that intraoperative blood loss is an independent predictable factor to the tumor recurrence and survival rates [27]. Furthermore, although resection margin status was not significantly different between both groups in our analysis, there were other different preoperative and postoperative factors, such as Child–Pugh classification, amount of blood loss, and resected liver volume between LLR and OLR groups which might have influenced the recurrence rate [14, 28–31]. Therefore, the recurrence rate between both groups was not significantly different after restricting the analysis to propensity score-matched studies.

The second international consensus conference rated the quality of evidence supporting the superiority of LLR as low since most of the evidence derived from observational studies comparing LLR versus OLR [8, 32, 33]. The jury of the conference strongly recommended launching studies comparing between LLR and OLR in a head-to-head randomized fashion. Currently, there are a few ongoing randomized controlled trials randomizing patients with HCC to LLR versus OLR (NCT01768741), (NCT00606385), and (NCT02526043). Hopefully, these studies can provide a valid, non-biased evidence regarding the superiority of either strategy.

Our meta-analysis demonstrated a favorable survival rate at 5 years in LLR in all-studies analysis, and this survival benefit persisted even after restricting the analysis to propensity score-matched studies. Previous studies that investigated the correlation between resection margin and the OS and DFS concluded that resection margin can significantly predict the prognosis of HCC [34, 35]. Our meta-analysis showed a non-significant difference between both groups in terms of resection margin, therefore, the difference in survival benefits was most probably driven by other postoperative clinical outcomes, such as blood loss, postoperative complications, morbidity and 30-days mortality. Furthermore, the more manipulation and compression of the tumor during OLR might have resulted in more dissemination of tumor cells through portal vein to systematic circulation and



A Operative time

Study name	Total OLR	Total LLR	Difference in means	Standard error	Lower limit	Upper limit	p-Value	Relative weight
Ahn 2016	93	32	-27.20	15.73	-58.03	3.63	0.08	4.17
Lai	33	28	-39.60	14.33	-67.68	-11.52	0.01	4.25
Jiang HT	50	50	-9.80	6.97	-23.46	3.86	0.16	4.54
Takahara	387	387	23.40	15.97	-7.89	54.69	0.14	4.16
Xiao	86	41	7.03	12.99	-18.42	32.48	0.59	4.31
Cho	19	24	251.30	50.51	152.31	350.29	0.00	2.16
Siniscalchi	133	23	10.00	18.44	-26.14	46.14	0.59	4.02
Yamashita	99	63	12.10	16.54	-20.31	44.51	0.46	4.13
Ahn 2014	51	51	8.70	19.71	-29.93	47.33	0.66	3.95
Kim SJ	76	70	-66.80	16.95	-100.03	-33.57	0.00	4.11
Ai	178	97	20.00	771.04	-1491.22	1531.22	0.98	0.02
Hu	30	30	10.00	10.08	-9.76	29.76	0.32	4.44
Ker	208	116	-34.60	22.58	-78.85	9.65	0.13	3.77
Truant	53	36	-22.40	20.55	-62.68	17.88	0.28	3.90
Aldrighetti	16	16	-90.00	33.44	-155.54	-24.46	0.01	3.08
Tranchart	42	42	11.30	15.99	-20.04	42.64	0.48	4.16
Sarpel	56	20	-4.00	12.87	-29.22	21.22	0.76	4.32
Laurent	14	13	85.00	26.36	33.33	136.67	0.00	3.53
Jun-hua Ai	178	97	20.00	13.83	-7.11	47.11	0.15	4.27
Amato B	18	11	-6.00	17.17	-39.66	27.66	0.73	4.09
Wenda Li	87	133	88.10	6.41	75.53	100.67	0.00	4.55
Xu 2017	59	50	23.23	10.88	1.91	44.55	0.03	4.40
Tarantino	51	13	18.00	21.81	-24.74	60.74	0.41	3.82
Yoon 2017	33	33	121.00	22.27	77.35	164.65	0.00	3.79
YueZhang Rt	42	35	176.00	24.97	127.06	224.94	0.00	3.62
YueZhang Lt	25	20	6.00	9.75	-13.10	25.10	0.54	4.45
			18.29	10.14	-1.58	38.15	0.07	

B Blood loss in ml

Study name	Total OLR	Total LLR	Difference in means	Standard error	Lower limit	Upper limit	p-Value	Relative weight
Lai	33	28	-510.00	328.79	-1154.43	134.43	0.12	0.87
Jiang HT	50	50	-211.00	26.91	-263.74	-158.26	0.00	7.13
Xiao	86	41	-177.92	56.98	-289.60	-66.24	0.00	6.10
Yamashita	99	63	19.10	84.71	-146.93	185.13	0.82	4.99
Ahn 2014	51	51	-5.20	74.71	-151.63	141.23	0.94	5.39
Ai	178	97	6.00	806.00	-1573.73	1585.73	0.99	0.16
Hu	30	30	40.00	10.03	20.35	59.65	0.00	7.44
Ker	208	116	-1008.50	155.00	-1312.30	-704.70	0.00	2.79
Truant	53	36	5.00	75.35	-142.68	152.68	0.95	5.36
Aldrighetti	16	16	-359.00	117.81	-589.91	-128.09	0.00	3.80
Tranchart	42	42	-359.40	109.42	-573.86	-144.94	0.00	4.08
Laurent	14	13	-100.00	75.15	-247.28	47.28	0.18	5.37
Jun-hua Ai	178	97	6.00	48.91	-89.86	101.86	0.90	6.42
Amato B	18	11	-112.00	26.71	-164.35	-59.65	0.00	7.14
Xu 2017	59	50	-22.84	17.62	-57.37	11.69	0.19	7.33
Tarantino	51	13	-83.00	74.19	-228.41	62.41	0.26	5.41
Yoon 2017	33	33	-6.50	50.49	-105.46	92.46	0.90	6.36
YueZhang Rt	42	35	-140.00	48.55	-235.16	-44.84	0.00	6.43
YueZhang Lt	25	20	-170.00	10.95	-191.45	-148.55	0.00	7.43
			-124.09	32.71	-188.21	-59.97	0.00	

C Blood transfusion

Study name	Events / Total OLR	Events / Total LLR	Odds ratio	Lower limit	Upper limit	p-Value	Relative
Cheung 2016	19 / 330	3 / 110	0.46	0.13	1.58	0.22	4.85
Ahn 2016	18 / 93	2 / 32	0.28	0.06	1.27	0.10	3.98
Xiang	42 / 207	23 / 128	0.86	0.49	1.51	0.60	7.32
Lai	17 / 33	7 / 28	0.31	0.11	0.94	0.04	5.34
Han	23 / 88	18 / 88	0.73	0.36	1.47	0.37	6.81
Komatsu	1 / 38	2 / 38	2.06	0.18	23.68	0.56	2.17
Xiao	12 / 86	3 / 41	0.49	0.13	1.83	0.29	4.56
Yoon 2014	13 / 174	2 / 58	0.44	0.10	2.02	0.29	3.98
Siniscalchi	36 / 133	0 / 23	0.06	0.00	0.96	0.05	1.73
Yamashita	2 / 99	4 / 63	3.29	0.58	18.51	0.18	3.45
Ahn 2014	5 / 51	3 / 51	0.58	0.13	2.54	0.47	4.07
Kim SJ	31 / 76	17 / 70	0.47	0.23	0.95	0.04	6.78
Ai	5 / 178	4 / 97	1.49	0.39	5.68	0.56	4.52
Lee KF	5 / 50	2 / 33	0.58	0.11	3.19	0.53	3.51
Truant	2 / 53	1 / 36	0.73	0.06	8.35	0.80	2.17
Aldrighetti	6 / 16	4 / 16	0.56	0.12	2.54	0.45	3.99
Tranchart	7 / 42	4 / 42	0.53	0.14	1.95	0.34	4.60
Alemi	9 / 25	4 / 28	0.30	0.08	1.13	0.07	4.52
Laurent	4 / 14	1 / 13	0.21	0.02	2.18	0.19	2.30
Shimada	4 / 38	1 / 17	0.53	0.05	5.14	0.59	2.41
Chen J	22 / 33	6 / 126	0.03	0.01	0.07	0.00	5.35
Jun-hua Ai	5 / 178	4 / 97	1.49	0.39	5.68	0.56	4.52
Cheung TT	8 / 120	0 / 20	0.32	0.02	5.81	0.44	1.67
Xu 2018	3 / 32	1 / 32	0.31	0.03	3.17	0.32	2.34
Sotiropouos	19 / 21	4 / 11	0.06	0.01	0.40	0.00	3.06
			0.45	0.30	0.69	0.00	

Fig. 2 Forest plot showing: **A** the mean difference of operative time in minutes in laparoscopic liver resection (LLR) in comparison with open liver resection (OLR), **B** The mean difference of blood loss in ml in LLR in comparison with OLR, and **C** The rate of blood transfusion in LLR) in comparison with OLR

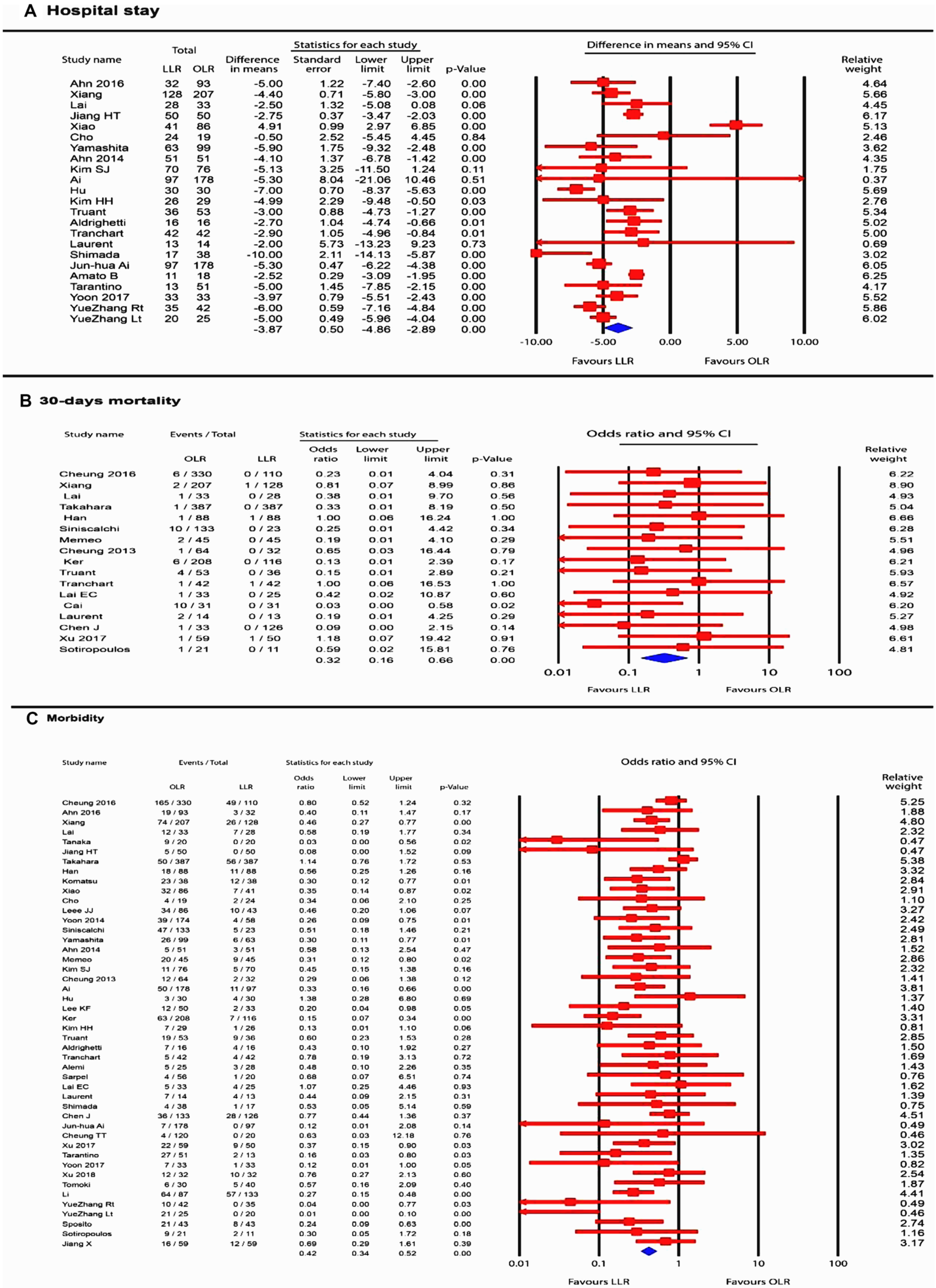


Fig. 3 Forest plot showing: **A** the mean difference of hospital stay in days in in laparoscopic liver resection (LLR) in comparison with open liver resection (OLR), **B** the 30-days mortality rate in LLR group comparing with OLR group, and **C** The morbidity rate in LLR in comparison with OLR

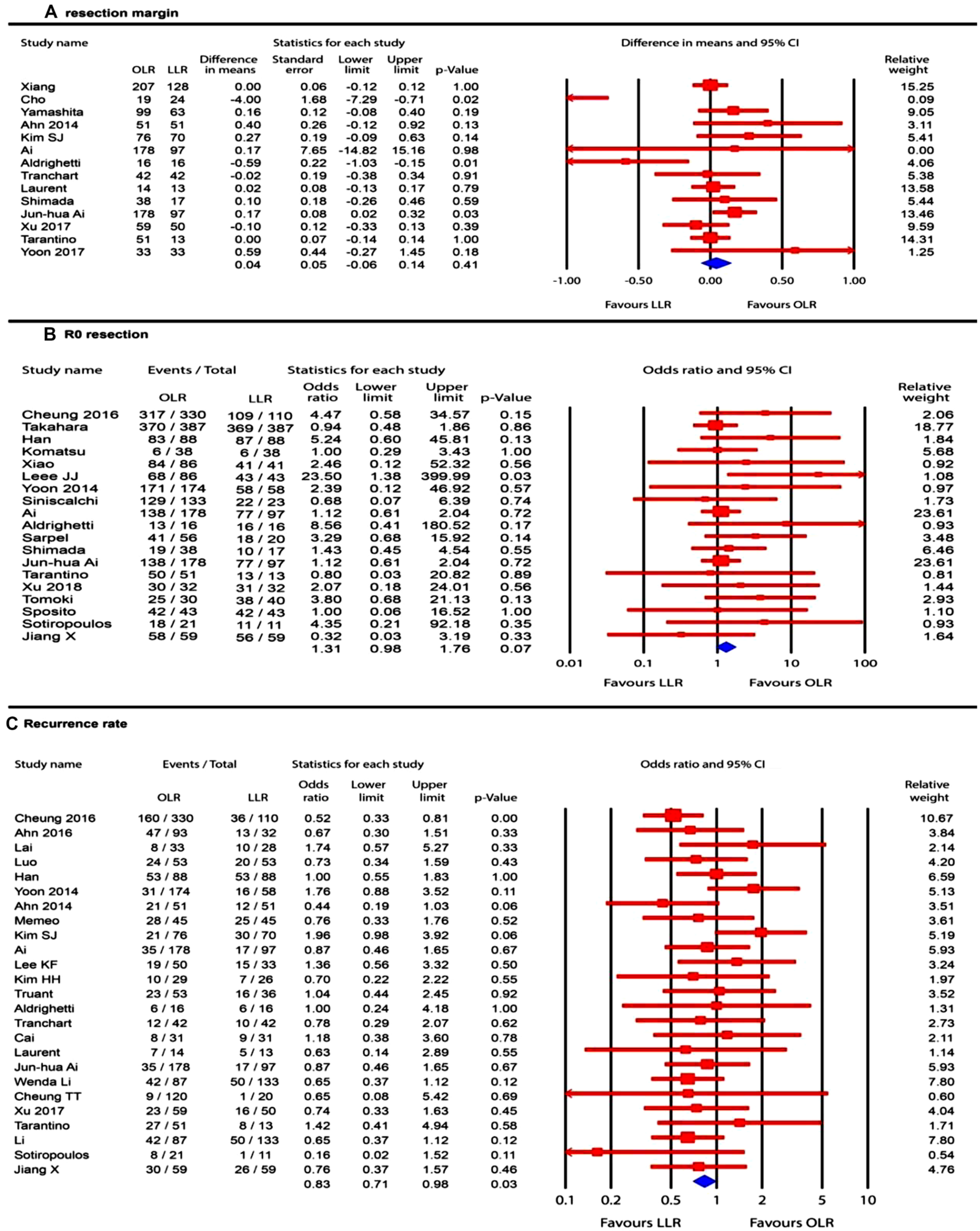


Fig. 4 Forest plot showing: **A** the mean difference of resection margin in CM in laparoscopic liver resection (LLR) in comparison with open liver resection (OLR), **B** the R0 resection rate in LLR in comparison with OLR, and **C** The recurrence rate in LLR in comparison with OLR

this could have impacted the survival rate [36]. Our results are inconsistent with Poon et al's findings that concluded that the resection margin was not associated with postoperative recurrence pattern and subsequently survival rate [37].

Our study did not find a statistically significant difference between LLR and OLR regarding 3-OS which might be explained by the limited number of studies reported 3-OS in comparison to studies reported 1-OS. Although there was a limited number of studies reported 5-OS, this

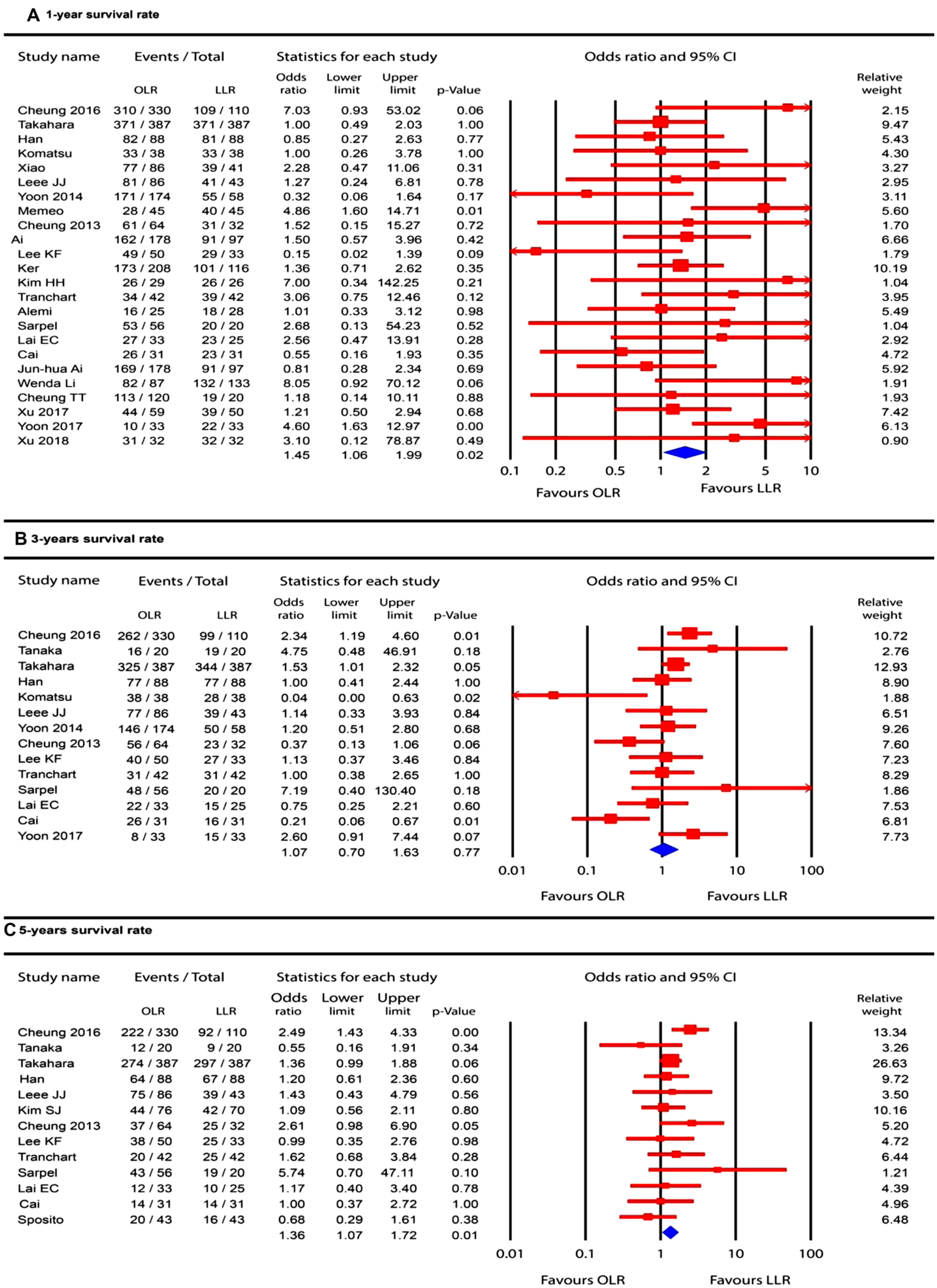
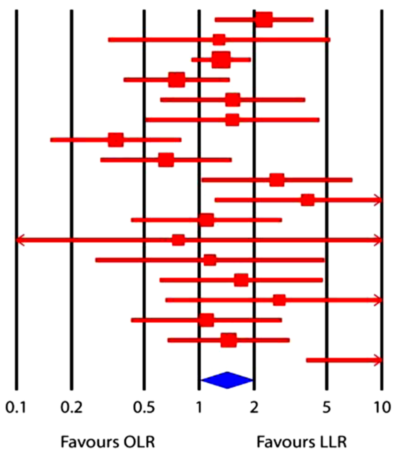


Fig. 5 Forest plot showing: **A** 1-year overall survival rate, **B** 3-years overall survival rate, and **C** 5-years overall survival rate

A Disease-free survival 1 year

Study name	Events / Total OLR	Events / Total LLR	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Cheung 2016	248 / 330	96 / 110	2.267	1.227	4.189	2.614	0.009	8.10
Tanaka	14 / 20	15 / 20	1.286	0.319	5.175	0.354	0.724	3.67
Takahara	308 / 387	324 / 387	1.319	0.915	1.902	1.483	0.138	9.97
Han	66 / 88	61 / 88	0.753	0.389	1.460	-0.840	0.401	7.73
Komatsu	18 / 38	22 / 38	1.528	0.618	3.779	0.917	0.359	6.03
Xiao	71 / 86	36 / 41	1.521	0.512	4.518	0.755	0.450	4.98
Leee JJ	70 / 86	26 / 43	0.350	0.154	0.792	-2.519	0.012	6.61
Yoon 2014	153 / 174	48 / 58	0.659	0.290	1.496	-0.998	0.318	6.59
Memeo	27 / 45	36 / 45	2.667	1.039	6.847	2.039	0.041	5.80
Cheung 2013	41 / 64	28 / 32	3.927	1.224	12.595	2.300	0.021	4.61
Ai	164 / 178	90 / 97	1.098	0.427	2.818	0.193	0.847	5.80
Kobayashi	26 / 27	20 / 21	0.769	0.045	13.067	-0.182	0.856	1.17
Kim HH	24 / 29	22 / 26	1.146	0.272	4.819	0.186	0.853	3.52
Tranchart	30 / 42	34 / 42	1.700	0.613	4.717	1.019	0.308	5.35
Lai EC	24 / 33	22 / 25	2.750	0.659	11.480	1.387	0.165	3.54
Jun-hua Ai	164 / 178	90 / 97	1.098	0.427	2.818	0.193	0.847	5.80
Xu 2017	30 / 59	30 / 50	1.450	0.677	3.107	0.956	0.339	7.00
Yoon 2017	13 / 33	30 / 33	15.385	3.882	60.969	3.891	0.000	3.72
			1.426	1.032	1.972	2.150	0.032	

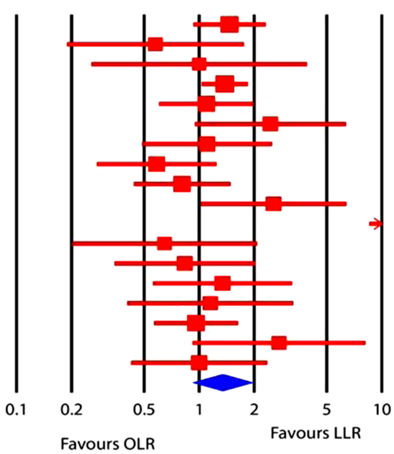
Odds ratio and 95% CI



B Diseas-free survival 3

Study name	Events / Total OLR	Events / Total LLR	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Cheung 2016	186 / 330	72 / 110	1.467	0.936	2.299	1.672	0.095	6.95
Lai	25 / 33	18 / 28	0.576	0.190	1.747	-0.974	0.330	4.50
Tanaka	6 / 20	6 / 20	1.000	0.259	3.867	0.000	1.000	3.73
Takahara	195 / 387	226 / 387	1.382	1.041	1.836	2.235	0.025	7.43
Han	44 / 88	46 / 88	1.095	0.606	1.978	0.302	0.763	6.45
Komatsu	11 / 38	19 / 38	2.455	0.953	6.325	1.859	0.063	5.08
Xiao	59 / 86	29 / 41	1.106	0.491	2.492	0.243	0.808	5.60
Leee JJ	57 / 86	23 / 43	0.585	0.277	1.236	-1.405	0.160	5.85
Yoon 2014	108 / 174	33 / 58	0.807	0.441	1.475	-0.698	0.485	6.40
Cheung 2013	32 / 64	23 / 32	2.556	1.025	6.369	2.014	0.044	5.21
Ai	19 / 178	64 / 97	16.230	8.604	30.615	8.607	0.000	6.28
Kobayashi	17 / 27	11 / 21	0.647	0.203	2.062	-0.736	0.462	4.33
Lee KF	28 / 50	17 / 33	0.835	0.346	2.017	-0.401	0.688	5.33
Tranchart	23 / 42	26 / 42	1.342	0.562	3.204	0.663	0.507	5.37
Lai EC	16 / 33	13 / 25	1.151	0.407	3.257	0.265	0.791	4.74
Jun-hua Ai	119 / 178	64 / 97	0.962	0.570	1.623	-0.147	0.883	6.70
Yoon 2017	7 / 33	14 / 33	2.737	0.927	8.084	1.822	0.068	4.59
Sposito	19 / 43	19 / 43	1.000	0.427	2.342	0.000	1.000	5.45
			1.349	0.939	1.938	1.621	0.105	

Odds ratio and 95% CI



C Disease-free survival 5 years

Study name	Events / Total OLR	Events / Total LLR	Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	Relative weight
Cheung 2016	247 / 330	57 / 110	0.361	0.231	0.566	-4.442	0.000	13.02
Takahara	152 / 387	58 / 387	0.273	0.193	0.385	-7.369	0.000	13.60
Han	36 / 88	37 / 88	1.048	0.575	1.909	0.153	0.878	12.04
Leee JJ	50 / 86	23 / 43	0.828	0.396	1.730	-0.502	0.616	11.07
Kim SJ	41 / 76	36 / 70	0.904	0.472	1.732	-0.305	0.761	11.68
Cheung 2013	28 / 64	17 / 32	1.457	0.622	3.416	0.866	0.386	10.24
Lee KF	28 / 50	15 / 33	0.655	0.271	1.585	-0.939	0.348	10.02
Tranchart	16 / 42	19 / 42	1.342	0.562	3.204	0.663	0.507	10.12
Sposito	5 / 43	11 / 43	2.613	0.821	8.309	1.627	0.104	8.20
			0.793	0.480	1.310	-0.906	0.365	

Odds ratio and 95% CI

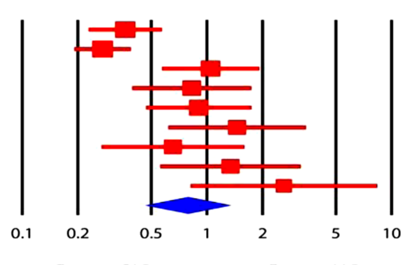
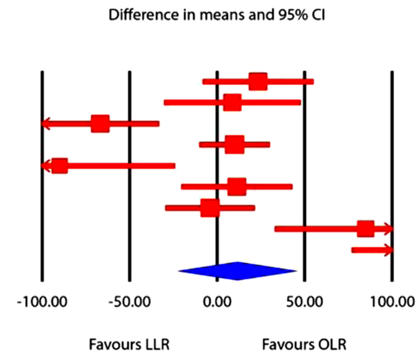


Fig. 6 Forest plot showing: **A** 1-year disease-free survival rate, **B** 3-years disease-free survival rate, and **C** 5-years disease-free survival rate

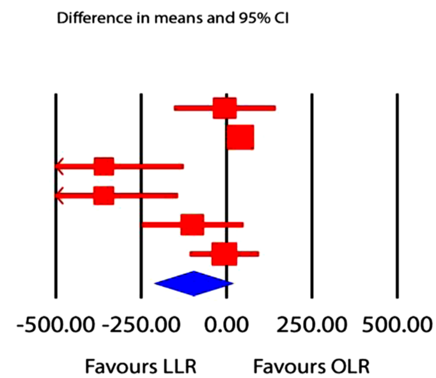
A Operative time

Study name	Difference in means	Standard error	Lower limit	Upper limit	p-Value
Takahara	23.40	15.97	-7.89	54.69	0.14
Ahn 2014	8.70	19.71	-29.93	47.33	0.66
Kim SJ	-66.80	16.95	-100.03	-33.57	0.00
Hu	10.00	10.08	-9.76	29.76	0.32
Aldrighetti	-90.00	33.44	-155.54	-24.46	0.01
Tranchart	11.30	15.99	-20.04	42.64	0.48
Sarpel	-4.00	12.87	-29.22	21.22	0.76
Laurent	85.00	26.36	33.33	136.67	0.00
Yoon 2017	121.00	22.27	77.35	164.65	0.00
	11.64	16.17	-20.06	43.33	0.47



B Blood loss

Study name	Difference in means	Standard error	Lower limit	Upper limit	p-Value
Ahn 2014	-5.20	74.71	-151.63	141.23	0.94
Hu	40.00	10.03	20.35	59.65	0.00
Aldrighetti	-359.00	117.81	-589.91	-128.09	0.00
Tranchart	-359.40	109.42	-573.86	-144.94	0.00
Laurent	-100.00	75.15	-247.28	47.28	0.18
Yoon 2017	-6.50	50.49	-105.46	92.46	0.90
	-95.62	56.40	-206.17	14.93	0.09



C Blood transfusion

Study name	Odds ratio	Lower limit	Upper limit	p-Value
Cheung 2016	0.46	0.13	1.58	0.22
Han	0.73	0.36	1.47	0.37
Komatsu	2.06	0.18	23.68	0.56
Yoon 2014	0.44	0.10	2.02	0.29
Ahn 2014	0.58	0.13	2.54	0.47
Kim SJ	0.47	0.23	0.95	0.04
Lee KF	0.58	0.11	3.19	0.53
Aldrighetti	0.56	0.12	2.54	0.45
Tranchart	0.53	0.14	1.95	0.34
Laurent	0.21	0.02	2.18	0.19
Cheung TT	0.32	0.02	5.81	0.44
Xu 2018	0.31	0.03	3.17	0.32
	0.54	0.38	0.78	0.00

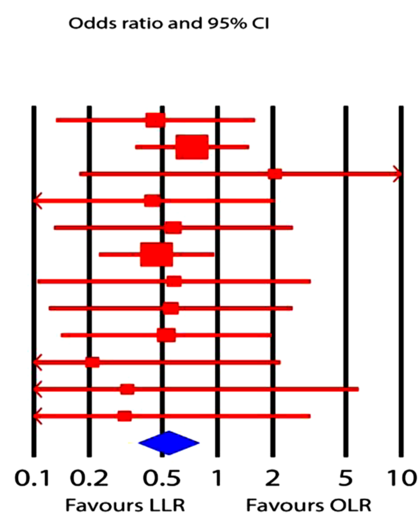


Fig. 7 Forest plot showing: **A** the mean operative time of laparoscopic liver resection (LLR) in comparison with open liver resection (OLR) in propensity score-matched studies, **B** The mean blood loss in ml in LLR in comparison with OLR in propensity score matched studies, and **C** The rate of blood transfusion in LLR in comparison with OLR in propensity score matched studies

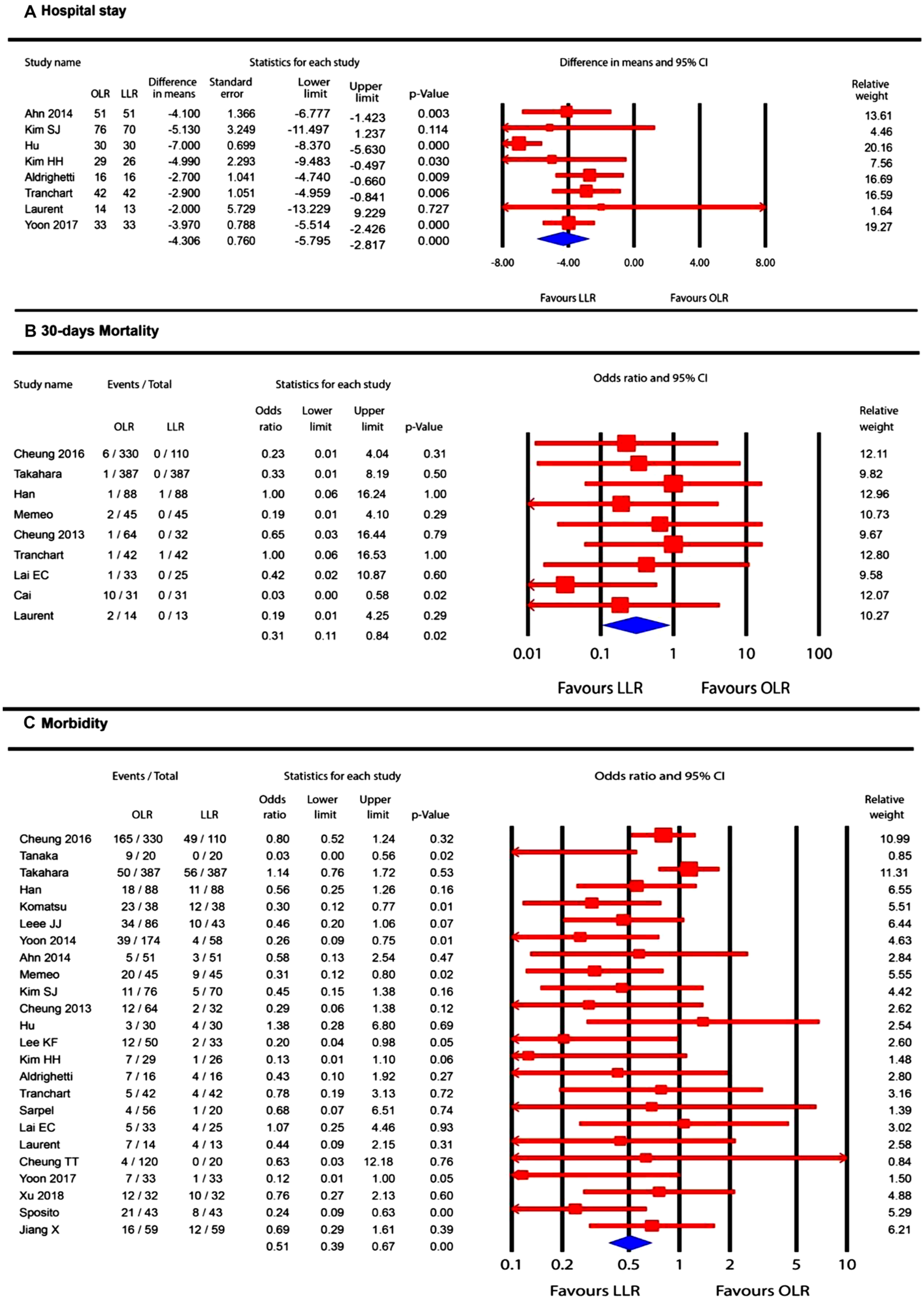


Fig. 8 Forest plot showing: **A** the mean difference of hospital stay in days in laparoscopic liver resection (LLR) in comparison with open liver resection (OLR) in propensity score matched studies, **B** The 30-days mortality rate of LLR in comparison with OLR in propensity score-matched studies, and **C** The rate of morbidity in LLR in comparison with OLR in propensity score-matched studies

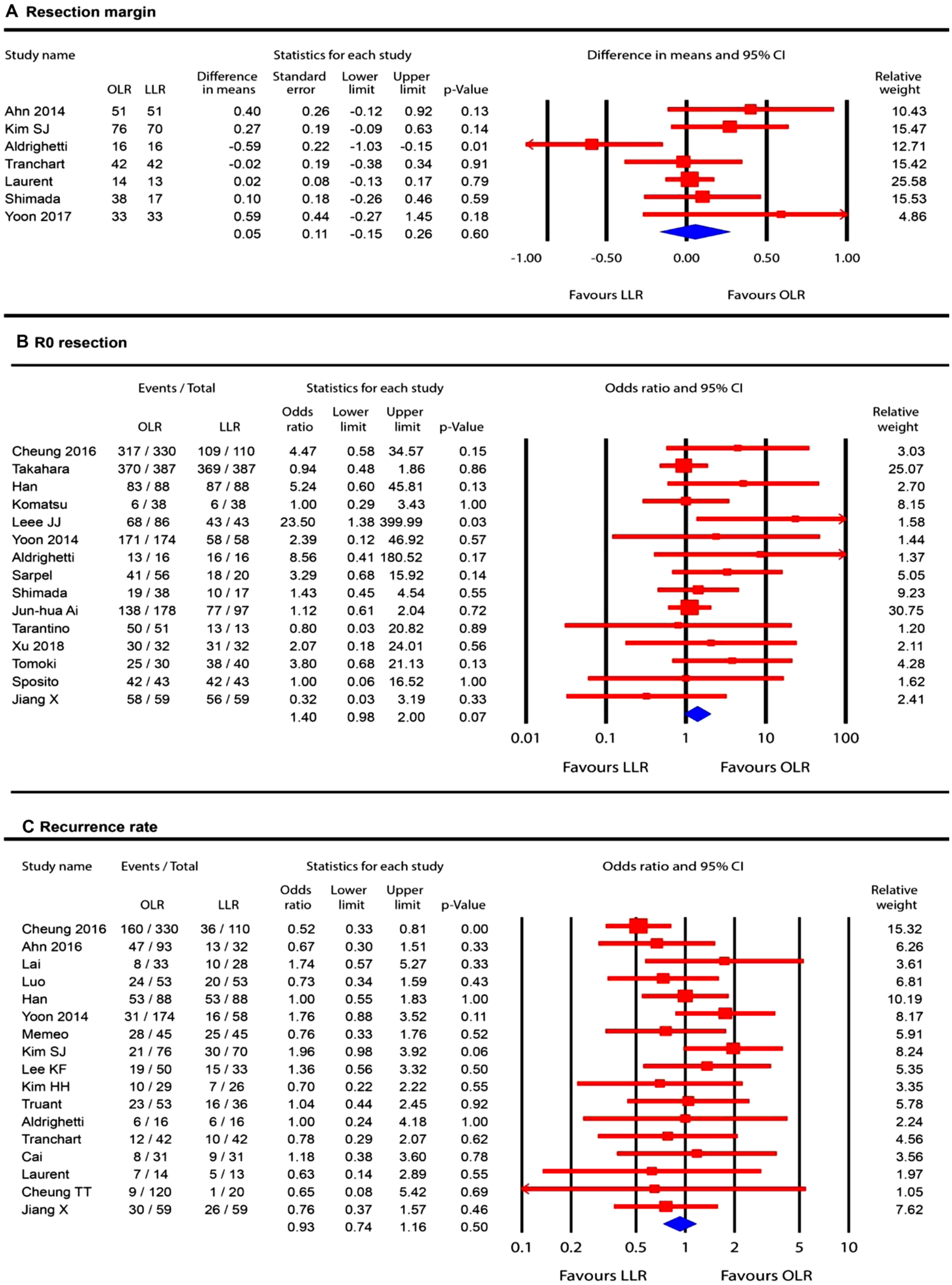


Fig. 9 Forest plot showing: **A** the mean difference of resection margin in CM of laparoscopic liver resection (LLR) in comparison with open liver resection (OLR) in propensity score-matched studies, **B** The R0 resection rate of LLR in comparison with OLR in propensity score-matched studies, and **C** The recurrence in LLR in comparison with OLR in propensity score-matched studies

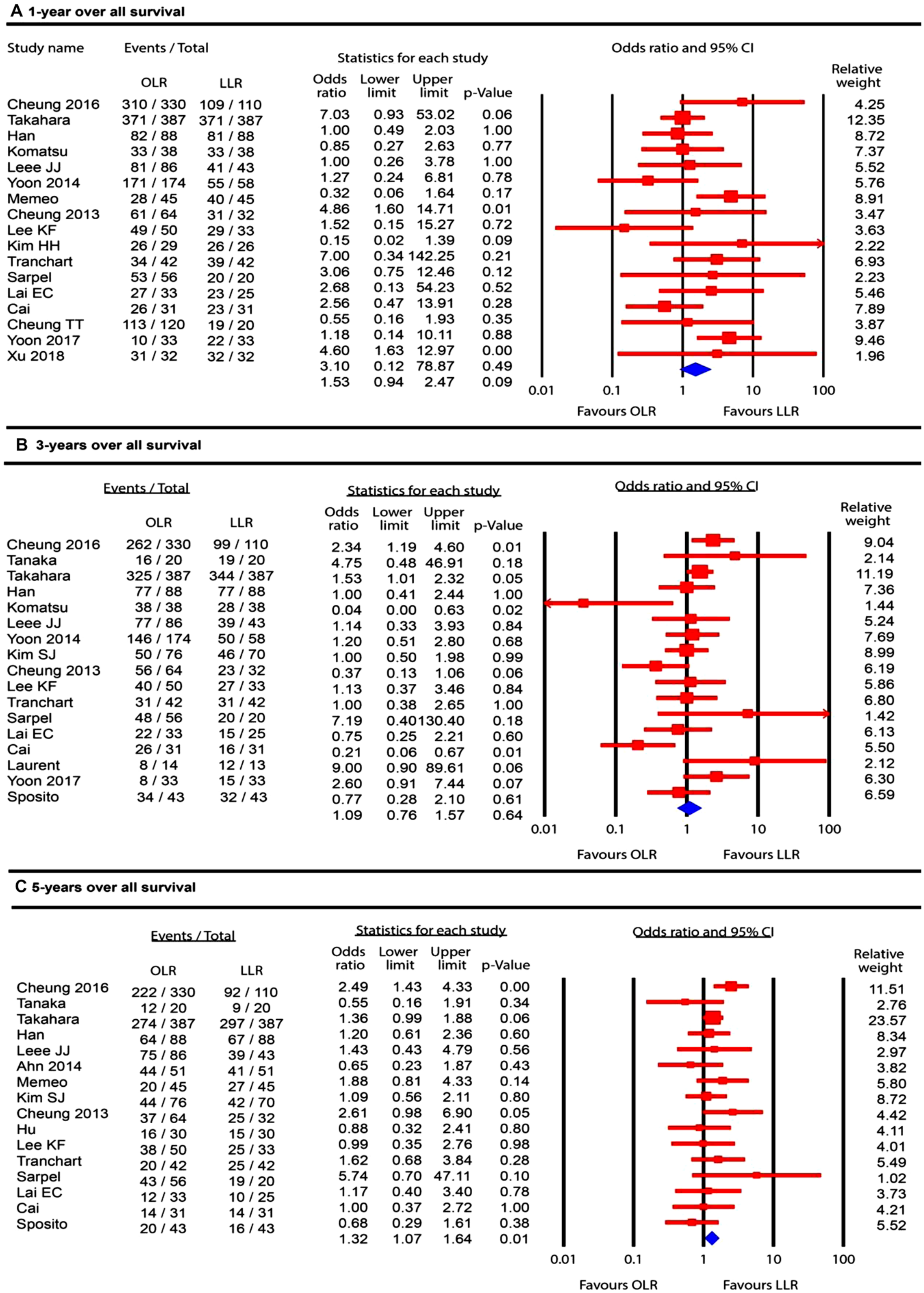
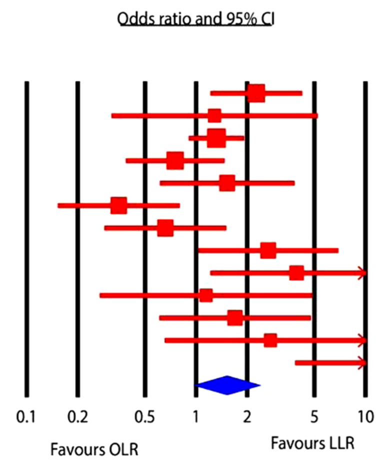


Fig. 10 Forest plot showing: **A** 1-year overall survival rate in propensity score matched studies, **B** 3-years overall survival rate in propensity score-matched studies, and **C** 5-years overall survival rate in propensity score matched studies

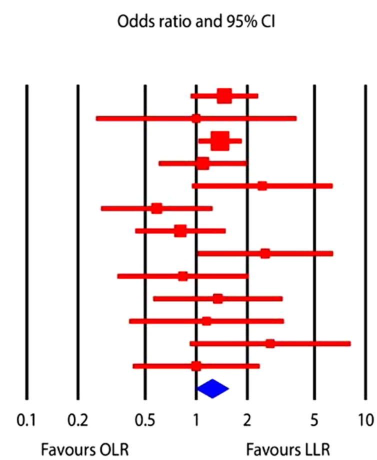
A Disease-free survival 1 year

Study name	Events / Total OLR	Events / Total LLR	Odds ratio	Lower limit	Upper limit	p-Value	Relative weight
Cheung 2016	248 / 330	96 / 110	2.267	1.227	4.189	0.009	10.07
Tanaka	14 / 20	15 / 20	1.286	0.319	5.175	0.724	5.41
Takahara	308 / 387	324 / 387	1.319	0.915	1.902	0.138	11.62
Han	66 / 88	61 / 88	0.753	0.389	1.460	0.401	9.74
Komatsu	18 / 38	22 / 38	1.528	0.618	3.779	0.359	8.09
Leee JJ	70 / 86	26 / 43	0.350	0.154	0.792	0.012	8.68
Yoon 2014	153 / 174	48 / 58	0.659	0.290	1.496	0.318	8.66
Memeo	27 / 45	36 / 45	2.667	1.039	6.847	0.041	7.85
Cheung 2013	41 / 64	28 / 32	3.927	1.224	12.595	0.021	6.54
Kim HH	24 / 29	22 / 26	1.146	0.272	4.819	0.853	5.22
Tranchart	30 / 42	34 / 42	1.700	0.613	4.717	0.308	7.37
Lai EC	24 / 33	22 / 25	2.750	0.659	11.480	0.165	5.25
Yoon 2017	13 / 33	30 / 33	15.385	3.882	60.969	0.000	5.48
			1.527	0.996	2.342	0.052	



B Disease-free survival 3 year

Study name	Events / Total OLR	Events / Total LLR	Odds ratio	Lower limit	Upper limit	p-Value	Relative weight
Cheung 2016	186 / 330	72 / 110	1.467	0.936	2.299	0.095	14.75
Tanaka	6 / 20	6 / 20	1.000	0.259	3.867	1.000	2.29
Takahara	195 / 387	226 / 387	1.382	1.041	1.836	0.025	24.75
Han	44 / 88	46 / 88	1.095	0.606	1.978	0.763	9.88
Komatsu	11 / 38	19 / 38	2.455	0.953	6.325	0.063	4.45
Leee JJ	57 / 86	23 / 43	0.585	0.277	1.236	0.160	6.73
Yoon 2014	108 / 174	33 / 58	0.807	0.441	1.475	0.485	9.57
Cheung 2013	32 / 64	23 / 32	2.556	1.025	6.369	0.044	4.75
Lee KF	28 / 50	17 / 33	0.835	0.346	2.017	0.688	5.05
Tranchart	23 / 42	26 / 42	1.342	0.562	3.204	0.507	5.17
Lai EC	16 / 33	13 / 25	1.151	0.407	3.257	0.791	3.75
Yoon 2017	7 / 33	14 / 33	2.737	0.927	8.084	0.068	3.48
Sposito	19 / 43	19 / 43	1.000	0.427	2.342	1.000	5.38
			1.246	1.010	1.537	0.040	



C Disease-free survival 5 year

Study name	Events / Total OLR	Events / Total LLR	Odds ratio	Lower limit	Upper limit	p-Value	Relative weight
Cheung 2016	247 / 330	57 / 110	0.361	0.231	0.566	0.000	10.05
Takahara	152 / 387	58 / 387	0.273	0.193	0.385	0.000	10.51
Han	36 / 88	37 / 88	1.048	0.575	1.909	0.878	9.27
Leee JJ	50 / 86	23 / 43	0.828	0.396	1.730	0.616	8.50
Ahn 2014	28 / 51	35 / 51	1.797	0.800	4.034	0.156	8.10
Memeo	10 / 45	9 / 45	0.875	0.318	2.411	0.796	6.97
Kim SJ	41 / 76	36 / 70	0.904	0.472	1.732	0.761	8.99
Cheung 2013	28 / 64	17 / 32	1.457	0.622	3.416	0.386	7.85
Lee KF	28 / 50	15 / 33	0.655	0.271	1.585	0.348	7.67
Tranchart	16 / 42	19 / 42	1.342	0.562	3.204	0.507	7.75
Sposito	5 / 43	11 / 43	2.613	0.821	8.309	0.104	6.25
Jiang X	44 / 59	42 / 59	0.842	0.374	1.899	0.679	8.07
			0.856	0.555	1.321	0.482	

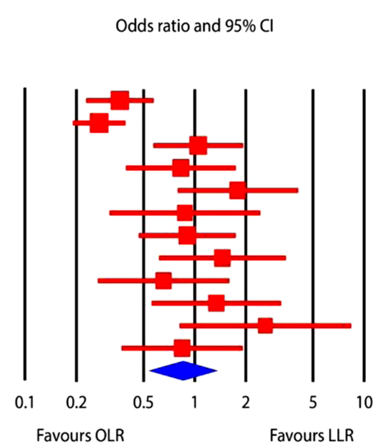


Fig. 11 Forest plot showing: **A** 1-year disease-free survival rate in propensity score matched studies, **B** 3-years disease-free survival rate in propensity score-matched studies, and **C** 5-years disease-free survival rate in propensity score matched studies

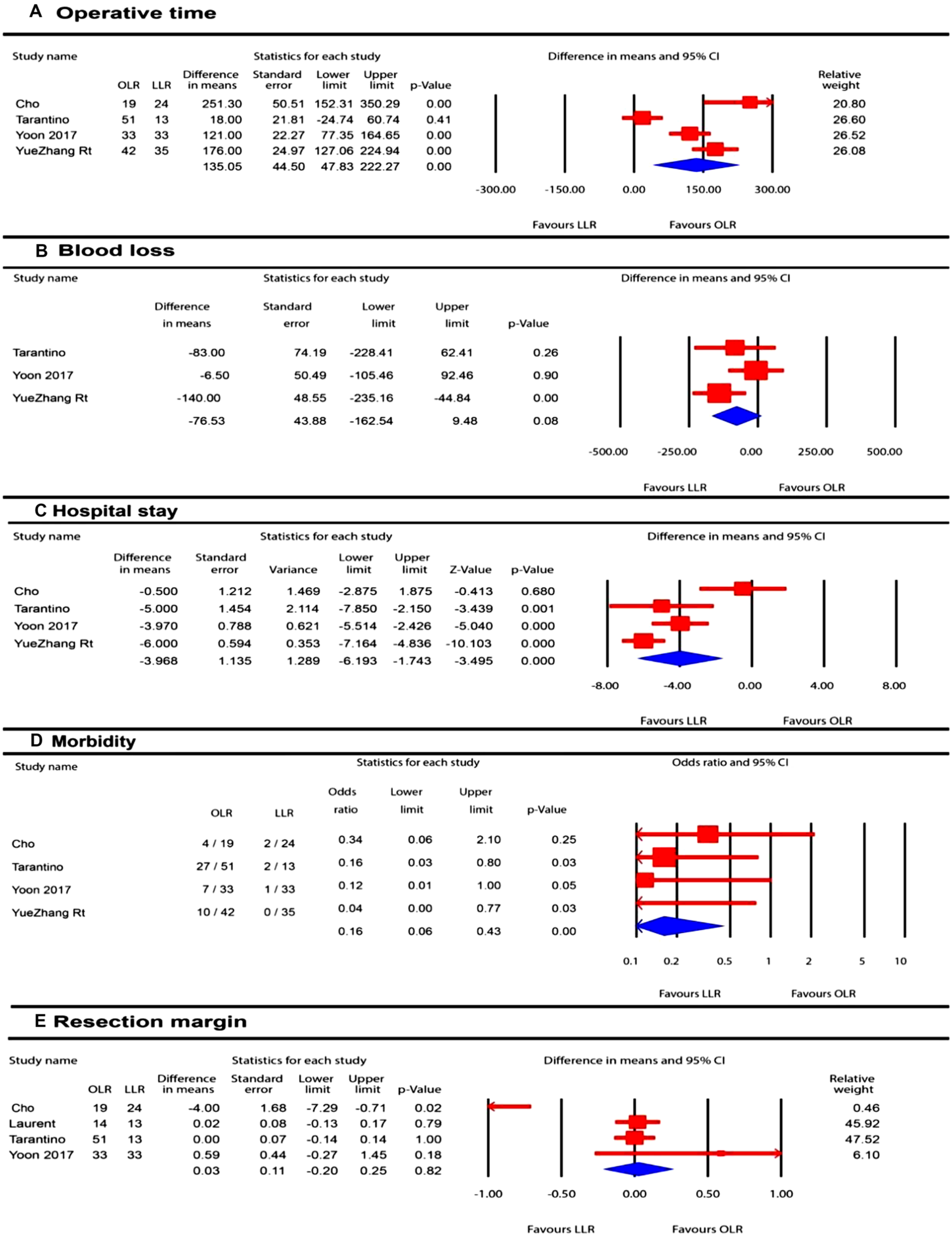


Fig. 12 Forest plot showing: **A** The mean difference of operative time in minutes in laparoscopic liver resection (LLR) in comparison with open liver resection (OLR) in right hepatectomy, **B** The mean difference of blood loss in ML in LLR in comparison with OLR in right hepatectomy, **C** The mean difference of hospital stay in days in LLR in comparison with OLR in right hepatectomy, **D** The morbidity rate in LLR comparing with OLR in right hepatectomy, and **E** the mean difference of resection margin in CM in LLR in comparison with OLR in right hepatectomy

Table 3 Egger's test to assess for potential publication bias

Outcome	Egger's regression intercept	95% CI	*P* value
Operative time in minutes	0.65	− 2.81 to 4.11	0.7
Blood loss in ML	− 1.9	− 5.6 to 1.7	0.27
Blood transfusion rate	− 0.64	− 2.1 to 0.81	0.37
Hospital stay in days	− 0.54	− 2.64 to 1.55	0.59
30-days mortality	− 2.2	− 6.3 to 1.94	0.27
Morbidity	− 1.37	− 2.06 to − 0.68	0.001
Resection margin	− 0.25	− 1.7 to 1.20	0.71
R0 resection	0.88	0.18 to 1.57	0.015
Recurrence rate	0.38	− 0.91 to 1.688	0.54
1-year overall survival	0.51	− 0.7 to 1.7	0.39
3-years overall survival	− 1.0	− 2.9 to 0.86	0.25
5-years overall survival	− 0.19	− 1.7 to 1.3	0.78
1-year disease-free survival	0.71	− 1.12 to 2.5	0.42
3-years disease-free survival	− 0.3	− 2.9 to 2.3	0.8
5-years disease- free survival	5.56	3.38 to 7.74	0.001

might be compensated by the relatively large number of events over at 5 years follow-up.

Our meta-analysis has several limitations; (1) none of the included studies were a randomized controlled trial which makes our study has a risk of confounding and selection bias, however we run a subgroup analysis focused on propensity score-matched studies to mitigate the inherent risk of confounding bias associated with observational studies. RCTs comparing between both resection approaches are needed to accurately identify the superiority of either strategy. (2) there was an inherent heterogeneity regarding the definition of clinical outcomes across the included studies. (3) Despite our extensive literature search, we found a limited number of studies recruited patients with right hepatectomy, therefore, the results of our study should be interpreted carefully regarding the safety and efficacy of LLR in comparison with OLR in right hepatectomy. Further studies investigating the clinical outcomes of both approaches in right hepatectomy are still needed. (4) We could not run a subgroup analysis based on tumor classification since most of the studies did not stratify the HCC into stages or based on Endmondson classification and report clinical outcomes accordingly. (5) Our results regarding morbidity, R0 resection, and 5-DFS should be interpreted with caution since our analysis found a potential publication bias with these outcomes. The potential publication bias might have arisen from that tertiary care centers, that are well equipped, are more likely to publish data about LLR than community hospitals.

In conclusion, LLR was significantly associated with shorter operative time, less blood loss, less blood transfusion rate, shorter hospital stay in days, lower 30-days mortality rate, and lower morbidity. There was no significant difference between LLR and OLR regarding resection margin. There was no significant difference between both groups in terms of 3-DFS, 5-DFS, 3-OS, nevertheless LLR was associated with a significantly higher 1-OS, 5-OS and 1-DFS rates. RCTs are needed to identify the efficacy and safety of LLR in comparison with OLR in patients with HCC. Further studies investigating LLR in right hepatectomy are needed.

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Compliance with ethical standard

Disclosures Drs. Meng Xiangfei, Xu Yinzhe, Pan Yingwei, Lu Shichun and Duan Weidong have no conflicts of interest or financial ties to disclose.

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