

## Meta-analysis of laparoscopic vs open liver resection for hepatocellular carcinoma

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### Abstract

**AIM:** To conduct a meta-analysis to determine the safety and efficacy of laparoscopic liver resection (LLR) and open liver resection (OLR) for hepatocellular carcinoma (HCC).

**METHODS:** PubMed (Medline), EMBASE and Science Citation Index Expanded and Cochrane Central Register of Controlled Trials in the Cochrane Library were searched systematically to identify relevant comparative studies reporting outcomes for both LLR and OLR

for HCC between January 1992 and February 2012. Two authors independently assessed the trials for inclusion and extracted the data. Meta-analysis was performed using Review Manager Version 5.0 software (The Cochrane Collaboration, Oxford, United Kingdom). Pooled odds ratios (OR) or weighted mean differences (WMD) with 95%CI were calculated using either fixed effects (Mantel-Haenszel method) or random effects models (DerSimonian and Laird method). Evaluated endpoints were operative outcomes (operation time, intraoperative blood loss, blood transfusion requirement), postoperative outcomes (liver failure, cirrhotic decompensation/ascites, bile leakage, postoperative bleeding, pulmonary complications, intraabdominal abscess, mortality, hospital stay and oncologic outcomes (positive resection margins and tumor recurrence).

**RESULTS:** Fifteen eligible non-randomized studies were identified, out of which, 9 high-quality studies involving 550 patients were included, with 234 patients in the LLR group and 316 patients in the OLR group. LLR was associated with significantly lower intraoperative blood loss, based on six studies with 333 patients [WMD: -129.48 mL; 95%CI: -224.76-(-34.21) mL;  $P = 0.008$ ]. Seven studies involving 416 patients were included to assess blood transfusion requirement between the two groups. The LLR group had lower blood transfusion requirement (OR: 0.49; 95%CI: 0.26-0.91;  $P = 0.02$ ). While analyzing hospital stay, six studies with 333 patients were included. Patients in the LLR group were found to have shorter hospital stay [WMD: -3.19 d; 95%CI: -4.09-(-2.28) d;  $P < 0.00001$ ] than their OLR counterpart. Seven studies including 416 patients were pooled together to estimate the odds of developing postoperative ascites in the patient groups. The LLR group appeared to have a lower incidence of postoperative ascites (OR: 0.32; 95%CI: 0.16-0.61;  $P = 0.0006$ ) as compared with OLR patients. Similarly, fewer patients had liver failure in the LLR group than in the OLR group (OR: 0.15; 95%CI: 0.02-0.95;  $P =$

0.04). However, no significant differences were found between the two approaches with regards to operation time [WMD: 4.69 min; 95%CI: -22.62-32 min;  $P = 0.74$ ], bile leakage (OR: 0.55; 95%CI: 0.10-3.12;  $P = 0.50$ ), postoperative bleeding (OR: 0.54; 95%CI: 0.20-1.45;  $P = 0.22$ ), pulmonary complications (OR: 0.43; 95%CI: 0.18-1.04;  $P = 0.06$ ), intra-abdominal abscesses (OR: 0.21; 95%CI: 0.01-4.53;  $P = 0.32$ ), mortality (OR: 0.46; 95%CI: 0.14-1.51;  $P = 0.20$ ), presence of positive resection margins (OR: 0.59; 95%CI: 0.21-1.62;  $P = 0.31$ ) and tumor recurrence (OR: 0.95; 95%CI: 0.62-1.46;  $P = 0.81$ ).

**CONCLUSION:** LLR appears to be a safe and feasible option for resection of HCC in selected patients based on current evidence. However, further appropriately designed randomized controlled trials should be undertaken to ascertain these findings.

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**Key words:** Hepatocellular carcinoma; Laparoscopy; Open liver resection; Hepatectomy; Meta-analysis

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## INTRODUCTION

Hepatocellular carcinoma (HCC) is the fifth most common primary cancer worldwide<sup>[1]</sup>, and the third most common cause of cancer-related deaths with about 600 000 patients dying from the disease annually<sup>[2]</sup>. The potential treatment options for HCC include: surgical resection<sup>[3]</sup>, liver transplantation<sup>[4]</sup>, chemotherapy and local ablative therapy<sup>[5]</sup>. Surgery, either through hepatic resection or liver transplantation, is the best hope for a cure, but is not suitable for those patients who also suffer from significant background cirrhosis<sup>[5]</sup>. Liver transplantation should be considered in any patient with cirrhosis and a small (5 cm or less single nodule or up to three lesions of 3 cm or less) HCC. Hepatic resection, on the other hand, should be considered as a primary therapy in every patient with HCC and a non-cirrhotic liver (including fibrolamellar variant). Resection can also be carried out in highly selected patients with hepatic cirrhosis and well preserved hepatic function (Child-Pugh A) who are unsuitable for liver transplantation<sup>[6]</sup>.

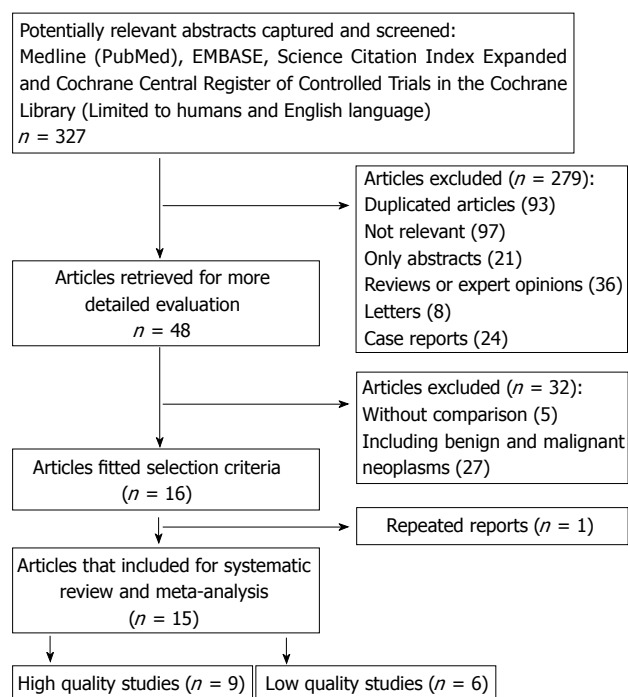
Open liver resection (OLR) has traditionally been accepted as the preferred treatment for resectable HCC in patients with adequate liver reserves<sup>[7]</sup>. However, most patients with HCC have significant underlying co-morbidities, including liver diseases such as chronic hepatitis and liver cirrhosis, and hence are at very high risk of developing significant postoperative complications. Laparoscopic surgery is considered to be a safe alternative to open surgical intervention in numerous surgical procedures. Since the first successful report of laparoscopic liver wedge resection in 1992<sup>[8]</sup>, improvement in surgical instrumentation and experience in laparoscopic treatment for the majority of surgical gastrointestinal conditions, including benign liver diseases, have led to a growing interest in its application for HCC. Recent studies have suggested that the laparoscopic liver resection (LLR) has a number of advantages such as reduction of postoperative pain, operative morbidity, and length of hospitalization, especially for cirrhotic patients with HCC<sup>[9-12]</sup>. However, the current literature on LLR for HCC exists in the form of few comparative studies. General application of this approach for treating this disease is still a matter of debate because it is new and data regarding long-term oncologic outcomes (e.g., recurrence) are not robust.

Three published meta-analysis<sup>[13-15]</sup> have investigated the advantages and disadvantages of the LLR for HCC. These meta-analyses have reported that LLR was associated with decreased blood loss and requirement for blood transfusion, lower overall postoperative morbidity and shorter hospital stay compared with the OLR. In addition, there was no difference between groups in oncologic outcomes such as positive resection margins and tumor recurrence. Since these meta-analysis included a limited number of studies with fewer cases, data reported were not sufficient to derive conclusions with regards to the overall efficacy and safety of LLR. In the interim, several high-quality studies<sup>[16-20]</sup> with more participants have been published. We have therefore undertaken an analysis of 15 studies including 1105 hepatic resections to provide an update on the efficacy of LLR vs OLR for HCC.

## MATERIALS AND METHODS

### Study selection

PubMed (Medline), EMBASE and Science Citation Index Expanded and Cochrane Central Register of Controlled Trials in the Cochrane Library were searched systematically for all articles published from January 1992 to February 2012 comparing LLR and OLR for HCC. The following medical search headings and keywords were used: "laparoscopy" or "laparoscopic" or "minimally invasive surgery" and "hepatectomy" or "liver resection" or "hepatic resection" and "primary liver carcinoma" or "hepatocellular carcinoma" or "HCC". Only human studies published in English language as full text articles were considered for inclusion. Reference lists of selected articles were also examined to find relevant studies which were not identified during the initial data-



**Figure 1** Flow diagram depicting the process of identification and inclusion of selected studies.

base searches. Final inclusion of articles was determined by consensus from two authors; when this failed, a third author adjudicated.

### Inclusion and exclusion criteria

Two authors identified and screened the aforementioned databases for potentially eligible studies.

**Inclusion criteria:** (1) Clear documentation of the operative techniques as “laparoscopic” or “open”; (2) Studies with at least one of the outcomes mentioned; and (3) Where multiple studies came from the same institute and/or authors, either the one of higher quality or the most recent publication was included in the analysis.

**Exclusion criteria:** (1) Abstracts, letters, editorials, expert opinions, case reports, reviews and studies lacking control groups; (2) Studies with no clearly reported outcomes of interest; (3) Studies dealing with HCC recurrence after hepatectomy; and (4) Studies including patients with benign lesions or other types of malignant liver tumors.

### Outcomes of interest

The following outcomes were evaluated in the two approaches.

**Operative outcomes:** Operative time, intraoperative blood loss and requirement for blood transfusions.

**Postoperative outcomes:** Hospital stay, liver failure, cirrhotic decompensation/ascites, bile leakage, postoperative bleeding, pulmonary complications (including pleural

effusion and pneumonia), intra-abdominal abscess and mortality.

**Oncologic outcomes:** Positive resection margins and tumor recurrence.

### Data extraction and quality assessment

Data were extracted by two independent observers using standardized forms. The recorded data included patient and study characteristics and surgical details. The quality of studies was assessed using the Newcastle-Ottawa Scale<sup>[21]</sup>, by examining three factors: patient selection, comparability of the study groups and assessment of outcome. Studies were matched for age, American Society of Anesthesiologists status, presence of cirrhosis, size of tumor and type of hepatic resection undertaken. The maximum numbers of stars in the selection, comparability, and outcome categories were four, two, and three, respectively. Studies achieving six or more stars were considered to be of higher quality<sup>[22]</sup>. Only these were included in the final analysis to have the best estimate of the outcome measure.

### Statistical analysis

Meta-analysis was performed using Review Manager Version 5.0 software (The Cochrane Collaboration, Oxford, United Kingdom). For continuous variables, treatment effects were expressed as weighted mean difference (WMD) with corresponding 95%CI. For categorical variables, treatment effects were expressed as odds ratio (OR) with corresponding 95%CI. Heterogeneity was evaluated using the  $\chi^2$  test, and a  $P$  value  $< 0.1$  was considered significant<sup>[23]</sup>. The fixed-effects model was initially calculated for all outcomes<sup>[24]</sup>. If the test rejected the assumption of homogeneity of studies, random-effects analysis was performed<sup>[25]</sup>. Sensitivity analysis were performed by removing individual studies from the data set and analyzing the effect on the overall results to identify sources of significant heterogeneity. Subgroup analysis were also undertaken by including low-quality studies to present cumulative evidence. Funnel plots were constructed to evaluate potential publication bias<sup>[26]</sup> based on the operative time, hospital stay and tumor recurrence.

## RESULTS

### Description of included trials in the meta-analysis

The search strategy initially generated 327 relevant clinical trials. Finally, 16 articles<sup>[10-12,16-20,27-34]</sup> were selected for further investigation. Of these, two studies<sup>[12,30]</sup> were published by the same institute and had overlapping patient populations; therefore, the higher-quality study<sup>[30]</sup> was included. In total, 15 non-randomized comparative studies were identified for final inclusion, out of which 9 were found to be of high quality<sup>[10,11,17,18,20,28,30,32,33]</sup>. These were included in the final analyses. Figure 1 shows the process of selecting comparative studies included in our meta-analysis.

Table 1 Characteristics of studies included in the meta-analysis

Study	Year	Country	Group	n	Male/female	Age (yr) (mean $\pm$ SD)	Matching <sup>b</sup>	Study quality
Shimada <i>et al</i> <sup>[27]</sup>	2001	Japan	LLR	17	15/2	62 $\pm$ 9	1,3,4	*****
Laurent <i>et al</i> <sup>[28]</sup>	2003	France	OLR	38	24/14	63 $\pm$ 79	1,3,4,5	*****
			LLR	13	10/3	62.6 $\pm$ 9.5		
Kaneko <i>et al</i> <sup>[29]</sup>	2005	Japan	OLR	14	10/4	65.9 $\pm$ 5.5	1,2,3,4,5	*****
			LLR	30	18/12	59 $\pm$ 8		
Belli <i>et al</i> <sup>[30]</sup>	2007	Italy	OLR	28	18/10	61 $\pm$ 10	1,2,3,4,5	*****
			LLR	23	13/10	59.5 $\pm$ 6.84		
Endo <i>et al</i> <sup>[31]</sup>	2009	Japan	OLR	23	14/9	62.4 $\pm$ 7.7	3,4	****
			LLR	10	8/2	72 $\pm$ 4		
Lai <i>et al</i> <sup>[32]</sup>	2009	China	OLR	11	8/3	64 $\pm$ 2	1,3,4	*****
			LLR	25	18/7	59 (35-79) <sup>a</sup>		
Sarpel <i>et al</i> <sup>[11]</sup>	2009	United States	OLR	33	21/12	59 (38-77) <sup>a</sup>	1,3,4	*****
			LLR	20	15/5	63.8 $\pm$ 10.3		
Aldrighetti <i>et al</i> <sup>[33]</sup>	2010	Italy	OLR	56	45/11	58.3 $\pm$ 11.0	1,2,3,4,5	*****
			LLR	16	11/5	65 $\pm$ 10		
Tranchart <i>et al</i> <sup>[10]</sup>	2010	France	OLR	16	12/4	71 $\pm$ 6	1,2,3,4,5	*****
			LLR	42	15/27	63.7 $\pm$ 13.1		
Nguyen <i>et al</i> <sup>[34]</sup>	2011	United States	OLR	42	14/28	65.7 $\pm$ 7.1	1,3,4,5	*****
			LLR	17	12/5	68		
Hu <i>et al</i> <sup>[16]</sup>	2011	China	OLR	20	12/8	65	1,3,4	****
			LLR	30	20/10	46 $\pm$ 12		
Ker <i>et al</i> <sup>[19]</sup>	2011	China	OLR	30	19/11	48 $\pm$ 15	1,2	****
			LLR	116	92/24	58.31 $\pm$ 12.7		
Kim <i>et al</i> <sup>[20]</sup>	2011	South Korea	OLR	208	156/52	57.9 $\pm$ 11.2	1,2,3,4,5	*****
			LLR	26	18/8	57.84 $\pm$ 9.66		
Lee <i>et al</i> <sup>[17]</sup>	2011	China	OLR	29	20/9	57.08 $\pm$ 9.78	1,2,4	*****
			LLR	33	24/9	59 (36-85) <sup>a</sup>		
Truant <i>et al</i> <sup>[18]</sup>	2011	France	OLR	50	40/10	58.5 (32-81) <sup>a</sup>	1,2,3,4	*****
			LLR	36	31/5	60.6 $\pm$ 10.2		
			OLR	53	47/6	63.3 $\pm$ 7.6		

LLR: Laparoscopic liver resection; OLR: Open liver resection. <sup>a</sup>Median with range; <sup>b</sup>1: Age; 2: American Society of Anesthesiologists physical status score; 3: Presence of cirrhosis; 4: Tumor size; 5: Type of liver resection.

### Study and patient characteristics

The characteristics and quality assessments of included studies are shown in Table 1. A total of 550 patients were included: 234 patients in the LLR and 316 patients in the OLR group. The characteristics of patients and surgical details are summarized in Table 2. The sample size of the included studies varied from 21 to 89 patients. The rate of conversion, from laparoscopic to open procedure, ranged from 0% to 19.4%. Patients in most of studies had concurrent hepatitis B infection.

### Meta-analysis results

Results of the analyses are shown in Figure 2 and summarized in Table 3.

**Operative outcomes:** Six high-quality studies<sup>[10,11,18,28,30,33]</sup> reported mean operation time, analysis of which showed no statistically significant difference between the two groups (patients 354; WMD: 4.69 min; 95%CI: -22.62-32 min;  $P = 0.74$ ). Similarly, six high-quality studies<sup>[10,18,20,28,30,33]</sup> provided detailed data for estimation of blood loss between the two groups. We found that LLR had significantly less intraoperative blood loss compared to OLR [patients 333; WMD: -129.48 mL; 95%CI: -224.76-(-34.21) mL;  $P = 0.008$ ]. Furthermore, the rate of blood transfusions requirement was identified to be significantly lower in the

LLR group as opposed to OLR (trials: 7; patients 416; OR: 0.49; 95%CI: 0.26-0.91;  $P = 0.02$ ). Addition of low-quality trials to these groups did not affect the results.

**Postoperative outcomes:** Six high-quality studies<sup>[10,18,20,28,30,33]</sup> reported on length of hospital stay. Pooled outcome measure favored LLR [patients 333; WMD: -3.19 d; 95%CI: -4.09-(-2.28) d;  $P < 0.00001$ ]. A lower incidence of liver failure was observed in patients undergoing LLR (trials 2, patients 116; OR: 0.15; 95%CI: 0.02-0.95;  $P = 0.04$ ). The incidence of postoperative ascites in seven high-quality trials (patients 416; OR: 0.32; 95%CI: 0.16-0.61;  $P = 0.0006$ ) was found to be significantly lower in LLR group. Six high-quality trials<sup>[10,17,18,20,28,30]</sup> revealed no statistically significant difference in the incidence of pulmonary complications between the two groups (patients 384; OR: 0.43; 95%CI: 0.18-1.04;  $P = 0.06$ ). However, when two low-quality trials<sup>[27,31]</sup> were also pooled together to get a cumulative result, LLR group seemed to have a lower incidence (patients 460; OR: 0.43; 95%CI: 0.19-0.96;  $P = 0.04$ ).

No significant differences were observed between two operative techniques in terms of other postoperative complications, such as bile leakage (trials 3; patients 205; OR: 0.55; 95%CI: 0.10-3.12;  $P = 0.50$ ), postoperative bleeding (trials 5; OR: 0.54; 95%CI: 0.20-1.45;  $P = 0.22$ ) and mortality (trials 5; patients 474; OR: 0.46; 95%CI:



Table 2 Characteristics of patients and surgical details

Study	Group	Cirrhosis <i>n</i> (%)	Tumor size (cm)	Type of hepatectomy
Shimada <i>et al</i> <sup>[27]</sup>	LLR	13 (76.4)	2.6 ± 0.9	a = 7, b = 10
	OLR	28 (73.6)	2.5 ± 1.0	NA
Laurent <i>et al</i> <sup>[28]</sup>	LLR	NA	3.35 ± 0.89	a = 3, b = 7, c = 3
	OLR	NA	3.43 ± 1.05	a = 4, b = 7, c = 3
Kaneko <i>et al</i> <sup>[29]</sup>	LLR	13 (43.3)	3.0 ± 0.8	a = 10, b = 20
	OLR	NA	3.1 ± 0.9	a = 8, b = 20
Belli <i>et al</i> <sup>[30]</sup>	LLR	23 (100)	3.1 ± 0.7	a = 5, b = 3, c = 15
	OLR	23 (100)	3.24 ± 0.70	a = 6, b = 5, c = 12
Endo <i>et al</i> <sup>[31]</sup>	LLR	6 (60)	3.0 ± 1.5	NA
	OLR	9 (81.8)	4.1 ± 0.8	NA
Lai <i>et al</i> <sup>[32]</sup>	LLR	23 (92)	2.5 (1-7) <sup>1</sup>	a = 6, b = 8, c = 10, d = 1
	OLR	31 (93.9)	2.6 (1-8) <sup>1</sup>	a = 2, b = 18, c = 13
Sarpel <i>et al</i> <sup>[11]</sup>	LLR	9 (45)	4.3 ± 2.1	NA
	OLR	27 (48.2)	4.3 ± 2.2	NA
Aldrighetti <i>et al</i> <sup>[33]</sup>	LLR	9 (56.3)	4 ± 2.2	a = 5, b = 2, c = 9
	OLR	9 (56.3)	4.6 ± 2.5	a = 5, b = 2, c = 9
Tranchart <i>et al</i> <sup>[10]</sup>	LLR	31 (73.8)	3.58 ± 1.75	a = 9, b = 15, c = 10, d = 3, e = 2, f = 3
	OLR	34 (80.9)	3.68 ± 2.09	a = 7, b = 13, c = 10, d = 3, e = 2, f = 7
Nguyen <i>et al</i> <sup>[34]</sup>	LLR	44 (65)	3.0	a = 6, b = 5, e = 6
	OLR	23 (35)	4.5	a = 6, b = 8, e = 6
Hu <i>et al</i> <sup>[16]</sup>	LLR	25 (83.3)	6.7 ± 3.1	NA
	OLR	NA	8.7 ± 2.3	a = 10, b = 20
Ker <i>et al</i> <sup>[19]</sup>	LLR	NA	2.5 ± 1.2	a = 7, c = 97, e = 4, g = 8
	OLR	NA	5.4 ± 3.5	NA
Kim <i>et al</i> <sup>[20]</sup>	LLR	NA	3.15 (1-8) <sup>1</sup>	a = 4, b = 4, c = 13, d = 4, e = 1
	OLR	NA	3.6 (1-19) <sup>1</sup>	a = 3, b = 10, c = 9, d = 5, e = 2
Lee <i>et al</i> <sup>[17]</sup>	LLR	28 (84.8)	2.5 (1.5-9) <sup>1</sup>	a = 18, h = 15
	OLR	32 (64)	2.9 (1.2-9) <sup>1</sup>	a = 10, h = 40
Truant <i>et al</i> <sup>[18]</sup>	LLR	NA	2.9 ± 1.2	a = 22, b or f = 14
	OLR	NA	3.1 ± 1.2	a = 26, b or f = 27

<sup>1</sup>Median and (range). LLR: Laparoscopic liver resection; OLR: Open liver resection; NA: Not available; a: Left lateral segmentectomy; b: Segmentectomy; c: Subsegmentectomy; d: Right hepatectomy; e: Left hepatectomy; f: Bisegmentectomy; g: Right anterior sectorectomy; h: Nonanatomical resection.

0.14-1.51;  $P = 0.20$ ).

Two high-quality trials<sup>[20,30]</sup> reported intra-abdominal abscess formation in their patient populations. However, one of these did not have any events in both the groups and was subsequently excluded. A subgroup analysis was therefore undertaken including a low-quality study, which also did not show an association of intra-abdominal abscess formation with the type of operative technique (patients 122; OR: 0.72; 95%CI: 0.12-4.54;  $P = 0.73$ ).

**Oncologic outcomes:** We did not find any significant differences in the rate of positive margins (trials 4; patients 287; OR: 0.59; 95%CI: 0.21-1.62;  $P = 0.31$ ) and tumor recurrence (trials 6; patients 416; OR: 0.95; 95%CI: 0.62-1.46;  $P = 0.81$ ).

### Sensitivity and subgroup analysis

Sensitivity analyses were carried out by excluding each in-

dividual study from each outcome measure. These exclusions did not alter the results obtained from cumulative analyses. Additionally, the pooled result of included outcomes was not affected, when either fixed effects or random effects models were used. Subgroup analyses were undertaken for all outcome measures by including low-quality studies as well. These are summarized in Table 3.

### Publication bias

The funnel plot was based on the operation time, hospital stay and tumor recurrence, which is shown in Figure 3. As no study lies outside the limits of the 95%CI, there was no evidence of publication bias.

## DISCUSSION

LLR is a challenging technique for surgeons as the liver has unique anatomical features which present technical difficulties for parenchymal transections-massive hemorrhage and bile leak from intrahepatic vessels<sup>[11,29]</sup>. Presence of cirrhosis in patients undergoing LLR makes parenchymal transection an even more delicate and demanding procedure<sup>[11]</sup>. Rare but fatal complications such as a gas embolism caused by the pneumoperitoneum through hepatic venous branches on the hepatic stump during parenchymal division of the liver have also been reported<sup>[27]</sup>. On the contrary, increased experience, technical refinement and improvement in surgical equipment have increased the safety of liver resection as a curative treatment for benign or malignant liver lesions<sup>[35-38]</sup>. In spite of these advancements, LLR has not been very popular for HCC, partly because of the controversies related to resection margins, tumor seeding, incision related metastasis, and long-term survival<sup>[32]</sup>. However, the difference in outcomes between LLR and OLR in HCC has not been evaluated in a randomized controlled trial. Most reported studies are retrospective, single-institution series with a small number of patients, which makes it difficult to interpret outcomes appropriately. In order to overcome these limitations, we have endeavored to pool all the relevant available data and perform a meta-analysis. Although our result is similar to previously reports<sup>[13-15]</sup> in some aspects, such as operative blood loss, blood transfusion requirement, length of hospital stay and tumor recurrence, our analysis included more high-quality case-matched studies as well as more patients and therefore, provides an up to date and high-quality evidence regarding the perioperative and long-term outcomes of patients with HCC undergoing LLR vs OLR.

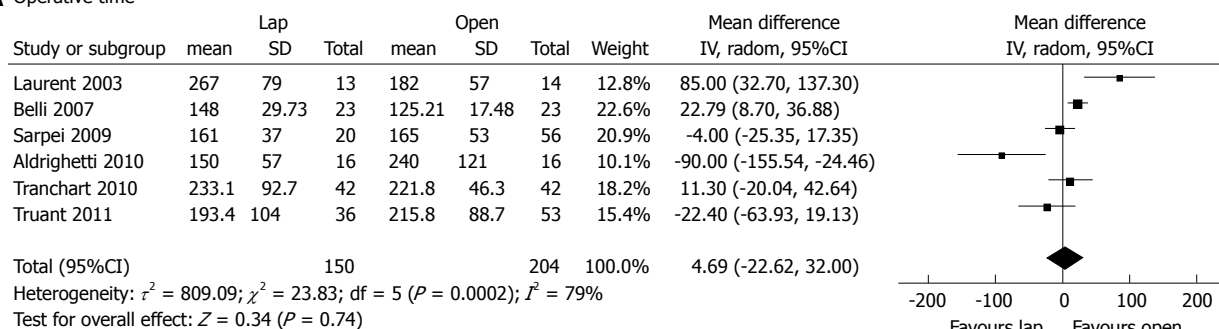
We found no significant difference in the 30-d mortality between the two groups. The results from this analysis indicate that LLR was successfully completed in most patients, with a rate of conversion to open surgery ranging from 0% to 19.4%. These results point towards the feasibility of LLR for patients with HCC.

There was no significant difference in operative time between the two techniques, based on our analysis, which can be explained by current advances in surgical instru-

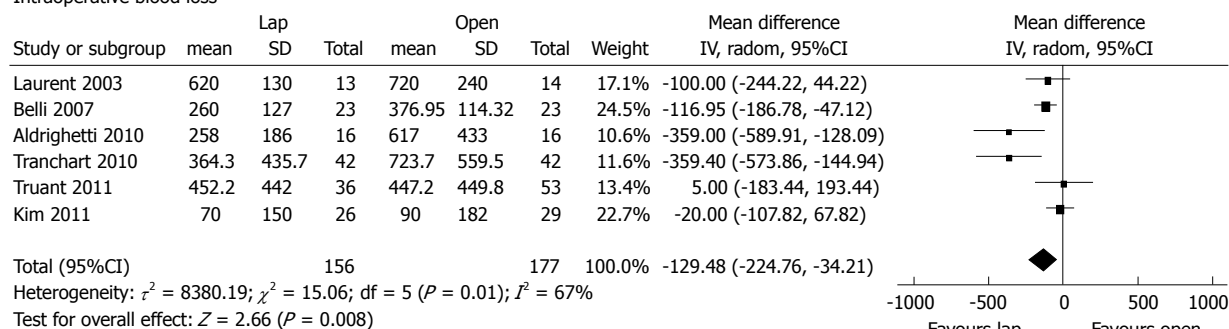
**Table 3** Results of meta-analysis comparing laparoscopic vs open hepatectomy (only high-quality studies)

Outcome of interest	No. of studies	No. of patients	OR/WMD	95%CI	P value	Heterogeneity P value	I <sup>2</sup> (%)
<b>Operative outcomes</b>							
Operation time (min)	6	354	4.69	-22.62, 32.00	0.74	0.0002	79
Intraoperative blood loss (mL)	6	333	-129.48	-224.76, -34.21	0.008	0.01	67
Blood transfusions requirement	7	416	0.49	0.26, 0.91	0.02	0.89	0
<b>Postoperative outcomes</b>							
Liver failure	2	116	0.15	0.02, 0.95	0.04	1.00	0
Cirrhotic decompensation/ascites	7	416	0.32	0.16, 0.61	0.001	0.95	0
Bile leakage	3	205	0.55	0.10, 3.12	0.50	0.86	0
Postoperative bleeding	5	287	0.54	0.20, 1.45	0.22	0.83	0
Pulmonary complications	6	384	0.43	0.18, 1.04	0.06	0.46	0
Intra-abdominal abscess	2	101	0.21	0.01, 4.53	0.32	-	-
Mortality	8	474	0.46	0.14, 1.51	0.20	0.64	0
Hospital stay	6	333	-3.19	-4.09, -2.28	< 0.00001	0.91	0
<b>Oncologic outcomes</b>							
Surgery margin positive rate	5	287	0.59	0.21, 1.62	0.31	0.65	0
Tumor recurrence	7	416	0.95	0.62, 1.46	0.81	0.93	0

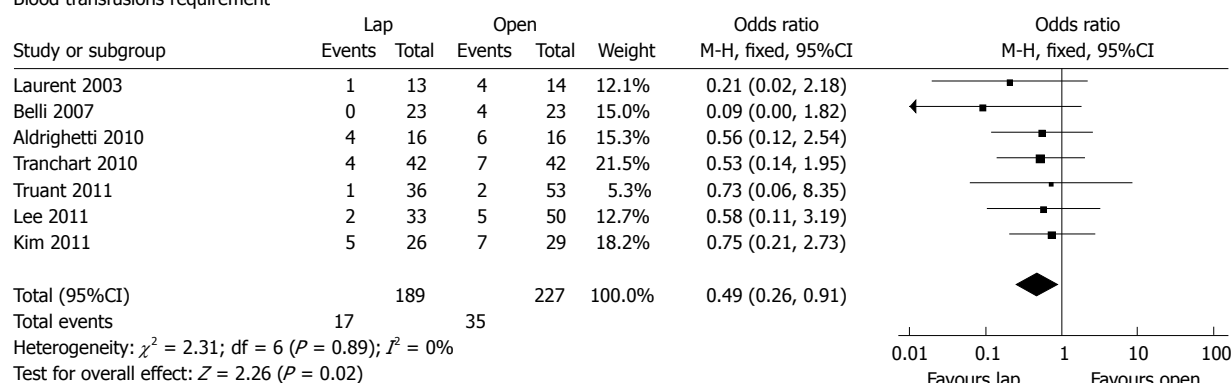
WMD: Weighted mean difference; OR: Odds ratio.

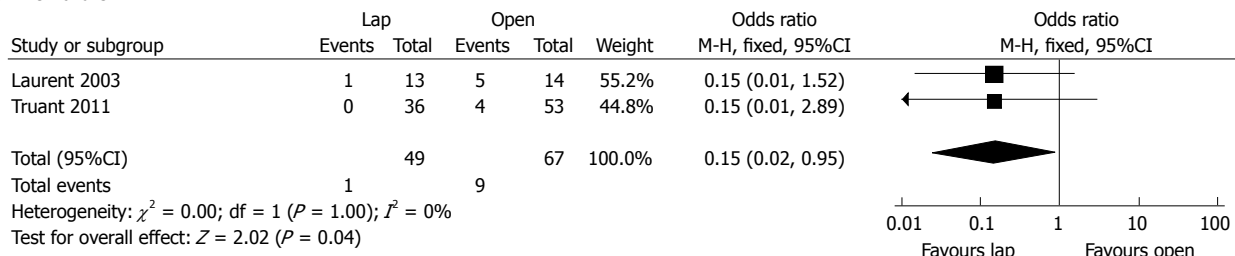
**A** Operative time

## Intraoperative blood loss

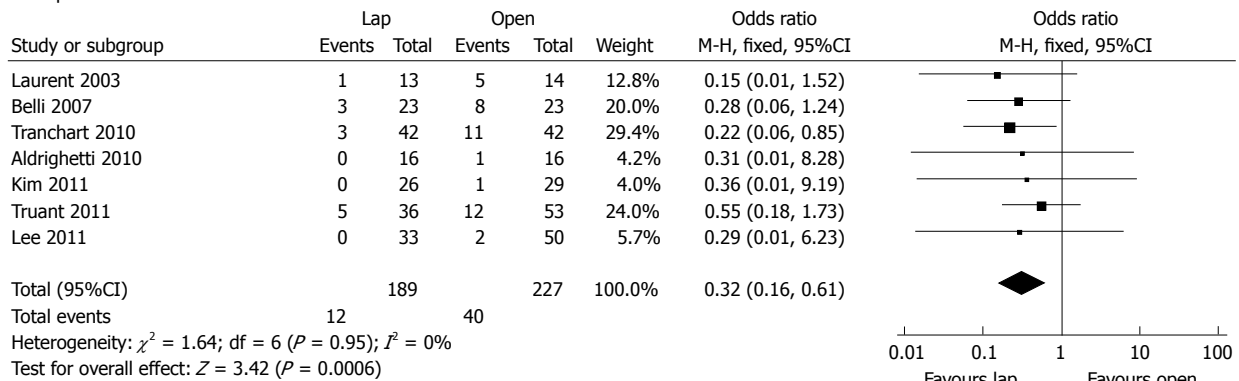


## Blood transfusions requirement

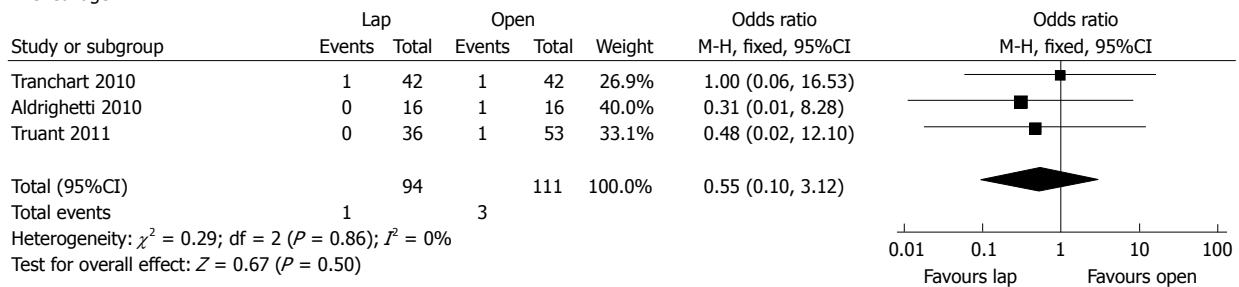


**B** Liver failure

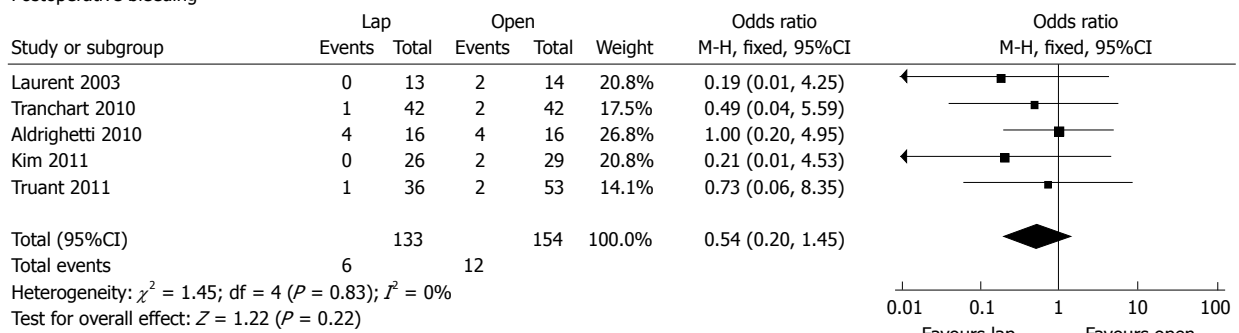
## Postoperative ascites



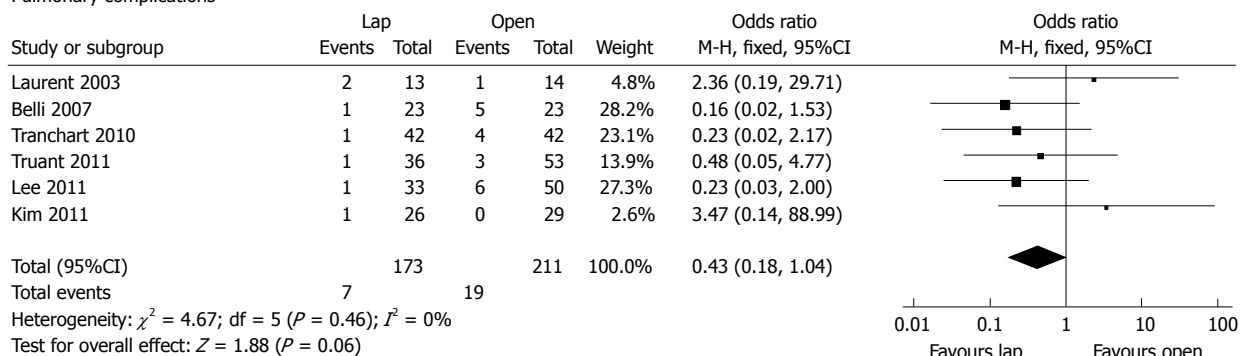
## Bile leakage



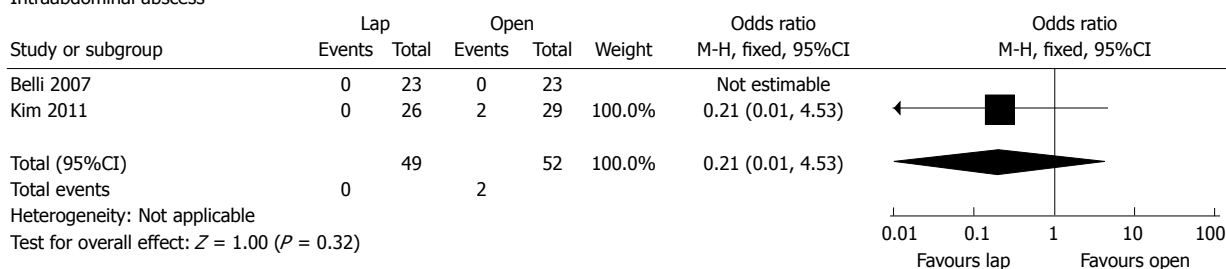
## Postoperative bleeding



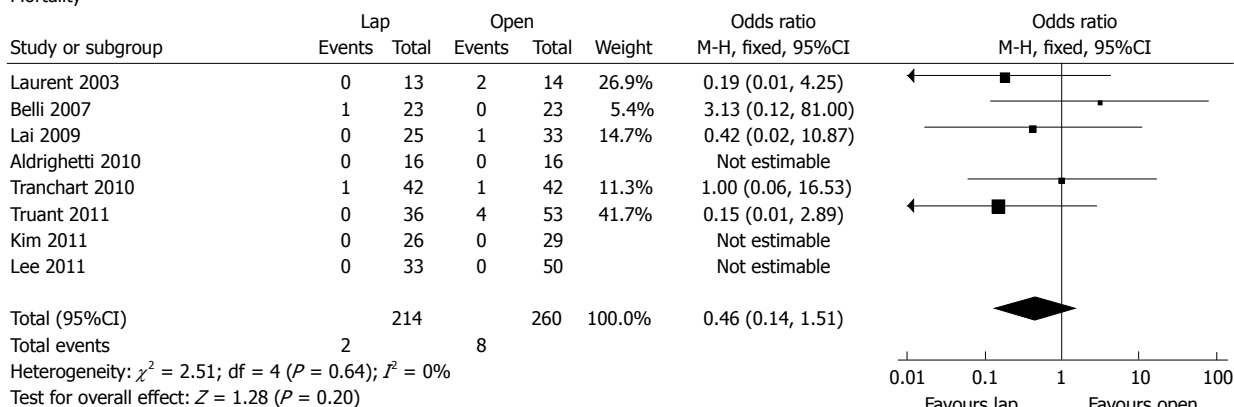
## Pulmonary complications



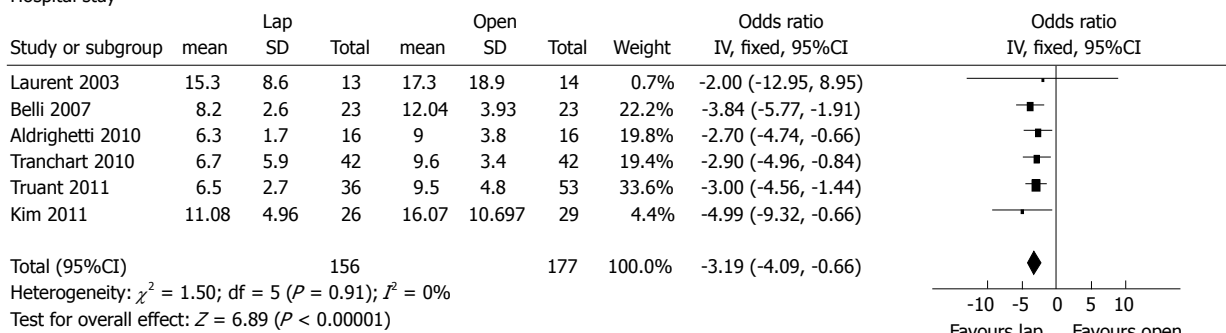
## Intraabdominal abscess



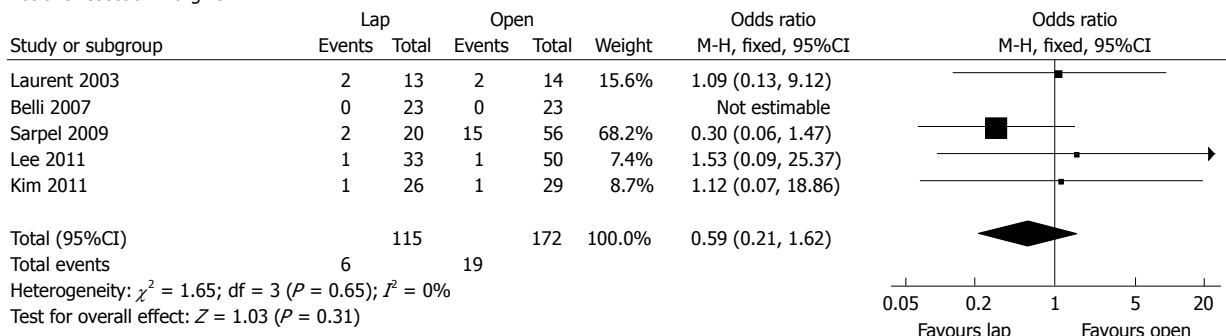
## Mortality



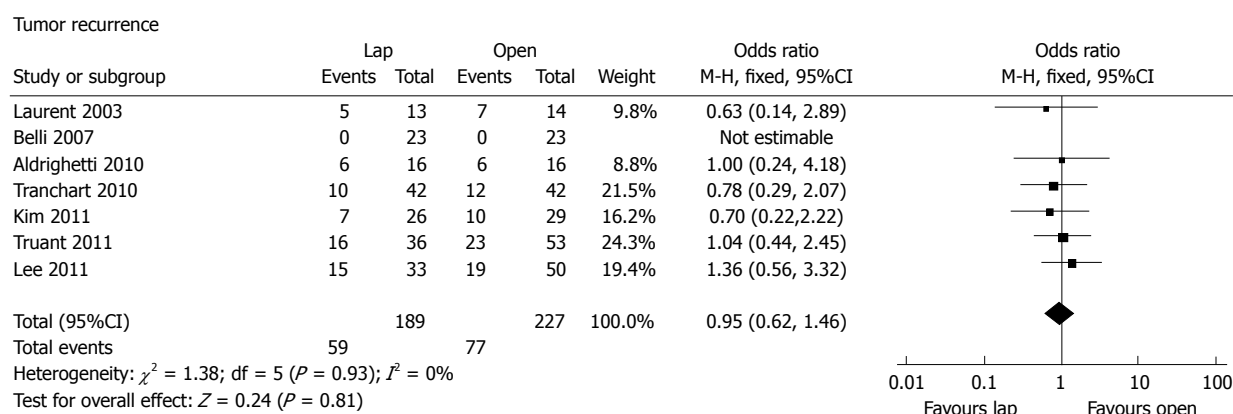
## Hospital stay



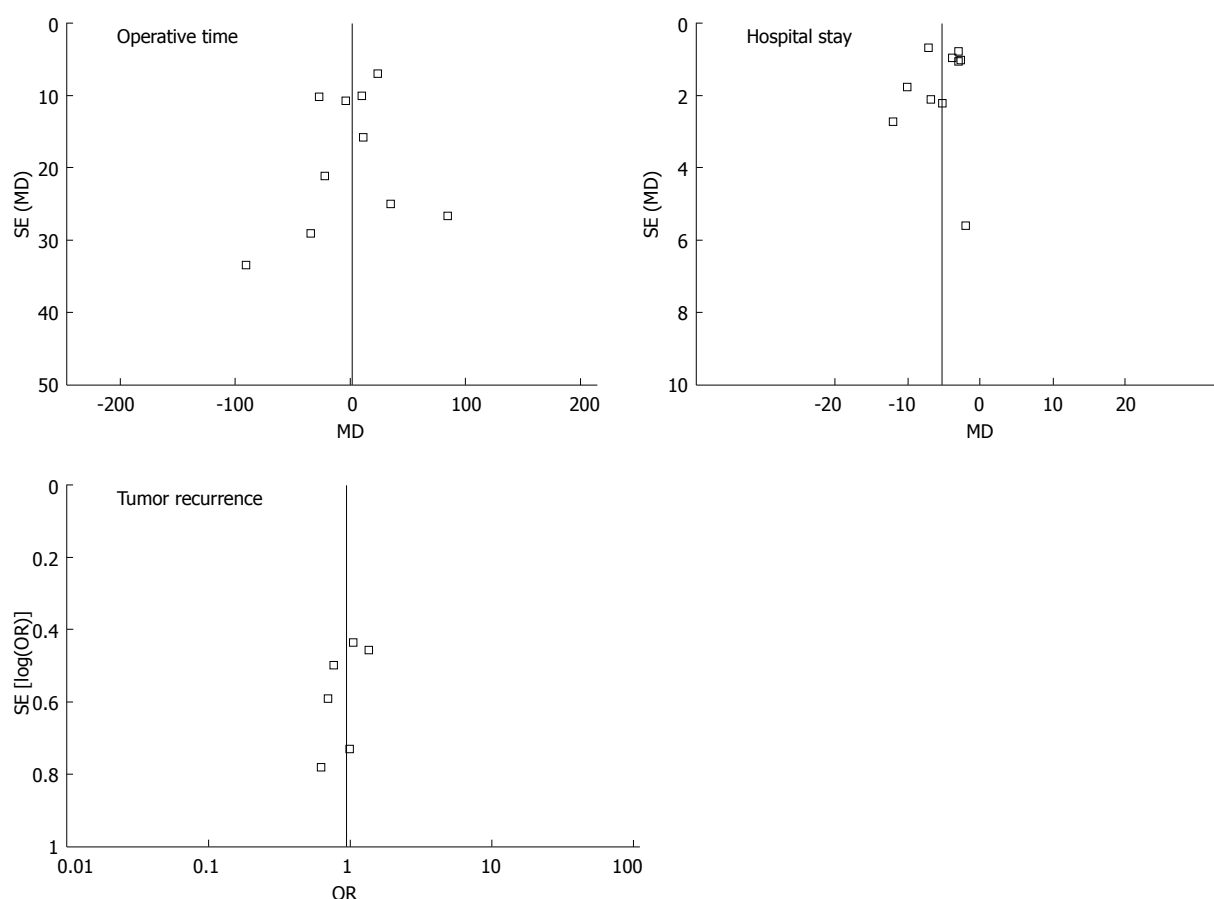
## C Positive resection margins







**Figure 2 Forest plots demonstrating operative, postoperative and oncologic outcomes.** A: Forest plots illustrating results of operative outcomes in the form of meta-analysis comparing laparoscopic vs open resection for hepatocellular carcinoma (high-quality studies only); B: Forest plots illustrating results of postoperative outcomes in the form of meta-analysis comparing laparoscopic vs open resection for hepatocellular carcinoma (high-quality studies only); C: Forest plots illustrating results of oncologic outcomes in the form of meta-analysis comparing laparoscopic vs open resection for hepatocellular carcinoma (high quality studies only). Pooled weighted mean difference or odds ratio with 95%CI was calculated using the fixed-effects or random effects model. IV: Inverse variance; M-H: Mantel-Haenszel.



**Figure 3 Funnel plot to investigate publication bias.** The laparoscopic vs the open group: A funnel plot showing the operation time, hospital stay and tumor recurrence. OR: Odds ratio; MD: Mean difference.

mentation and technology, as well as surgeons' experience and learning curve<sup>[39]</sup>. Our results demonstrate that LLR is associated with significantly less intraoperative blood loss and blood transfusion requirement, which can partly be explained by the hemostatic effect of pneumoperitoneum on the hepatic vein branches<sup>[30,40]</sup> and also image magnification during LLR<sup>[33]</sup>. There have been some re-

ports in literature indicating that significant intraoperative blood loss and blood transfusion are associated with recurrence and survival rates after resection of HCC<sup>[41-43]</sup>. Hence reduced blood loss in LLR is favorable. Results from this meta-analysis also reveal a significant reduction in the postoperative hospital stay in the LLR group. These findings are consistent with laparoscopic procedures

where patients have faster ambulation, early oral intake and reduced analgesic requirements<sup>[11,33]</sup>.

There is growing evidence to suggest that LLR is associated with less postoperative morbidity particularly with regards to developing postoperative ascites and liver failure. The reduction in the incidence of postoperative ascites in LLR might be due to preservation of the abdominal wall collateral circulation, by avoiding long abdominal incisions and preservation of the round ligament, which may contain significant collateral veins, thereby reducing portal hypertension and intraoperative fluid requirements<sup>[44]</sup>. Other favorable factors associated with LLR include less frequent mobilization and manipulation of the liver, reduced fluid requirements, decreased blood loss, early ambulation and oral food intake and reduced third space accumulation leading to hyperaldosteronism<sup>[28,30,45-47]</sup>.

Incomplete tumor resection with positive resection margins is perceived to be a potential disadvantage in LLR<sup>[33]</sup>. However, our results reveal no significant difference in the margin positive rate between the LLR and OLR groups. Further analysis revealed no difference in recurrence between the two groups. These findings can be attributed to the use of intraoperative ultrasonography in LLR or OLR. Intraoperative ultrasonography is a sensitive tool for accurate identification of lesions and orientation of borders for non-tumorous tissue<sup>[48,49]</sup>. The other consideration for laparoscopic resection of malignancies is the potential of peritoneal dissemination, or port-site metastasis<sup>[50-52]</sup>. However we did not encounter any case of peritoneal dissemination or port-site metastasis in our analysis.

Although our analysis shows apparent advantages of LLR over OLR for HCC, it is important to highlight that most of the patients included in our meta-analysis underwent segmentectomy or subsegmentectomy for peripheral lesions located in the anterolateral segments of the liver. Although it is encouraging that our results have been consistent throughout the sensitivity analyses, this meta-analysis also has some limitations which should be considered when interpreting its results and warrants a discussion. Firstly, all of the studies included were non-randomized, retrospective trials, which inevitably add a degree of selection bias to the results and can lead to over/under estimation of the measured effect. Since factors such as tumor location, extent of liver cirrhosis and tumor size are important determinants of outcome, we matched the two groups based on these important factors to eliminate bias and improve the validity of our results<sup>[53]</sup>.

Secondly, we observed some heterogeneity in certain outcome measures. This might be explained by differences in surgical techniques, retrospective nature of the studies, and limited blinded outcome assessment in some of the trials. However investigation of heterogeneity using meta-regression was not possible due to small number of studies.

Thirdly, there was inconsistency in the definition of some outcomes in different studies, making it difficult

to pool the results together. Using standardized guidelines to report outcomes can potentially overcome this problem and would allow more studies to be included in meta-analyses, leading to more reliable conclusions.

Finally, it is important to note that surgeons' experience and volume of cases operated in a particular hospital may affect these outcome measures tremendously. Unfortunately, none of the studies included in this analysis provided details of these factors and therefore, we were unable to assess the effect in such settings. Future trials should carefully consider such stratification while designing their studies and interpreting their data.

In conclusion, the results of this comprehensive, high-quality up to date meta-analysis indicate that LLR is feasible and safe for the treatment of HCC. LLR should be performed in selected patients by expert surgeons in high volume centers. Further research by undertaking well designed, prospective randomized controlled trials can confirm the advantages of LLR for the management of HCC.

## COMMENTS

### Background

Laparoscopic liver resection (LLR) is an attractive treatment for liver benign tumor comparing with open liver resection (OLR) because of good cosmetic results and less trauma, but its role remains controversial when LLR is applied to hepatocellular carcinoma (HCC) because of a lack of high-quality randomized controlled trials in this area.

### Research frontiers

In order to compare the safety and effectiveness between the LLR and OLR, the meta-analysis was used to evaluate operative, postoperative and oncologic outcomes of these two surgical methods for HCC in this study.

### Innovations and breakthroughs

Although previous meta-analysis had compared the outcomes of these two surgical methods, which included a limited number of studies with fewer cases, many high-quality studies with more participants have been published since. Therefore, it is important to provide an up to date analysis of these outcomes. This meta-analysis reported that LLR had significant advantage over OLR in terms of intraoperative blood loss, blood transfusions requirement, hospital stay, postoperative ascites and liver failure compared with OLR for HCC. Meanwhile, incidences of operation time, bile leakage, postoperative bleeding, pulmonary complications, intra-abdominal abscess, mortality, positive resection margins and tumor recurrence were similar between LLR and OLR.

### Applications

The results of this meta-analysis show that LLR appears to be a safe and feasible option for HCC in selected patients based on current evidence. Therefore, LLR may be an alternative treatment for HCC. However, the experience of the operating surgeon and volume of operated cases in a particular centre has to be taken into consideration.

### Terminology

HCC is the fifth most common primary cancer worldwide with high malignant potential.

### Peer review

The paper investigates the safety and effectiveness of LLR on HCC. The statistical analysis used in the study is appropriate and the results suggest that there are some advantages in LLR. This paper should be of interest to surgeons in the field of the hepato-biliary-pancreatic surgery worldwide.

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