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Original Article

The safety and efficacy of laparoscopic and open hepatectomy in hepatocellular carcinoma patients with liver cirrhosis: a systematic review

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Abstract: Background: Compared with open hepatectomy (OH), laparoscopic hepatectomy (LH) had better short-term outcomes in normal hepatocellular carcinoma (HCC) patients. Since liver cirrhosis is the major risk of HCC, serve postoperative complications can be observed after LH in HCC patients with cirrhosis. We conducted this systematic review to analysis the safety and the efficiency of LH in HCC patients with liver cirrhosis. Methods: MEDLINE, EMBASE, the Cochrane Library, the Chinese National Knowledge Infrastructure database, and clinical trial registries were searched through March 2015. Risk ratios (RRs), weigh mean difference (WMD) and 95% confidence intervals (CIs) were calculated. Results: The analysis included 7 retrospective trials, altogether involving 828 patients. Patients in LH group had wider tumor margin (WMD = 0.12, 95% CI 0.04 to 0.21, *P* = 0.003), less blood loss (WMD = -157.25, 95% CI -295.05 to -19.45, *P* = 0.03), less blood transfusion (RR = 0.41, 95% CI 0.22 to 0.74, *P* = 0.004), less postoperative mobility (RR = 0.48, 95% CI 0.35 to 0.66, *P*<0.001) and less hospital stay (WMD = -4.11, 95% CI -6.23 to -1.98, *P*<0.001). Overall survival (OS) and disease free survival (DFS) were similar between 2 groups, except LH had a better 5-year survival rate (RR = 1.28, 95% CI 1.01 to 1.62, *P* = 0.04). Conclusion: In HCC patients with liver cirrhosis, LH have short-term outcomes advantages of tumor margin, blood loss, blood transfusion, postoperative mobility, and hospital stay. OS and DFS were similar between LH and OH. LH is safe in HCC patients with liver cirrhosis.

Keywords: Hepatocellular carcinoma, meta-analysis, laparoscopic, open hepatectomy, surgery

Introduction

Hepatocellular carcinoma (HCC) is the sixth most common type of cancer worldwide and the third leading cause of cancer-related death [1]. Increasing incidence of HCC associated with the development of cirrhosis [2]. Nearly 80% of HCC develop the tumor from such chronic liver diseases [3]. Among varies therapies for HCC patients, hepatectomy is the most curative therapy [3, 4]. Traditional surgical therapy is open hepatectomy (OH). Since the first laparoscopic use was reported in 1987 as laparoscopic cholecystectomy, laparoscopic surgery has been increasingly popular in all fields of general surgery [5].

For cirrhotic HCC patients, more postoperative adverse events (ADEs) would develop including infections, pleural effusion, or liver failure [6, 7]. Compared with OH, laparoscopic hepatectomy (LH) seems to get decreased postoperative pain, less blood loss and shorter hospital stay [8-12]. No significant difference in survival outcomes is presented between LH and OH in normal HCC patients [13-19]. However, with the difficulties in techniques and bleeding control, LH should be carefully chosen for patients with liver cirrhosis. For liver cirrhosis patients, hepatectomy may lead to several serious ADEs related to poor hepatic function [20, 21].

At present, several trials studied the safety and efficiency of LH comparing OH in patients with liver cirrhosis [7, 8, 22-24]. Meanwhile, a recent meta-analysis figured out that LH is safe and would improve outcomes [25]. Nevertheless, long-term outcomes were not clearly described and sensitivity analysis was not conducted.

In order to clearly described the short-/long-term outcomes in HCC patients with liver cirrhosis in LH and OH. We conducted this systematic review to evaluate the safety and efficacy of LH comparing OH.

Methods

This meta-analysis was conducted according to PRISMA guidelines (Checklist S1).

Literature search strategy

Systematic searches of the following electronic databases were conducted through March 2015 without language restrictions: MEDLINE, EMBASE, the Cochrane Library, and the Chinese National Knowledge Infrastructure (CNKI). We also searched five primary clinical trial registries recognized by the WHO International Clinical Trial Registry Platform: Australia and New Zealand Clinical Trial Registry (www.anzctr.org.au/), Chinese Clinical Trial Register (www.chictr.org), ISRCTN (www.controlled-trials.com/isrctn/), U.S. National Institutes of Health Clinical Trials Database (www.clinicaltrials.gov/), and Clinical Trials Registry-India (www.ctri.in:8080/Clinicaltrials/index.jsp) [26, 27]. Eligible studies were identified using any of the following index words: hepatocellular carcinoma or HCC or hepatic tumor or liver tumor or hepatic cancer or liver cancer; open surgery or open hepatectomy or open liver resection or traditional surgery or traditional hepatectomy or traditional liver resection; laparoscopic surgery or laparoscopic hepatectomy or laparoscopic liver resection.

Relevant reviews and meta-analyses comparing OH and LH for HCC were manually examined in order to identify additional eligible studies.

Inclusion criteria

In order to be concluded, studies had to satisfy the following criteria: (1) the trial should conducted two kinds of hepatectomy for HCC patients which is LH and OH; (2) HCC patients in the trials should have liver cirrhosis (New European classification system was used to diagnose liver cirrhosis [28]); (3) the trial reported data on short-/long-term outcomes; (4) the trial reported sufficient data to allow calculation of risk ratios (RRs) or weigh mean difference (WMD) with 95% confidence intervals (CIs); (5) retrospective studies.

Types of outcome measures

Intraoperative outcomes were tumor margin, operative time, blood loss, and blood transfusion. Short-term outcomes were postoperative morbility and mortality, curative resection, and length of hospital stay. Long-term outcomes concluded overall survival and disease free survival.

Data extraction

Two reviewers (J.C. and T.B.) independently read potentially eligible studies and extracted the following data respectively: authors, publication year, study design, patient characteristics, and outcomes. Any disagreements were arbitrated by a third reviewer (L.Q.L.) [27].

Quality assessment

Two reviewers (J.C. and T.B.) independently assess the risk for every included trials using modified criteria suggested by the Newcastle-Ottawa quality assessment tool (NOS) [29]. Sensitivity analysis is conducted by omitting the biggest weigh trials.

Statistical analysis

All statistical calculations were performed using Review Manager 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.). Mantel-Haenszel RRs with corresponding 95% CIs were calculated for dichotomous, while WMD with 95% CIs were calculated for continuous variable. Medians were converted to means using the technique described by Hozo et al. [30]. *P* value of < 0.05 was considered statically significant.

Meta-analysis was carried out on an 'intention-to-treat' basis which means all patients were evaluated according to their initial group allocation. Patients with unknown endpoints were considered to have died or lost to follow up. Heterogeneity was assessed by calculating I^2. When I^2 was less than 50%, we used a fixed-effects model for meta-analysis; when I^2 was more than 50%, a random-effects model was used. Homogeneity between trials was assessed using the χ^2 test with the significance threshold set at $P > 0.1$. Moreover, $I^2 < 25\%$ was defined to represent low heterogeneity, moderate heterogeneity was defined as a value between 25 and 50%, and $I^2 > 50\%$ was of a

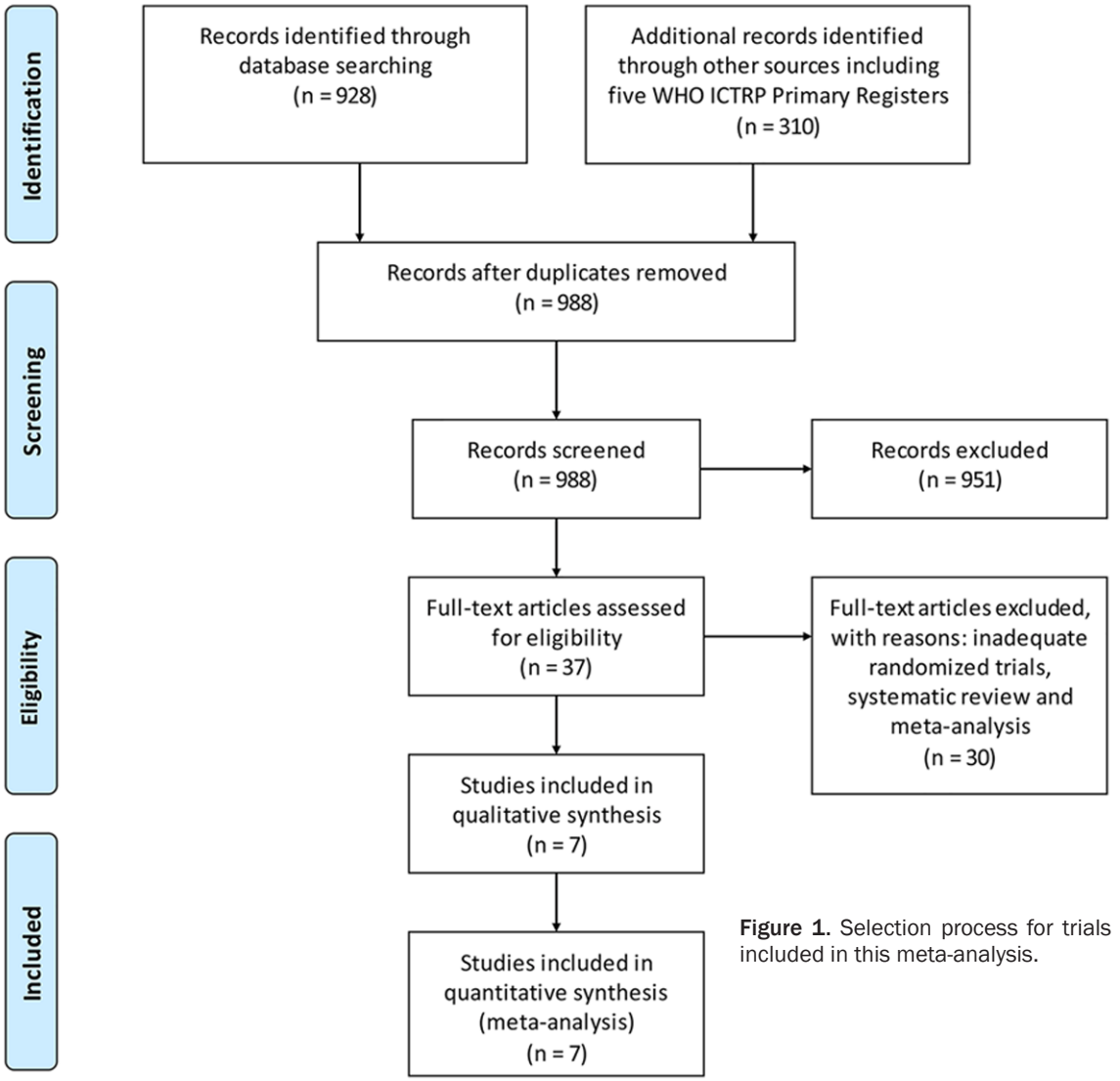

Figure 1. Selection process for trials included in this meta-analysis.

high heterogeneity [31]. Subgroup was conducted depending on retrospective and retrospective matched trials. To evaluate the robustness of meta-analysis results, we repeated all meta-analyses using the other type of model (fixed- or random-effects); if both models gave the same meta-analysis results, we judged the result to be reliable.

Results

Characteristics of the included studies

After searching the database and trial registries, 928 published trials and 310 registered studies were initially presented (**Figure 1**). We removed 250 duplicates, and left with 988 trials (887 published and 101 registered trials), which were potentially eligible. With the screening of the titles and abstracts, 856 published trials and 101 registered studies were excluded because the design or outcomes data were not satisfied with the inclusion criteria (not related with our topic). The remaining 37 published trials were fully read, and 30 published trials were excluded. It is because the trials were systematic reviews, or meta-analyses. Finally, 7 trials involving 828 patients were included (Belli et al. [22], Cheung et al. [23], Kanazawa et al. [7], Memeo et al. [24], Siniscalchi et al. [32], Truant et al. [8] and Yamashita et al. [33]). In 828 patients, 281 patients were with LH, another 547 patients were under OH. The number of HCC patients ranged from 56 to 179. A total of 605 patients were men. All HCC patients had liver cirrhosis. Conversion rate of LH to OH

Table 1. Characteristics of included studies comparing LH and OH to treat HCC patients with liver cirrhosis

Study	Study design	No. of patients		Mean age, y		Child-Pugh (A/B)		Convention to open, (n, %)
		LH (M, %)	OH (M, %)	LH	OH	LH	OH	
Belli *et al.*	R	54 (31, 57.4%)	125 (78, 62.4%)	63.3±6.1*	61.5±7.8	49/5	117/8	4, 7.0%
Cheung *et al.*	RM	32 (22, 68.8%)	64 (50, 78.1%)	59.5 (39-79)**	61 (29-82)	32/0	62/4	3, 18.8%
Kanazawa *et al.*	R	28 (16, 57.1%)	28 (17, 60.7%)	69 (40-85)	68 (29-82)	20/8	21/7	3, 10.7%
Memeo *et al.*	RM	45 (37, 82.2%)	45 (35, 77.8%)	60 (43-80)	62 (34-75)	43/2	44/1	NA
Siniscalchi *et al.*	R	23 (15, 65.2%)	133 (104. 78.2%)	57.9 (30-73)	63.3 (41-77)	NA	NA	NA
Truant *et al.*	RM	36 (31, 86.1%)	53 (47, 88.7%)	60.6±10.2	63.3±7.6	36/0	53/0	7, 19.4%
Yamashita *et al.*	R	63 (48, 76.2%)	99 (74, 74.7%)	67.5±9.5	65.2±10.1	59/4	96/3	NA

Abbreviations: LH = laparoscopic hepatectomy; OH = open hepatectomy; R = retrospective study; RM = retrospective matching study; NA = not available. *Mean ± SD. **Median (range).

Table 2. Intraoperative data and surgical results comparing LH and OH to treat HCC patients with liver cirrhosis

Outcomes / Study	Tumor margin (cm)		Operative time (min)		Blood loss (ml)		Blood transfusion (n, %)	
	LH	OH	LH	OH	LH	OH	LH	OH
Belli *et al.*	NA	NA	167±36*	185±61.3	297±134	580±120	6 (11.1%)	32 (25.6%)
Cheung *et al.*	0.95 (0-3)	0.8 (0-3.5)	232.5 (70-450)**	204.5 (67-705)	150 (10-1460)	300 (50-2700)	0 (0.0%)	3 (4.7%)
Kanazawa *et al.*	0.5 (0-1.8)	0.3 (0-1.5)	228 (69-515)	236 (95-376)	88 (0-900)	505 (80-1150)	0 (0.0%)	4 (14.3%)
Memeo *et al.*	1 (0-5)	0.6 (0-5.8)	140 (45-360)	180 (90-360)	200 (0-1500)	200 (0-2000)	0 (0.0%)	0 (0.0%)
Siniscalchi *et al.*	NA	NA	175±91	165±80	NA	NA	0 (0.0%)	36 (27.4%)
Truant *et al.*	0.95±0.28	0.86±0.17	193.4±104	215.8±88.7	452.2±442	447.2±449.8	1 (2.8%)	2 (3.8%)
Yamashita *et al.*	0.74±0.87	0.58±0.69	299.5±127.6	287.4±83.2	436.6±320.7	455.7±741.9	4 (6.3%)	2 (2.0%)

Abbreviations: LH = laparoscopic hepatectomy; OH = open hepatectomy; HCC = hepatocellular carcinoma; NA = not available. *Mean ± SD. **Median (range).

ranged 7.0% to 19.4%. The characteristics of the included studies are shown in **Table 1**.

Quality assessment results were presented as Supplementary Table 1. NOS was used to assess the risk of bias for quality assessment of non-randomized studies. Overall quality of the included studies was of good quality that the NOS scores varied between 7 and 8 out of 9.

Therapy outcomes

Intraoperative outcomes: During surgery, tumor margin was significantly wider in LH than OH (WMD = 0.12, 95% CI 0.04 to 0.21, P = 0.002, I^2 = 0%). Operating time seems to be similar between LH and OH (WMD = -10.36, 95% CI -26.21 to 5.49, P = 0.20, I^2 = 36%). Patients in LH get less blood loss (WMD = -157.25, 95% CI -295.05 to -19.45, P = 0.03, I^2 = 84%) and blood transfusion (RR = 0.41, 95% CI 0.22 to 0.74, P = 0.004, I^2 = 40%) than patients in OH. (**Tables 2** and **3**; Supplementary Figure 1).

Postoperative outcomes: Postoperative mobility was significantly decreased in LH (RR = 0.48, 95% CI 0.35 to 0.66, P<0.0001, I^2 = 40%. Postoperative mortality was similar between LH and OH (RR = 0.72, 95% CI 0.28 to 1.81, P = 0.48, I^2 = 19%). Curative resection in LH was no significantly better than patients in OH (RR = 1.15, 95% CI 0.90 to 1.47, P = 0.26, I^2 = 90%). Patients in OH had significantly longer hospital stay than LH (WMD = -4.11, 95% CI -6.23 to -1.98, P = 0.0002, I^2 = 82%) (**Tables 3** and **4**; Supplementary Figure 2).

Belli et al. [22] reported 8 patients suffered postoperative ascites, 2 patients developed postoperative haemorrhage, 1 patient had infectious and 1 patient had cardiovascular complications, and one patient had an abdominal wall complication. In Cheung et al. [23], 2 patients suffered chest infections, 11 patients had pleural effusion, and 1 patient suffered subphrenic abscess. In Yamashita et al. [33], 3 patients suffered bile leakage, 7 patients had ascites, and 11 patients had infections.

Overall survival

Patients in LH got similar 1-year survival (RR = 1.13, 95% CI 0.96 to 1.34, P = 0.15, I^2 = 83%) and 3-year survival (RR = 1.06, 95% CI 0.73 to

Table 3. Subgroup analysis of outcomes depending on retrospective studies and retrospective match studies

Comparison	Pooled estimates	95% CI	*P*	I^2
Tumor margin	WMD 0.12	0.04-0.21	0.03	28%
Studies with RM	WMD 0.10	0.01-0.20	0.06	7%
Studies without RM	WMD 0.18	0.02-0.35	0.03	0%
Omit Truant *et al.*	WMD 0.19	0.05-0.33	0.01	0%
Operating time	WMD -10.36	-26.21-5.49	0.20	36%
Studies with RM	WMD -15.95	-52.86-20.96	0.40	60%
Studies without RM	WMD -8.06	-23.80-7.69	0.32	17%
Omit Belli *et al*.	WMD -6.12	-27.66-15.43	0.58	42%
Blood loss	WMD -157.25	-295.05-19.45	0.03	84%
Studies with RM	WMD -41.11	-151.95-69.74	0.47	0%
Studies without RM	WMD -250.12	-420.36-79.89	0.004	85%
Omit Belli *et al.*	WMD -121.63	-308.77-65.50	0.20	83%
Blood transfusion	RR 0.41	0.22-0.74	0.004	40%
Studies with RM	RR 0.47	0.08-2.86	0.41	0%
Studies without RM	RR 0.45	0.10-1.98	0.29	63%
Omit Belli *et al.*	RR 0.38	0.16-0.93	0.20	83%
Postoperative morbility	RR 0.48	0.35-0.66	< 0.001	40%
Studies with RM	RR 0.52	0.33-0.81	0.004	0%
Studies without RM	RR 0.45	0.17-1.16	0.10	71%
Omit Belli *et al.*	RR 0.48	0.26-0.86	0.01	52%
Death	RR 0.72	0.28-1.81	0.48	19%
Studies with RM	RR 1.10	0.35-3.49	0.87	47%
Studies without RM	RR 0.36	0.07-1.98	0.24	0%
Omit Truant *et al.*	RR 0.96	0.34-2.70	0.68	36%
Curative resection	RR 1.15	0.90-1.47	0.26	90%
Studies with RM	RR 1.13	0.98-1.30	0.08	NA
Studies without RM	RR 1.17	0.72-1.91	0.52	95%
Omit Siniscalchi *et al.*	RR 1.25	0.99-1.58	0.06	75%
Length of hospital stay	WMD -4.11	-6.23-1.98	< 0.001	82%
Studies with RM	WMD -3.11	-4.42-1.80	< 0.001	0%
Studies without RM	WMD -5.23	-9.70-0.76	0.02	88%
Omit Belli *et al.*	WMD -4.78	-6.68-2.88	< 0.001	50%

Abbreviations: LH = laparoscopic hepatectomy; OH = open hepatectomy; RM = retrospective matching study; RR = risk ratio; WMD = weigh mean difference CI = confidence interval.

1.55, P = 0.75, I^2 = 85%) as patients in OH. However, 5-year survival in LH seemed to be significantly higher than OH (RR = 1.28, 95% CI 1.01 to 1.62, P = 0.04, I^2 = 62%) (**Figure 2**).

Disease-free survival

Patients in LH got similar results as OH no matter 1-year disease free survival (RR = 1.21, 95% CI 0.99 to 1.48, P = 0.07, I^2 = 61%), 3-year disease free survival (RR = 1.19, 95% CI 0.85 to 1.68, P = 0.31, I^2 = 62%) or 5-year disease free survival (RR = 0.97, 95% CI 0.75 to 1.25, P = 0.81, I^2 = 0%) (**Figure 3**).

Subgroup analysis

According to the trials were retrospective or retrospective matched studies, subgroup analysis were conducted. Different results were found in blood loss, blood transfusion, and postoperative morbility (**Table 3**).

Sensitivity analysis

Omitting the trial which has the biggest weigh (**Table 3**). Different results were found in blood loss.

Discussion

LH has been proved to have better short-term outcomes and have similar long-term outcomes as OH in normal HCC patients [14, 17, 18, 34-38]. Initially, ascribe to the difficulties of technique, LH should be carefully for liver cirrhosis patients [15, 39]. With the huge development of laparoscopic technique and equipment, LH seemed to provide reduced surgical trauma comparing with OH in HCC patients with cirrhotic liver [8, 23, 24, 32]. Our systematic reviews suggest LH could perform better short-term outcomes, and may prolong survival benefit.

For the intraoperative outcomes in HCC patients with liver cirrhosis, Patients in LH group have significantly wide tumor margin, less blood loss and blood transfusion. Meanwhile, operating time was similar between LH and OH. This result may associate with the study design. Since the study design is not randomized, selection bias may be presented.

Table 4. Short-term outcomes comparing LH and OH to treat HCC patients with liver cirrhosis

Study \ Outcomes	Postoperative morbility (n, %)		Postoperative mortality (n, %)		Curative resection (n, %)		Length of hospital stay (d)	
	LH	OH	LH	OH	LH	OH	LH	OH
Belli *et al.*	10 (18.5%)	45 (36.0%)	1 (1.9%)	5 (4.0%)	45 (83.3%)	74 (59.2%)	8.4±2.5*	9.2±3.1
Cheung *et al.*	2 (6.3%)	12 (18.8%)	0 (0.0%)	1 (1.6%)	NA	NA	4 (2-16)**	7 (4-42)
Kanazawa *et al.*	3 (10.7%)	20 (71.4%)	0 (0.0%)	0 (0.0%)	NA	NA	10 (6-25)	19 (8-49)
Memeo *et al.*	9 (20.0%)	20 (44.4%)	5 (11.1%) 1 m	1 (2.2%) 1 m	43 (95.0%)	38 (85.0%)	7 (0-69)	12 (0-34)
Siniscalchi *et al.*	NA	NA	0 (0.0%)	10 (7.5%)	22 (95.6%)	129 (97.0%)	7.61 (3-29)	14.38 (4-166)
Truant *et al.*	9 (25.0%)	19 (35.8%)	0 (0.0%)	4 (7.5%)	NA	NA	6.5±2.7	9.5±4.8
Yamashita *et al.*	6 (9.5%)	9 (9.0%)	0 (0.0%)	0 (0.0%)	NA	NA	10.3±4.4	16.2±13.4

Abbreviations: LH = laparoscopic hepatectomy; OH = open hepatectomy; HCC = hepatocellular carcinoma; NA = not available. *Mean ± SD. **Median (range).

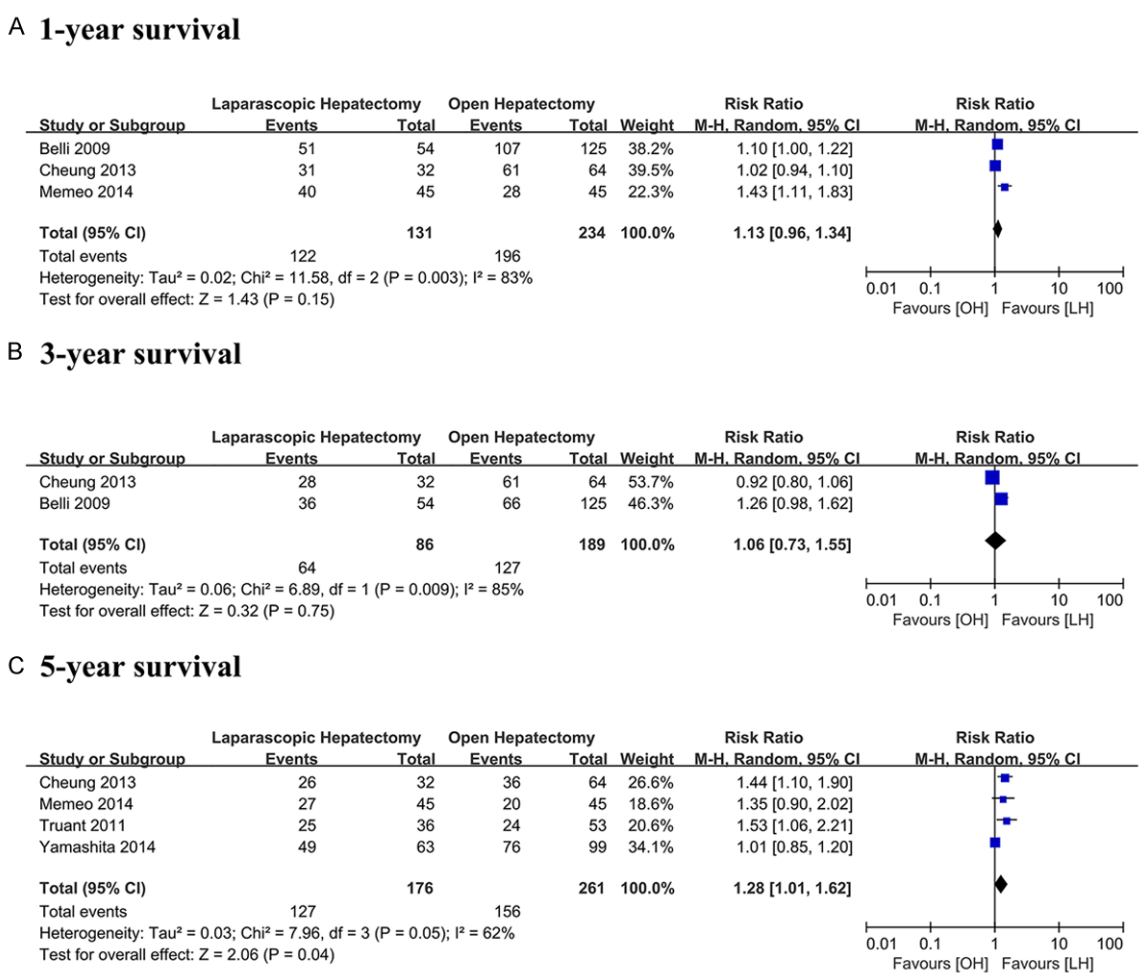

Figure 2. Meta-analysis of data on overall survival in LH and OH.

Surgeons would like to perform preoperative evaluation; patients with huge HCC, higher degree of cirrhosis, improper tumor location that had high risk of blood loss and life threaten were inclined to perform OH. For LH, patients with solitary lesion, 5 cm or less, located in liver segment 2-6 would be suitable [40]. Patients in LH group suffer less postoperative morbility, and shorter hospital stay than OH. Curative resection and postoperative mortality was similar between OH and LH. LH has the advantage of reduction of surgery-induced injuries [36, 41], thus patients are more likely to have less postoperative complications and to recover

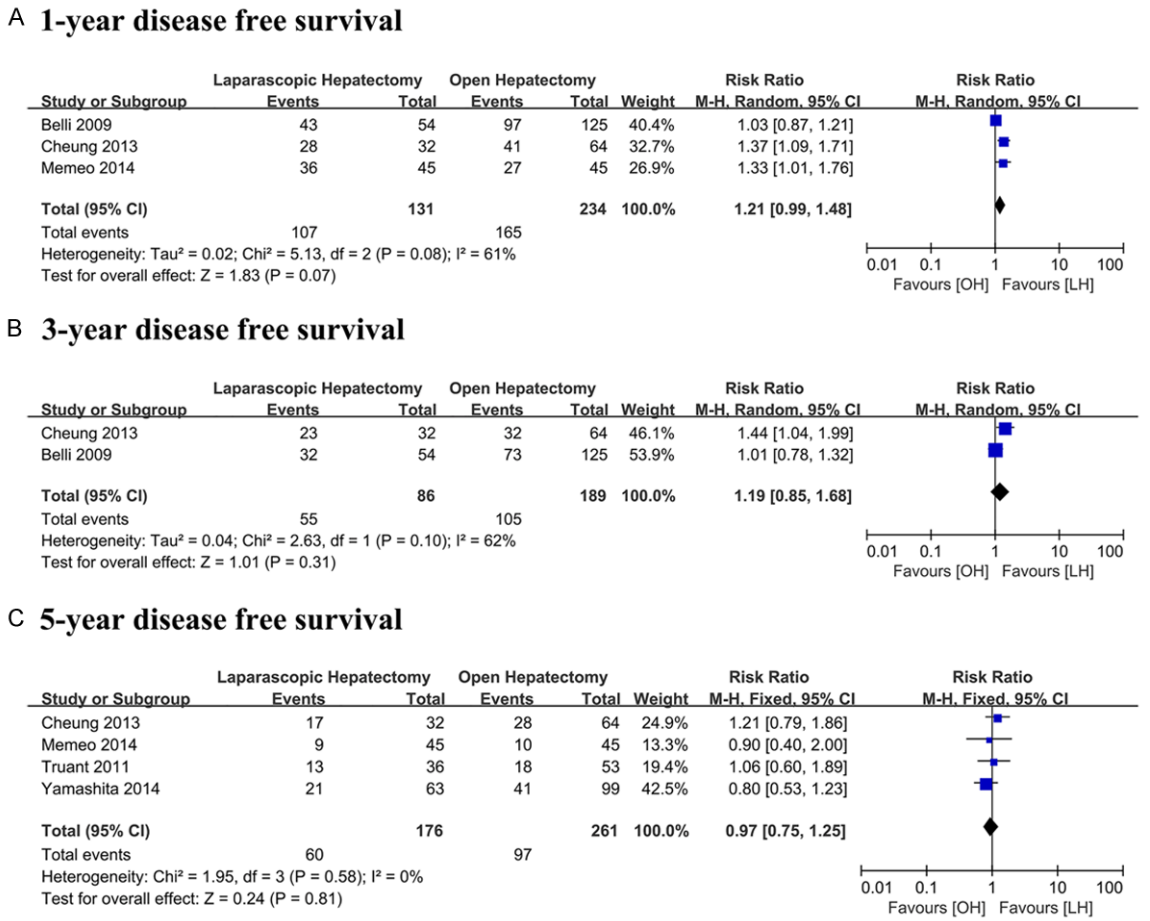

Figure 3. Meta-analysis of data on disease free survival in LH and OH.

soon. Compared with OH, LH has other advantages in several studies. LH make subsequent surgical procedures easier which could reduce the adhesion [42, 43]. Also, LH used as repeat operation could also perform better short-term outcomes [12, 44].

Survival benefit was also familiar between LH and OH, except 5-year survival (RR = 1.26, 95% CI 1.01 to 1.62, P = 0.04, I^2 = 62%). We conducted sensitivity analysis, it showed LH had better 5-year survival (RR = 1.44, 95% CI 1.18 to 1.76, P < 0.001, I^2 = 0%). It may associated with laparoscopic equipment which make us more easily detect micro-vascular invasion. Integrity resection of micro invasion may prolong the survival. Moreover, in HCC patients under LH, the locations of tumors were more easier than patients under OH. Thus sometimes it would be more curative. But a high heterogeneity was observed, and limited sample size, the results still need to be confirmed. If the original data could be collected and analyzed hazard ratio could be calculated, the result would be more convincible. Thus the results need further certifications.

Compared with normal HCC patients, patients with liver cirrhosis have more serious postoperative ADEs. In our included trials, several serious ADEs were reported above. In Cheung et al. [23], Truant et al. [8], and Kanazawa et al. [33], Clavien-Dindo score system [45] was performed to evaluate postoperative complications between 2 groups. However, no significant difference was found. We often concern gas embolization and blood controlling in LH. The risk of gas embolism due to lesions of the hepatic veins has been suggested during parenchymal transection. However, the incidence of this ADE is relatively low [46, 47]. The main technical challenge of LH remains intra-

operative bleeding when parenchymal transection happens. These were mainly related to hepatic veins injuries [48-50]. In our systematic review, the rate of convention to OH is from 7% to 19.4%. Main reasons are technically related issues (difficult exposure, or fragile tumor with risk of rupture) and difficulties of bleeding control [50].

A recent meta-analysis [25] is performed in HCC patients with liver cirrhosis between LH and OH. Several results were different from us because some points in their review may be improper. In Twaij et al. [25], standard mean difference (WMD) was performed to calculate continues variable. However, SMD is recommended when different easurement scales in the studies are used to reflect the outcomes [31]. Here WMD is more suitable which studies use the same scale to report the outcomes. In our study, we use WMD to calculate the variables and add several new trials. In addition, we performed sensitivity analysis to test the robustness of our results which showed our results was reliable. In their review, no details were about survival benefits. As for the original data was not available, we only calculate the given data, and showed LH had similar survival benefit as OH. Another systematic review comparing LH and OH in normal HCC patients also showed similar results as ours like the outcome of postoperative morbility and blood loss [51]. This global analysis not only testify the safety and efficiency of LH in normal HCC patients but also convinced our results in liver cirrhosis HCC patietns.

Sensitivity analysis result (omitting Belli et al. [22]) was different on the outcome of blood transfusion and 1-year disease free survival. This may cause by patient compose in Belli et al. [22]. In Belli et al. [22], patients were without serve portal hypertension, which may result in better liver function inefficiency endurance. It could explain why only 7% convention rate was observed in their study. And Belli et al. [22]'s study had the largest sample size, its results would affect the final results a lot.

The biggest limitation in our systematic review is the included trials were retrospective, non-randomized studies which would increase the selection bias. Moreover, the sample size is small which decrease the reliability of the final results. We select trials carefully with strict include and exclude criteria. Newcastle-Ottawa quality assessment tool [29] was performed to evaluate the quality which our final quality is high. In addition, subgroup analysis was performed to list the detail data of our review. Sensitivity analysis was conducted to conformed the reliability of the pooled estimates in the meta-analysis. And the basic characteristics between 2 groups was almost no significantly different. Thus, the selection bias would play little role in our final results. With the limitations shown in our systematic review, further large sample size, well designed randomized or controlled trials should perform.

In conclusion, LH may provide better intraoperative and short-term outcomes than OH in HCC patients with liver cirrhosis. However, no significant survival benefit was shown between them. But a tendency to have better survival benefit still could be found of LH in HCC patients with liver cirrhosis.

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Disclosure of conflict of interest

None.

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Checklist S1. PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract:			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8

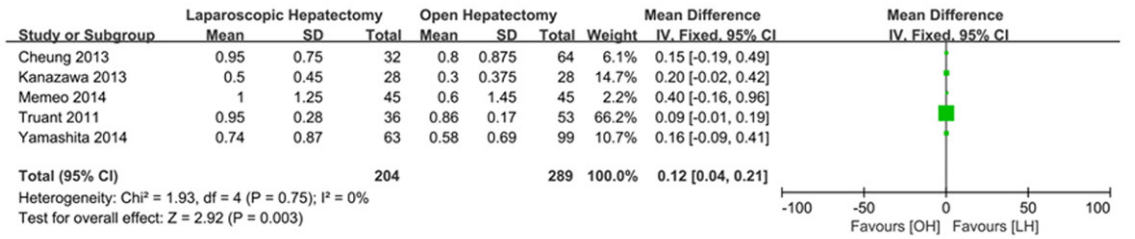
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9-10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10-11
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-11
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097. For more information, visit: www.prisma-statement.org.

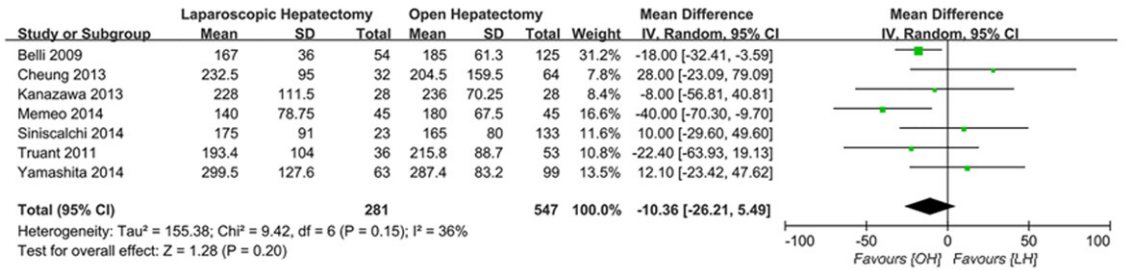
Supplementary Table 1. Risk of bias of included trials

Study	Representative of exposed cohort	Selection of non-exposed cohort	Exposure	Outcome of interest not present at start	Comparability of LH *vs.* OH	Assessment of outcome	Follow up	Adequacy of follow-up/missing data	Score
Belli *et al.*	Truly representative	Same	Surgical records	Yes	Restrictions in exophytic or subcapsular tumors, not matched	Record linkage	3 yr	Unclear	7
Cheung *et al.*	Truly representative	Same	Surgical records	Yes	No restrictions, matched	Record linkage	5 yr	None	8
Kanazawa *et al.*	Truly representative	Same	Surgical records	Yes	No restrictions, not matched	Record linkage	5 yr	Unclear	7
Memeo *et al.*	Truly representative	Same	Surgical records	Yes	No restrictions, matched	Record linkage	10 yr	Unclear	7
Siniscalchi *et al.*	Truly representative	Same	Surgical records	Yes	Restrictions in tumors diameters and should located in the anterior or lateral segments II-VI, not matched	Record linkage	7 d	Clear	7
Truant *et al.*	Truly representative	Same	Surgical records	Yes	Restrictions in subcapsular tumors located in the anterior or lateral segments II-VI, matched	Record linkage	5 yr	None	7
Yamashita *et al.*	Truly representative	Same	Surgical records	Yes	No restrictions, not matched	Record linkage	5 yr	Unclear	7

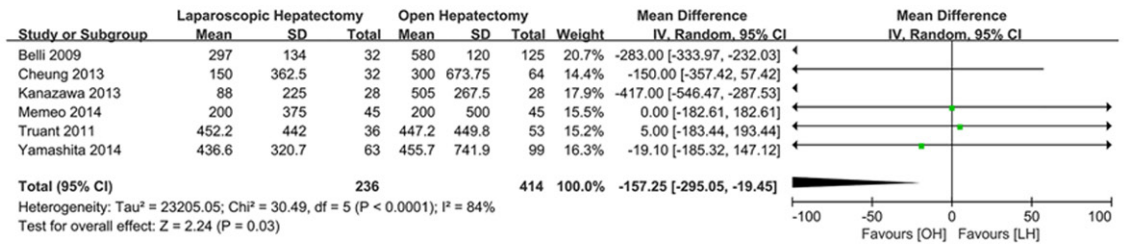
A **Tumor margin**



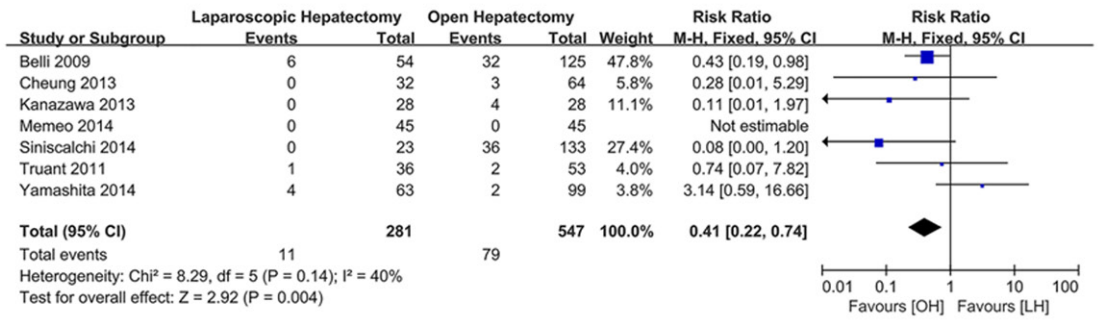
B **Operative time**



C **Blood loss**

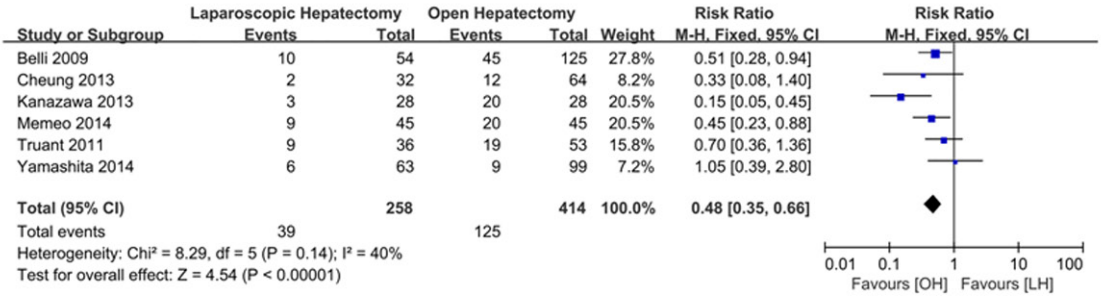


D **Blood transfusion**

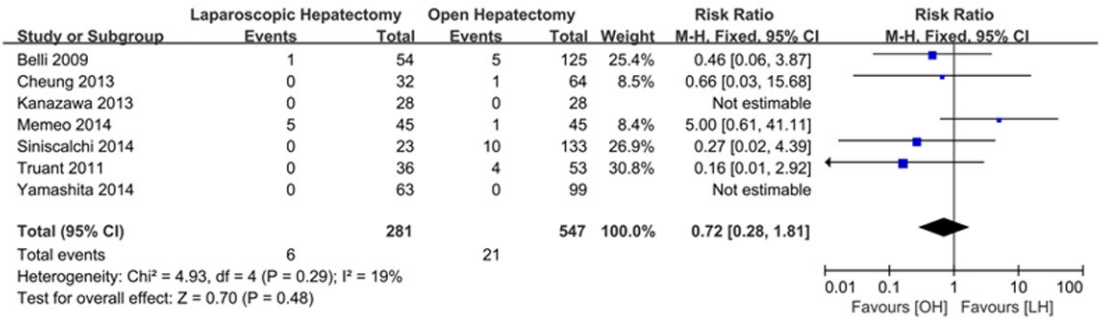


Supplementary Figure 1. Meta-analysis of data on opeartion outcomes in LH and OH.

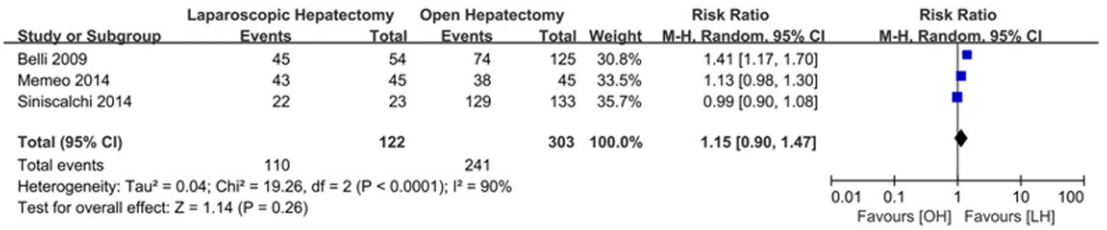
A **Postoperative mobility**



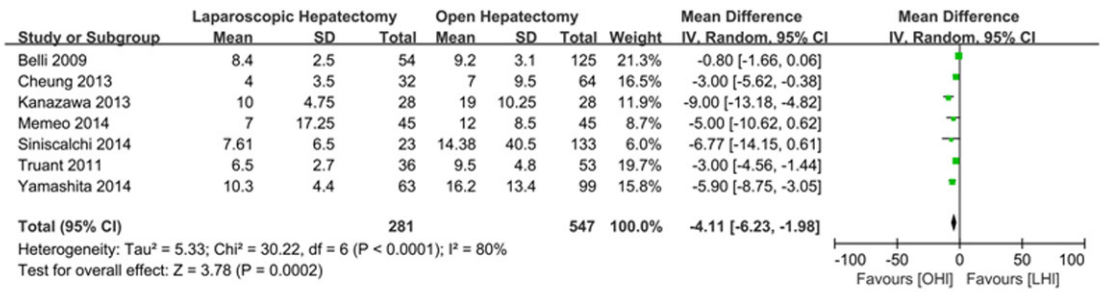
B **Postoperative mortality**



C **Curative resection**



D **Length of hospital stay**



Supplementary Figure 2. Meta-analysis of data on short-term outcomes in LH and OH.