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# Systematic review and meta-analysis of laparoscopic versus open repeat hepatectomy for recurrent liver cancer

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ABSTRACT

*Background:* Repeat hepatectomy plays a key role in recurrent hepatic tumors. However, it is still unknown whether laparoscopic hepatectomy is suitable for recurrent liver cancers. The aim of this meta-analysis is to evaluate the efficacy and feasibility of laparoscopic repeat hepatectomy (LRH) compared with open repeat hepatectomy (ORH).

*Methods:* Several databases, including Web of Science, PubMed, The Cochrane Library and Ovid, were retrieved from date of inception to 31st March 2018. All articles comparing LRH and ORH were identified. Tumor characteristics and perioperative outcomes including resection type, operation time, blood loss, transfusion, complications and hospital stay were evaluated. Data were extracted and calculated using random- or fixed-effect models.

*Results:* A total of seven non-randomized observational clinical articles including 443 patients were analyzed. LRH was associated with significantly lower blood loss (WMD = −389.09, 95% CI -628.34 to −149.84, $P = 0.001$), transfusion (OR 0.16, 95% CI 0.03–0.74, $P = 0.019$) as well as limited hospital stay (WMD = −4.00, 95% CI -6.58 to −1.42, $P = 0.002$). No statistical difference was found in the field of tumor characteristics and other perioperative outcomes. In the sensitivity analysis of case-match studies, LRH was associated with significant limited hospital stay, but with significant longer operation time. There were 8 (1.8%, range 0–13.3%) cases of conversion in LRH group.

*Conclusions:* Based on the results of these limited data, LRH is as feasible and efficient as ORH by expert surgeons in selected patients, whose cancer is resectable at the time of surgery and who have Child-Pugh A or B cirrhosis.

## 1. Introduction

Hepatectomy is an effective treatment for live tumors, including hepatocellular carcinoma (HCC), intrahepatic cholangiocarcinoma and metastatic cancer. However, postoperative recurrence, which is reported 5-year recurrence rate of 50–70%, frequently undermines the long-term survival outcomes of hepatectomy [1,2]. Salvage treatment is often anticipated by surgeons [3]. Although recurrent liver tumors can be treated by various therapeutic modalities including repeated hepatectomy, transarterial chemoembolization (TACE) and radiofrequency ablation (RFA), liver re-resection is a potential curative therapy [4,5]. Comparing with initial resection, liver re-resection is generally more technically challenging due to deformation of the liver, changes in anatomical landmarks and postoperative adhesions [6].

Since the first successful laparoscopic liver resection (LLR) reported by Reich et al. [7] in 1991, LLR has gradually gained acceptance. Recently, laparoscopic hepatectomy has been increasingly adopted as a choice of treatment for HCC [8]. Additionally, several meta-analyses have proved that LLR offered some short-term advantages for liver cancer including lower blood loss and perioperative blood transfusions, fewer postoperative complications and shorter hospital stay without increasing operative time and mortality [9–11]. However, laparoscopic repeat hepatectomy (LRH) has not been widely adopted because of technical challenge for recurrent tumors in patients with a history of

*Abbreviations:* HCC, hepatocellular carcinoma; LRH, laparoscopic repeat hepatectomy; ORH, open repeat hepatectomy; TACE, transarterial chemoembolization; RFA, radiofrequency ablation; OCS, observational clinical study; RCT, randomized controlled trial; BMI, body mass index; NOS, Newcastle-Ottawa Scale; *Ph*, *P*-value of heterogeneity; SSI, surgical site infection; DFS, disease-free survival; OS, overall survival; LLR, laparoscopic liver resection

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liver resection. It is still unknown whether LRH is as feasible and safe as ORH for recurrent liver cancers, although several observational studies have reported LRH for rHCC [12–18]. Herein, we performed this meta-analysis in order to investigate whether LRH is feasible and safe for recurrent liver cancers.

## 2. Methods

### 2.1. Study selection

Several databases, including Web of Science, PubMed, The Cochrane Library and Ovid, were retrieved with the following combinations of search terms: "laparoscopic," "laparoscopic assisted," "minimally invasive," "repeat hepatectomy," "liver re-resection," "repeat liver resection," "liver surgery," "recurrent liver cancer," "recurrent hepatocellular carcinoma," "hepatic metastatic tumor". The search was updated to 31st March 2018. References of the eligible studies were manually retrieved in order to gain additional studies. PRISMA guideline was followed [19].

### 2.2. Inclusion and exclusion criteria

Each acquired study in this meta-analysis must satisfy the following standard: (1) clinical controlled articles of LRH and ORH including observational clinical studies (OCSs) or randomized controlled trials (RCTs); (2) at least one interest data should be reported; (3) if the same authors and/or institutions published more than one publication of the same databases, the study quality, publication year and sample size were considered, and only one article with high quality was selected. Exclusion criteria were as follows: (1) editorials, expert opinions, abstracts, letters, case reports and reviews without original data; (2) studies in non-English languages; (3) studies without available data.

### 2.3. Data extraction and quality assessment

All candidate articles were independently assessed and extracted by two authors. The following data were used: first author; year of publication; number of patients; gender and age of patients; body mass index (BMI); Child-Pugh grade; liver cirrhosis; previous hepatectomy; tumor characteristics and perioperative outcomes. Inconsistencies were resolved through discussion, or came to an agreement with a third reviewer. If means and standard deviations of continuous variable data were not provided by the selected study in this meta-analysis, the means and standard deviations were imputed from medians and ranges via the method reported by Hozo et al. [20]. Two reviewers independently assessed the quality of non-randomized studies using the Newcastle-Ottawa Scale (NOS), which was developed for non-randomized studies considered for systematic reviews and meta-analyses [21]. The total scaled scores (0–9 scores) contained three parts: including selection (0–4 scores), outcome assessment (0–3 scores) and comparability (0–2 scores). Jadad standards were used to evaluate the quality of RCTs [22]. The overall scores of Jadad standards range from 0 to 5.

### 2.4. Outcomes of interest

Outcomes of interest were separately extracted by us from the selected non-randomized articles: approach of primary surgery, tumor characteristics (pathological diagnosis, recurrent tumor location, tumor numbers, size of primary tumor, size of recurrent tumor and tumor of segment VII or VIII), intraoperative outcomes (operative time, type of resection, resection margin, intraoperative blood loss, transfusion and conversion rate) and post-operative outcomes (overall postoperative complications, bleeding, bile leakage, intra-abdominal effusion or abscess, delayed gastric emptying, wound infection, reoperation, mortality and length of hospital stay). In addition, the data of inpatient costs and long-term oncological parameters including tumor recurrence, disease-free survival (DFS) and overall survival (OS) were also extracted from the selected studies as soon so possible.

### 2.5. Statistical analysis

Data analysis was performed using Stata SE 12.0 software. $I^2$ statistics and chi-square Q test were used to identify the heterogeneity of the acquired data. A *P*h (*P*-value of heterogeneity) $< 0.10$ or $I^2 > 50\%$ indicated significant heterogeneity among the acquired data, and the random-effects model was adopted [23]. Otherwise, a fixed-effect model was used. Furthermore, sensitivity analyses according to the design of case match and non-case match studies were performed in order to minimize case selection bias. Exclusion method of sensitivity analysis was conducted, in order to assess any single study that may affect the pooled result. Publication bias was not performed due to the fact that less than 10 studies were included in this meta-analysis. A *P*-value less than 0.05 was considered to have statistical significance.

## 3. Results

A total of 638 published studies were initially found in the article review. The flow of reference selection was outlined in Fig. 1. Seven articles with 443 patients were included in the present meta-analysis, after meticulous inspection of the articles. There were 172 and 271 patients in the LRH and ORH groups, respectively. And four case-match studies [12–15] were found among the seven included studies. Therefore, sensitivity analysis according to the design of the included studies was performed, in order to find the potential advantages of the laparoscopic approach. The quality assessment scores and study characteristics were outlined in Table 1. In addition, characteristics of recurrent liver tumors in the selected articles were listed in Table 2. The results of the meta-analysis, which were pooled from eligible parameters, were listed in Table 3.

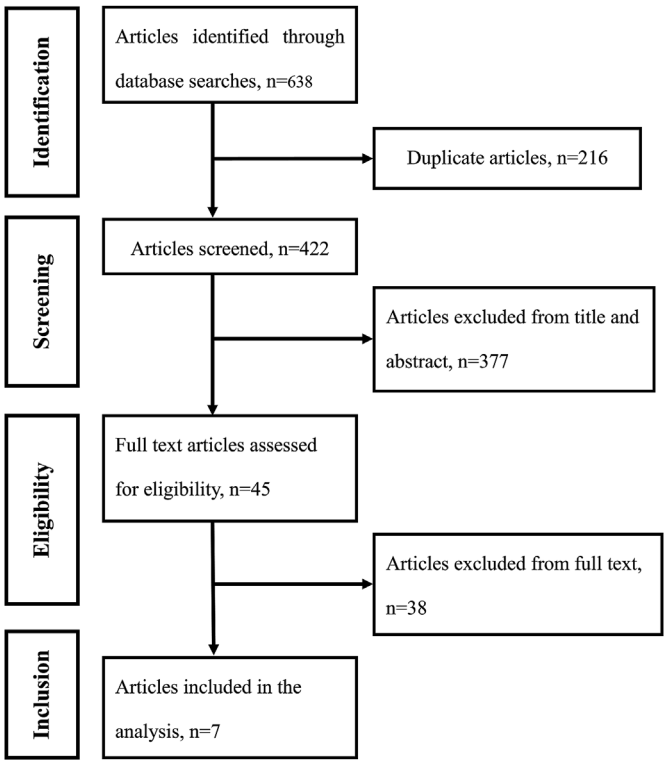


**Fig. 1.** Flow diagram depicting the process of identifying and selecting studies for inclusion.

**Table 1**
Characteristics of included studies.

| Authors | Year | Group | No.of patients | Gender (M/F) | Age (yrs) | BMI (kg/m$^2$) | Child-Pugh grade(A/B) | Liver cirrhosis (Yes/No) | Type of study | Quality scores |
|---|---|---|---|---|---|---|---|---|---|---|
| Chan et al. [12] | 2014 | LRH | 11 | 8/3 | 61 (43–80) | NA | NA | NA | Retrospective | 6 |
| | | ORH | 22 | 16/6 | 62(43–76) | NA | NA | NA | Matched | |
| Hallet et al. [13] | 2017 | LRH | 27 | 20/7 | 63.6 (59.0–70.9) | NA | NA | NA | Prospective Matched | 8 |
| | | ORH | 81 | 50/31 | 62.8 (57.5–70.3) | NA | NA | NA | | |
| Kanazawa et al. [l4] | 2013 | LRH | 20 | 15/5 | 70(46–83) | NA | 19/1 | 7/13 | Retrospective | 7 |
| | | ORH | 20 | 19/1 | 65(43–74) | NA | 17/3 | 7/13 | Matched | |
| Liu et al. [l5] | 2017 | LRH | 30 | 23/7 | 56.5(27–79) | NA | 30/0 | 26/4 | Prospective Matched | 9 |
| | | ORH | 30 | 28/2 | 48.5(28–79) | NA | 27/3 | 26/4 | | |
| Noda et al. [16] | 2018 | LRH | 20 | 15/5 | 68.8 ± 9.7 | 22.3 ± 2.8 | 19/1 | 8/12 | Retrospective | 8 |
| | | ORH | 48 | 39/9 | 67.2 ± 8.4 | 22.7 ± 3.5 | 44/4 | 16/32 | | |
| Ome et al. [17] | 2018 | LRH | 33 | 26/7 | 73(45–84) | 23.3(17.3–32.9) | 33/0 | 13/20 | Prospective | 8 |
| | | ORH | 37 | 27/10 | 71(45–84) | 23.6(16.0–31.8) | 36/1 | 10/27 | | |
| Zhang et al. [18] | 2016 | LRH | 31 | 26/5 | 54(37–66) | 24.4 (19.1–31.0) | NA | NA | Prospective | 7 |
| | | ORH | 33 | 27/6 | 59.5(34–65) | 25.0 (21.8–29.9) | NA | NA | | |

M male, F female, yrs years, BMI body mass index, LRH laparoscopic repeat hepatectomy, ORH open repeat hepatectomy, NA not available

### 3.1. Clinical characteristics of the patients

Pre-operative clinical characteristics of the patients were listed in Tables 1 and 3 One study [13] of the selected studies came from France and the rest six selected studies from Asia, including 3 studies from China [12,15,18] and 3 studies from Japan [14,16,17]. As shown in Table 3, there were no significant difference between LRH and ORH in the field of clinical characteristics of the patients, including age (WMD = 1.00, 95% CI -0.28 to 2.28, $P = 0.127$), gender (OR 0.32, 95% CI 0.08–1.30, $P = 0.112$), BMI (WMD = −0.37, 95% CI-1.33 to 0.59, $P = 0.448$), Child-Pugh classification (OR 0.31, 95% CI 0.09–1.14, $P = 0.078$), cirrhosis (OR 1.32, 95% CI 0.73–2.37, $P = 0.354$) and approach of primary surgery (OR 2.35, 95% CI 0.81–6.84, $P = 0.117$; Fig. 2). In the group of non-case match studies, however, the rate of previous laparoscopic hepatectomy (LH) was significantly higher in the LRH group (OR 9.17, 95% CI 3.17–26.56, $P < 0.001$) compared with ORH group.

### 3.2. Characteristics of recurrent liver tumors

Characteristics of recurrent liver tumor in the selected articles were listed in Table 2. Five studies [12,14–16,18] reported recurrent tumor locations. And the pooled data revealed that no significant difference was discovered between LRH and ORH (OR 0.78, 95% CI 0.46–1.32, $P = 0.349$; Fig. 3A). No significant difference was also found in the sensitivity analysis. In addition, four studies [12,14–16] reported tumor of segment VII or VIII, and the results of our meta-analysis showed that no significant difference was observed in both groups (OR 0.62, 95% CI 0.32–1.21, $P = 0.161$; Table 3). Six studies [12,14–18] reported the size of recurrent tumors, the pooled data of meta-analysis also showed no obvious difference between LRH and ORH groups (WMD = −0.56, 95% CI -1.19 to 0.08, $P = 0.336$; Fig. 3B), but with an $I^2$ of 70.6% (higher than 50%) and *P*h of 0.004 (lower than 0.1). Then, sensitivity analysis according to the design of case match and non-case match studies was performed; the results showed that no obvious difference between LRH and ORH was found in case-match studies (WMD = −0.28, 95% CI -0.68 to 0.13, $P = 0.179$) and non-case-match studies (WMD = −1.63, 95% CI -4.74 to 1.48, $P = 0.304$). However, no obvious heterogeneity was found in both case-match studies ($I^2 = 27.7\%$; *P*h = 0.251) and non-case-match studies ($I^2 = 43.3\%$; *P*h = 0.171). There were four studies [12,14–16] reported number of tumors (solitary *vs.* multiple), and no significant difference between these two groups was found in the pooled data (OR 0.75, 95% CI 0.33–1.73, $P = 0.502$; Fig. 3C). No significant difference was also presented in the sensitivity analysis.

### 3.3. Intraoperative outcomes

The resection type relying on the characteristics of recurrent liver tumor (anatomical resection *vs.* non-anatomical resection) between this

**Table 2**
Characteristics of recurrent tumors.

| Authors | Group | Tumor size (cm) | No. of tumors (S/M) | Tumor location (L/R) | Pathological diagnosis | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | HCC | CCC | Combined HCC and CCC | Metastatic tumor | Others |
| Chan et al. [12] | LRH | 2 (1.0–4.5) | 10/1 | 7/4 | 11 | 0 | 0 | 0 | 0 |
| | ORH | 2 (1.0–5.0) | 20/2 | 14/8 | 22 | 0 | 0 | 0 | 0 |
| Hallet et al. [13] | LRH | NA | 18/9 | NA | 0 | 0 | 0 | 27 | 0 |
| | ORH | NA | 25/56 | NA | 0 | 0 | 0 | 81 | 0 |
| Kanazawa et al. [l4] | LRH | 1.7 (0.7–3.5) | 4/16 | 13/7[b] | 20 | 0 | 0 | 0 | 0 |
| | ORH | 2.2(1.3–4.1) | 2/18 | 13/7[b] | 20 | 0 | 0 | 0 | 0 |
| Liu et al. [l5] | LRH | 2.1(1.0–5.0) | 28/2 | 18/12[b] | 30 | 0 | 0 | 0 | 0 |
| | ORH | 2.45(1.0–4.3) | 25/5 | 15/15[b] | 30 | 0 | 0 | 0 | 0 |
| Noda et al. [16] | LRH | 24.1 ± 12.6 | 3/17 | 16/4[b] | 15 | 0 | 0 | 5 | 0 |
| | ORH | 22.1 ± 10.9 | 11/37 | 29/19[b] | 36 | 0 | 0 | 12 | 0 |
| Ome et al. [17] | LRH | 18.0 (4–45) | 1 (1–3)[a] | NA | 16 | 0 | 2 | 15 | 0 |
| | ORH | 24.0 (7–55) | 1 (1–4)[a] | NA | 16 | 1 | 2 | 16 | 2 |
| Zhang et al. [18] | LRH | 2.5 ± 1.0 | NA | 16/15 | 31 | 0 | 0 | 0 | 0 |
| | ORH | 3.8 ± 1.1 | NA | 19/14 | 33 | 0 | 0 | 0 | 0 |

*S* solitary, *M* multiple, *L* left lobe, *R* right lobe, *HCC* hepatocellular carcinoma, *CCC* cholangiocellular carcinoma.
[a] Values were median (range).
[b] Tumor location in these studies was grouped in different ways.

**Table 3**
Results of the meta-analysis.

| Outcomes of interest | No. of studies | No. of patients | OR or WMD (95% CI) | *P* | Heterogeneity | | |
|---|---|---|---|---|---|---|---|
| | | | | | $I^2$ (%) | *Ph* | Model |
| Clinical characteristics of the patients | | | | | | | |
| Age (y) | 7 | 172/271 | 1.00(-0.28–2.28) | 0.127 | 0.0 | 0.660 | Fixed effects |
| Gender (Male:Female) | 7 | 172/271 | 0.32(0.08–1.30) | 0.112 | 71.2 | 0.004 | Random effects |
| BMI | 3 | 84/118 | −0.37(-1.33–0.59) | 0.448 | 0.0 | 0.705 | Fixed effects |
| CPC (A:B) | 5 | 114/157 | 0.31(0.09–1.14) | 0.078 | 0.0 | 0.889 | Fixed effects |
| Cirrhosis (Yes:No) | 4 | 103/135 | 1.32(0.73–2.37) | 0.354 | 0.0 | 0.893 | Fixed effects |
| Approach of primary surgery (LH:OH) | 6 | 145/190 | 2.35(0.81–6.84) | 0.117 | 66.1 | 0.019 | Random effects |
| Recurrent tumor characteristics | | | | | | | |
| Tumor location (AR:NAR) | 5 | 112/153 | 0.78(0.46–1.32) | 0.349 | 0.0 | 0.667 | Fixed effects |
| Size of tumor (cm) | 6 | 145/190 | −0.56(-1.19–0.08) | 0.336 | 70.6 | 0.004 | Random effects |
| Tumor numbers (S:M) | 4 | 81/120 | 0.75(0.33–1.73) | 0.502 | 0.0 | 0.521 | Fixed effects |
| Tumor of segment VII or VIII (Yes:No) | 4 | 81/120 | 0.62(0.32–1.21) | 0.161 | 0.0 | 0.506 | Fixed effects |
| Intraoperative outcomes | | | | | | | |
| Resection type (S:M) | 5 | 125/170 | 0.83(0.48–1.43) | 0.499 | 0.0 | 0.960 | Fixed effects |
| Operation time (h) | 7 | 172/271 | −12.38(-43.69–18.93) | 0.438 | 77.0 | < 0.001 | Random effects |
| Blood loss (ml) | 6 | 145/190 | −389.09(-628.34～ −149.84) | 0.001 | 88.5 | < 0.001 | Random effects |
| Transfusion (Yes:No) | 5 | 121/190 | 0.16(0.03–0.74) | 0.019 | 59.9 | 0.058 | Random effects |
| Resection margin (P:N) | 4 | 91/160 | 0.57(0.28–1.19) | 0.136 | 0.0 | 0.927 | Fixed effects |
| Postoperative outcomes | | | | | | | |
| Complications (Yes:No) | 6 | 141/238 | 0.32(0.08–1.30) | 0.112 | 71.2 | 0.004 | Random effects |
| Bile leak (Yes:No) | 5 | 121/218 | 0.80(0.31–2.05) | 0.644 | 0.0 | 0.477 | Fixed effects |
| Ascites (Yes:No) | 4 | 81/120 | 0.36(0.10–1.21) | 0.099 | 0.0 | 0.800 | Fixed effects |
| SSI (Yes:No) | 4 | 97/181 | 0.69(0.32–1.50) | 0.351 | 47.2 | 0.128 | Fixed effects |
| Hospital stay (d) | 7 | 172/271 | −4.00(-6.58～ −1.42) | 0.002 | 84.9 | < 0.001 | Random effects |

*OR* odds ratio, *WMD* weighted mean difference, *CI* confidence interval, *Ph* *P*-value of heterogeneity, *BMI* body mass index, *CPC* Child–Pugh classification, *SSI* surgical site infection, *LH* laparoscopic hepatectomy, *OH* open hepatectomy, *AR* anatomical resection, *NAR* non-anatomical resection, *S* solitary, *M* multiple, *P* positive, *N* negative.

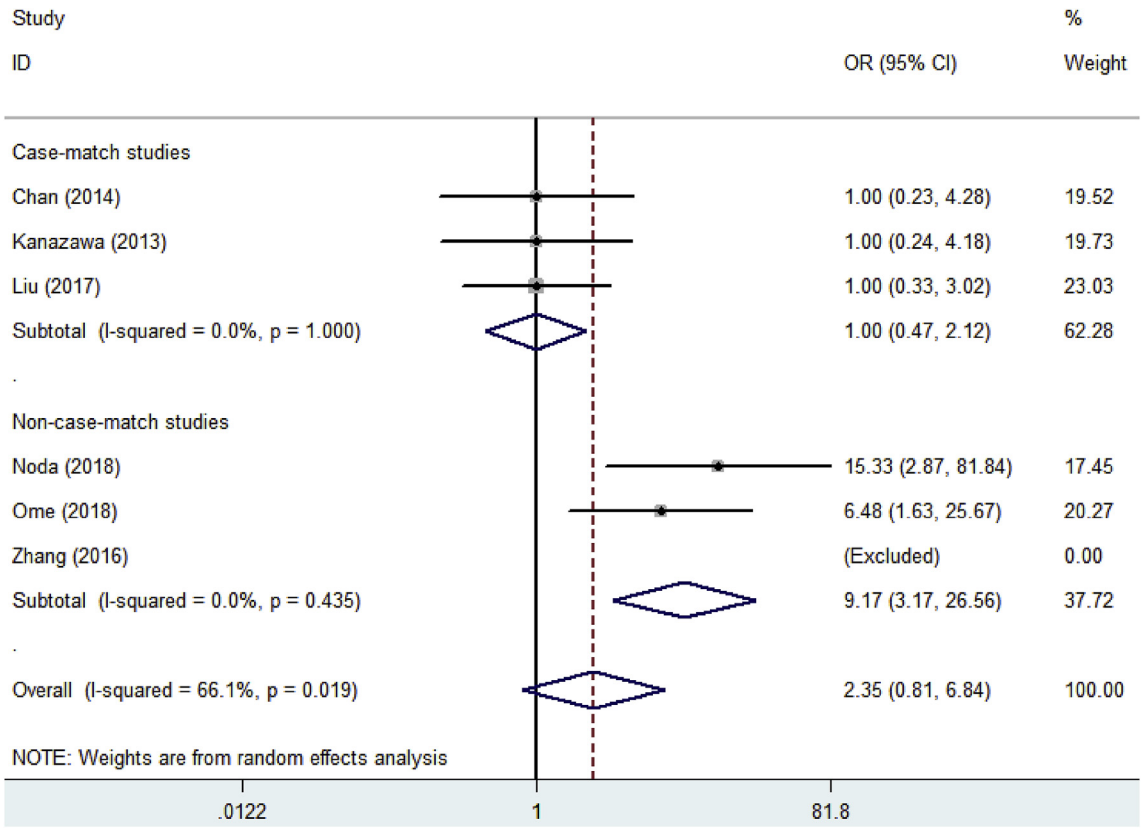


**Fig. 2.** Forest plots illustrating approach of primary surgery show no significant difference between the both groups. In the sensitivity of non-case match studies, however, the rate of previous LH is significantly higher in the LRH group compared with that of ORH group.

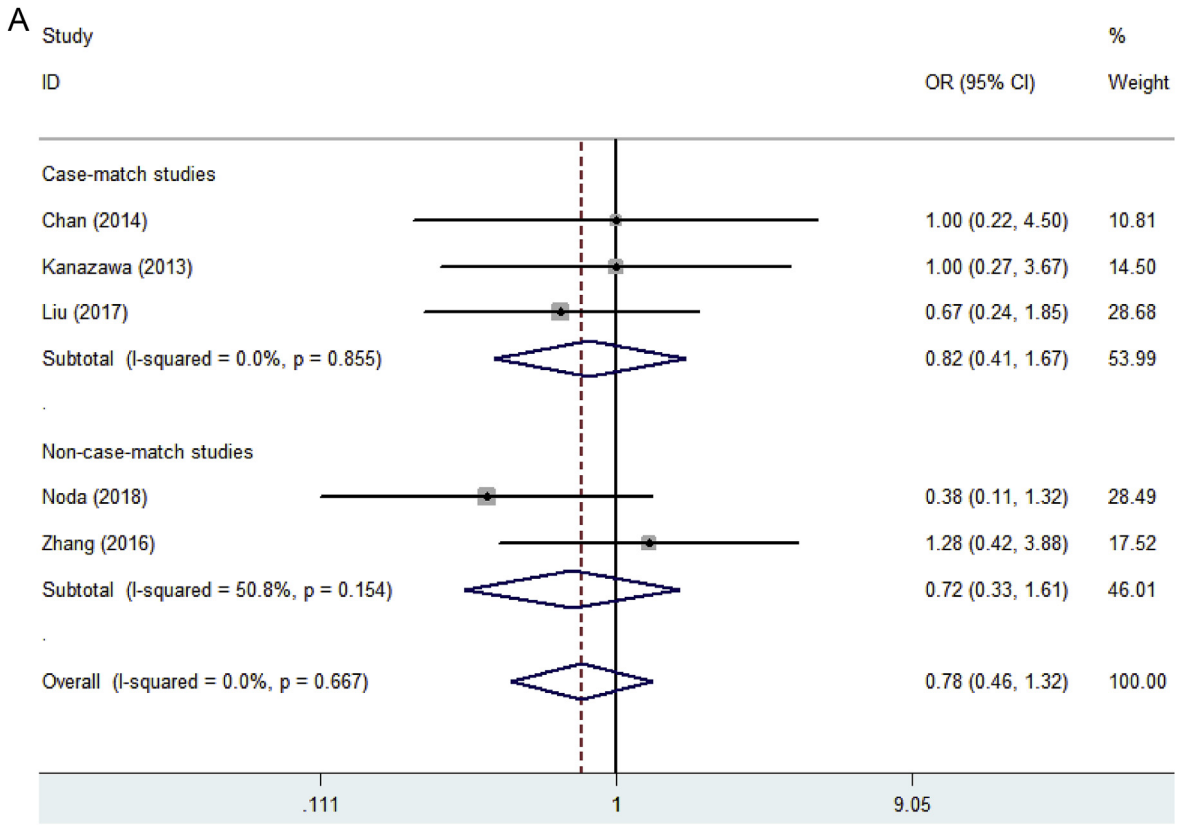


**Fig. 3.** Forest plots illustrating characteristics of recurrent tumor results show no significant difference between the both groups: **A** recurrent tumor location; **B** tumor of segment VII or VIII; **C** size of recurrent tumor; **D** number of tumors.

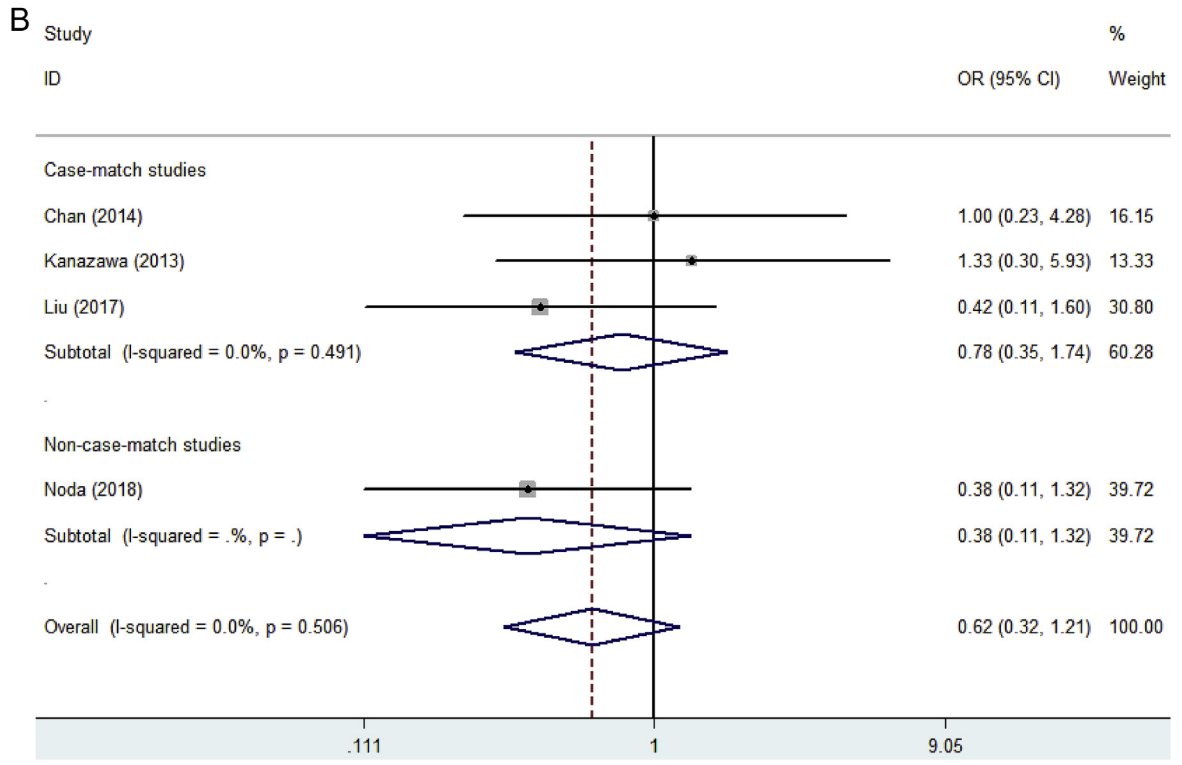


**Fig. 3.** (*continued*)

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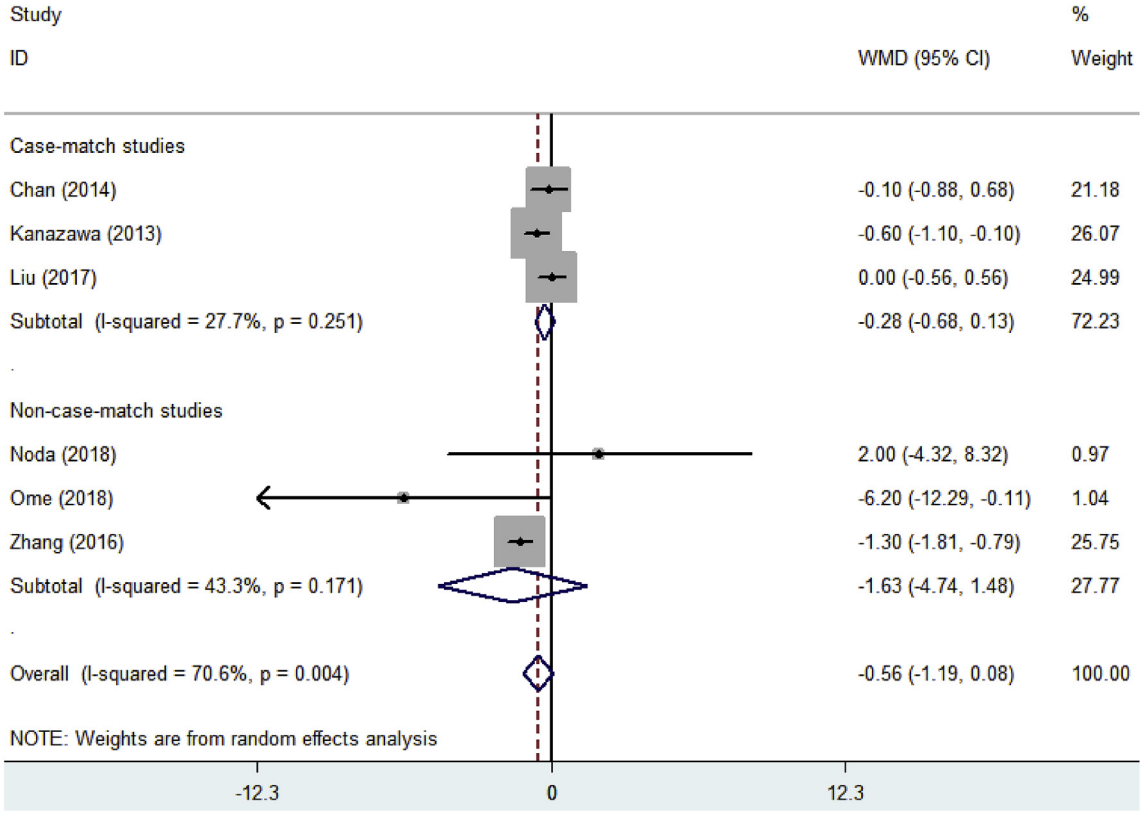


**Fig. 3.** (*continued*)

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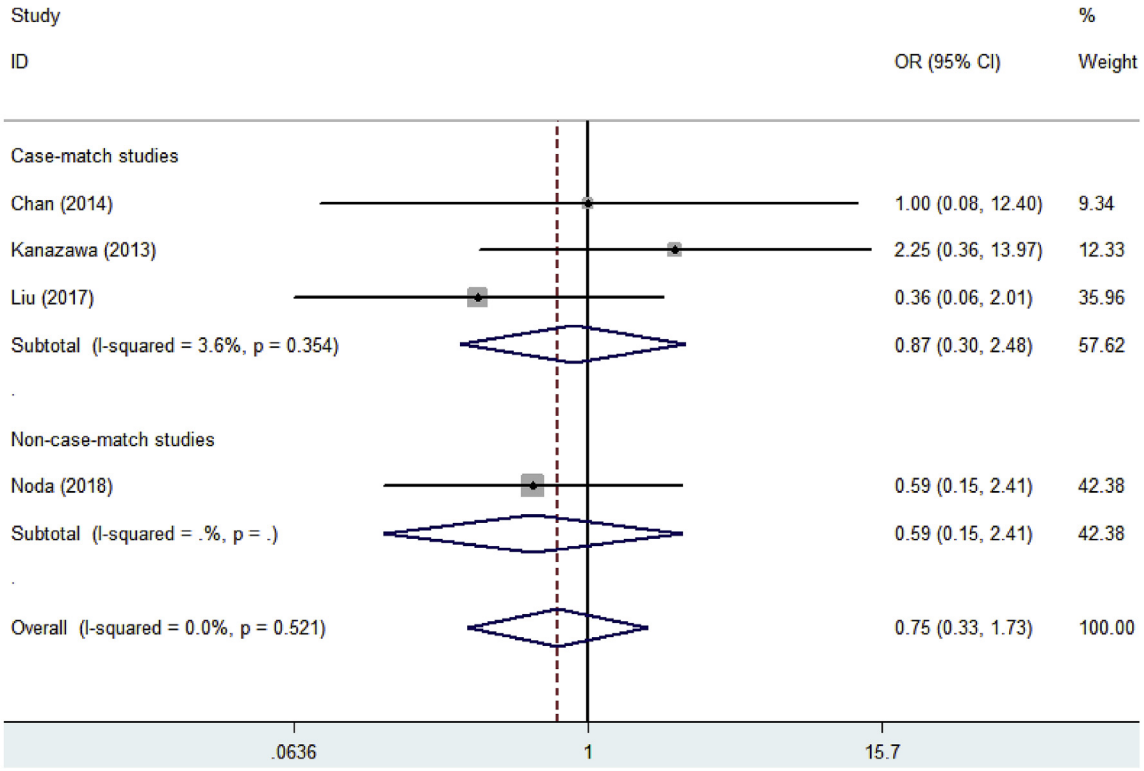


**Fig. 3.** (*continued*)

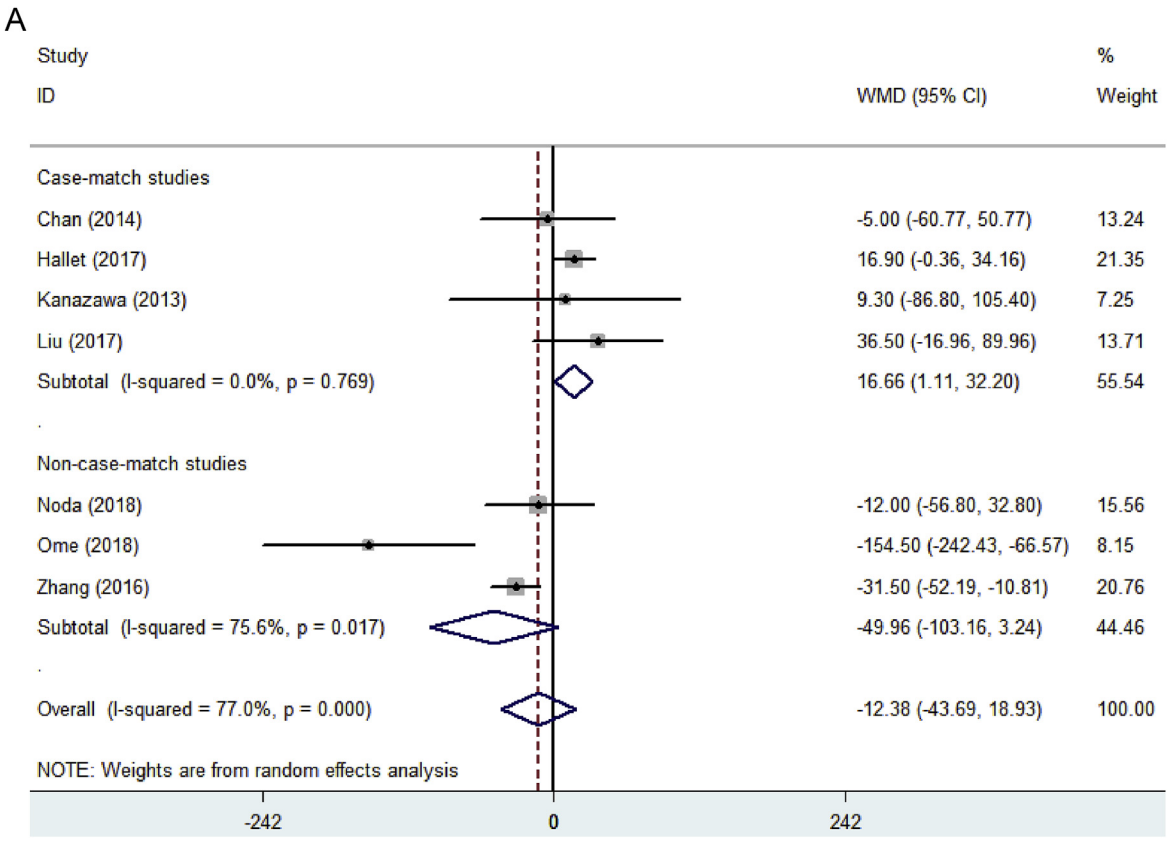


**Fig. 4.** Forest plots illustrating intraoperative outcomes: **A** operation time shows no significant difference between the both groups, but LRH was associated with significant longer operation time in the sensitivity of case match studies; **B** blood loss favors laparoscopy, but no significant difference is found between the both groups in the case match sensitivity analysis; **C** transfusion favors laparoscopy; **D** resection margin show no significant difference between the both groups.

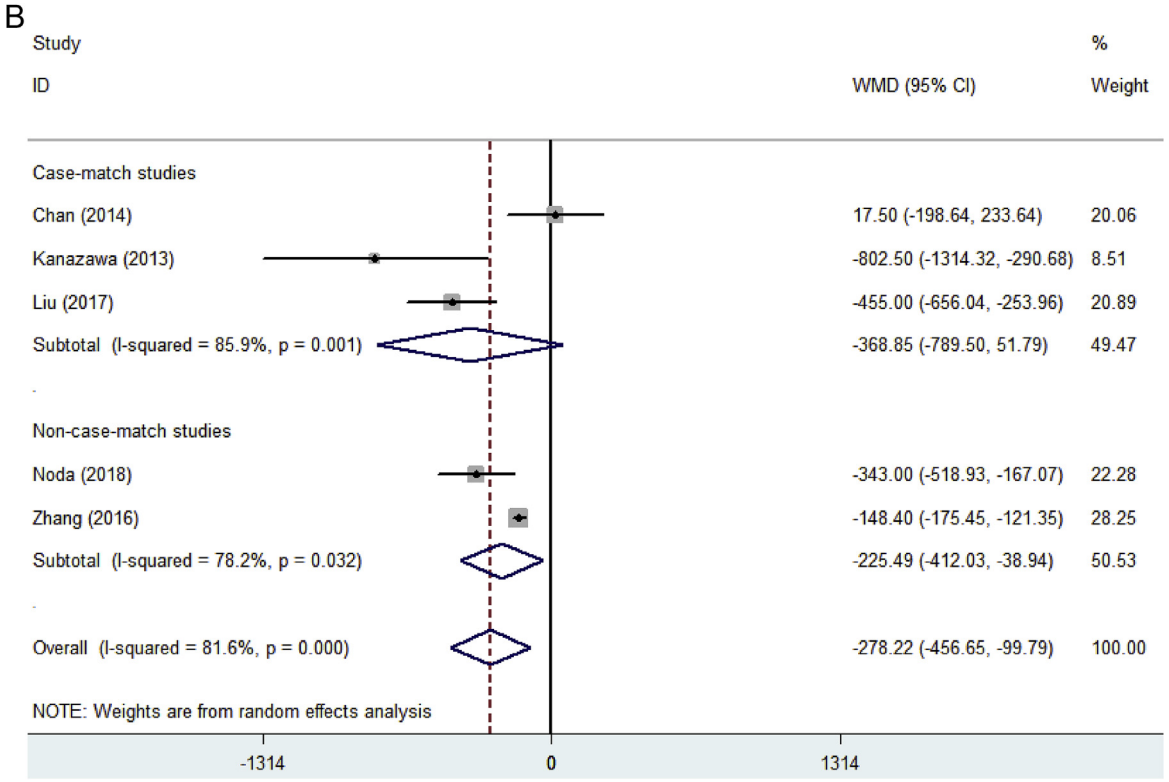


**Fig. 4.** (*continued*)

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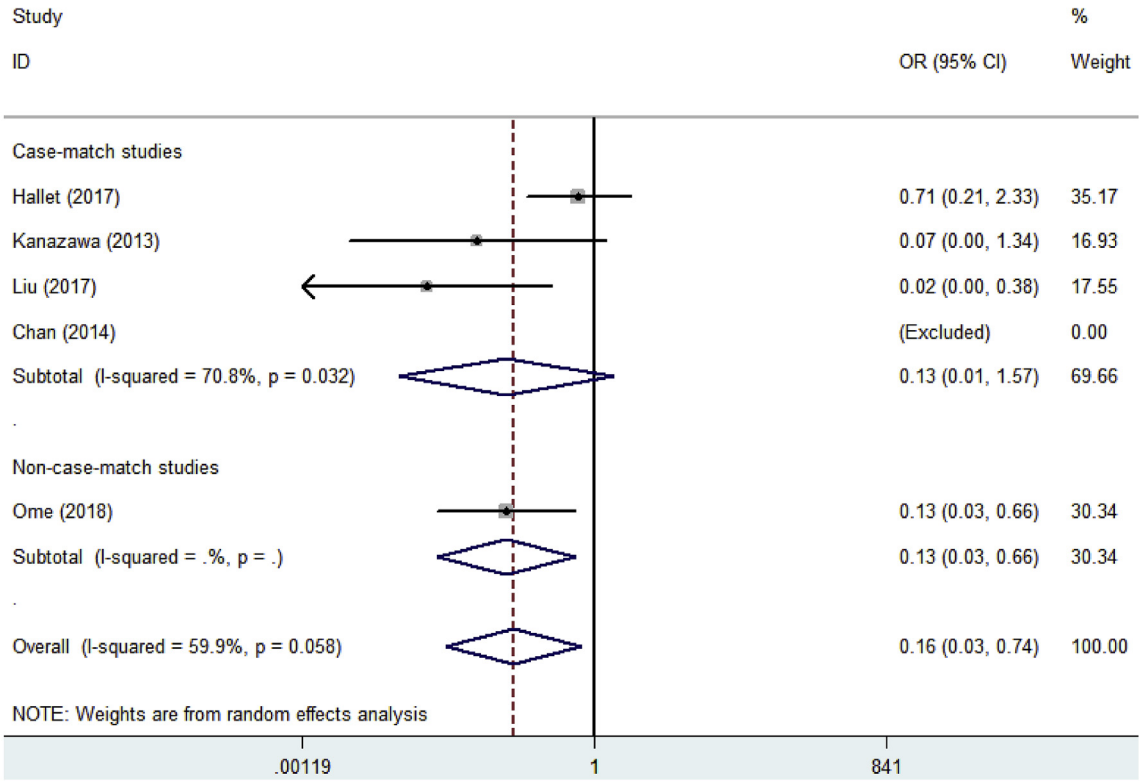


**Fig. 4.** (*continued*)

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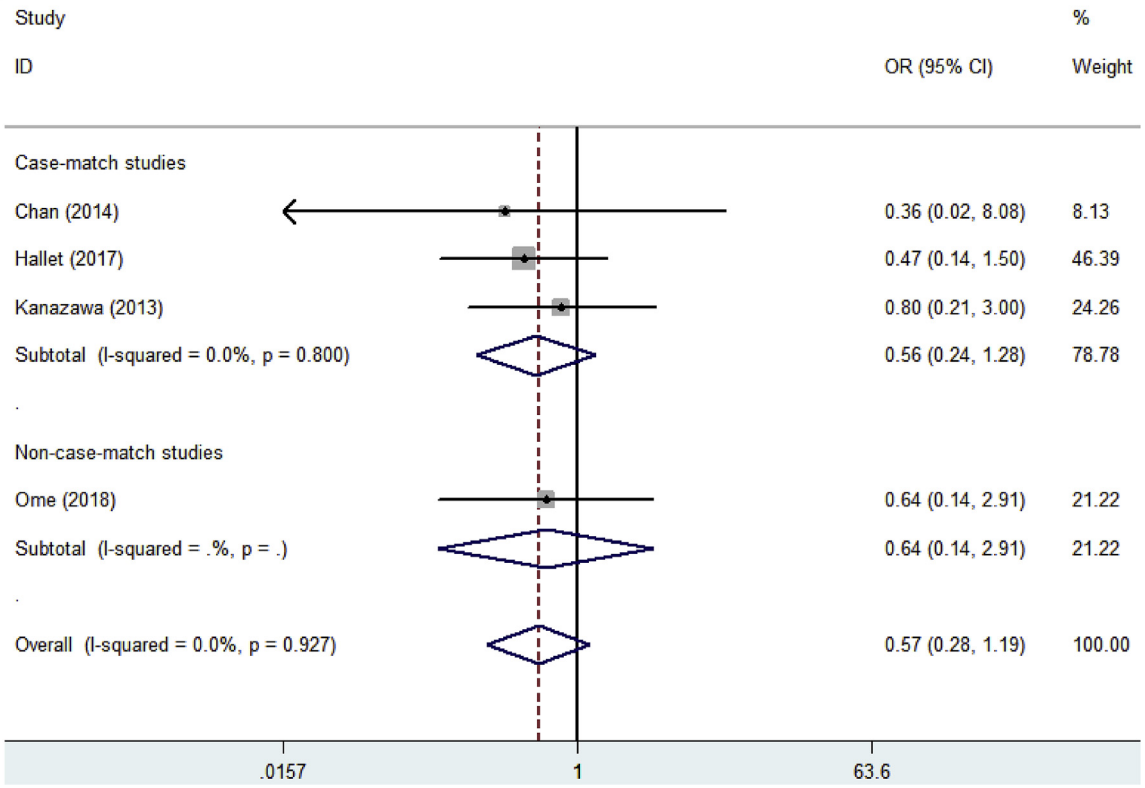


**Fig. 4.** (*continued*)

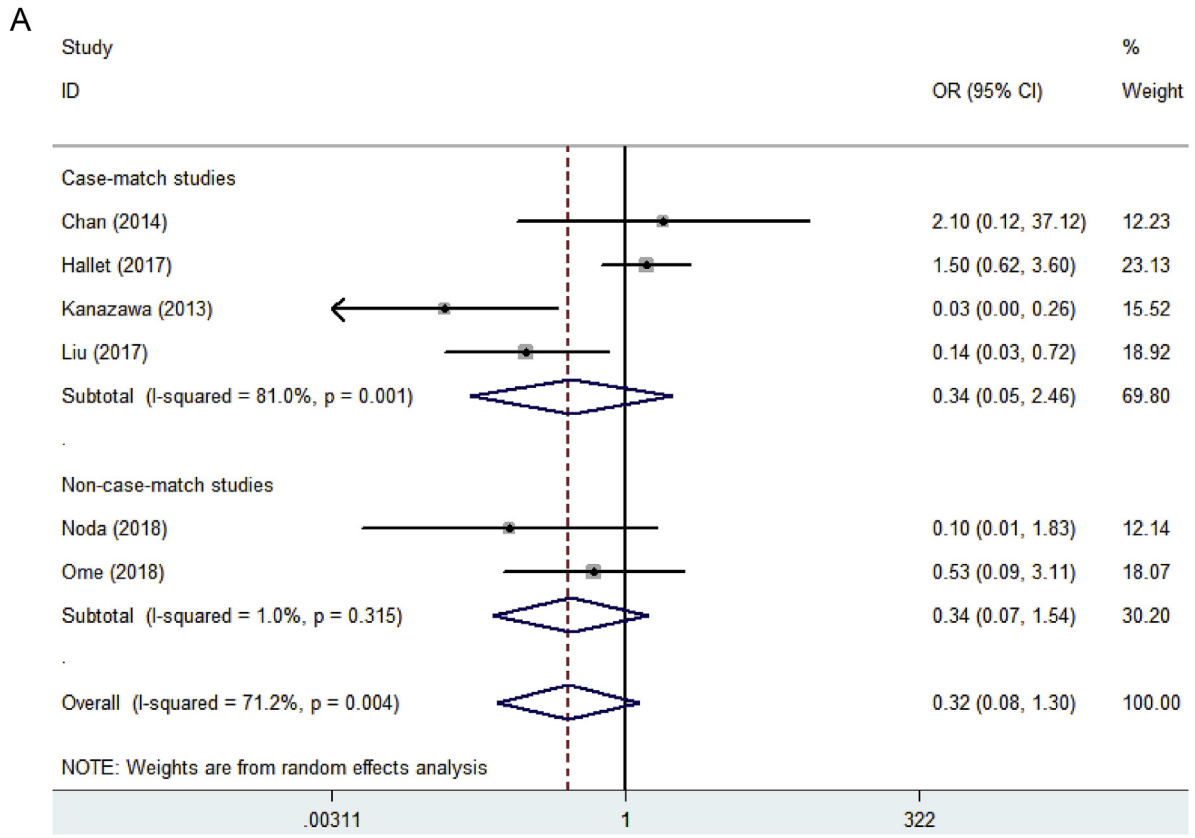


**Fig. 5.** Forest plots illustrating post-operative outcomes: **A** postoperative overall complications show no significant difference between the both groups; **B** hospital stay favors laparoscopy.

two groups showed no remarkable difference (OR 0.83, 95% CI 0.48–1.43, $P = 0.960$; Table 3), and no remarkable difference was also found in the sensitivity analysis. All seven studies reported operation time, and the furnishing data indicated that no remarkable difference was observed between LRH and ORH groups (WMD = −12.38, 95% CI -43.69 to 18.93, $P = 0.438$; Fig. 4A), but with significant heterogeneity ($I^2 = 77.0\%$; $Ph < 0.001$). Then, sensitivity analysis according to the design of case match and non-case match studies was performed; the results showed that LRH was associated with longer operation time in case-match studies (WMD = 16.7, 95% CI 1.11 to 32.20, $P = 0.036$; Fig. 4A). No significant heterogeneity was found in case-match studies ($I^2 = 0.0\%$; $Ph = 0.769$; Fig. 4A). In addition, exclusion method of sensitivity analysis was conducted, in order to assess any single study that may affect the pooled result. We found that one study reported by Ome et al. [17] had important effects on the result. After excluding the study of Ome et al., no obvious heterogeneity was found ($I^2 = 35.6\%$; $Ph = 0.184$), but operation time of LRH was remarkably lower than that of ORH (WMD = −18.65, 95% CI -52.19 to −10.81, $P = 0.028$). Compared with ORH group, LRH had a significant lower blood loss (WMD = −389.09, 95% CI -628.34 to −149.84, $P = 0.001$; Fig. 4B) with significant heterogeneity ($I^2 = 88.5\%$; $Ph < 0.001$). However, sensitivity analysis showed that no obvious difference between LRH and ORH was found in case match studies (WMD = −368.85, 95% CI -789.50 to 51.79, $P = 0.086$; Fig. 4B). Although sensitivity analysis was performed, the reasons of heterogeneity were not found. In addition, LRH group had significant less transfusion in comparing with ORH (OR 0.16, 95% CI 0.03–0.74, $P = 0.019$; Fig. 4C). However, the results of sensitivity analysis showed that no significant difference was found in case-match studies. Resection margin was reported by four studies [12–14,17], and the result showed that no significant difference was found between ORH and LRH (OR 0.57, 95% CI 0.28–1.19, $P = 0.136$; Fig. 4D). There were 8 (1.8%, range 0–13.3%) cases of conversion in LRH group. All the 8 patients were conversed from pure laparoscopic hepatectomy to hybrid hepatectomy due to failure to progress for tumors location in posterior segments [16] and severe intra-abdominal adhesions [13,16,17].

### 3.4. Postoperative outcomes

All the seven studies reported postoperative overall complications, but only six studies [12–17] provided the data. According to the pooled data, no significant difference was found in both groups (OR 0.32, 95% CI 0.08–1.30, $P = 0.112$; Fig. 5A) with significant heterogeneity ($I^2 = 71.2\%$; $Ph = 0.004$). Although sensitivity analysis was performed, the reasons of heterogeneity were not found. Furthermore, there were at least three studies had provided complications, including bile leak, ascites and surgical site infection (SSI). Then, a meta-analysis of these complications was performed. No dramatic difference was found in the complications of bile leak (OR 0.80, 95% CI 0.31–2.05, $P = 0.644$; Table 3), ascites (OR 0.36, 95% CI 0.10–1.21, $P = 0.099$; Table 3) and surgical site infection (OR 0.69, 95% CI 0.32–1.50, $P = 0.351$; Table 3). Postoperative hospital stay was reported by all of the seven studies; the meta-analysis indicated that ORH had an obvious longer hospital stay that of LRH (WMD = −4.00, 95% CI -6.58 to −1.42, $P = 0.002$; Fig. 5B). Sensitivity analysis also showed that ORH had an obvious longer hospital stay that of LRH in both case-match studies and no case-match studies. Although postoperative mortality was reported by all studies, only one patient died after operation in LRH group and two in ORH, respectively.

### 3.5. Long-term oncological outcomes and inpatient costs

Although four studies [12,13,15,18] have reported short- and long-term oncological outcomes, the data of HR with 95%CI for disease-free

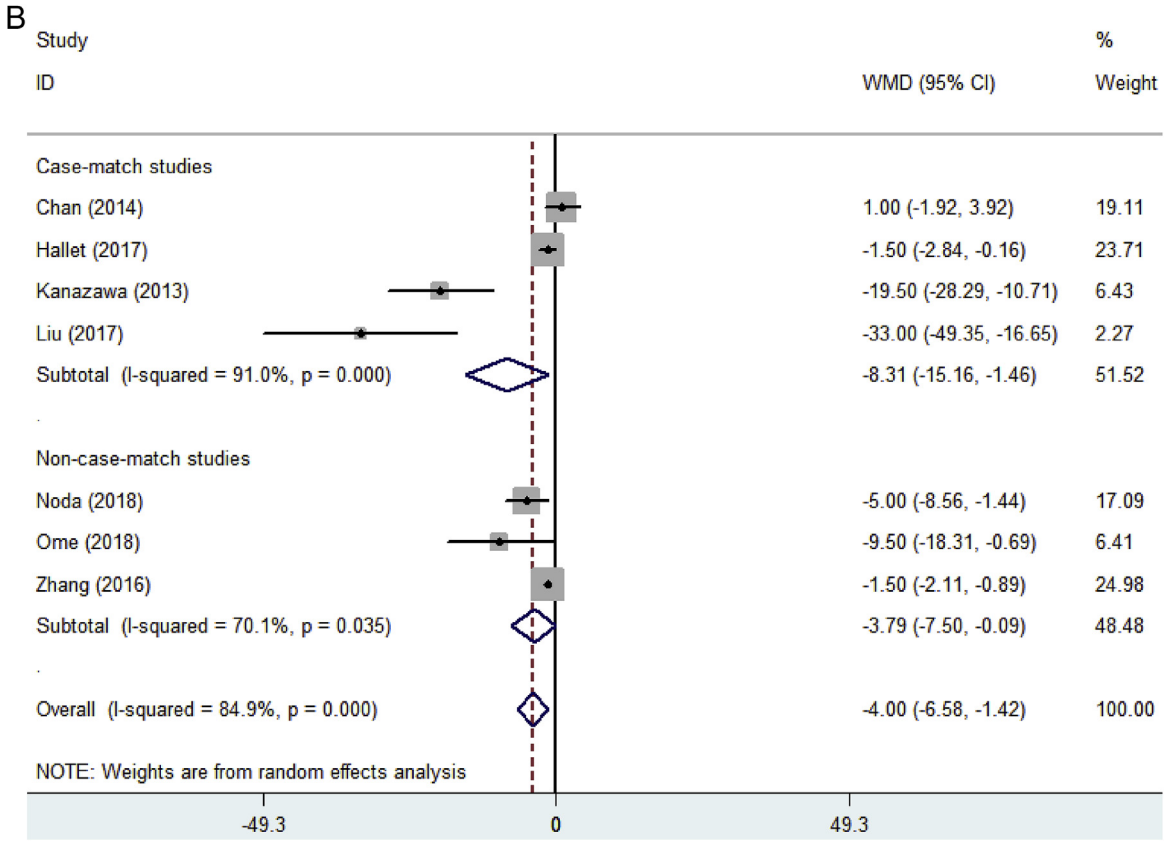


**Fig. 5.** (*continued*)

survival (DFS) and overall survival (OS) were not provided. Therefore, meta-analysis was not performed while a system review was performed. Chan et al. [12] have reported 3-year OS (LRH *vs.* ORH = 60.0% *vs.* 89.3%) and DFS (LRH *vs.* ORH = 18.9% *vs.* 45.7%) rates of LRH and ORH; and no significant difference was found between LRH and ORH groups. Among the study of Zhang et al. [18], there was no significant difference DFS between LRH and ORH. Liu et al. [15] and Hallet et al. [13] also provided 1-year, 3-year, 5-year OS and DFS rates between LRH and ORH groups and no obvious difference existed. However, just one study reported inpatient costs among all the seven study. And the result of this study showed that the expenses of the both groups were almost the same [18].

### 3.6. Publication bias

Publication bias was not performed, due to the fact that just six studies were included.

## 4. Discussion

Laparoscopic hepatic surgery is now a common operation for liver benign or malignant tumors [24,25], due to the rapid improvement of surgical equipment and procedures. The present meta-analysis demonstrated that the advantages of laparoscopy could also be applied to recurrent tumors in selected patients with prior liver resection. However, adhesions after abdominal surgery develop in 67–93% of patients [26]. Apart from significantly prolong operative time, adhesions may increase intraoperative blood loss as well as perioperative blood transfusion. In addition, several studies have reported that increased perioperative blood transfusion and intraoperative blood loss might play key roles in postoperative lethal complications, including liver failure and tumor recurrence after liver re-resection [27–30]. Therefore, it may be a technical challenge for surgeons to perform LRH, which is difficult to deal with densely or vascular-rich adhesions around the hepatic hilum or major vessels. This meta-analysis study discounts the belief that laparoscopic approach for recurrent liver cancer is more difficult compared to the open technique. In this meta-analysis, there were just two studies reported adhesions after surgery [15,18], and no significant difference of abdominal adhesions was found between the two groups. With regard to operative time, no remarkable difference was observed between LRH and ORH groups. Moreover, the present meta-analysis showed that LRH favored in perioperative blood transfusion and intraoperative blood loss in comparison with ORH. The main reasons of LRH to control intraoperative blood loss for patients with recurrent liver cancer may be the positive pressure of $CO_2$ pneumoperitoneum, image magnification of laparoscopic approach and state of the art transaction devices [31,32]. In regard to significant heterogeneity of operation time and unstable outcomes of intraoperative blood loss, however, the result of operation time and intraoperative blood loss should be interpreted with caution.

With regard to the data on post-operative outcomes, the present meta-analysis showed that no dramatic difference was found in post-operative overall complications, the complications of bile leak, surgical site infection (SSI) and ascites between the two groups. Interesting, the length of hospital stay in the LRH group was significant shorter than ORH group, which might be the results of advantages and low post-operative overall complications of laparoscopic surgery. Unfortunately, only four studies reported short- or long-term oncological outcomes without providing the data of HR with 95%CI for DFS and OS. In order to prove the advantages of LRH, additional carefully designed studies with short- or long-term oncological outcomes are required in the future.

There are a number of limitations in the present meta-analysis of non-randomized studies, which should be acknowledged and considered when interpreting the results. Firstly, all studies included in the meta-analysis are single-centre non-randomized controlled trials

(NRCTs) in design, which may be inclined to cause selection bias and exaggerate the effect of the approaches. For example, no significant difference was found between both groups in approach of primary surgery. In the sensitivity of non-case match group, however, the rate of previous laparoscopic hepatectomy (LH) was significantly higher in the LRH group compared with ORH group. It is a debated topic in the field of meta-analysis to pool data from NRCTs. Nevertheless, several pieces of evidence deriving from studies of well-designed NRCTs may be reliable [33,34]. In order to minimize case selection bias, sensitivity analyses according to the design of case match and non-case match studies are performed in the present meta-analysis. Secondly, characteristics of the populations as well as recurrent tumors, transaction devices in laparoscopic surgery, the learning curve of the surgeons and definition of the outcomes vary considerably among the included studies, which may bring heterogeneity and impact the reliability of our results. Thirdly, most patients included in the meta-analysis were Asians. Additionally, publication bias may exist. Finally, due to the included studies having limited or nonexistent descriptive statistics, it is impossible to generate more in-depth comparative results, such as the grade of adhesions, the major/minor hepatectomy of the two groups during the first hepatectomy, additional organ removal (colon, diaphragm) during first and the repeat hepatectomy, previous tumor location and sizes, the location of the recurrence after repeat heaptectomy, costs and short- or long-term oncological outcomes.

In conclusion, the results of our meta-analysis indicate that LRH is as feasible and efficient as ORH, and possesses some perioperative advantages, including lower transfusion and fewer post-operative complications. However, because of the small proportion of patients included in this meta-analysis and lack of high-quality RCTs, the evidence is still limited. Therefore, in order to further define the role of LRH for patients with recurrent liver cancers, additional prospective and multicentre RCTs are needed.

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## Conflicts of interest

None.

## Author contributions

Jiaqing Cao and Shengxun Mao conceived the study; Long Peng collected the data, performed the data analysis and wrote the paper; Zhiyong Zhou edited the paper; all authors read and approved the final manuscript.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.suronc.2018.10.010.

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