Efficacy of Laparoscopic Hepatectomy versus Open Surgery for Hepatocellular Carcinoma With Cirrhosis: A Meta-analysis of Case-Matched Studies

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Background: The role of laparoscopic hepatectomy (LH) in hepatocellular carcinoma (HCC) with cirrhosis remains controversial and needs to be further assessed. The present meta-analysis aimed to compare the surgical and oncological outcomes of LH with those of open hepatectomy (OH) for HCC with cirrhosis.

Methods: The PubMed, Embase, and Cochrane Library databases were searched for studies comparing LH and OH until Mar 2021. Weighted mean differences (WMDs), odds ratios (ORs), and hazard ratios (HRs) were calculated for continuous, dichotomous, and long-term variables, respectively, with 95% confidence intervals (CIs). Subgroup analysis was performed according to different resection types: major resection and minor resection. The meta-analysis was performed using the STATA 12.0.

Results: A total of 16 case-matched studies (784 patients in the LH group and 1,191 patients in the OH group) were included in this meta-analysis. In terms of primary outcomes, LH was associated with decreased overall complication rate (OR 0.57; 95% CI 0.46 to 0.71; P < 0.01), major complication rate (OR 0.52; 95% CI 0.33 to 0.82; P < 0.01), postoperative mortality (OR 0.27; 95% CI 0.11 to 0.73; P < 0.01), 1-y overall survival (OS) rate (HR 0.48; 95% CI 0.31 to 0.73; P < 0.01), 2-y OS (HR 0.61; 95% CI 0.45 to 0.83; P < 0.01), and 5-y OS (0.67; 95% CI 0.53 to 0.85; P < 0.01). With respect to secondary outcomes, blood loss (WMD −69.16; 95% CI −101.72 to −36.61; P < 0.01), length of hospitalization (LOH) (WMD −2.65; 95% CI −3.41 to −1.89; P < 0.01), minor complication rate (OR 0.70; 95% CI 0.53 to 0.94; P = 0.02), postoperative liver failure (OR 0.60; 95% CI 0.38 to 0.95; P = 0.03), and postoperative ascites (OR 0.44; 95% CI 0.28 to 0.72; P < 0.01) was lower in LH than in OH. No significant differences in operation time (P = 0.07), transfusion rate (P = 0.05), 1-, 2-, and 5-year DFS rate (1-year, P = 0.08; 2-year, P = 0.08; 5-year, P = 0.23) were noted between LH and OH. Subgroup analysis based on minor resection revealed that LH had similar favored outcomes in comparison with those in the overall pooled analysis. However, LH had a longer operation time than OH in the setting of major resection (P < 0.01).
INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary cancer of the liver and one of the leading causes of cancer-related deaths worldwide (1, 2). Hepatectomy is the commonly used curative treatment strategy for very early- and early-stage HCC patients with preserved liver function. In the early 1990s, with the inception of laparoscopic techniques, initial reports on laparoscopic hepatectomy (LH) were published (3, 4). Since then, the laparoscopic approach has been increasingly accepted in the field of liver surgery. Laparoscopic techniques have been shown to expedite recovery, improve postoperative pain, and result in better cosmesis than the open approach. In the statement of the First International Consensus Conference for Laparoscopic Liver Resection, laparoscopic left lateral segmentectomy was identified as the gold standard approach (5). In 2014, the Second International Consensus Conference for Laparoscopic Liver Resection recommended laparoscopic minor hepatectomy as the standard surgical practice (6).

Most patients with HCC commonly have chronic hepatitis and cirrhosis making liver resection technically demanding. Liver resection is a challenging procedure in the setting of cirrhosis owing to elevated portal pressure and impaired coagulation function in patients with this condition. A retrospective study by Neeff et al. reported that the severity of cirrhosis was correlated with perioperative mortality after hepatectomy (7). The development of devices and techniques for hemostasis has allowed bleeding control in LH. Several efforts have been made to promote the adoption of LH in the treatment of HCC with cirrhosis (8–11). Given the advantages of laparoscopic surgery in terms of minimal invasiveness, LH is expected to be more beneficial for HCC patients with cirrhosis. Several meta-analyses have reported that patients with cirrhosis undergoing LH experienced less blood loss, fewer postoperative complications, and shorter hospital stays than those undergoing open resection (12, 13). Most studies included in these meta-analyses were retrospective and limited to laparoscopic minor resection. Since then, one randomized clinical trial (RCT) and several case-matched studies focusing on HCC with cirrhosis have reported the favored surgical outcomes of LH (14–16). Furthermore, major liver resection is an important curative modality for HCC. Recently, laparoscopic major hepatectomy (LMH) for selected patients with cirrhosis has been reported by several experienced surgeons in a few medical centers (17, 18). Hence, in this study, we aimed to compare the surgical and oncological outcomes of LH with those of open hepatectomy (OH) for HCC with cirrhosis by collecting high-quality case-matched studies.

Conclusion: LH is technically feasible and safe for selected HCC patients with cirrhosis. LH can achieve favored short-term and long-term oncological outcomes in minor liver resection. Laparoscopic major hepatectomy (LMH) seems to offer some advantages over the open approach; however concerns about surgical and oncological safety remain. More evidence on LMH is warranted before expanding its indication to patients with cirrhosis.

Keywords: laparoscopic hepatectomy, hepatocellular carcinoma, cirrhosis, prognosis, meta-analysis

METHODS

Search Strategy
This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (19). Electronic databases including PubMed, Embase, and Cochrane Library were searched. The search strategy for Pubmed was as follows: (((“Minimally Invasive Surgical Procedures”[Mesh]) OR “Laparoscopy”[Mesh]) AND “Liver Cirrhosis”[Mesh]) AND “Liver Neoplasms”[Mesh]) and similar strategy was performed in other databases. The references of the retrieved results were also manually reviewed to obtain more related articles as possible. The final search was conducted in March 2021. No institutional review board approval or patient written consent was necessary because only published data were used.

Study Selection
Case-matched studies written in English and comparing the outcomes of OH vs LH for HCC in patients with cirrhosis were considered for inclusion. The exclusion criteria were as follows: (i). reviews, editorials, case reports, abstracts, or letters; (ii). studies including patients without cirrhosis or those with unproven cirrhosis; (iii). studies including patients who underwent robotic or hybrid procedures; (iv). overlapped studies; (v). studies that did not report at least three of the primary outcomes.

Data Extraction
After the initial screening, full-text versions of the selected articles were obtained. Two reviewers (SX and KC), as well as an independent third reviewer (YP) in cases in which consensus could not be reached, individually assessed each article and rejected those that failed to meet the inclusion criteria. The following items were extracted: year of publication, study design, sample size, country of study, patient characteristics, and outcome measures. The primary outcomes were overall complication rate, major complication rate, postoperative mortality, overall survival (OS) rate, and disease-free survival (DFS) rate. The secondary outcomes were operation time, blood loss, transfusion rate, length of hospitalization (LOH), minor complication rate, postoperative ascites, and postoperative liver failure (POLF). The Newcastle-Ottawa scale (NOS) was used to evaluate the quality of observational studies (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). The NOS scores were ≥7, were considered of high quality. According to previous studies, minor resection was defined as hepatectomy of fewer than three sections.
and major resection was defined as hepatectomy of more than three sections (20–22). Clavien–Dindo classification was used to grade postoperative complications and a major complication was defined as Clavien–Dindo ≥3; otherwise, the complication was defined as minor (23).

**Statistical Analysis**

Dichotomous variables were evaluated using odds ratios (ORs) with 95% confidence intervals (95% CIs), and continuous variables were analyzed using the weighted mean differences (WMDs) with 95% CIs. The hazard ratio (HR) was used as a summary statistic for long-term outcomes (survival analysis), as described by Tierney et al. (24). Medians were converted to means using the formula described by Hozo et al. (25). According to the Higgins I² statistic, heterogeneities <25, 25 to 50, and >50% were defined as low, moderate, and high, respectively (26). A fixed-effects model was used for studies with low or moderate statistical heterogeneity (27), whereas a random-effects model was used for studies with high statistical heterogeneity (28). Subgroup analysis was performed according to different resection types: major resection and minor resection. Funnel plots were used to estimate the potential publication bias. P<0.05 was considered statistically significant. The meta-analysis was performed using the STATA 12.0.

**RESULTS**

**Study Characteristics**

This meta-analysis was registered to PROSPERO (https://www.crd.york.ac.uk/prospero/) with an ID of CRD42020161775. The search strategy initially retrieved 501 records. After the exclusion of irrelevant studies by screening the abstracts, the full texts of 28 potentially relevant articles were obtained for assessment. Twelve studies were excluded due to overlapping data, inclusion of patients without cirrhosis, unavailable statistical data, non-comparative studies, non-case matched studies (8, 9, 29–38). Sixteen studies were eventually included (15–18, 39–50). The PRISMA flowchart of the literature review is presented in Figure 1.

The characteristics of the included studies are summarized in Table 1. A total of 1,975 patients from both Eastern and Western countries were pooled in this meta-analysis: 784 patients in the LH group and 1,191 patients in the OH group. To balance the basic characteristics, the propensity score matching method was used in 12 out of 16 retrospective studies, whereas the case-matched method was used in the others. Detail of matched characteristics was summarized in Supplementary Table 1. Nine studies focused on minor liver resection, and five studies reported outcomes limited to patients who underwent major liver resection. Ten studies reported the conversion rate of LH,
| study        | year | Country | Study design | sample size (LH/OH) | Mean age (LH/OH) | Gender (M/F) (LH/OH) | Childs-Pugh A:B ratio (LH/OH) | tumor size (LH/OH) | tumor pattern (LH/OH) | conversion rate | resection type | Matched method |
|--------------|------|---------|--------------|---------------------|------------------|---------------------|--------------------------|------------------|---------------------|-----------------|---------------|----------------|
| Belli et al. | 2007 | Italy   | R            | 23 vs 23            | 59.5 vs 62.4     | 13/10 vs 14/9       | 3.1 vs 3.2               | NA               | NA                  | 0               | minor          | M              |
| Truant et al.| 2011 | France  | R            | 36 vs 53            | 60.6 vs 63.3     | 31/5 vs 47/6        | 2.9 vs 3.1               | 34/2 vs 44/9     | NA                  | NA              | minor          | M              |
| Memet et al. | 2014 | France  | R            | 45 vs 45            | 62 vs 60         | 35/10 vs 37/8       | 3.2 vs 3.7               | NA               | NA                  | 0               | minor          | M              |
| Komatsu et al.| 2016 | Japan   | R            | 38 vs 38            | 61.5 vs 61.7     | 34/4 vs 33/5        | 4.75 vs 8.5              | 19/19 vs 22/16   | 34.21%             | major           | M              |
| Cheung et al.| 2016 | China   | R            | 110 vs 330         | 60 vs 61         | 80/30 vs 258/72     | 2.6 vs 2.85              | 100/10 vs 292/38 | 5.5%               | minor           | PSM            |
| Jiang et al. | 2016 | China   | R            | 59 vs 59           | 51 vs 50         | 42/17 vs 3821       | 3 vs 3                   | 59/0 vs 59/0     | 5.1%               | minor           | PSM            |
| Yoon et al.  | 2017 | Korea   | R            | 33 vs 33           | 56.03 vs         | 23/10 vs 26/7       | 3.31 vs NA               | NA               | NA                  | major           | PSM            |
| Xu et al.    | 2018 | China   | R            | 32 vs 32           | 53.5 vs 52       | 28/4 vs 28/4        | 4 vs 6.2                 | 29/3 vs 29/3     | NA                  | major           | PSM            |
| Kim et al.   | 2018 | Korea   | R            | 18 vs 36           | 55.7 vs 54.6     | 13/5 vs 22/14       | 2.9 vs 3.66              | 18/0 vs 36/0     | 0                   | minor           | PSM            |
| Sandro et al.| 2018 | Italy   | R            | 75 vs 75           | 68.6 vs 67.1     | 33/4/2 vs 24/51     | 2.5 vs 2.5               | 66/9 vs 65/10    | 7.6%               | minor           | PSM            |
| Delvecchio et al. | 2020 | RM      | R            | 38 vs 84           | 75 vs 74.3       | 29/9 vs 6/23        | 4 vs 7                   | 33/5 vs 68/18    | NA                  | major           | PSM            |
| Cheung et al.| 2020 | China   | R            | 24 vs 96           | 63 vs 62         | 20/4 vs 8/15        | 4.5 vs 4.8               | 18/6 vs 75/21    | NA                  | major           | PSM            |
| Hobeika et al.| 2020 | France  | R            | 124 vs 124         | 63 vs 63         | 98/26 vs 101/13     | NA                       | NA               | 16.8%              | minor           | PSM            |
| Yamamoto et al.| 2020 | Japan   | R            | 58 vs 58           | 71 vs 72         | 39/19 vs 30/28      | 1.7 vs 1.6               | NA               | NA                  | minor           | PSM            |
| Inoue et al. | 2020 | Japan   | R            | 28 vs 28           | 73 vs 72         | 19/9 vs 18/10       | 2.4 vs 2.4               | NA               | 12.70%             | NA              | PSM            |
| Fu et al.    | 2021 | China   | R            | 43 vs 77           | 52 vs 56         | 33/10 vs 59/18      | 2.5 vs 2.5               | NA               | 2.0%               | NA              | PSM            |

LH laparoscopic hepatectomy, OH open hepatectomy, M male, F female, NA not available, R retrospective, RM retrospective multicenter, PSM propensity score-matched.
which ranged from 0 to 34.21%. Surgical techniques including inflow occlusion method, parenchymal transection technique, and hemostasis method, were summarized in Supplementary Table 2. All studies were considered to be of adequate quality for the meta-analysis, as presented in Table 2.

**Intraoperative Outcomes**

All 16 pooled studies reported the operation time. Compared with the OH group, the LH group achieved a comparable operation time (WMD 19.33, 95% CI −1.67 to 40.34; P = 0.07; Figure 2A). According to 15 studies reporting intraoperative blood loss, our meta-analysis found blood loss was less in the LH than that in the OH groups (WMD −69.16; 95% CI −101.72 to −36.61; P < 0.01; Figure 2B). Similarly the occurrence of transfusion in LH was less than that in OH (OR 0.63; 95% CI 0.52 to 0.82; P < 0.01; Figure 2C).

**Postoperative Outcomes**

A shorter LOH was observed in LH (WMD −2.65; 95% CI −3.41 to −1.89; P < 0.01; Figure 3A). Postoperative complications were recorded in fifteen studies. The LH group had a decreased risk of overall postoperative complications (OR 0.57; 95% CI 0.46 to 0.71; P < 0.01; Figure 3B). Moreover, 15 studies reported postoperative mortalities. On the basis of these data, LH had a lower mortality rate (OR 0.27; 95% CI 0.11 to 0.66; P < 0.01; Figure 3C). To clarify the influence of LH on postoperative complications, we classified postoperative complications into minor complications and major complications.

With respect to the overall postoperative complications, the LH group had more favorable minor complication rate (OR 0.72; 95% CI 0.53 to 0.94; P = 0.02; Figure 4A) and major complication rate (OR 0.52; 95% CI 0.33 to 0.82; P < 0.01; Figure 4B) than OH. We also evaluated some detailed complications specifically associated with liver resection in patients with cirrhosis, including POLF and ascites. The LH group had less POLF (OR 0.60; 95% CI 0.38 to 0.95; P = 0.03; Figure 4C) and ascites (OR 0.44; 95% CI 0.28 to 0.72; P < 0.01; Figure 4D) than the OH group.

**Long-Term Outcomes**

Twelve studies reported the long-term outcomes including OS and DFS rates. The data showed that LH had more favorable 1-, 2-, and 5-year OS rate (1-year: HR 0.48; 95% CI 0.31 to 0.73; P < 0.01; Figure 5A; 2-year: HR 0.61; 95% CI 0.45 to 0.83; P < 0.01; Figure 5C; 5-year: HR 0.67; 95% CI 0.53 to 0.85; P < 0.01; Figure 5E) than OH. As for the DFS rate, LH had comparable outcomes to OH in terms of 1-, 2-, and 5-year DFS rates (1-year: HR 0.73; 95% CI 0.52 to 1.04; P = 0.08; Figure 5B; 2-year: HR 0.86; 95% CI 0.73 to 1.02; P = 0.08; Figure 5D; 5-year: HR 0.90; 95% CI 0.75 to 1.07; P = 0.23; Figure 5F).

**Subgroup Analysis**

Given that the included studies enrolled patients who underwent different extents of liver resection, subgroup analysis was conducted according to the resection extent (major or minor resection), as shown in Table 3. In accordance with the overall analysis, LH was associated with less blood loss, shorter LOH, fewer postoperative complications and mortalities, better 1-year, 2-year, and 5-year OS rate in minor resection subgroup analysis. Notably, in the major resection subgroup analysis, the LH group had a longer operation time, shorter LOH, and fewer postoperative complications than the OH group. Moreover, there was no difference in the OS and DFS rates between the LH and OH groups in the major resection subgroup analysis.

**Sensitivity Analysis and Publication Bias**

Sensitivity analyses were conducted by excluding the highest-weighted study in each pooled analysis. These exclusions did not alter the results of cumulative analyses. A funnel plot based on overall postoperative complications was performed to assess...
FIGURE 2 | Forest plots of intraoperative outcomes, (A) operation time, (B) blood loss, (C) transfusion rate.
FIGURE 3 | Forest plots of postoperative outcomes, (A) length of postoperative hospitalization, (B) overall postoperative complication, (C) postoperative mortality.
publication bias. No significant publication bias was detected by visual inspection of the funnel plot, in which the pooled studies were almost symmetrical and none of them were outside the 95% CI (Figure 6).

DISCUSSION

OH is a well-established curative treatment for HCC. However, patients with poor liver functional reserve, such as those with cirrhosis, are at higher risk of undergoing OH with a large surgical incision, wide extent of resection, and relatively large amount of blood loss. LH is emerging as a promising alternative approach for HCC patients with cirrhosis. Several previous meta-analyses have evaluated the advantages and disadvantages of LH (Table 4). Studies by Twaij et al. and Chen et al. identified significantly decreased overall postoperative complications, mortality, blood loss, and LOH in the LH group (12, 13). Goh et al. reported that LH was associated with better oncological outcomes (51). However, most studies included in those meta-analyses were retrospective studies with small sample sizes, which are prone to biases. Recently, several high-quality articles comparing LH and OH for HCC with cirrhosis have been published (14–18). To minimize the selection bias, this systematic review and meta-analysis pooled 16 case-matched retrospective studies. Comparisons were made between LH and OH for HCC in patients with cirrhosis, along with subgroup analysis according to different surgical extents.

Consistent with previous studies, the main findings obtained from our meta-analysis showed that patients who underwent LH presented notable oncological advantages in terms of 1-, 2-, and 5-year OS and 1-year DFS. In addition, our meta-analysis showed that LH was associated with lower postoperative morbidity, lower mortality, less blood loss, and shorter LOH than OH.

The primary concern with LH was bleeding control during transection in the setting of cirrhosis. The impact of cirrhosis on portal vein pressure and coagulation, and the movement restriction in laparoscopic surgery, make bleeding control challenging and increase the conversion risk. Truant et al. reported that uncontrolled bleeding accounted for 57.1% (4/7) of total conversion (42). Similarly, Sandro et al. also reported that one-third (2/7) of patients underwent conversion because of bleeding (15). With the accumulation of surgical experience, bleeding control during transection has been established by using the Pringle maneuver, compression with or without hemostatic material, clipping, suturing, temporary clamp for vessels, and various energy devices. Simultaneously, decreased intraoperative blood loss has been achieved with the application of appropriate pneumoperitoneum pressure, which reduces venous bleeding, and a magnified operating view, which allows meticulous manipulation. In this meta-analysis, the blood loss in the LH group was less than that in the OH group, as reported in previous studies. The considerable decrease in blood loss with the LH procedure means a decreased risk of transfusion. Accordingly, a lower transfusion rate in the LH group was observed in the present study.
Decreased blood loss, avoidance of large incisions and meticulous manipulation alleviate the surgical trauma. The minimally invasive approach reduces the risk of acute or delayed systematic adverse events and subsequent postoperative morbidity and mortality. The overall complication rate of LH was approximately 22.8% (169/741), which was significantly lower than that of OH (34.9%, 389/1,114). Recently, Goh et al. examined 400 cases of LH and reported a postoperative morbidity of 18.8%, which is equivalent to the present study (52). A similar result was observed in that OH had a nearly four-fold risk of postoperative death in comparison with LH (OR = 0.28).

Hepatectomy can lead to refractory ascites in patients with cirrhosis, which can be fatal. By preserving the integrity of the abdominal wall and reducing surgery-induced injury to the area surrounding the liver, disruption of collateral blood and lymphatic flow is minimized in the laparoscopic approach. Further analysis of postoperative complications revealed that the LH group had less postoperative ascites. The LH group had fewer major and minor complications as than the OH group. Furthermore, in the setting of LH, minor complications were predominant, accounting for 75.8% (91/120) of the overall complications, which was significantly higher than that in OH (68.2%, 176/258). Therefore, it can be deduced that LH is technically safe and tends to have fewer and milder complications.

Reduced surgical trauma, fewer postoperative events, and enhanced recovery resulted in shorter LOH and lower medical costs. More importantly, the present study demonstrated that patients undergoing LH had better oncological outcomes, including 1-, 2-, 5-year OS and 1-year DFS. Although no statistical difference was found in 2- and 5-year DFS owing to the inclusion of limited studies, a trend of favoring LH was observed. We speculated that the better prognosis of LH patients might lie in the less compression during laparoscopic manipulation, which prevented tumor cell metastasis. In addition, the minimally invasive approach resulted in faster recovery of the immune and nutritional status, which may also contribute to better prognosis.

**FIGURE 5** Forest plots of long-term outcomes, (A) 1-y overall survival rate, (B) 1-y disease-free survival rate, (C) 2-y overall survival rate, (D) 2-y disease-free survival rate, (E) 5-y overall survival rate, (F) 5-y disease-free survival rate.
| Outcomes               | Included studies | Sample size | I2  | Pooled mode | Pooled effect       | P value |
|-----------------------|-----------------|-------------|-----|-------------|---------------------|---------|
| **Operation time**    |                 |             |     |             |                     |         |
| All                   | 16              | 1975        | 93.7%| Random      | WMD:19.33(-1.67,40.34) | 0.07    |
| Minor resection       | 9               | 1351        | 93.9%| Random      | WMD:14.80(-11.24,40.85) | 0.27    |
| Major resection       | 5               | 448         | 84.7%| Random      | WMD:47.24(5.52,89.00) | 0.03    |
| **Blood loss**        |                 |             |     |             |                     |         |
| All                   | 15              | 1853        | 57.0%| Random      | WMD:-69.16(-101.72,-36.61) | <0.01   |
| Minor resection       | 9               | 1351        | 34.3%| Fixed       | WMD:-84.75(-112.22,-57.29) | <0.01   |
| Major resection       | 4               | 326         | 0.0% | Fixed       | WMD:-1.97(-65.34,61.40) | 0.95    |
| **Transfusion**       |                 |             |     |             |                     |         |
| All                   | 10              | 1381        | 7.3% | Fixed       | OR:0.63(0.40,1.00)   | 0.05    |
| Minor resection       | 4               | 823         | 0.0% | Fixed       | OR:0.52(0.27,1.02)   | 0.06    |
| Major resection       | 4               | 382         | 0.0% | Fixed       | OR:0.71(0.34,1.49)   | 0.36    |
| **LOH**               |                 |             |     |             |                     |         |
| All                   | 16              | 1975        | 69.4%| Random      | WMD:-2.65(-3.41,-1.88) | <0.01   |
| Minor resection       | 9               | 1351        | 70.8%| Random      | WMD:-2.45(-3.33,-1.57) | <0.01   |
| Major resection       | 5               | 448         | 4.8% | Random      | WMD:-2.99(-4.11,-1.86) | <0.01   |
| **Overall complication** |             |             |     |             |                     |         |
| All                   | 15              | 1859        | 0.0% | Fixed       | OR:0.57(0.46,0.71)   | <0.01   |
| Minor resection       | 9               | 1351        | 0.0% | Fixed       | OR:0.61(0.48,0.78)   | <0.01   |
| Major resection       | 5               | 448         | 0.0% | Fixed       | OR:0.47(0.30,0.75)   | <0.01   |
| **Minor complication**|                 |             |     |             |                     |         |
| All                   | 8               | 1295        | 0.0% | Fixed       | OR:0.70(0.53,0.94)   | 0.02    |
| Minor resection       | 6               | 1099        | 0.0% | Fixed       | OR:0.76(0.55,1.03)   | 0.08    |
| Major resection       | 2               | 196         | 0.0% | Fixed       | OR:0.41(0.18,0.95)   | 0.04    |
| **Major complication**|                 |             |     |             |                     |         |
| All                   | 10              | 1467        | 0.0% | Fixed       | OR:0.52(0.33,0.82)   | <0.01   |
| Minor resection       | 7               | 1215        | 0.0% | Fixed       | OR:0.57(0.34,0.94)   | 0.03    |
| Major resection       | 2               | 196         | 0.0% | Fixed       | OR:0.54(0.19,1.56)   | 0.26    |
| **Mortality**         |                 |             |     |             |                     |         |
| All                   | 10              | 1425        | 0.0% | Fixed       | OR:0.27(0.11,0.66)   | <0.01   |
| Minor resection       | 6               | 1063        | 0.0% | Fixed       | OR:0.26(0.08,0.83)   | 0.02    |
| Major resection       | 3               | 306         | 0.0% | Fixed       | OR:0.34(0.06,1.94)   | 0.22    |
| **POLF**              |                 |             |     |             |                     |         |
| All                   | 10              | 1352        | 0.0% | Fixed       | OR:0.60(0.38,0.95)   | 0.03    |
| Minor resection       | 5               | 914         | 0.0% | Fixed       | OR:0.63(0.33,1.21)   | 0.17    |
| Major resection       | 4               | 382         | 0.0% | Fixed       | OR:0.68(0.31,1.17)   | 0.14    |
| **Ascites**           |                 |             |     |             |                     |         |
| All                   | 11              | 971         | 0.00%| Fixed       | OR:0.44(0.28,0.72)   | <0.01   |
| Minor resection       | 7               | 663         | 0.00%| Fixed       | OR:0.48(0.27,0.86)   | 0.01    |
| Major resection       | 3               | 252         | 0.00%| Fixed       | OR:0.43(0.18,1.02)   | 0.05    |
| **1-year OS**         |                 |             |     |             |                     |         |
| All                   | 11              | 1367        | 32.90%| Fixed       | HR:0.48(0.31,0.73)   | <0.01   |
| Minor resection       | 7               | 985         | 0%   | Fixed       | HR:0.42(0.26,0.68)   | <0.01   |
| Major resection       | 4               | 382         | 36.4%| Fixed       | HR:0.72(0.30,1.74)   | 0.46    |
| **2-year OS**         |                 |             |     |             |                     |         |
| All                   | 12              | 1433        | 0.00%| Fixed       | HR:0.61(0.45,0.83)   | <0.01   |
| Minor resection       | 7               | 985         | 0%   | Fixed       | HR:0.59(0.42,0.85)   | <0.01   |
| Major resection       | 5               | 448         | 31.7%| Fixed       | HR:0.66(0.37,1.17)   | 0.16    |
| **5-year OS**         |                 |             |     |             |                     |         |
| All                   | 7               | 1127        | 31.70%| Fixed       | HR:0.67(0.53,0.85)   | <0.01   |
| Minor resection       | 5               | 885         | 35%  | Fixed       | HR:0.69(0.53,0.90)   | <0.01   |
| Major resection       | 2               | 242         | 55.8%| Random      | HR:0.57(0.26,1.30)   | 0.18    |
| **1-year DFS**        |                 |             |     |             |                     |         |
| All                   | 11              | 1387        | 59.70%| Random      | HR:0.73(0.52,1.04)   | 0.08    |
| Minor resection       | 6               | 939         | 67.10%| Random      | HR:0.63(0.41,0.98)   | 0.03    |
| Major resection       | 5               | 448         | 22.3%| Fixed       | HR:1.03(0.69,1.56)   | 0.88    |
| **2-year DFS**        |                 |             |     |             |                     |         |
| All                   | 11              | 1387        | 0%   | Fixed       | HR:0.86(0.73,1.02)   | 0.08    |
| Minor resection       | 6               | 939         | 0%   | Fixed       | HR:0.87(0.72,1.05)   | 0.15    |
| Major resection       | 5               | 448         | 0%   | Fixed       | HR:0.83(0.59,1.17)   | 0.29    |
| **5-year DFS**        |                 |             |     |             |                     |         |
| All                   | 6               | 781         | 23.80%| Fixed       | HR:0.90(0.75,1.07)   | 0.23    |
Unlike previous meta-analyses on this issue, the present study performed subgroup analysis based on the surgical extent, which was necessary to eliminate such heterogeneity among the studies. The present study found that the results of subgroup analysis based on minor resection were in line with the results of the overall analysis, however, the results of subgroup analysis based on major resection should be cautiously interpreted, although only three studies were included. As expected, LMH was a potential alternative to its open counterpart, and it maintained the advantage of shorter LOH and fewer postoperative complications as in laparoscopic minor hepatectomy. However, LMH had a longer operation time than the open approach, suggesting that this procedure is technically demanding. Notably, Komatsu et al. reported a conversion rate of 34.21% in the LMH group, reflecting the steep learning curve of LMH in the setting of HCC with cirrhosis. Comprehensive liver function assessment and a good understanding of the liver anatomy, as well as ample surgical expertise, are the most important factors for successful LMH. Emerging evidence proving the value of LMH may lead to the expansion of the indication of LH to HCC patients with cirrhosis.

Our review has notable strengths as follows: (i) all included studies were case-matched studies, which balanced the baseline

### TABLE 3 | Continued

| Outcomes                          | Included studies | Sample size | I² | Pooled mode | Pooled effect         | P value |
|-----------------------------------|------------------|-------------|----|-------------|-----------------------|---------|
| Minor resection                   | 4                | 735         | 0% | Fixed       | HR:0.87(0.71,1.06)    | 0.16    |
| Major resection                   | 2                | 242         | 81.9% | Random     | HR:0.95(0.37,2.44)    | 0.91    |

LOH length of hospitalization, CI confidence interval, WMD weighted mean difference, OR odds ratio, POLF postoperative liver failure, HR hazard ratio, OS overall survival, DFS disease-free survival.

### TABLE 4 | Summary of outcomes reported by previous meta-analysis and present meta-analysis.

| Study          | Latest literature search | Included studies | Study characteristics | Operation time | Blood loss | Blood transfusion | postoperative morbidity | postoperative mortality | LOH | 1-year OS | 5-year OS | 1-year DFS | 5-year DFS |
|----------------|--------------------------|------------------|-----------------------|----------------|------------|-------------------|------------------------|------------------------|-----|----------|-----------|-----------|-----------|
| Twaij et al.   | 2013.8                   | 4                | R&R, RM              | E              | FLH        | FLH               | FLH                    | NA                     | FLH | NA       | NA        | NA        | NA        |
| Chen et al.    | 2015.3                   | 7                | R&R, RM              | E              | FLH        | FLH               | FLH                    | E                      | FLH | E        | E         | E         | E         |
| Goh et al.     | 2016.11                  | 5                | R&R, RM              | NA             | NA         | NA                | NA                     | NA                     | NA  | FLH      | FLH       | FLH       | E         |
| Present study  | 2021.3                   | 16               | RM                   | E              | FLH        | FLH               | FLH                    | FLH                    | FLH | FLH      | FLH       | E         | E         |

LOH length of hospitalization, OS overall survival, DFS disease-free survival, R retrospective study, RM retrospective matched study, RCT randomized clinical trial, E equivalent, FLH favors laparoscopic hepatectomy, NA not available.

**FIGURE 6** | Funnel plots of postoperative complication.

**FIGURE 6** | Begg's funnel plot with pseudo 95% confidence limits.
CONCLUSION

In summary, this systematic review and meta-analysis comparing LH and OH demonstrated that LH can be safely performed in selected HCC patients with cirrhosis. LH offers favorable short-term outcomes and long-term oncological outcomes in minor liver resections. Although LMH seems to favor short-term outcomes and long-term oncological outcomes, concerns about surgical and oncological safety remain. More evidence on LMH is warranted before expanding its indication to patients with cirrhosis.

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DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

This research was an analysis of published data and did not require informed consent. Ethics approval and consent to participate were not applicable in this research.

AUTHOR CONTRIBUTIONS

Conception and design: X-JC and YP. Administrative support: X-JC. Provision of study material or patients: YP, KC, and S-JX. Collection and assembly of data: KC, S-JX, and J-QC. Data analysis and interpretation: YP. Manuscript writing: all authors. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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