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META-ANALYSIS

Laparoscopic *vs* open radical resection in management of gallbladder carcinoma: A systematic review and meta-analysis

Shilin He, Tu-Nan Yu, Jia-Sheng Cao, Xue-Yin Zhou, Zhe-Han Chen, Wen-Bin Jiang, Liu-Xin Cai, Xiao Liang

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Abstract

BACKGROUND

Radical resection offers the only hope for the long-term survival of patients with gallbladder carcinoma (GBC) above the T1b stage. However, whether it should be performed under laparoscopy for GBC is still controversial.

AIM

To compare laparoscopic radical resection (LRR) with traditional open radical resection (ORR) in managing GBC.

METHODS

A comprehensive search of online databases, including Medline (PubMed), Cochrane Library, and Web of Science, was conducted to identify comparative studies involving LRR and ORR in GBCs till March 2023. A meta-analysis was subsequently performed.

RESULTS

A total of 18 retrospective studies were identified. In the long-term prognosis, the LRR group was comparable with the ORR group in terms of overall survival and tumor-free survival (TFS). LRR showed superiority in terms of TFS in the T2/tumor-node-metastasis (TNM) II stage subgroup *vs* the ORR group (P = 0.04).

In the short-term prognosis, the LRR group had superiority over the ORR group in the postoperative length of stay (POLS) ($P < 0.001$). The sensitivity analysis showed that all pooled results were robust.

CONCLUSION

The meta-analysis results show that LRR is not inferior to ORR in all measured outcomes and is even superior in the TFS of patients with stage T2/TNM II disease and POLS. Surgeons with sufficient laparoscopic experience can perform LRR as an alternative surgical strategy to ORR.

Key Words: Gallbladder carcinoma; Laparoscopic radical resection; Open radical resection; Outcome; Systematic review; Meta-analysis

Core Tip: Using laparoscopic surgery to treat gallbladder carcinoma (GBC) is still controversial. This is the first meta-analysis to directly compare laparoscopic radical resection and open radical resection in GBC. Unlike previous similar meta-analyses, we excluded interference from simple cholecystectomy cases in our study and conducted a subgroup analysis. We also tested the publication bias and conducted a sensitivity analysis.

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INTRODUCTION

Gallbladder carcinoma (GBC) carries one of the most dismal prognoses among all types of malignancies. The 5-year survival rates range from 5% to 15%[1,2]. The most common pathological type of GBC is adenocarcinoma, which accounts for more than 80% of all GBCs[3,4]. Others types include adenosquamous carcinoma, squamous carcinoma, neuroendocrine carcinoma, and so forth. It has a remarkable propensity to spread early by invading the liver and other adjacent organs directly or metastasizing to lymph nodes. Thus, it is generally believed that simple cholecystectomy (SC) is not sufficient for GBC staged T1b and above. Radical resection, which includes partial hepatectomy and lymph node dissection, offers the only hope for long-term survival[5,6].

Systemic therapy has consistently played an essential role in treating GBC and biliary tract cancer (BTC), considering the low resection rate at the diagnosis. The main chemotherapy regimen employed for advanced GBC, even today, remains cisplatin combined with gemcitabine (CisGem)[7]. In the last decade, immune checkpoint inhibitors (ICIs) have made major breakthroughs in the field of cancer treatment and changed the treatment pattern of several malignant tumors, especially malignancies with deficient mismatch repair, high tumor mutational burden, or high microsatellite instability[8-10]. However, the role of ICIs in BTC needs further exploration. Also, their combination with other anti-cancer drugs (chemotherapy, targeted agents, *etc.*) may be a more promising direction[10-15]. Additionally, researchers are actively investigating the relationship between ICIs and other therapeutic targets, such as breast cancer susceptibility genes (BRCA) 1/2 mutations (BRCAm), to provide patients with more personalized and precise treatment[16].

Laparoscopic surgery has been widely performed in most cancers, including colon, gastric, and liver cancers. Compared with traditional open surgery, laparoscopic radical surgery shows the advantage of minimal invasion and achieves satisfactory long-term survival[17-20]. However, for a long time, laparoscopic surgery has only been recommended for treating benign gallbladder diseases, staging and biopsying of GBC, or resecting GBC in very early stages (Tis and T1a)[21-23]. GBC with T1b stage or above has always been considered contraindicated, requiring a radical resection. In recent years, many surgeons have tried to apply laparoscopic technology to manage GBCs. Several meta-analyses have discussed this issue and reached optimistic conclusions[24-27]. However, whether laparoscopic radical resection (LRR) is feasible in treating GBC staged T1b and above still has not been fully demonstrated because the studies included in these meta-analyses contained several SC cases. Thus, a new meta-analysis focusing on the feasibility of LRR by excluding all SC cases should be performed.

MATERIALS AND METHODS

Search strategy and study selection

A systematic review of the published studies till March 2023 was performed to screen studies comparing the outcomes of patients who underwent LRR *vs* open radical resection (ORR) for GBCs. We searched the abstracts in PubMed, Cochrane Library, and Web of Science using the following keywords: Laparoscopic OR minimally invasive AND gallbladder cancer

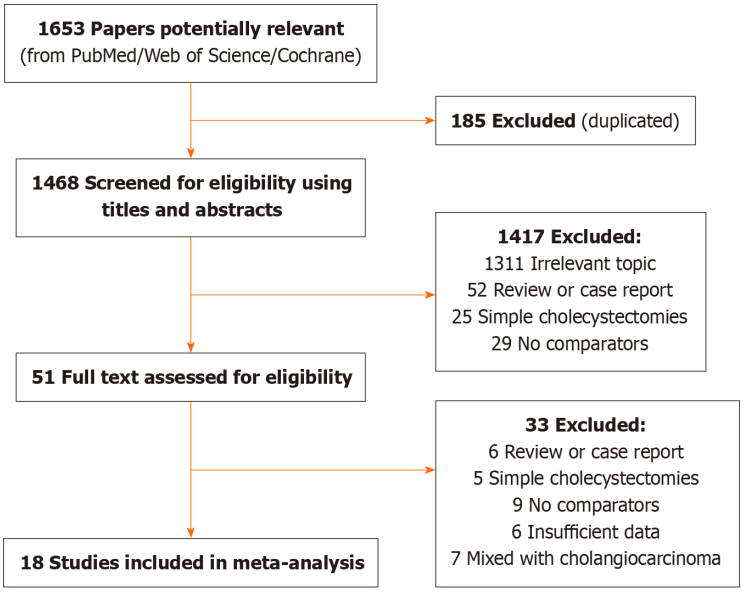

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Figure 1 Search strategy and identification of studies for the systematic review and meta-analysis.

OR GBC OR gallbladder neoplasm. Searches were limited to human studies and English-language publications. The citation lists of retrieved studies were manually filtered to identify other studies. Two researchers independently searched for studies and compared the results.

Study selection

Eligible studies were required to meet the following criteria: (1) The study must have a comparative design and evaluate LRR and ORR for GBC; and (2) the study should be a human study published in English.

The study was excluded from the analysis for the following reasons: (1) Case report or case series studies; (2) studies enrolling patients who just underwent laparoscopic simple cholecystectomy (LSC) or whose surgical method was unclear; and (3) studies including other tumors, such as intrahepatic bile duct cancer, in which GBC data could not be extracted separately. The literature search and selection strategy are demonstrated in Figure 1. The modified Newcastle-Ottawa scale was used to assess the quality of included studies[28].

Data extraction and outcome measures

The data extraction was performed independently by two authors. The following details were extracted: Study period, study design, country/region, number of patients, sex, age, type of surgery, tumor stage, operation time, blood loss, complications, postoperative length of stay (POLS), resection margin, and so forth.

The primary outcomes were overall survival (OS) and tumor-free survival (TFS). If the hazard ratio (HR) and 95% confidence interval (CI) of survival were not reported, they were extracted from the survival curve using Engauge Digitizer 11.1 software. Subsequently, the HR and 95%CI were calculated and converted into lnHR and its standard error for further analysis[29]. The secondary outcomes included the following: The number of lymph nodes harvested (No. LNH), operation time, blood loss, R0 resection rate, POLS, and complication rate. In cases where the aforementioned information was a a median (range) for a continuous variable, it was converted into the mean ± SD using established methods[30,31]. Two authors independently extracted and compared the data to eliminate the errors. Due to unavailable data, not all included studies could participate in every outcome analysis.

Statistical analysis

The studies from which valid data could be extracted were included in the final meta-analysis. For dichotomous data, the odds ratio (OR) and 95%CI were calculated; for continuous data, the mean difference (MD) and 95%CI were calculated. For survival data, we calculated HR and 95%CI. The χ^2 and I^2 statistic were used to measure heterogeneity. For example, the χ^2 $P < 0.05$ or $I^2 > 50\%$ indicated significant heterogeneity. In this case, a random-effects model was adopted when appropriate; otherwise, a fixed-effects model was used. All meta-analyses were performed using the statistical software [Review Manager (RevMan) version 5.3, Copenhagen, Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration; 2014]. A P value < 0.05 indicated a statistically significant difference.

Risk of bias

Begg's and Egger's tests were used to evaluate potential publication bias quantitatively. A P value or corrected P value of < 0.05 in the test indicated the presence of significant statistical publication bias. The results are shown in Table 1. Besides, sensitivity analysis was conducted to assess the stability of the pooled results of major measured outcomes. The results of the sensitivity analysis are presented in Figure 2. Begg's test, Egger's test, and sensitivity analysis were conducted using

Table 1 Publication bias test of major measured outcomes

	No. of studies	No. of patients		Egger's test		Begg's test (continuity corrected)	
		LRR	ORR	*t*	*P* > |*t*|	z	*P* > |z|
No. LNH	17	799	1209	-5.1	< 0.001	0.37	0.711
Operation time	16	564	764	1.57	0.139	0.86	0.392
Blood loss	14	489	689	-2.18	0.050	1.86	0.063
POLS	17	799	1209	-3.03	0.008	0.04	0.967
R0 rate	8	1609	1705	1.64	0.162	0.00	1.000
Complications	15	511	703	-1.67	0.119	1.29	0.198
Complications (Clavien-Dindo 3-4)	8	244	245	-1.85	0.162	0.73	0.462
OS	15	1299	1936	0.3	0.767	0.68	0.499
TFS	10	339	338	-1.04	0.329	0.36	0.721

No. LNH: Number of lymph node harvested; POLS: Postoperative length of stay; OS: Overall survival; TFS: Tumor-free survival; LRR: Laparoscopic radical resection; ORR: Open radical resection.

Stata software (version 17.0).

Subgroup analysis

Subgroup analysis was conducted to reduce interference from tumor stage and other factors. Based on the available data, we found that fewer data on T1/tumor-node-metastasis (TNM) **I**stage and T3/TNM III stage could be extracted. Therefore, we conducted a subgroup analysis for T1/TNM I + T2/TNM II stage**,** T2/TNM II stage, and T2/TNM II + T3/TNM III stage. In addition, we also conducted a subgroup analysis of the data after propensity score matching (PSM).

RESULTS

Study selection and characteristics

Eighteen retrospective studies were identified after screening based on the inclusion criteria and assessing the full text of potentially eligible studies[32-49]. The characteristics and quality evaluation of the 18 included studies for meta-analysis are summarized in Table 2. These studies included 3513 patients with GBC who underwent surgery with curative intention, of which 1422 were in the LRR group and 2091 in the ORR group. The details about these patients are listed in Table 3. One study[33] included 12 cases of LSC; we retained this study and only included data from its T2 and T3 subgroups comprising no LSC cases. Another study[47] initially included eight LSC cases. However, the laparoscopic and open surgery groups were reduced to four cases following PSM. This adjustment had less impact on the analysis results, thus warranting the retention of this study. The data after PSM was available in 6 of the 18 studies.

Long-term outcomes

OS and TFS: The OS data were available in 1615 studies, and no significant heterogeneity existed [χ^2 = 17.31, *df* = 15 (*P* = 0.30), I^2 = 13%]. Therefore, a fixed-effects model was used. The result showed no difference in OS between the LRR and ORR groups (HR: 0.92, 95%CI: 0.80 to 1.05, *P* = 0.22; Figure 3A).

The TFS data were available in 10 studies, and no significant heterogeneity existed [χ^2 = 9.32, *df* = 9 (*P* = 0.41), I^2 = 3%]. Therefore, a fixed-effects model was used. The result showed no difference in TFS between the LRR and ORR groups (HR: 0.93, 95%CI: 0.66 to 1.31, *P* = 0.70; Figure 3B).

OS and TFS after PSM: The OS data after PSM were available in five studies, and no significant heterogeneity existed [χ^2 = 1.15, *df* = 4 (*P* = 0.89), I^2 = 0%]. Therefore, a fixed-effects model was used. The result showed no difference in OS between the LRR and ORR groups (HR: 0.71, 95%CI: 0.39 to 1.30, *P* = 0.27; Figure 3C).

The TFS data after PSM were available in four studies, and no significant heterogeneity existed [χ^2 = 0.96, *df* = 3 (*P* = 0.81), I^2 = 0%]. Therefore, a fixed-effects model was used. The result showed no difference in TFS between the LRR and ORR groups (HR: 1.00, 95%CI: 0.63 to 1.57, *P* = 0.99; Figure 3D).

OS and TFS in T2/TNM II subgroup: The OS data of patients with stage T2/TNM II disease were available in seven studies, and no significant heterogeneity existed [χ^2 = 3.66, *df* = 6 (*P* = 0.72), I^2 = 0%]. Therefore, a fixed-effects model was used. The result showed no difference in OS between the LRR and ORR groups for the T2/TNM II subgroup (HR: 0.94, 95%CI: 0.53 to 1.65, *P* = 0.83; Figure 4A).

Table 2 Characteristics of included comparative studies

Ref.	Year	Country	Study design	NOS	Group	Patient (*n*)	Age	F/M	T stage/TNM stage(*n*)	Follow-up (mo)
Agarwal *et al*[32]	2015	India	Retrospective	7	LRR	24	44 (21-61)	17/7	I: 3; II: 10; III: 11	18 (6-34)
					ORR	46	49 (23-70)	34/12	I: 5; II: 10; III: 31	
Feng *et al* [33]	2019	China	Retrospective	7	LRR	41	64 ± 14	17/24	Tis: 9; T1: 10; T2: 14; T3: 8	12 (2-93)
					ORR	61	66 ± 10	22/39	Tis: 4; T1: 9; T2: 1 32; T3: 16	
Itano *et al* [34]	2015	Japan	Retrospective	6	LRR	16	68.1 ± 19.9	7/9	T1: 3; T2: 13	37
					ORR	14	71.5 ± 13.2	9/5	T1-T2: 14	48
Jang *et al*[35]	2019	Korea	Retrospective	7	LRR	55	70.1 ± 8.1	36/19	T2: 55	35.2 (3-139)
					ORR	44	65.5 ± 10.5	21/23	T2: 44	38.6 (4-160)
Nag *et al*[36]	2019	India	Retrospective	7	LRR	30	49.6 ± 12.8	27/3	T1: 8; T2: 8; T3: 8; T4: 2	NA
					ORR	38	49 ± 10.1	23/15	T1: 6; T2: 17; T3: 15; T4: 0	NA
Ong *et al*[37]	2017	United States	Retrospective	6	LRR	623	70 (61-79)	442/181	T1 + T2: 461; T3: 146; UKN: 16	NA
					ORR	882		587/295	T1 + T2: 469; T3: 374; UKN: 39	NA
Vega *et al* [38]	2019	United StatesChile	Retrospective	8	LRR	65	68 (59-76)	49/141	T1: 14; T2: 43; T3: 8	Survivors: 70.8 (95%CI: 53.6 to 87.3)
					ORR	190		11/54	T1: 5; T2: 126; T3: 39	
Cao *et al*[46]	2021	China	Retrospective	8	LRR	53	61 (48-77)	35	T1b: 3; T2: 50	NA
					ORR	61	64 (39-79)	47	T1b: 5; T2: 56	NA
Dou *et al*[48]	2022	China	Retrospective	7	LRR (PSM)	30	> 60: 21	23	T2: 9; T3: 21	NA
					ORR (PSM)	30	> 60: 19	25	T2: 10; T3: 20	NA
Lee *et al*[43]	2022	Korea	Retrospective	8	LRR	20	71.85 ± 9.11	15	T1: 4; T2: 12; T3: 4	NA
					ORR	24	68.08 ± 10.64	13	T1: 5; T2: 16; T3: 3	NA
Navarro *et al*[41]	2020	Korea	Retrospective	7	LRR (PSM)	43	66.7 ± 10.3	18	T2: 43	32 (2-125)
					ORR (PSM)	43	65.4 ± 7.6	15	T2: 43	
Regmi *et al* [40]	2020	China	Retrospective	7	LRR	20	> 70y: 4	13	T1b: 10; T2: 10	21.28 (12-29)
					ORR	30	> 70y: 3	19	T1b: 13; T2: 17	20.4 (12.25-29.50)
Huang *et al* [44]	2022	China	Retrospective	8	LRR (PSM)	35	58.7 ± 10.5	19	T3: 35	NA
					ORR (PSM)	35	60.4 ± 10.6	18	T3: 35	NA
D'Silva *et al* [45]	2021	China	Retrospective	7	LRR (PSM)	12	68.5 ± 10.56	7	T2: 7;T3: 9	21.5 (9-80)

					ORR (PSM)	12	67.5 ± 12.88	7	T2: 5;T3: 3	
Lee *et al*[42]	2022	Korea	Retrospective	8	LRR (PSM)	56	62.0 ± 13.7	27	T2: 56	26.2
					ORR (PSM)	56	62.5 ± 15.0	28	T2: 56	
Wang *et al* [39]	2020	China	Retrospective	8	LRR	45	62.6 (45-76)	29	Tb: 30; T2: 15	38 (3-84)
					ORR	61	65.2 (51-82)	37	Tb: 35;T2: 26	33 (6-72)
AlMasri *et al* [49]	2020	United States	Retrospective	8	LRR	235	66.1 ± 11.8	64	I: 24; II: 78; III: 133	NA
					ORR	445	65.8 ± 11.2	294	I: 29; II: 114; III: 302	NA
Cho *et al*[47]	2022	Korea	Retrospective	7	LRR (PSM)	19	69.9 ± 9.1	11	T2: 19	26
					ORR (PSM)	19	66.7 ± 7.8	7	T2: 19	70

UKN: Unknown; LRR: Laparoscopic radical resection; ORR: Open radical resection; PSM: Propensity score matching; NOS: The modified Newcastle–Ottawa scale; TNM: Tumor-node-metastasis; NA: Not available; F: Female; M: Male; CI: Confidence interval.

The TFS data of patients with stage T2/TNM II disease were available in five studies, and no significant heterogeneity existed [χ^2 = 4.12, *df* = 4 (*P* = 0.39), I^2 = 3%]. Therefore, a fixed-effects model was used. The LRR group showed a better TFS than the ORR group for the T2/TNM II subgroup (HR: 0.50, 95%CI: 0.26 to 0.96, *P* = 0.04; Figure 4B).

OS and TFS in T1/TNM I + T2/TNM II subgroup: The OS data of patients with stage T1/TNM I or T2/TNM II disase were available in 11 studies, and no significant heterogeneity existed [χ^2 = 7.06, *df* = 11 (*P* = 0.79), I^2 = 0%]. Therefore, a fixed-effects model was used. The result showed no difference in OS between the LRR and ORR groups for the T1/TNM I + T2/TNM II subgroup (HR: 1.35, 95%CI: 0.95 to 1.92, *P* = 0.09; Figure 4C).

The TFS data of patients with stage T1/TNM I or T2/TNM II disease were available in seven studies, and no significant heterogeneity existed [χ^2 = 8.23, *df* = 6 (*P* = 0.22), I^2 = 27%]. Therefore, a fixed-effects model was used. A significant difference was detected in TFS between the LRR and ORR groups for the T1/TNM I or T2/TNM II subgroup (HR: 0.83, 95%CI: 0.54 to 1.27, *P* = 0.39; Figure 4D).

OS and TFS in T2/TNM II + T3/TNM III subgroup: The OS data of patients with stage T2/TNM II or T3/TNM III disease were available in nine studies, and no significant heterogeneity existed [χ^2 = 4.56, *df* = 10 (*P* = 0.92), I^2 = 0%]. Therefore, a fixed-effects model was used. The result showed no difference in OS between the LRR and ORR groups for the T2/TNM II + T3/TNM III subgroup (HR: 0.82, 95%CI: 0.64 to 1.05, *P* = 0.12; Figure 4E).

The TFS data of patients with stage T2/TNM II or T3/TNM III disease was available in seven studies, and no significant heterogeneity existed [χ^2 = 7.79, *df* = 6 (*P* = 0.25), I^2 = 23%]. Therefore, a fixed-effects model was used. A significant difference was detected in TFS between the LRR and ORR groups for the T2/TNM II + T3/TNM III subgroup (HR: 0.81, 95%CI: 0.52 to 1.24, *P* = 0.32; Figure 4F).

Short-term outcomes

Number of LNH: The data regarding the No. LNH were reported in 17 studies. Significant heterogeneity existed between these studies [χ^2 = 131.34, *df* = 16 (*P* < 0.001), I^2 = 88%]. Therefore, a random-effects model was used. The results showed no significant difference in the No. LNH between the LRR and ORR groups (MD: -0.73, 95%CI: -1.87 to 0.41, *P* = 0.21; Figure 5A).

The data regarding the No. LNH after PSM were reported in six studies. Significant heterogeneity was found between these studies [χ^2 = 78.43, *df* = 5 (*P* < 0.001); I^2 = 94%]. Therefore, a random-effects model was used. The results showed no significant difference in the No. LNH between the LRR and ORR groups (MD: -1.52, 95%CI: -4.20 to 1.15, *P* = 0.26; Figure 6A).

Operation time: The data on operation time were reported in 16 studies. Significant heterogeneity existed between these studies [χ^2 = 288.26, *df* = 15 (*P* < 0.001), I^2 = 95%]. Therefore, a random-effects model was used. The results showed no significant difference in the operation time between the LRR and ORR groups (MD: 7.72, 95%CI: -16.28 to 31.72, *P* = 0.53; Figure 5B).

The data on operation time after PSM were reported in six studies. Significant heterogeneity existed between these studies [χ^2 = 81.27, *df* = 5 (*P* < 0.001), I^2 = 94%]. Therefore, a random-effects model was used. The results showed no significant difference in the operation time between the LRR and ORR groups (MD: 22.69, 95%CI: -12.93 to 58.31, *P* = 0.21; Figure 6B).

Table 3 Perioperative outcomes of included comparative studies

Ref.	Group	Pts	No. LNH	R0 margin(*n*)	Operation time (min)	Blood loss (mL)	POLS	Complications	Complications(Clavien-Dindo 3-4)
Agarwal *et al*[32]	LRR	24	12.5 ± 5.4	NA	270 (180-340)	200 (100-850)	5 (3-16)	3	NA
	ORR	46	12.9 ± 5.4	NA	240 (180-360)	275 (100-800)	5 (3-17)	8	NA
Feng *et al*[33]	LRR	41	5 ± 3	33	137 ± 92	358 ± 390	5 ± 3	3	NA
	ORR	61	5 ± 3	47	168 ± 51	386 ± 391	11 ± 5	6	NA
Itano *et al*[34]	LRR	16	12.6 ± 3.1	NA	368 ± 73	152 ± 90	9.1 ± 1.6	1	NA
	ORR	14	10.2 ± 4.0	NA	352 ± 75	777 ± 392	21.6 ± 9.0	3	NA
Jang *et al*[35]	LRR	55	7.6 ± 3.4	NA	231.0 ± 95.2	225.1 ± 328.6	5.8 ± 5.3	7	4
	ORR	44	9.9 ± 6.8	NA	252.5 ± 76.1	310.5 ± 260.9	9.5 ± 4.8	6	3
Nag *et al*[36]	LRR	30	11.9 ± 5.2	30	286.5 ± 71.6	158.6 ± 85.7	6.4 ± 3.1	5	0
	ORR	38	12.7 ± 4.2	37	274.2 ± 96.3	219.4 ± 87.7	9 ± 8.0	12	5
Ong *et al*[37]	LRR	623	NA	484	NA	NA	NA	NA	NA
	ORR	882	NA	664	NA	NA	NA	NA	NA
Vega *et al*[38]	LRR	65	6 (0-19)	62	240 (120-275)	300 (30-1200)	4 (2-18)	12	NA
	ORR	190	6 (0-27)	172	240 (60-600)	200 (50-2000)	6 (1-52)	38	NA
Cao *et al*[46]	LRR	53	6 (1-16)	NA	238.4	257 ± 6.3	10.4 ± 18.6	NA	NA
	ORR	61	8 (1-42)	NA	215.7	256.2 ± 6.3	11.3 ± 18.6	NA	NA
Dou *et al*[48]	LRR (PSM)	30	10.12 ± 0.90	NA	328.12 ± 21.53	256.74 ± 39.21	10.43 ± 0.97	6	3
	ORR (PSM)	30	7.92 ± 0.57	NA	245.82 ± 15.18	484.36 ± 64.67	14.23 ± 1.07	4	2
Lee *et al*[43]	LRR	20	5.75 ± 3.54	19	186.60 ± 88.14	320.00 ± 451.72	10.95 ± 4.82	2	2
	ORR	24	6.75 ± 4.17	23	231.67 ± 82.97	593.75 ± 912.04	12.80 ± 4.87	5	5
Navarro *et al*[41]	LRR (PSM)	43	6.12 ± 5.78	NA	139.05 ± 97.09	71.63 ± 178.77	6.05 ± 9.846	0	0
	ORR(PSM)	43	11.93 ± 7.03	NA	211.16 ± 91.36	208.14 ± 242.165	12.58 ± 5.504	4	0
Regmi *et al*[40]	LRR	20	5.4 ± 3.5	20	258.25 ± 72.50	242 ± 108.5	6.2 ± 2.4	3	NA
	ORR	30	5.8 ± 2.1	30	227.00 ± 59.81	401 ± 130.3	8.6 ± 2.3	6	NA
Huang *et al*[44]	LRR (PSM)	35	8.4 ± 4.6	34	245.0 (183.0-285.0)	50.0 (50.0-150.0)	6.0 (6.0-7.0)	4	1
	ORR (PSM)	35	8.1 ± 3.9	33	160.0 (125.0-230.0)	50.0 (50.0-150.0)	7.0 (6.0-8.0)	6	2
Silva *et al*[45]	LRR (PSM)	12	6.5 (4-9.5)	NA	237.5 (120-520)	300 (150-1750)	4.5 (2-12)	1	0
	ORR (PSM)	12	8.5 (4.5-14.5)	NA	272.5 (180-560)	275 (100-1800)	8 (5-32)	4	0

Lee *et al*[42]	LRR (PSM)	56	4.6 ± 4.1	NA	171.7 ± 64.1	NA	5.7 ± 4.2	4	NA
	ORR (PSM)	56	6.9 ± 4.9	NA	98.0 ± 53.2	NA	9.8 ± 4.9	7	NA
Wang *et al* [39]	LRR	45	19.8 ± 7.9	NA	115 ± 32.5	100 ± 25.4	3.5 ± 1.9	3	NA
	ORR	61	17.3 ± 5.7	NA	100 ± 20.4	200 ± 45.6	5.6 ± 2.7	8	NA
AlMasri *et al* [49]	LRR	235	6.5 ± 14.6	195	NA	NA	7.0 ± 13.0	NA	NA
	ORR	445	6.7 ± 13.5	348	NA	NA	8.8 ± 10.9	NA	NA
Cho *et al*[47]	LRR (PSM)	19	5.3 ± 6.6	NA	218.9 ± 145.0	NA	8.4 ± 5.9	4	0
	ORR (PSM)	19	7.3 ± 5.5	NA	316.8 ± 80.3	NA	14.4 ± 6.0	2	0

Pts: Patients; No. LNH: Number of lymph node harvested; LRR: Laparoscopic radical resection; ORR: Open radical resection; POLS: Postoperative length of stay; NA: Not available; PSM: Propensity score matching.

Intraoperative blood loss: The data on intraoperative blood loss were reported in 14 studies. Significant heterogeneity existed between these studies [χ^2 = 516.12, *df* = 13 (*P* < 0.001), I^2 = 97%]. Therefore, a random-effects model was used. The LRR group showed lesser intraoperative blood loss than the ORR group (MD: -60.58, 95%CI: -102.94 to -18.23, *P* = 0.005; Figure 5C).

The data on intraoperative blood loss after PSM were reported in four studies. Significant heterogeneity existed between these studies [χ^2 = 237.8, *df* = 3 (*P* < 0.001), I^2 = 99%]. Therefore, a random-effects model was used. The results showed no significant difference in the intraoperative blood loss between the LRR and ORR groups (MD: -94.71, 95%CI: -262.26 to 72.83, *P* = 0.27; Figure 6C).

POLS: The data regarding POLS were reported in 17 studies. Significant heterogeneity existed between these studies [χ^2 = 212.98, *df* = 16 (*P* < 0.001), I^2 = 92%]. Therefore, a random-effects model was used. The LRR group showed a shorter POLS than the ORR group (MD: -3.31, 95%CI: -4.38 to -2.24, *P* < 0.001; Figure 5D).

The data regarding POLS after PSM were reported in six studies. Significant heterogeneity was found between these studies [χ^2 = 139.03, *df* = 5 (*P* < 0.001);, I^2 = 96%]. Therefore, a random-effects model was used. The LRR group showed a shorter POLS than the ORR group (MD: -4.11, 95%CI: -6.10 to 2.12, *P* < 0.001; Figure 6D).

Complications: The data on complications were reported in 15 studies. No significant heterogeneity existed [χ^2 = 7.68, *df* = 14 (*P* = 0.91); I^2 = 0%]. Therefore, a fixed-effects model was used. The LRR group showed a lower complication rate than the ORR group (OR: 0.69, 95%CI: 0.49 to 0.96, *P* = 0.03; Figure 5E).

The data on complications after PSM were reported in six studies. No significant heterogeneity existed [χ^2 = 18.04, *df* = 15 (*P* = 0.26), I^2 = 17%]. Therefore, a fixed-effects model was used. The results showed no significant difference in the complications between the LRR and ORR groups (OR: 1.00, 95%CI: 0.78 to 1.28, *P* = 1.00; Figure 6E).

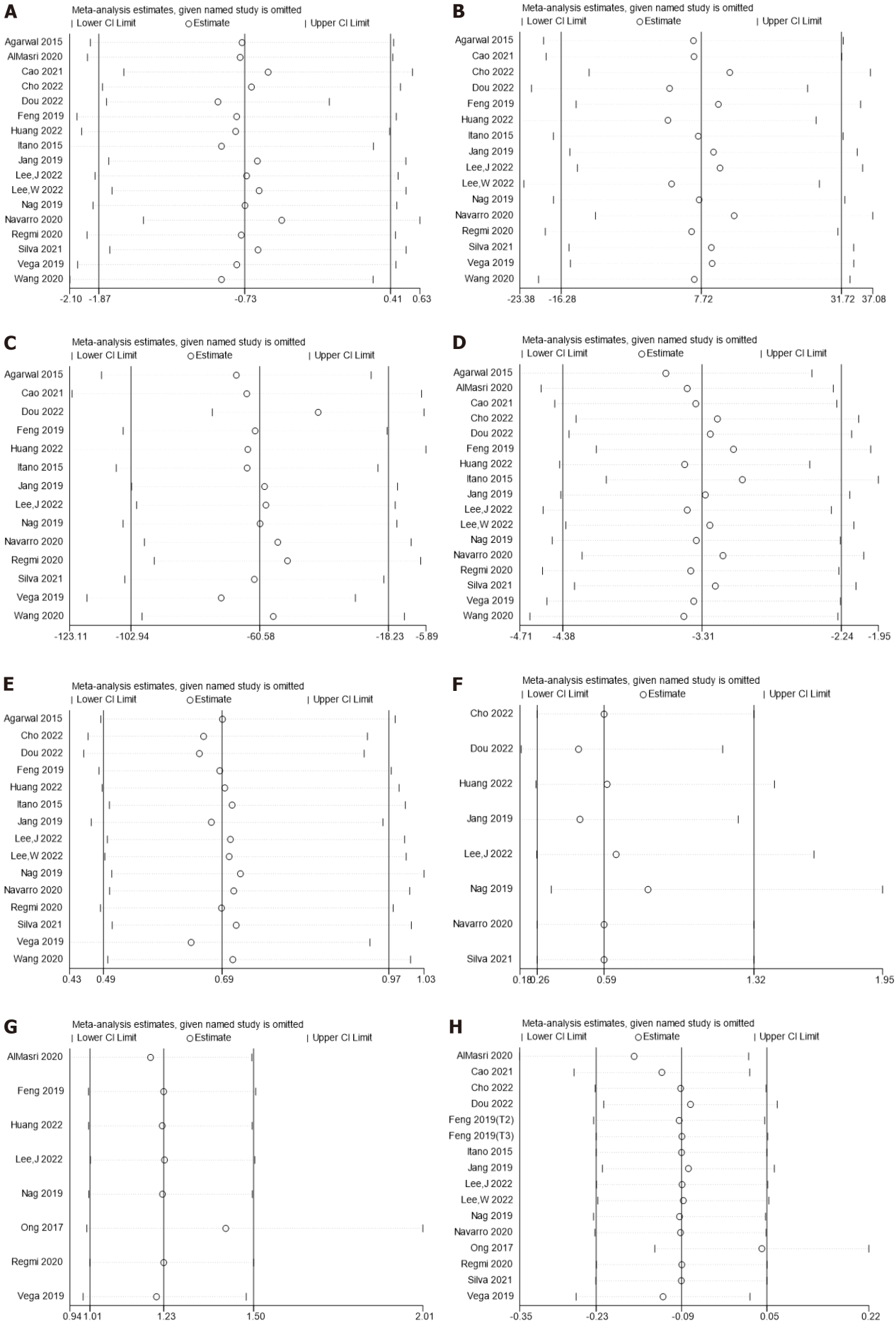
Complications (Clavien-Dindo 3-4): The data on complications (Clavien-Dindo 3-4) were reported in eight studies. No significant heterogeneity existed [χ^2 = 3.18, *df* = 4 (*P* = 0.53), I^2 = 0%]. Therefore, a fixed-effects model was used. The results showed no significant difference in the complications (Clavien-Dindo 3-4) between the LRR and ORR groups (OR: 0.59, 95%CI: 0.26 to 1.32, *P* = 0.20; Figure 5F).

The data on complications (Clavien-Dindo 3-4) after PSM were reported in five studies. No significant heterogeneity existed [χ^2 = 0.55, *df* = 1 (*P* = 0.46); I^2 = 0%]. Therefore, a fixed-effects model was used. The results showed no significant difference in the complications (Clavien-Dindo 3-4) between the LRR and ORR groups (OR: 1.00, 95%CI: 0.24 to 4.19, *P* = 1.00; Figure 6F).

R0 resection rate: The data regarding the R0 resection rate were reported in eight studies. No significant heterogeneity existed [χ^2 = 1.77, *df* = 6 (*P* = 0.94), I^2 = 0%]. Therefore, a fixed-effects model was used. The LRR group showed a significantly higher R0 resection rate compared with the ORR group (OR: 1.23, 95%CI: 1.01 to 1.50, *P* = 0.04; Figure 5G). The data of the R0 resection rate after PSM were not enough for pooled analysis.

Early-stage rate

We defined the T1-2 stage and TNM I-II stage as the early-stage group, and the T3-4 stage and TNM III-IV stage as the late-stage group. Of the 18 studies included, 9 comprised only early-stage or late-stage cases. We included the remaining nine studies for analysis. Significant heterogeneity existed between these studies [χ^2 = 17.40, *df* = 8 (*P* = 0.03), I^2 = 54%]. Therefore, a random-effects model was used. The LRR group showed a significantly higher early-stage rate compared with the ORR group (OR: 1.54, 95%CI: 1.08 to 2.18, *P* = 0.02; Figure 5H).


A
Meta-analysis estimates, given named study is omitted
Lower CI Limit
Estimate
Upper CI Limit
Agarwal 2015
AlMasri 2020
Cao 2021
Cho 2022
Dou 2022
Feng 2019
Huang 2022
Itano 2015
Jang 2019
Lee,J 2022
Lee,W 2022
Nag 2019
Navarro 2020
Regmi 2020
Silva 2021
Vega 2019
Wang 2020
-2.10 -1.87 -0.73 0.41 0.63
B
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Lower CI Limit
Estimate
Upper CI Limit
-23.38 -16.28 7.72 31.72 37.08
C
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Lower CI Limit
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-123.11 -102.94 -60.58 -18.23 -5.89
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Lower CI Limit
Estimate
Upper CI Limit
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Estimate
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F
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Lower CI Limit
Estimate
Upper CI Limit
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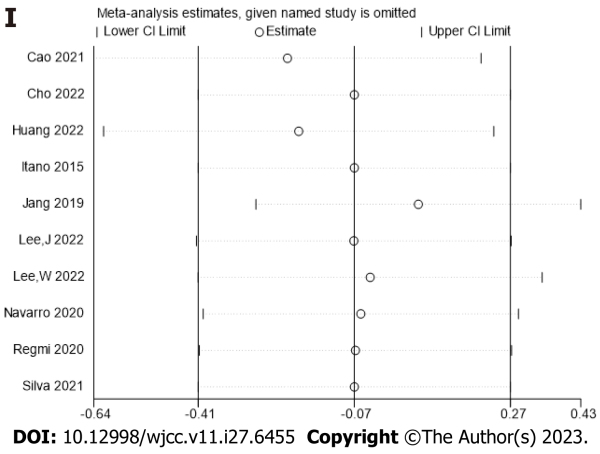
G
Meta-analysis estimates, given named study is omitted
Lower CI Limit
Estimate
Upper CI Limit
AlMasri 2020
Feng 2019
Huang 2022
Lee,J 2022
Nag 2019
Ong 2017
Regmi 2020
Vega 2019
0.94 1.01 1.23 1.50 2.01
H
Meta-analysis estimates, given named study is omitted
Lower CI Limit
Estimate
Upper CI Limit
Feng 2019(T2)
Feng 2019(T3)
-0.35 -0.23 -0.09 0.05 0.22



DOI: 10.12998/wjcc.v11.i27.6455

Figure 2 Results of sensitivity analysis on major measured outcomes. A: Number of lymph nodes harvested; B: Operation time; C: Intraoperative blood loss; D: Postoperative length of stay; E: Postoperative complications; F: Postoperative complications (Clavien-Dindo 3-4); G: R0 resection rate; H: Overall survival; I: Tumor-free survival.

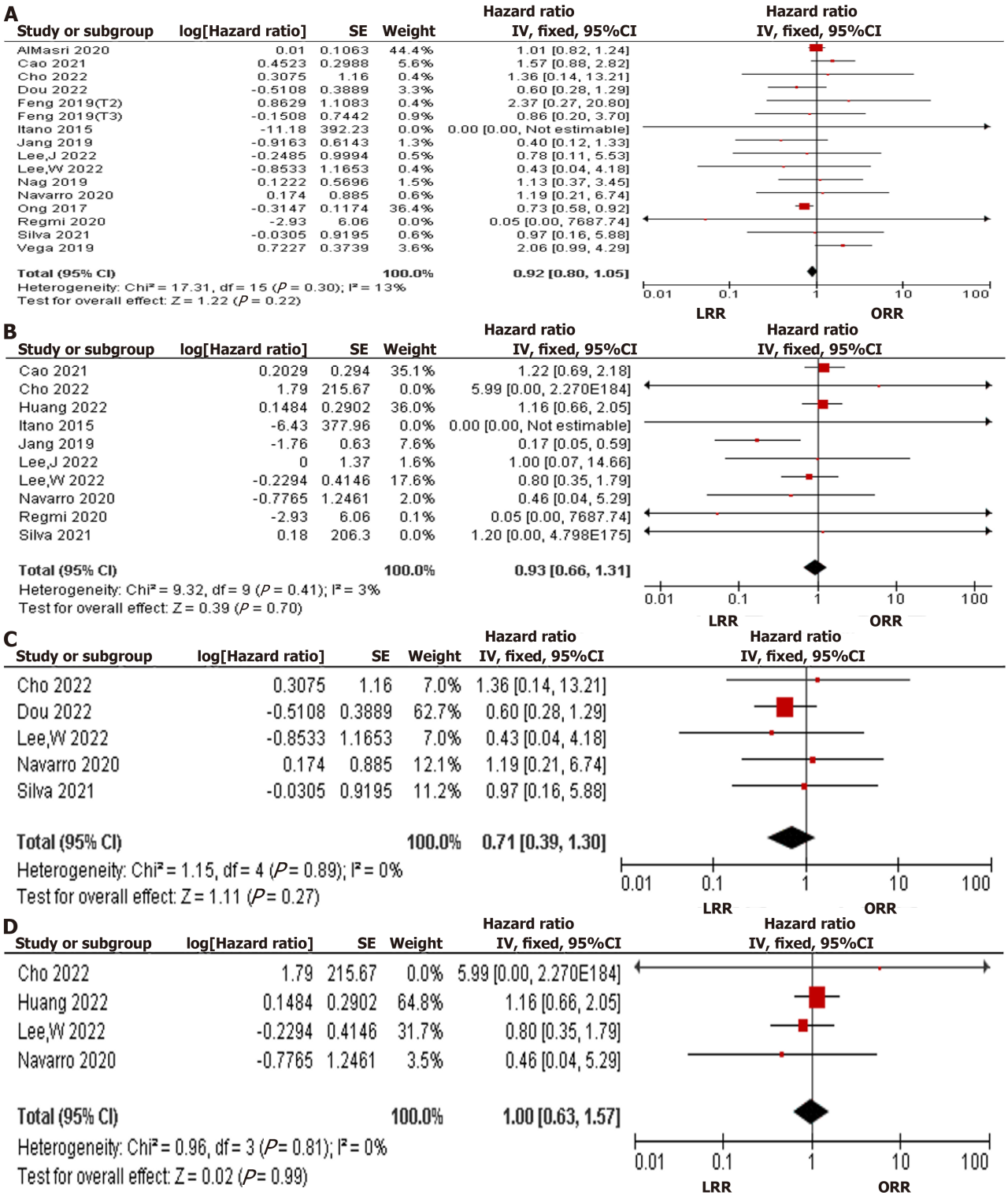
Evaluation of publication bias and sensitivity analysis

Egger's test, Begg's test, and sensitivity analysis were performed to evaluate major measured outcomes, including the No. LNH, operation time, blood loss, POLS, complications, complications (Clavien-Dindo 3-4), R0 resection rate, OS, and TFS. A remarkable asymmetry was detected using Egger's test in the No. LNH, operation time, and POLS; however, no publication bias was detected using Begg's test in all measured outcomes. The results of Egger's and Begg's tests are presented in Table 1. The sensitivity analysis showed that the pooled results of all of the major outcomes were stable and robust. The results of the sensitivity analysis are presented in Figure 6.

DISCUSSION

In the analysis of long-term prognosis, the LRR group was comparable with the ORR group in terms of OS and TFS. The same result was obtained even after PSM. Then, the subgroup analysis on T2/TNM II stage, T1/TNM I + T2/TNM II stage, and T2/TNM II + T3/TNM III stage was performed. The results showed that the LRR group had a superiority over the ORR group in terms of TFS only in the T2/II stage subgroup (P = 0.04). In the analysis of short-term prognosis, the LRR group had superiority over the ORR group in terms of blood loss (P = 0.005), POLS (P < 0.001), complication rate (P = 0.03), and R0 resection rate (P = 0.04). After PSM, the advantage in the POLS persisted (P < 0.001), but the differences in the blood loss (P = 0.27) and complication rate (P = 0.29) were no longer significant. The R0 resection rate could not be analyzed after PSM due to the unavailability of data. The LRR and ORR groups did not exhibit significant differences in other short-term outcomes, such as No. LNH, surgical time, and complication rate (Clavien-Dindo 3-4), regardless of whether PSM was done. Although Egger's and Begg's tests indicated the presence of publication bias, the sensitivity analysis confirmed the stability and robustness of all pooled results.

In recent years, several meta-analyses have been published comparing laparoscopic and open surgery for treating GBC, and similar results were obtained[24-27]. However, we believed that conducting this meta-analysis was necessary because it significantly differed from previous studies. First, all previous meta-analyses included numerous studies with a substantial number of SC cases. For example, the study by Jang *et al*[50] included 197 cases. However, in their study, 94 cases in the laparoscopic group and 30 in the open surgery group just underwent SC, and only 73 cases in the open surgery group underwent ORR. This study aimed to explore the feasibility of LSC for T1 GBC. In the study performed by Goetze and Paolucci[51], 837 patients were included. A total of 492 patients underwent LSC, 200 underwent open surgery, and 142 initially underwent LSC using the primary access technique, but required conversion to open surgery. Furthermore, among the 300 patients who underwent re-resection, the stratification was based on the primary surgical approach, and whether LRR was performed was not clearly mentioned. Based on the content and time of the research, it was highly likely that the re-resection procedures were carried out as open surgery. This study aimed to explore the impact of the primary access technique (laparoscopy *vs* primary open surgery) on the prognosis of GBCs. The aforementioned two studies were included in all of the previous meta-analyses and made important contributions to the pooled results because of their large sample sizes. Similar situations existed in many other included studies[52-61], and they did not discuss the impact of the approach of radical resection on the prognosis of GBC. Therefore, these studies were not included based on our inclusion criteria. This is the biggest difference between our meta-analysis and the previous meta-analyses. Second, we analyzed the results of TFS, which were not used in the previous meta-analyses. The results of the overall recurrence rate were pooled in the meta-analysis performed by Lv *et al*[26] and Nakanishi *et al*[27]. However, we presumed that it was unreasonable to directly pool the overall recurrence rate results because the follow-up times of the included studies were not the same and the HR used in our study was more reasonable. Third, we analyzed the data after PSM to minimize the influence of other factors on the results, which was not reported in the previous meta-analyses.



DOI: 10.12998/wjcc.v11.i27.6455

Figure 3 Forest plots of pooled hazard ratio for survival outcomes. A: Overall survival (OS); B: Tumor-free survival (TFS); C: OS after propensity score matching (PSM); D: TFS after PSM. LRR: Laparoscopic radical resection; ORR: Open radical resection; CI: Confidence interval.

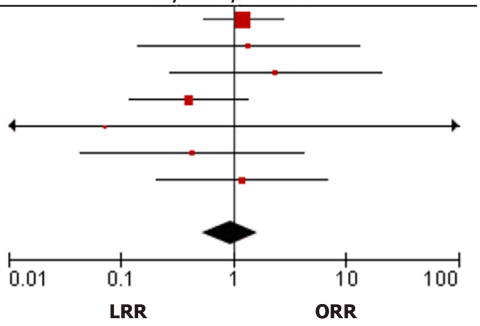
Fourth, we pooled the staging data and found that the cases included in the LRR group had an earlier stage than those in the ORR group. Tumor staging is one of the most important factors affecting the prognosis, suggesting that our interpretation of the overall results should be conservative and that we should pay more attention to subgroup analysis.

Laparoscopic surgery has been thought to worsen the prognosis of GBC, which was first described in the 1990s[62-64]. Since then, it has been controversial, and the focus is on the possible port-site recurrence and peritoneal metastasis after laparoscopic surgery, which was considered to be associated with intraoperative gallbladder perforation and pneumoperitoneum and suggested a poor prognosis[65-67]. The submucosa of the gallbladder wall is absent, and the muscularis propria is extremely thin. Thus, gallbladder perforation is more likely to occur in laparoscopic surgery.

A

Study or subgroup	log[Hazard ratio]	SE	Weight	Hazard ratio IV, fixed, 95%CI
AlMasri 2020(II)	0.1989	0.4158	48.2%	1.22 [0.54, 2.76]
Cho 2022	0.3075	1.16	6.2%	1.36 [0.14, 13.21]
Feng 2019(T2)	0.8629	1.1083	6.8%	2.37 [0.27, 20.80]
Jang 2019	-0.9163	0.6143	22.1%	0.40 [0.12, 1.33]
Lee,J 2022	-2.64	226.46	0.0%	0.07 [0.00, 4.136E191]
Lee,W 2022	-0.8533	1.1653	6.1%	0.43 [0.04, 4.18]
Navarro 2020	0.174	0.885	10.6%	1.19 [0.21, 6.74]
Total (95% CI)			**100.0%**	**0.94 [0.53, 1.65]**

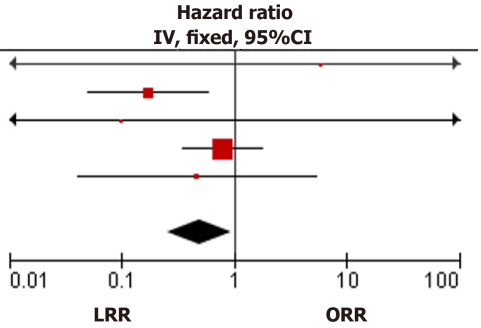
Heterogeneity: Chi² = 3.66, df = 6 (*P* = 0.72); I² = 0%
Test for overall effect: Z = 0.22 (*P* = 0.83)



B

Study or subgroup	log[Hazard ratio]	SE	Weight	Hazard ratio IV, fixed, 95%CI
Cho 2022	1.79	215.67	0.0%	5.99 [0.00, 2.270E184]
Jang 2019	-1.76	0.63	28.1%	0.17 [0.05, 0.59]
Lee,J 2022	-2.3	226.47	0.0%	0.10 [0.00, 5.926E191]
Lee,W 2022	-0.2294	0.4146	64.8%	0.80 [0.35, 1.79]
Navarro 2020	-0.7765	1.2461	7.2%	0.46 [0.04, 5.29]
Total (95% CI)			**100.0%**	**0.50 [0.26, 0.96]**

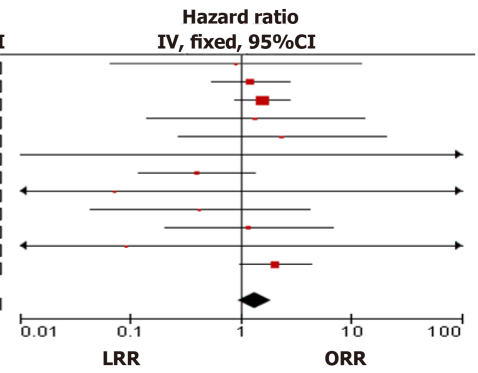
Heterogeneity: Chi² = 4.12, df = 4 (*P* = 0.39); I² = 3%
Test for overall effect: Z = 2.09 (*P* = 0.04)



C

Study or subgroup	log[Hazard ratio]	SE	Weight	Hazard ratio IV, fixed, 95%CI
AlMasri 2020(I)	-0.1	1.33	1.8%	0.90 [0.07, 12.27]
AlMasri 2020(II)	0.1989	0.4158	18.7%	1.22 [0.54, 2.76]
Cao 2021	0.4523	0.2988	36.2%	1.57 [0.88, 2.82]
Cho 2022	0.3075	1.16	2.4%	1.36 [0.14, 13.21]
Feng 2019(T2)	0.8629	1.1083	2.6%	2.37 [0.27, 20.80]
Itano 2015	-11.18	392.23	0.0%	0.00 [0.00, Not estimable]
Jang 2019	-0.9163	0.6143	8.6%	0.40 [0.12, 1.33]
Lee,J 2022	-2.64	226.46	0.0%	0.07 [0.00, 4.136E191]
Lee,W 2022	-0.8533	1.1653	2.4%	0.43 [0.04, 4.18]
Navarro 2020	0.174	0.885	4.1%	1.19 [0.21, 6.74]
Regmi 2020	-2.39	6.06	0.1%	0.09 [0.00, 13192.21]
Vega 2019	0.7227	0.3739	23.1%	2.06 [0.99, 4.29]
Total (95% CI)			**100.0%**	**1.35 [0.95, 1.92]**

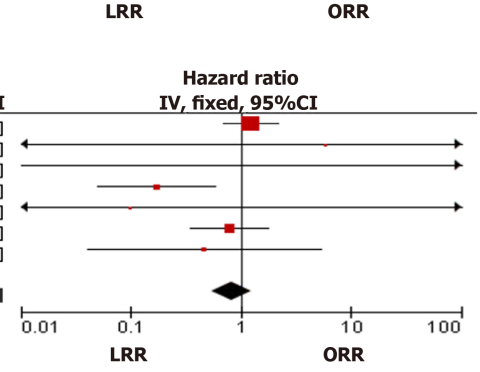
Heterogeneity: Chi² = 7.06, df = 11 (*P* = 0.79); I² = 0%
Test for overall effect: Z = 1.68 (*P* = 0.09)



D

Study or subgroup	log[Hazard ratio]	SE	Weight	Hazard ratio IV, fixed, 95%CI
Cao 2021	0.2029	0.294	56.3%	1.22 [0.69, 2.18]
Cho 2022	1.79	215.67	0.0%	5.99 [0.00, 2.270E184]
Itano 2015	-6.43	377.96	0.0%	0.00 [0.00, Not estimable]
Jang 2019	-1.76	0.63	12.3%	0.17 [0.05, 0.59]
Lee,J 2022	-2.3	226.47	0.0%	0.10 [0.00, 5.926E191]
Lee,W 2022	-0.2294	0.4146	28.3%	0.80 [0.35, 1.79]
Navarro 2020	-0.7765	1.2461	3.1%	0.46 [0.04, 5.29]
Total (95% CI)			**100.0%**	**0.83 [0.54, 1.27]**

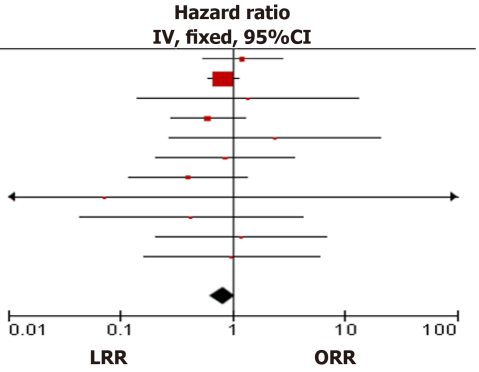
Heterogeneity: Chi² = 8.23, df = 6 (*P* = 0.22); I² = 27%
Test for overall effect: Z = 0.87 (*P* = 0.39)

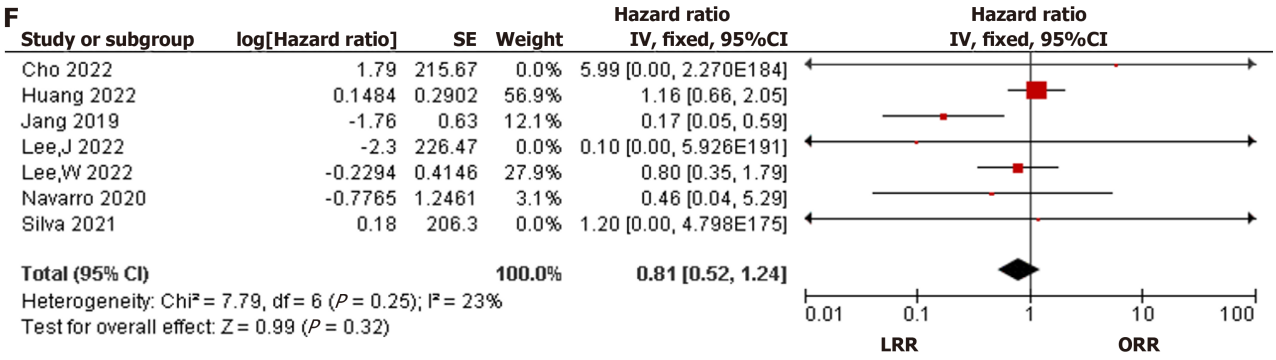


E

Study or subgroup	log[Hazard ratio]	SE	Weight	Hazard ratio IV, fixed, 95%CI
AlMasri 2020(II)	0.1989	0.4158	9.5%	1.22 [0.54, 2.76]
AlMasri 2020(III)	-0.2	0.16	64.3%	0.82 [0.60, 1.12]
Cho 2022	0.3075	1.16	1.2%	1.36 [0.14, 13.21]
Dou 2022	-0.5108	0.3889	10.9%	0.60 [0.28, 1.29]
Feng 2019(T2)	0.8629	1.1083	1.3%	2.37 [0.27, 20.80]
Feng 2019(T3)	-0.15	0.73	3.1%	0.86 [0.21, 3.60]
Jang 2019	-0.9163	0.6143	4.4%	0.40 [0.12, 1.33]
Lee,J 2022	-2.64	226.46	0.0%	0.07 [0.00, 4.136E191]
Lee,W 2022	-0.8533	1.1653	1.2%	0.43 [0.04, 4.18]
Navarro 2020	0.174	0.885	2.1%	1.19 [0.21, 6.74]
Silva 2021	-0.0305	0.9195	1.9%	0.97 [0.16, 5.88]
Total (95% CI)			**100.0%**	**0.82 [0.64, 1.05]**

Heterogeneity: Chi² = 4.56, df = 10 (*P* = 0.92); I² = 0%
Test for overall effect: Z = 1.57 (*P* = 0.12)





DOI: 10.12998/wjcc.v11.i27.6455

Figure 4 Forest plots of pooled hazard ratio for survival outcomes in subgroup analysis. A: Overall survival (OS) in the T2/tumor-node-metastasis (TNM) II subgroup; B: Tumor-free survival (TFS) in the T2/TNM II subgroup; C: OS in the T1/TNM I + T2/TNM II subgroup; D: TFS in the T1/TNM I + T2/TNM II subgroup; E: OS in the T2/TNM II + T3/TNM III subgroup; F: TFS in the T2/TNM II + T3/TNM III subgroup. LRR: Laparoscopic radical resection; ORR: Open radical resection; CI: Confidence interval.

Around the 2000s, the gallbladder perforation rate in laparoscopic surgery was reported to be 20%-36%[64,67-69]. However, currently, gallbladder perforation is not as common as earlier, which may be attributed to the improvement in the operation skills of the surgeons. Of the 18 studies included in our meta-analysis, only the study by Feng *et al*[33] reported perforations caused by gallbladder decompression due to incarcerated gallstones or severe inflammation, and the incidence showed no difference between the laparoscopic and open surgery groups. Besides, the routine use of retrieval bags avoided the direct contact between the surgical specimen and the extraction port, significantly reduced the risk of port-site metastasis[64]. In the 1990s, the incidence of port-site metastases in incidental GBC was reported as high as 17%[70]. However, the incidence decreased to 10% in a recent systematic review, and the recurrence rate of incisions after open surgery remained at about 7%[71]. Further, the incidence of peritoneal carcinomatosis was even higher in the ORR group than in the LRR group in the study by Vega *et al*[38].

Another concern is about whether laparoscopic surgery is competent for the radical resection of GBC, which includes partial hepatectomy (wedge resection/IVb + V segment resection) and lymph node dissection. In the past, such a complicated surgery was not appropriate to be performed in laparoscopy. However, the development of laparoscopic surgery for other cancers has changed this view. Numerous reports have been published regarding the use of laparoscopic techniques in complex liver resections, including procedures like right hemi-hepatectomy, caudate lobe resection, and so forth. These reports consistently demonstrate improved short-term prognosis and comparable long-term survival [72-74]. The laparoscopic techniques have also been reported in live liver donation[75,76]. More extensive lymph node dissection is performed under laparoscopy for treating gastric cancer[17,77]. Thus, from a purely technical perspective, the current laparoscopic techniques can fully meet the requirements of radical resection for elective GBC, and it seems that LRR should no longer be considered a contraindication for GBC.

The treatment of GBC will be a comprehensive pattern based on surgery, with chemotherapy, immunotherapy, and targeted therapy combined. And it is developing towards the trend of being minimally invasive, precise, and individualized. In this study, LRR not only provided satisfactory survival, but also demonstrated the advantages of minimally invasive and enhanced postoperative recovery. It may inevitably play a more critical role in treating of GBC. In addition, the rapid development of targeted agents and immunotherapy may provide more treatment options for GBC.

This meta-analysis had some limitations. First, all included studies were retrospective, and no randomized controlled or prospective studies were included. Second, significant heterogeneities were found in some analyses, the reasons for which were difficult to find; we could only reduce their impact by choosing random-effects models. Third, we found using Egger' test that a publication bias might exist, which was difficult to eliminate. Fourth, the estimated HR extracted from the survival curve was rough and might introduce bias. Fifth, related confounding factors were difficult to extract from the study, and few studies were included in the subgroup analysis of staging and the analysis after PSM. Sixth, most of the included studies did not report detailed adjuvant therapy data, therefore it was difficult to judge the impact of adjuvant therapy on long-term prognosis. This study was not impeccable; however, it truly described the current state in this field and provided reasonable support for the further exploration of LRR in treating GBC.

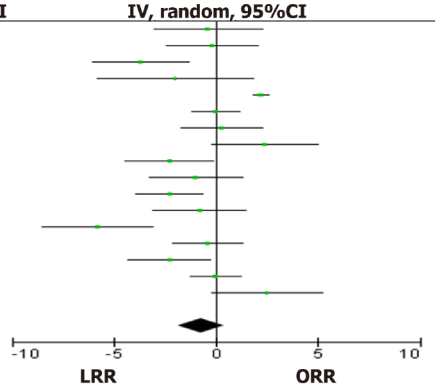
CONCLUSION

Our analysis enrolled a large number of comparative studies. This is the first study to compare LRR and ORR in treating GBC. While excluding the interference of SC cases, the data after PSM was analyzed for the first time. The results of the meta-analysis showed that LRR was not inferior to ORR in all measured outcomes and even showed superiority in the TFS of patients with stage T2/TNM II disease and POLS. Surgeons with sufficient laparoscopic experience can perform LRR as an alternative surgical strategy to ORR. This may not be the final conclusion, and a more comprehensive meta-analysis is necessary.

A

Study or subgroup	LRR Mean	LRR SD	LRR Total	ORR Mean	ORR SD	ORR Total	Weight	Mean difference IV, random, 95%CI
Agarwal 2015	12.5	5.4	24	12.9	5.4	46	5.3%	-0.40 [-3.07, 2.27]
AlMasri 2020	6.5	14.6	235	6.7	13.5	445	5.8%	-0.20 [-2.45, 2.05]
Cao 2021	6.4	3.3	53	10.1	8.8	61	5.6%	-3.70 [-6.08, -1.32]
Cho 2022	5.3	6.6	19	7.3	5.5	19	4.0%	-2.00 [-5.86, 1.86]
Dou 2022	10.12	0.9	30	7.92	0.57	30	7.4%	2.20 [1.82, 2.58]
Feng 2019	5	3	41	5	3	61	6.9%	0.00 [-1.19, 1.19]
Huang 2022	8.4	4.6	35	8.1	3.9	35	6.1%	0.30 [-1.70, 2.30]
Itano 2015	12.6	3.1	16	10.2	4	14	5.4%	2.40 [-0.19, 4.99]
Jang 2019	7.6	3.4	55	9.9	6.8	44	5.8%	-2.30 [-4.50, -0.10]
Lee,J 2022	5.75	3.54	20	6.75	4.17	24	5.7%	-1.00 [-3.28, 1.28]
Lee,W 2022	4.6	4.1	56	6.9	4.9	56	6.4%	-2.30 [-3.97, -0.63]
Nag 2019	11.9	5.2	30	12.7	4.2	38	5.7%	-0.80 [-3.09, 1.49]
Navarro 2020	6.12	5.78	43	11.93	7.03	43	5.2%	-5.81 [-8.53, -3.09]
Regmi 2020	5.4	3.5	20	5.8	2.1	30	6.4%	-0.40 [-2.11, 1.31]
Silva 2021	6.6	1.7	12	8.9	3.1	12	6.1%	-2.30 [-4.30, -0.30]
Vega 2019	6.5	4.1	65	6.5	5	190	6.9%	0.00 [-1.22, 1.22]
Wang 2020	19.8	7.9	45	17.3	5.7	61	5.2%	2.50 [-0.22, 5.22]
Total (95% CI)			**799**			**1209**	**100.0%**	**-0.73 [-1.87, 0.41]**

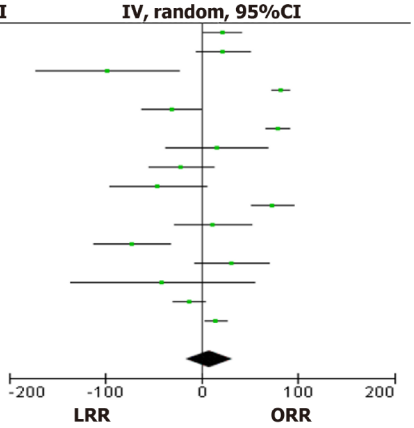
Heterogeneity: Tau² = 4.54; Chi² = 131.34, df = 16 (P < 0.00001); I² = 88%
Test for overall effect: Z = 1.26 (P = 0.21)



B

Study or subgroup	LRR Mean	LRR SD	LRR Total	ORR Mean	ORR SD	ORR Total	Weight	Mean difference IV, random, 95%CI
Agarwal 2015	267.3	41.1	24	245.5	40.7	46	7.0%	21.80 [1.58, 42.02]
Cao 2021	238.4	74	53	215.7	74	61	6.8%	22.70 [-4.54, 49.94]
Cho 2022	218.9	145	19	316.8	80.3	19	4.3%	-97.90 [-172.43, -23.37]
Dou 2022	328.12	21.53	30	245.82	15.18	30	7.3%	82.30 [72.87, 91.73]
Feng 2019	137	92	41	168	51	61	6.6%	-31.00 [-61.93, -0.07]
Huang 2022	242.6	24.3	35	163.8	25	35	7.3%	78.80 [67.25, 90.35]
Itano 2015	368	73	16	352	75	14	5.4%	16.00 [-37.13, 69.13]
Jang 2019	231	95.2	55	252.5	76.1	44	6.5%	-21.50 [-55.24, 12.24]
Lee,J 2022	186.6	88.14	20	231.67	82.97	24	5.5%	-45.07 [-96.00, 5.86]
Lee,W 2022	171.7	64.1	56	98	53.2	56	7.0%	73.70 [51.88, 95.52]
Nag 2019	286.5	71.6	30	274.2	96.3	38	6.1%	12.30 [-27.62, 52.22]
Navarro 2020	139.05	97.09	43	211.16	91.36	43	6.1%	-72.11 [-111.96, -32.26]
Regmi 2020	258.25	72.5	20	227	59.81	30	6.2%	31.25 [-7.06, 69.56]
Silva 2021	269.1	122.3	12	309.8	116.2	12	3.4%	-40.70 [-136.15, 54.75]
Vega 2019	233.7	33.1	65	246.5	99.3	190	7.2%	-12.80 [-29.05, 3.45]
Wang 2020	115	32.5	45	100	20.4	61	7.3%	15.00 [4.21, 25.79]
Total (95% CI)			**564**			**764**	**100.0%**	**7.72 [-16.28, 31.72]**

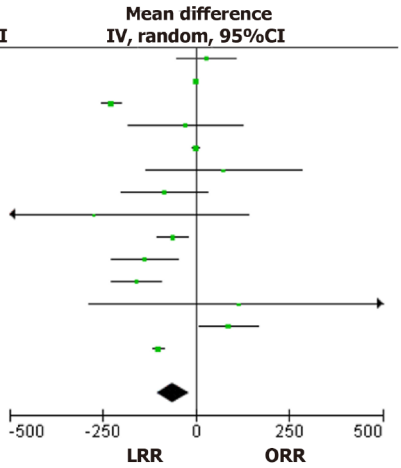
Heterogeneity: Tau² = 2027.93; Chi² = 288.26, df = 15 (P < 0.00001); I² = 95%
Test for overall effect: Z = 0.63 (P = 0.53)



C

Study or subgroup	LRR Mean	LRR SD	LRR Total	ORR Mean	ORR SD	ORR Total	Weight	Mean difference IV, random, 95%CI
Agarwal 2015	274.1	192.6	24	245.5	40.7	46	8.0%	28.60 [-49.35, 106.55]
Cao 2021	257	6.3	53	256.2	6.3	61	10.9%	0.80 [-1.52, 3.12]
Dou 2022	256.74	39.21	30	484.36	64.67	30	10.4%	-227.62 [-254.68, -200.56]
Feng 2019	358	390	41	386	391	61	4.5%	-28.00 [-182.53, 126.53]
Huang 2022	60.9	23.8	35	60.9	23.8	35	10.8%	0.00 [-11.15, 11.15]
Itano 2015	152	90	16	77	392	14	3.0%	75.00 [-135.02, 285.02]
Jang 2019	225.1	328.6	55	310.5	260.9	44	6.0%	-85.40 [-201.52, 30.72]
Lee,J 2022	320	451.72	20	593.75	912.04	24	1.0%	-273.75 [-688.88, 141.38]
Nag 2019	158.6	85.7	30	219.4	87.7	38	9.9%	-60.80 [-102.25, -19.35]
Navarro 2020	71.63	178.77	43	208.14	242.17	43	7.3%	-136.51 [-226.48, -46.54]
Regmi 2020	242	108.5	20	401	130.3	30	8.6%	-159.00 [-225.60, -92.40]
Silva 2021	548.9	489.3	12	433.4	519.9	12	1.0%	115.50 [-288.44, 519.44]
Vega 2019	346.9	249.7	65	259.8	358.7	190	7.9%	87.10 [7.81, 166.39]
Wang 2020	100	25.4	45	200	45.6	61	10.8%	-100.00 [-113.64, -86.36]
Total (95% CI)			**489**			**689**	**100.0%**	**-60.58 [-102.94, -18.23]**

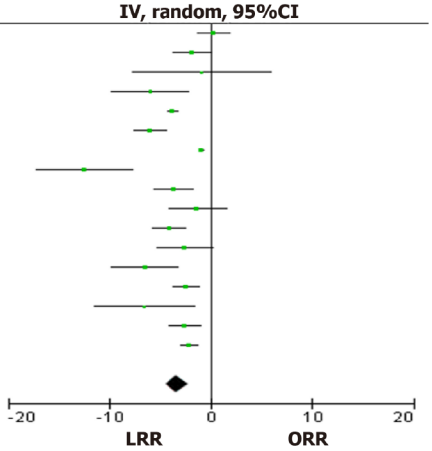
Heterogeneity: Tau² = 4279.07; Chi² = 516.12, df = 13 (P < 0.00001); I² = 97%
Test for overall effect: Z = 2.80 (P = 0.005)



D

Study or subgroup	LRR Mean	LRR SD	LRR Total	ORR Mean	ORR SD	ORR Total	Weight	Mean difference IV, random, 95%CI
Agarwal 2015	6.2	3.3	24	5.9	3.2	46	7.0%	0.30 [-1.31, 1.91]
AlMasri 2020	7	13	235	8.8	10.9	445	6.5%	-1.80 [-3.75, 0.15]
Cao 2021	10.4	18.6	53	11.3	18.6	61	1.9%	-0.90 [-7.75, 5.95]
Cho 2022	8.4	5.9	19	14.4	6	19	4.1%	-6.00 [-9.78, -2.22]
Dou 2022	10.43	0.97	30	14.23	1.07	30	8.2%	-3.80 [-4.32, -3.28]
Feng 2019	5	3	41	11	5	61	7.1%	-6.00 [-7.55, -4.45]
Huang 2022	6.1	0.2	35	7	0.5	35	8.3%	-0.90 [-1.08, -0.72]
Itano 2015	9.1	1.6	16	21.6	9	14	3.1%	-12.50 [-17.28, -7.72]
Jang 2019	5.8	5.3	55	9.5	4.8	44	6.5%	-3.70 [-5.69, -1.71]
Lee,J 2022	10.95	4.82	20	12.28	4.87	24	5.2%	-1.33 [-4.20, 1.54]
Lee,W 2022	5.7	4.2	56	9.8	4.9	56	6.9%	-4.10 [-5.79, -2.41]
Nag 2019	6.4	3.1	30	9	8	38	5.3%	-2.60 [-5.37, 0.17]
Navarro 2020	6.05	9.85	43	12.58	5.5	43	4.6%	-6.53 [-9.90, -3.16]
Regmi 2020	6.2	2.4	20	8.6	2.3	30	7.4%	-2.40 [-3.74, -1.06]
Silva 2021	5.46	3.06	12	12.02	8.26	12	3.0%	-6.56 [-11.54, -1.58]
Vega 2019	4.9	3.4	65	7.5	9.4	190	7.1%	-2.60 [-4.17, -1.03]
Wang 2020	3.5	1.9	45	5.6	2.7	61	7.9%	-2.10 [-2.98, -1.22]
Total (95% CI)			**799**			**1209**	**100.0%**	**-3.31 [-4.38, -2.24]**

Heterogeneity: Tau² = 3.59; Chi² = 212.98, df = 16 (P < 0.00001); I² = 92%
Test for overall effect: Z = 6.05 (P < 0.00001)



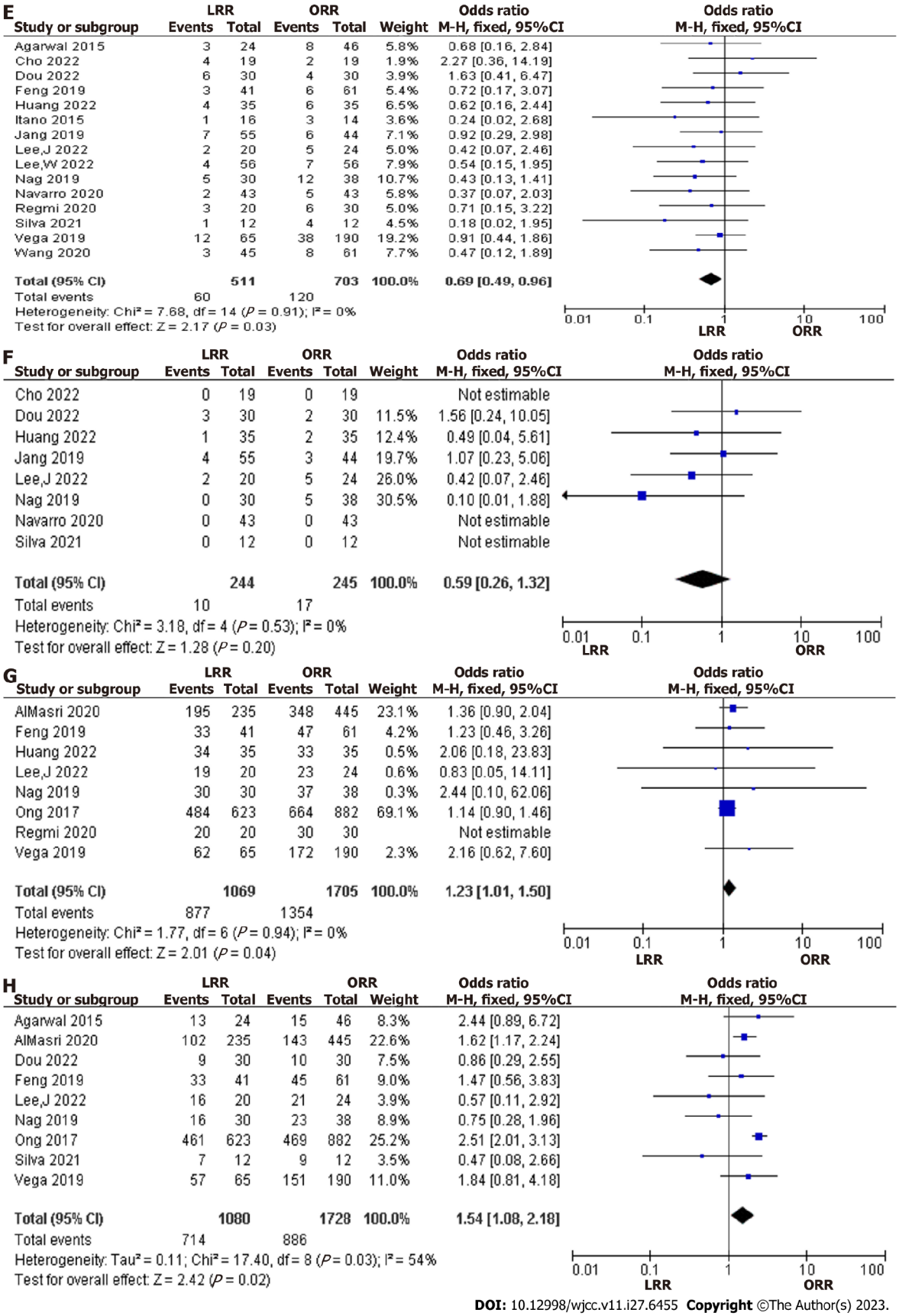


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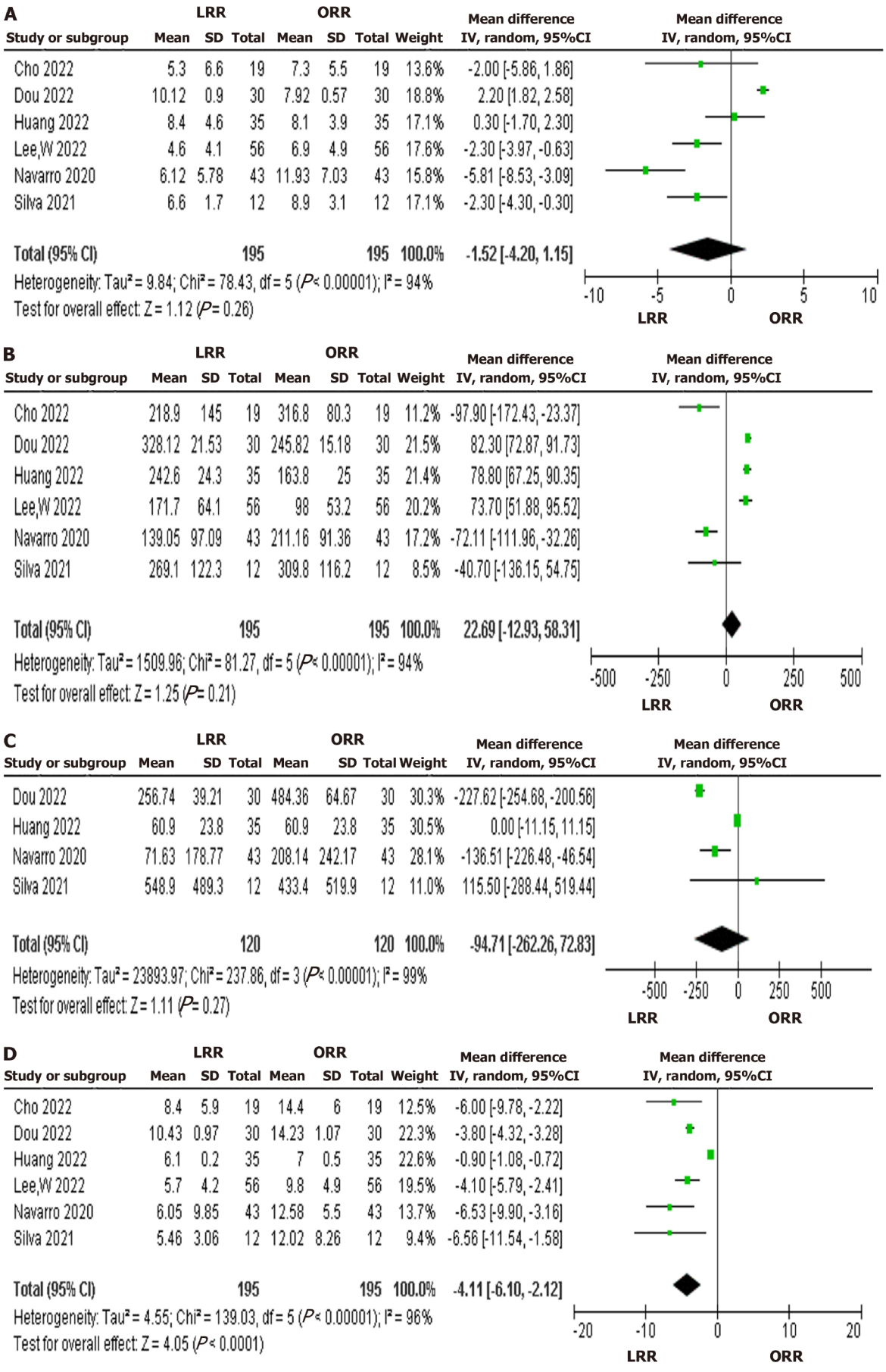
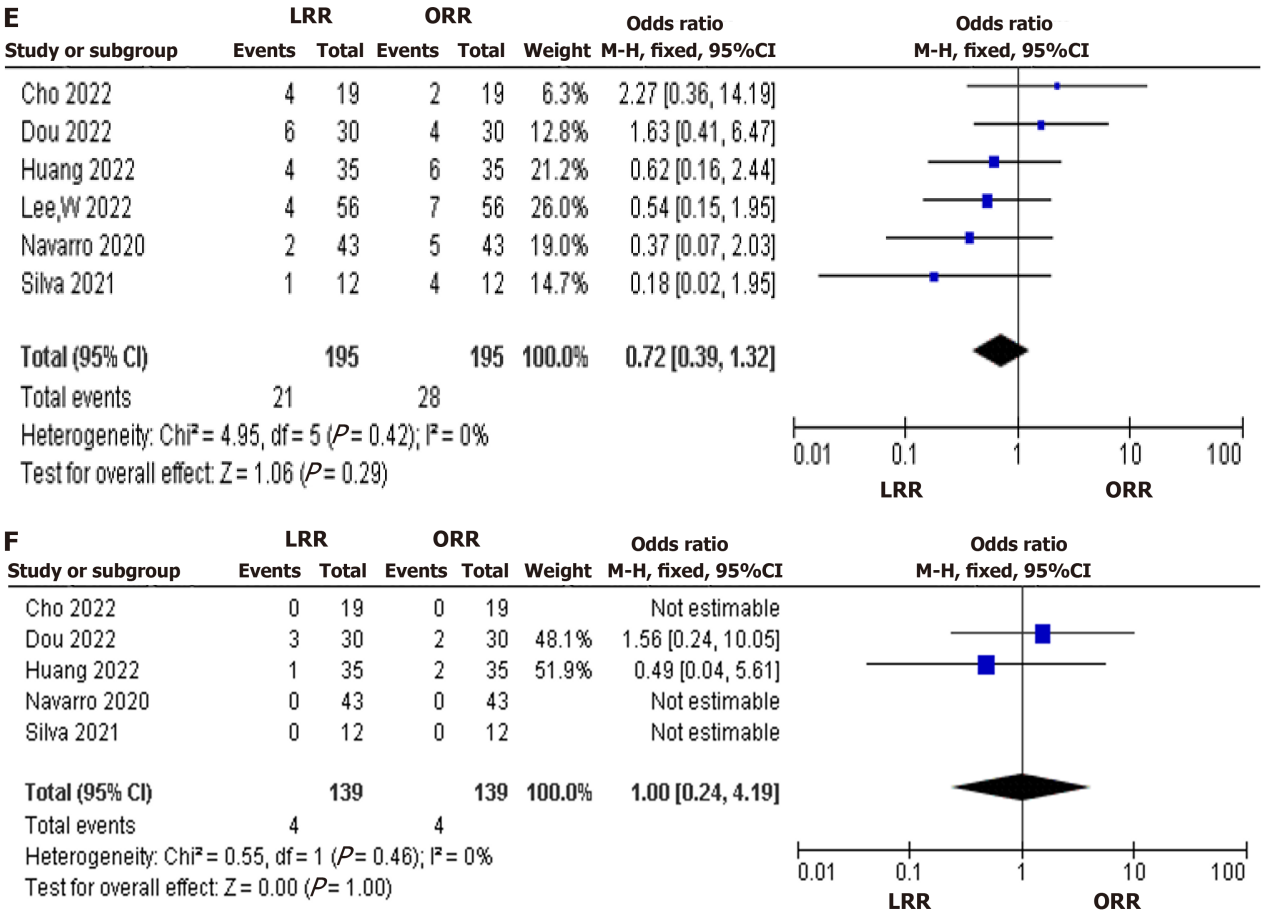
Figure 5 Forest plots of pooled odds ratio or weighted mean difference of short-term outcomes. A: Number of lymph nodes harvested; B: Operation time; C: Intraoperative blood loss; D: Postoperative length of stay; E: Postoperative complications; F: Postoperative complications (Clavien-Dindo 3-4); G: R0 margin rate; H: Early-stage rate (≤ T2/tumor-node-metastasis II stage). LRR: Laparoscopic radical resection; ORR: Open radical resection; CI: Confidence interval.


A
LRR
ORR
Mean difference
Mean difference
Study or subgroup Mean SD Total Mean SD Total Weight IV, random, 95%CI
IV, random, 95%CI
Cho 2022 5.3 6.6 19 7.3 5.5 19 13.6% -2.00 [-5.86, 1.86]
Dou 2022 10.12 0.9 30 7.92 0.57 30 18.8% 2.20 [1.82, 2.58]
Huang 2022 8.4 4.6 35 8.1 3.9 35 17.1% 0.30 [-1.70, 2.30]
Lee,W 2022 4.6 4.1 56 6.9 4.9 56 17.6% -2.30 [-3.97, -0.63]
Navarro 2020 6.12 5.78 43 11.93 7.03 43 15.8% -5.81 [-8.53, -3.09]
Silva 2021 6.6 1.7 12 8.9 3.1 12 17.1% -2.30 [-4.30, -0.30]
Total (95% CI) 195 195 100.0% -1.52 [-4.20, 1.15]
Heterogeneity: Tau² = 9.84; Chi² = 78.43, df = 5 (P < 0.00001); I² = 94%
Test for overall effect: Z = 1.12 (P = 0.26)
-10 -5 0 5 10
LRR ORR
B
LRR
ORR
Mean difference
Mean difference
Study or subgroup Mean SD Total Mean SD Total Weight IV, random, 95%CI
IV, random, 95%CI
Cho 2022 218.9 145 19 316.8 80.3 19 11.2% -97.90 [-172.43, -23.37]
Dou 2022 328.12 21.53 30 245.82 15.18 30 21.5% 82.30 [72.87, 91.73]
Huang 2022 242.6 24.3 35 163.8 25 35 21.4% 78.80 [67.25, 90.35]
Lee,W 2022 171.7 64.1 56 98 53.2 56 20.2% 73.70 [51.88, 95.52]
Navarro 2020 139.05 97.09 43 211.16 91.36 43 17.2% -72.11 [-111.96, -32.26]
Silva 2021 269.1 122.3 12 309.8 116.2 12 8.5% -40.70 [-136.15, 54.75]
Total (95% CI) 195 195 100.0% 22.69 [-12.93, 58.31]
Heterogeneity: Tau² = 1509.96; Chi² = 81.27, df = 5 (P < 0.00001); I² = 94%
Test for overall effect: Z = 1.25 (P = 0.21)
-500 -250 0 250 500
LRR ORR
C
LRR
ORR
Mean difference
Mean difference
Study or subgroup Mean SD Total Mean SD Total Weight IV, random, 95%CI
IV, random, 95%CI
Dou 2022 256.74 39.21 30 484.36 64.67 30 30.3% -227.62 [-254.68, -200.56]
Huang 2022 60.9 23.8 35 60.9 23.8 35 30.5% 0.00 [-11.15, 11.15]
Navarro 2020 71.63 178.77 43 208.14 242.17 43 28.1% -136.51 [-226.48, -46.54]
Silva 2021 548.9 489.3 12 433.4 519.9 12 11.0% 115.50 [-288.44, 519.44]
Total (95% CI) 120 120 100.0% -94.71 [-262.26, 72.83]
Heterogeneity: Tau² = 23893.97; Chi² = 237.86, df = 3 (P < 0.00001); I² = 99%
Test for overall effect: Z = 1.11 (P = 0.27)
-500 -250 0 250 500
LRR ORR
D
LRR
ORR
Mean difference
Mean difference
Study or subgroup Mean SD Total Mean SD Total Weight IV, random, 95%CI
IV, random, 95%CI
Cho 2022 8.4 5.9 19 14.4 6 19 12.5% -6.00 [-9.78, -2.22]
Dou 2022 10.43 0.97 30 14.23 1.07 30 22.3% -3.80 [-4.32, -3.28]
Huang 2022 6.1 0.2 35 7 0.5 35 22.6% -0.90 [-1.08, -0.72]
Lee,W 2022 5.7 4.2 56 9.8 4.9 56 19.5% -4.10 [-5.79, -2.41]
Navarro 2020 6.05 9.85 43 12.58 5.5 43 13.7% -6.53 [-9.90, -3.16]
Silva 2021 5.46 3.06 12 12.02 8.26 12 9.4% -6.56 [-11.54, -1.58]
Total (95% CI) 195 195 100.0% -4.11 [-6.10, -2.12]
Heterogeneity: Tau² = 4.55; Chi² = 139.03, df = 5 (P < 0.00001); I² = 96%
Test for overall effect: Z = 4.05 (P < 0.0001)
-20 -10 0 10 20
LRR ORR



DOI: 10.12998/wjcc.v11.i27.6455

Figure 6 Forest plots of pooled odds ratio or weighted mean difference of short-term outcomes after propensity score matching. A: Number of lymph nodes harvested; B: Operation time; C: Intraoperative blood loss; D: Postoperative length of stay; E: Postoperative complications; F: Postoperative complications (Clavien-Dindo 3-4). LRR: Laparoscopic radical resection; ORR: Open radical resection; CI: Confidence interval.

ARTICLE HIGHLIGHTS

Research background

Laparoscopic surgery has been widely used in the treatment of a variety of tumors, but it is still controversial in the treatment of gallbladder cancer. This is the first meta-analysis to compare laparoscopic radical resection (LRR) and open radical resection (ORR) in gallbladder carcinoma (GBC) directly.

Research motivation

This study compared LRR with traditional ORR in the management of GBC. It aimed to resolve the disputes faced by LRR and provide support for further research.

Research objectives

This study aimed to clarify the feasibility of LRR in GBC treatment, and encourage more surgeons to further carry out research on LRR, and move the minimally invasive treatment of gallbladder cancer forward.

Research methods

We systematically reviewed the literature on the LRR and ORR in GBC, and integrated the available data for meta-analysis. The Begg's test and Egger's test were used to assess potential publication bias, and sensitivity analysis was performed to evaluate the stability of the results.

Research results

This study found that the LRR group was comparable with the ORR group in long-term and short-term prognosis, and even showed advantages in some aspects, such as tumor-free survival (TFS) in the T2/tumor-node-metastasis (TNM) II stage subgroup and postoperative length of stay (POLS). Although there is still a lack of support from randomized controlled trials (RCTs), this result will encourage surgeons to conduct further and more in-depth research.

Research conclusions

The meta-analysis results showed that LRR was not inferior to ORR in all measured outcomes and even showed superiority in the TFS of patients with stage T2/TNM II disease and POLS. It is the first meta-analysis that excluded interference from simple cholecystectomy cases, and it is also the first time to conduct a subgroup analysis of the data after propensity score matching.

Research perspectives

LRR will inevitably play a more important role in the treatment of GBC, considering its minimally invasive characteristics and the advantage of enhanced postoperative recovery. But it requires further research, such as RCT or research on the combination of LRR and adjuvant therapy.

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FOOTNOTES

Author contributions: He S acquired, analyzed, and interpreted the data, drafted the manuscript, and approved the final manuscript; Yu TN, Cao JS, and Cai LX revised the manuscript and approved the final manuscript; Zhou XY and Chen ZH interpreted the data, revised the manuscript, and approved the final manuscript; Jiang WB acquired and interpreted the data, and approved the final manuscript; Liang X conceptualized and designed the study, critically revised the manuscript, and approved the final manuscript.

Conflict-of-interest statement: The authors deny any conflict of interest for this article.

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