

Laparoscopic Versus Abdominal Radical Hysterectomy for Cervical Cancer

A Meta-analysis of Randomized Controlled Trials

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BACKGROUND

Cervical cancer is one of the most common malignant tumors that seriously threaten women's health, and its incidence ranks third among female malignant tumors in the world, second only to breast cancer and colorectal cancer.^{1,2} There are about 500,000 new cases of cervical cancer every year in the world, 85% of which are in developing countries, and about 250,000 people die of cervical cancer each year.^{3,4} In China, 140,000 new cases are discovered every year, accounting for about one third of the global patients with cervical cancer, and about 50,000 patients die of cervical cancer every year.^{5,6} In recent years, the incidence of cervical cancer has a younger trend.^{7,8} Therefore, the treatment and care of cervical cancer is of great significance to the prognosis of patients.

Radical hysterectomy and lymph node dissection are the surgical methods recommended by the International Federation of Obstetrics and Gynaecology (FIGO) for the treatment of early-stage cervical cancer.⁹ Since the first successful laparoscopic pelvic lymph node dissection for cervical cancer in 1989, minimally invasive techniques have developed rapidly. In 1991, laparoscopy was first used for pelvic lymph node dissection combined with vaginal hysterectomy in the treatment of early cervical cancer. Laparoscopy has been used for total hysterectomy and pelvic lymph node dissection in the treatment of cervical cancer. Since then, many studies^{10–12} have shown that laparoscopic surgery has the advantages of less trauma, faster recovery, and less pain for patients after surgery, which has been valued by the majority of obstetrics and gynecologists. In recent years, many researchers have conducted many studies on the clinical efficacy and safety of laparoscopic surgery for cervical cancer. However, because of the small number of independent research samples and uneven research quality limits the results promotion. So far, no large-sample, multi-center clinical trials have been reported. To this end, we aimed to conduct a meta-analysis to compare the efficacy and safety of laparoscopic radical hysterectomy (LRH) and open abdominal radical hysterectomy (ARH) in the treatment of cervical cancer to provide a reliable basis for the selection of clinical surgical methods for cervical cancer treatment.

METHODS

This meta-analysis and systematic review was conducted in comply with the statement of preferred reporting items for systematic reviews and meta-analyses¹³ (Supplemental Digital Content 1, <http://links.lww.com/AJCO/A427> and Supplemental Digital Content 2, <http://links.lww.com/AJCO/A428>).

Search Strategy

The 2 authors independently searched PubMed, Web of Science, EMBase, Cochrane Library, China Biomedical Database,

Background: Laparoscopic radical hysterectomy (LRH) and open abdominal radical hysterectomy (ARH) have been used for cervical cancer treatment. We aimed to perform a meta-analysis to compare the efficacy and safety of LRH and ARH in the treatment of cervical cancer to provide reliable evidence to the clinical cervical cancer treatment.

Methods: Two investigators independently searched PubMed and other databases for randomized controlled trials (RCTs) comparing LRH and ARH for cervical cancer treatment up to May 31, 2022. The risk of bias assessment tool recommended by Cochrane library was used for quality assessment. RevMan 5.3 software was used for meta-analysis.

Results: Fourteen RCTs with a total of 1700 patients with cervical cancer were finally included. Meta-analyses indicated that compared with ARH, LRH reduced the intraoperative blood loss (mean difference [MD] = -58.08; 95% CI, -70.91, -45.24), the time to first passage of flatus (MD = -14.50; 95% CI, -16.55, -12.44) (all $P < 0.05$), and increase the number of lymph nodes removed (MD = 3.47; 95% CI, 0.51, 6.43; $P = 0.02$). There were no significant differences in the duration of surgery (MD = 27.62; 95% CI, -6.26, 61.49), intraoperative complications (odds ratio [OR] = 1.10; 95% CI, 0.17, 7.32), post-operative complications (OR = 0.78; 95% CI, 0.33, 1.86), relapse rate (OR = 1.45; 95% CI, 0.56, 3.74), and survival rate (OR = 0.75; 95% CI, 0.52, 1.08) between LRH group and ARH group (all $P > 0.05$).

Conclusions: LRH has more advantages over ARH in the treatment of cervical cancer. Still, the long-term effects and safety of LRH and ARH need more high-quality, large-sample RCTs to be further verified.

Key Words: laparoscopic, abdominal, radical hysterectomy, cervical cancer, treatment, care

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In this study, all methods were performed in accordance with the relevant guidelines and regulations. Ethics approval and consent to participate is not necessary, as our study is a meta-analysis and systematic review.

F.Z. designed research; F.Z. and X.S. conducted research; F.Z. and X.S. analyzed data; F.Z. and X.S. wrote the first draft of manuscript; F.Z. and X.S. had primary responsibility for final content.

The authors declare no conflicts of interest.

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Chinese National Knowledge Infrastructure (CNKI), Wanfang, and Weipu databases for randomized controlled trials (RCTs) on the efficacy and safety of LRH and ARH for cervical cancer treatment. The retrieval time limit is from the establishment of the database to May 31, 2022. The language was limited to Chinese or English. The search terms used were as following: (“cervical cancer” OR “cervical carcinoma” OR “uterine cervical neoplasms” OR “invasive carcinoma of cervix uteri”) AND (“laparoscopy” OR “laparotomy” OR “surgery” OR “abdominal” OR “open”).

Inclusion and Exclusion Criteria

The inclusion criteria for this meta-analysis were as follows: (1) the type of study was a RCT, the language was limited to Chinese and English, (2) the patients were clinically diagnosed with cervical cancer confirmed by pathology and underwent radical hysterectomy (3) LRH was used for the intervention measures in the experimental group, and ARH was used for the intervention measures in the control group, (4) The article reported relevant outcome indicators, such as operation time, intraoperative blood loss, number of lymph node biopsies, recurrence rate, and survival rate. The exclusion criteria for this meta-analysis were as follows: (1) review, case, and basic experimental studies; (2) duplicate published literature reports; (3) research reports for which data could not be extracted.

Quality Assessment

The RCTs included in this study were assessed using the risk of bias assessment tool for RCTs recommended by Cochrane library.¹⁴ The evaluated items in this tool include (1) the method of generating random sequences; (2) whether the allocation scheme is hidden; (3) whether the personnel is blinded; (4) whether the outcome assessment is blinded; (5) whether the outcome data is complete; (6) whether the results are selectively reported; and (7) whether there is any other bias. For each study result, a choice was made on the above 7 items, including “Yes” (low bias), “No” (high bias), and “Unclear” (lack of relevant information or uncertain bias).

Literature Screening and Data Extraction

In this meta-analysis, 2 reviewers independently screened the literature and extracted data and cross-checked them. In case of disagreement, a third party was consulted to assist in judgment, and the first original authors would be contacted as much as possible to supplement the lack of data. We extracted the following data: basic information of included studies, including research title, first author, publication journal and time, etc.; basic characteristics of research subjects, including age, number of cases, FIGO stage; Key elements of study design type, and quality assessment; relevant outcome data.

Statistical Analysis

This study used RevMan 5.3 software for meta-analysis. For enumeration data, odd ratio (OR) and its 95% confidence interval (CI) were used as effect size. For measurement data, mean difference (MD) and its 95% CI were used as effect size. The χ^2 test was used to analyze the heterogeneity between the results of the studies. If there was no statistical heterogeneity among the results of each study ($P > 0.10$, $I^2 \leq 50\%$), a fixed-effects model was used for meta-analysis; otherwise, a random-effects model was used for meta-analysis. Publication bias was evaluated by the demonstration of funnel plots, and asymmetry was assessed by means of the Egger regression test. $P < 0.05$ indicated that the difference between groups was statistically significant.

TABLE 1. The Characteristics of Included Randomized Controlled Trials

Study	Country	Sample Size		Age (y)		Pathological Type (Squamous Cell Carcinoma/Other, Case)		Clinical Stage (Ia/Ib/IIa/IIb/III, Case)			Outcomes
		LRH	ARH	LRH	ARH	LRH	ARH	LRH	ARH	ARH	
Campos et al ¹⁸	Portugal	14	19	56 (36-69)						0/0/0/15/17	0②
Campos et al ¹⁷	Portugal	16	14	56 (36-69)		27/5	NA	NA		0/0/0/30/0	0②
Dai ²⁷	China	20	20	60.06±9.28	61.22±10.08	NA	NA	NA	0/0/0/9/11	0/0/0/10/10	0⑥⑦⑧
Dong ²⁵	China	40	40	60.9±7.1	58.8±9.4	32/8	35/5	NA	NA	NA	0⑥⑥
Guo ²²	China	50	50	62(40~75)		NA	NA	NA	NA	NA	0③③⑥⑧
Li ²⁸	China	25	25	58.05±10.22	56.18±8.43	20/5	21/4	NA	0/0/2/1/4/9	0/1/4/14/6	0⑦
Lin ¹⁵	China	72	72	59.21±10.05		60/12	62/10	NA	NA	NA	0⑧
Ma ²⁶	China	51	51	55.96±6.11	56.04±9.27	NA	NA	NA	NA	NA	0②⑥⑥
Panici et al ²³	Italy	56	56	47±21	48.5±18.8	NA	NA	NA	0/0/0/24/32	0/0/0/30/26	①
Ramirez et al ²⁴	US	312	312	46.0±10.6	46.1±11.0	210/109	214/98	NA	25/287/0/0/0	26/293/0/0/0	⑥⑧
Song ¹⁹	China	76	76	62.8±10.5	59.2±9.6	65/11	66/10	NA	NA	NA	0③⑥⑧
Sun ¹⁶	China	45	45	46.12 ± 6.84	48.51±6.82	NA	NA	NA	NA	NA	0②③
Wang ²¹	China	28	28	60.44±9.12		NA	NA	NA	NA	NA	0③③⑦
Zhao ²⁰	China	40	40	57.15±8.05	58.08±9.24	33/7	32/8	NA	0/0/0/21/19	0/0/1/22/17	0⑤⑥⑧

①duration of surgery; ②intraoperative blood loss; ③number of lymph nodes removed; ④intraoperative complications; ⑤postoperative complications; ⑥the time to first passage of flatus; ⑦relapse rate; ⑧survival rate. ARH indicates abdominal radical hysterectomy; LRH, laparoscopic radical hysterectomy; NA, not available.

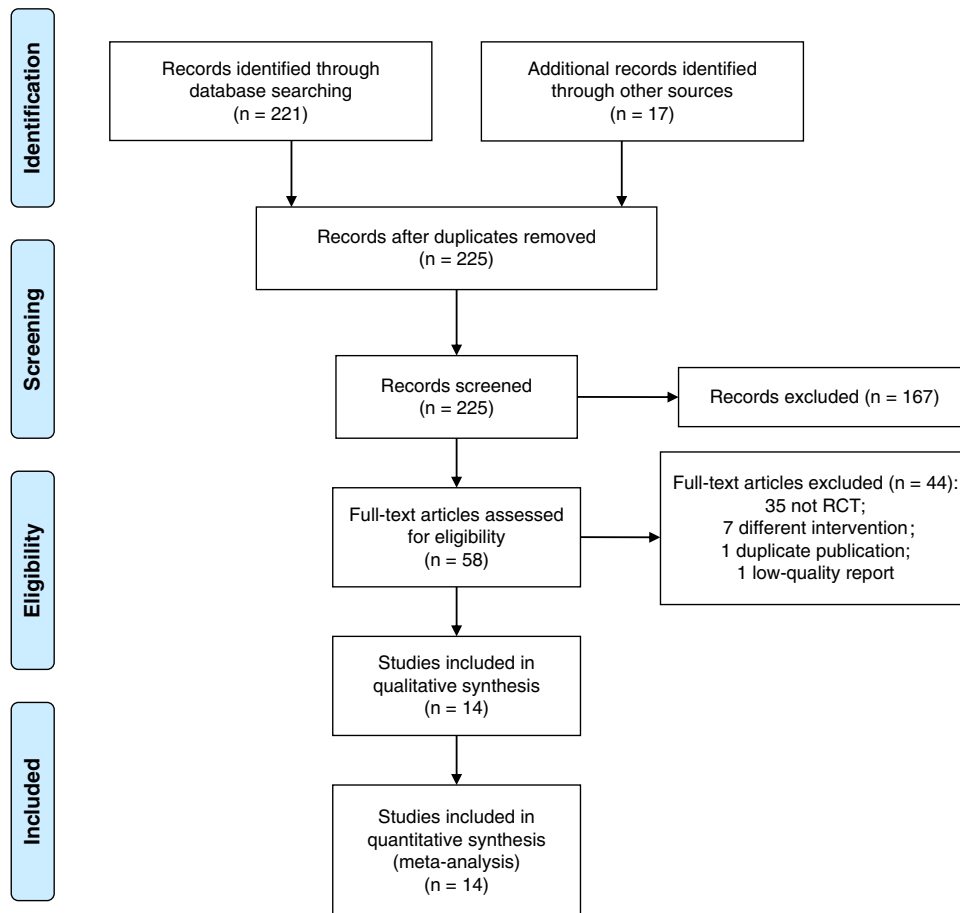


FIGURE 1. Preferred reporting items for systematic reviews and meta-analyses flow diagram of randomized controlled trial selection. full color online

RESULTS

RCT Selection

A total of 238 literatures were initially detected in the first literature search. After reading the titles and abstracts, 58 papers were included after excluding the literatures that did not meet the inclusion criteria. After reading the full text of the literature, 14 RCTs¹⁵⁻²⁸ were finally included (Fig. 1). Of the included 14 RCTs, a total of 1700 patients with cervical cancer were involved, 852 patients underwent

LRH treatment, 848 patients underwent ARH treatment. The basic characteristics of the included studies are shown in Table 1.

Literature Quality Evaluation

Of all the 14 included RCTs, 11 RCTs^{15-22,24-26} described specific methods for generating random sequences, and another 3 RCTs did not mention specific randomization methods. Only 6 RCTs reported specific allocation concealment methods. Blinding of participants and personnel and

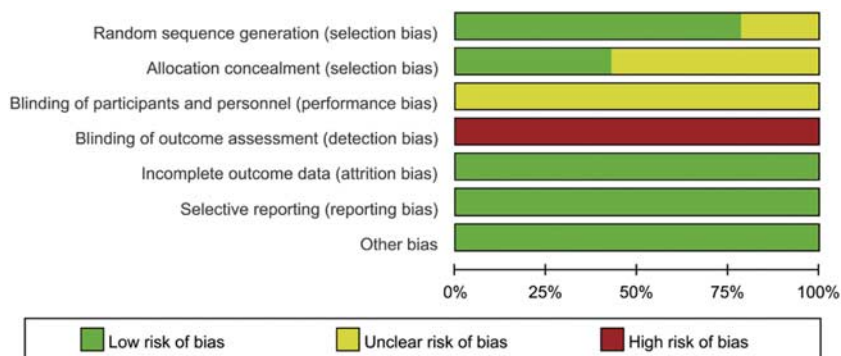


FIGURE 2. Risk of bias graph. full color online

outcome assessment (detection bias) were not stated in the included RCTs. No loss to follow-up and selective outcomes were reported. The results of the literature quality evaluation are shown in Figures 2 and 3.

Meta-analysis

Duration of Surgery

Eleven included RCTs^{16,18–23,25–28} reported the duration of surgery. Meta-analysis of random effects model showed that there was no significant difference in the duration of surgery between LRH group and ARH group (MD=27.62; 95% CI, -6.26, 61.49; *P*=0.11, Fig. 4A), with evidence of heterogeneity (*P*<0.001, *I*² = 99%).

Intraoperative Blood Loss

Ten included RCTs^{16,19–23,25–28} reported the intraoperative blood loss. Meta-analysis of random effects model showed that the intraoperative blood loss in the LRH group was significantly less than that of ARH group (MD=-58.08; 95% CI, -70.91, -45.24; *P*<0.001, Fig. 4B), with evidence of heterogeneity (*P*<0.001, *I*² = 73%).

Number of Lymph Nodes Removed

Eight included RCTs^{16,18,19,21–23,25,26} reported the number of lymph nodes removed. Meta-analysis of random effects model showed that the number of lymph nodes removed in the LRH group was significantly more than that of ARH group (MD=3.47; 95% CI, 0.51, 6.43; *P*=0.02, Fig. 4C), with evidence of heterogeneity (*P*<0.001, *I*² = 97%).

The Time to First Passage of Flatus

Seven included RCTs^{16,19,20,22,25–27} reported the time to first passage of flatus. Meta-analysis of random effects model showed that the time to first passage of flatus in the LRH group was significantly less than that of ARH group (MD=-14.50; 95% CI, -16.55, -12.44; *P*<0.001, Fig. 4D), with evidence of heterogeneity (*P*=0.003, *I*² = 70%).

Intraoperative Complications

Three included RCTs^{18,21,22} reported the intraoperative complications. Meta-analysis of random effects model showed that there was no significant difference in intraoperative complications between LRH group and ARH group (OR=1.10; 95% CI, 0.17, 7.32; *P*=0.92, Fig. 5A), with evidence of heterogeneity (*P*=0.12, *I*² = 53%).

Postoperative Complications

Three included RCTs^{18,20,21} reported the postoperative complications. Meta-analysis of fixed effects model showed that there was no significant difference in postoperative complications between LRH group and ARH group (OR=0.78; 95% CI, 0.33, 1.86; *P*=0.57, Fig. 5B), with no evidence of heterogeneity (*P*=0.21, *I*² = 37%).

Relapse Rate

Five included RCTs^{15,21,24,27,28} reported the relapse rate. The meta-analysis of random effects model showed that there was no significant difference in the relapse rate between LRH group and ARH group (OR=1.45; 95% CI, 0.56, 3.74; *P*=0.44, Fig. 5C), with evidence of heterogeneity (*P*=0.07, *I*² = 54%).

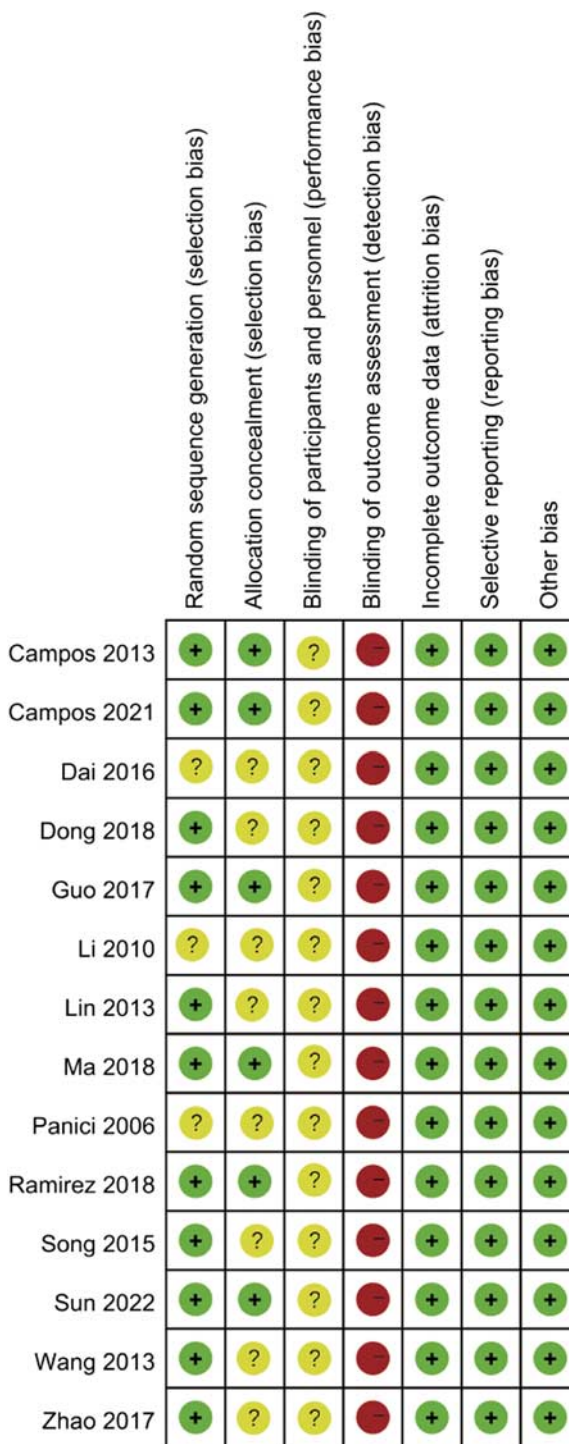


FIGURE 3. Risk of bias summary. full color online

Survival Rate

Six included RCTs^{15,19,20,22,24,27} reported the survival rate. The meta-analysis of fixed effects model showed that there was no significant difference in the survival rate between LRH group and ARH group (OR=0.75; 95% CI, 0.52, 1.08; *P*=0.12, Fig. 5D), with evidence of heterogeneity (*P*=0.08, *I*² = 48%).

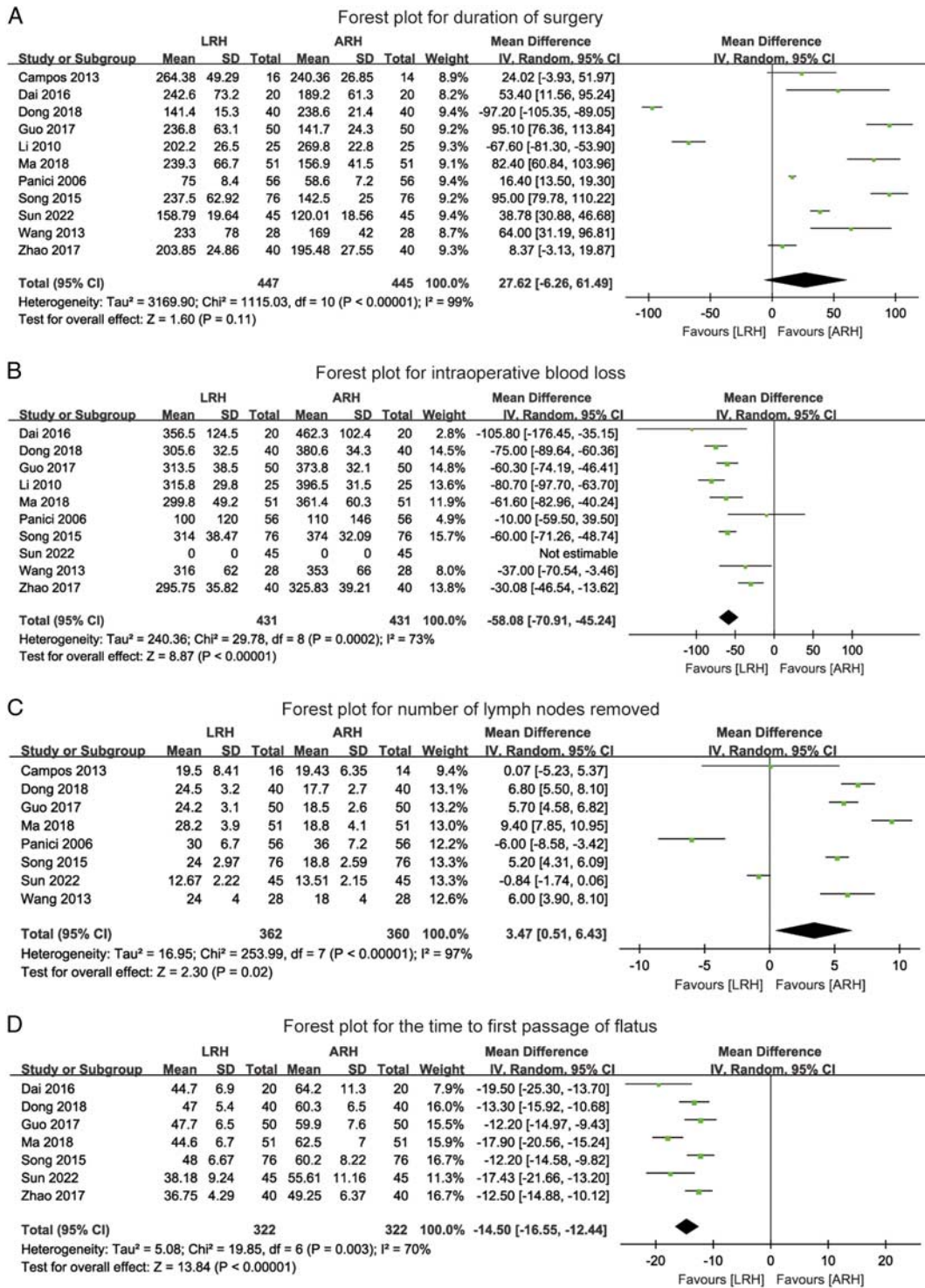


FIGURE 4. Forest plots for synthesized outcomes. ARH indicates abdominal radical hysterectomy; CI, confidence interval; LRH, laparoscopic radical hysterectomy. [full color online](#)

Publication Bias

As showed in Figures 6 and 7, the dots in the funnel plots for synthesized outcomes were evenly distributed, and the results of Egger regression tests indicated that there was no publication bias in the synthesized outcomes (all P > 0.05).

Sensitivity Analyses

Sensitivity analyses that assess the impact of single 1 study on the overall risk estimate by removing 1 study in each turn. No significant change of the overall risk estimates by removing any single study was found.

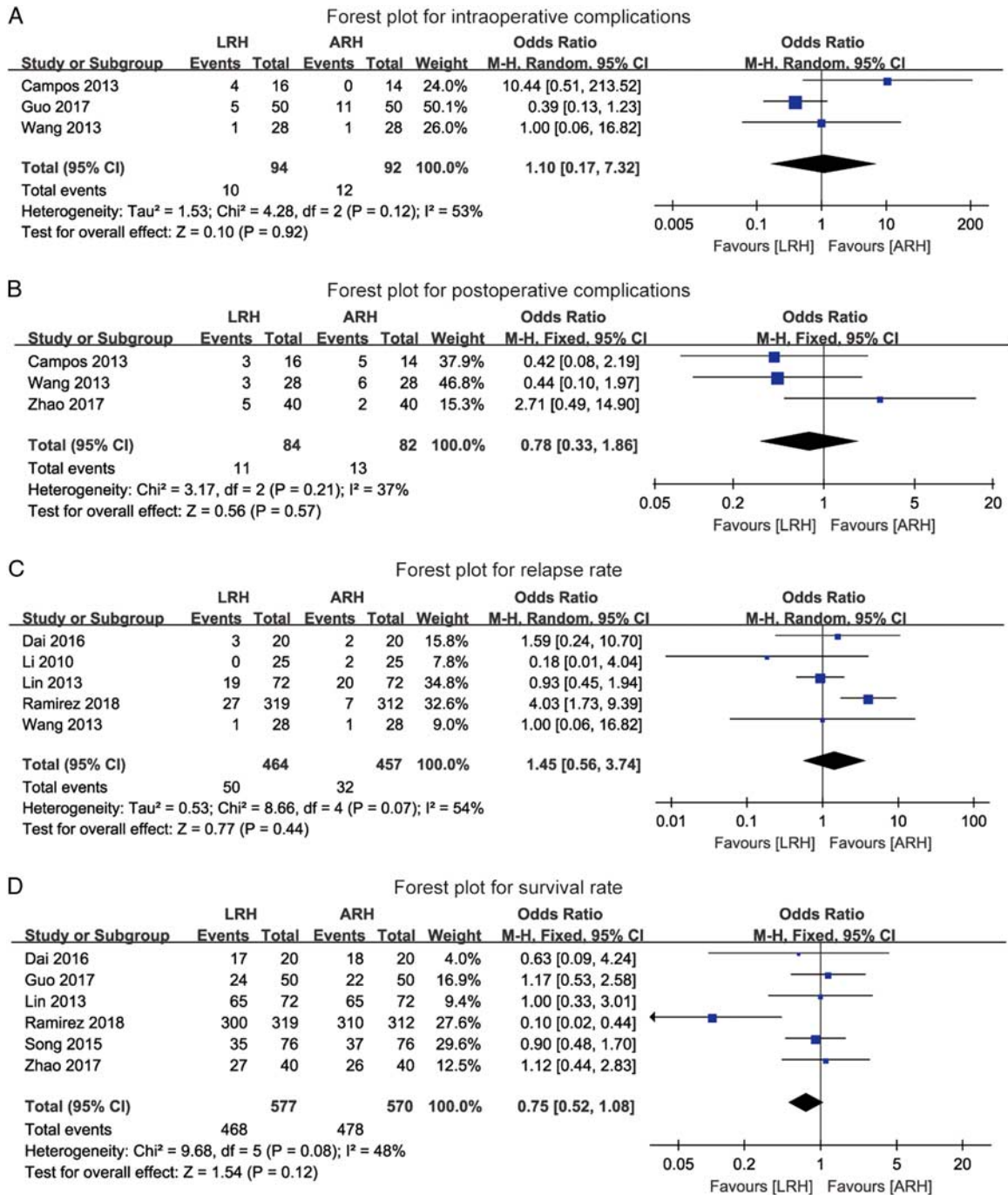


FIGURE 5. Forest plots for synthesized outcomes.

DISCUSSIONS

The treatment of cervical cancer should be based on the patient’s age, general condition, tumor stage, histologic type, lymph node metastasis, and fertility requirements to formulate the best treatment plan.^{29,30} For the diagnosis and treatment of cervical cancer, not only we must follow the basic principles of diagnosis and treatment guidelines, but also pay attention to individualized treatment, so the choice of specific treatment plan often requires the comprehensive judgment of clinicians.³¹ The results of clinical studies^{32–34} so far have shown that for

patients with early stage of cervical cancer FIGO clinical stage compared with radiotherapy alone, surgical treatment has the advantages of reducing the mortality rate of cervical cancer and the probability of tumor recurrence, and improving the quality of life of patients after surgery. At the same time, the possibility of permanent damage to ovarian function and other normal organs around the tumor by radiation therapy should be considered.³⁵ Therefore, for patients with early-stage cervical cancer, surgery is still the first choice for treatment. This meta-analysis has included 14 RCTs comparing ARH and LRH in the

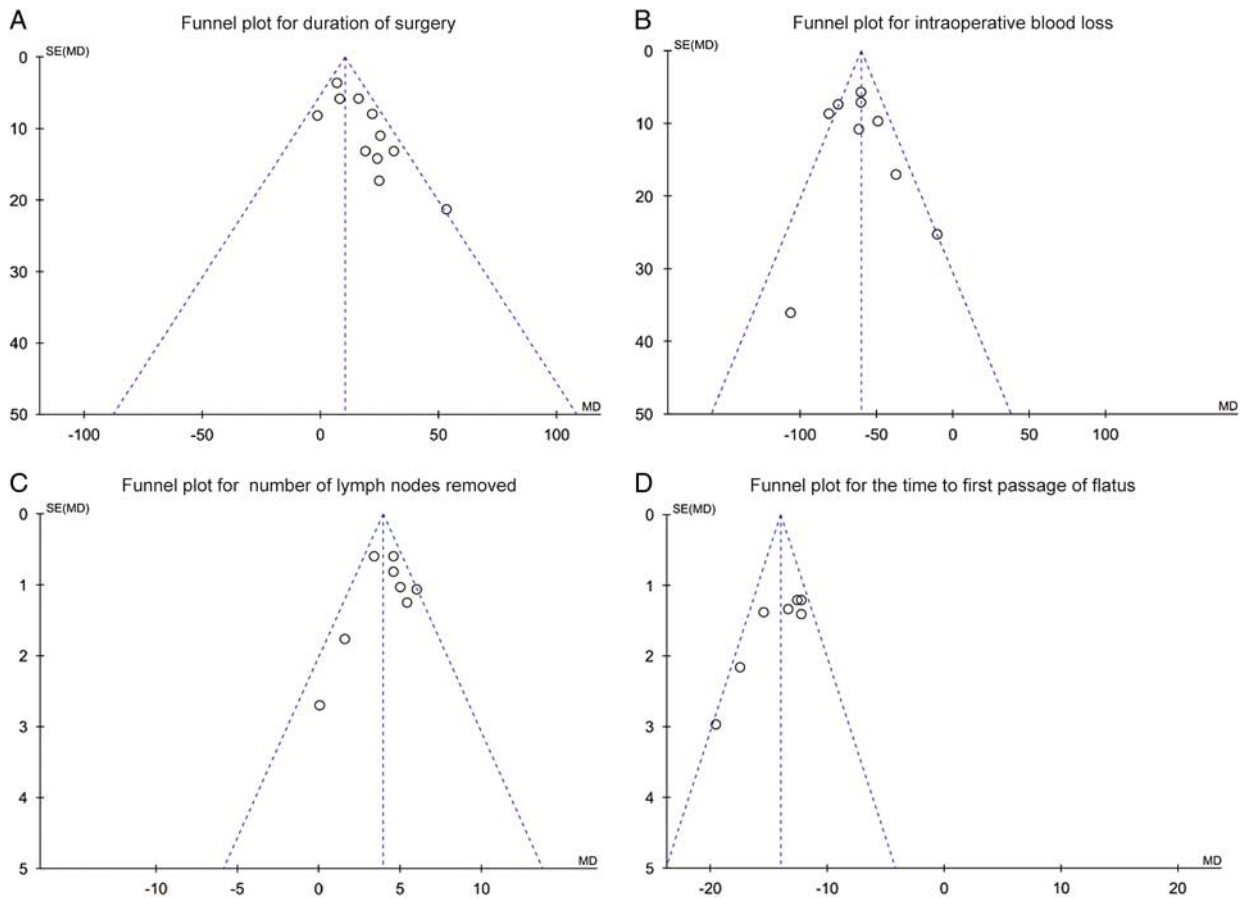


FIGURE 6. Funnel plots for synthesized outcomes. MD indicates mean difference; OD, odd ratio. [full color online](#)

treatment of cervical cancer. The results have showed that compared with the ARH, the LRH in the treatment of early cervical cancer can reduce the intraoperative blood loss, significantly increase the number of lymph nodes removed, and shorten the time to first passage of flatus. There are no significant differences between the ARH and LRH in terms of duration of surgery, intraoperative complications, postoperative complications, postoperative relapse rate, and survival rate.

We have not found the difference in the duration of surgery between ARH and LRH. On the one hand, the laparoscopic surgery is a new development technology, and the publication time of the included studies in this meta-analysis is different. In earlier studies, the laparoscopic surgery was carried out for a short period of time. ARH is a traditional operation, the surgeon may have higher technical level and richer surgical experience.³⁶ On the other hand, the “learning curve” of the surgeon also affects the duration of surgery.^{37–39} As none of the included studies reported the surgeon’s proficiency in LRH and the number of previous surgeries, the learning curve of the surgeons also contributed to the statistical heterogeneity among the included studies. Finally, none of the included studies have reported whether the patients had a history of multiple operations in the lower abdomen, which may cause adhesions between the pelvic and abdominal organs and tissues, leading to longer duration of surgery.

The intraoperative blood loss of LRH is less than that of ARH, and the difference was statistically significant. LRH has a small incision, whereas ARH has a larger incision. The process

of entering the abdominal cavity through the skin layer by layer damages more blood vessels and increases the bleeding of the incision.⁴⁰ When laparoscopic ultrasonic scalpel is used for tissue separation during surgery, it can not only cut tissue but also stop bleeding in a timely and effective manner, reducing unnecessary bleeding.^{41,42} Because of the magnifying effect of laparoscopic equipment, it is easier and clearer for the operator to identify important tissue structures such as blood vessels and nerves and the local anatomical relationship between them during surgical operations.^{43–45} When the laparoscopic eyepiece is close to the observation target, the surgical details can be observed for better and finer operation, and the bleeding-prone tissue can be effectively and preventively avoided. When the laparoscopic eyepiece is retreated, the surgical field of view can be expanded, and the operator’s awareness of the operation can be improved. The overall grasp of the visual field avoids the omission of small active bleeding foci in the surgical field of view, and can effectively stop bleeding in time, thereby significantly reducing the amount of bleeding on the surgical wound and avoiding the occurrence of major bleeding.^{46–48}

The results of this study have showed that the time of the time to the first passage of flatus in the LRH is earlier than that of ARH. The possible reason for the difference may be that laparoscopic surgery avoids the touch of the abdominal retractor, gauze and operator’s gloves on the intestine, and the less intestinal tract manipulations in the LRH reduce irritation to the patient’s gastrointestinal tract. In addition, laparoscopic surgery is performed in a relatively closed abdominal cavity,

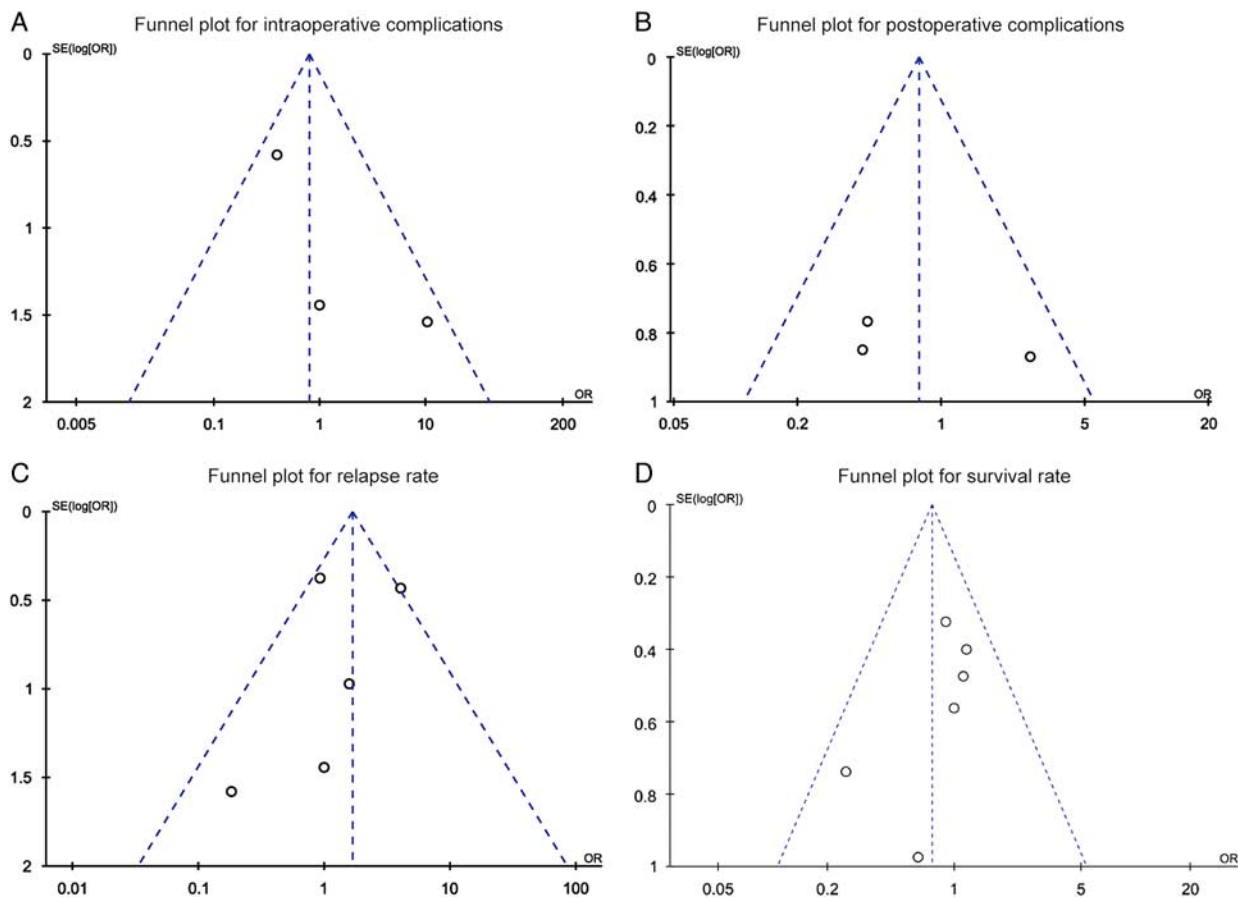


FIGURE 7. Funnel plots for synthesized outcomes. OD indicates odd ratio. [full color online](#)

and the pelvic and abdominal organs do not need to be exposed for a long time, and the intestinal tract will not be dry and cold, so that the patient's gastrointestinal motility function can be quickly recovered after surgery.^{49–51}

There are no significant differences in recurrence and survival between LRH and ARH. A long-term follow-up study⁵² has found that the 5-year survival rate after LRH was basically the same as that of laparotomy. In a retrospective case-control study,⁵³ 2 groups of cervical cancer patients with different surgical procedures were followed up for 5 years. The results showed that compared with laparoscopic surgery, the 5-year overall survival rates were 95.2% and 96.4%, respectively, the 5-year recurrence-free survival rates were 92.8% and 94.4%, and the 5-year tumor-specific survival rates were 89.6% and 90.7%, respectively. In recent years, some researchers^{54–56} have compared the 5-year overall survival rate and 5-year disease-free survival rate of laparoscopic surgery and traditional laparotomy in the treatment of cervical cancer, and have found that there is no significant difference between the 2 groups. We have evaluated the data from English versus Chinese reports, there is a difference in the survival rate between the English versus Chinese reports. Heretofore, the predominance of English data suggests an adverse survival rate associated with a minimally invasive approach. For patients with cervical cancer, whether different surgical methods will improve their postoperative survival rate and which method is more advantageous, there is still no clear conclusion. Therefore,

long-term follow-up results of multiple large-sample RCTs are still needed to confirm and evaluate the effect of LRH and ARH.

There are certain limitations in this study that must be considered. First, because surgery cannot be blinded, this may increase the measurement and performance bias of the study and increase the clinical heterogeneity among included RCTs. Second, some of the measurement indicators in this study were subject to the surgeon's learning curve and clinical experience, and none of the included studies reported whether the surgeons were proficient in LRH and the number of previous surgeries. Third, we included patients not only limited to early stage, we tried to conduct subgroup analysis based on the disease stage, yet the data were limited for subgroup analysis. In addition, most of the included studies had small sample sizes, which may affect the internal validity of the results. It is recommended that randomization methods, allocation concealment, and blinding design should be reported in detail in future clinical trials to reduce selection bias and measurement bias.

CONCLUSIONS

In conclusion, the results of this meta-analysis have found that LRH is beneficial to reduce the intraoperative blood loss, shorten the recovery time of postoperative gastrointestinal function, and increase the number of lymph nodes removed in patients with cervical cancer compared with ARH. Future research should be based on the patients' safety and quality of life, focusing on postoperative overall survival time, tumor-free survival time, and quality of life of patients with cervical cancer. It is suggested that

more RCTs should be carried out on the efficacy of LRH and ARH on postoperative quality of life and other outcomes with larger sample size and longer follow-up.

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