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Short- and long-term outcomes of laparoscopic versus open surgery for rectal cancer

A systematic review and meta-analysis of randomized controlled trials

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Abstract

Objectives: The present meta-analysis aimed to evaluate the short- and long-term outcomes of laparoscopic surgery (LS) versus open surgery (OS) for rectal cancer.

Methods: PubMed, Web of Science, and Cochrane Library, were searched for eligible randomized controlled trials (RCTs) published up to June 2017. Operation related index, postoperative complication, and long-term survival rate and disease-free survival rate were evaluated by meta-analytical techniques.

Result: Nine RCTs enrolling 4126 patients were included in the present meta-analysis. Compared to OS, LS had similar positive circumferential resection margin (CRM) and number of lymph nodes extracted (LNE) as well as long term 5 years survival rate and disease-free survival rate, but of which the risk tendency was higher in LS group. The short-term outcomes of major and total postoperative complication were lower in LS group.

Conclusions: LS for rectal cancer was as safe and effective as OS in terms of long-term outcomes, but with lower postoperative complication.

Abbreviations: 95% CI = confidence interval, APR = abdominoperineal resection, AR = anterior resection, BMI = body mass index, CRM = circumferential resection margin, ES = effect size, F = female, HR = hazard ratio, LAR = lower anterior resection, LHC = left hemicolectomy, LNE = lymph nodes extracted, LS = laparoscopic surgery, M = male, OS = open surgery, PICOS = population, intervention, compare, outcomes, study, PME = partial mesorectal excision, RCTs = randomized controlled trials, RHC = right hemicolectomy, RR = risk ratio, SC = Sigmoid colectomy, SWD = standardized mean difference, TME = total mesorectum excision.

Keywords: laparoscopic surgery, open surgery, randomized controlled trials, rectal cancer, systematic review

1. Introduction

Laparoscopic resection has been introduced to treat rectal cancer for decades.[1] Although some studies have demonstrated improved outcomes after laparoscopic-assisted resection of rectal cancer,[2–4] it is still controversial because of long skill learning, technical challenges related to the anatomical position of the rectum in the pelvis and lack of high quality published data regarding postoperative complications, oncologic safety, and long-term survival.

Recently, several randomized controlled research reported that laparoscopic resection for rectal show less blood loss, quicker recovery, shorter hospital stay, less complications, and a better quality of life compare with open surgery.[5–7] Meta-analysis can be used to evaluate the existing literature in a quantitative way by comparing and combining the results of different studies considering variations between studies.[4,8,9] In the present paper, we use meta-analytical techniques to compare the short- and long-term outcomes of LS and OS for rectal cancer from RCTs.

2. Material and methods

2.1. Study selection

A Web of Science, PubMed, and Cochrane library database search was performed on all studies between January 1986 and June 2017 to compare laparoscopic and open surgery for rectal cancer. We utilized the search terms in "PICOS" principle included the following: "colon neoplasm," "rectum neoplasm," "colonic," "rectal," "open surgery," "laparoscopic surgery," "laparoscopic operation," "open operation," "outcomes,"

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"complication," "transfer," "randomized," "controlled," and "randomly". We used both free text and MeSH as searches keywords. The "related articles" function was used to broaden the search, and all abstracts, studies, and citations scanned were reviewed. Only full-text papers in English and the results of LS and OS resection compared were considered. If data sets overlapped, only the most recent information was included. All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

2.2. Data extraction

Data were independently extracted by 2 investigators reviewed the titles, abstracts, and full texts of retrieved articles. Disagreements were resolved with a third reviewer. The following information was collected from each study: author, year, study design, characteristics of the study population, operation time, estimated blood loss, length of hospital stay, number of lymph nodes extracted, distance to distal circumferential resection margin, postoperative (1year) mortality, first time intake of solids, long-term mortality(5 year), long-term disease-free survival rate (5 year), etc.

2.3. Statistical analysis

RevMan version 5.3 and Stata version 12.0 were used to conduct the quality assessment and meta-analysis. Statistical analysis for categorical variables was performed by using the risk ratio (RR) or hazard ratio (HR) with 95% confidence interval (95% CI) and continuous variables were analyzed with standardized mean difference (SWD). If only the median, range, and size of the trial were reported in the literature, the means and standard deviations were calculated as described by Wan et al.[10] According to the Higgins' I^2 statistic, heterogeneity <25%, 25% to 50%, and ≥50% were defined as low, moderate and high, respectively.[11] Subgroup analyses would be taken if the synthesis results with high heterogeneity for the individual variation existing between the inclusion studies. A fixed-effect model was used for studies with low or moderate statistical heterogeneity, and a random-effect model was used for studies with high statistical heterogeneity. The value of $P<.05$ was considered statistically significant. Sources of heterogeneity were explored using sensitivity and subgroup analyses. Publication bias was quantitatively evaluated using funnel plots.

3. Results

3.1. Studies selected

The process of studies selected shown in the flow diagram, in brief, a total of 1026 studies were identified by the search strategy on line.

3.2. Study characteristics and qualities

A total of 9RCTs studies based on comparing the results of laparoscopic versus open resection for rectal cancer were eligible for the meta-analysis. Four thousand twenty 6 rectal cancer patients were included, of these, 2379 patients underwent LS and 1747 patients underwent OS. As Table 1 shown, 5 of the studies were randomized multicenter clinical studies and long-term follow-up were conducted in all studies.

Methodological quality of included trials was assessed using the Cochrane Collaboration's tool for evaluating risk of bias. In these studies, blinding techniques were hardly feasible because of the different treatment procedures and the associated adverse effects. However, the 2 reviewers judge that the outcome is not likely to be influenced by lack of blinding. All of the studies had a moderate risk of bias (Fig. 1A and B).

3.3. Short-term outcomes of laparoscopic surgery versus open surgery

The meta-analysis results for short-term outcomes indicated no significance between laparoscopic surgery and open surgery as Table 2 shown, except for transfusion [RR=0.344, 95%CI (0.175, 0.675), $I^2=0$, $P=.002$], incision length [SWD=−1.487, 95%CI (−2.639, −0.334), $I^2=99.5\%$, $P=.011$], blood loss [SWD=−0.475, 95%CI (−0.918, −0.032), $I^2=96.9\%$, $P=.036$], operation time [SWD=1.099, 95%CI (0.517, 1.682), $I^2=98.3\%$, $P=.000$], wound infection [RR=0.762, 95%CI

Table 1

Characteristics of the studies included in meta-analysis.

Author (year)	Leung K.L. (2004)	Marco B. (2007)	Simon S. M. (2008)	Liang X.B. (2011)	Green B.L. (2012)	V.D.Pas M.H. (2013)	Jeong S.Y. (2014)	Fleshman J. (2015)	Andrew R. L. (2015)
Country	Hong Kong	Italy	Hong Kong	China	England	Sweden	Korea	USA	Australasian
Multicenter	No	No	No	No	Yes	Yes	Yes	Yes	Yes
Experienced	Yes	Yes	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes
Gender (M/F)									
LS	55/28	37/39	31/20	104/65	296/230	162/98	110/60	156/86	160/67
OS	64/21	48/29	30/18	92/82	145/123	77/48	110/60	158/81	151/64
Age, years									
LS	62.8±12.6	66.5±11.9	63.7±11.8	57.3±14.1	69.0±11.0	67.4±0.4	57.8±11.1	57.7±11.5	66.6±0.6
OS	65.3±10.3	65.7±12	63.5±12.6	57.4±13.1	69.0±12.0	65.0±3.0	59.1±9.9	57.2±12.1	65.0±2.83
BMI (kg/m^2)									
LS	Unclear	Unclear	Unclear	Unclear	25±4.0	26.0±4.5	24.1±3.2	57.2±12.1	27.0±1.0
OS	Unclear	Unclear	Unclear	Unclear	26±4.0	26.5±0.3	26.4±4.0	26.8±4.2	26.0±1.0
Chemotherapy	portion	portion	No	Unclear	Portion	Portion	Yes	Yes	Portion
Resection type	AR	TME	APR	LAR,APR	AR, RHC,SC, APR,LHC	PEM,TEM	TME	TME, PME	LAR,APR
AJCC stage	I–IV	I–IV	I–IV	I–IV	I–IV	I–IV	I–IV	I–III	I–III

APR=abdominoperineal resection, AR=anterior resection, BMI=body mass index, F=female, LAR=lower anterior resection, LHC=left hemicolectomy, LS=laparoscopic surgery, M=male, OS=open surgery, PME=partial mesorectal excision, RHC=right hemicolectomy, SC=sigmoid colectomy, TME=total mesorectum excision.

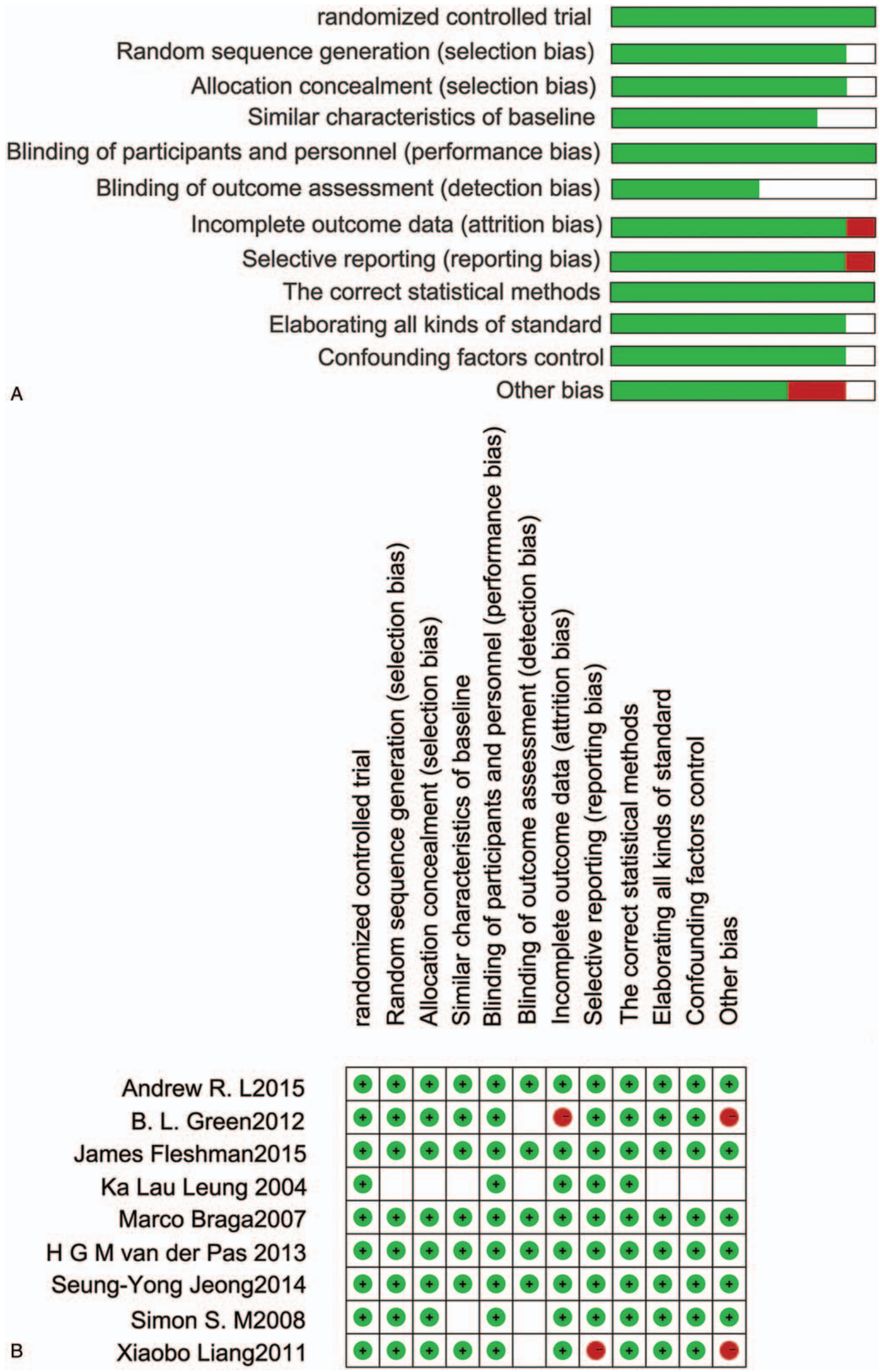

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies. (A) Risk of bias summary: review authors' judgements about each risk of bias item for each included study (B).

(0.605, 0.960), $I^2=0$, $P=.021$], first bowel movement [SWD = −1.278, 95%CI (−2.257, −0.299), $I^2=99.4\%$, $P=.011$], major complication[effect size (ES) = 0.794, 95%CI (0.663, 0.950), $I^2=38.8\%$, $P=.012$] and total complication [ES = 0.884, 95%CI (0.800, 0.977), $I^2=0\%$, $P=.015$].

3.4. Long term outcomes of laparoscopic surgery versus open surgery

Six studies analysed 5 year survival rate between the 2 groups, which involved 1715 patients (986 laparoscopic group and 729 open group), and it revealed no significantly difference [Hazard

Table 2

Results of meta-analysis of short outcomes and individual postoperative complications.

Outcome measures	No. of studies	Patients (LS/OS)	I^2 (%)	RR/ WMD	95% CI	*P* value
Transfusion	3	422/429	0.0%	0.3	0.2,0.7	.002*
Incision length	7	1919/1539	99.5%	−1.5	−2.6,−0.3	.011*
CRM	6	1686/1327	53.4%	0.013	−0.1,0.1	.820
Positive CRM	7	1609/1183	0.0%	1.2	0.9,1.6	.121
Blood loss	7	1684/1305	96.9%	−0.5	−0.9,−0.0	.036*
Operation time	8	1853/802	98.3%	1.1	0.5,1.7	.000*
Hospital stay	7	1669/1297	95.3%	−0.3	−0.7,0.0	.057
First bowel movement	8	2296/1662	99.4%	−1.3	−2.3,−0.3	.011*
Wound infection	9	2307/1695	0.0%	0.8	0.6,1.0	.021*
Anastomotic leak	7	1621/1251	0.0%	1.1	0.8,1.5	.546
LNE	7	1599/1209	92.1%	−0.2	−0.5,0.1	.111
TRND	5	1220/958	97.0%	−0.5	−1.0,0.0	.053
1 year mortality	7	1854/1248	0.0%	0.9	0.7,1.1	.330
Major complication	8	2136/1511	38.8%	0.8	0.7,0.95	.012*
Total complication	8	2140/1508	0.0%	0.9	0.8,1.0	.015*

CRM = circumferential resection margin, LNE = the number of lymph nodes extracted, LS = laparoscopic surgery, OS = open surgery, RR = risk ratio, TRND = time to resume normal diet.
$I^2 \leq 25\%$ (fixed analysis model), $I^2 > 25\%$ (random analysis model).

ratio (HR) = 0.915, 95%CI (0.816, 1.025), I^2 = 0, *P* = .124, Fig. 2A; RR = 0.998, 95%CI (0.928,1.037), I^2 = 0, *P* = .947]. A total of 1538 patients (878 laparoscopic group and 660 open group in 5 studies) were included in the analyses of 5 year disease-free survival, and this difference was also not significant [HR = 0.909, 95%CI (0.807, 1.023), I^2 = 0, *P* = .114, Fig. 2B; RR = 0.963, 95%CI (0.896, 1.036), I^2 = 0, *P* = .314].

3.5. Subgroup analysis

As indicated in multicenter subgroup analysis, the result of first bowel movement [3 studies in singer central, SWD = −0.324, 95%CI (−0.460, −0.189), I^2 = 0, *P* = .000; 4 studies in multicenter, SWD = −1.858, 95%CI (−3.289, −0.427), I^2 = 99.6%, *P* = .011, Fig. 3A] were significantly lower for LS group, and the number of lymph nodes extracted [4 studies in singer central, SWD = −0.109, 95%CI (−0.232, −0.014), I^2 = 0, *P* = .083; 3 studies in multicenter, SWD = −0.436, 95%CI (−0.880, −0.008), I^2 = 94.7%, *P* = 0.054, Fig. 3B] has no significance between these 2 groups.

In the experienced doctor surgery subgroup where blood loss [6 studies, SWD = −0.288, 95%CI (−0.433, −0.143), I^2 = 58.3%, *P* = .000, Fig. 4A], the incision length [3 studies, SWD = 0.021, 95%CI (−0.102, 0.142), I^2 = 0.0%, *P* = 0.324, Fig. 4B] and the rate of major complication [ES = 0.805, 95%CI (0.670, 0.967), I^2 = 0%, *P* = .021, Fig. 4C] were significantly lower in LS group with low heterogeneity.

3.6. Sensitivity analysis and publication bias

Sensitivity analysis was performed by trim and fill method, of which results are similar and steady for long-term outcomes and complication between pre-trim and post-trim (Fig. 5). Funnel plot analysis (Fig. 5) of the studies was performed in the meta-analysis for detecting the publication bias of the main outcomes such as 5 year mortality (Harbord test, *P* = .656), 5 year disease-free survival

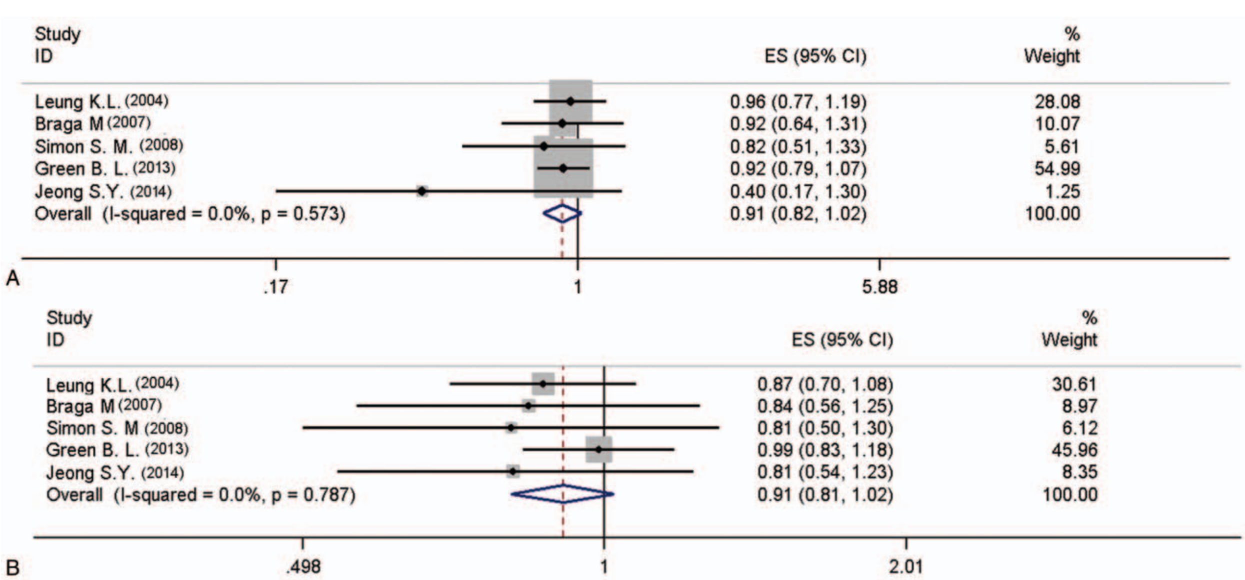

Figure 2. Meta-analysis of the pooled data: 5 year survival rate (A) 5 year disease-free survival (B).

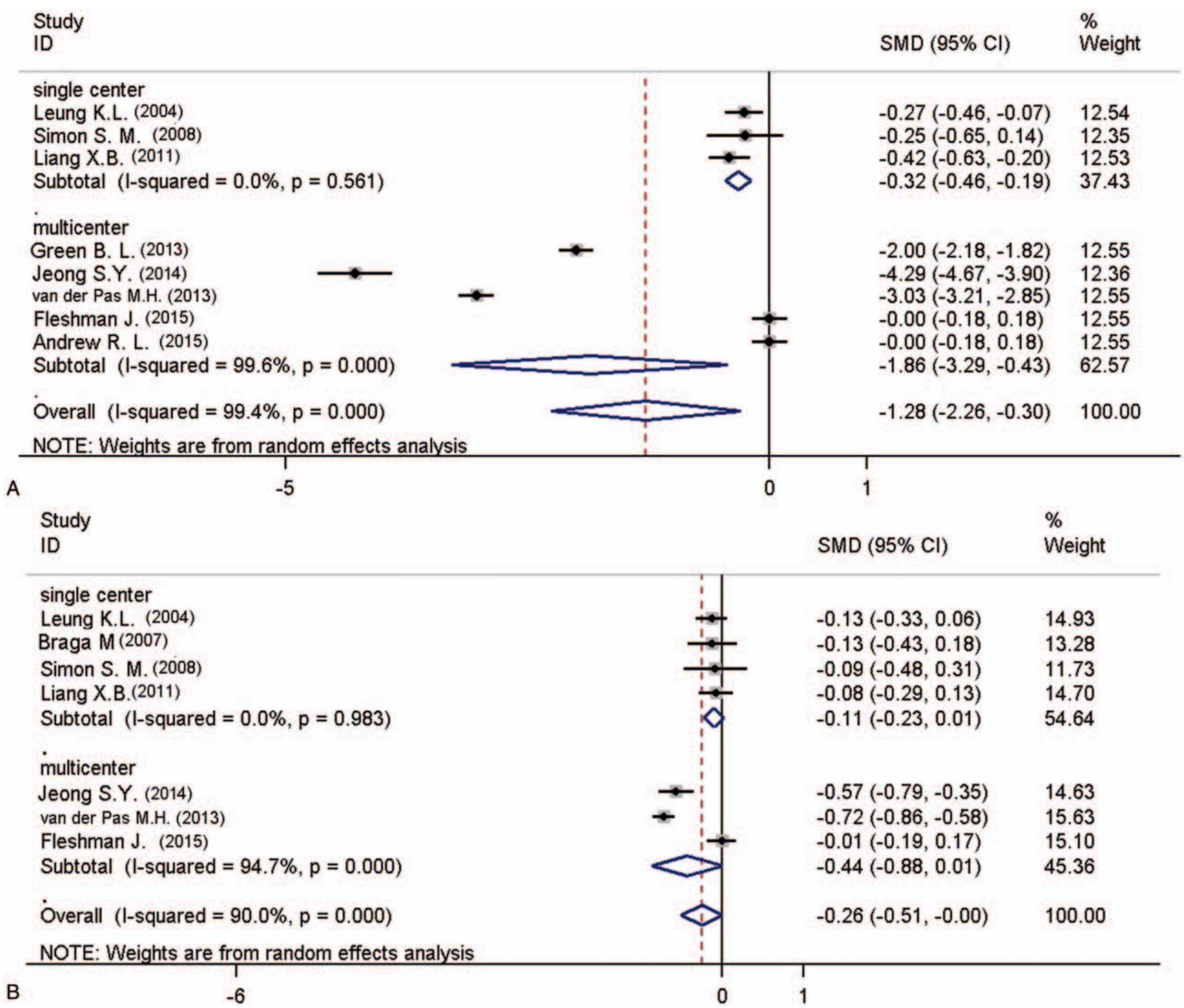

Figure 3. Subgroup analysis of the pooled data: first bowel movement (A) number of lymph nodes extracted (B).

(Harbord test, $P=.747$), total complication (Harbord test, $P=.656$) and major complication (Harbord test, $P=.052$), None of the studies were outside of the limits of the 95%CI, and there was no evidence of publication bias or heterogeneity among the studies.

4. Discussion

A total of 4126 patients from 9 RCTs considered low risk of bias were analyzed in the present meta-analysis (LS 2379 vs OS 1747). In this analysis, long-term outcome shown no statistical significant differences and similar with previous reports[6,7,12,13] between the 2 groups regarding 5 year survival rate and disease-free survival,[3,14] but of which the risk trend were higher in LS group. The short term outcome of major complication and total complication were lower in LS group compared with OS group.[15] It is confident that the original data of the synthetic results come from high quality RCTs. The selection and publication biases have not been detected by bias risk analysis and sensitivity analysis shown a stable profile for these long-term outcome.

Amount studies reported optimal operation information in LS versus OS. A faster postoperation recovery would well compensate the relatively long operating time (Table 2) for the laparoscopic approach for rectal cancer as most of other studies related.[6,16,17] For considering the high heterogeneity ($I^2=98.5\%$), we applied a subgroup analysis of random-effects model to take into consideration the study variation, of which result shown different area may be as one important reason for the differences of the results from different studies (Asian, $I^2=7.2\%$; occidental, $I^2=99.2\%$).[18,19] The blood loss was significant lower in LS group with moderate heterogeneity taking surgical experience as grouping factors (surgical experience group, $I^2=58.3\%$), which indicates that ultrasonic scalpel and magnification instruments applied by highly skilled doctors would enable better identification and dissection of the vessels and significantly reduce operation bleeding.[20,21]

The positive CRM and retrieved lymph node numbers are related to local recurrence and long term survival.[22–24] In this analysis, we did not find significant differences between LS and OS at the result (Table 2) of positive CRM (RR=1.2, $P=.121$; $I^2=0.0\%$,) and lymph node numbers (WMD=−0.2, $P=.111$; $I^2=92.1.0\%$) as James Fleshman and Andrew reported indicated that the resection outcomes of LS were comparable to that of OS.[7,25] We attributed the high heterogeneity in the synthetic results of lymph node numbers to different operation criteria

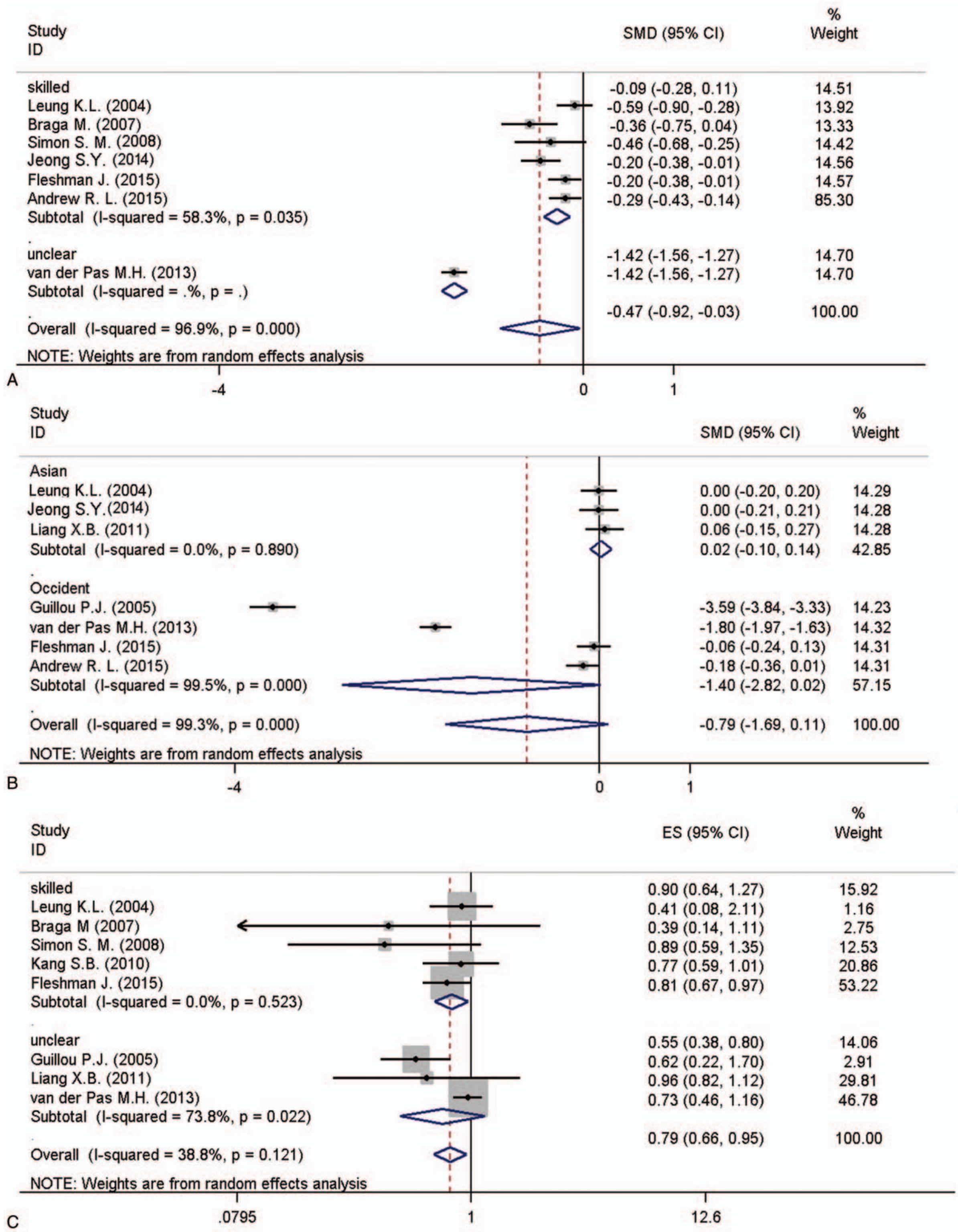

Figure 4. Subgroup analysis of the pooled data: blood loss (A) incision length (B) major complication (C).

from hospitals because of lower heterogeneity detected in single center subgroup ($I^2=0.0\%$, $P=.083$).[4,26]

Postoperative complication rate is a crucial index for evaluating the quality of operation. In the present analysis, no significant differences were detected for anastomotic leak[27,28] and 1 year mortality[3,29,30] (Table 2) between LS and OS groups as other studies concerns, but the rates of major postoperative complication and total postoperative complication were lower in LS group implied that LS treatment reduced postoperative complication compared to OS for rectal cancer. In the subgroup analysis, we identified skilled operation team was the main connections for the occurrence of major postoperative

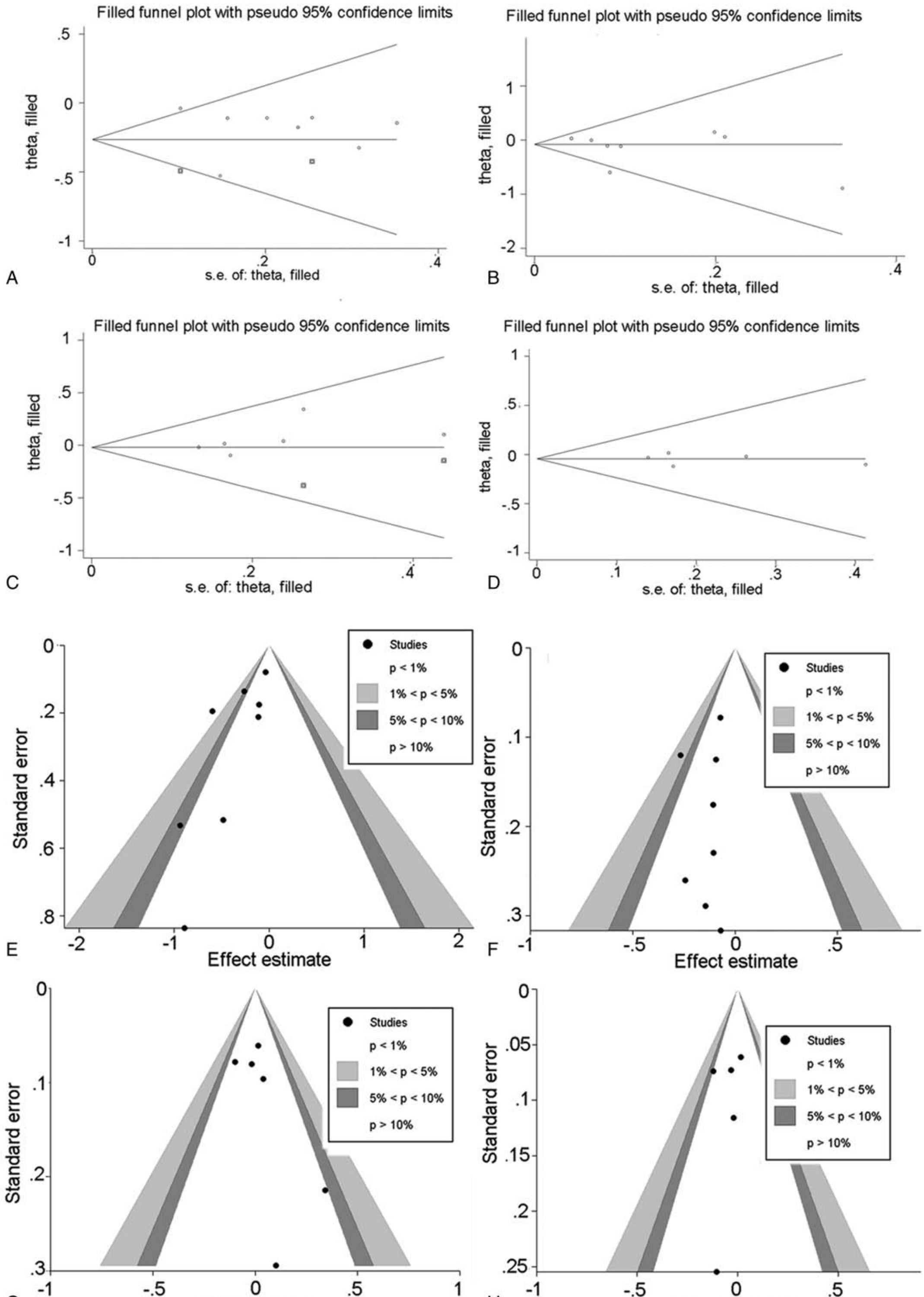

Figure 5. Post-trim plots of the synthetic results: major complication (A) total complication (B) 5 year survival rate (C) 5 year disease-free survival (D) funnel plots of the synthetic results: major complication (E) total complication (F) 5 year survival rate (G) 5 year-disease-free survival (H).

complication (skilled operation team, $I^2=0\%$; unclear team, $I^2=38.8\%$).[31]

In summary, our study indicated that laparoscopic surgery for rectal cancer was as safe and effective as open surgery in terms of long-term outcomes. Moreover, laparoscopic surgery reduced hospital stay, wound infection, total and major post- operative complication.

This meta-analysis has several limitations that should be considered regarding interpretation. Firstly, the small number of included RCTs may limit the statistical power. Although it is ideal for a meta-analysis to include RCTs only, the inclusion of high-quality non-RCT can improve the statistical power while maintaining an acceptable level of evidence. Secondly, high heterogeneity exists in several synthetic results (Table 2), therefore more details relating the bias between different studies, such as the race of the patients, the operation team, randomization, blinding and the oncologic results, should be recorded. Furthermore, improved standardized judgment method and reporting form of functional outcomes should be considered in the future RCTs.

Author contributions

Contribution of authors: All of the authors participated in the design, interpretation of the studies, analysis of the data and review of the manuscript; Conception and design: Zhong Lin, Qiang- Qiang Ge; Search literature: Zhong Lin, Qiang-Qiang Ge, Zheng-Li Jiang, Dan-Yang Chen; Collection and assembly of data: Zhong Lin, Qiang-Qiang Ge, Zheng-Li Jiang, Min-Fang Chen, Li-Hua Chen; Data analysis and interpretation: Peng-Zhou, Ai-Xiao Xia, Yan-Wu Zhu; Manuscript writing: Zhong Lin, Qiang-Qiang Ge, Zheng-Li Jiang; Final approval of manuscript: All authors.

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