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META-ANALYSIS

Genitourinary function and defecation after colorectal cancer surgery with low- and high-ligation of the inferior mesenteric artery: A meta-analysis

Xiao Bai, Chun-Dong Zhang, Jun-Peng Pei, Dong-Qiu Dai

ORCID number: Xiao Bai 0000-0001-5964-0289; Chun-Dong Zhang 0000-0003-1804-1356; Jun-Peng Pei 0000-0002-1876-3204; Dong-Qiu Dai 0000-0002-1154-3276.

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Xiao Bai, Chun-Dong Zhang, Jun-Peng Pei, Dong-Qiu Dai, Department of Gastrointestinal Surgery, the Fourth Affiliated Hospital of China Medical University, Shenyang 110032, Liaoning Province, China

Chun-Dong Zhang, Department of Gastrointestinal Surgery, Graduate School of Medicine, The University of Tokyo, Tokyo 113-0033, Japan

Dong-Qiu Dai, Cancer Center, the Fourth Affiliated Hospital of China Medical University, Shenyang 110032, Liaoning Province , China

Corresponding author: Dong-Qiu Dai, MD, PhD, Professor, Department of Gastrointestinal Surgery, the Fourth Affiliated Hospital of China Medical University, No. 4 Chongshan East Road, Shenyang 110032, Liaoning Province, China. daidq63@163.com

Abstract

BACKGROUND

The effect of low ligation (LL) *vs* high ligation (HL) of the inferior mesenteric artery (IMA) on functional outcomes during sigmoid colon and rectal cancer surgery, including urinary, sexual, and bowel function, is still controversial.

AIM

To assess the effect of LL of the IMA on genitourinary function and defecation after colorectal cancer (CRC) surgery.

METHODS

EMBASE, PubMed, Web of Science, and the Cochrane Library were systematically searched to retrieve studies describing sigmoid colon and rectal cancer surgery in order to compare outcomes following LL and HL. A total of 14 articles, including 4750 patients, were analyzed using Review Manager 5.3 software. Dichotomous results are expressed as odds ratios (ORs) with 95% confidence intervals (CIs) and continuous outcomes are expressed as weighted mean differences (WMDs) with 95%CIs.

RESULTS

LL resulted in a significantly lower incidence of nocturnal bowel movement (OR = 0.73, 95%CI: 0.55 to 0.97, P = 0.03) and anastomotic stenosis (OR = 0.31, 95%CI: 0.16 to 0.62, P = 0.0009) compared with HL. The risk of postoperative urinary

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dysfunction, however, did not differ significantly between the two techniques. The meta-analysis also showed no significant differences between LL and HL in terms of anastomotic leakage, postoperative complications, total lymph nodes harvested, blood loss, operation time, tumor recurrence, mortality, 5-year overall survival rate, or 5-year disease-free survival rate.

CONCLUSION
Since LL may result in better bowel function and a reduced rate of anastomotic stenosis following CRC surgeries, we suggest that LL be preferred over HL.

Key Words: Low ligation; High ligation; Colorectal cancer; Genitourinary function; Defecatory function; Meta-analysis

Core Tip: It remains unclear whether the benefits of low ligation of the inferior mesenteric artery (IMA) during sigmoid colon and rectal cancer surgeries extend to improved genitourinary and defecatory function. We conducted this meta-analysis to compare low ligation and high ligation of the IMA in terms of functional outcomes, as well as other surgical and long-term survival outcomes.

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INTRODUCTION

Colorectal cancer (CRC) ranks third in global cancer incidence, accounting for 10.0% of the total number of cancer cases, and ranks second in mortality[1]. Two techniques, which differ mainly in the level of inferior mesenteric artery (IMA) ligation, are used during curative surgery for cancer of the sigmoid colon and rectum. Which of high ligation (HL), which does not preserve the left colic artery, or low ligation (LL), which does preserve the left colic artery, is the better technique has been controversial since 1908[2]. Compared with LL, HL may allow a greater total number of lymph nodes to be harvested, facilitating more accurate assessment of tumor stage, and guiding adjuvant treatment. HL may be easier to achieve surgically and has been advocated by Girard *et al*[3]. Because HL will increase urogenital and defecation disorders, others have recently suggested that LL be preferred[4,5]. Some studies, however, showed no significance between LL and HL in terms of surgical or oncological outcomes[6,7].

Because of the ongoing controversy, previous reviews have explored the relationship between the two different approaches to IMA ligation and patient outcomes. Harjinder *et al*[8] found no difference between the two techniques in terms of rate of anastomotic leakage, total number of lymph nodes harvested, or survival rates. Other meta-analyses[9,10], however, found that LL of the IMA is associated with a lower risk of anastomotic leakage. At present, when completing sigmoid colon and rectal cancer surgery, it remains unclear whether the benefits of LL extend to improved genitourinary and defecatory function.

To address this, we carried out this meta-analysis to systemically compare LL and HL of the IMA in terms of functional outcomes, including urinary, sexual, and bowel function, as well as other surgical and survival outcomes.

MATERIALS AND METHODS

Search strategy

This meta-analysis was conducted according to the guidelines for Preferred Reporting

Items of Systematic Reviews and Meta-Analyses (PRISMA)[11]. The search terms "ligation" and "colorectal surgery" were used to retrieve all relevant articles from the Cochrane library, PubMed, EMBASE, and Web of Science (search last updated in December, 2020). References cited by articles identified in the initial search were used to identify additional relevant articles.

Primary outcomes

Genitourinary functional outcomes, including sexual function, urinary function, and defecation, were regarded as primary outcomes.

Secondary outcomes

The secondary outcomes were total number of lymph nodes harvested, anastomotic stenosis, anastomotic leakage, postoperative complications, operation time, blood loss, mortality, recurrence, 5-year overall survival, and disease-free survival.

Study selection and data extraction

The following criteria were used for inclusion: (1) Studies having at least one main result; (2) Randomized controlled trials (RCTs) or non-randomized studies in patients with sigmoid colon and rectal cancer; and (3) Studies comparing high and low ligation in radical resection, regardless of surgical approach. Where several reports described the same clinical study, the publication with the most complete data set was included in the meta-analysis. Articles in any language were included.

The exclusion criteria were as follows: (1) Studies having no control group; (2) Full text unavailable; and (3) Review articles, case reports, letters, or meta-analyses.

Two authors independently checked and evaluated the titles and/or abstracts of the articles and excluded any that were obviously irrelevant. The suitability of the remaining articles for inclusion in the analysis was assessed by inspection of the full article. Relevant details on research design, baseline characteristics, and outcomes were then collected. Differences in opinion between the two authors were resolved through discussion. The following data were retrieved from each article: Year of publication, first author's name, country where the study was conducted, and the number of patients, together with age and gender. If available, supplementary information was obtained for each article included in the study.

Quality assessment

The Newcastle-Ottawa Scale[12], based on comparability between groups, quality of patient selection, patient results, and determination of exposure, was used to evaluate the quality of non-randomized studies. The Cochrane Collaborative Bias Risk Tool was used to evaluate the quality of RCTs. Research areas covered allocation concealment, selective reporting of results, sequence generation, incomplete results, blinding, and other sources of bias. The bias risk of each study was sorted as high, ambiguous, or low. Differences were settled through consensus discussions.

Statistical analysis

Statistical analyses were performed using Review Manager 5.3 software (The Cochrane Collaboration; Copenhagen, Denmark). Continuous outcomes are expressed as weighted mean differences (WMDs), with 95% confidence intervals (CIs). Dichotomous outcomes are expressed as odds ratios (ORs), with 95%CIs. Heterogeneity between studies was evaluated using the χ^2 test (Cochran Q test) and I^2 statistics. The random effects model was used for meta-analysis where the P value was less than 0.10 or I^2 was greater than 50%; otherwise the fixed effects model was used.

RESULTS

Study selection

Our initial search identified 458 studies. After removal of duplicates and assessment of eligibility for inclusion, 14 clinical trials, which included an LL treatment group and an HL treatment group, were included in the final analysis (Figure 1). These studies involved a total of 4750 patients, with 1984 patients in the LL group and 2766 patients in the HL group. The baseline characteristics of the 14 eligible studies[4,5,7,13-23] are shown in Table 1. Quality assessments of the included studies are shown in Table 2 and Figure 2, and all endpoints are listed in Table 3.

Table 1 Characteristics of studies included

Ref.	Year	Country	Design	Surgical treatment (No. patients)		Male (%) LL/HL	Age, yr[1]		Diagnosis	Stage (No. patients) LL/HL			
				LL	HL		LL	HL		I	II	III	IV
AlSuhaimi *et al*[15]	2019	South Korea	Retrospective cohort	378	835	63.8/66.2	60.2 ± 11.5	60.6 ± 10.8	Rectal cancer	NA			
Chen *et al*[4]	2020	China	Retrospective cohort	227	235	51.5/54.0	58.6 ± 8.9	57.9 ± 9.1	Rectal cancer	19/24	111/95	97/116	
Dimitri *et al*[18]	2018	Greece	Retrospective cohort	44	76	68.2/51.3	72 (64-77.8)	70 (63-79)	Rectosigmoid and rectal cancer	9/17	16/27	14/26	
Fiori *et al*[5]	2020	Italy	RCT	24	22	58.3/54.4	68 ± 11	68 ± 9	Rectal cancer	24/22			
Fujii *et al*[7]	2019	Japan	RCT	108	107	63.0/63.6	66 (35-88)	66 (30-86)	Rectal cancer	43/45	20/20	36/36	4/3
Kverneng Hultberg *et al*[20]	2017	England	Retrospective cohort	432	373	52.5/63.0	NA		Rectal cancer	118/86	138/128	137/122	25/24
Lee *et al*[17]	2018	South Korea	Retrospective cohort	83	51	71.1/66.7	66.6 ± 10.7	66.1 ± 11.5	Sigmoid colon cancer	NA			
Matsuda *et al*[23]	2015	Japan	RCT	49	51	69.4/64.7	67 (45-89)	69 (45-85)	Rectal cancer	17/7	17/15	13/23	2/4
Park *et al*[14]	2020	South Korea	Retrospective cohort	163	613	65.0/66.4	62 (31-88)	62 (30-86)	Distal sigmoid colon and rectal cancer	51/175	35/146	52/229	10/30
Wang *et al*[22]	2015	China	RCT	65	63	64.6/60.3	58.6 ± 13.7	56.8 ± 14.2	Rectal cancer	NA			
Yasuda *et al*[21]	2016	Japan	Retrospective cohort	147	42	62.6/61.9	68 ± 9.1	64.5 ± 9.6	Sigmoid colon and rectal cancer	38/2	44/21	65/19	
You *et al*[13]	2020	China	Retrospective cohort	148	174	66.2/67.2	58.1 ± 10.8	57.2 ± 10.5	Rectal cancer	28/38	59/77	59/58	
You *et al*[19]	2017	China	Retrospective cohort	64	72	56.3/58.3	60.1 ± 10.8	58.1 ± 10.9	Rectal cancer	14/16	20/22	29/23	
Zhou *et al*[16]	2018	China	RCT	52	52	61.5/59.6	53.9 ± 13.5	52.7 ± 12.9	Rectal cancer	4/2	23/27	25/23	

[1]Data expressed as the mean ± SD or median (range). LL: Low ligation; HL: High ligation; NA: Not available; RCT: Randomized clinical trial.

Genitourinary function outcomes

No significant differences in urinary dysfunction (OR = 1.23, 95%CI: 0.95 to 1.59, P = 0.12; Figure 3A)[4,7,16-18,20,21] or urinary retention (OR = 1.51, 95%CI: 0.85 to 2.68, P = 0.16; Figure 3B)[5,14,22,23] were found between the LL and HL groups. The LL group did, however, have a lower risk of urinary infection (OR = 0.29, 95%CI: 0.16 to 0.54, P < 0.0001; 3C)[7,15,21] and a decreased risk of genitourinary dysfunction (OR = 0.32, 95%CI: 0.17 to 0.61, P = 0.0006; Figure 3D), compared with the HL group[13,19].

Defecatory function outcomes

Nocturnal bowel movement was lower in the LL group than in the HL group (OR = 0.73, 95%CI: 0.55 to 0.97, P = 0.03; Figure 3E)[20,22,23], but there was no difference between the two groups in terms of need for antidiarrheal or laxative drugs (OR = 0.70, 95%CI: 0.37 to 1.30, P = 0.26; Figure 3F)[22,23] or Wexner's incontinence score (WMD, −0.01, 95%CI: −0.71 to 0.70, P = 0.99; Figure 3G)[5,22,23].

Table 2 Quality assessment of included non-randomized trials based on Newcastle-Ottawa scoring system

Ref.	Year	Selection of the research object	Comparability	Measurement	NOS score
AlSuhaimi *et al*[15]	2019	3	1	3	7
Chen *et al*[4]	2020	3	2	2	7
Dimitriou *et al*[18]	2018	2	1	3	6
Kverneng Hultberg *et al*[20]	2017	3	1	2	6
Lee *et al*[17]	2018	2	2	2	6
Park *et al*[14]	2020	3	1	3	7
Yasuda *et al*[21]	2016	2	2	3	7
You *et al*[13]	2020	3	2	3	8
You *et al*[19]	2017	2	1	3	6

NOS: Newcastle-Ottawa scale.

Table 3 Endpoints of this meta-analysis

Endpoint	No. of patients	No. of studies	LL	HL	OR WMD (95CI)	I^2(%)	*P* value
Functional outcomes							
Urinary dysfunction	2029	7	1093	936	OR, 1.23 (0.95-1.59)	25	0.12
Urinary retention	1050	4	301	749	OR, 1.51 (0.85-2.68)	0	0.16
Urinary infection	1617	3	633	984	OR, 0.29 (0.16-0.54)	0	< 0.0001
Genitourinary dysfunction	458	2	212	246	OR, 0.32 (0.17-0.61)	0	0.0006
Nocturnal bowel movement	884	3	461	423	OR, 0.73 (0.55-0,97)	0	0.03
Need for antidiarrheal or laxative drugs	187	2	94	93	OR, 0.70 (0.37-1.30)	14	0.26
Wexner's incontinence score	274	3	138	136	MD, -0.01 (-0.71-0.70)	76	0.99
Safety outcomes							
Anastomotic leakage	4574	13	1830	2744	OR, 0.69 (0.45-1.07)	50	0.10
Anastomotic stenosis	686	4	326	360	OR, 0.31 (0.16-0.62)	46	0.0009
Postoperative complication	2622	5	892	1730	OR, 1.07 (0.66-1.72)	62	0.79
Mortality	822	6	394	428	OR, 2.70 (0.64-11.40)	0	0.18
Operative time	2491	7	996	1495	MD, 4.42 (-2.05-10.89	80	0.18
Blood loss	2357	6	913	1444	MD, -0.63 (-4.01-2.76)	76	0.72
Oncological outcomes							
Total lymph nodes harvested	2491	7	996	1495	MD, 0.68 (-1.03-2.38)	94	0.44
Recurrence	1340	8	706	634	OR, 0.97 (0.73-1.30)	0	0.85
5-year overall survival	2821	7	1035	1786	OR, 0.94 (0.61-1.44)	61	0.77
5-year disease-free survival	1523	5	602	921	OR, 0.86 (0.65-1.14)	0	0.29

LL: Low ligation; HL: High ligation; WMD: Weighted mean difference.

Safety outcomes

Although the LL group had a lower incidence of anastomotic stenosis than the HL group (OR = 0.31, 95%CI: 0.16 to 0.62, *P* = 0.0009; Figure 3H)[13,19,22,23], there were no significant differences in the anastomotic leakage rate (OR = 0.69, 95%CI: 0.45 to 1.07, *P* = 0.10; Figure 3I)[4,7,13-23], postoperative complication rate (OR = 1.07, 95%CI: 0.66 to 1.72, *P* = 0.79; Figure 3J)[7,14,15,18,21], or mortality (OR = 2.70, 95%CI: 0.64 to 11.40, *P* = 0.18; Figure 3K)[5,7,16,18,22,23] between the two groups. There were no

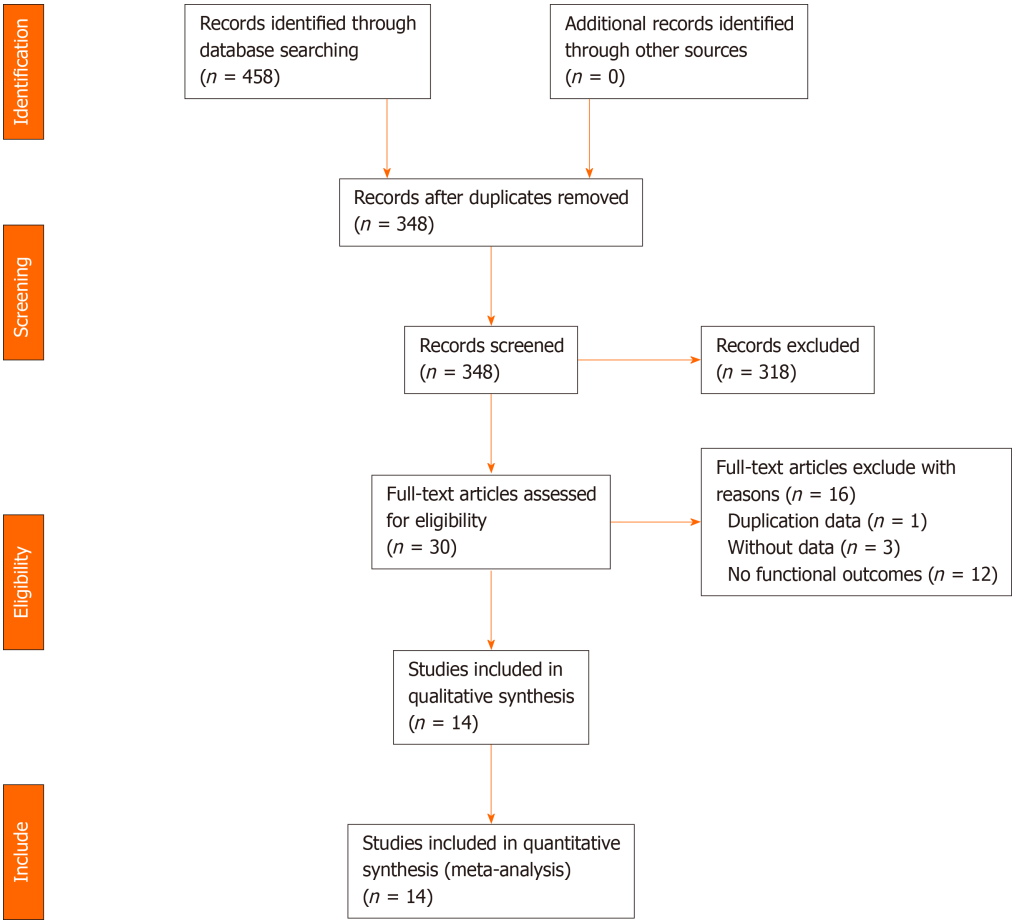


Figure 1 Flow diagram of literature search.

differences in operative time (WMD, 4.42, 95%CI: −2.05 to 10.89, P = 0.18; Figure 3L)[4,13,15-19] or blood loss (WMD, −0.63, 95%CI: −4.01 to 2.76, P = 0.72; Figure 4A)[4,13,15,16,18,19] between the two groups.

Oncological outcomes

There were no differences in the total number of lymph nodes harvested (WMD, 0.68, 95%CI: −1.03 to 2.38, P = 0.44; Figure 4B)[4,13,15-19], recurrence rate (OR = 0.97, 95%CI: 0.73 to 1.30, P = 0.85; Figure 5)[7,13,17-19,21-23], 5-year overall survival (OR = 0.94, 95%CI: 0.61 to 1.44, P = 0.77; Figure 6A)[7,14,15,17,18,21,23], or 5-year disease-free survival (OR = 0.86, 95%CI: 0.65 to 1.14, P = 0.29; Figure 6B)[7,14,17,21,23] between the LL and HL groups.

DISCUSSION

Radical resection is the most efficient way to surgically treat sigmoid colon and rectal cancer. However, the best ligation site of the IMA has been controversial for more than 100 years. The current controversy mainly involves the influence on lymph node dissection, anastomotic blood supply, postoperative autonomic function, and prognosis. Some safety and oncological outcomes following LL and HL have been investigated in previous reviews[8-10,24,25], all of which reported that LL decreased the incidence of anastomotic leakage, except for one meta-analysis that included only RCTs. A meta-analysis carried out by Hajibandeh *et al*[8] demonstrated that there was no significant difference in anastomotic leakage rate between the two ligation positions of the IMA. These earlier reviews also found no difference in terms of the number of lymph nodes harvested or the survival rate. Our meta-analysis, on the other hand, mainly evaluated functional outcomes and found that LL was associated with a lower risk of anastomotic stenosis, which was also related to anastomotic tension and anastomotic blood supply.

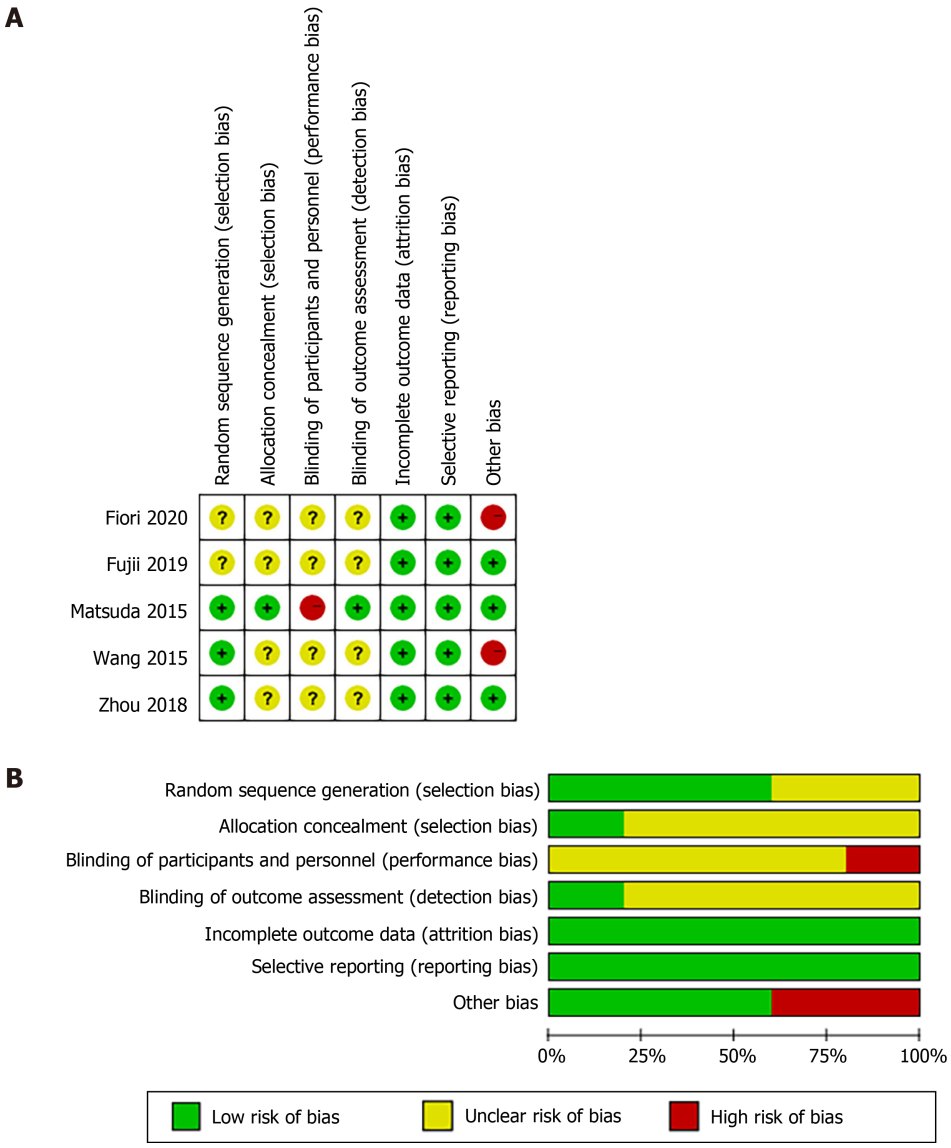


Figure 2 Summary of methodologic quality assessment. A: Risk of bias summary; B: Risk of bias graph.

Urinary and sexual dysfunction after CRC surgery are inevitable problems, associated with injury to the superior hypogastric plexus[26]. Some studies[5,6] demonstrated that LL was associated with a lower risk of postoperative genitourinary dysfunction. One randomized study, however, found that LL was not superior to HL in preserving urinary function in an anterior resection and the authors believed that LL was a more complex procedure[7]. Although we found that LL was associated with a decreased risk of urinary infection, we found no difference between the two techniques regarding urinary dysfunction and urinary retention. Our conclusion is opposite to that of Si *et al*[10], who found that LL was associated with less postoperative urinary dysfunction. Two clinical trials used genitourinary dysfunction to evaluate both sexual and voiding dysfunction; this limitation did not allow us to draw a definitive conclusion on sexual dysfunction.

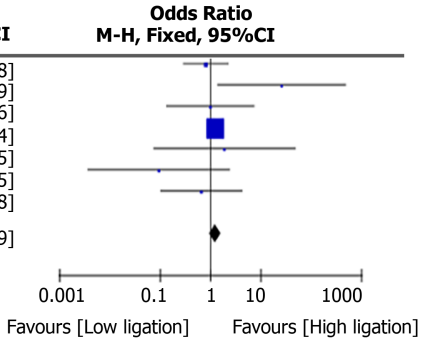
Impaired bowel function is also a common complication after CRC surgery. Factors affecting bowel function are complex and include rectal compliance, anal sphincter function, and pelvic floor muscle contraction. The regulation of defecatory function is closely controlled by the sympathetic and parasympathetic nerves from the superior and inferior hypogastric plexus[26]. Although previous trials acquired the data at different months after surgery, acute peripheral nerve injury may take up to 6 mo to heal[27]. We therefore used Wexner's incontinence score[28], nocturnal bowel movement, and the number of patients using antidiarrheals and laxatives 1 year after surgery to compare bowel function following the two ligation techniques.

A

Study or Subgroup	Low Ligation Events	Low Ligation Total	High Ligation Events	High Ligation Total	Weight	Odds Ratio M-H, Fixed, 95%CI
Chen 2020	7	227	9	235	8.3%	0.80 [0.29, 2.18]
Dimitriou 2018	6	44	0	76	0.3%	25.83 [1.42, 470.59]
Fujii 2019	2	108	2	107	1.9%	0.99 [0.14, 7.16]
Kverneng Hultberg 2017	185	432	141	373	83.8%	1.23 [0.93, 1.64]
Lee 2018	1	83	0	51	0.6%	1.87 [0.07, 46.85]
Yasuda 2016	0	147	1	42	2.2%	0.09 [0.00, 2.35]
Zhou 2018	2	52	3	52	2.8%	0.65 [0.10, 4.08]
Total (95%CI)		1093		936	100.0%	1.23 [0.95, 1.59]
Total events	203		156			

Heterogeneity: Chi² = 7.96, df = 6 (P = 0.24); I^2 = 25%

Test for overall effect: Z = 1.56 (P = 0.12)

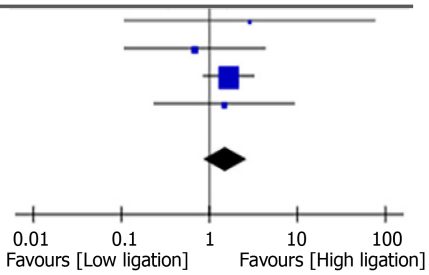


B

Study or Subgroup	Low Ligation Events	Low Ligation Total	High Ligation Events	High Ligation Total	Weight	Odds Ratio M-H, Fixed, 95%CI
Fiori 2020	1	24	0	22	2.7%	2.87 [0.11, 74.26]
Matsuda 2015	2	49	3	51	15.7%	0.68 [0.11, 4.26]
Park 2020	14	163	33	613	70.7%	1.65 [0.86, 3.17]
Wang 2015	3	65	2	63	10.8%	1.48 [0.24, 9.14]
Total (95%CI)		301		749	100.0%	1.51 [0.85, 2.68]
Total events	20		38			

Heterogeneity: Chi² = 0.95, df = 3 (P = 0.81); I^2 = 0%

Test for overall effect: Z = 1.42 (P = 0.16)

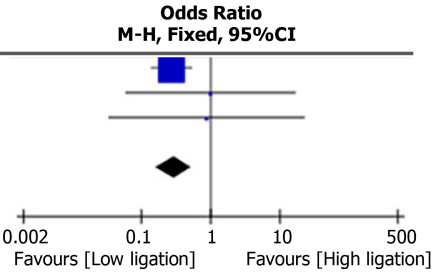


C

Study or Subgroup	Low Ligation Events	Low Ligation Total	High Ligation Events	High Ligation Total	Weight	Odds Ratio M-H, Fixed, 95%CI
Alsuhaimi 2019	11	378	83	835	96.6%	0.27 [0.14, 0.52]
Fujii 2019	1	108	1	107	1.9%	0.99 [0.06, 16.05]
Yasuda 2016	1	147	0	42	1.5%	0.87 [0.03, 21.76]
Total (95%CI)		633		984	100.0%	0.29 [0.16, 0.54]
Total events	13		84			

Heterogeneity: Chi² = 1.23, df = 2 (P = 0.54); I^2 = 0%

Test for overall effect: Z = 3.97 (P < 0.0001)

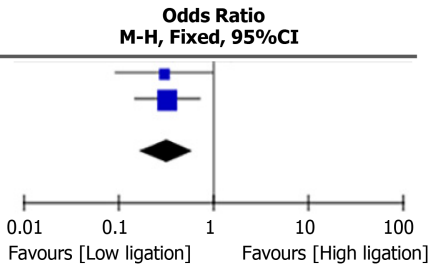


D

Study or Subgroup	Low Ligation Events	Low Ligation Total	High Ligation Events	High Ligation Total	Weight	Odds Ratio M-H, Fixed, 95%CI
You 2017	4	64	13	72	31.4%	0.30 [0.09, 0.98]
You' 2020	9	148	29	174	68.6%	0.32 [0.15, 0.71]
Total (95%CI)		212		246	100.0%	0.32 [0.17, 0.61]
Total events	13		42			

Heterogeneity: Chi² = 0.01, df = 1 (P = 0.93); I^2 = 0%

Test for overall effect: Z = 3.45 (P = 0.0006)

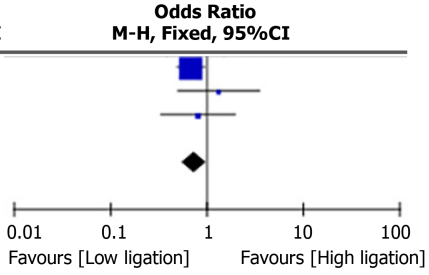


E

Study or Subgroup	Low Ligation Events	Low Ligation Total	High Ligation Events	High Ligation Total	Weight	Odds Ratio M-H, Fixed, 95%CI
Kverneng Hultberg 2017	232	367	237	330	83.1%	0.67 [0.49, 0.93]
Matsuda 2015	13	36	12	40	6.6%	1.32 [0.51, 3.44]
Wang 2015	13	58	14	53	10.3%	0.80 [0.34, 1.92]
Total (95%CI)		461		423	100.0%	0.73 [0.55, 0.97]
Total events	258		263			

Heterogeneity: Chi² = 1.74, df = 2 (P = 0.42); I^2 = 0%

Test for overall effect: Z = 2.16 (P = 0.03)

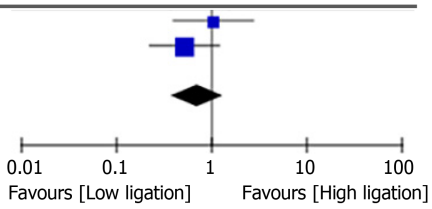


F

Study or Subgroup	Low Ligation Events	Low Ligation Total	High Ligation Events	High Ligation Total	Weight	Odds Ratio M-H, Fixed, 95%CI
Matsuda 2015	12	36	13	40	34.8%	1.04 [0.40, 2.71]
Wang 2015	13	58	19	53	65.2%	0.52 [0.22, 1.19]
Total (95%CI)		94		93	100.0%	0.70 [0.37, 1.30]
Total events	25		32			

Heterogeneity: Chi² = 1.16, df = 1 (P = 0.28); I^2 = 14%

Test for overall effect: Z = 1.13 (P = 0.26)

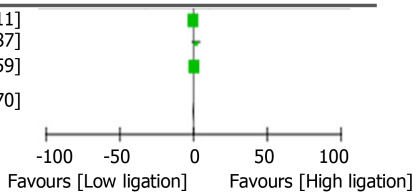


G

Study or Subgroup	Low Ligation Mean	Low Ligation SD	Low Ligation Total	High Ligation Mean	High Ligation SD	High Ligation Total	Weight	Mean Difference IV, Random, 95%CI
Fiori 2020	0.1	0.3	24	0.6	0.9	22	45.8%	-0.50 [-0.89, -0.11]
Matsuda 2015	3.8	5.8	49	2.2	5.8	51	8.2%	1.60 [-0.67, 3.87]
Wang 2015	3.2	1.3	65	3	0.9	63	46.1%	-0.20 [-0.19, 0.59]
Total (95%CI)			138			136	100.0%	-0.01 [-0.71, 0.70]

Heterogeneity: Tau² = 0.24; Chi² = 8.39, df = 2 (P = 0.02); I^2 = 76%

Test for overall effect: Z = 0.02 (P = 0.99)

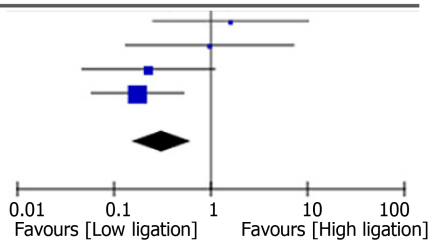


H

Study or Subgroup	Low Ligation Events	Low Ligation Total	High Ligation Events	High Ligation Total	Weight	Odds Ratio M-H, Fixed, 95%CI
Matsuda 2015	3	49	2	51	5.5%	1.60 [0.26, 10.00]
Wang 2015	2	65	2	63	5.9%	0.97 [0.13, 7.09]
You 2017	2	64	9	72	24.5%	0.23 [0.05, 1.09]
You' 2020	4	148	24	174	64.1%	0.17 [0.06, 0.51]
Total (95%CI)		326		360	100.0%	0.31 [0.16, 0.62]
Total events	11		37			

Heterogeneity: Chi² = 5.58, df = 3 (P = 0.13); I^2 = 46%

Test for overall effect: Z = 3.31 (P = 0.0009)

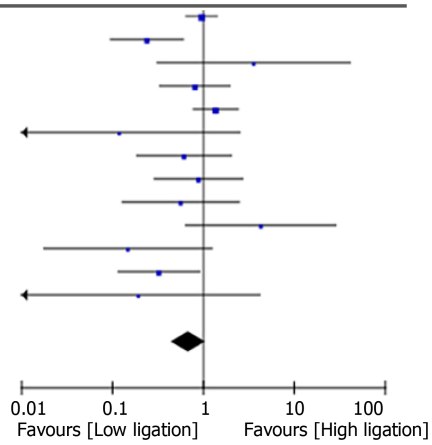


I

Study or Subgroup	Low Ligation Events	Low Ligation Total	High Ligation Events	High Ligation Total	Weight	Odds Ratio M-H, Random, 95%CI
Alsuhaimi 2019	41	378	94	835	17.1%	0.96 [0.65, 1.41]
Chen 2020	6	227	24	235	10.6%	0.24 [0.10, 0.60]
Dimitriou 2018	2	44	1	76	2.8%	3.57 [0.31, 40.57]
Fujii 2019	10	108	12	107	10.9%	0.81 [0.33, 1.96]
Kverneng Hultberg 2017	34	432	22	373	15.0%	1.36 [0.78, 2.37]
Lee 2018	0	83	2	51	1.8%	0.12 [0.01, 2.52]
Matsuda 2015	5	49	8	51	8.0%	0.61 [0.19, 2.02]
Park 2020	4	163	17	613	8.7%	0.88 [0.29, 2.66]
Wang 2015	3	65	5	63	6.1%	0.56 [0.13, 2.45]
Yasuda 2016	3	17	2	42	4.2%	4.29 [0.65, 28.37]
You 2017	1	64	7	72	3.5%	0.15 [0.02, 1.23]
You' 2020	5	148	17	174	9.5%	0.32 [0.12, 0.90]
Zhou 2018	0	52	2	52	1.8%	0.19 [0.01, 4.11]
Total (95%CI)		1830		2744	100.0%	0.69 [0.45, 1.07]
Total events	114		213			

Heterogeneity: Tau² = 0.25; Chi² = 23.97, df = 12 (P = 0.02); I^2 = 50%

Test for overall effect: Z = 1.65 (P = 0.10)

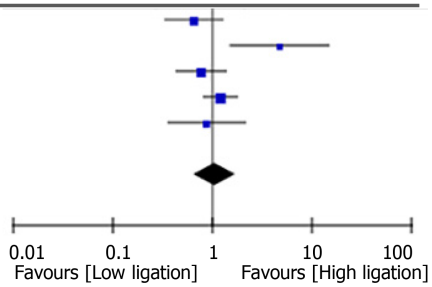


J

Study or Subgroup	Low Ligation Events	Low Ligation Total	High Ligation Events	High Ligation Total	Weight	Odds Ratio M-H, Random, 95% CI
Alsuhaimi 2019	12	378	40	835	20.9%	0.65 [0.34, 1.26]
Dimitriou 2018	11	44	5	76	11.8%	4.73 [1.52, 14.72]
Fujii 2019	26	160	33	164	23.2%	0.77 [0.44, 1.36]
Park 2020	47	163	154	613	28.1%	1.21 [0.82, 1.77]
Yasuda 2016	25	147	8	42	15.9%	0.87 [0.66, 1.72]
Total (95%CI)		892		1730	100.0%	1.07 [0.66, 1.72]
Total events	121		240			

Heterogeneity: Tau² = 0.18; Chi² = 10.60, df = 4 (P = 0.03); I^2 = 62%

Test for overall effect: Z = 0.62 (P = 0.79)



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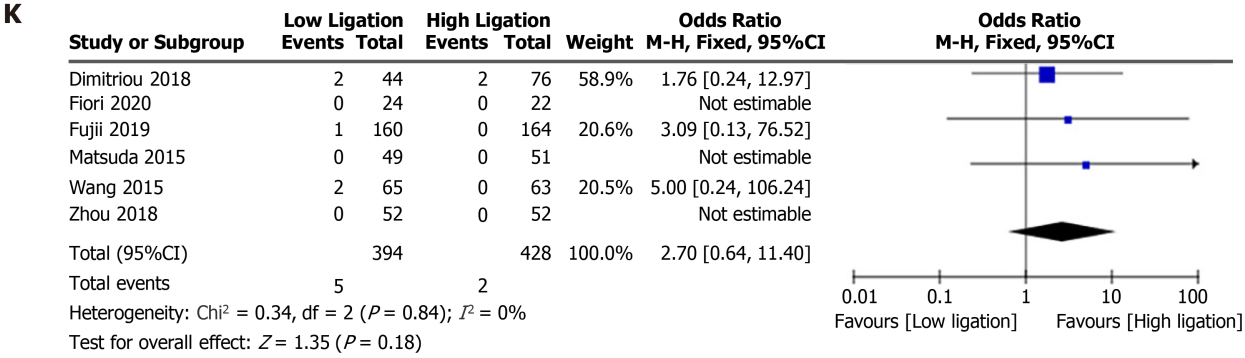

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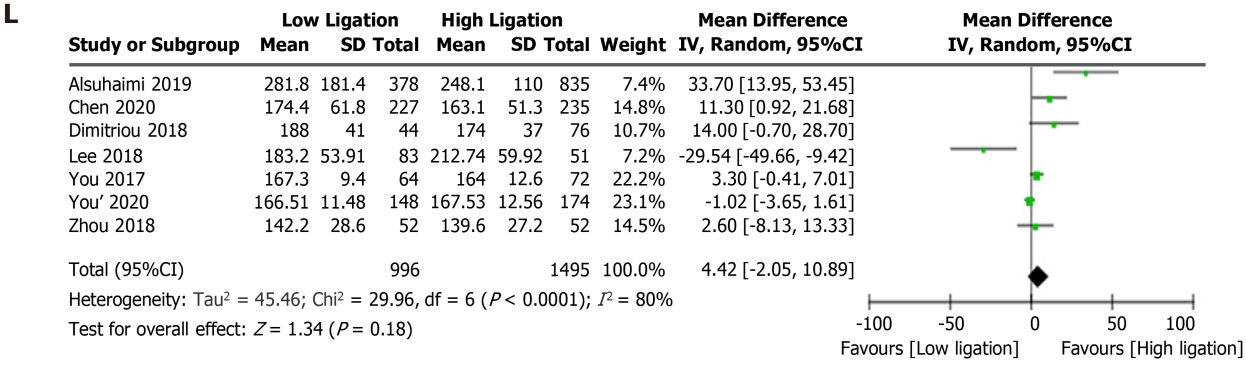
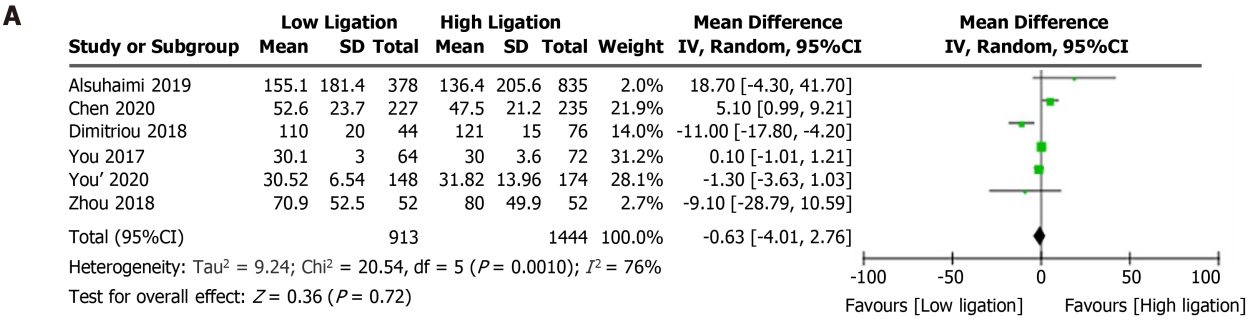


Figure 3 Forest plots for various function parameters with low ligation and high ligation. A: Urinary dysfunction; B: Urinary retention; C: Urinary infection; D: Genitourinary dysfunction; E: Nocturnal bowel movement; F: Need for antidiarrheal or laxative drugs; G: Wexner's incontinence score; H: Anastomotic stenosis; I: Anastomotic leakage; J: Postoperative complications; K: Mortality; L: Operative time.

A



B

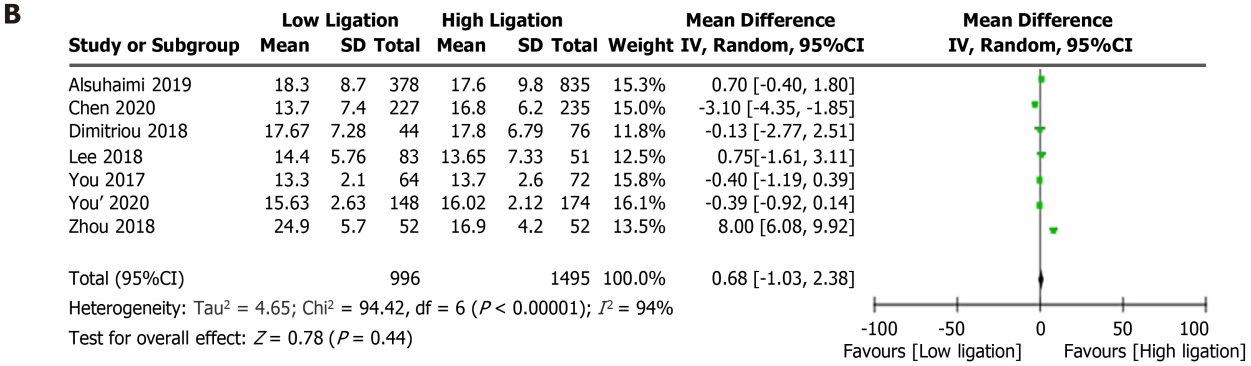


Figure 4 Forest plots for intraoperative indexes of low ligation and high ligation. A: Blood loss; B: Total lymph nodes harvested.

Motility of the neorectum is closely associated with defecatory function and it has been suggested that long denervation of the neorectum following HL leads to impaired bowel function[29]. Less propagated contraction and more spastic micro-contraction were observed in patients with long denervation. Although other indicators related to bowel function were difficult to analyze because of the limitation

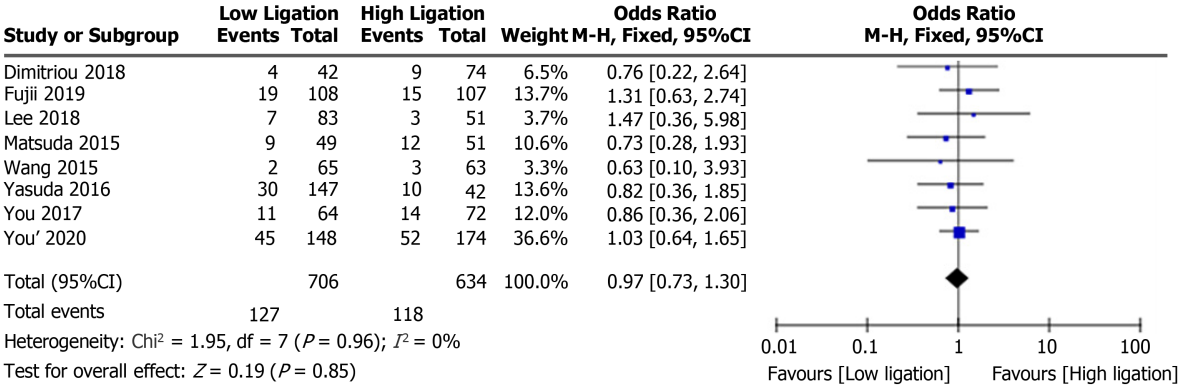
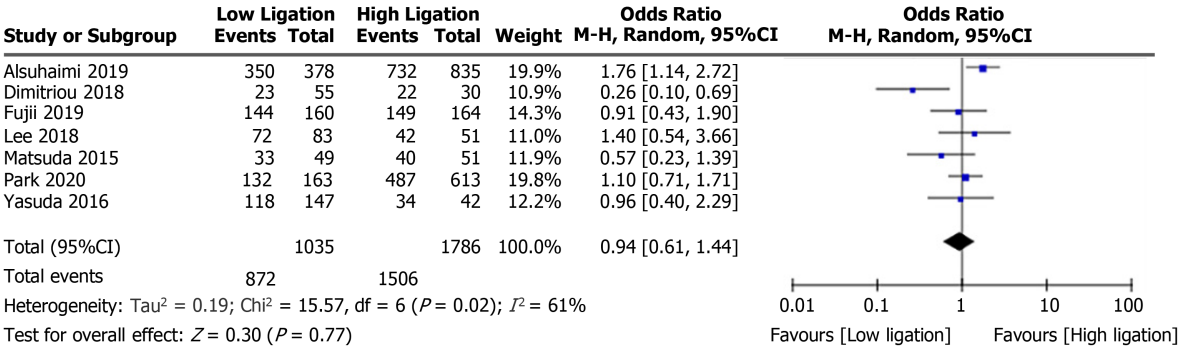


Figure 5 Forest plot for tumor recurrence following low ligation and high ligation.

A



B

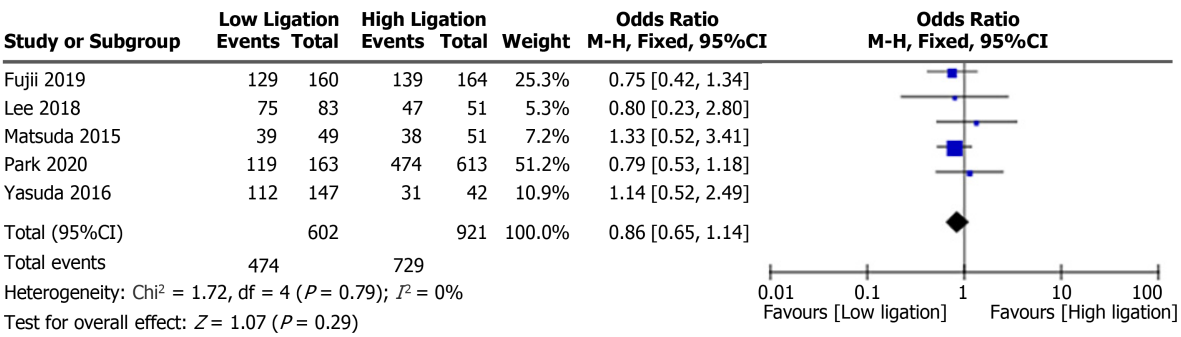


Figure 6 Forest plots for 5-year overall survival following low ligation and high ligation. A: 5-year overall survival; B: 5-year disease-free survival.

of data extraction, we found that the LL may result in better bowel control.

Anastomotic stenosis, which is one factor used to evaluate the quality of life of patients who have undergone colorectal surgery, is similar to anastomotic leakage. When the diameter of the anastomosis is less than 12 mm, with or without intestinal obstruction, it is defined as an anastomotic stenosis, whose pathological basis is the hyperplasia of fibrous tissue caused by hypoxia[30]. Anastomotic leakage is also regarded as an essential cause of anastomotic stenosis[31]. Our results showed no difference in the incidence of anastomotic leakage, but LL was associated with a lower incidence of anastomotic stenosis. Although the analyses of anastomotic leakage and anastomotic stenosis included 13 studies and 4 studies, respectively, they did not have high heterogeneity.

From an oncological perspective, some surgeons believe that HL during radical resection of sigmoid CRC can allow removal of more lymph nodes and improve the prognosis of patients. Others, however, believe that metastasis of apical lymph nodes is rare, and that the survival rate following LL is not inferior to that following HL. There was little difference in total recurrence rate, number of lymph nodes harvested, 5-year overall survival, or 5-year disease-free survival between the two levels of ligation of the IMA in our meta-analysis.

Since autonomic function could greatly affect the quality of life of patients, we compared the outcomes of two levels of ligations of the IMA on postoperative urinary, sexual, and defecatory function. This meta-analysis can provide surgeons with suggestions for the best IMA ligation technique during radical resection of sigmoid CRC. Our meta-analysis has some limitations and there are several confounding factors, such as neoadjuvant therapy, adjuvant therapy, tumor stage, operative approach, surgical technology, and preventive stoma. Functional outcomes were not completely clear because some studies did not evaluate the preoperative genitourinary and bowel function of the patients and functional outcomes were not determined at a consistent time after surgery. Both of these factors may affect the judging of functional outcomes and we hope that future studies will address these issues.

CONCLUSION

LL may result in better bowel function and reduce the rate of anastomotic stenosis. The risk of urinary dysfunction and anastomotic leakage, however, seems to be equivalent between the two IMA ligation techniques. Since LL is less invasive and does not increase operative time, we recommend LL of the IMA in sigmoid colon and rectal cancer surgery. Future studies are needed to confirm our conclusions.

ARTICLE HIGHLIGHTS

Research background

Whether the benefits of low ligation (LL) of the inferior mesenteric artery (IMA) during colorectal cancer (CRC) surgeries extend to improved genitourinary and defecatory function is still controversial.

Research motivation

Previous studies have demonstrated that LL was associated with a lower risk of postoperative genitourinary and defecatory dysfunction in patients with CRC. One randomized study, however, found that LL was not superior to high ligation (HL) in preserving urinary function. Therefore, we carried out a meta-analysis to systemically compare functional outcomes of patients with CRC between LL and HL of the IMA.

Research objectives

To evaluate the effect of LL of the IMA on genitourinary function and defecation for patients after CRC surgeries.

Research methods

The meta-analysis methods were adopted to realize the objectives. And statistical analyses were performed using Review Manager 5.3 software.

Research results

LL resulted in a significantly lower incidence of nocturnal bowel movement (OR = 0.73, 95%CI: 0.55 to 0.97, P = 0.03) and anastomotic stenosis (OR = 0.31, 95%CI: 0.16 to 0.62, P = 0.0009) compared with HL. The risk of postoperative urinary dysfunction, however, did not differ significantly between the two techniques. The meta-analysis also showed no significant differences between LL and HL in terms of anastomotic leakage, postoperative complications, total lymph nodes harvested, blood loss, operation time, tumor recurrence, mortality, 5-year overall survival rate, or 5-year disease-free survival rate.

Research conclusions

Since LL may result in better bowel function and a reduced rate of anastomotic stenosis following CRC surgeries, we suggest that LL be preferred over HL.

Research perspectives

Some limitations in this meta-analysis should be addressed carefully. First, since both randomized controlled trials and non-randomized studies were included, the randomization in the original research was limited. Second, several studies did not evaluate the preoperative genitourinary and bowel function of the patients and functional

outcomes were not determined at a consistent time after surgery. In addition, there were differences in the neoadjuvant therapy, adjuvant therapy, surgical approach, and preventive stoma in this analysis. All of these factors may affect the results. Future studies are needed to address these issues.

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