META-ANALYSIS

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

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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
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

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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 defecatory 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.

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**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 weighed 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 $\chi^2$ 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          | LL (No. patients) | Male (%) | Age, yr | Diagnosis                        | Stage (No. patients) LL/HL |
|------|------|---------|-----------------|-------------------|----------|---------|----------------------------------|----------------------------|
| Alsuhaimi et al [15] | 2019 | South Korea | Retrospective cohort | 378/835 | 63.8/66.2 | 60.2 ± 11.5 | Rectal cancer | NA |
| Chen et al [4] | 2020 | China | Retrospective cohort | 227/235 | 51.5/54.0 | 58.6 ± 8.9 | 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) | Rectosigmoid and rectal cancer | 9/17 | 16/27 | 14/26 |
| Fiori et al [3] | 2020 | Italy | RCT | 24/22 | 58.3/54.4 | 68 ± 11 | Rectal cancer | 24/22 |
| Fujii et al [7] | 2019 | Japan | RCT | 108/107 | 63.0/63.6 | 66 (55-88) | 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 | Sigmoid colon cancer | NA |
| Matsuda et al [23] | 2015 | Japan | RCT | 49/51 | 69.4/64.7 | 67 (45-89) | 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) | 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 | Rectal cancer | NA |
| Yasuda et al [21] | 2016 | Japan | Retrospective cohort | 147/42 | 62.6/61.9 | 68 ± 9.1 | 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 | 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 | 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 | Rectal cancer | 4/2 | 23/27 | 25/23 |

1Data 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) or urinary retention (OR = 1.51, 95% CI: 0.85 to 2.68, P = 0.16; Figure 3B) 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) 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), 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) or Wexner’s incontinence score (WMD, −0.01, 95% CI: −0.71 to 0.70, P = 0.99; Figure 3G).
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) | I² (%) | 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 3I)[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 3I)[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
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**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 Hajibande 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.
Urinary and sexual dysfunction after CRC surgery are inevitable problems, associated with injury to the superior hypogastric plexus\textsuperscript{[26]}. Some studies\textsuperscript{[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\textsuperscript{[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\textsuperscript{[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\textsuperscript{[26]}. Although previous trials acquired the data at different months after surgery, acute peripheral nerve injury may take up to 6 mo to heal\textsuperscript{[27]}. We therefore used Wexner’s incontinence score\textsuperscript{[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.
### Table A

| Study or Subgroup | Low Ligation Events | Total | High Ligation Events | 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]        |
| Fuji 2019         | 2                   | 108   | 2                    | 107   | 1.9%   | 0.99 [0.14, 7.16]           |
| Kveneng 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); I² = 25%
Test for overall effect: Z = 1.56 (P = 0.12)

### Table B

| Study or Subgroup | Low Ligation Events | Total | High Ligation Events | 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); I² = 0%
Test for overall effect: Z = 1.42 (P = 0.16)

### Table C

| Study or Subgroup | Low Ligation Events | Total | High Ligation Events | Total | Weight | Odds Ratio M-H, Fixed, 95%CI |
|-------------------|---------------------|-------|----------------------|-------|--------|-----------------------------|
| Alkuhami 2019     | 11                  | 378   | 83                   | 835   | 96.6%  | 0.27 [0.14, 0.52]           |
| Fuji 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); I² = 0%
Test for overall effect: Z = 3.97 (P < 0.0001)

### Table D

| Study or Subgroup | Low Ligation Events | Total | High Ligation Events | 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); I² = 0%
Test for overall effect: Z = 3.45 (P = 0.0006)

### Table E

| Study or Subgroup | Low Ligation Events | Total | High Ligation Events | Total | Weight | Odds Ratio M-H, Fixed, 95%CI |
|-------------------|---------------------|-------|----------------------|-------|--------|-----------------------------|
| Kveneng Hultberg 2017 | 222              | 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); I² = 0%
Test for overall effect: Z = 2.16 (P = 0.03)
### F

| Study or Subgroup | Low Ligation Events | High Ligation Events | Odds Ratio |
|-------------------|---------------------|----------------------|------------|
|                   | Total               | Total                | M-H, Fixed, 95%CI |
| Matsuoka 2015     | 12                  | 36                   | 34.8%      | 1.04 [0.40, 2.71] |
| Wang 2015         | 13                  | 58                   | 53         | 65.2% | 0.52 [0.22, 1.19] |
| Total (95%CI)     | 94                  | 93                   | 100.00%    | 0.70 [0.37, 1.30] |
| Total events      | 25                  | 32                   |             |             |

Heterogeneity: $\chi^2 = 11.6$, 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 | SD | Total | High Ligation Mean | SD | Total | Mean Difference |
|-------------------|-------------------|-----|-------|-------------------|-----|-------|-----------------|
|                   | Weight IV, Random, 95%CI | | | Weight IV, Random, 95%CI | | | |
| Flion 2020        | 0.1               | 0.3 | 24    | 0.6              | 0.9 | 22    | -0.50 [-0.89, -0.11] |
| Matsuoka 2015     | 3.8               | 5.8 | 49    | 2.2              | 5.8 | 51    | 1.60 [0.67, 3.87] |
| Wang 2015         | 3.2               | 1.3 | 65    | 3.0              | 9.9 | 63    | -0.20 [-0.19, 0.59] |
| Total (95%CI)     | 138               | 136 | 100.00% | | | | -0.01 [-0.71, 0.70] |

Heterogeneity: $\tau^2 = 0.24$; $\chi^2 = 8.39$, 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 | Total | High Ligation Events | Total | Weight | Odds Ratio |
|-------------------|---------------------|-------|----------------------|-------|--------|------------|
|                   | M-H, Fixed, 95%CI   |       | M-H, Fixed, 95%CI   |       |        |            |
| Matsuoka 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   | 100.00%             | | | 0.31 [0.16, 0.62] |
| Total events      | 11                  | 37    |                     | | |             |

Heterogeneity: $\chi^2 = 5.58$, 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 | Total | High Ligation Events | Total | Weight | Odds Ratio |
|-------------------|---------------------|-------|----------------------|-------|--------|------------|
|                   | M-H, Random, 95%CI  |       | M-H, Random, 95%CI  |       |        |            |
| Atsuhaimi 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] |
| Matsuoka 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   | 100.00%             | | | 0.69 [0.45, 1.07] |
| Total events      | 114                 | 213    |                     | | |             |

Heterogeneity: $\tau^2 = 0.25$; $\chi^2 = 23.97$, 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 | Total | High Ligation Events | Total | Weight | Odds Ratio |
|-------------------|---------------------|-------|----------------------|-------|--------|------------|
|                   | M-H, Random, 95%CI  |       | M-H, Random, 95%CI  |       |        |            |
| Atsuhaimi 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, 1.17] |
| Total (95%CI)     | 892                 | 1730   | 100.00%             | | | 1.07 [0.66, 1.72] |
| Total events      | 121                | 240   |                     | | |             |

Heterogeneity: $\tau^2 = 0.18$; $\chi^2 = 10.60$, df = 4 ($P = 0.03$); $I^2 = 62$

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

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021; 71: 209-249 [PMID: 35538338 DOI: 10.3322/caac.21660]

2. Miles WE. A method of performing abdomino-perineal excision for carcinoma of the rectum and of the terminal portion of the pelvic colon (1908). CA Cancer J Clin 1971; 21: 361-364 [PMID: 5001853 DOI: 10.3322/canclin.21.6.361]

3. Girard E, Trilling B, Rabattu PY, Sage PY, Taton N, Robert Y, Chaffanjon P, Faucheron JL. Level of inferior mesenteric artery ligation in low rectal cancer surgery: high tie preferred over low tie. Tech Coloproctol 2019; 23: 267-271 [PMID: 30963345 DOI: 10.1007/s10151-019-01931-0]

4. Chen JN, Liu Z, Wang ZJ, Zhao FQ, Wei FZ, Mei SW, Shen HY, Li J, Pei W, Wang Z, Yu J, Liu Q. Low ligation has a lower anastomotic leakage rate after rectal cancer surgery. World J Gastrointest Oncol 2020, 12: 632-641 [PMID: 32699578 DOI: 10.4251/wjgo.v12.i6.632]

5. Fiori E, Crocetti D, Lamazza A, DE Felice F, Sterpetti AV, Irace L, Mingoli A, Sapienza P, DE Toma G. Is Low Inferior Mesenteric Artery Ligation Worthwhile to Prevent Urinary and Sexual Dysfunction After Total Mesorectal Excision for Rectal Cancer? Anticancer Res 2020; 40: 4223-4228 DOI: 10.21873/anticancer.14423]

6. Mari GM, Crippa J, Cocozza E, Berselli M, Livraghi L, Carzaniga P, Valenti F, Roscio F, Ferrari G, Mazzola M, Magistro C, Origi M, Forgione A, Zuliani W, Scandroglio I, Pugliese R, Costanzi ATM, Maggioni D. Low Ligation of Inferior Mesenteric Artery in Laparoscopic Anterior Resection for Rectal Cancer Reduces Genitourinary Dysfunction: Results From a Randomized Controlled Trial (HIGHLOW Trial). Ann Surg 2019; 269: 1018-1024 [PMID: 31082897 DOI: 10.1097/SLA.0000000000002947]

7. Fujii S, Ishibe A, Ota M, Suwa H, Watanabe J, Kunisaki C, Endo I. Short-term and long-term results of a randomized study comparing high tie and low tie inferior mesenteric artery ligation in laparoscopic rectal anterior resection: subanalysis of the HTLT (High tie vs. low tie) study. Surg Endosc 2019; 33: 1100-1110 [PMID: 30027510 DOI: 10.1007/s00464-018-6367-1]

8. Hajibande S, Hajibande S, Maw A. Beta-analysis and Trial Sequential Analysis of Randomized Controlled Trials Comparing High and Low Ligation of the Inferior Mesenteric Artery in Rectal Cancer Surgery. Dis Colon Rectum 2020; 63: 988-999 [PMID: 32243350 DOI: 10.1097/DCR.0000000000001693]

9. Zeng J, Su G. High ligation of the inferior mesenteric artery during sigmoid colon and rectal cancer surgery increases the risk of anastomotic leakage: a meta-analysis. World J Surg Oncol 2018; 16: 157 [PMID: 30071856 DOI: 10.1186/s12957-018-1458-7]

10. Si MB, Yan PJ, Du ZY, Li LY, Tian HW, Jiang WJ, Jing WT, Yang J, Han CW, Shi XE, Yang KH, Guo TK. Lymph node yield, survival benefit, and safety of high and low ligation of the inferior mesenteric artery in colorectal cancer surgery: a systematic review and meta-analysis. Int J Colorectal Dis 2019; 34: 947-962 [PMID: 30997603 DOI: 10.1007/s00384-019-03291-2]

11. Page MJ, Moher D, Bousquet PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, McKenzie JE. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ 2021; 372: n160 [PMID: 33781993 DOI: 10.1136/bmj.n160]

12. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010; 25: 603-605 [PMID: 20652370 DOI: 10.1007/s10654-010-9491-z]

13. You X, Liu Q, Wu J, Wang Y, Huang C, Cao G, Dai J, Chen D, Zhou Y. High vs low ligation of inferior mesenteric artery during laparoscopic radical resection of rectal cancer: A retrospective cohort study. Medicine (Baltimore) 2020; 99: e19437 [PMID: 32195939 DOI: 10.1097/MD.0000000000019437]

14. Park SS, Park B, Park EY, Park SC, Kim MJ, Sohn DK, Oh JH. Outcomes of high vs low ligation of the inferior mesenteric artery with lymph node dissection for distal sigmoid colon or rectal cancer. Surg Today 2020; 50: 560-568 [PMID: 31907664 DOI: 10.1007/s11295-019-01942-2]

15. AlSuhaimi MA, Yang SY, Kang JH, Alsabitah IF, Hur H, Kim NK. Operative safety and oncologic
outcomes in rectal cancer based on the level of inferior mesenteric artery ligation: a stratified analysis of a large Korean cohort. *Ann Surg Treat Res* 2019; 97: 254-260 [PMID: 31742210 DOI: 10.4174/astr.2019.97.5.254]

16 Zhou J, Zhang S, Huang J, Huang P, Peng S, Lin J, Li T, Wang J, Huang M. [Accurate low ligation of inferior mesenteric artery and root lymph node dissection according to different vascular typing in laparoscopic radical resection of rectal cancer]. *Zhonghua Wei Chang Wai Ke Za Zhi* 2018; 21: 46-52 [PMID: 29354809]

17 Lee KH, Kim JS, Kim JY. Feasibility and oncologic safety of low ligation of inferior mesenteric artery with D3 dissection in cT3N0M0 sigmoid colon cancer. *Ann Surg Treat Res* 2018; 94: 209-215 [PMID: 29629356 DOI: 10.4174/astr.2018.94.4.209]

18 Dimitrion N, Felekouras E, Karavokyros I, Pikoulis E, Vergadis C, Nonni A, Griniatsos J. High vs low ligation of inferior mesenteric vessels in rectal cancer surgery: A retrospective cohort study. *J BUON* 2018; 23: 1350-1361 [PMID: 30570858]

19 You X, Wang Y, Chen Z, Li W, Xu N, Liu G, Zhao X, Huang C. [Clinical study of preserving left colic artery during laparoscopic total mesorectal excision for the treatment of rectal cancer]. *Zhonghua Wei Chang Wai Ke Za Zhi* 2017; 20: 1162-1167 [PMID: 29103232]

20 Kverneng Hultberg D, Afshar AA, Rutegård J, Lange M, Haapamäki MM, Matthiessen P, Rutegård M. Level of vascular tie and its effect on functional outcome 2 years after anterior resection for rectal cancer. *Colorectal Dis* 2017; 19: 987-995 [PMID: 28544473 DOI: 10.1111/col.13745]

21 Yasuda K, Kawai K, Ishihara S, Murono K, Otani K, Nishikawa T, Tanaka T, Kiyomatsu T, Hata K, Nozawa H, Yamaguchi H, Aoki S, Mishima H, Maruyama T, Sako A, Watanabe T. Level of arterial ligation in sigmoid colon and rectal cancer surgery. *World J Surg Oncol* 2016; 14: 99 [PMID: 27036117 DOI: 10.1186/s12957-016-0819-3]

22 Wang Q, Zhang C, Zhang H, Wang Y, Yuan Z, Di C. [Effect of ligation level of inferior mesenteric artery on postoperative defaecatory function in patients with rectal cancer]. *Zhonghua Wei Chang Wai Ke Za Zhi* 2015; 18: 1132-1135 [PMID: 26616809]

23 Matsuda K, Hotta T, Takiufi K, Yokoyama S, Oka Y, Watanabe T, Mitani Y, Jeda J, Mizumoto Y, Yamaue H. Randomized clinical trial of defaecatory function after anterior resection for rectal cancer with high vs low ligation of the inferior mesenteric artery. *Br J Surg* 2015; 102: 501-508 [PMID: 25764287 DOI: 10.1002/bjs.9739]

24 Fan YC, Ning FL, Zhang CD, Dai DQ. Preservation vs non-preservation of left colic artery in sigmoid and rectal cancer surgery: A meta-analysis. *Int J Surg* 2018; 52: 269-277 [PMID: 29501795 DOI: 10.1016/j.ijsu.2018.02.054]

25 Ciocchi R, Trastulli S, Farinella E, Desiderio J, Vettoretto N, Parisi A, Boselli C, Noya G. High tie vs low tie of the inferior mesenteric artery in colorectal cancer: a RCT is needed. *Surg Oncol* 2012; 21: e111-e123 [PMID: 22770982 DOI: 10.1016/j.suronc.2012.04.004]

26 Lemos N, Souza C, Marques RM, Kamergorodsky G, Schor E, Girão MJ. Laparoscopic anatomy of the autonomic nerves of the pelvis and the concept of nerve-sparing surgery by direct visualization of autonomic nerve bundles. *Fertil Steril* 2015; 104: e11-e12 [PMID: 26260200 DOI: 10.1016/j.fertnstert.2015.07.1138]

27 Houdek MT, Shin AY. Management and complications of traumatic peripheral nerve injuries. *Hand Clin* 2015; 31: 151-163 [PMID: 25934193 DOI: 10.1016/j.hcl.2015.01.007]

28 Jorge JM, Wexner SD. Etiology and management of fecal incontinence. *Dis Colon Rectum* 1993; 36: 77-97 [PMID: 8416784 DOI: 10.1007/BF02050307]

29 Koda K, Saito N, Seike K, Shimizu K, Kosugi C, Miyazaki M. Denervation of the neorectum as a potential cause of defecatory disorder following low anterior resection for rectal cancer. *Dis Colon Rectum* 2005; 48: 210-217 [PMID: 1571859 DOI: 10.1007/s10350-004-0814-6]

30 Suchan KL, Muldner A, Manegold BC. Endoscopic treatment of postoperative colorectal anastomotic strictures. *Surg Endosc* 2003; 17: 1110-1113 [PMID: 12728381 DOI: 10.1007/s00464-002-8926-3]

31 Guyton KL, Hymon NH, Alverdy JC. Prevention of perioperative Anastomotic Healing Complications: Anastomotic Stricture and Anastomotic Leak. *Adv Surg* 2016; 50: 129-141 [PMID: 27520868 DOI: 10.1016/j.asu.2016.03.011]
