Technical Feasibility and Oncological Safety of Low and High Ligation of the Inferior Mesenteric Artery in Colorectal Cancer Surgery for Asian Populations: a Systematic Review and Meta-analysis

Weipeng Ye
Fujian Medical University
Zhipeng Zhu
First Hospital of Xiamen: The First Affiliated Hospital of Xiamen University
Xiaofang Wu
Fujian Medical University
Sihao Lin
First Hospital of Xiamen: The First Affiliated Hospital of Xiamen University
Jiuhua Xu
Fujian Medical University
Lulu Li
First Hospital of Xiamen: The First Affiliated Hospital of Xiamen University
Zhengjie Huang (huangzhengjie@xmu.edu.cn)
Xiamen University and Fujian Medical University Affiliated First Hospital https://orcid.org/0000-0001-6298-8112

Research

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Abstract

Background: The level of ligation of the inferior mesenteric artery (IMA) is controversial. There is still no consensus on whether to preserve the left colon artery (LCA). The aim of this updated meta-analysis was to compare the technical feasibility and oncological safety of low ligation (LL) and high ligation (HL) of IMA in the treatment of colorectal cancer for Asian populations.

Methods: A systematic search was conducted in the PubMed, Embase, Web of Science and China Biomedical Literature Database (CBM) for relevant studies that compared HL and LL for sigmoid or rectal cancer were published between January 2010 and August 2020 from Asian countries. The outcomes of interest include anastomotic leak, operation time, blood loss, early complications, the postoperative first anal exhaust time, lymph node yield outcomes and involvement state, 5-year overall survival (OS), 5-year disease-free survival (DFS), and overall recurrence.

Results: Twenty-one studies including 8 randomized controlled trials (RCTs) and 13 retrospective cohort studies (non-RCTs) with a total of 5947 patients (2519 patients in LL group and 3428 patients in HL group) were involved in this meta-analysis. LL group showed a lower incidence of anastomotic leakage (WMD=0.59; 95%CI=0.46~0.76; P<0.05) and earlier postoperative first anal exhaust time (WMD=-4.55; 95%CI=-8.87~-0.24; P<0.05). In term of operation time, blood loss, early complications, the first postoperative anal exhaust time, lymph node yield outcomes and involvement state, 5-year OS, 5-year DFS, and overall recurrence, there were no significant differences between LL and HL group.

Conclusions: Compared with HL, LL significantly reduced the incidence of anastomotic leakage and accelerated the postoperative recovery time of bowel function in Asian populations. What's more, LL can obtain equivalent lymph node yield and long-term survival benefit as compared to HL.

Introduction

In 2018, there were 18.1 million new cancer cases and 9.6 million deaths worldwide, of which Asia accounted for 48.4 percent and 57.3 percent, respectively. In terms of the incidence of new cancers in 2018, colorectal cancer ranked third, accounting for 10.2 percent of all new cases, and cancer mortality ranked second, accounting for 9.2 percent of all deaths[1]. The basic principle of the treatment of colorectal cancer is based on surgical operation, including tumor resection, dissection of regional lymph nodes, extensive mesenteric resection, ligation of inferior mesenteric veins and arteries and other vessels[2]. Currently, the level of ligation of the inferior mesenteric artery (IMA) is still controversial. The controversy is whether to preserve the left colon artery (LCA)[3–5]. The preservation of the left colonic artery is known as low ligation (LL), which refers to the ligation below the origin of the left colonic artery. The non-preservation of the left colonic artery is known as high ligation (HL), which refers to the ligation at the origin of the inferior mesenteric artery from the abdominal aorta.

Some studies have recommended high ligation, suggesting that this technique can more thoroughly remove lymph nodes and improve lymph nodes harvest rates, thus contributing to more accurate tumor staging and better disease prognosis[6, 7]. Secondly, high ligation may achieve sufficient colonic length for a tension-free anastomosis[8]. Some other scholars believe that after the lower ligation, LCA and its branches can be preserved, which can provide more adequate blood perfusion to the anastomotic stoma, thus reducing the risk of anastomotic leakage, and this technique has little risk of injury to the autonomic nerve[9–11]. However, in terms of surgical difficulty and operative time, lower ligation and lymph nodes dissection at the root of IMA may require more surgical steps[12]. Although several randomized controlled trials and retrospective cohort studies have been published in recent years to examine the oncological outcomes and safety of HL and LL, it is worth noting that the conclusions of these studies remain controversial. Si et al. and Fan et al. reported that low ligation significantly reduced the risk of anastomotic leakage, whereas pooled data from the studies of Hajibandeh et al. and Yang et al. showed that there was no significant difference in the incidence of anastomotic leakage with the two approaches[1, 5, 13, 14] High-quality meta-analysis is increasingly recognized as one of the key tools for obtaining evidence. Therefore, it is necessary to do an updated systematic review and meta-analysis, including recently published studies, to compare the efficacy and safety of HL and LL.

Methods

Search strategy

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines[15]. The comprehensive publications were identified by searching medical electronic databases PubMed, Embase, Web of Science and China Biomedical Literature Database (CBM), which published from January 2010 to August 2020. The following MeSH terms and non-MeSH terms were used: “rectal” or “rectum” or “sigmoid” or “sigmoid” or “colon” or “colorectal” and “cancer” or “carcinoma” or “tumor” or “malignancy” or “neoplasm” and “left colic artery” or “inferior mesenteric artery” or “superior rectal artery” or “high lie” or “high ligation” or “low tie” or “low ligation”. The last search was performed on September 23. The references of the relevant articles and previous meta-analysis studies were identified as additional articles. Title and abstracts of each identified article were screened, and the full text of the screened articles was assessed for eligibility. Three authors researched and reviewed independently and thoroughly through the above-mentioned search strategy.

Inclusion criteria

The inclusion criteria for our study were as follows:

1. Patients definitely diagnosed with sigmoid or rectal cancer by enhanced computed tomography, colonoscopy, and pathological biopsy.
2. Clinical studies containing randomized controlled trials (RCTs) and retrospective cohort studies (non-RCTs).
3. Clinical studies having compared high ligation with low ligation of the IMA for sigmoid or rectal cancer surgery, regardless of the cause of colorectal cancer, surgical procedure (open or laparoscopic) and surgical urgency (limited or emergency).

Exclusion criteria

The exclusion criteria for this study were as follows:

1. case report, letter, reply, comment, conference proceeding, and review article;
2. single arm study;
3. insufficient information concerning the outcomes of interest;
4. full-text not available;
5. published by non-Asian countries.

Data extraction

Clinical data was extracted independently and evaluated critically by two authors. The relevant data included first author, publication year, country, study design, patient recruitment period, tumor location, surgical procedure, sample, BMI, TNM stage, and outcomes of interest. Anastomotic leak, lymph node yield outcomes and involvement state were regarded as primary outcome measures. In addition, operation time, blood loss, early complications, the postoperative first anal exhaust time, 5-year overall survival (OS), 5-year disease-free survival (DFS), and overall recurrence were considered as secondary outcome measures. Any discrepancies between the two reviewers were resolved by discussion to reach agreement, if an agreement between the two reviewers could not be reached, a third person was involved.

Quality assessment

All studies were independently assessed by two investigators for quality and validity. We used the Newcastle-Ottawa Quality Assessment Scale (NOS) for non-RCT[16]. NOS contains 3 categories including selection, comparability, and outcome, which were scaled by eight elements; high-quality elements are awarded by adding a star, no more than one stars could be added into the elements of selection and outcome, and no more than two stars could be added into the elements of comparability; then, studies were compared according to the number of stars, total score was 9 stars, 0–5 stars was considered as low-quality and 6–9 stars was considered as high quality. The Jadad scale (JCS) was used to assess the bias risk and quality of the RCTs[17]. This scoring system is based on three specific items: randomization, blinding, and withdrawals and dropouts. The total score ranges from 0 to 5; a score of ≤ 2 indicates poor-quality evidence and a score of ≥ 3 indicates high-quality evidence. The results of this assessment are shown respectively in Table 1 and Table 2. Disagreements in the quality assessment were resolved by consensus.

Table 1
Basic characteristics of the included studies

First author, yr	Country	Study design	Patient recruitment period	Tumor location	Surgical procedure	Sample		BMI		NOS score
						LL	HL	LL	HL	
Lee, 2017	UK	Non-RCT	2008.1-2013.12	Sigmoid or rectosigmoid colon cancer	Laparoscopy	83	51	24.03 ± 3.08	23.87 ± 3.15	8
You, 2020	China	Non-RCT	2010.1-2017.12	Rectal cancer	Laparoscopy	148	174	NA	NA	7
Yasuda, 2016	Japen	Non-RCT	1997.1-2007.3	Sigmoid and rectal cancer	open	147	42	NA	NA	7
Chen, 2020	China	Non-RCT	2017.1-2019.7	Rectal cancer	Laparoscopy	227	235	23.7 ± 3.1	24.1 ± 2.6	8
Guo, 2015	China	RCT	2013.2-2013.12	Sigmoid and rectal cancer	Laparoscopy	28	29	NA	NA	-
Kim, 2018	UK	Non-RCT	2011.1-2015.7	Sigmoid and rectal cancer	Laparoscopy or open	97	97	NA	NA	8
Matsuda, 2017	Japen	RCT	2008.2-2011.12	Rectal cancer	Laparoscopy or open	49	51	NA	NA	-
AlSuhaimi, 2019	UK	Non-RCT	2007.1-2013.3	Rectal cancer	Laparoscopy or open	378	835	23.2 ± 3.4	23.4 ± 3.2	7
Park, 2020	UK	Non-RCT	2010.4-2013.12	Sigmoid and rectal cancer	Laparoscopy	163	613	NA	NA	9
Fujii, 2018	Japen	RCT	2006.6-2012.9	Rectal cancer	Laparoscopy or open	160	164	22.4 ± 3.5	23.0 ± 3.2	-
Fujii, 2019	Japen	RCT	2006.6-2012.9	Rectal cancer	Laparoscopy	108	107	NA	NA	-
Hinoi, 2013	Japen	Non-RCT	1994.5-2006.2	Rectal cancer	Laparoscopy or open	155	256	23.4 ± 4.7	22.4 ± 3.8	8
Yamamoto, 2014	Japen	Non-RCT	1998–2009	Sigmoid or rectosigmoid colon cancer	Laparoscopy	120	91	NA	NA	8
Zhang, 2016	China	Non-RCT	2015.5-2016.1	Rectal cancer	Laparoscopy	61	42	23.48 ± 3.60	24.22 ± 7.45	7
Zhou, 2018	China	RCT	2015.10-2016.6	Rectal cancer	Laparoscopy	52	52	25.9 ± 2.0	25.4 ± 2.5	-
Luo, 2017	China	Non-RCT	2015.1-2016.12	Rectal cancer	Laparoscopy	203	320	NA	NA	6
Zhang, 2016	China	Non-RCT	2010.6-2015.1	Rectal cancer	Laparoscopy or open	132	84	NA	NA	7
Wang, 2015	China	RCT	2012.1-2013.12	Rectal cancer	Laparoscopy or open	65	63	21.5 ± 4.0	21.7 ± 3.8	-
Wu, 2017	China	RCT	2014.7-2016.7	Rectal cancer	Laparoscopy	46	50	22.5 ± 1.2	23.8 ± 1.6	-
Niu, 2016	China	RCT	2009.3-2015.3	Rectal cancer	Laparoscopy	52	45	NA	NA	-
Sekimoto, 2011	Japen	Non-RCT	2007.1-2009.6	Sigmoid and rectal cancer	Laparoscopy	45	27	NA	NA	7

LL = low ligation, HL = high ligation, BMI = body mass index, RCT = randomized controlled trial, non-RCT = non-randomized controlled trial, NOS = Newcastle-Ottawa Scale, NA = not available

Table 2
Assessment of quality of RCTs (Jadad scale)

References	Year	Randomization	Blinding	Withdraw and dropout	Total score
Guo	2015	2	1	1	4
Matsuda	2017	2	1	1	4
Fujii	2018	2	0	1	3
Fujii	2019	2	0	1	3
Zhou	2018	2	0	1	3
Wang	2015	2	0	1	3
Wu	2017	2	0	0	2
Niu	2016	1	0	1	2

Randomization: randomization was described with appropriate method — 2 score, randomization was described without appropriate method — 1 score, no randomization — 0 score. Blinding: blinding was performed on all doctors and patients — 2 score, blinding was partially performed on doctors and patients — 1 score, no blinding—0 score. Withdraw and dropout: the reason of withdraw and dropout was described—1 score, the reason of withdraw and dropout was not described — 0 score. Quality: high-quality trials should score ≥ 3, moderate-quality trials should score ≥ 2

Statistical analysis

STATA 12.0 for window was performed for this study. Dichotomous data was calculated by relative risks (RR) with 95% confidence intervals and continuous variables were calculated by Weighted mean differences (WMD) with 95% (CI). Meanwhile, χ^2 test was used to assess heterogeneity, with an I^2 of 25–50%, 50–75% or > 75% that were considered with low, moderate or high heterogeneity[18]. Studies with low heterogeneity adopted fixed-effect model, while those with high heterogeneity adopted random-effect model and subgroup analysis based on the type of study design (RCTs or non-RCTs). Funnel plots and Egger's linear regression test were used to assess the publication bias. $P < 0.05$ was considered to indicate statistical significance.

Results

Description of study selection

The study selection process is summarized in the flowchart (Fig. 1).A total of 459 studies were obtained according to the initial search strategy. After removing duplicates, 362 studies remained. After reviewing the titles and abstracts, 299 irrelevant studies were excluded, and 63 studies were further evaluated. Among them, 16 studies were review articles, comments, letters, case reports, and 7 studies underwent resection only with low ligation or high ligation. There were 40 full-text articles assessed for eligibility. Among them, 8 studies failed to provide sufficient data and 11 studies published by non-Asian countries. Finally, 21 studies including 8 RCTs and 13 non-RCTs published between 2010 and 2020 were included in this systematic review and meta-analysis[4, 7, 9, 19–36]. A total of 5947 patients (2519 patients in LL group and 3428 patients in HL group) were involved in the study. Among the 21 studies, 10 studies originated from China, 7 studies originated from Japan, 4 studies originated from UK. Detailed information for basic characteristics of included studies is shown in Table 1 and the tumor stage is shown in Table 3. The results of interest are shown in Tables 4 and 5.

Table 3
The tumor stage of the included studies

Reference	Sample Size		TNM Stage		
	LL	HL	Stage 0-II	Stage III	Stage IV
Lee, 2017	83	51			
You, 2020	148	174	60% vs 67%	40% vs 33%	
Yasuda, 2016	147	42	56% vs 55%	44% vs 45%	
Chen, 2020	227	235			
Guo, 2015	28	29			
Kim, 2018	97	97			
Matsuda, 2017	49	51	69% vs 47%	27% vs 45%	4% vs 8%
AlSuhaimi, 2019	378	835			
Park, 2020	163	613	61% vs 58%	33% vs 37%	6% vs 5%
Fujii, 2018	160	164	60% vs 63%	35% vs 33%	5% vs 4%
Fujii, 2019	108	107	63% vs 63%	33% vs 34%	4% vs 3%
Hinoi, 2013	155	256	65% vs 64%	32% vs 28%	3% vs 8%
Yamamoto, 2014	120	91			
Zhang, 2016	62	42			
Zhou, 2018	52	52	52% vs 56%	48% vs 44%	
Luo, 2017	203	320	62% vs 63%	33% vs 32%	5% vs 5%
Zhang, 2016	132	84			
Wang, 2015	65	63			
Wu, 2017	46	50	72% vs 74%	28% vs 26%	
Niu, 2016	52	45	85% vs 80%	15% vs 20%	
Sekimoto, 2011	27	45			

LL = low ligation, HL = high ligation

Table 4
Surgical outcomes of LL and HL

Reference	Anastomotic leakage		Operation time (min)		Blood loss (ml)		Early complications		Postoperative first anal exhaust time(h)	
	LL	HL	LL	HL	LL	HL	LL	HL	LL	HL
Lee, 2017	0	2	183.20 ± 53.91	212.74 ± 59.92	-	-	8	4	-	-
You, 2020	5	17	166.51 ± 11.48	167.53 ± 12.56	30.52 ± 6.54	31.82 ± 13.96	4	24	35.92 ± 4.33	35.95 ± 8.05
Yasuda, 2016	3	2	-	-	-	-	25	8	-	-
Chen, 2020	6	24	174.4 ± 61.8	163.1 ± 51.3	52.6 ± 23.7	47.5 ± 21.2	-	-	45.6 ± 19.2	50.4 ± 14.4
Guo, 2015	1	3	180.00 ± 10.80	166.00 ± 9.15	-	-	-	-	-	-
Kim, 2018	5	14	170.8 ± 51.4	185.3 ± 58.1	-	-	30	22	-	-
Matsuda, 2017	5	8	-	-	-	-	-	-	-	-
AlSuhaimi, 2019	41	94	281.8 ± 181.4	248.1 ± 110	155.1 ± 181.4	136.4 ± 205.6	12	40	-	-
Park, 2020	4	17	-	-	-	-	47	154	-	-
Fujii, 2018	26	29	206.00 ± 59	209 ± 67	152 ± 289	155 ± 299	56	61	-	-
Fujii, 2019	10	12	-	-	-	-	26	33	-	-
Hinoi, 2013	11	37	303 ± 84	262 ± 83	140 ± 158	152 ± 198	42	62	-	-
Yamamoto, 2014	2	2	-	-	-	-	-	-	-	-
Zhang, 2016	2	3	103.8 ± 16.1	104.4 ± 15.8	94.6 ± 23.1	93.6 ± 24.1	-	-	64.8 ± 16.8	69.6 ± 12.0
Zhou, 2018	0	2	142.2 ± 28.6	139.6 ± 27.2	70.9 ± 52.5	80.0 ± 49.9	-	-	69.6 ± 26.4	69.6 ± 26.4
Luo, 2017	17	47	-	-	-	-	-	-	-	-
Zhang, 2016	0	2	159.3 ± 3.35	141.7 ± 3.10	-	-	-	-	36.4 ± 7.6	45.7 ± 9.3
Wang, 2015	3	5	-	-	-	-	-	-	-	-
Wu, 2017	0	5	118.7 ± 13.6	116.0 ± 15.8	41.8 ± 21.2	42.1 ± 27.2	-	-	-	-
Niu, 2016	0	3	121.4 ± 17.5	97.0 ± 19.2	60.2 ± 4.3	55.1 ± 5.7	-	-	60.0 ± 16.8	67.2 ± 19.2
Sekimoto, 2011	1	0	-	-	-	-	-	-	-	-

LL = low ligation, HL = high ligation

Table 5
Lymph node yield, lymph node involvement state, and oncological outcomes for LL and HL

Reference	Total harvested lymph nodes		Harvested root lymph nodes of IMA		Total lymph node involvement (n)		Root lymph node of IMA involvement (n)		5-year OS (%)		5-year DFS (%)		Overall recurrence (%)	
	LL	HL	LL	HL	LL	HL	LL	HL	LL	HL	LL	HL	LL	HL
Lee, 2017	14.40 ± 5.76	13.65 ± 7.33	0.61 ± 1.36	0.84 ± 1.73	49	37			87.50%	84.10%	91.10%	92.60%	8.80%	7.40%
You, 2020	15.63 ± 2.63	16.02 ± 2.12							77.02%	77.01%			31.12%	29.71%
Yasuda, 2016					64	20			80.30%	82.40%	76.20%	75.60%	17.0%	19.0%
Chen, 2020	13.7 ± 7.4	16.8 ± 6.2												
Guo, 2015	17.71 ± 1.36	16.21 ± 1.08	2.96 ± 0.47	2.96 ± 0.39										
Kim, 2018	20.2 ± 9.2	20.9 ± 13.2											39.20%	23.70%
Matsuda, 2017									83.00%	79.30%	80.70%	74.90%	22.40%	25.50%
AlSuhaimi, 2019	18.3 ± 8.7	17.6 ± 9.8							92.60%	87.70%	96.10%	92.10%		
Park, 2020									81.30%	79.60%	73.30%	77.40%		
Fujii, 2018	24.1 ± 12.2	26.4 ± 11.4	2.9 ± 2.7	2.8 ± 2.1	56	59	5	3	89.40%	87.20%	77.60%	76.30%		
Fujii, 2019									90.20%	91.30%	81.20%	85.30%	17.60%	14.00%
Hinoi, 2013	18.9 ± 9.8	19.0 ± 10.1	0.9 ± 1.8	1.5 ± 3.4										
Yamamoto, 2014									90.00%	91.20%			15.00%	16.50%
Zhang, 2016	15.5 ± 7.2	16.1 ± 6.8	4.3 ± 1.7	4.2 ± 1.7			3	4						
Zhou, 2018	24.9 ± 5.7	16.9 ± 4.2	2.4 ± 1.1	1.5 ± 0.8	17	15	2	1						
Luo, 2017	13.03 ± 0.39	12.16 ± 0.23			71	113	1	24						
Zhang, 2016	14.3 ± 2.4	14.9 ± 2.9	3.21 ± 1.4	3.0 ± 1.1			10	6						
Wang, 2015													3.10%	4.80%
Wu, 2017	15.8 ± 2.8	15.7 ± 2.9	5.5 ± 1.6	6.2 ± 1.8										
Niu, 2016			4.2 ± 1.5	3.6 ± 1.7									7.80%	11.10%
Sekimoto, 2011														

LL = low ligation, HL = high ligation, IMA = inferior mesenteric artery, n = number of patients, OS = overall survival, DFS = disease-free survival

Anastomotic leakage

The pooled anastomotic leakage rate was 5.5% (132/2411) in the low ligation group and 9.5% (316/3321) in the high ligation group. The meta-analysis of 20 trials reporting this data indicated that there was a significant difference between the two groups (RR = 0.59; 95%CI = 0.46 ~ 0.76; $P < 0.05$; Fig. 2) with low heterogeneity (I^2=16.6%). Subgroup analysis based on published years indicated a similar result in both subgroups. The pooled data showed LL-treated patients had a lower incidence of anastomotic leakage compared to HL-treated patients.

Operation time

The meta-analysis of 13 trials reporting this data indicated that there was a significant difference between the two groups (WMD = 7.71; 95%CI = 0.96 ~ 14.46; $P < 0.05$; Fig. 3) with significant heterogeneity (I^2=89.6%), and so the random effects model was adopted. However, the subgroup analysis based on clinical study type indicated no statistically significant difference in the non-RCT group (WMD = 7.03; 95%CI=-2.70 ~ 16.75; $P > 0.05$) and the RCT group (WMD = 8.93; 95%CI=-0.14 ~ 18.01; $P > 0.05$). Therefore, it cannot be concluded that the operation time of high ligation is longer than that of low ligation. More high-quality research will need to be included in the discussion.

Blood loss

The meta-analysis of 9 trials reporting this data indicated that there was no significant difference between the two groups (WMD = 2.20; 95%CI=-1.40 ~ 5.80; $P > 0.05$; Fig. 4) with certain heterogeneity (I^2=64.3%), and so the random effects model was adopted.

Early complication

The meta-analysis of 9 trials reporting this data indicated that there was no significant difference between the two groups (RR = 0.96; 95%CI = 0.75 ~ 1.23; $P > 0.05$; Fig. 5) with certain heterogeneity (I^2=52.9%), and so the random effects model was adopted.

The postoperative first anal exhaust time

The meta-analysis of 6 trials reporting this data indicated that there was a significant difference between the two groups (WMD=-4.55; 95%CI=-8.87~-0.24; $P < 0.05$; Fig. 6) with high heterogeneity (I^2=89.6%), and so the random effects model was adopted. The heterogeneity may be caused by different units of measurement. Pooled analysis showed shorter recovery time of bowel function in LL group than that of HL group.

Lymph node yield outcomes

Total number of harvested lymph nodes

The meta-analysis of 12 trials reporting this data indicated that there was no significant difference between the two groups (WMD = 0.29; 95%CI = − 0.83 ~ 1.41; $P > 0.05$; Fig. 7). The value for I^2 suggested high level of heterogeneity (I^2=90.9%). A random-effects model was used for analysis, and subgroup analysis based on clinical study type showed the difference was not statistically significant in non-RCT subgroup (WMD=-0.57; 95%CI = − 1.39 ~ 0.26; $P > 0.05$) and RCT subgroup (WMD = 1.86; 95%CI = − 1.02 ~ 4.75; $P > 0.05$).

The number of harvested lymph nodes around the root of the IMA

The meta-analysis of 9 trials reporting this data indicated that there was no significant difference between the two groups (WMD = 0.07; 95% CI = − 0.25 ~ 0.38; $P > 0.05$; Fig. 8) with certain heterogeneity (I^2=77.5%). A random-effects model was used for analysis, and subgroup analysis based on clinical study type showed the difference was not statistically significant in two subgroups.

Lymph node involvement state

Total lymph node involvement

The pooled rate of total lymph node involvement was 39.8% (257/645) in the low ligation group and 38.8% (244/629) in the high ligation group. The meta-analysis of 5 trials reporting this data indicated that there was no significant difference between the two groups (RR = 0.95; 95%CI = 0.83 ~ 1.09; $P > 0.05$; Fig. 9) without heterogeneity (I^2=0%).

Lymph node involvement around the root of the IMA

The pooled rate of lymph node involvement around the root of the IMA was 5.9% (36/608) in the low ligation group and 6.1% (38/662) in the high ligation group. The meta-analysis of 5 trials reporting this data indicated that there was no significant difference between the two groups (RR = 1.06; 95%CI = 0.68 ~ 1.66; $P > 0.05$; Fig. 10) without heterogeneity (I^2=0%).

Long-term prognosis

5-year overall survival

Eight studies compared the 5-year overall survival. There was no heterogeneity among the studies (I^2=0%). Pooled analysis showed no statistically significant difference between the high ligation group and the low ligation group (RR = 0.85; 95%CI = 0.70 ~ 1.02; $P > 0.05$; Fig. 11).

5-year disease-free survival

Six studies compared the 5-year disease-free survival. There was certain heterogeneity among the studies (I^2=39.9%), and so the random effects model and subgroup analysis was adopted. Pooled analysis showed no statistically significant difference between the high ligation group and the low ligation group (RR = 0.90; 95%CI = 0.68 ~ 1.19; $P > 0.05$; Fig. 12).

Overall recurrence

Nine studies compared the recurrence rates. There was no significant heterogeneity among the studies (I^2=0.6%). Pooled analysis showed no statistically significant difference between the high ligation group and the low ligation group (RR = 1.02; 95%CI = 0.83 ~ 1.25; $P > 0.05$; Fig. 13).

Sensitivity analysis

We performed a sensitivity analysis by investigating the influence of a single study on the overall pooled estimates. This was achieved by eliminating one study at a time and repeating the analyses, which producing the similar outcomes. The heterogeneity may be caused by different surgical proficiency, individual anatomical differences and outcomes measured by different methods.

Assessment of publication Bias

We only analyzed publication bias for outcomes included in 8 or more studies. After viewing the funnel plots and Egger's tests, it was concluded that there was no obvious publication bias among the studies. A funnel plot of the studies used in the meta-analysis reporting on 5-year OS after colorectal resection with low ligation and high ligation was shown in Fig. 14. None of the studies lay outside the limits of the 95% confidence interval.

Discussion

Recently, a technique involving LL and lymph nodes dissection around the root of the IMA to achieve D3 lymph nodes dissection has been widely used clinically, especially in Asian countries[37]. To compare the efficacy and safety of LL and HL, A total of 5947 patients (2519 patients in LL group and 3428 patients in HL group) were involved in this meta-analysis. The first objective of this meta-analysis was to understand whether the two ligation methods of IMA had a certain impact on the incidence of anastomotic leakage. It has been reported that the incidence of anastomotic leakage is 2.2%~12%[38]. There are many risk factors for anastomotic leakage, however, blood perfusion and anastomotic tension are of primary concern to surgeons because good blood supply and tension-free anastomosis are critical in radical resection of colorectal cancer[8, 39, 40]. The colon below the root of IMA is perfused by IMA and the limbic artery from the middle colon artery(MCA)[8, 41]. Some studies have shown that in patients receiving HL treatment, since the LCA and its ascending branches are ligated, the perfusion of the distal colon is completely dependent on the limbic artery from the MCA, leading to a significant impact on the perfusion of the distal colon[22]. Dworkin et al. used Doppler flowmeter to make measurements and found that HL significantly reduced blood perfusion in the distal colon[42, 43]. This undoubtedly increases the incidence of anastomotic leakage in HL patients. However, other studies suggest that HL can provide enough colon length for tension-free anastomosis, and the limbic artery can provide sufficient blood supply to the remaining colon[44, 45].

In some previously published meta-analyses, Fan et al. reported that low ligation significantly reduced the risk of anastomotic leakage, whereas Yang et al. reported that there was no significant difference in the incidence of anastomotic leakage with the two approaches[5, 14]. However, there are significant limitations to their findings. In the meta-analysis published by Yang Y et al., not enough studies on anastomotic leakage were included. In the meta-analysis published by Fan et al., the included studies were basically retrospective studies, lacking RCT data, and the results lacked stability and reliability. In our meta-analysis, we included the latest high-quality literature from Asian countries, including 8 RCTs and 13 non-RCTs, to evaluate the technical feasibility and oncological safety of low and high ligation of the inferior mesenteric artery in colorectal cancer surgery for Asian populations. The pooled anastomotic leakage rate was 5.5% (132/2411) in the low ligation group and 9.5% (316/3321) in the high ligation group. The meta-analysis of 20 trials reporting this data indicated that there was a significant difference between the two groups($p < 0.05$). The results showed LL-treated patients had a lower incidence of anastomotic leakage compared to HL-treated patients. This finding is consistent with a meta-analysis recently published by Si et al[1]. From an anatomical point of view, the left branch of the MCA and the ascending branch of the LCA form anastomotic branches near the splenic flexion through the Riolan arch. However, this region is usually relatively thin and is absent in 5% of the cases[29]. Furthermore, postoperative systemic blood perfusion decline, elderly patients or patients with metabolic diseases and especially the increasing number of patients with vascular lesions, may become risk factors for anastomotic blood supply deficiency. Thus, low ligation is of great advantage in improving anastomotic blood supply and reducing anastomotic leakage.

Our meta-analysis confirmed that there were no significant differences between LL group and HL group in terms of operation time, blood loss, and early complications. This is consistent with the previously published meta-analysis[13, 46]. However, we found that regarding postoperative first anal exhaust time, LL group was earlier than HL group, which was rarely reported in previous studies. It may be because LL retains the LCA and provides better blood perfusion at the anastomosis, thus promoting the recovery time of bowel function.

Lymph node yield and involvement state, especially around the root of IMA, is a key prognostic factor for colorectal cancer[47, 48]. Some studies suggest that high ligation can more thoroughly remove lymph nodes and improve lymph nodes harvest rate, thus contributing to more accurate tumor stage and better disease prognosis[6, 7]. This may be because in those studies, LL group did not undergo IMA root lymph node dissection. Moreover, with the development of laparoscopic-assisted radical resection of colorectal cancer, the techniques of low ligation and IMA root lymph node dissection to achieve D3 lymph node dissection are increasingly mature. This meta-analysis shows that, the pooled rate of total lymph node involvement was 39.8% (257/645) in the low ligation group and 38.8% (244/629) in the high ligation group, and the pooled rate of lymph node involvement around the root of the IMA was 5.9% (36/608) in the low ligation group and 6.1% (38/662) in the high ligation group. We observed that there was no statistical difference between LL group and the HL group either in terms of the harvested number of lymph nodes or the involvement state of lymph node($p > 0.05$). And, the metastasis rate of the IMA root lymph nodes is stable and low. This indicated that the number of lymph nodes dissected by low ligation was similar to that by high ligation, and the oncological safety was comparable. It is not surprising, therefore, that we observed similarities in 5-year OS and 5-year DFS between the two groups($p > 0.05$). Because of the differences in physical fitness and dietary culture between Eastern and Western people, we only included Asian patients to assess the long-term prognosis of tumors[37]. Our meta-analysis confirmed that HL did not significantly improve the long-term prognosis of tumors in patients with radical resection of colorectal cancer compared with LL, which was consistent with previous studies[6, 12, 49]. However, the meta-analysis published by Singh et al. showed no significant difference in OS among all case groups, while HL over LL had a significant OS benefit in the IMA positive lymph nodes group[50]. Si et al. recently published a meta-analysis that compared stage II and III patients in greater depth and found no difference in survival between the two IMA ligation techniques[1]. Therefore, based on the available evidence, LL of IMA is recommended in colorectal cancer surgery for Asian populations regardless of tumor stage.

Some limitations exist that should not be neglected for this meta-analysis. First, many studies related with the theme are non-randomized retrospective trials. Therefore, we have analyzed both the RCTs and non-RCTs to avoid lack of samples. Second, the data including postoperative defecation, urinary and sexual function are obviously insufficient in the literatures, so the functional results are not analyzed. Third, Individual differences in patient anatomy and the skill of surgeon, as well as differences in measurement methods, led to a high degree of heterogeneity in some of the results, which may affect the quality of evidence to some extent. Finally, the meta-analysis was limited to literature in English and the studies from China accounting for a larger proportion, which is a potential source of bias.

Conclusion

In conclusion, this meta-analysis showed that compared with high ligation, low ligation reduced the incidence of anastomotic leakage and accelerated the postoperative recovery time of intestinal function for Asian populations. There were no significant differences between the two groups in terms of operation time, blood loss, early complications, number of harvested lymph nodes, and lymph node involvement status, 5-year OS, 5-year DFS and overall recurrence. It shows that LL can obtain equivalent lymph node yield and long-term survival benefit as compared to HL. More high-powered, well-designed RCTs, with extensive follow-up, will be need in the future to confirm and update the results of this analysis.

Abbreviations

IMA: inferior mesenteric artery

LCA: left colon artery

MCA: middle colon artery

LL: low ligation

HL: high ligation

OS: over survival

DFS: disease-free survival

RCTs: randomized controlled trials

Non-RCTs: retrospective cohort studies

NOS: Newcastle—Ottawa Quality Assessment Scale

JCS: Jadad scale

RR: relative risks

WMD: weighted mean differences

CI: confidence interval

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

WPY designed and performed the study. XFW and ZPZ compiled the literature selection criteria and developed the literature search. JHX and LLL extracted the original data. WPY, ZPZ performed the statistical analysis. XFW and SHL processed the related figures and tables. WPY, XFW and ZPZ drafted the manuscript. All authors approved the final manuscript.

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Figures

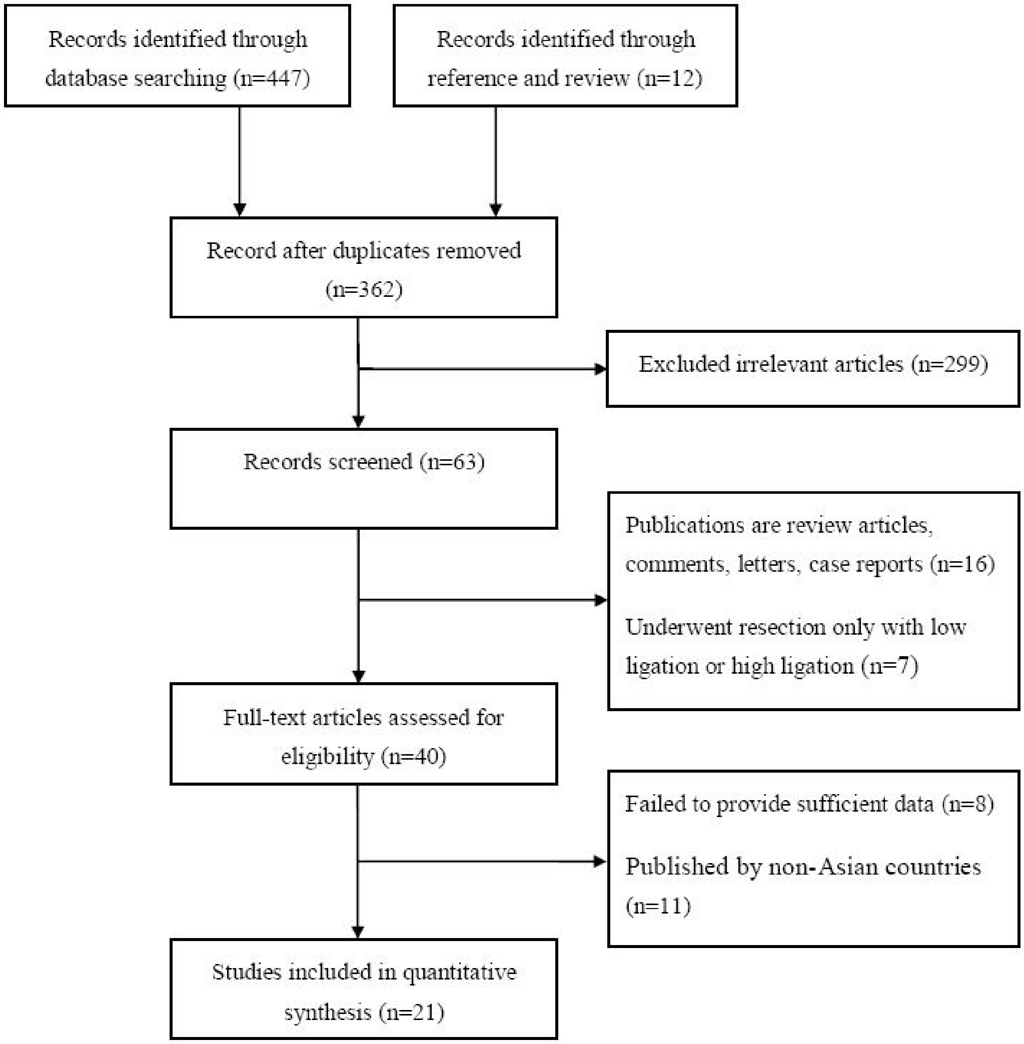

Figure 1

Flowchart of the study selection

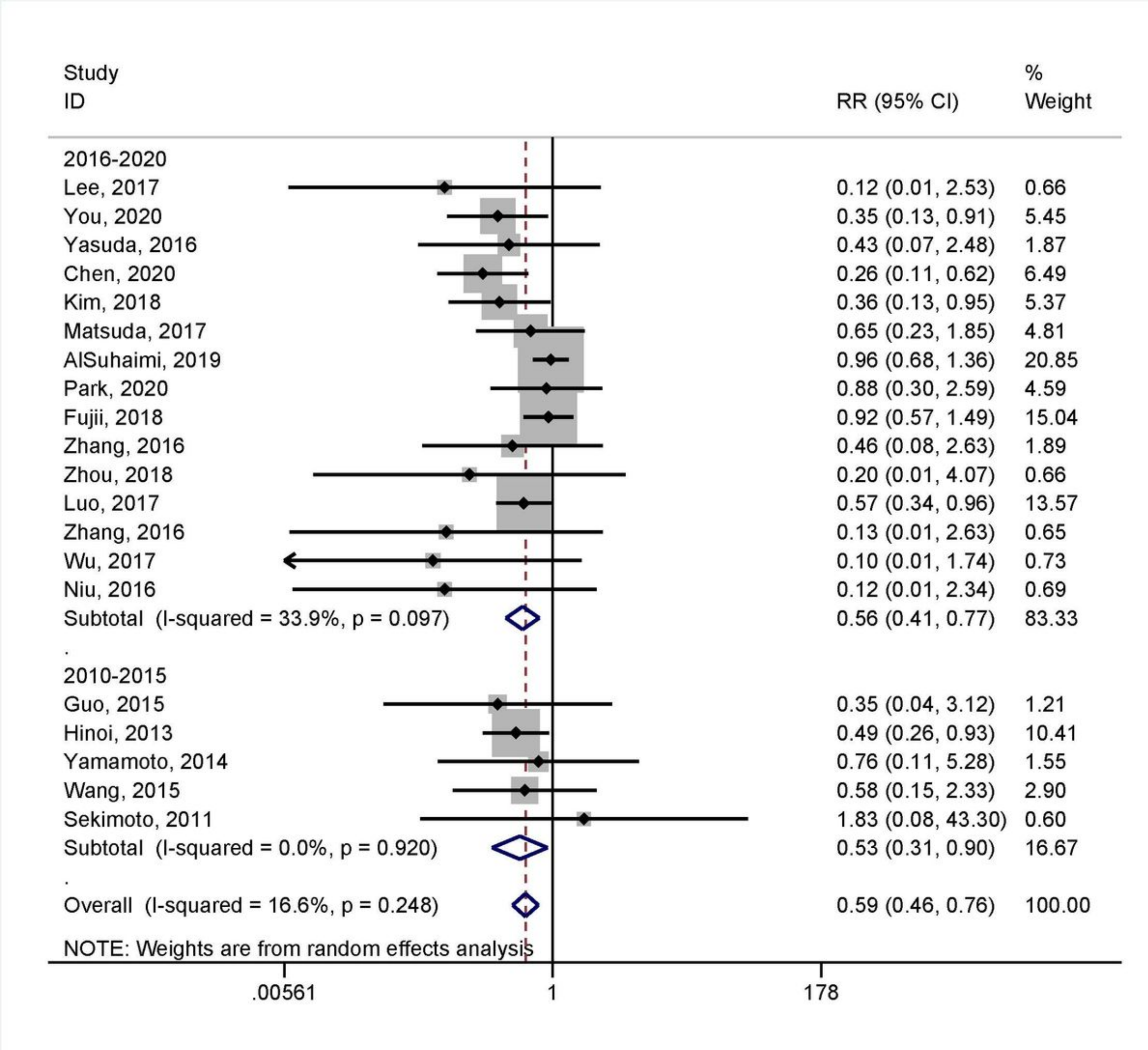

Figure 2

Forest plot of anastomotic leakage

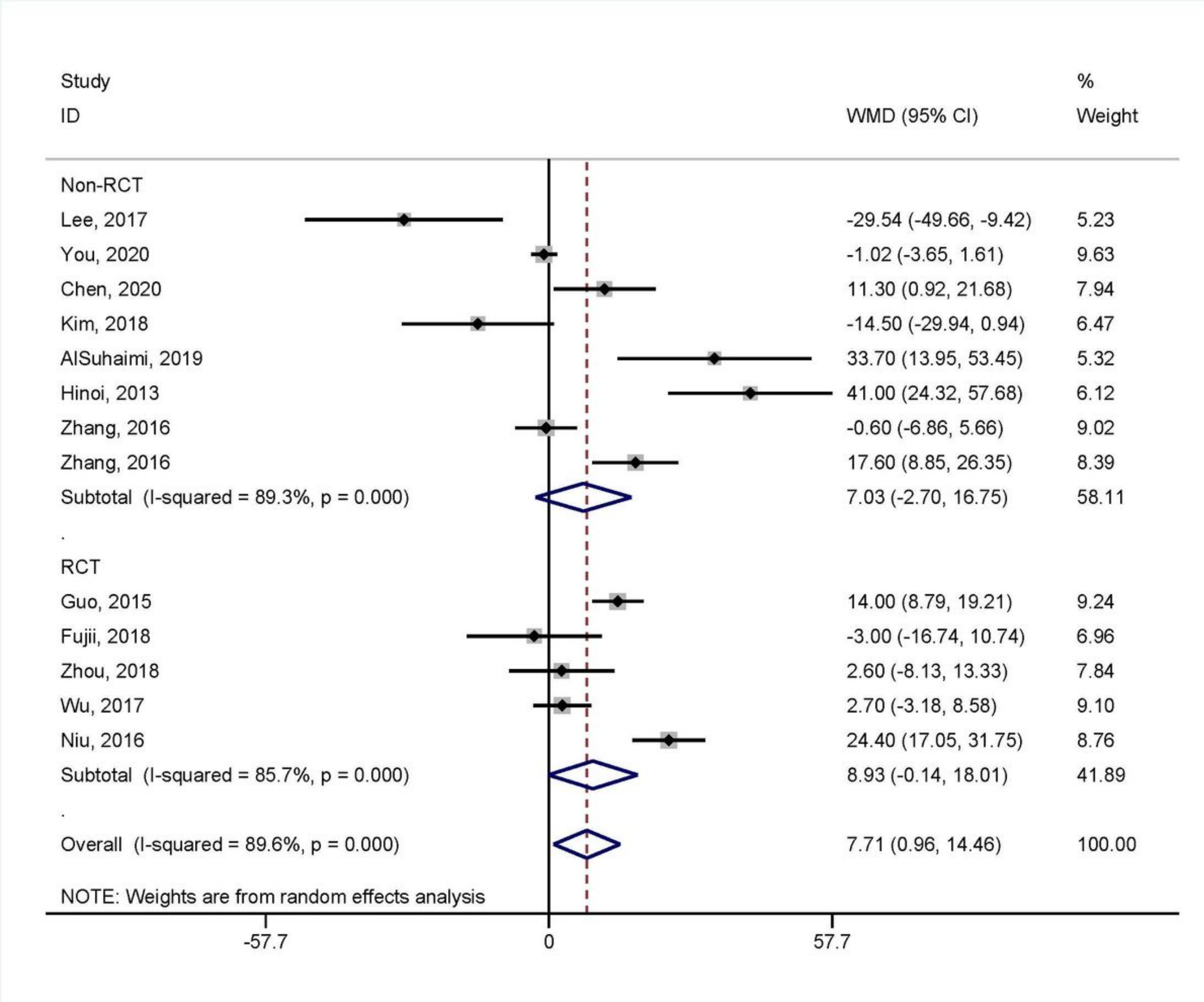

Figure 3

Forest plot of operation time.

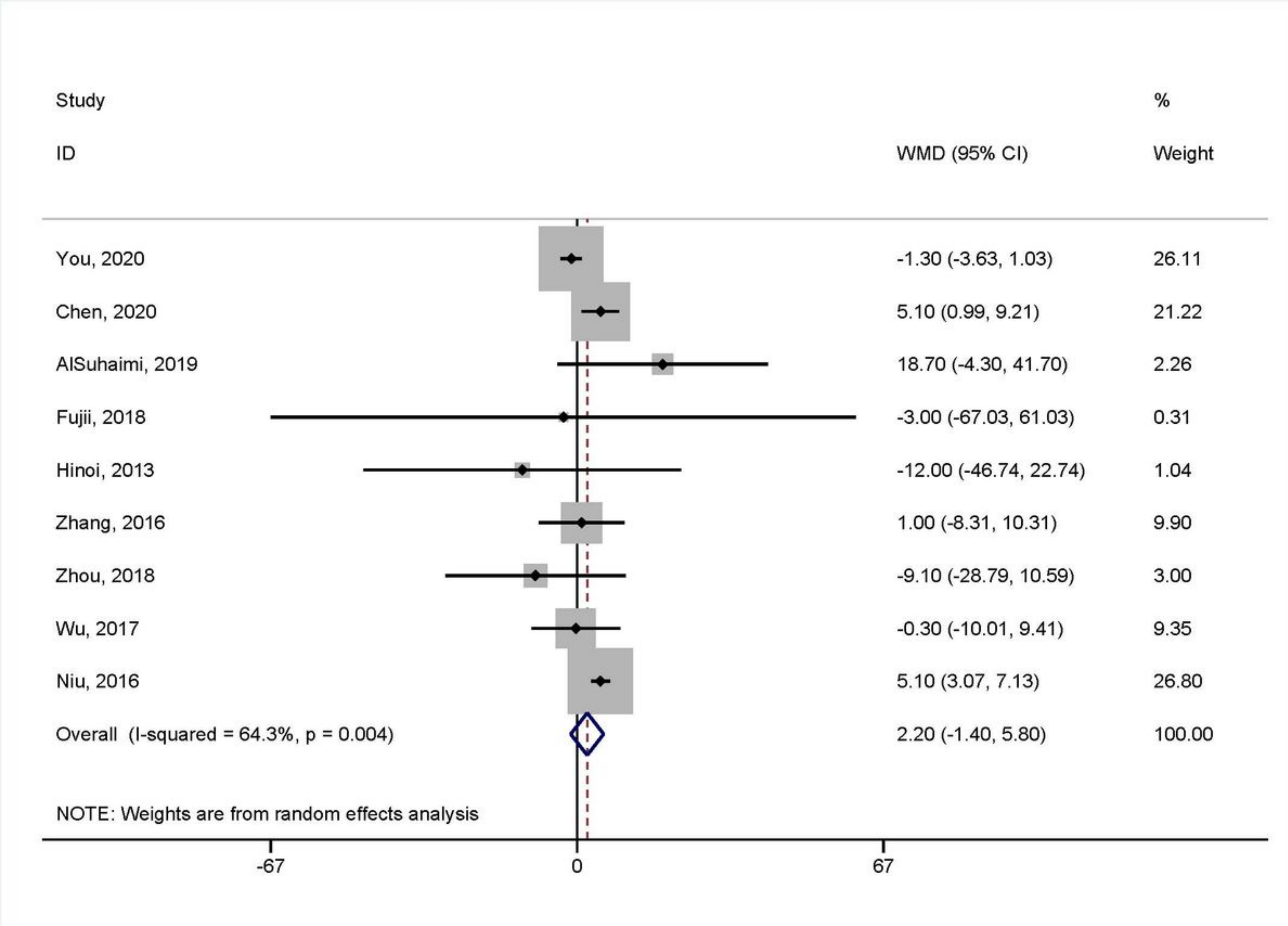

Figure 4

Forest plot of blood loss

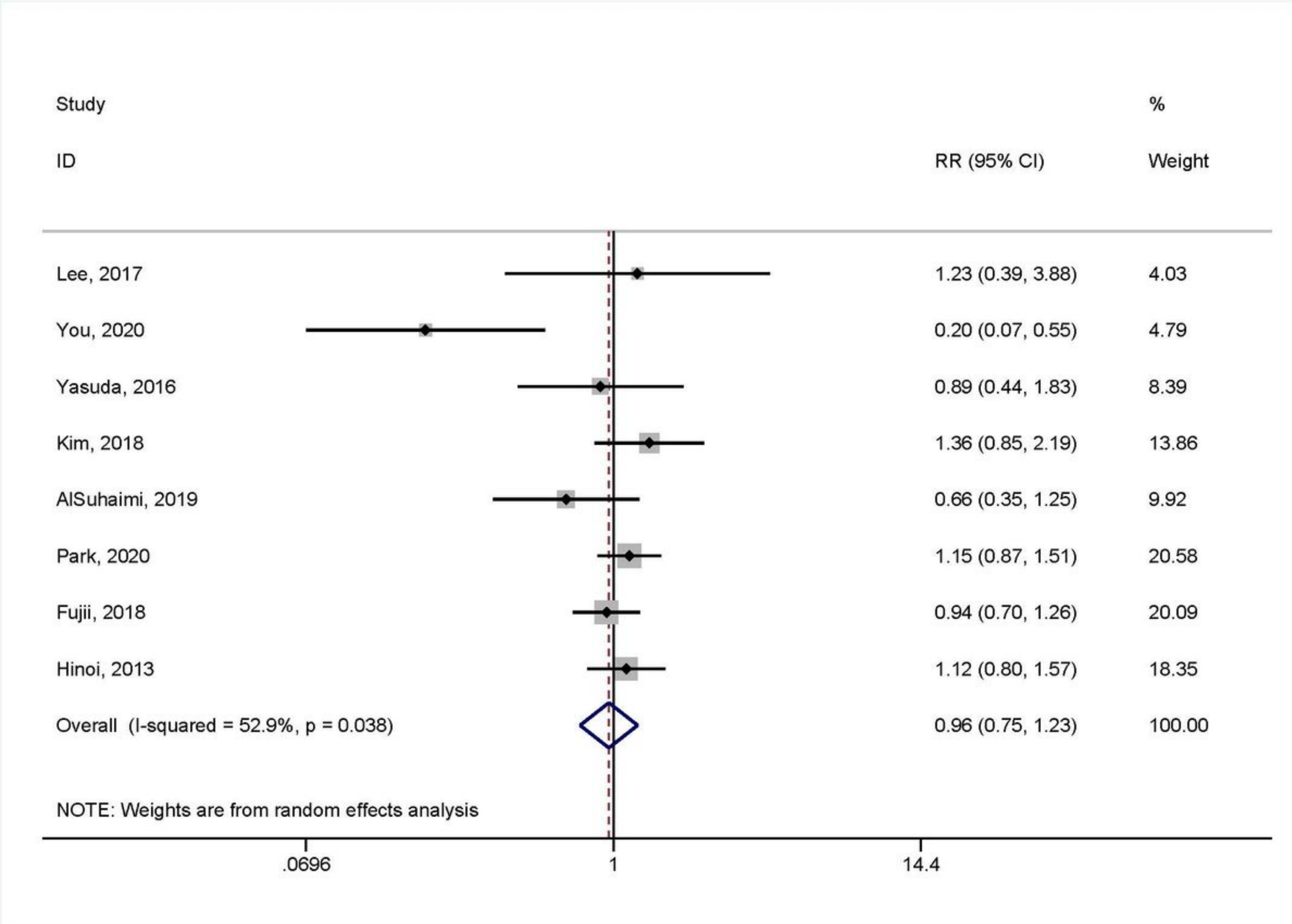

Figure 5

Forest plot of early complication

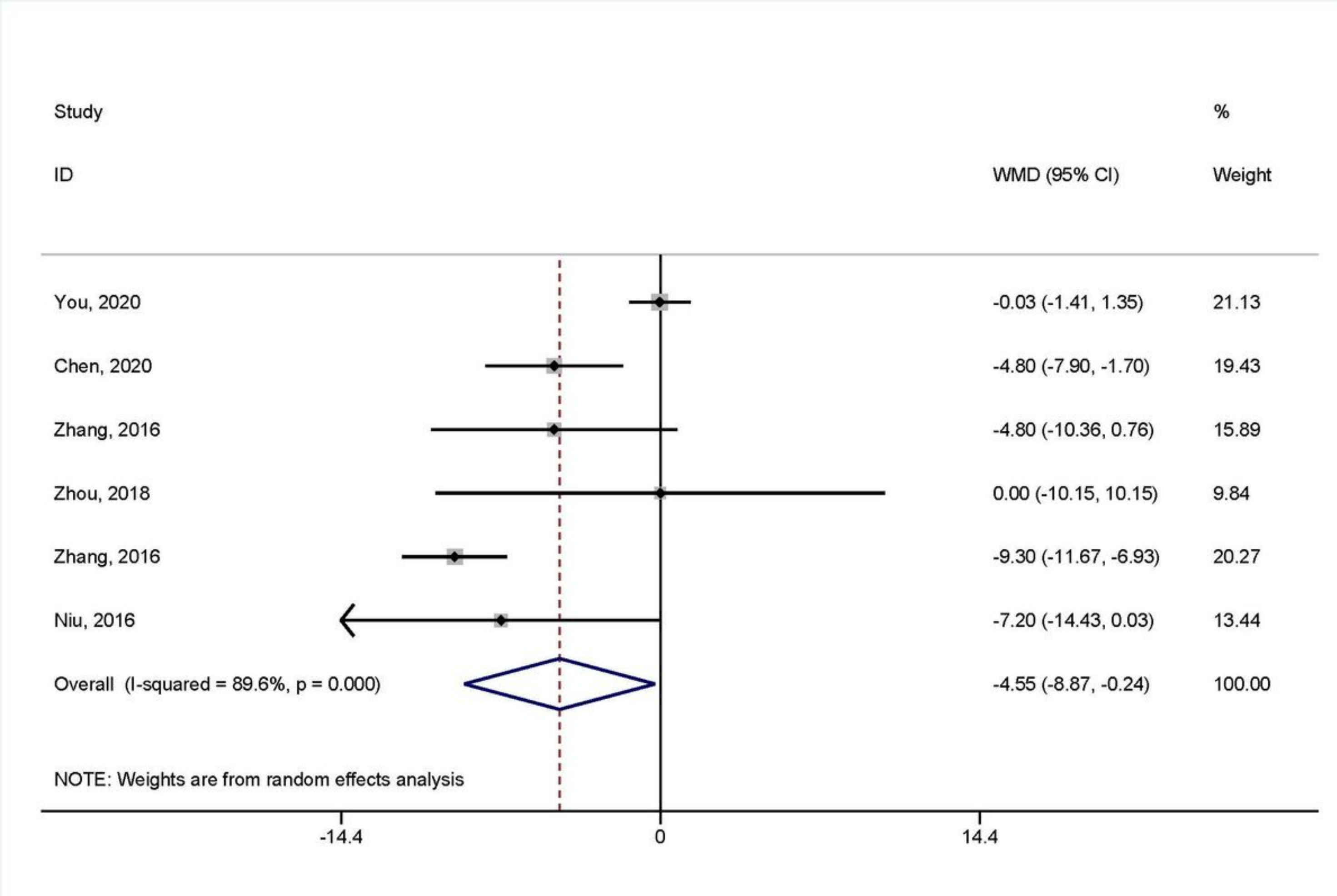

Figure 6

Forest plot of the postoperative first anal exhaust time

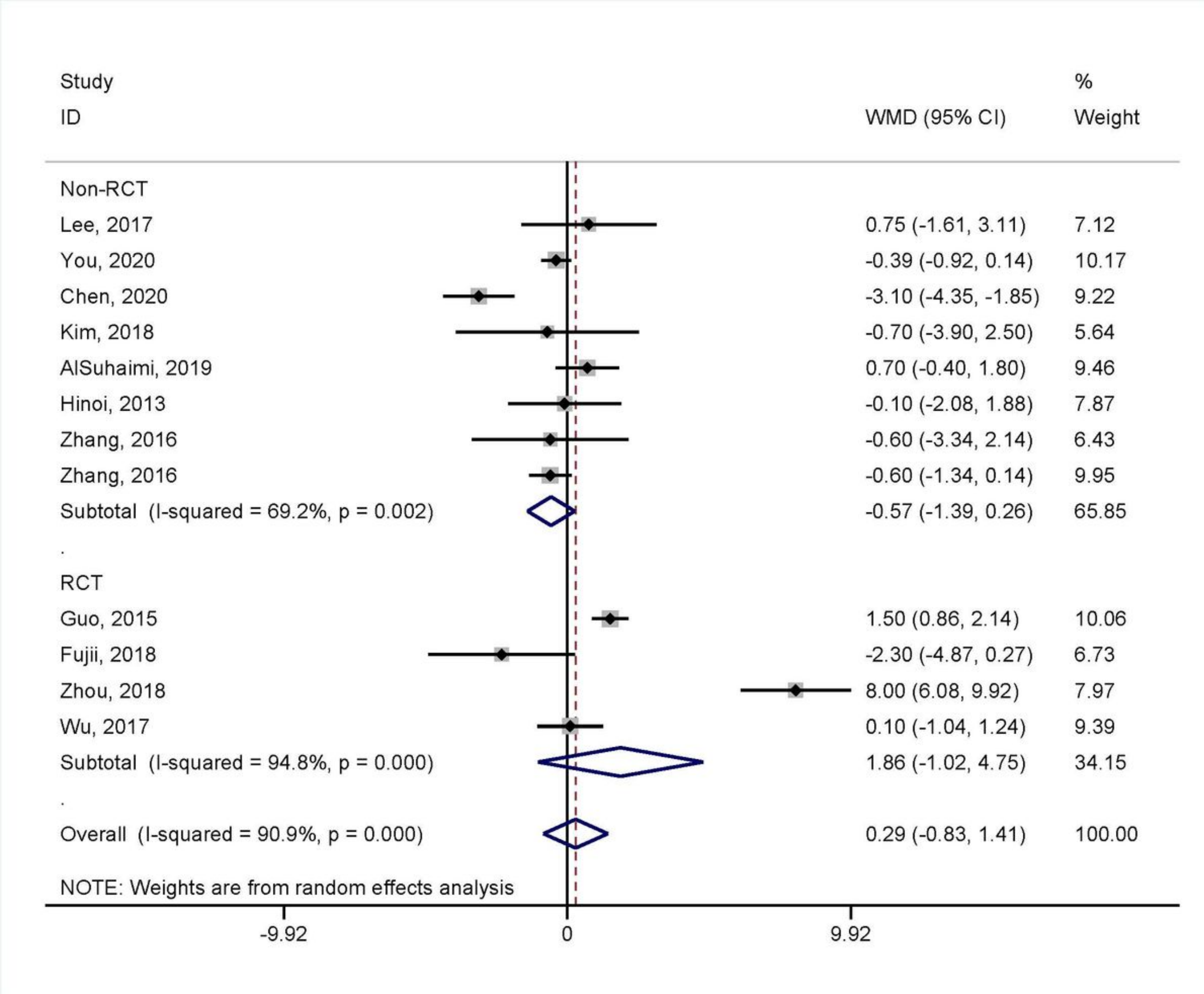

Figure 7

Forest plot of total number of harvested lymph nodes

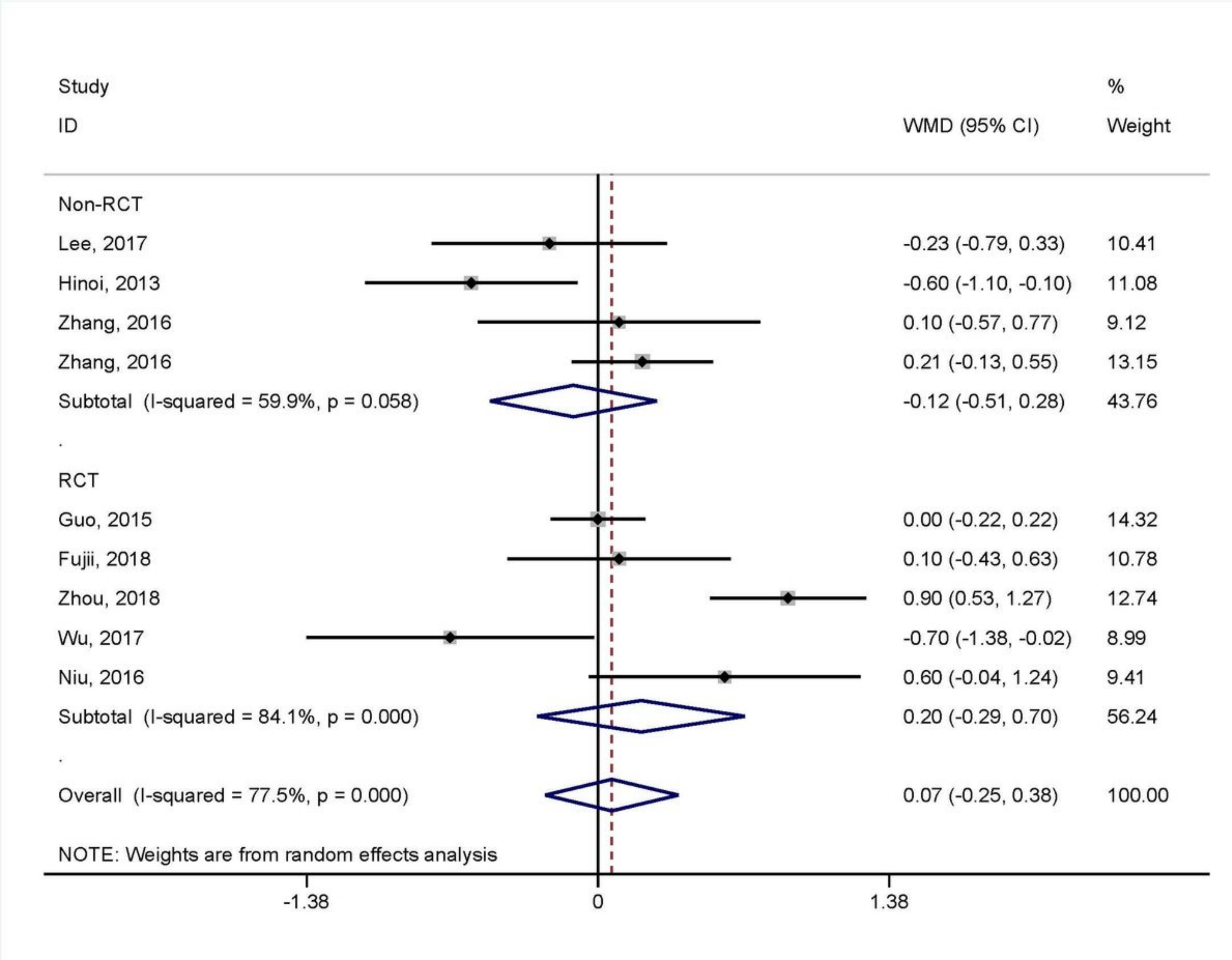

Figure 8

Forest plot of the number of harvested lymph nodes around the root of the IMA

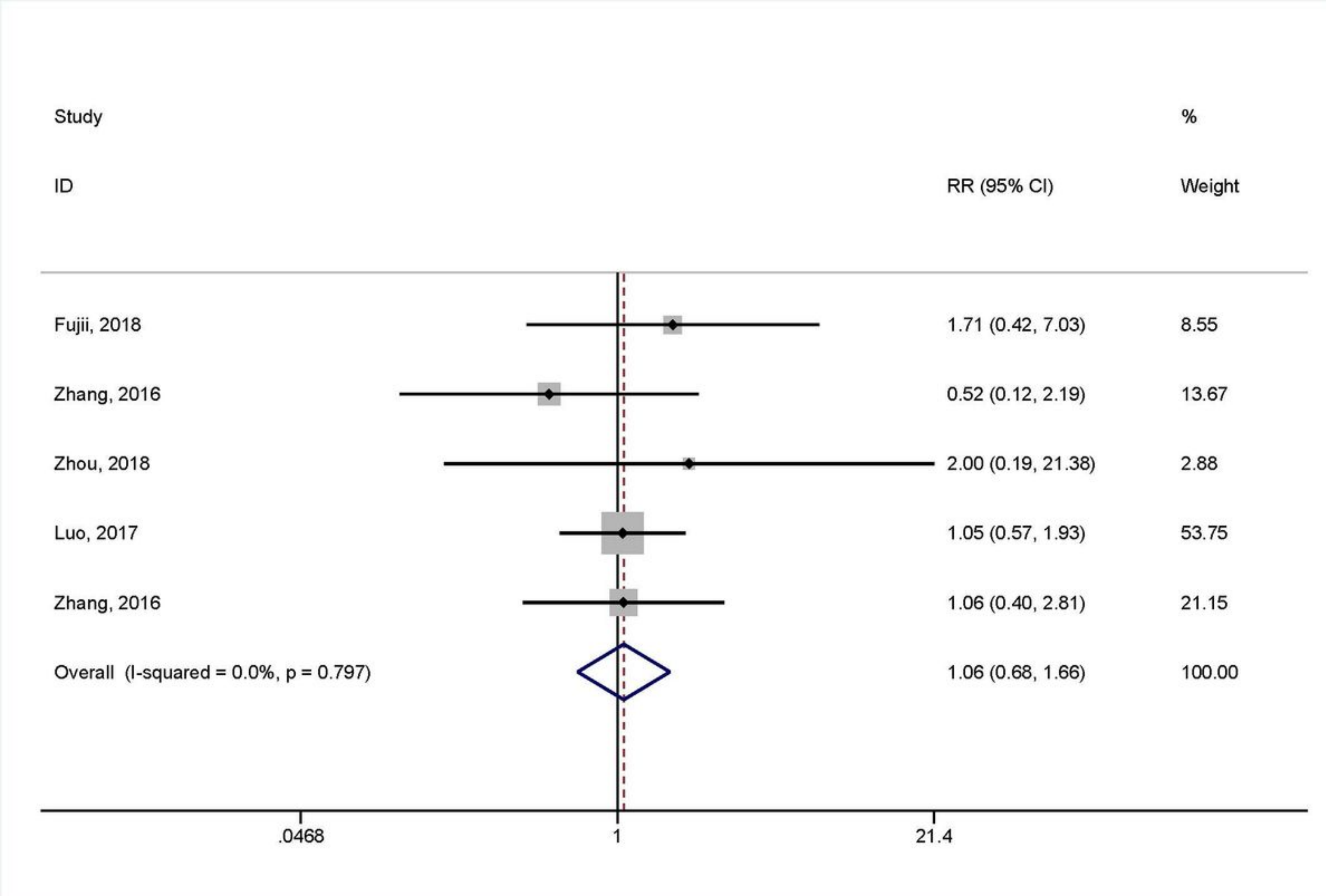

Figure 10

Forest plot of lymph node involvement around the root of the IMA

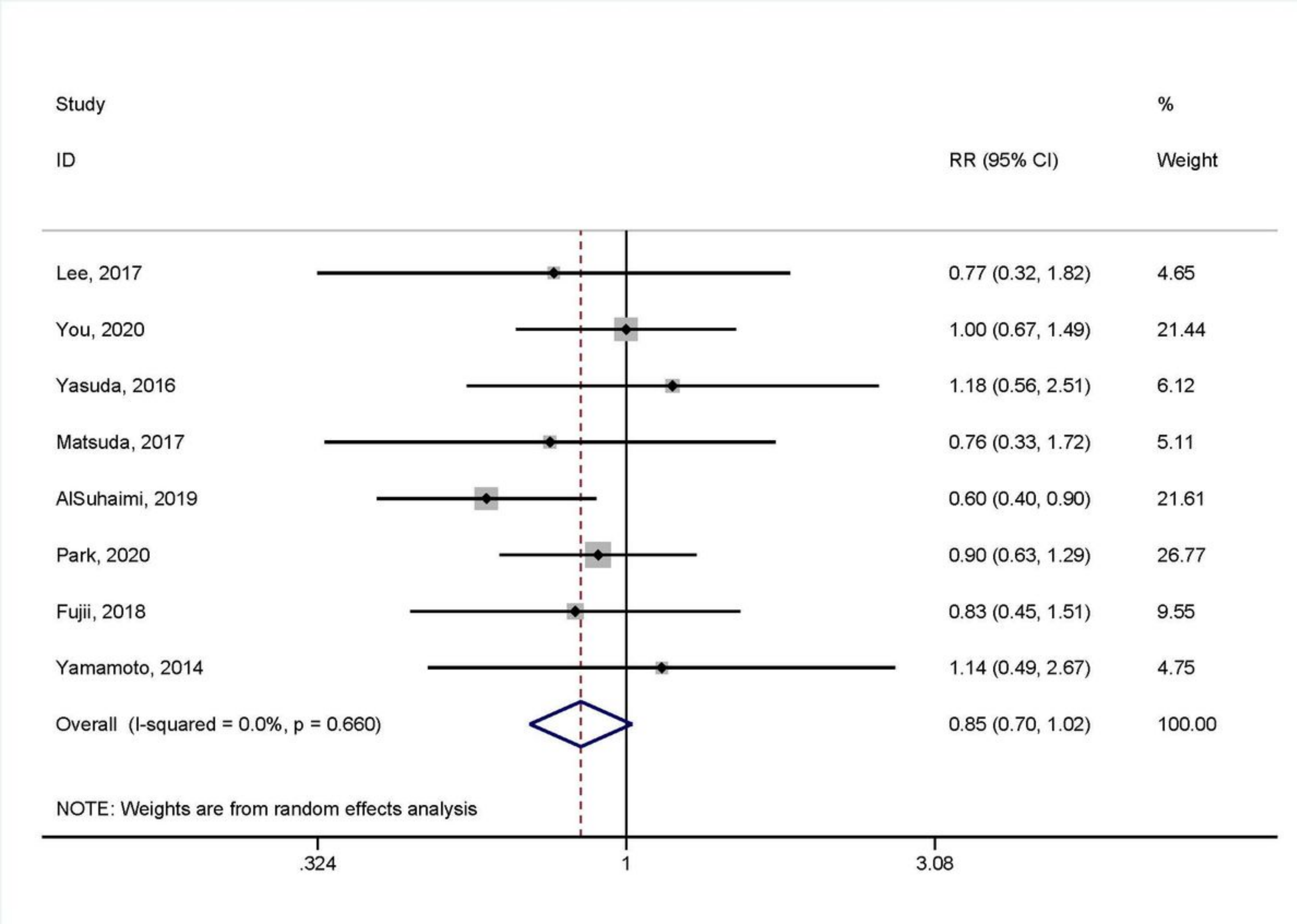

Figure 11

Forest plot of 5-year overall survival

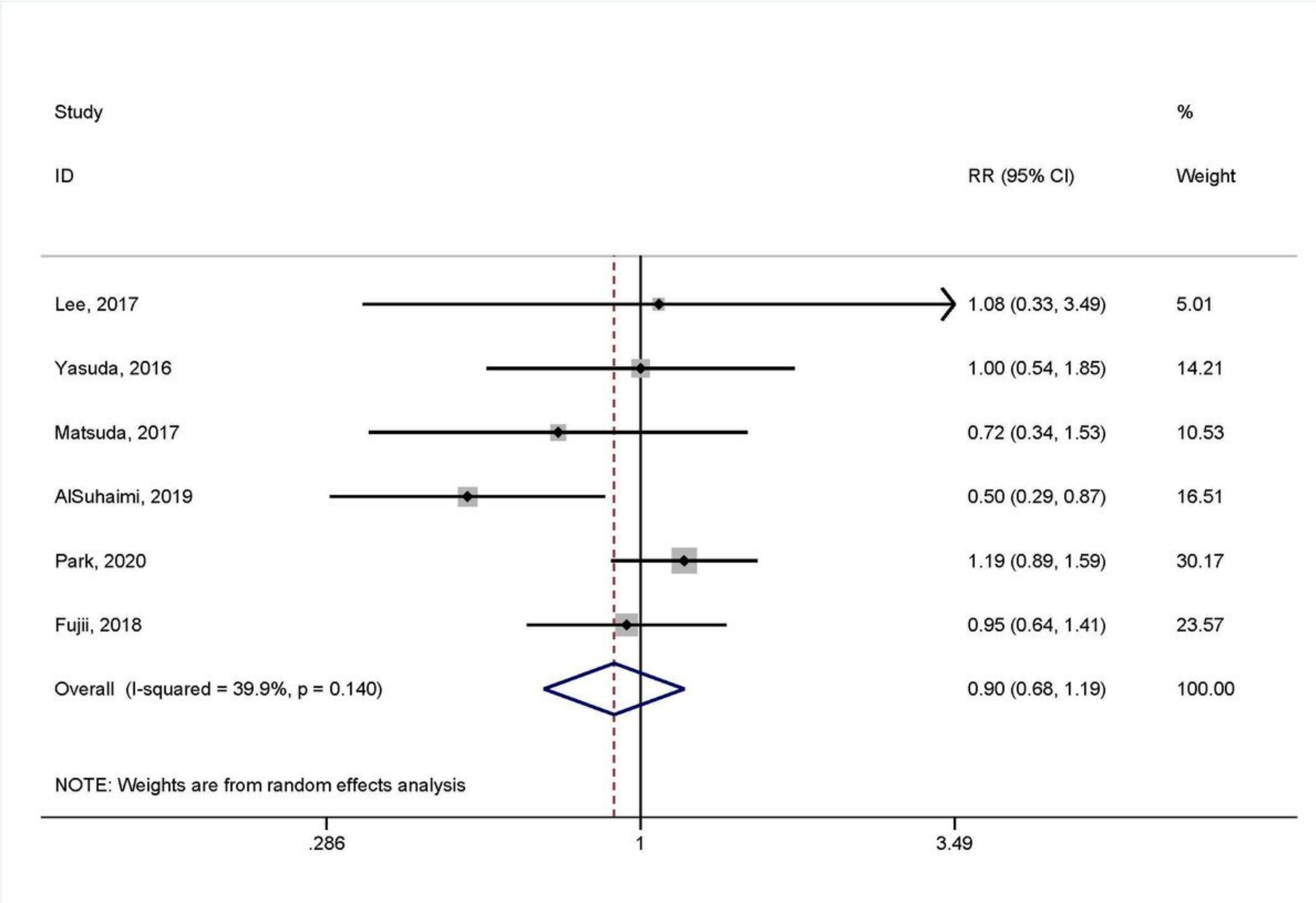

Figure 12

Forest plot of 5-year disease-free survival

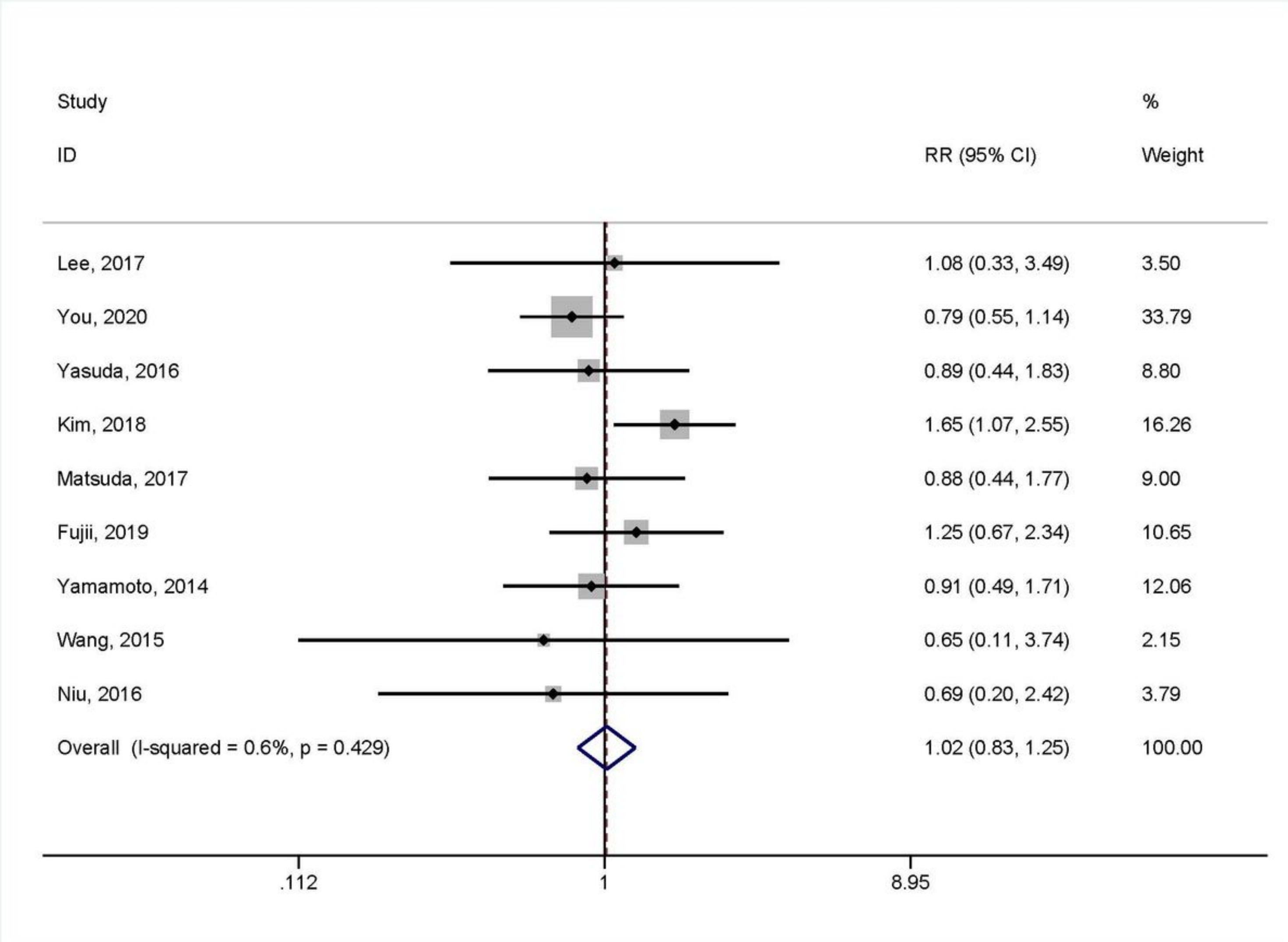

Figure 13

Forest plot of overall recurrence

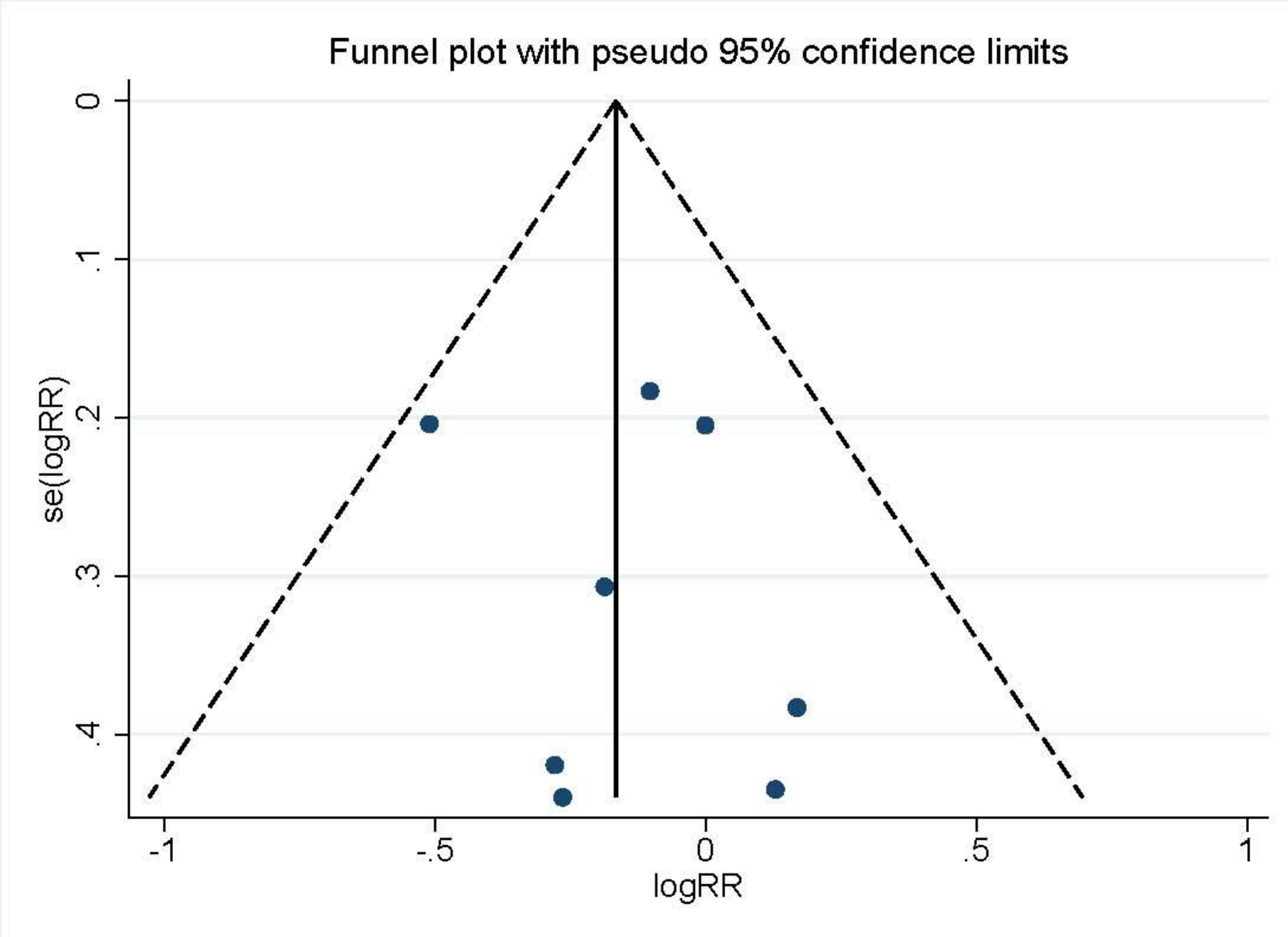

Figure 14

Funnel plot of 5-year overall survival