Park *et al*. *Mini-invasive Surg* 2020;4:87
DOI: 10.20517/2574-1225.2020.87

Mini-invasive Surgery

Meta-Analysis

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A systematic review and meta-analysis comparing intracorporeal anastomosis and extracorporeal anastomosis in minimally invasive colectomies

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How to cite this article: Park SSW, Feng D, Smith S. A systematic review and meta-analysis comparing intracorporeal anastomosis and extracorporeal anastomosis in minimally invasive colectomies. *Mini-invasive Surg* 2020;4:87.
DOI: 10.20517/2574-1225.2020.87

Received: 30 Aug 2020 **First Decision**: 12 Oct 2020 **Revised**: 19 Oct 2020 **Accepted**: 30 Oct 2020 **Published**: 5 Dec 2020

Academic Editor: Simon Ng **Copy Editor**: Cai-Hong Wang **Production Editor**: Jing Yu

Abstract

Aim: This systemic review aims to determine if intracorporeal anastomosis (IA) adds value to patient outcomes without compromising operative and oncological safety when compared to extracorporeal anastomosis (EA) in laparoscopic colectomies. This is the first systematic review with meta-analysis to evaluate the outcomes in a combined fashion including both laparoscopic right and left colectomies.

Methods: A systematic review of Medline, EMBASE, Cochrane Library, and PubMed was performed on studies analysing direct comparison between IA and EA. The primary outcome was anastomotic leakage. Quality assessment was carried out using a modified Institute of Health Economics appraisal tool. Meta-analysis was performed using a random-effects model.

Results: A total of 24 papers with 2,674 patients were included in the analysis. No significant difference was found in anastomotic leakage (OR = 0.84; 95%CI: 0.54-1.31; P = 0.44) and short-term mortality (OR = 0.56; 95%CI: 0.20-1.58; P = 0.27) between the IA and EA cohorts. The IA cohort was associated with faster return of bowel function [MD = -0.53 days; 95%CI: -0.67-(-0.39); P < 0.00001] and lower incidence of surgical site infection

(OR = 0.52; 95%CI: 0.31-0.85; P = 0.009). The number of lymph nodes harvested was higher in IA (MD = 1.05; 95%CI: 0.19-1.91; P = 0.02; I^2 = 83%) with considerable heterogeneity.

Conclusion: Intracorporeal anastomosis can be considered a safe alternative technique in laparoscopic colectomies, with potential benefits in patient outcomes. A lack of randomised studies and heterogeneity need to be addressed by additional high-quality trials.

Keywords: Laparoscopic, intracorporeal, extracorporeal, colectomy, outcome

INTRODUCTION

Laparoscopic colectomy has been increasingly performed worldwide since its introduction and it is currently considered the "gold standard" surgical care for benign and malignant colon resections[1]. The most common indication for the colon resection is malignancy, which is the second leading cause of cancer death worldwide, with a lifetime incidence of approximately 6%[2].

In general, the term "laparoscopic colectomy" refers to laparoscopic-assisted colectomy with extracorporeal anastomosis (EA). Extracorporeal anastomosis is the preferred technique as intracorporeal anastomosis (IA) is considered more technically challenging due to the need for laparoscopic suturing and the potential risk of intra-abdominal spillage[3,4]. Subsequently, there has been concern about a greater likelihood of anastomotic leak[5]. However, IA is less invasive, and there is accumulating data to support its safety and potential short-term benefits in the post-operative period[6,7]. Unfortunately, available meta-analyses are limited to right colectomies based on limited observational studies while there is a paucity of data on left colectomies.

Traditionally, left colectomy is perceived to be more challenging than right colectomy due to the need for extensive posterior dissection during mobilisation of the splenic flexure and its anatomic characteristics of multiple lymphatic drainage. However, a study by Iorio *et al.*[8], investigating direct comparison of surgical outcomes in laparoscopic IA approach between right-sided and left-sided tumours, concluded that the location of the tumour itself did not have significant impact on patient clinical outcome, including anastomotic leakage.

The aim of this study was, therefore, to conduct a comprehensive systematic review to perform a combined meta-analysis of left and right-sided colectomies in order to broaden the existing understanding on the safety and potential benefits of IA in laparoscopic colectomy, irrespective of its primary location.

METHODS

Study design

Literature search and data extraction

A systematic literature search was carried out by two independent researchers using electronic databases including Medline, EMBASE, Cochrane Library, and PubMed. The following search strategy was used for database extraction using Endnote (Version X8, Clarivate Analytics®): "intracorporeal" OR "extracorporeal" OR "anastomosis" OR "laparoscopic assisted" OR "totally laparoscopic" AND "colectomy" and ("laparoscopy" or "laparoscopic"). The search was performed without any restriction on language or publication status. Studies published in a language other than English were excluded unless its full article was available in an English edition.

Inclusion and exclusion criteria

The following inclusion criteria were prerequisite to be included in the meta-analysis: (1) direct comparison of the pre-determined outcomes of IA with EA involving right-sided and/or left-sided colectomies; and (2) reported data concerning at least the primary endpoint (i.e., anastomotic leakage). If two studies were reported by the same institution and/or authors, the one with more comprehensive data was included, unless the studies were of different design and encompassed distinctive study population.

Non-comparative studies such as case series, description of particular techniques, along with animal studies, conference abstracts, review articles, opinions and editorials were excluded from the analysis. Furthermore, studies with inadequate data or that described other types of resections (e.g., single-incision approach, purely robotic, sub-total colectomy, primary rectosigmoid resection, and palliative resection) were excluded as well. The natural orifice extraction studies were excluded as it is currently not a widely practiced method and its validity is still to be confirmed[9].

Outcome measures

The primary endpoint was anastomotic leakage since the safety of a surgical technique is considered the most vital. An anastomotic leak was defined as a defect in the intestinal wall integrity at the anastomotic site leading to a communication between the intraluminal and extraluminal compartments either clinically or radiologically[10].

With regard to the secondary outcomes, we chose the following clinical endpoints to best reflect crucial clinical consequences of colonic resection:

Intraoperative:
(1) Operative time
(2) Number of lymph nodes harvested

Post-operative:
(1) Mortality, defined as any deaths occurred during hospitalisation or within 30 days post-operatively
(2) Need for re-intervention
(3) Time to first flatus
(4) Surgical site infections
(5) Incidence of post-operative incisional hernia

Data analysis

Statistical analysis

The meta-analysis was performed using Review Manager 5.3 (Cochrane Community) and was conducted in accordance with recommendations from the Cochrane Collaboration and Meta-Analysis of Observational Studies in Epidemiology Guidelines.

The statistical analysis for dichotomous variables was summarised by calculating odds ratios (OR) with a confidence interval (CI) of 95%. Mantel-Haenszel method was used to calculate the effect size by combining the odds ratios of the outcomes using a random-effects model. Odds ratio < 1 favoured the IA group while odds ratio > 1 favoured the EA group. This was considered statistically significant if $P < 0.05$ and if the confidence interval did not include 1. Continuous variables were statistically analysed by calculating the weighted mean difference (WMD) with a 95% confidence interval. A positive WMD indicated that the pooled mean value of the outcome was higher in the IA group and was considered statistically significant if $P < 0.05$. Study heterogeneity was evaluated using I^2 statistics. $I^2 > 50\%$ was considered substantial (i.e., serious heterogeneity) while $I^2 < 50\%$ was considered low-moderate risk of heterogeneity. In studies which

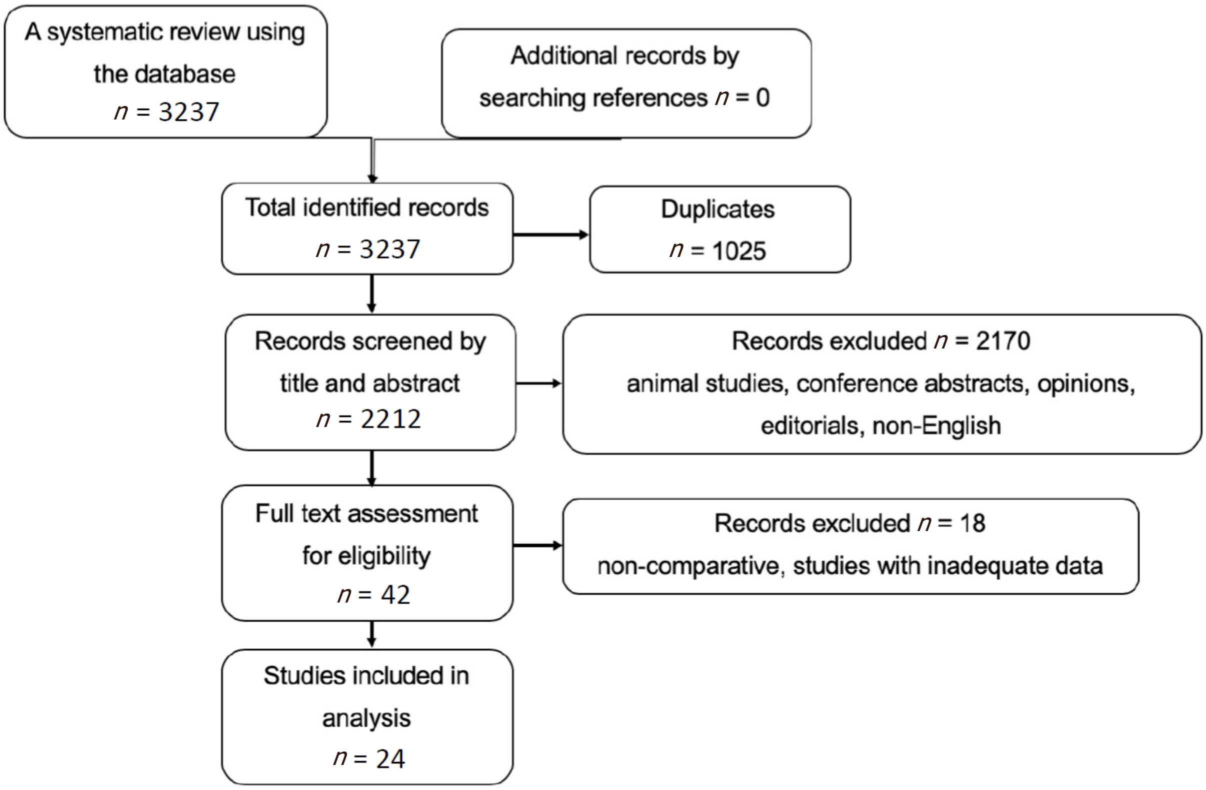


Figure 1. PRISMA flowchart for the systematic review of literature

included median with range, a dedicated mathematical conversion to mean and standard deviation was carried out using methods from Wan *et al.*[11].

Forest plots were constructed for meta-analysis on pre-determined outcomes by evaluating the total colectomies combined. A meta regression analysis and leave-one-out analysis were performed for the primary outcome to identify potential heterogeneity. Publication bias was assessed using Begg's and Egger's test.

RESULTS

Included articles

The flow chart on search results of the literature in accordance with the PRISMA statement are displayed in Figure 1. The search identified a total number of 3,237 potential articles published between 1991 and 2019. A total of 42 articles met initial inclusion criteria and full-text articles were reviewed. After thorough process of literature review and discussion between two independent reviewers, 24 papers were determined to be eligible for data extraction and subsequent statistical analysis. Cross-checking of all references of the included papers did not identify any additional studies.

The included studies for final analysis resulted in a total of 2,674 patients who had undergone laparoscopic colectomy. This was split into 1,412 patients (52.8%) in the intervention group (i.e., intracorporeal anastomosis) and 1,262 (47.2%) in the control group (i.e., extracorporeal anastomosis). The study design and characteristics of each study included are described in Table 1.

Two papers were identified to have been published by the same author, Vignali *et al.*[12,13]. After a thorough review, both studies were considered for inclusion in our analysis as they were of different study design, with Vignali *et al.*[12] evaluating the outcomes in a specific patient cohort, the obese population, as evident

Table 1. Study characteristics and demographic data

	Year	Recruitment	Country	Study design	Location	IA (*n*)	EA (*n*)	Multi-centre	IHE quality score	Age (IA)	Age (EA)	BMI (IA)	BMI (EA)	Malignant (IA)	Malignant (EA)	Anastomosis
Allaix *et al.*[14]	2019	2017-2018	Italy	Double-blind randomised	Right	70	70	N		70.5 ± 3	71.5 ± 3	24.8 ± 1.6	25.6 ± 1.6	77.1%	87.1%	Side-to-Side Linear Stapler for IA; Variations in EA
Anania *et al.*[15]	2012	2006-2010	Italy	Retrospective	Right	39	33	N	23	74.5 ± 9	74 ± 12	27.4 ± 4.3	28.3 ± 4.3	64.1%	84.8%	Side-to-Side Linear Stapler
Biondi *et al.*[16]	2017	2006-2016	Italy	Retrospective	Right	54	54	N	22	69.5 ± 12.7	68.6 ± 9.8	25.6 ± 4.7	26.3 ± 3.2	88.9%	100%	Side-to-Side Linear Stapler; Isoperistaltic
Chaves *et al.*[17]	2011	2004-2010	Spain	Retrospective	Right	35	25	N	24	62.2 ± 13.4	58.9 ± 12.9	25.9 ± 3.1	26.7 ± 3.9	62.9%	72%	Side-to-Side Linear Stapler; Isoperistaltic
Jian-Cheng *et al.*[18]	2016	2011-2015	China	Retrospective	Right	56	29	N	22	68 ± 8.3	69 ± 6.5	20.3 ± 2	20.6 ± 1.7	NR	NR	Linear Stapler
Erguner *et al.*[19]	2013	NR	Turkey	Retrospective	Right	15	15	N	23	65.4 ± 9.6	63.3 ± 13	27 ± 3.5	25.8 ± 3.2	100%	100%	Side-to-Side Linear Stapler; Isoperistaltic
Fabozzi *et al.*[20]	2010	2001-2009	Italy	Retrospective	Right	50	50	N	21	62.1 ± 8.3	59.4 ± 9.5	21.4 ± 2.3	22.1 ± 1.6	100%	100%	Linear Stapler; Isoperistaltic
Franklin *et al.*[21]	2004	1991-2002	USA	Retrospective	Right	82	10	N	24	NR	NR	NR	NR	100%	100%	Linear Stapler
Grams *et al.*[22]	2010	2006-2008	USA	Retrospective	Right	54	51	N	22	45	50	23.8	23.4	24.1%	29.4%	Side-to-Side Linear or Circular Stapler
Hanna *et al.*[23]	2015	2005-2014	USA	Retrospective	Right	86	109	Y	27	66 ± 4	59 ± 4.5	26.1 ± 1.1	25.5 ± 1.4	82.6%	65.1%	Side-to-Side Linear Stapler; Isoperistaltic
Hellan *et al.*[24]	2009	2004-2008	USA	Retrospective	Right	23	57	N	25	65.8 ± 8.8	66.5 ± 14	28.8 ± 5.3	28.5 ± 5	65.2%	63.2%	Side-to-Side Linear Stapler
Lee *et al.*[25]	2013	2005-2010	USA	Retrospective	Right	51	35	Y	27	70 ± 11.8	66 ± 11.3	29 ± 7.1	28.6 ± 6.8	100%	100%	Side-to-Side Linear Stapler; Anti-peristaltic
Magistro *et al.*[26]	2013	2009-2011	Italy	Prospective	Right	40	40	N	25	70.9 ± 13.4	71.2 ± 10.5	24.8 ± 2.8	23.9 ± 4.4	100%	100%	Side-to-Side Linear Stapler; Isoperistaltic
Marchesi *et al.*[27]	2013	2006-2010	Italy	Retrospective	Right	28	27	N	24	66.2	67.7	26.1	26.2	60.7%	63%	Side-to-Side Linear Stapler; Isoperistaltic
Mari *et al.*[28]	2018	2015-2016	Italy	Prospective randomised	Right	30	30	N		64.3 ± 10.3	65 ± 14.5	24.3 ± 5.9	26.1 ± 3.3	NR	NR	Linear Stapler
Milone *et al.*[7]	2015	2005-2012	Italy	Prospective	Right	286	226	Y	28	66.7 ± 12.6	65.6 ± 11.4	25.2 ± 3.8	25.4 ± 3.8	100%	100%	Side-to-Side Linear Stapler
Milone *et al.*[29]	2018	2005-2015	Italy	Retrospective	Left	92	89	Y	28	66 ± 10.9	68.7 ± 10.2	29.5 ± 4.3	24.7 ± 4.2	100%	100%	Side-to-Side Linear Stapler
Roscio *et al.*[30]	2012	2006-2011	Italy	Retrospective	Right	42	30	N	25	63.5 ± 10.3	63.7 ± 10.3	26 ± 4	26.3 ± 3.8	100%	100%	Side-to-Side Linear Stapler; Isoperistaltic
Scatizzi *et al.*[31]	2010	2006-2009	Italy	Retrospective	Right	40	40	N	24	65.7 ± 11	68.5 ± 10	27	28	100%	100%	Side-to-Side Linear Stapler; Isoperistaltic
Shapiro *et al.*[32]	2016	2006-2014	Israel	Prospective	Right	91	100	Y	26	72 ± 7.5	72 ± 6.8	27.8 ± 4.6	26.9 ± 4.3	100%	100%	Side-to-Side Linear Stapler; Isoperistaltic
Swaid *et al.*[33]	2016	2005-2014	Israel	Retrospective	Left	33	19	N	22	64.2 ± 12.4	72.7 ± 2.1	25.4 ± 3.9	25 ± 3.6	100%	100%	Side-to-Side Linear Stapler; Isoperistaltic
Vergis *et al.*[34]	2015	2008-2009	Canada	Retrospective	Right	21	29	N	22	65	69	21.7	28.6	NR	NR	Side-to-Side Linear Stapler
Vignali *et al.*[13]	2016	2008-2015	Italy	Prospective randomised	Right	30	30	N		67.4 ± 1.8	64.7 ± 2.9	24.6 ± 4.3	24.8 ± 3.4	100%	100%	Side-to-Side Linear Stapler; Isoperistaltic
Vignali *et al.*[12]	2018	2008-2015	Italy	Retrospective	Right	64	64	N	24	61.3 ± 13.3	63.5 ± 13.5	31.4 ± 2	31.6 ± 2.2	82.8%	85.9%	Side-to-Side Linear Stapler; Isoperistaltic

IA: intracorporeal anastomosis; EA: extracorporeal anastomosis; BMI: body mass index; IHE: Institute of Health Economics

Study or Subgroup	Intracorporeal Events	Intracorporeal Total	Extracorporeal Events	Extracorporeal Total	Weight	Odds Ratio M-H, Random, 95% CI
Allaix 2019	6	70	2	70	7.2%	3.19 [0.62, 16.37]
Anania 2012	2	39	2	33	4.7%	0.84 [0.11, 6.30]
Biondi 2017	0	54	2	54	2.1%	0.19 [0.01, 4.11]
Chaves 2010	3	35	0	25	2.1%	5.49 [0.27, 111.23]
Cheng 2016	0	56	0	29		Not estimable
Erguner 2012	1	15	2	15	3.0%	0.46 [0.04, 5.75]
Fabozzi 2010	0	50	3	50	2.2%	0.13 [0.01, 2.67]
Franklin 2004	0	82	0	10		Not estimable
Grams 2010	0	54	1	51	1.9%	0.31 [0.01, 7.76]
Hanna 2015	4	86	9	109	13.1%	0.54 [0.16, 1.82]
Hellan 2009	1	23	1	57	2.4%	2.55 [0.15, 42.51]
Lee 2013	4	51	2	35	6.2%	1.40 [0.24, 8.12]
Magistro 2013	0	40	0	40		Not estimable
Marchesi 2013	0	28	0	27		Not estimable
Mari 2018	0	30	1	30	1.8%	0.32 [0.01, 8.24]
Milone 2014	12	286	12	226	28.6%	0.78 [0.34, 1.77]
Milone 2018	2	92	1	89	3.3%	1.96 [0.17, 21.96]
Roscio 2012	1	42	1	30	2.4%	0.71 [0.04, 11.78]
Scatizzi 2010	0	40	0	40		Not estimable
Shapiro 2015	1	91	4	100	3.9%	0.27 [0.03, 2.43]
Swaid 2015	1	33	0	19	1.8%	1.80 [0.07, 46.40]
Vergis 2014	1	21	1	29	2.4%	1.40 [0.08, 23.74]
Vignali 2016	2	30	0	30	2.0%	5.35 [0.25, 116.31]
Vignali 2017	3	64	5	64	8.8%	0.58 [0.13, 2.54]
Total (95% CI)		**1412**		**1262**	**100.0%**	**0.84 [0.54, 1.31]**
Total events	44		49			

Heterogeneity: Tau² = 0.00; Chi² = 12.24, df = 18 (P = 0.83); I^2 = 0%
Test for overall effect: Z = 0.77 (P = 0.44)

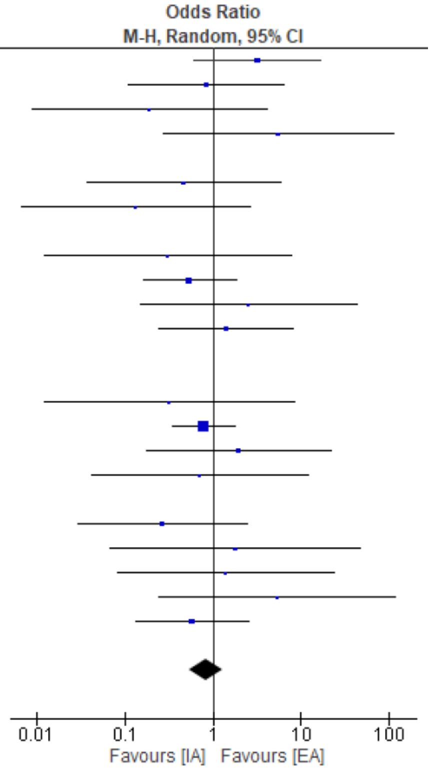


Figure 2. Meta-analysis of anastomotic leakage

by the significant difference in average body mass index (BMI) of the patient cohort included in the study [Table 1][12].

Study characteristics and demographic data

The surgical technique used to perform IA anastomosis was similar in all included studies. A mechanical linear stapler was the method of choice for bowel anastomosis for both intracorporeal and extracorporeal approach, reported in all 24 articles. However, a large variation was noted among published literature for the closure of enterotomies and the length of anastomosis.

The overall mean age, reported in twenty-three articles, was 65.7 years in the IA group and 66.0 years in the EA group. The male to female ratio was 1.1:1 for IA cohort and 1:1 for the EA. The average BMI, reported in 23 papers, was 25.8 kg/m^2 for the IA cohort and 26.0 kg/m^2 for the EA group.

Quality assessment: modified Institute of Health Economics quality appraisal tool

The modified Institute of Health Economics (IHE) quality appraisal tool used is displayed in Supplement Table 1[35]. The assessment was conducted for 21 comparative, non-randomised studies. The mean score was 24.2 (range 21-28) out of a total of 30 points. Study with a score ≥ 26 was considered of high quality.

Meta-analysis

Primary outcome

Anastomotic Leakage: The overall rate of anastomotic leakage [Figure 2] reported in 24 articles was 3.1% (44 cases) for the IA and 3.9% (49 cases) for the EA. The meta-analysis did not reveal a statistically significant difference (OR = 0.84; 95%CI: 0.54-1.31; P = 0.44; I^2 = 0%).

Secondary outcomes

Operative time: The operative time [Figure 3] was reported in 21 studies. It was 10 min longer for IA (MD = 9.99 min; 95%CI: 3.68-16.31; P = 0.002; I^2 = 85%), which was statistically significant.

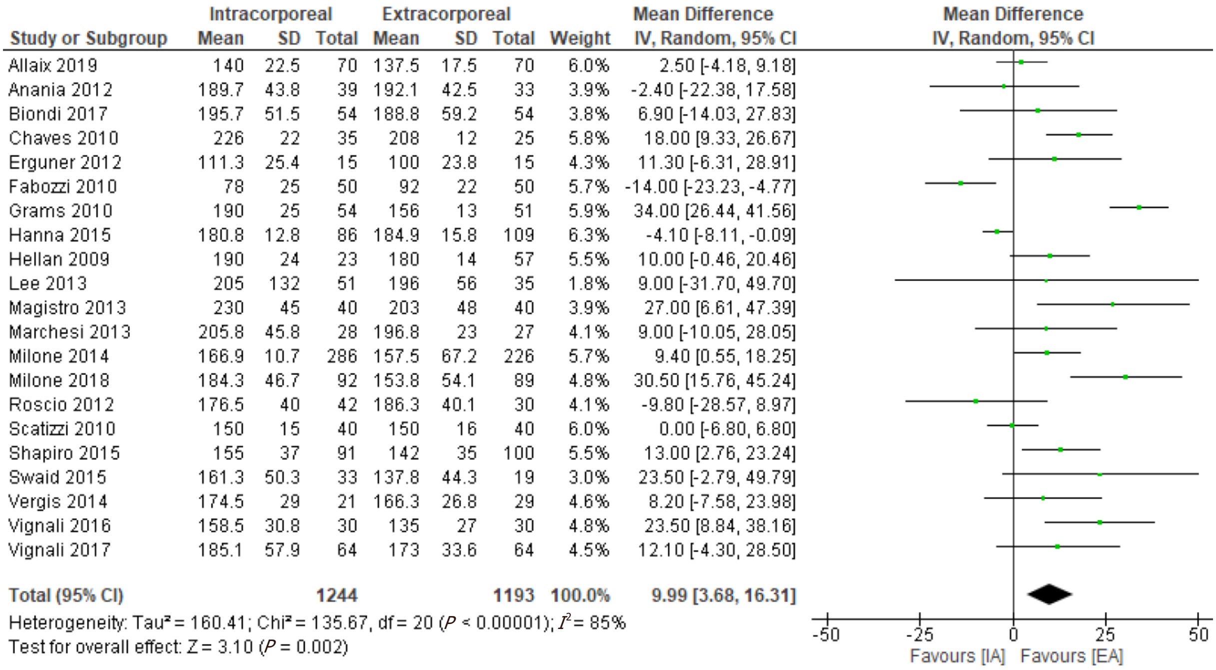


Figure 3. Meta-analysis of operative time

Lymph node harvesting: The number of lymph nodes harvested [Figure 4] in oncological resections was documented in 19 studies. Meta-analysis demonstrated that IA was associated with higher number of lymph nodes harvested (MD = 1.05; 95%CI: 0.19-1.91; P = 0.02; I^2 = 83%). This was statistically significant but with considerable heterogeneity.

Mortality: Mortality was reported in 22 studies [Figure 5]. There were 3 deaths in the IA group and 8 in the EA group. No statistically significant difference was observed between the two groups (OR = 0.56; 95%CI: 0.20-1.58; P = 0.27; I^2 = 0%).

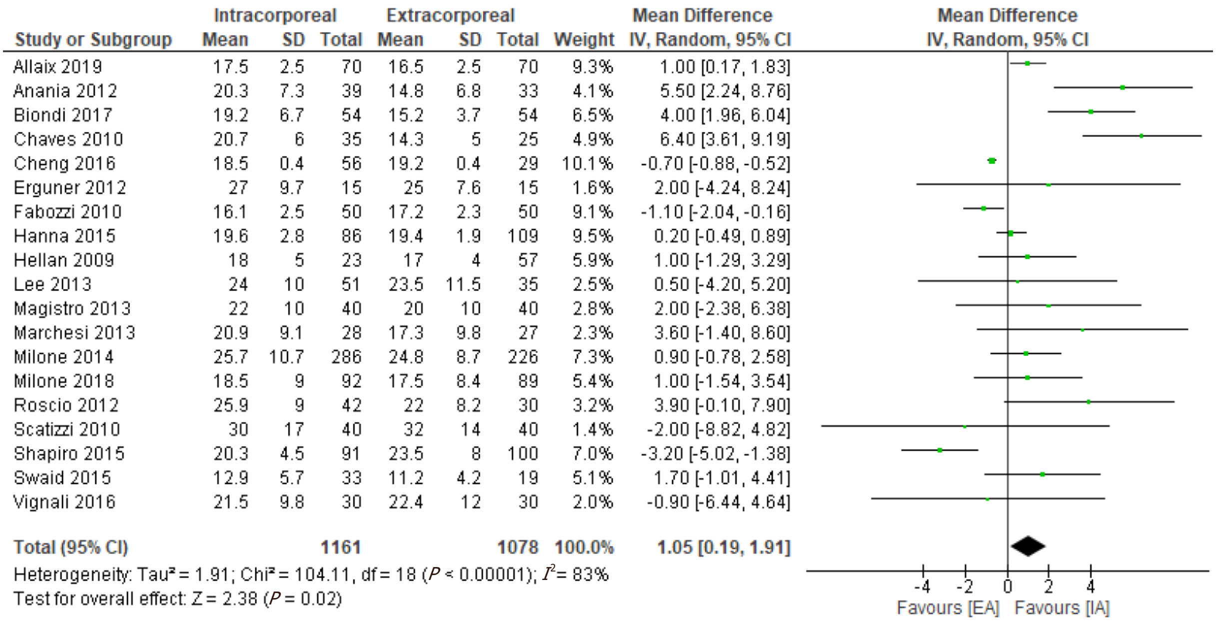
Post-operative surgical complications: The indicators of post-operative complications were comprised of the incidence of surgical site infection, incisional hernia, and the need for re-intervention.

Post-operative surgical site infection [Figure 6] was investigated in 20 studies. The rate of post-operative wound infection was 3.7% (46 cases) in IA and 7.7% (90 cases) in EA. The incidence of post-operative incisional hernia [Figure 7] was evaluated in 12 articles, and the rate of incisional hernia development was 2.8% (17 cases) in IA and 10.9% (67 cases) in EA. Meta-analysis demonstrated that the incidence of surgical site infection (OR = 0.52; 95%CI: 0.31-0.85; P = 0.009; I^2 = 27%) and incisional hernia (OR = 0.30; 95%CI: 0.17-0.53; P < 0.0001; I^2 = 0%) was significantly lower in IA group.

The need for re-intervention [Figure 8] demonstrated no statistically significant difference between the two groups (OR = 0.72; 95%CI: 0.45-1.16; P = 0.18; I^2 = 0%).

Return of bowel function outcomes: Time to first flatus was reported in 13 studies [Figure 9]. The analysis demonstrated that the patients in IA group had faster return to gut function as measured by first flatus [MD = -0.53 days; 95%CI: -0.67-(-0.39); P < 0.00001; I^2 = 56%].

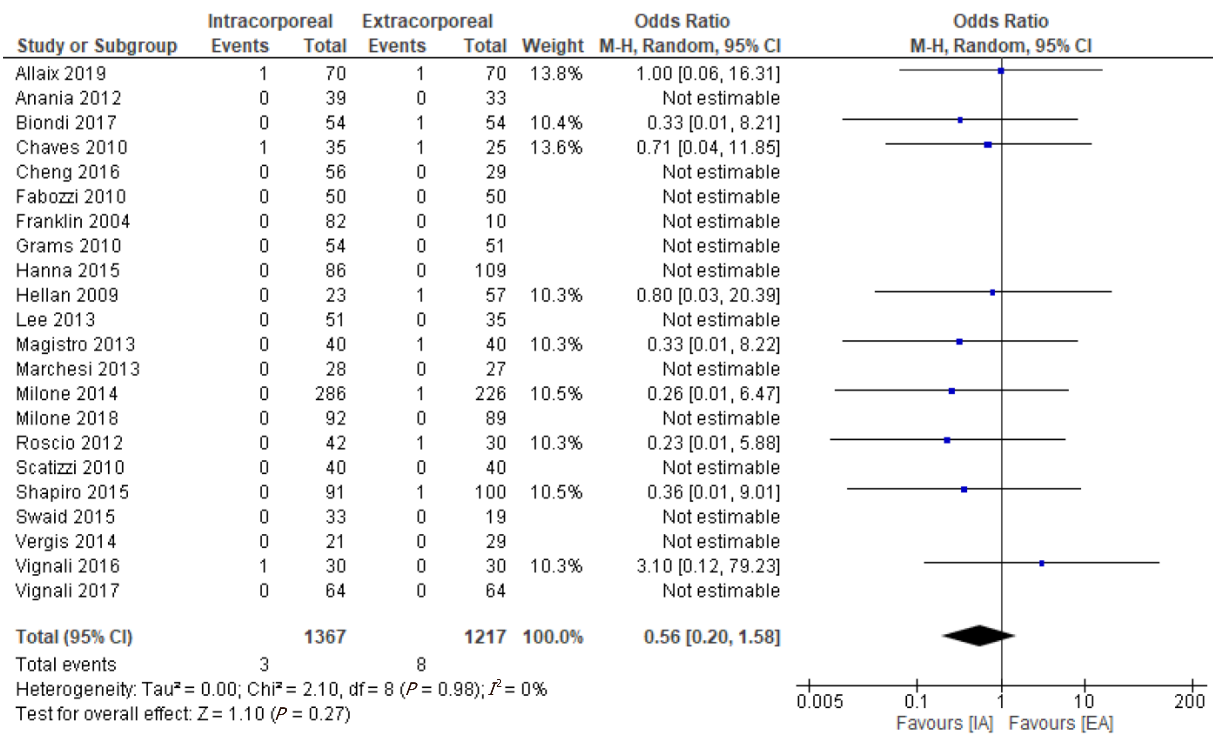
Heterogeneity: The heterogeneity was low for the primary endpoint (i.e., I^2 = 0 for anastomotic leakage). However, it was variable for the secondary outcomes. The heterogeneity was low for mortality, surgical



Study or Subgroup	Intracorporeal Mean	SD	Total	Extracorporeal Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Allaix 2019	17.5	2.5	70	16.5	2.5	70	9.3%	1.00 [0.17, 1.83]
Anania 2012	20.3	7.3	39	14.8	6.8	33	4.1%	5.50 [2.24, 8.76]
Biondi 2017	19.2	6.7	54	15.2	3.7	54	6.5%	4.00 [1.96, 6.04]
Chaves 2010	20.7	6	35	14.3	5	25	4.9%	6.40 [3.61, 9.19]
Cheng 2016	18.5	0.4	56	19.2	0.4	29	10.1%	-0.70 [-0.88, -0.52]
Erguner 2012	27	9.7	15	25	7.6	15	1.6%	2.00 [-4.24, 8.24]
Fabozzi 2010	16.1	2.5	50	17.2	2.3	50	9.1%	-1.10 [-2.04, -0.16]
Hanna 2015	19.6	2.8	86	19.4	1.9	109	9.5%	0.20 [-0.49, 0.89]
Hellan 2009	18	5	23	17	4	57	5.9%	1.00 [-1.29, 3.29]
Lee 2013	24	10	51	23.5	11.5	35	2.5%	0.50 [-4.20, 5.20]
Magistro 2013	22	10	40	20	10	40	2.8%	2.00 [-2.38, 6.38]
Marchesi 2013	20.9	9.1	28	17.3	9.8	27	2.3%	3.60 [-1.40, 8.60]
Milone 2014	25.7	10.7	286	24.8	8.7	226	7.3%	0.90 [-0.78, 2.58]
Milone 2018	18.5	9	92	17.5	8.4	89	5.4%	1.00 [-1.54, 3.54]
Roscio 2012	25.9	9	42	22	8.2	30	3.2%	3.90 [-0.10, 7.90]
Scatizzi 2010	30	17	40	32	14	40	1.4%	-2.00 [-8.82, 4.82]
Shapiro 2015	20.3	4.5	91	23.5	8	100	7.0%	-3.20 [-5.02, -1.38]
Swaid 2015	12.9	5.7	33	11.2	4.2	19	5.1%	1.70 [-1.01, 4.41]
Vignali 2016	21.5	9.8	30	22.4	12	30	2.0%	-0.90 [-6.44, 4.64]
Total (95% CI)			**1161**			**1078**	**100.0%**	**1.05 [0.19, 1.91]**

Heterogeneity: Tau² = 1.91; Chi² = 104.11, df = 18 (*P* < 0.00001); I^2 = 83%
Test for overall effect: Z = 2.38 (*P* = 0.02)

Figure 4. Meta-analysis of lymph node harvesting



Study or Subgroup	Intracorporeal Events	Total	Extracorporeal Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Allaix 2019	1	70	1	70	13.8%	1.00 [0.06, 16.31]
Anania 2012	0	39	0	33		Not estimable
Biondi 2017	0	54	1	54	10.4%	0.33 [0.01, 8.21]
Chaves 2010	1	35	1	25	13.6%	0.71 [0.04, 11.85]
Cheng 2016	0	56	0	29		Not estimable
Fabozzi 2010	0	50	0	50		Not estimable
Franklin 2004	0	82	0	10		Not estimable
Grams 2010	0	54	0	51		Not estimable
Hanna 2015	0	86	0	109		Not estimable
Hellan 2009	0	23	1	57	10.3%	0.80 [0.03, 20.39]
Lee 2013	0	51	0	35		Not estimable
Magistro 2013	0	40	1	40	10.3%	0.33 [0.01, 8.22]
Marchesi 2013	0	28	0	27		Not estimable
Milone 2014	0	286	1	226	10.5%	0.26 [0.01, 6.47]
Milone 2018	0	92	0	89		Not estimable
Roscio 2012	0	42	1	30	10.3%	0.23 [0.01, 5.88]
Scatizzi 2010	0	40	0	40		Not estimable
Shapiro 2015	0	91	1	100	10.5%	0.36 [0.01, 9.01]
Swaid 2015	0	33	0	19		Not estimable
Vergis 2014	0	21	0	29		Not estimable
Vignali 2016	1	30	0	30	10.3%	3.10 [0.12, 79.23]
Vignali 2017	0	64	0	64		Not estimable
Total (95% CI)		**1367**		**1217**	**100.0%**	**0.56 [0.20, 1.58]**
Total events	3		8			

Heterogeneity: Tau² = 0.00; Chi² = 2.10, df = 8 (*P* = 0.98); I^2 = 0%
Test for overall effect: Z = 1.10 (*P* = 0.27)

Figure 5. Meta-analysis of mortality

site infection, incisional hernia, and the need for re-intervention. On the other hand, it was considered substantial for operative time, time to first flatus, and lymph node harvesting.

Meta-regression analysis: Four covariates were assessed to determine their influences on heterogeneity, including median year of patient recruitment, retrospective *vs*. prospective study, study quality, and left

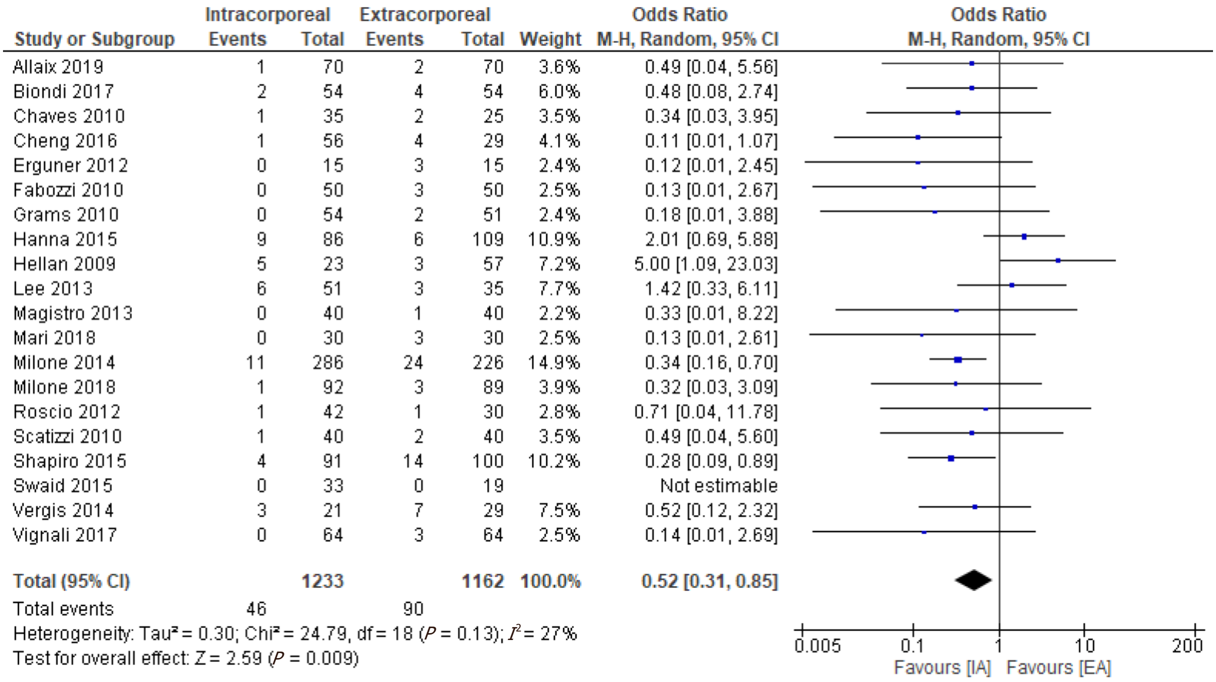


Figure 6. Meta-analysis of surgical site infection

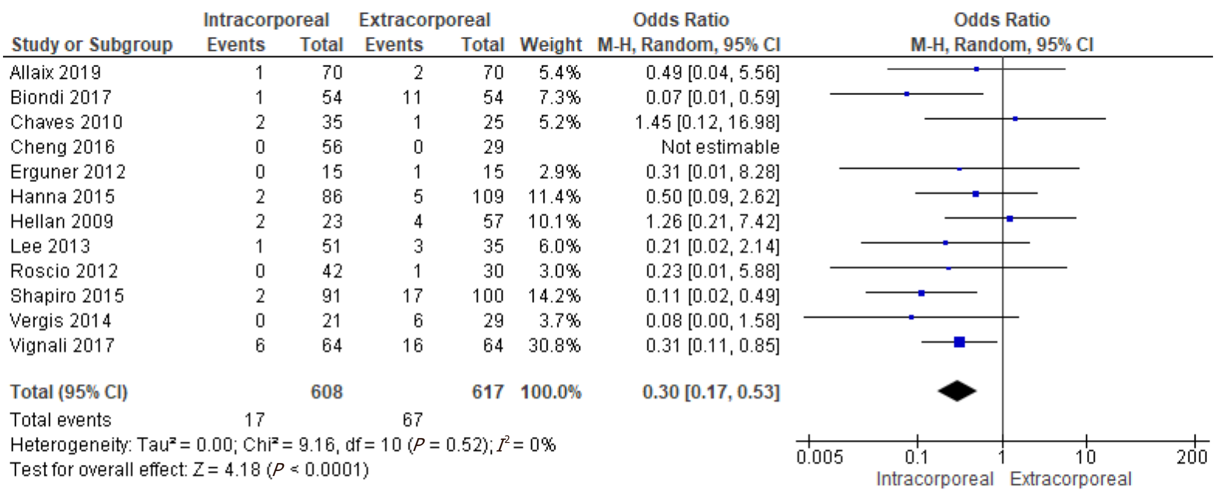


Figure 7. Meta-analysis of incisional hernia

vs. right colectomy. Univariable meta-regression did not identify any of these covariates to be a significant influence for the primary outcome.

Publication bias: No evidence of publication bias was found for the primary outcome (Begg's P = 0.520; Egger's P = 0.640). Visual examination of funnel plots for those outcomes did not demonstrate asymmetry, as evidenced in Figure 10.

Leave-one-out analysis for the primary outcome, anastomotic leakage [Figure 11], was conducted to evaluate the odds ratio when individual studies were removed. No major changes to the results were observed for anastomotic leakage (OR = 0.84; 95%CI: 0.54-1.32).

Study or Subgroup	Intracorporeal Events	Intracorporeal Total	Extracorporeal Events	Extracorporeal Total	Weight	Odds Ratio M-H, Random, 95% CI
Biondi 2017	0	54	1	54	2.2%	0.33 [0.01, 8.21]
Cheng 2016	0	56	0	29		Not estimable
Erguner 2012	1	15	3	15	4.0%	0.29 [0.03, 3.12]
Fabozzi 2010	0	50	5	50	2.6%	0.08 [0.00, 1.52]
Grams 2010	1	54	3	51	4.3%	0.30 [0.03, 3.00]
Hanna 2015	1	86	2	109	3.9%	0.63 [0.06, 7.06]
Hellan 2009	0	23	3	57	2.5%	0.33 [0.02, 6.67]
Magistro 2013	0	40	0	40		Not estimable
Marchesi 2013	1	28	1	27	2.8%	0.96 [0.06, 16.21]
Mari 2018	0	30	1	30	2.2%	0.32 [0.01, 8.24]
Milone 2014	14	286	16	226	41.3%	0.68 [0.32, 1.42]
Milone 2018	4	92	2	89	7.6%	1.98 [0.35, 11.08]
Roscio 2012	1	42	1	30	2.9%	0.71 [0.04, 11.78]
Scatizzi 2010	0	40	0	40		Not estimable
Shapiro 2015	0	91	7	100	2.7%	0.07 [0.00, 1.21]
Swaid 2015	1	33	0	19	2.1%	1.80 [0.07, 46.40]
Vergis 2014	1	21	0	29	2.1%	4.32 [0.17, 111.32]
Vignali 2016	2	30	1	30	3.7%	2.07 [0.18, 24.15]
Vignali 2017	6	64	4	64	13.1%	1.55 [0.42, 5.78]
Total (95% CI)		**1135**		**1089**	**100.0%**	**0.72 [0.45, 1.16]**
Total events	33		50			

Heterogeneity: Tau² = 0.00; Chi² = 11.73, df = 15 (P = 0.70); I^2 = 0%
Test for overall effect: Z = 1.35 (P = 0.18)

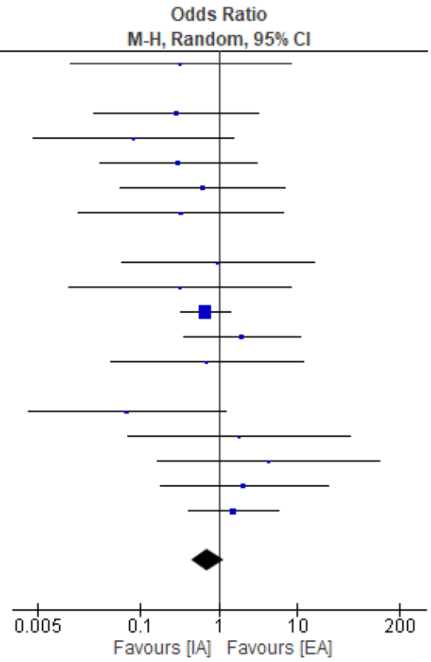


Figure 8. Meta-analysis of need for re-intervention

Study or Subgroup	Intracorporeal Mean	Intracorporeal SD	Intracorporeal Total	Extracorporeal Mean	Extracorporeal SD	Extracorporeal Total	Weight	Mean Difference IV, Random, 95% CI
Allaix 2019	2.25	0.25	70	2.75	0.25	70	17.3%	-0.50 [-0.58, -0.42]
Anania 2012	3.3	1.3	39	3.5	1.3	33	4.0%	-0.20 [-0.80, 0.40]
Biondi 2017	2.5	0.9	54	3.2	1	54	8.1%	-0.70 [-1.06, -0.34]
Fabozzi 2010	3.1	1.2	50	4.4	1.6	50	4.6%	-1.30 [-1.85, -0.75]
Grams 2010	2	1	54	2.4	2	51	4.0%	-0.40 [-1.01, 0.21]
Magistro 2013	2.2	0.6	40	2.6	0.8	40	9.5%	-0.40 [-0.71, -0.09]
Mari 2018	1.8	0.5	30	2.3	0.9	30	7.9%	-0.50 [-0.87, -0.13]
Milone 2014	1.7	1	286	2.3	0.8	226	14.9%	-0.60 [-0.76, -0.44]
Milone 2018	2.6	1.1	92	3.4	1.2	89	8.8%	-0.80 [-1.14, -0.46]
Scatizzi 2010	2	1	40	2	1	40	6.4%	0.00 [-0.44, 0.44]
Swaid 2015	2.9	1.3	33	2.5	1.3	19	2.9%	0.40 [-0.33, 1.13]
Vignali 2016	1.8	0.8	30	2.3	1.2	30	5.1%	-0.50 [-1.02, 0.02]
Vignali 2017	1.8	1.4	64	2.6	1.1	64	6.4%	-0.80 [-1.24, -0.36]
Total (95% CI)			**882**			**796**	**100.0%**	**-0.53 [-0.67, -0.39]**

Heterogeneity: Tau² = 0.03; Chi² = 27.31, df = 12 (P = 0.007); I^2 = 56%
Test for overall effect: Z = 7.58 (P < 0.00001)

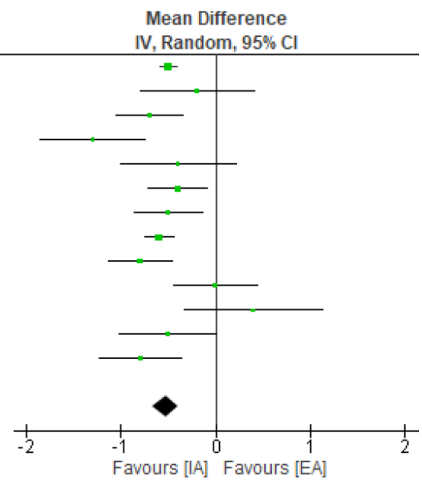


Figure 9. Meta-analysis of time to first flatus

Subgroup analysis on left colectomy

In our systematic review, only three studies were found to have met the search criteria with direct comparison on anastomotic leakage between intracorporeal and extracorporeal anastomosis in left-sided colectomy. After a careful review, only two studies[29,33] were eligible for further analysis, with a total number of 233 patients (125 IA *vs.* 108 EA). A meta-analysis was conducted for the primary outcome of anastomotic leak, which did not demonstrate a significant difference between the two cohorts (OR = 1.90; 95%CI: 0.27-13.21; P = 0.52; I^2 = 0%) [Figure 12]. However, these studies were non-randomised with a lack of long-term follow-up, and it was perceived that further subgroup meta-analysis on left colectomy alone, with Milone *et al.*[29] imposing significantly higher weight (64.4%), would be unlikely to produce meaningful results and therefore was not conducted.

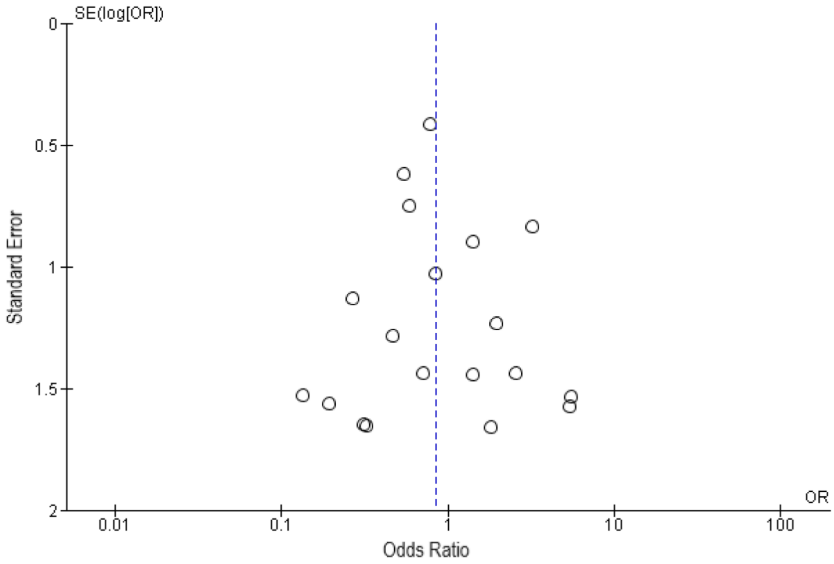


Figure 10. Funnel plot for anastomotic leak

Study	Odds Ratio [95% CI]
Omitting Allaix 2019	OR 0.76 [0.48, 1.20]
Omitting Anania 2012	OR 0.84 [0.54, 1.32]
Omitting Biondi 2017	OR 0.87 [0.56, 1.35]
Omitting Chaves 2010	OR 0.81 [0.52, 1.26]
Omitting Cheng 2016	OR 0.84 [0.54, 1.31]
Omitting Erguner 2012	OR 0.86 [0.55, 1.34]
Omitting Fabozzi 2010	OR 0.88 [0.56, 1.37]
Omitting Franklin 2004	OR 0.84 [0.54, 1.31]
Omitting Grams 2010	OR 0.86 [0.55, 1.34]
Omitting Hanna 2015	OR 0.90 [0.56, 1.44]
Omitting Hellan 2009	OR 0.82 [0.53, 1.28]
Omitting Lee 2013	OR 0.81 [0.52, 1.28]
Omitting Magistro 2013	OR 0.84 [0.54, 1.31]
Omitting Marchesi 2013	OR 0.84 [0.54, 1.31]
Omitting Mari 2018	OR 0.86 [0.55, 1.33]
Omitting Milone 2014	OR 0.87 [0.52, 1.46]
Omitting Milone 2018	OR 0.82 [0.52, 1.28]
Omitting Roscio 2012	OR 0.85 [0.54, 1.32]
Omitting Scatizzi 2010	OR 0.84 [0.54, 1.31]
Omitting Shapiro 2015	OR 0.88 [0.56, 1.38]
Omitting Swaid 2015	OR 0.83 [0.53, 1.29]
Omitting Vergis 2014	OR 0.83 [0.53, 1.30]
Omitting Vignali 2016	OR 0.81 [0.52, 1.26]
Omitting Vignali 2017	OR 0.87 [0.55, 1.38]
Random Effect Model	OR 0.84 [0.54, 1.32]

Figure 11. Leave one out analysis for anastomotic leak

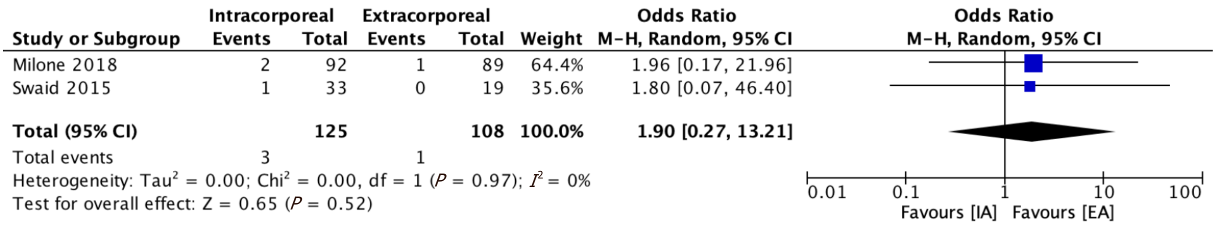


Figure 12. Subgroup meta-analysis of anastomotic leak in left colectomy

DISCUSSION

There is a growing body of evidence in the literature that intracorporeal anastomosis is a safe alternative to extracorporeal anastomosis in laparoscopic right hemicolectomy[3-5]. However, we found that currently published systematic reviews and meta-analyses have not included more recently published studies, and have only compared right sided colectomies, with little research into left colectomies. As a result, we have carried out a new meta-analysis in an attempt to evaluate the clinical and oncological appropriateness of intracorporeal anastomosis technique, combining data on right-sided and left-sided laparoscopic colectomies and including more recently published studies. The strengths of this meta-analysis are that it provides more power to the analysis, allows for identification of more patients in each study arm through meticulous methodology, and offers thorough selection process and critical analysis of the results. To the best of our knowledge, this is the first systematic review with meta-analysis of the literature evaluating comprehensive peri-operative outcomes between IA and EA in a combined fashion including both laparoscopic right and left colectomies. Twenty-four studies were included for analysis, with an overall sample size of 2,674 patients (1,412 in the IA and 1,262 in the EA arm).

In terms of the primary outcome, the analysis supports the surgical safety of performing intracorporeal anastomosis in laparoscopic colectomy, with no statistically significant difference observed for the rate of anastomotic leakage. The quality of data is reinforced by an adequate sample size as well as an absence of heterogeneity and publication bias.

Concerning the secondary outcomes, our results from meta-analysis appear to favour IA when compared to EA, as evidenced by improved patient recovery with earlier return of bowel function, and lower rates of surgical site infections and incisional hernia, all of which were statistically significant. Moreover, this was without compromising oncological safety and short-term mortality.

Since the most common indication for laparoscopic colon resection is malignancy, it is imperative to consider the oncological safety of a surgical technique. We have selected the number of lymph nodes harvested as a surrogate marker for appropriateness of oncological radicality as the data was readily available in the literature but also an area of debate for many years. Our analysis revealed that IA was associated with slightly higher number of lymph nodes harvested. However, we acknowledge that the number of lymph nodes harvested alone does not truly represent the adequacy of oncological resection, and other crucial factors known to determine oncological safety such as clear multi-dimensional resection margins, minimal intraoperative manipulation of the tumour, and wound protection during specimen extraction all need to be considered. Therefore, we believe oncological safety would be better reflected by long-term survival and recurrence outcome. Unfortunately, only two studies, Hanna *et al.*[36] and Lee *et al.*[25], published meaningful long-term survival outcome with Kaplan-Meier graphs. Those studies demonstrated that there was no significant difference in both disease-free survival and overall survival at 5 years and 3 years between IA and EA cohorts respectively.

Our data demonstrated that operative time was significantly longer with the IA technique by 10 min on weighted mean difference when compared to the EA technique. Although this was statistically significant, large variations in operative time reported in included studies were reflected by serious heterogeneity in our analysis (I^2 = 85%). Operative time can be influenced by a multitude of factors beyond technical aspects alone, which may include fat distribution in individual patient, adhesions from previous abdominal surgery, extension of the tumour, and/or experience of individual surgeon to account for the learning curve effect. Unfortunately, however, these potential confounders were not easily identifiable in the available studies.

The lower rates of surgical site infections and incisional hernia observed in the IA cohort may be chiefly attributed to the extraction site. The IA approach allows flexibility when choosing the location of the incision for specimen extraction. In our analysis, the most common extraction site in the IA cohort (described explicitly in 15 studies) was through Pfannenstiel incision on the suprapubic port site, which is well recognised to result in good cosmetic satisfaction with low morbidity, less pain, and lower rates of incisional hernias[37].

The return of bowel function was faster in the IA cohort, which is consistent with the widely accepted theory that patients undergoing IA are expected to undergo reduced manipulation of the colon and mesentery. This notion is gaining considerable attention, especially in the era of growing obese population among surgical patients. A totally laparoscopic approach is thought to minimise traction injuries and risk of micro-lacerations when exteriorising the bowel through thicker abdominal walls, which is known to worsen the outcome in bowel anastomosis[5,17]. However, the paucity in research is reflected by the fact that only one study, Vignali *et al.*[12], 2018, was dedicated to a direct comparison between IA with EA in obese population, which did not demonstrate significant difference between the two groups in terms of peri-operative outcomes, except for the lower incidence of incisional hernia in the IA group. Further studies are thus warranted to validate this notion, which would be valuable for evidence-based safe surgical practice in an obese population.

In addition, there are two growing areas of interest for which IA could provide superior outcomes, robotic surgery and patients undergoing emergency colectomy. A 2020 meta-analysis by Genova *et al.*[38] showed that robotic right colectomy is superior to the laparoscopic approach in terms of length of stay, time to first flatus, and overall rate of complications. Part of this difference was attributed to the rate of IA in robotic colectomy, which was 10 times higher than in laparoscopic colectomy, and when a subgroup analysis was carried out for EA in both groups, the advantages of robotic colectomy disappeared, suggesting that IA may be a strong reason for superior outcome. Di Saverio *et al.*[39] recently published a case series of 59 emergent laparoscopic colectomies with intracorporeal anastomosis, showing that such a technique is feasible and likely safe in acute surgery. The case series demonstrated an anastomotic leak rate of 3.4% and a re-intervention rate of 3.4%, both of which are comparable to the data found by this meta-analysis. This is a novel area that warrants further research.

However, this analysis should not be taken at its face value as it is not without limitations on closer inspection. In terms of the secondary outcomes, the data collected by the studies included in this meta-analysis are overall substantially heterogeneous, making it challenging to draw robust conclusions. The lack of standardised experimental conditions is likely to have impacted on the clinical outcome measures. For example, Anania *et al.*[15] reported that the authors did not standardise the surgical steps of extracorporeal anastomosis in right hemicolectomy, although the intracorporal technique was uniform. Additionally, it is unclear whether some of the peri-operative measures known to improve patient outcomes were implemented. For example, it was unknown if the ERAS (enhanced-recovery-after-surgery) protocol, pre-operative bowel preparation, or prophylactic antibiotics were administered.

Therefore, we suggest that prudential interpretation around clinical significance rather than statistical significance is considered. Most available studies included in our analysis are merely observational without randomisation and are of retrospective design, the quality of which was assessed to be not very high based on IHE assessment.

In conclusion, this systematic review and meta-analysis on the comparative studies between IA and EA in laparoscopic colectomies has demonstrated IA can be safely considered by laparoscopic surgeons for resection of benign and malignant pathology in right and left colon without compromising oncological radicality. However, various limitations in the current data identified by this study need to be addressed by high-quality randomised trials involving longer follow-up.

DECLARATIONS

Authors' contributions

Study conception and design, data acquisition: Park SSW, Smith S
Data analysis and interpretation, drafting the article, critical revision of article, final approval of manuscript: Park SSW, Feng D, Smith S

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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