



Intracorporeal Versus Extracorporeal Anastomosis in Laparoscopic Colectomy: A Meta-Analysis and Systematic Review

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Abstract

Purpose of Review Laparoscopic hemicolectomy (LHC) is widely used to treat benign and malignant colorectal disease. However, the optimal method to restore intestinal continuity is still controversial; hence, this study aims to compare the safety and efficacy of intracorporeal anastomosis (IA) with extracorporeal anastomosis (EA).

Recent Findings Current literature comprises largely of retrospective cohort studies and three significant randomized controlled trials examining the differences between IA and EA in mostly right-sided colectomies. The evidence points to superior intraoperative and postoperative outcomes such as reduced incision length, incidence of wound infection and length of stay for IA, but with incongruous findings on outcomes such as anastomotic leakage and lymph node yield. Likewise, existing meta-analyses have reached differing conclusions about some of these key outcomes.

Summary This paper provides a timely update to existing reviews and shows that IA is associated with superior intraoperative, postoperative and long-term recovery outcomes. We provide more conclusive evidence that lymph node yield for cancer patients is improved in IA. Furthermore, lymph node yield and lowered readmission rate appeared to be more pronounced in patients with higher BMI through regression analysis. Our key recommendation is for surgeons to acquire a high level of proficiency in performing IA to improve patient outcomes.

Keywords Colorectal surgery · Laparoscopic right hemicolectomy · Intracorporeal anastomosis · Extracorporeal anastomosis · Meta-analysis

Introduction

Since its inception in the 1990s [1], laparoscopic hemicolectomy (LHC) is widely acknowledged as the standard of care in the treatment of benign and malignant colorectal diseases. Currently, extracorporeal anastomosis (EA) is the most common technique for anastomotic closure in LHC [2].

It entails exteriorisation of the bowel outside the abdominal cavity, which facilitates visual assessment of bowel viability for anastomosis and decreases the risk of colonic content leakage [3]. However, the increased mesenteric tractions can result in serosal injuries, mesenteric bleeding and devascularisation that contributes to postoperative ileus [4]. This increased traction is further associated with other morbidities such as pain-associated reduction in pulmonary function and wound infections leading to prolonged hospital stay [5–7]. In addition, the midline extraction site, an option chosen more frequently as compared to other sites for the accommodation of the transverse colon extraction in EA, is associated with higher rates of incisional hernias [8].

In contrast, by obviating the need for external bowel mobilisation, intracorporeal anastomosis (IA) confers notable advantages such as a decreased risk of ileus [4]. Moreover, a midline extraction site is not a requirement for IA. However, IA is known to be technically demanding as it

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requires a mastery of skills in laparoscopic surgery especially in hand-sewn suturing [9]. Other drawbacks include an inability to perform bowel palpation prior to transection as well as exposure of peritoneum to potential intraluminal contamination [10]. Nevertheless, a majority of previous meta-analyses that compared IA and EA showed better postoperative recovery and fewer complications [11, 12, 13, 14, 15, 16] when IA is used.

However, existing meta-analysis have not extensively analysed clinically important outcomes such as lymph node yield and have reached differing conclusions about the impact of IA on anatomic leak rates [16]. This review provides an updated comparison between IA and EA by including papers published in the previous 2 years, utilising a more comprehensive search that comprises both right- and left-sided, robotic assisted, and laparoscopic hemicolectomies, and analysing hitherto unreported outcomes such as lymph node yield. Sensitivity analysis was conducted, when appropriate (at least two papers in a subgroup is required), to reduce biases and better estimate the true effect-size. Meta-regression which was lacking in previous reviews was used to examine the potential sources of heterogeneity in our findings and to identify patient characteristics most suited for IA.

Materials and Methods

Search Strategy

This systematic review and meta-analysis follows the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines [17]. Relevant articles were identified by searching Medline, Embase and Cochrane electronic databases from inception through 21 September 2020. Search terms consisted of MeSH terms and keywords relating to “Colectomy” or “Laparoscopy” or “Intracorporeal anastomosis” and “Extracorporeal anastomosis”. The detailed search strategies are presented in Online Resource 1. All relevant abstracts were imported into EndNote X9 and duplicates were removed.

Criteria for the Selection of Studies

Studies were eligible for inclusion if (1) patients underwent elective laparoscopic or robotic right- or left-sided hemicolectomies, (2) studies compared outcomes of interest between intracorporeal and extracorporeal anastomosis, (3) studies were randomized controlled trials (RCTs) or observational studies (cohort and case-control studies only), and (4) written in the English language. Studies were excluded if they (1) were review articles,

conference abstracts, non-human studies, case reports, or cross-sectional studies; (2) included emergency surgeries; (3) lacked comparison between intracorporeal and extracorporeal anastomosis; (4) included only open surgery in comparison; (5) did not analyse postoperative complications; or (6) were written in languages apart from the English language.

Intraoperative, postoperative and long-term recovery outcomes were extracted and analysed. Intraoperative outcomes included operation time, incision size, conversion to open surgery, number of lymph nodes harvested and intraoperative blood loss. A broad range of postoperative complications were examined, encompassing anastomotic leak rate, surgical site infections, dehiscence, intra-abdominal abscess, pneumonia, deep vein thrombosis, pulmonary embolism, acute myocardial infarction, overall bleeding, anastomotic bleeding, intra-abdominal bleeding, gastrointestinal bleeding, evisceration, ileus, bowel obstruction, *Clostridioides difficile* colitis, postoperative blood transfusions, urinary tract infections, urinary retention, reoperations, time to oral feeding, time to bowel movement, time to flatus, time to mobilisation, time to intestinal recovery and length of hospital stay. Long-term recovery outcomes comprised incidence of hernia formation and readmissions.

Data Extraction and Assessment of Quality

Predefined data were extracted from the selected articles into a structured proforma by TL and SAU independently. Data extracted from each paper included the general information of the study (author’s name, article title, publication year, geographical region of the study, study design and indication for surgery), patient demographics (age, gender and body mass index (BMI)), clinical characteristics, operative details and outcomes of interest, as defined above. For continuous outcomes where mean and SD were not available, available data were transformed according to existing formulae; median and range were transformed using formulae of Hozo et al. [18], while median and interquartile range were transformed using calculations formulae of Wan et al. [19]. Quality assessment for the included articles was done by two independent authors using the Newcastle–Ottawa Quality Assessment Form for Cohort Studies [20] and the Jadad Scale [21] for clinical trials. The Newcastle–Ottawa Quality Assessment Form for Cohort Studies [20] is designed to assess the quality of nonrandomised studies in meta-analyses and evaluates studies on three domains: the selection of the study groups; the comparability of the groups; the outcome of interest for cohort studies. The Jadad scale [21] for randomised controlled trials is created to assess the

methodological quality of a clinical trial, by assessing the effectiveness of blinding.

Statistical Analysis

Meta-analyses and sensitivity analyses were performed with Cochrane Review Manager 5.3 [22] while meta-regression analyses were conducted using RStudio [23]. OR and corresponding 95% CIs were calculated for dichotomous variables while weighted mean differences (WMD) and corresponding 95% CI were calculated for continuous variables. The DerSimonian–Laird (DL) random-effects method [24] was then used to estimate pooled ORs and pooled WMDs regardless of inter-study heterogeneity as assessed by Cochran Q statistics and I^2 statistics. Significance was determined by $p < 0.05$. Studies were characterised based on study type (RCT or observational study) and location of colectomy (right or left sided) for sensitivity analyses in several outcomes including lymph node yield, anastomotic leak rate, reoperations and readmissions. Meta-regression analyses were subsequently conducted for selected outcomes with variance estimates obtained using the DL approach and

Knapp–Hartung method. Publication bias was assessed by visual inspection of funnel plots (Online Resource 2).

Results

Study and Patient Characteristics

A summary of the study selection process can be found in Fig. 1. The search strategy yielded 579 records, of which the full texts of 367 manuscripts were evaluated. Forty-one retrospective cohort studies [25–65], three RCTs [66••, 67, 68] and three case–control studies [69–71] that fulfilled the predefined inclusion criteria were incorporated for final analysis, with 19 studies from Italy, 13 from the USA, three studies from Canada, two from Spain, two from Israel, and one each from France, China, Japan, Poland, Romania, Turkey, Argentina and Portugal. These 47 articles reported on 7001 patients of which 3152 underwent IA (45%) and 3849 underwent EA (55%). The key characteristics and quality assessments of included studies as well as demographic and operative variables of the patient population are detailed in Table 1. Most patients

Fig. 1 PRISMA flow diagram

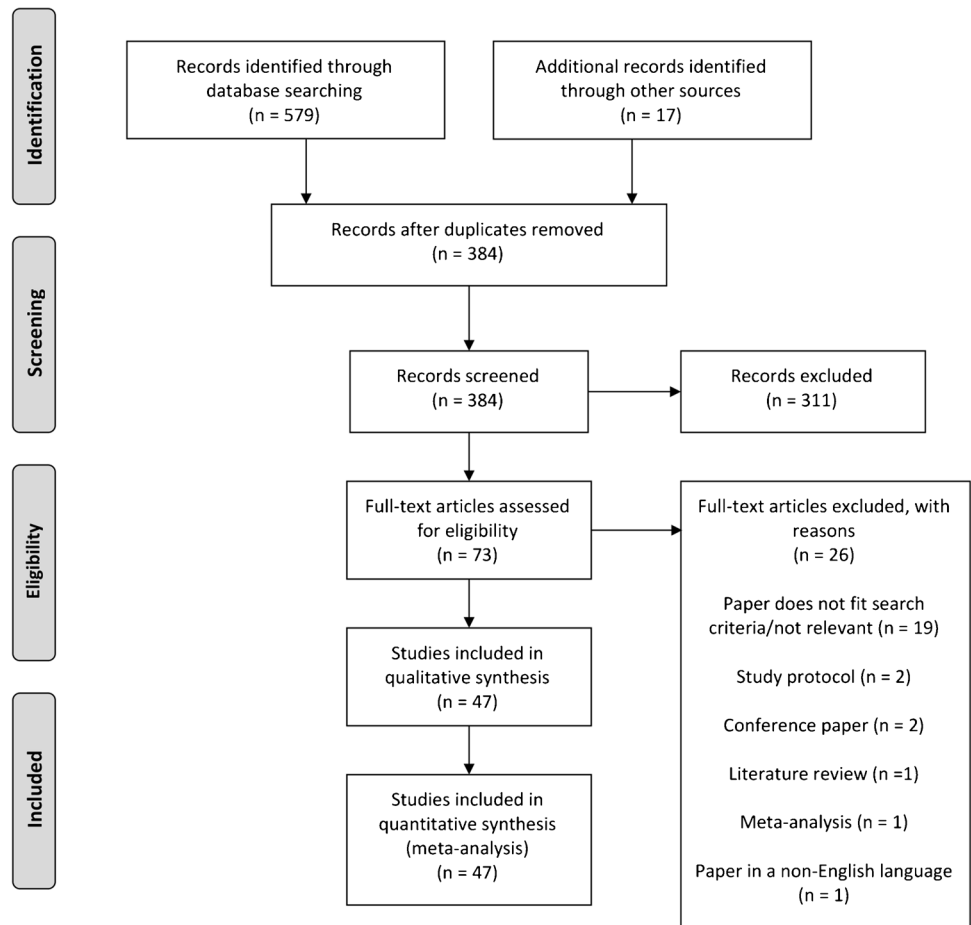


Table 1 Patient demographics, clinical characteristics and study details

Author	Year	Country	Study characteristics	Location of colectomy	Type of anastomosis	Procedure (Robo vs. Lap)	No. of patients	Sex (M)	BMI (kg/m ²)	Benign disease	Malignant disease	Quality assessment
Akram et al. [1]	2018	USA	Retrospective PSM comparison	RS	IA	R	55	0.5	27.600	25	30	8*
Allaix et al. [2]	2019	Italy	Randomised controlled trial	RS	EA	R	55	0.6	27.964	25	30	5 [#]
Anania et al. [3]	2012	Italy	Retrospective cohort study	RS	EA	L	70	0.557	25.030	16	54	7*
Arredondo et al. [4]	2010	Spain	Case-control study	RS	EA	L	70	0.586	25.767	9	61	7*
Bollo et al. [5]	2019	Spain	Randomised controlled trial	RS	EA	L	39	0.615	26.300	14	25	7*
Saleh et al. [6]	2020	France	Retrospective cohort study	RS	EA	L	33	0.606	28.100	11	22	7*
Carlini et al. [7]	2016	Italy	Retrospective cohort study	SFR	EA	L	35	0.54	25.900	13	22	7*
Cleary et al. [8]	2018	USA	Retrospective cohort study	RS	EA	R+L [†]	25	0.56	26.700	7	18	4 [#]
Fagarasan et al. [9]	2020	Romania	Retrospective cohort study	RS	EA	R+L [‡]	69	0.493	27.400	0	69	6*
Franklin et al. [10]	2004	USA	Retrospective cohort study	RS	EA	L	70	0.557	26.300	0	70	6*
Grams et al. [11]	2010	USA	Retrospective cohort study	MX	EA	L	150	0.61	26.000	33	117	7*
Grieco et al. [12]	2019	Italy	Retrospective cohort study	SFR	EA	L	447	0.48	24.000	114	333	6*
Hanna et al. [13]	2016	USA	Retrospective cohort study	RS	EA	L	9	NR	NR	0	9	6*
Hellian et al. [14]	2009	USA	Retrospective cohort study	RS	EA	L	11	NR	NR	0	11	7*
Jian-Cheng et al. [15]	2016	China	Retrospective cohort study	RS	EA	L	379	0.475	29.600	198	178	7*
Kayano et al. [16]	2019	Japan	Retrospective cohort study	MX	EA	L	650	0.514	28.200	345	298	7*
Kelley et al. [17]	2018	USA	Retrospective cohort study	RS	EA	L	8	NR	NR	NR [§]	NR [§]	7*
Krouchev et al. [18]	2018	Canada	Retrospective cohort study	RS	EA	L	8	NR	NR	NR	NR	7*
Kwiatkowski et al. [19]	2019	Poland	Retrospective cohort study	RS	EA	L	82	NR	NR	0	82	7*
							10	NR	NR	0	10	7*
							54	0.352	23.800	41	13	7*
							51	0.549	23.400	36	15	8*
							36	0.528	25.300	0	36	7*
							36	0.639	26.000	0	36	7*
							86	0.477	26.200	30	56	7*
							109	0.422	25.567	52	57	7*
							23	0.696	29.300	6	17	8*
							57	0.509	28.667	19	38	8*
							56	0.571	20.300	0	56	8*
							29	0.69	20.600	0	29	8*
							44	0.5	22.400	0	44	8*
							61	0.508	22.500	0	61	8*
							27	0.63	28.000	6	21	8*
							87	0.38	27.00	20	67	7*
							18	0.667	NR	0	18	7*
							56	0.554	NR	0	56	7*
							51	0.608	27.900	8	43	7*
							34	0.647	27.600	6	28	7*

Table 1 (continued)

Author	Year	Country	Study characteristics	Location of colectomy	Type of anastomosis	Procedure (Robo vs. Lap)	No. of patients	Sex (M)	BMI (kg/m ²)	Benign disease	Malignant disease	Quality assessment
Lee et al. [20]	2013	USA	Retrospective cohort study	RS	IA	L	51	0.49	25.700	0	51	8*
Lujan et al. [21]	2018	USA	Retrospective cohort study	RS	EA	L	35	0.371	25.400	0	35	8*
Magistro et al. [22]	2013	Italy	Retrospective cohort study	RS	EA	R	89	0.539	28.400	42	47	8*
Malerba et al. [23]	2020	Italy	Retrospective cohort study	RS	EA	L	135	0.452	27.100	53	82	7*
Mari et al. [24]	2018	Italy	Retrospective cohort study	RS	EA	L	40	0.5	24.800	0	40	7*
Martinek et al. [25]	2018	USA	Retrospective cohort study	RS	EA	L	30	0.45	23.900	0	40	9*
Milone et al. [26]	2018	Italy	Retrospective cohort study	LS	EA	L	29	NR	NR	NR [§]	NR [§]	9*
Milone et al. [27]	2015	Italy	Retrospective cohort study	RS	EA	L	30	NR	NR	NR [§]	NR [§]	9*
Morpurgo et al. [28]	2013	Italy	Case-control study	RS	EA	L	30	0.633	24.300	0	30	7*
Rawlings et al. [29]	2007	USA	Retrospective cohort study	RS	EA	L	30	0.533	26.100	0	30	6*
Reitz et al. [30]	2018	USA	Retrospective cohort study	RS	EA	L	195	0.426	28.600	56	139	6*
Scatizzi et al. [31]	2010	Italy	Case-control study	RS	EA	L	195	0.446	27.400	47	148	6*
Scotton et al. [32]	2018	Italy	Retrospective cohort study	RS	EA	L	92	0.587	29.500	0	92	6*
Shapiro et al. [33]	2016	Israel	Retrospective cohort study	RS	EA	L	89	0.528	24.700	0	89	7*
Swaid et al. [34]	2016	Israel	Retrospective cohort study	LS	EA	L	286	0.507	25.200	0	286	7*
Trastulli et al. [35]	2015	Italy	Retrospective cohort study	RS	EA	L	226	0.531	25.400	0	226	6*
Vergis et al. [36]	2015	Canada	Retrospective cohort study	RS	EA	L	48	0.563	25.000	0	48	6*
Vignali et al. [37]	2016	Italy	Randomised controlled trial	RS	EA	L	48	0.333	28.000	0	48	7*
Vignali et al. [38]	2017	Italy	Retrospective cohort study	RS	EA	L	17	0.471	25.700	14	3	6*
							15	0.4	28.300	9	6	7*
							29	0.38	30.300	17	12	6*
							20	0.5	28.800	8	12	6*
							40	0.45	27.000	0	40	8*
							40	0.475	28.000	0	40	8*
							206	0.52	26.000	0	206	8*
							160	0.5	25.600	0	160	8*
							91	0.418	27.800	21	70	9*
							100	0.48	26.900	30	70	9*
							33	0.667	25.400	0	33	6*
							19	0.421	25.000	0	19	6*
							40	0.625	26.600	8	32	7*
							94	0.553	25.400	6	88	7*
							21	0.619	27.670	NR [§]	NR [§]	8*
							29	0.448	28.640	NR [§]	NR [§]	8*
							30	0.54	24.600	0	30	4#
							30	0.46	24.800	0	30	4#
							64	0.672 [¶]	31.400 [¶]	11	53	7*
							64	0.672 [¶]	31.600 [¶]	9	55	7*

Table 1 (continued)

Author	Year	Country	Study characteristics	Location of colectomy	Type of anastomosis	Procedure (Robo vs. Lap)	No. of patients	Sex (M)	BMI (kg/m ²)	Benign disease	Malignant disease	Quality assessment
Widmar et al. [39]	2018	USA	Retrospective cohort study	RS	IA	R	67	0.42	NR	8	59	8*
Fabozzi et al. [40]	2010	Italy	Retrospective cohort study	RS	EA	R	97	0.48	NR	15	82	9*
Erguner et al. [41]	2012	Turkey	Retrospective cohort study	RS	EA	L	50	0.42	21.400	0	50	9*
Roscio et al. [42]	2012	Italy	Retrospective cohort study	RS	EA	L	15	0.34	22.100	0	50	8*
Uriburu et al. [43]	2016	Argentina	Retrospective cohort study	RS	EA	L	15	0.533	27.000	0	15	8*
Biondi et al. [44]	2017	Italy	Retrospective cohort study	RS	EA	L	15	0.467	25.75	0	15	8*
Gil et al. [45]	2018	Portugal	Retrospective cohort study	RS	EA	L	42	0.5	26.000	0	42	8*
Anania et al. [46]	2020	Italy	Retrospective cohort study	RS	EA	L	30	0.4	26.300	0	30	8*
Trepanier et al. [47]	2019	Canada	Retrospective cohort study	RS	EA	L	30	0.4	28.260	10	15	8*
							28	0.357	28.540	9	14	8*
							54	0.574	25.620	6	48	8*
							54	0.519	26.340	6	48	8*
							31	0.548	NR	NR [§]		7*
							84	0.548	NR	NR [§]		7*
							80	0.5	25.783	0	80	8*
							69	0.594	25.617	0	69	8*
							61	0.475	26.000	23	38	7*
							124	0.524	25.600	39	85	7*

Data are reported as mean

BMI, body mass index; EA, extracorporeal anastomosis; IA, intracorporeal anastomosis; L, laparoscopic; LS, left sided; M, male; MX, mixed; NR, not reported; RS, right sided; R, robotic; SFR, splenic flexure resection

*Newcastle–Ottawa Scale (NOS) for non-randomised cohort and case–control studies in meta-analysis (0–3: high risk of bias; 4–6: moderate risk of bias; 7–9: low risk of bias)

#Jadad Scale for reporting Randomised Control Trials (0: very poor–5: rigorous)

¶Vignali 2017 included only obese patients (body mass index > 30 kg/m²) in their study population

†R (335)+L (44)

‡R (253)+L (397)

§No breakdown of the number of patients with benign and malignant diseases was provided

underwent hemicolectomy for benign growths, malignant neoplasia or inflammatory bowel disease.

Complications between Patients in IA Group versus EA Group

Full results for all intraoperative, postoperative and long-term recovery outcomes are reported in Table 2. Key results are further detailed below.

Intraoperative Complications

Pooled analysis of 6570 patients (42 studies; 2957 with IA and 3613 with EA) revealed a significantly longer operative time in the IA group compared to the EA group ($p < 0.01$; WMD = 13.32 min; 95% CI, 6.57 to 20.06, $I^2 = 92\%$). Among the 2467 patients (21 studies; 1187 with IA and 1280 with EA) evaluated, a significantly smaller incision size was found in the IA group compared to the EA group ($p < 0.01$; WMD = -2.21 cm; 95% CI, -2.85 to -1.58 ,

Table 2 Summary of comparative meta-analysis

Outcome	OR/WMD (95% CI)	<i>P</i> value	<i>I</i> ² (%)	Favours
Intraoperative outcomes				
Operation time (min)	13.32 (6.57 to 20.06)	<0.01	92	EA
Incision size (cm)	-2.21 (-2.85 to -1.58)	<0.01	97	IA
Conversion to open	0.33 (0.24 to 0.46)	<0.01	56	IA
Blood loss (ml)	-15.73 (-21.53 to -9.93)	<0.01	49	IA
Lymph nodes harvested	1.29 (0.46 to 2.12)	<0.01	72	IA
Postoperative complications				
Anastomotic leakage	0.60 (0.42 to 0.87)	<0.01	0	IA
SSI and wound infection	0.62 (0.49 to 0.78)	<0.01	21	IA
Intra-abdominal abscess	0.71 (0.36 to 1.41)	0.33	0	NS
Ileus	0.76 (0.56 to 1.03)	0.07	23	NS
Bowel obstruction	0.55 (0.29 to 1.06)	0.07	0	NS
Postoperative blood transfusions	0.92 (0.53 to 1.63)	0.79	0	NS
Clavien–Dindo (grade 4 to 5)	0.75 (0.34 to 1.68)	0.49	0	NS
Dehiscence	5.49 (0.27 to 111.23)	0.27	NA	NS
Pneumonia	0.70 (0.25 to 1.96)	0.50	0	NS
Deep vein thrombosis	0.40 (0.06 to 2.58)	0.34	0	NS
Pulmonary embolism	0.9 (0.09 to 8.79)	0.93	0	NS
Acute myocardial infarction	1.07 (0.25 to 4.55)	0.92	0	NS
Bleeding	0.9 (0.61 to 1.33)	0.60	0	NS
Anastomotic bleeding	0.92 (0.34 to 2.44)	0.86	0	NS
Intra-abdominal bleeding	2.93 (0.12 to 72.99)	0.51	NA	NS
Gastrointestinal bleeding	0.27 (0.09 to 0.83)	0.02	0	IA
Evisceration	1.81 (0.12 to 28.31)	0.67	48	NS
<i>Clostridioides difficile</i> colitis	0.42 (0.09 to 1.98)	0.27	0	NS
Urinary tract infection	0.72 (0.23 to 2.23)	0.57	25	NS
Urinary retention	0.94 (0.37 to 2.39)	0.90	0	NS
Reoperations	0.60 (0.40 to 0.91)	0.02	0	IA
Time to oral feeding (days)	-0.74 (-1.09 to -0.39)	<0.01	73	IA
Time to first bowel movement (h)	-15.04 (19.11 to -10.96)	<0.01	71	IA
Time to first flatus (h)	-8.28 (-12.07 to -4.50)	<0.01	83	IA
Time to mobilisation (days)	-0.28 (-0.55 to -0.01)	0.04	79	IA
Time to intestinal recovery (days)	-1.12 (-2.29 to 0.06)	0.06	98	NS
Length of stay (days)	-0.83 (-1.08 to -0.57)	<0.01	67	IA
Long-term recovery outcomes				
Hernia	0.28 (0.18 to 0.44)	<0.01	0	IA
Readmissions	0.57 (0.37 to 0.89)	0.01	0	IA

EA, extracorporeal anastomosis; IA, intracorporeal anastomosis; NA, not applicable; NS, not significant; WMD, weighted mean difference

$I^2 = 97\%$). Evaluation of 4509 patients (24 studies; 2081 with IA and 2428 with EA) revealed that IA was associated with a significantly lower odds of conversion to open surgery compared to EA ($p < 0.01$; OR = 0.33; 95% CI, 0.24 to 0.46, $I^2 = 56\%$). Assessment of 3386 patients (21 studies; 1479 with IA and 1907 with EA) revealed a lower estimated blood loss for patients in the IA group compared with the EA group ($p < 0.01$; WMD = -15.73 ml; 95% CI, -21.53 to -9.93, $I^2 = 49\%$).

The number of lymph nodes harvested in pooled analysis of 3394 patients (25 studies; 1706 with IA and 1688 with EA) undergoing colectomy for colon cancer was significantly higher in the IA group compared with the EA group ($p < 0.01$; WMD = 1.29; 95% CI, 0.46 to 2.12, $I^2 = 72\%$; Fig. 2). Sensitivity analysis of right-sided colectomies confirmed that lymph node yield was greater in the IA groups ($p < 0.01$; WMD = 1.33; 95% CI, 0.43 to 2.22, $I^2 = 74\%$; Online Resource 4 (Supplementary Fig. 2b)).

Postoperative Complications

Analysis of 5839 patients (33 studies; 2579 with IA and 3260 with EA) showed a significantly lower odds of anastomotic leakage in the IA group compared to the EA group ($p < 0.01$; OR = 0.60; 95% CI, 0.42 to 0.87, $I^2 = 0\%$; Fig. 3). However, sensitivity analysis of three RCTs revealed no

significant difference in the odds of anastomotic leakage between the two approaches ($p = 0.47$; OR = 1.63; 95% CI, 0.43 to 6.22, $I^2 = 34\%$; Online Resource 4 (Supplementary Fig. 3c)). The odds of surgical site and wound infection among 6342 patients (38 studies; 2759 with IA and 3583 with EA) was lower in the IA group compared with the EA group ($p < 0.01$; OR = 0.62; 95% CI, 0.49 to 0.78, $I^2 = 21\%$; Fig. 4). The odds of other postoperative complications including intra-abdominal abscess, postoperative ileus, bowel obstruction, postoperative blood transfusion and grade 4 to 5 Clavien–Dindo complications were found to be similar in both groups. Out of 436 patients (4 studies; 193 with IA and 243 with EA) evaluated, the odds of gastrointestinal (GI) bleeding was found to be lower in the IA group compared to the EA group ($p = 0.02$; OR = 0.27; 95% CI, 0.09 to 0.83, $I^2 = 0\%$). Investigation of 3356 patients (18 studies; 1417 with IA and 1939 with EA) revealed that patients in the IA group had a significantly lower odds of undergoing reoperation compared with the EA group ($p = 0.02$; OR = 0.60; 95% CI 0.39 to 0.92, $I^2 = 0\%$; Online Resource 4 (Supplementary Fig. 5b)). Sensitivity analysis of right-sided colectomies likewise indicated reduced odds of reoperations in the IA group ($p = 0.02$; OR = 0.60; 95% CI 0.39 to 0.92, $I^2 = 0\%$; Online Resource 4 (Supplementary Fig. 5b)). Sensitivity analysis with solely RCTs was not possible because only Bollo et al. reported reoperation rates [72].

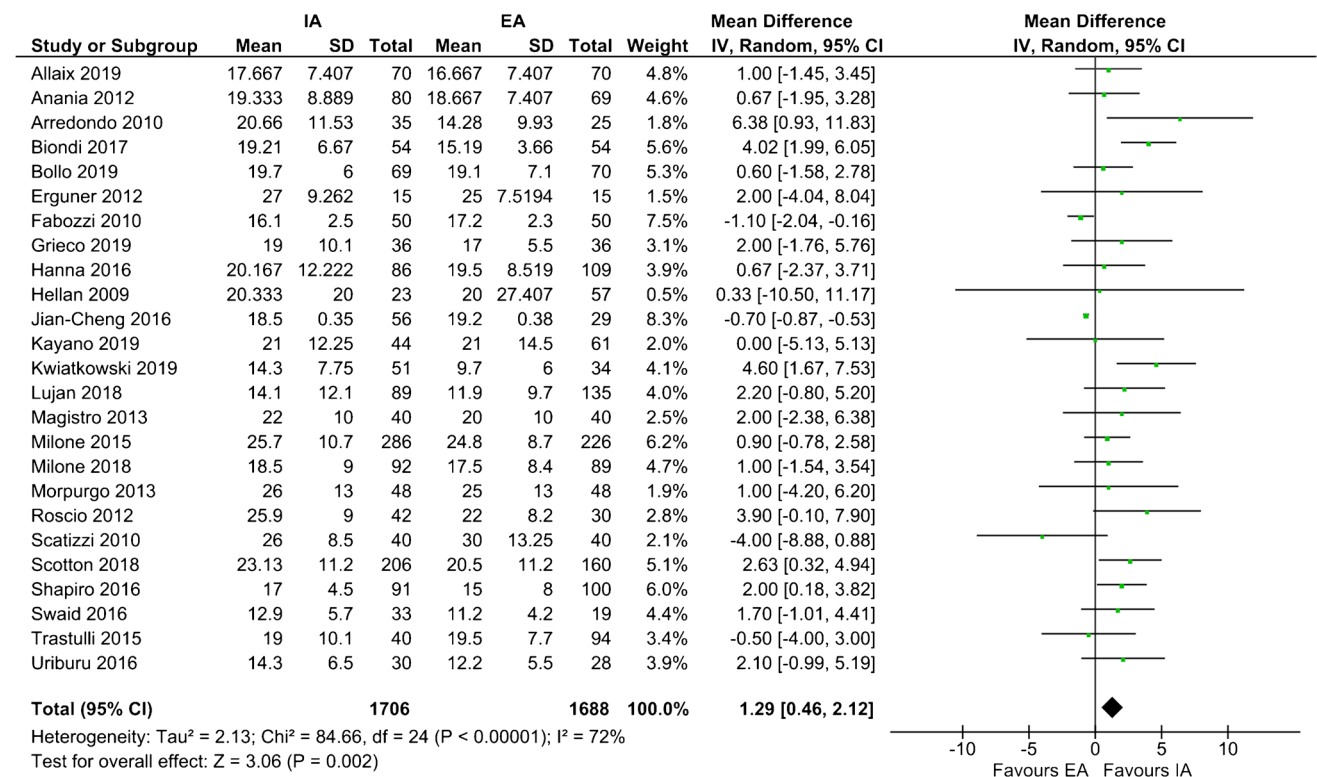
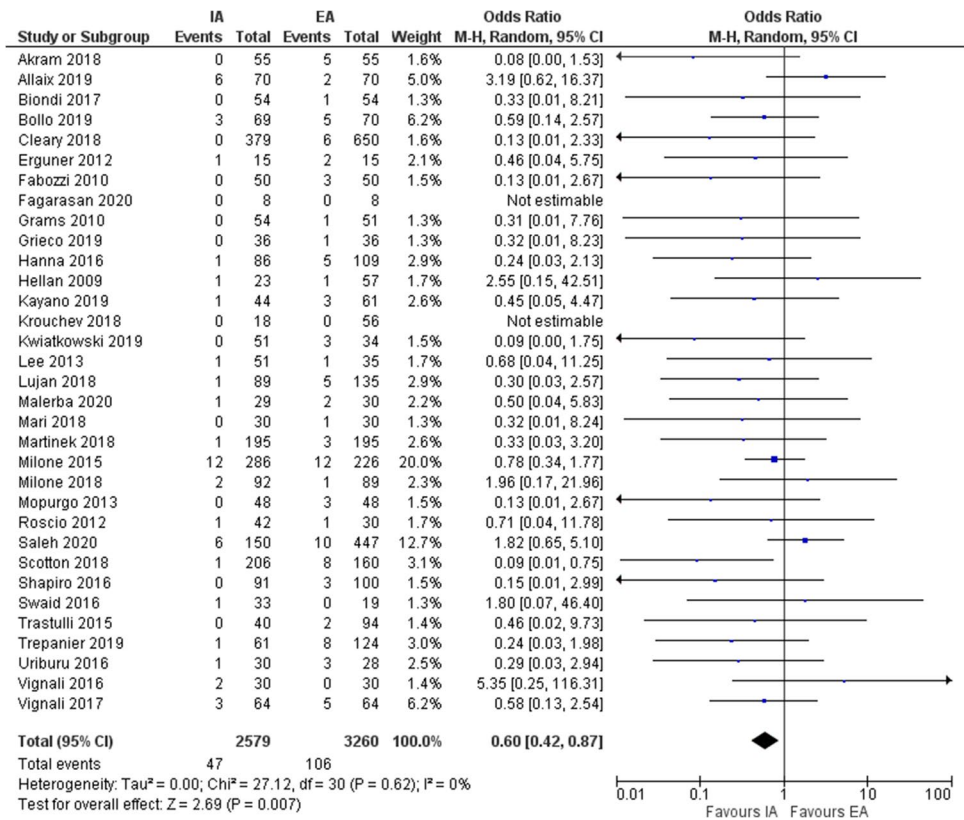


Fig. 2 Meta-analysis of lymph node yield

Fig. 3 Meta-analysis of anastomotic leak



Analysis of 2079 patients (13 studies; 862 with IA and 1217 with EA) revealed that IA was associated with a shorter time to oral feeding compared with EA ($p < 0.01$; WMD = -0.74 days; 95% CI, -1.09 to -0.39 , $I^2 = 73%$). Among the 4059 patients (22 studies; 1722 with IA and 2337 with EA), it was observed that a significantly shorter time to first bowel movement was found in the IA group compared to the EA group ($p < 0.01$; WMD = -15.04 h; 95% CI, -19.11 to -10.96 , $I^2 = 71%$). Pooled analysis of 3584 patients (24 studies; 1620 with IA and 1964 with EA) revealed that IA patients experienced significantly shorter time to first flatus compared to the EA patients ($p < 0.01$; WMD = -8.28 h; 95% CI, -12.07 to -4.50 , $I^2 = 83%$). Evaluating 1362 patients (4 studies; 564 with IA and 798 with EA), a significantly shorter time to mobilisation was found in the IA group compared with the EA group ($p = 0.04$; WMD = -0.28 days; 95% CI, -0.55 to -0.01 , $I^2 = 79%$). Investigations of 5848 patients (40 studies; 2534 with IA and 3314 with EA) revealed that IA was associated with a significantly shorter length of stay compared to the EA group ($p < 0.01$; WMD = -0.83 days; 95% CI, -1.08 to -0.57 , $I^2 = 67%$). Among the 199 patients (2 studies; 83 with IA and 116 with EA) evaluated, no significant difference was found in the time to intestinal function recovery between the IA group and the EA group ($p = 0.06$; WMD = -1.12 days; 95% CI, -2.29 to 0.06 , $I^2 = 98%$).

Long-Term Recovery

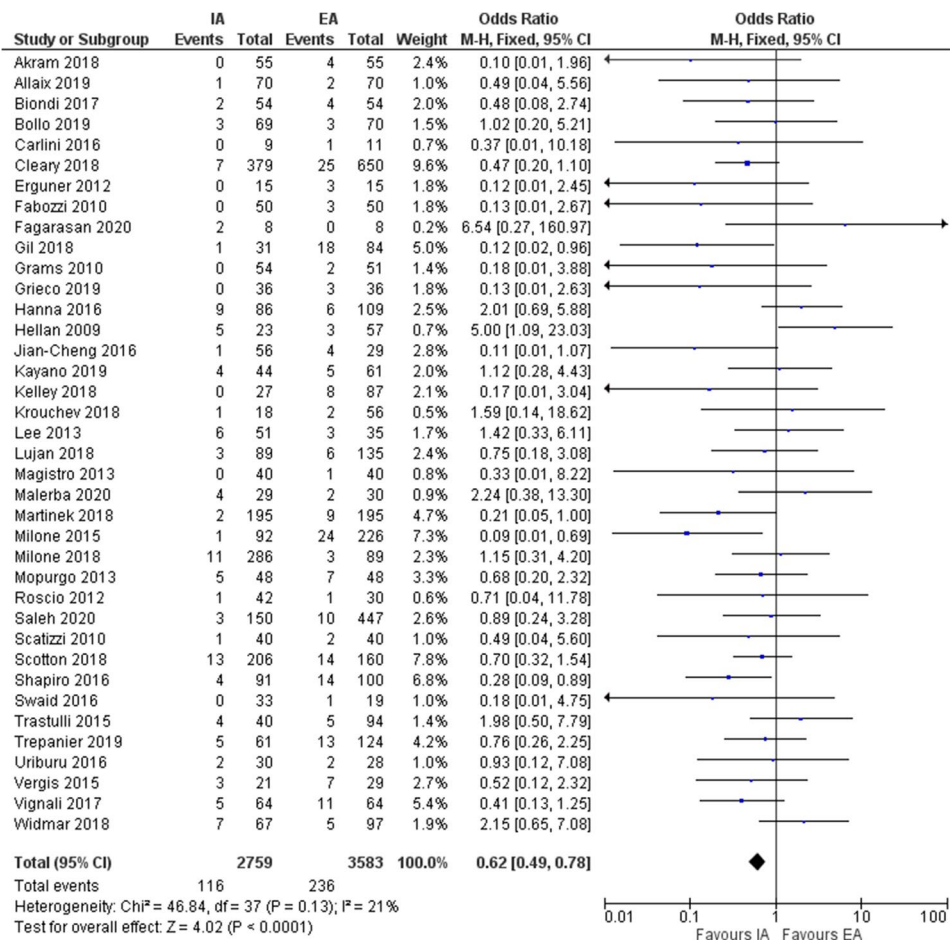
The odds of hernias in 1792 patients (16 studies; 880 with IA and 912 with EA) was significantly lower in the IA group compared to the EA group ($p < 0.01$; OR = 0.28; 95% CI, 0.18 to 0.44, $I^2 = 0%$). A total of 2081 patients (17 studies; 895 with IA and 1186 with EA) were evaluated, and it was found that patients in the IA group had a significantly lower odds of readmissions compared with the EA group ($p = 0.01$; OR = 0.57; 95% CI 0.37 to 0.89, $I^2 = 0%$; Fig. 6). However, sensitivity analysis of RCTs revealed no significant difference of the odds of readmissions between IA and EA ($p = 0.26$; OR = 0.32; 95% CI, 0.05 to 2.28, $I^2 = 30%$; Online Resource 4 (Supplementary Fig. 6c)).

Meta-Regression Analyses

Meta-regression analyses of study and patient characteristics (sample size, age, gender, BMI, aetiology, tumour size, prior abdominal surgery, ASA class) with key outcomes (operative time, anastomotic leak, number of lymph nodes harvested, readmissions and reoperations) were conducted and reported in Online Resource 3.

A significant association was found between BMI and mean number of lymph nodes harvested (25 studies;

Fig. 4 Meta-analysis for surgical site infection and wound infections



$\beta = 0.427$, $SE = 0.0992$, $p = 0.0003$; Online Resource 4 (Supplementary Fig. 2d)), showing that the increased lymph node yield seen in IA is more pronounced for patients with higher BMI. Rate of readmissions was also found to be significantly associated with BMI (14 studies; $\beta = -0.3628$, $SE = 0.1123$, $p = 0.0072$; Online Resource 4 (Supplementary Fig. 6d)) which indicates that the lowered readmission linked to IA is more evident in patients with increased BMI. Further analyses failed to highlight any significant associations between the remaining patient-specific factors and key outcomes.

Discussion and Conclusion

Minimally invasive surgery (MIS), which comprises laparoscopic and robotic approaches, has emerged as an increasingly popular alternative to open colectomies for the treatment of both benign and malignant colonic diseases. In MIS, resection is followed by an anastomotic procedure, either IA or EA, to restore intestinal continuity. The benefits of transitioning from the prevailing EA technique to its more modern IA counterpart have been reviewed by numerous studies but are still a matter of debate. This paper found a significant improvement

in intraoperative outcomes for the IA group pertaining to reduced blood loss, lower rates of conversion to open surgery and smaller incision sizes, in addition to a reduction in the risks of postoperative and long-term surgical complications such as hernias, SSI and wound infections (Table 2) which are largely consistent with current literature [15•, 16]. In the present study, a significantly improved lymph node yield in favour of IA was additionally found (Fig. 2). Not surprisingly, AL rates remained similar after subgroup analysis of RCTs (Online Resource 4 (Supplementary Fig. 3c)), which is contrary to previous meta-analysis [16], while meta-regression analysis further suggested that the advantages of IA may be more pronounced in patients with higher BMI.

Sufficient lymph node yield is important for precise cancer staging, containment of metastatic tumour spread [73, 74] and serves as an accurate prognostic marker [75], yet it has been poorly investigated in previous meta-analyses. The present study found only two reviews, Wu et al. and Ricci et al., that analysed the lymph node yield of 1006 patients from 8 studies and 1532 patients from 12 studies, respectively. Both separately concluded that there were no significant differences between IA and EA for this outcome [12, 76]. In contrast, this meta-analysis incorporated 3394 patients from 25 studies and, with improved

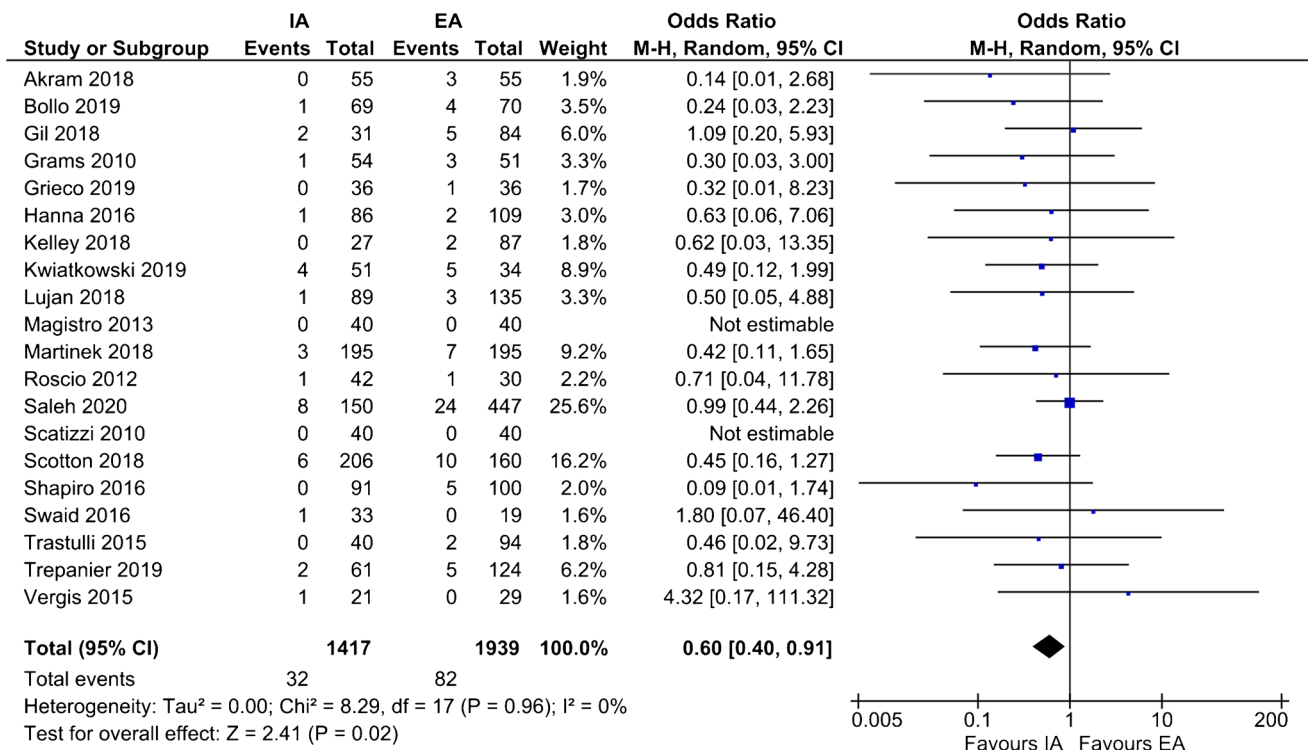


Fig. 5 Meta-analysis of reoperations

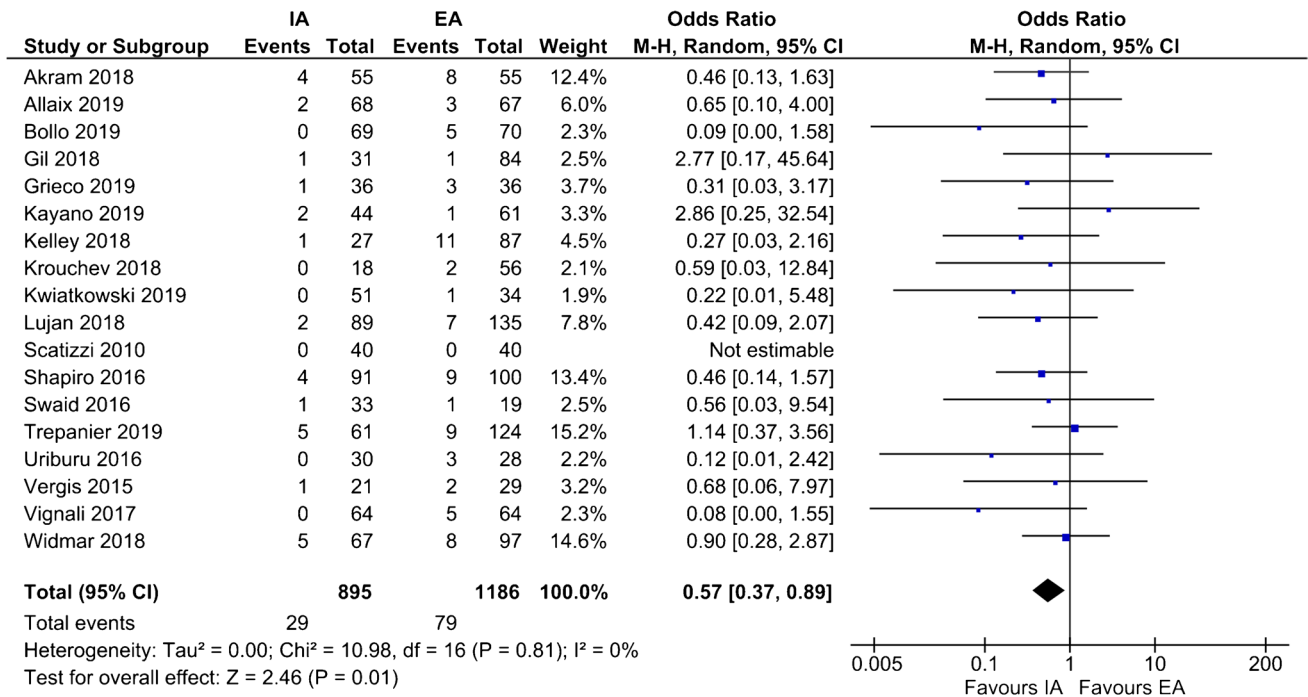


Fig. 6 Meta-analysis of readmissions

statistical power, found a significantly increased number of lymph nodes harvested in IA compared with EA (Fig. 2). While the anastomotic technique (IA or EA) itself is unlikely to have

a direct effect on the lymph node harvest, it is possible that the increased ease of performing central vascular ligation (CVL) in IA due to clearer visualisation of the mesenteric root when

the bowel is not externalized [77] plays a role. CVL involves central ligation of the main arteries and veins at their roots, thus allowing for more meticulous lymph node dissection [77]. Along with an increased uptake of intermediate and central nodes through higher ligation of the vascular pedicle [78], the improvement in the lymph node yield can be explained. These results contribute to the existing base of evidence supporting the use of IA for radical dissection of colonic neoplasms.

Another infrequently analysed outcome is the readmission rate which was lower in the IA group in the primary meta-analysis (Fig. 6). While this may be a consequence of improved intraoperative characteristics and reduced postoperative complications [79], a sensitivity analysis of three RCTs showed no significant difference between readmission rates (Online Resource 4 (Supplementary Fig. 6c)). Further large-scale RCTs are required to determine the true effect of IA on readmission rates.

Meta-regression analyses of cohort studies and RCTs additionally revealed that the advantages of increased lymph node yield and lowered readmission rate in IA are more prominent in patients with higher BMI (Online Resource 4 (Supplementary Fig. 2d) and Online Resource 4 (Supplementary Fig. 6d)), suggesting that IA may be especially beneficial for obese individuals. For patients with thicker abdominal walls as seen in those with higher BMI, the difference in incision lengths required for IA and EA is further pronounced. This is because intracorporeal dissection in IA enables extraction of specimens one limb at a time whereby a smaller incision can be made, while simultaneous evisceration of both limbs of the bowel to facilitate extracorporeal dissection in EA necessitates a longer incision. This translates to poorer postoperative outcomes such as readmission rates among patients with higher BMI. In addition, thickened abdominal pannus renders exteriorisation of the specimen difficult [80], making extracorporeal vessel root ligation and wider mesenteric dissection more challenging. As such, a larger number of lymph nodes can be harvested in IA for these patients.

IA was also associated with lower odds of GI bleeding and improved intestinal recovery which manifested as reduced time to oral feeding, time to first bowel movement, time to first flatus, time to mobilisation and length of stay. By obviating the need for bowel exteriorisation, a process that introduces additional tractional forces and physical trauma, intracorporeal anastomosis reduces the probability of traction injury to mesenteric blood supply and decreases the risk of serosal tears thereby improving postoperative function [16]. The present study also found that IA was also associated with decreased odds of hernia formation, SSI and wound infection (Fig. 4). The use of smaller incisions, and Pfannenstiel instead of midline incisions, may explain these results [81, 82]. Pfannenstiel incisions also provide superior cosmesis and reduced postoperative pain [83]; however, these outcomes could not be evaluated in this meta-analysis.

Emile et al. [16] and Aiolfi et al. [15•] conducted a meta-analysis of cohort studies and found that IA reduced AL rates but had no significant effect on reoperation rates. This study's primary analysis of cohort studies supports their AL finding (Fig. 3) but indicated that IA significantly reduces reoperation rates (Fig. 5). Sensitivity analysis of AL excluding all cohort studies, however, showed that the odds were not significantly different in combined analysis of the three included RCTs (Online Resource 4 (Supplementary Fig. 3c)). AL and reoperation rates are most commonly affected by factors affecting wound healing such as the surgical technique and experience, preoperative steroid use [84] as well as patient comorbidities [85]; there is no a priori reason why these factors would be affected by bowel exteriorisation. The decreased AL rate observed in the primary meta-analysis was instead likely due to methodological and operative differences between study groups that occur in non-randomised cohort studies, for instance an oversewing of the anastomosis in IA as suggested by Grams et al. [86]. A biased AL rate could additionally explain for biased reoperation rate, although this could not be confirmed due to insufficient RCTs included in this review. This meta-analysis thus suggests that the choice to restore intestinal continuity intracorporeally or extracorporeally does not affect the odds of AL or reoperation rates between IA and EA.

It has been suggested that intra-abdominal anastomosis formation could lead to increased risk of intraperitoneal opening of contaminated bowel [87], thereby increasing intra-abdominal abscess rates. However, this meta-analysis found no evidence to support this. Antibiotic prophylaxis [88–90] and mechanical bowel preparation [90, 91] thus appear to be adequate in curtailing the risk of infection when appropriate care and precautions are taken during surgery. Another major concern is the technical difficulty of laparoscopic suturing in IA as opposed to manual sewing in EA, which could increase the operative time of IA. This study confirms this finding and quantifies that IA takes 13 min longer than EA. While familiarisation with IA would help overcome the steep learning curve and should narrow the mean difference in operation time between the two groups [92], no significant association was found when total sample size was used as a surrogate measure for experience in meta-regression. Further studies are warranted to investigate this and should account for the overall surgical experience of the surgeon with precise characterisation of intraoperative and postoperative outcomes for individual surgeons.

Strengths and Limitations

This paper updates the preceding meta-analyses by including recent studies published in the past 2 years. By investigating a comprehensive range of outcomes and utilising a broadened search criterion, our review provides clarification on the clinical benefits of IA through more accurate

evaluation based on a larger pool of evidence. Sensitivity analysis of RCTs overcame selection and operative biases in non-randomised cohort studies to better estimate the true effect of IA for contentious outcomes. Meta-regression identified obese patients as a patient subtype for whom IA may be more efficacious, and this should be investigated in future studies. Separately, the use of meta-regression analyses also helped to identify potential confounding factors that may lead to biased findings.

This paper presents with a few principal limitations, mostly pertaining to significant heterogeneity (reflected by the high I^2 values of selected outcomes) across studies, which have been considered through subgroup and regression analysis. Included studies failed to provide details regarding the definition or clinical measurement of outcomes such as hernia formation as well as incision size, and in many cases did not standardise or report surgeon experience. Imprecise definitions of conversion to open surgery protocols as well as a lack of postoperative management protocol could have affected the postoperative recovery, complication rates and long-term recovery outcomes. However, it was likely that all colorectal surgery patients were managed by the same protocols, limiting the risk that differences in postoperative outcomes between IA and EA patients are due to such protocol differences. The vast majority of included studies are cohort studies which are inherently at risk for both case selection bias and possible surgeon bias. Sensitivity analysis of RCTs helped to mitigate this problem for selected outcomes. Lastly, we are unable to comment if the improvement in postoperative outcomes is clinically significant due to lack of well-defined minimal clinically important differences (MCID).

Conclusion

In the context of LHC, this updated meta-analysis strengthens existing findings that IA superior to EA and reveals for the first time that IA is associated with an ameliorated lymph node yield without a difference in anastomotic leak rates. The benefits of IA pertaining to readmission rate and lymph node yield may also be more pronounced in patients with higher BMI while large-scale, randomised controlled trials are warranted to further verify these findings.

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Declarations

Conflict of Interest Timothy Jia Rong Lam, Shamill Amedot Udonwa, Clyve Yu Leon Yaow, Kameswara Rishi Yeshayahu Nistala, and Choon Seng Chong have nothing to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
- Of major importance

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