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Systematic Review

Intracorporeal *versus* extracorporeal anastomosis in laparoscopic right colectomy: updated meta-analysis of randomized controlled trials

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Abstract

Background: Selection of intracorporeal anastomosis (IA) or extracorporeal anastomosis (EA) in laparoscopic right colectomy (LRC) remains controversial. This meta-analysis aimed to evaluate the effectiveness and safety of IA compared with EA in LRC patients.

Methods: Literature was searched systematically for randomized controlled trials (RCTs) that compared IA with EA in LRC patients until May 2021. The eligible studies for risk of bias were assessed using the Cochrane Risk of Bias Tool. Data were extracted and analysed for the following outcomes of interest: operative time, length of incision, nodal harvest, bowel function recovery, postoperative pain, postoperative complications (wound infection, anastomotic leak, ileus, obstruction, reoperation), death at 30 days, duration of hospital stay and 30-day readmission.

Results: Five RCTs, including a total of 559 patients, were eligible for meta-analysis. All of the trials reported adequate random sequence generation and allocation concealment. There were significantly better outcomes in the IA group than in the EA group in time to first flatus (mean difference (MD) −0.71 (95 per cent c.i. −1.12 to −0.31), $P = 0.0005$), time to first passage of stool (MD −0.53 (95 per cent c.i. −0.69 to −0.37), $P < 0.00001$), visual analogue scale of pain on postoperative day (POD) 3 (MD −0.76 (95 per cent c.i. −1.23 to −0.28), $P = 0.002$), POD 4 (MD −0.83 (95 per cent c.i. −1.46 to −0.20), $P = 0.01$), POD 5 (MD −0.60 (95 per cent c.i. −0.95 to −0.25), $P = 0.0007$), length of incision (MD −1.52 (95 per cent c.i. −2.30 to −0.74), $P = 0.0001$) and wound infection (relative risk 0.46 (95 per cent c.i. 0.23 to 0.91), $P = 0.02$). However, there were no statistically significant differences between the two groups in duration of hospital stay ($P = 0.47$), operative time ($P = 0.07$), number of lymph nodes harvested ($P = 0.70$), anastomotic leak ($P = 0.88$), postoperative ileus ($P = 0.48$), bleeding ($P = 0.15$), bowel obstruction ($P = 0.24$), reoperation ($P = 0.34$), readmission within 30 days ($P = 0.26$), and death ($P = 0.70$).

Conclusion: Compared with EA, IA shows a faster recovery of bowel function with fewer wound infections.

Introduction

The advantages of laparoscopic right colectomy (LRC) for colon carcinoma compared with open right colectomy (ORC) have been confirmed by several trials[1–3]. LRC is superior to ORC in early recovery and short-term complications and equivalent in oncological outcomes[4,5]. For the ileocolic anastomosis of LRC, extracorporeal anastomosis (EA) is used more frequently than intracorporeal anastomosis (IA), due to technical facilities and the shorter surgical time compared with IA[6,7]. However, EA requires greater mobilization and exteriorization of the bowel through the abdominal incision for further steps, which may lead to tissue injury to the mesentery and affect the recovery of bowel function[7]. IA was reported to have a longer operative time than EA in several retrospective studies, whereas a faster recovery after surgery was demonstrated because of the shorter incision and less traction and mobilization of the mesentery[8–10]. In recent years, IA has gained more and more attention because of the development of intracorporeal devices and suturing techniques (linear stapler and barbed suture, among others). However, the selection of IA *versus* EA remains controversial among surgeons, mainly depending on their expertise and personal preference. Aiming to provide a robust guideline for surgeons, a meta-analysis of RCTs was performed to evaluate the effectiveness and safety of IA compared with EA in LRC patients.

Methods

This study was conducted according to the recommendations of the PRISMA statement[11].

Literature search

A systematic literature search was performed up to 30 May 2021, using the terms ‘laparoscopic right colectomy/laparoscopic right hemicolectomy/laparoscopic right colon resection’, ‘intracorporeal

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anastomosis/anastomoses', and 'extracorporeal anastomosis/anastomoses' in the following databases: MEDLINE, EMBASE, the Cochrane Library, the Clinical Trials Database (ClinicalTrials.gov http://clinicaltrials.gov/, World Health Organization International Clinical Trials Registry http://apps.who.int/trialsearch/, ISRCTN Register http://www.isrctn.com/ and Chinese Clinical Trial Registry http://www.chictr.org.cn/index.aspx), China National Knowledge Infrastructure (CNKI, https://www.cnki.net/) and Wanfang Med Online (http://med.wanfangdata.com.cn/). The reference lists of the identified relevant articles, conference proceedings and ongoing trial databases were further screened for potentially relevant studies. There was no language restriction while screening for the relevant studies.

The titles and abstracts of all of the identified articles were screened, and the trials were included for analysis according to the following criteria: RCTs that compared IA with EA; patients with diseases that needed to be treated with LRC; and outcomes included effectiveness or postoperative complications. Studies were excluded if they were retrospective, had no randomization or had no control arm.

Data extraction and quality assessment

Two investigators independently extracted the following data from all the included trials: patient characteristics, study design, patient inclusion and exclusion criteria, surgery process, intraoperative results and postoperative outcomes. Details of randomization, allocation concealment, blinding, number of patients allocated to each arm, and procedures of IAs and EAs were recorded. If the important data were not reported, the authors were contacted as early as possible. The same reviewers assessed the methodological quality of each trial. A third reviewer was consulted if there were any discrepancies, and consensus was reached by discussion. The quality of each included study was determined using the Cochrane Collaboration's tool for assessing the risk of bias, a value of low risk, high risk or unclear was assigned to the seven domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias[12].

Data analysis and outcomes of interest

Data were extracted and analysed for the following primary outcomes: postoperative recovery (time to first flatus, time to first passage of stool, duration of hospital stay, postoperative pain); and operative data (length of incision, operative time and number of lymph nodes harvested).

Secondary outcomes (complications) were: anastomotic leak, wound infection, postoperative ileus, bleeding (gastrointestinal or anastomotic bleeding), bowel obstruction, reoperation, readmission within 30 days and death at 30 days.

A sensitivity analysis was also performed for eliminating the potential clinical heterogeneities of different types of ileocolic anastomosis. A subgroup analysis based on the peristaltic orientation of anastomosis was also performed.

Statistical analysis

Statistical analyses were performed with the recommendations of the Cochrane Collaboration Guidelines[12]. Review Manager software (RevMan, version 5.4.1 for Windows) was used to perform this meta-analysis[13]. Dichotomous outcomes were presented as relative risk (RR) and continuous outcomes were presented as mean difference (m.d.); 95 per cent confidence intervals were quantified for all the analyses. Data expressed as median with range were converted to mean with standard deviation for continuous outcomes using methods as described before[14]. Heterogeneity was assessed with Cochran's χ^2 test and the I^2 test. Statistically significant heterogeneity was considered when P was <0.100 and the I^2 test value was >50 per cent[15]. The fixed effects model was used if there was no significant statistical heterogeneity ($P > 0.100$ and $I^2 < 50$ per cent). If heterogeneity existed, the random effects model was applied[16]. Sensitivity analyses were performed with trials of performing side-to-side and stapled ileocolic anastomosis. Subgroup analysis was performed by stratifying the trials based on the peristaltic orientation of anastomosis (antiperistaltic anastomosis and isoperistaltic anastomosis).

Results

An initial screening resulted in the identification of a total of 1836 potentially relevant studies. Further analysis revealed that only five RCTs with 559 patients met all the inclusion criteria and these underwent a full analysis (*Fig. 1*)[17–21]. The characteristics of the included trials are shown in *Table 1*. In these five RCTs, IA was performed in 281 of 559 patients (50.3 per cent), while EA was performed in 278 patients (49.7 per cent). Most of the included patients were diagnosed with malignant tumours of the right colon (534 patients, 95.5 per cent). The sites of the tumour were as follows: 259 in the caecum (46.3 per cent), 171 in the ascending colon (30.6 per cent) and 129 in the colon liver flexure (23.1 per cent). For the type of ileocolic anastomosis, four trials reported that side-to-side (476 of 499 patients, 95.4 per cent), stapled (465 of 499 patients, 93.2 per cent), and anti-peristaltic (279 of 499 patients, 55.9 per cent) were the preferred choices[17–19,21]. Enterotomies were all closed with two layers of absorbable sutures. In the IA group, four trials reported that the incisions for specimen extraction were Pfannenstiel incision (160 of 251 patients, 63.7 per cent), midline (54 of 251 patients, 21.5 per cent), transverse (20 of 251 patients, 8.0 per cent) and others (17 of 251 patients, 6.8 per cent); in the EA group, the ratios of above-mentioned incisions were 0.8 per cent (2 of 248 patients), 43.1 per cent (107 of 248 patients), 48.0 per cent (119 of 248 patients) and 8.1 per cent (20 of 248 patients) respectively[17–19,21]. The length of the incision was significantly shorter in the IA group than in the EA group. The mesenteric defects were all closed in two trials[17,21]. These studies[17,21] plus another study[19], applied several recommendations of the enhanced recovery after surgery (ERAS) protocol[22], such as no perioperative mechanical bowel preparation, postoperative analgesia, early resumption of diet, removal of the urinary catheter on postoperative day (POD) 1 and early mobilization on POD 1; the full ERAS protocol was implemented in the other two trials[18,20].

Risk of bias in included trials

The Cochrane Risk of Bias Tool was used to assess the potential risk of bias in the included trials (*Fig. 2*). All of the trials reported adequate random sequence generation and allocation concealment. All of the patients were blinded to their treatment in four trials[17,18,20,21], one trial did not report blinding of patients[19], and two trials blinded the outcome assessors[17,21]. Surgeon blinding would have been inappropriate in all of the included trials. However, the randomization envelope was only opened to the surgeons at the beginning of the procedure or anastomosis. Attrition bias and reporting bias are both at low risk.

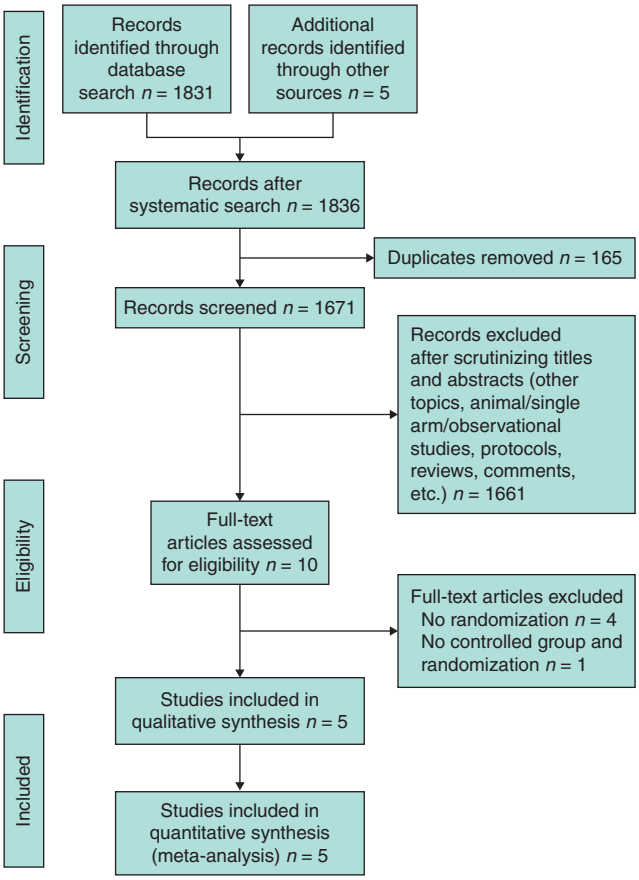


Fig. 1 Flow diagram of literature search

Primary outcomes

In the IA group, the time of the first flatus was significantly shorter than in the EA group (m.d. −0.71 (95 per cent c.i. −1.12 to −0.31), $P = 0.0005$). Three trials reported this outcome[17,20,21], with heterogeneity ($I^2 = 80$ per cent) (*Fig. 3a*).

In the IA group, the first passage of stool was significantly faster than in the EA group (m.d. −0.53 (95 per cent c.i. −0.69 to −0.37), $P < 0.00001$). Three trials reported this outcome[17,18,21], with no heterogeneity ($I^2 = 0$ per cent) (*Fig. 3b*).

Duration of hospital stay was not significantly different between the two groups (m.d. −0.07 (95 per cent c.i. −0.27 to 0.13), $P = 0.47$). Five trials reported the data, and significant heterogeneity was not observed between them ($I^2 = 48$ per cent) (*Fig. 3c*).

Postoperative pain was evaluated in three trials using a visual analogue scale (VAS) ranging from 0 to 10 (0 = no pain, 10 = maximal pain)[17,18,21]. The results of meta-analysis showed that patients in the IA group had a lower VAS score than those in the EA group on POD 3 (m.d. −0.76 (95 per cent c.i. −1.23 to −0.28), $P = 0.002$), POD 4 (m.d. −0.83 (95 per cent c.i. −1.46 to −0.20), $P = 0.01$) and POD 5 (m.d. −0.60 (95 per cent c.i. −0.95 to −0.25), $P = 0.0007$); however, no significant difference was found between two groups on POD 1 (m.d. −0.05 (95 per cent c.i. −0.27 to 0.17), $P = 0.66$) and POD 2 (m.d. −0.60 (95 per cent c.i. −1.44 to 0.25), $P = 0.17$) (*Fig. S1*).

The incision length was significantly shorter in the IA group than in the EA group (m.d. −1.52 (95 per cent c.i. −2.30 to −0.74), $P = 0.0001$). Four trials reported the data[17–19,21] and heterogeneity was observed between them ($I^2 = 88$ per cent) (*Fig. 3d*).

The operative time of the two groups was not significantly different (m.d. 12.41 (95 per cent c.i. −1.18 to 25.99), $P = 0.07$). Four trials reported the data[17–19,21] and heterogeneity was observed between them ($I^2 = 86$ per cent) (*Fig. 3e*).

The number of lymph nodes harvested was similar between the IA and EA groups (m.d. 0.40 (95 per cent c.i. −1.63 to 2.43), $P = 0.70$). Two trials, including only patients with malignant tumours, reported the data[18,21], with no heterogeneity ($I^2 = 0$ per cent) (*Fig. 3f*).

Secondary outcomes

A total of 15 (5.3 per cent) patients in the IA group and 14 (5.0 per cent) patients in the EA group experienced anastomotic leak (RR 1.05 (95 per cent c.i. 0.53 to 2.09), $P = 0.88$). Five trials reported the data, and no significant heterogeneity was seen between them ($I^2 = 11$ per cent) (*Fig. 4a*). Eleven (3.9 per cent) patients in the IA group and 24 (8.6 per cent) patients in the EA group experienced wound infection (RR 0.46 (95 per cent c.i. 0.23 to 0.91), $P = 0.02$). Five trials reported the data, with no significant heterogeneity ($I^2 = 23$ per cent) (*Fig. 4b*).

The incidence of postoperative ileus was similar between the IA group (33 patients, 11.7 per cent) and the EA group (44 patients, 15.8 per cent) (RR 0.72 (95 per cent c.i. 0.30 to 1.77), $P = 0.48$). Five trials reported this outcome, with heterogeneity ($I^2 = 58$ per cent) (*Fig. 4c*).

Five (3.0 per cent) patients in the IA group and 11 (6.5 per cent) patients in the EA group experienced bleeding (RR 0.48 (95 per cent c.i. 0.18 to 1.31), $P = 0.15$). Three trials reported the

Table 1 General characteristics of the included trials

Study	Anastomosis	No. of patients	Age (years)	Male N (%)	BMI, kg/m^2	Center	ERAS (complete/partial)
Allaix 2019[17]	IA	70	70 (65–77)†	39 (55.7)	24 (22.4–28.7)†	Single-centre	Partial
	EA	70	72 (65–77)†	41 (58.6)	25.2 (22.9–29.2)†		
Bollo 2020[18]	IA	69	72.7 (10.4)*	34 (49.3)	27.4 (5.4)*	Single-centre	Complete
	EA	70	70.9 (11.7)*	39 (55.7)	26.3 (4.7)*		
Ferrer 2021[19]	IA	82	70.51 (9.88)*	43 (52.4)	28.25 (4.69)*	Multi-centre	Partial
	EA	78	68.65 (12.51)*	39 (50.0)	28.67 (4.54)*		
Mari 2018[20]	IA	30	66 (42–83)†	19 (63.3)	24.3 (5.9)*	Single-centre	Complete
	EA	30	72 (39–87)†	16 (53.3)	26.1 (3.3)*		
Vignali 2016[21]	IA	30	67.4 (1.8)*	16 (53.3)	24.6 (4.3)*	Single-centre	Partial
	EA	30	64.7 (2.9)*	14 (46.7)	24.8 (3.4)*		

Study	Anastomosis	No. of patients	Tumour		Tumour location		
			Malignant	Benign	Caecum	Ascending colon	Colon liver flexure
Allaix 2019[17]	IA	70	54	16	39	18	13
	EA	70	61	9	41	12	17
Bollo 2020[18]	IA	69	69	0	29	21	19
	EA	70	70	0	27	12	31
Ferrer 2021[19]	IA	82	82	0	35	27	20
	EA	78	78	0	33	31	14
Mari 2018[20]	IA	30	30	0	12	16	2
	EA	30	30	0	14	14	2
Vignali 2016[21]	IA	30	30	0	14	9	7
	EA	30	30	0	15	11	4

Study	Anastomosis	No. of patients	Type of ileocolic anastomosis					
			Side-to-side	End-to-end	End-to-side	Stapled	Hand-sewn	Orientation
Allaix 2019[17]	IA	70	70	0	0	70	0	Anti-peristaltic
	EA	70	47	1	22	36	34	
Bollo 2020[18]	IA	69	69	0	0	69	0	Anti-peristaltic
	EA	70	70	0	0	70	0	
Ferrer 2021[19]	IA	82	82	0	0	82	0	Iso-peristaltic
	EA	78	78	0	0	78	0	
Mari 2018[20]	IA	30	NA	NA	NA	NA	NA	NA
	EA	30	NA	NA	NA	NA	NA	
Vignali 2016[21]	IA	30	30	0	0	30	0	Iso-peristaltic
	EA	30	30	0	0	30	0	

*Mean (s.d.), †Median (range). ERAS, enhanced recovery after surgery; NA, not available.

data[17,18,20], with no significant heterogeneity (I^2 = 49 per cent) (*Fig. 4d*).

One (1.0 per cent) patient in the IA group and four (4 per cent) patients in the EA group experienced bowel obstruction (RR 0.33 (95 per cent c.i. 0.05 to 2.06), $P = 0.24$). Two trials reported the data[17,21], with no heterogeneity ($I^2 = 0$ per cent) (*Fig. 4e*).

Thirteen (4.6 per cent) patients in the IA group and 18 (6.5 per cent) patients in the EA group experienced reoperation (RR 0.72 (95 per cent c.i. 0.37 to 1.41), $P = 0.34$). Five trials reported the data, with no significant heterogeneity ($I^2 = 33$ per cent) (*Fig. 4f*).

A total of seven (2.8 per cent) patients in the IA group and 12 (4.8 per cent) patients in the EA group experienced readmission within 30 days (RR 0.60 (95 per cent c.i. 0.25 to 1.45), $P = 0.26$). Four trials reported the data[17–19,21] and no significant heterogeneity was seen between them ($I^2 = 17$ per cent) (*Fig. 4g*).

Three (1.1 per cent) patients in the IA group and four (1.4 per cent) patients in the EA group died in the postoperative period (RR 0.76 (95 per cent c.i. 0.19 to 3.01), $P = 0.70$). Five trials reported the data, with no heterogeneity ($I^2 = 0$ per cent) (*Fig. 4h*).

Sensitivity analysis

One trial that did not report the type of ileocolic anastomosis[20] and one trial that included the mixed type of ileocolic anastomosis[17] were excluded from the sensitivity analysis. The other three trials, all performing side-to-side and stapled ileocolic anastomosis, were analysed. The analyses showed that the time to first passage of stool (m.d. −0.95 (95 per cent c.i. −1.58 to −0.32), $P = 0.003$), VAS scores of POD 2 (m.d. −1.04 (95 per cent c.i. −1.60 to −0.47), $P = 0.003$) and 4 (m.d. −0.51 (95 per cent c.i. −0.96 to −0.05), $P = 0.03$), length of incision (m.d. −1.86 (95 per cent c.i. −2.32 to −1.41), $P < 0.00001$) and bleeding (RR 0.20 (95 per cent c.i. 0.05 to 0.89), $P = 0.03$) favoured the IA group, while the operative time (m.d. 17.12 (95 per cent c.i. 1.47 to 32.78), $P = 0.03$) favoured the EA group. There was no significant difference in the other outcomes (*Table S1*).

Subgroup analysis

This analysis was focused on the peristaltic orientation of the anastomosis (antiperistaltic anastomosis, two RCTs, 279 patients[17,18]; and isoperistaltic anastomosis, two RCTs, 200 patients[19,21]). In the subgroup of antiperistaltic anastomosis, time to first flatus (m.d. −1.00 (95 per cent c.i. −1.08 to −0.92), $P < 0.00001$), time to first passage of stool (m.d. −0.50 (95 per cent c.i. −0.67 to −0.33), $P < 0.00001$), VAS scores on POD 3 (m.d. −0.74 (95 per cent c.i. −1.40 to −0.08), $P = 0.03$), POD 4 (m.d. −1.24 (95 per cent c.i. −1.33 to −1.16), $P < 0.00001$) and POD 5 (m.d. −0.75 (95 per cent c.i. −0.83 to −0.67), $P < 0.00001$), postoperative ileus (RR 0.46 (95 per cent c.i. 0.23 to 0.91), $P = 0.03$) and

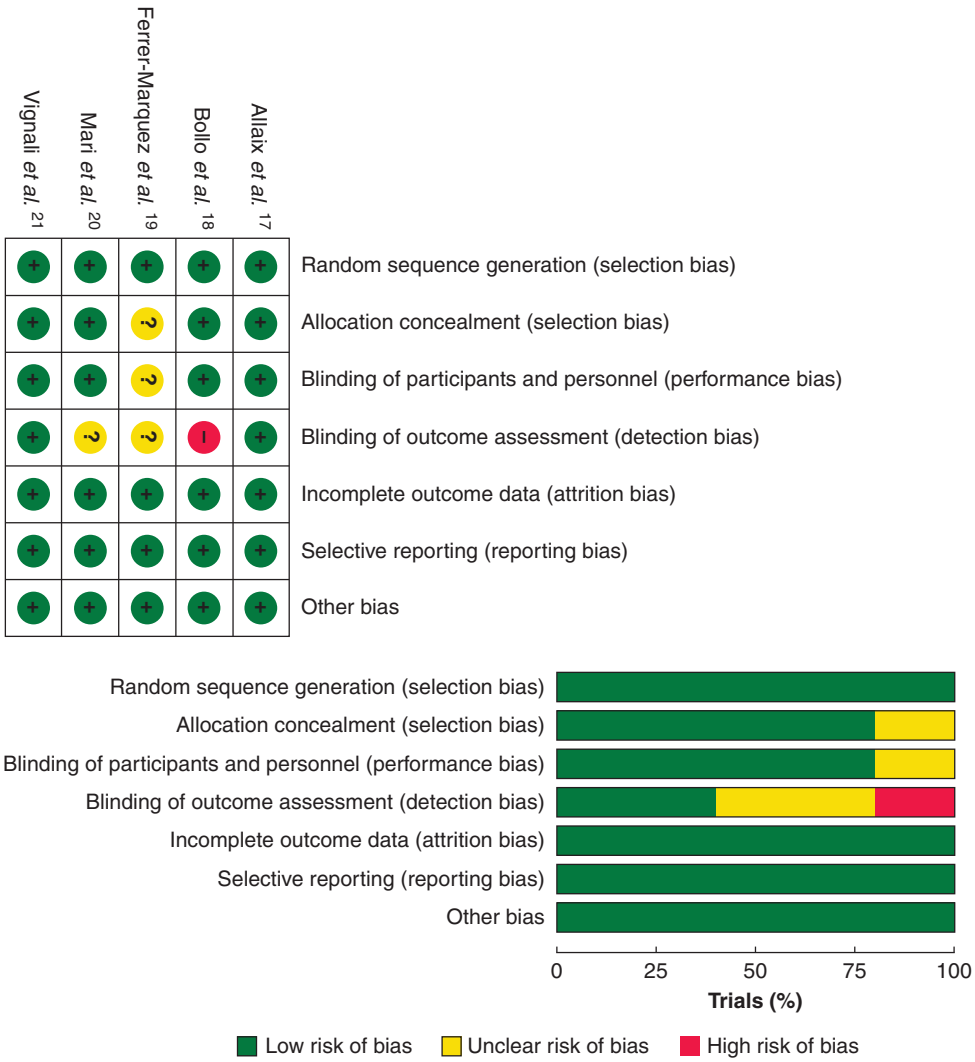


Fig. 2 Risk of bias summary and graph

Each risk of bias item for the included trials is presented as a percentage across all the included trials.

bleeding (RR 0.28 (95 per cent c.i. 0.08 to 0.96), $P = 0.04$) were all in favour of the IA group. In the subgroup of isoperistaltic anastomosis, time to first passage of stool (m.d. −0.90 (95 per cent c.i. −1.79 to −0.01), $P = 0.048$) and length of incision (m.d. −1.78 (95 per cent c.i. −2.61 to −0.96), $P < 0.0001$) were both in favour of the IA group. There was no significant difference in the other outcomes (*Table S2*).

Discussion

Laparoscopic colectomy is increasingly becoming a standard treatment for benign and malignant colonic disease in many centres around the world[23,24]. In LRC, IA and EA are the two main anastomotic techniques for restoration of bowel continuity. Several meta-analyses have been published comparing IA *versus* EA on short-term outcomes, morbidity and death in patients undergoing LRC[24–28]. Based on these initial conclusions, IA appears to be safe in terms of postoperative complications and is potentially more effective in recovery after surgery. However, most of the included studies were retrospective in the former meta-analyses, which made the level of evidence lower than in the meta-analysis of RCTs[29]. This may be one reason why surgeons do not perform IA routinely. Another reason is the technical difficulty of performing the laparoscopic hand-sewn suture[27]. However, new suturing techniques, such as barbed sutures, facilitate laparoscopic suturing because it is unnecessary to tie a knot[30]. The use of barbed sutures in laparoscopic colectomy for enterotomy closure is associated with a shorter operative time[31]. Several new RCTs of ileocolic anastomosis in LRC were published from 2016 to 2021, which provided a high level of evidence for the issue of IA *versus* EA[17–21].

In this meta-analysis involving 559 patients from five RCTs, patients treated with IA had faster recovery of flatus and defaecation, less postoperative pain, shorter length of the incision and fewer wound infections than patients treated using EA. The data demonstrated that IA was associated with a faster recovery of bowel function than EA, which is consistent with findings reported by others[27,28]. Although technically demanding and requiring advanced laparoscopic skills, IA does not require bowel exteriorization and reduces intestinal manipulation, leading to less traction on and fewer tissue injuries to the mesentery[7,32]. A past study demonstrated that tissue injury clearly had a major role in the surgical stress response (SSR), which may affect the recovery of bowel function, and elevated SSR in EA patients was shown by apparently higher levels of IL-6, C-reactive protein and

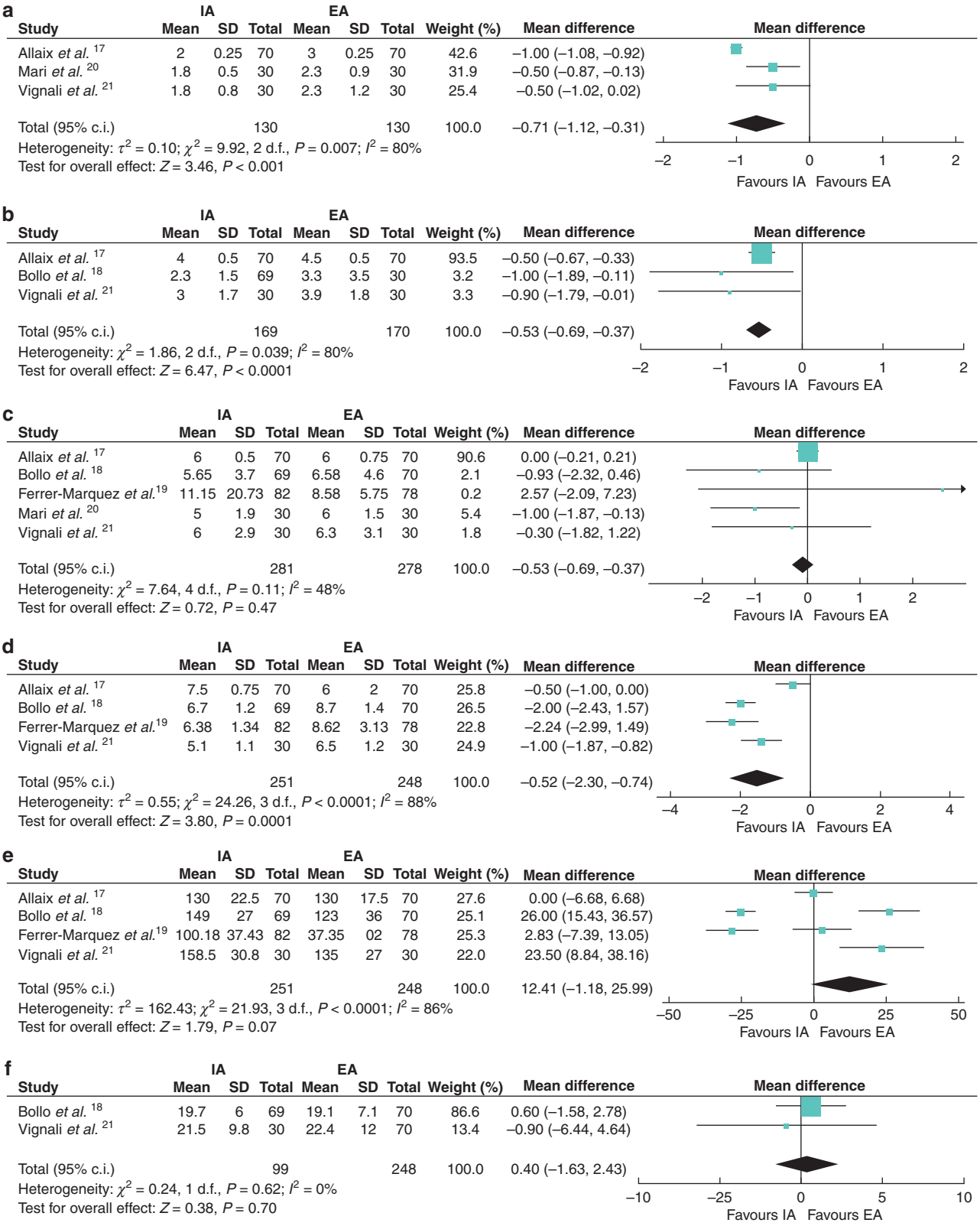


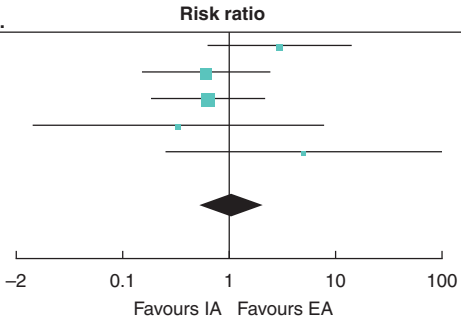
Fig. 3 Forest plots of primary outcomes (postoperative recovery and operative data)

a Time to first flatus; **b** time to first passage of stool; **c** duration of hospital stay; **d** length of incision; **e** operative time; and **f** lymph nodes harvested. IA, intracorporeal anastomosis; EA, extracorporeal anastomosis.

a

Study	IA Events	IA Total	EA Events	EA Total	Weight (%)	Risk ratio M-H, Fixed, 95% c.i.
Allaix *et al.* [17]	6	70	2	70	13.2	3.00 (0.63, 14.36)
Bollo *et al.* [18]	3	69	5	70	32.8	0.61 (0.15, 2.45)
Ferrer-Marquez *et al.*[19]	4	82	6	78	40.7	0.63 (0.19, 2.16)
Mari *et al.* [20]	0	30	1	30	9.9	0.33 (0.01, 7.87)
Vignali *et al.* [21]	2	30	0	30	3.3	5.00 (0.25, 99.95)
Total (95% c.i.)		281		278	100.0	1.05 (0.53, 2.09)
Total events	15		14			

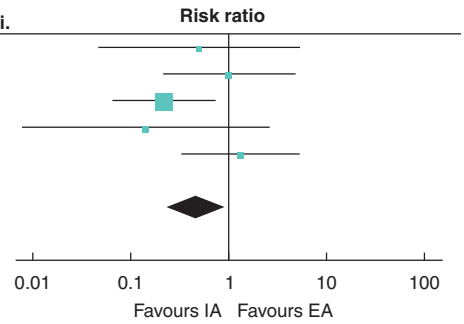
Heterogeneity: $\chi^2 = 4.52$, 4 d.f., $P = 0.34$; $I^2 = 11\%$
Test for overall effect: $Z = 0.15$, $P = 0.88$



b

Study	IA Events	IA Total	EA Events	EA Total	Weight (%)	Risk ratio M-H, Fixed, 95% c.i.
Allaix *et al.* [17]	1	70	2	70	8.1	0.50 (0.05, 5.39)
Bollo *et al.* [18]	3	69	3	70	12.0	1.01 (0.21, 4.85)
Ferrer-Marquez *et al.*[19]	4	82	13	78	53.7	0.22 (0.07, 0.74)
Mari *et al.* [20]	0	30	3	30	14.1	0.14 (0.01, 2.65)
Vignali *et al.* [21]	4	30	3	30	12.1	1.33 (0.33, 5.45)
Total (95% c.i.)		281		278	100.0	0.46 (0.23, 0.91)
Total events	11		24			

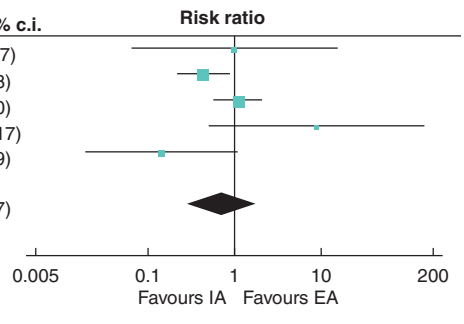
Heterogeneity: $\chi^2 = 5.21$, 4 d.f., $P = 0.27$; $I^2 = 23\%$
Test for overall effect: $Z = 2.24$, $P = 0.02$



c

Study	IA Events	IA Total	EA Events	EA Total	Weight (%)	Risk ratio M-H, Random, 95% c.i.
Allaix *et al.* [17]	1	70	1	70	8.5	1.00 (0.06, 15.67)
Bollo *et al.* [18]	9	69	21	70	34.1	0.43 (0.21, 0.88)
Ferrer-Marquez *et al.*[19]	18	82	15	78	36.0	1.14 (0.62, 2.10)
Mari *et al.* [20]	4	30	0	30	7.9	9.00 (0.51, 160.17)
Vignali *et al.* [21]	1	30	7	30	13.4	0.14 (0.02, 1.09)
Total (95% c.i.)		281		278	100.0	0.72 (0.30, 1.77)
Total events	33		44			

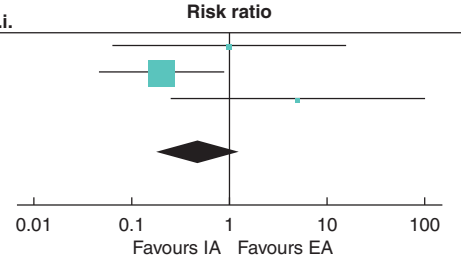
Heterogeneity: $\tau^2 = 0.48$; $\chi^2 = 9.56$, 4 d.f., $P = 0.05$; $I^2 = 58\%$
Test for overall effect: $Z = 0.71$, $P = 0.48$



d

Study	IA Events	IA Total	EA Events	EA Total	Weight (%)	Risk ratio M-H, Fixed, 95% c.i.
Allaix *et al.* [17]	1	70	1	70	.8	1.00 (0.06, 15.67)
Bollo *et al.* [18]	9	69	10	70	86.9	0.20 (0.05, 0.89)
Mari *et al.* [20]	18	30	0	80	4.4	5.00 (0.25, 99.95)
Total (95% c.i.)		169		170	100.0	0.48 (0.18, 1.31)
Total events	5		11			

Heterogeneity: $\chi^2 = 3.92$, 2 d.f., $P = 0.14$; $I^2 = 49\%$
Test for overall effect: $Z = 1.43$, $P = 0.15$



e

Study	IA Events	IA Total	EA Events	EA Total	Weight (%)	Risk ratio M-H, Fixed, 95% c.i.
Allaix *et al.* [17]	0	70	2	70	55.6	0.20 (0.01, 4.09)
Vignali *et al.* [21]	1	30	2	30	44.4	0.50 (0.05, 5.22)
Total (95% c.i.)		100		100	100.0	0.33 (0.05, 2.06)
Total events	1		4			

Heterogeneity: $\chi^2 = 0.22$, 1 d.f., $P = 0.64$; $I^2 = 0\%$
Test for overall effect: $Z = 1.18$, $P = 0.24$

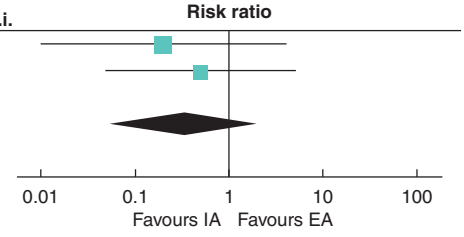


Fig. 4 Forest plots of secondary outcomes (complications)

a Anastomotic leak; **b** wound infection; **c** postoperative ileus; **d** bleeding; **e** bowel obstruction; **f** reoperation; **g** readmission within 30 days; and **h** death. IA, intracorporeal anastomosis; EA, extracorporeal anastomosis.

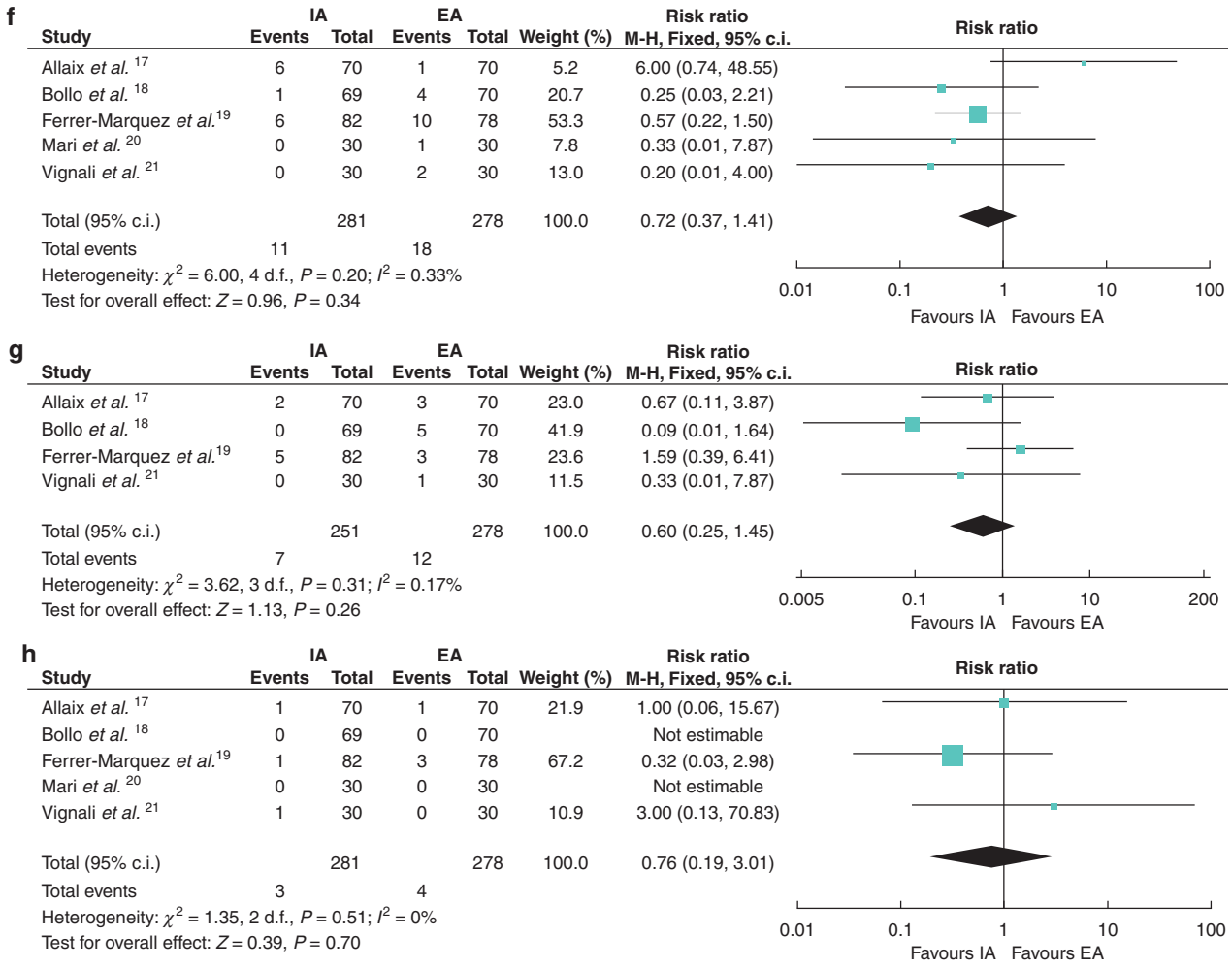


Fig. 4 (continued)

white blood cells than in IA patients[20]. Notably, it was difficult to exteriorize the transverse colon or terminal ileum in obese patients via a small abdominal incision owning to a short and thickened bowel mesentery[20,33,34]. To achieve EA in patients with high BMI, surgeons may need to perform excessive traction on the colon and terminal ileum, which leads easily to tissue injury to the mesentery. Conversely, IA was not affected by BMI, owing to its avoidance of mesenteric traction to externalize the bowel for anastomosis. An increased inflammatory response in postsurgical intestinal muscularis has also been demonstrated from excessive bowel handling *in vivo*, leading to an increase in or exacerbation of postoperative ileus[35]. In this meta-analysis of the antiperistaltic anastomosis subgroup, fewer cases of postoperative ileus were observed in IA patients than in EA patients. Obviously, the less the manipulation, the lower the incidence of postoperative ileus[18]. In addition, it has been reported that IA may reduce the likelihood of intestinal twisting because of a better view with laparoscopic visualization for performing the anastomosis, following a lower operative conversion rate[33,34,36,37]. However, high operative conversion rates with increased morbidity were reported in laparoscopically assisted colectomy with EA[38,39].

For IA, a small incision is enough to extract the specimen only. In the included trials, the abdominal incision length was significantly reduced in the IA group. This was also found in a meta-analysis of observational studies[28]. A midline incision was used for 43.1 per cent of patients in the EA group, which was associated with the highest risk of incisional hernia, as previously reported[24]. In the IA group, Pfannenstiel incision (63.7 per cent) was used in more than half of the patients; the incidence of incisional hernias and postoperative pain could be less in this group because of rapid wall suturing (fewer muscle layers) with reduced operative time and shorter length of incision[40,41]. A further potential advantage of Pfannenstiel incision is the cosmetic effect due to its invisibility. Owning to short follow-up, incisional hernia was not reported in any of the five included trials. Several other studies have shown a higher incidence of incisional hernia in the EA group than in the IA group[9,24,40]. Notably, IA with a Pfannenstiel incision could reduce the rate of incisional hernias compared with EA with a vertical midline incision[42].

All of the included patients routinely received postoperative multimodal analgesics based on ERAS recommendations for about 48 hours[22], and similar VAS pain scores were seen on PODs 1 and 2 between the IA and EA groups. However, lower VAS scores were shown on PODs 3, 4 and 5 of the IA group. Undoubtedly, a shorter incision was an important factor associated with less postoperative pain. The incidence of wound infection in the EA group was higher than in the IA group. Except for longer incisions, another potential reason may be wound contamination while performing EA through the incision[24]. Theoretically, intra-abdominal infection of the IA group is expected to be high because of the possibility of faecal spillage

when performing ileocolic anastomosis. However, a similar rate of abdominal abscess was observed between the IA and EA groups[8,19], which suggests that no significant intraperitoneal spillage occurred in the IA group before the enterotomies were closed. Some measures may be beneficial for preventing intra-abdominal infection, such as using atraumatic bulldogs to block spillage[43], administering prophylactic antibiotics[44], irrigating the abdominal cavity locally after anastomosis[45] and ensuring adequate nutritional support[46].

The anastomotic leak rate is an important measure to determine the success of each anastomotic technique[6]. IA was considered to have a greater likelihood of anastomotic leak due to the technical difficulty[26], whereas higher odds of the anastomotic leak were observed in the EA group previously reported[24]. One potential reason may be the shortage of anastomotic blood supply following mesenteric injuries caused by traction on the bowel ends through the extraction site incision[33]. Another reason is that hand-sewn anastomosis, which was reported to be associated with anastomotic leak more than with stapled anastomosis[47], was used more often in the EA group than in the IA group[24]. However, based on the present meta-analysis, LRCs with IA or EA were both safe, with no significant differences in the rate of anastomotic leak between the two groups. It should be added that stapled anastomosis was also used mostly in the EA group (214 of 248 patients, 86.3 per cent). The extensive experience of participant surgeons in laparoscopic colorectal surgery eliminated the impact of technical difficulty to some extent in the IA group. For an experienced laparoscopic surgeon, it has been reported that the learning curve of ileocolonic intracorporeal anastomosis was short, and the total operating time of the IA method was shorter than that of the EA method after a minimal learning curve period of about 18 cases[37]. Even for high-risk patients with obesity and high ASA grade, the surgical outcomes of total intracorporeal laparoscopic colectomy are equal to those of low-risk patients except for a longer operative time[34]. In this meta-analysis, similar operative time was demonstrated between the IA and EA groups. However, sensitivity analysis for patients undergoing side-to-side ileocolic anastomosis with a stapler showed a longer operative time in the IA group. Intracorporeal suturing to close the enterocolostomy is undoubtedly the most challenging procedure for surgeons, whereas the use of barbed suture facilitated the procedure and resulted in a similar surgical time between IA and EA[19].

In this meta-analysis, both the IA and EA groups obtained good oncological radicality owing to a similar number of lymph nodes harvested. Furthermore, it was demonstrated that the lengths of the distal and proximal margins were similar between the two groups[17,48]. Therefore, in the short term, the IA method is oncologically equivalent to the EA method; that is, the extent of tumour resection (length of resection and number of lymph nodes) is related to the short-term therapeutic effects. No significant difference in long-term outcomes was found in overall survival and disease-free survival at 3 years[8] and 5.7 years[49] of follow-up between the two groups.

There were several limitations to this meta-analysis. The ERAS protocol was not performed completely in all the included trials. Different experiences among surgeons probably led to variable operative time. Also, the ratio of the type of surgical incision was not the same between IA and EA groups. These factors may affect the recovery process of patients and surgical outcomes. Finally, the number of the included patients was small. Large RCTs comparing IA with EA are necessary in the future.

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Supplementary material

Supplementary material is available at *BJS Open* online.

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