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Post-surgical morbidity in early versus late closure of defunctioning ileostomy after rectal cancer surgery: A systematic review and meta-analysis of randomised controlled trials

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Abstract

Background A defunctioning ileostomy is frequently created to avert the implications of a colo-rectal anastomotic dehiscence in rectal cancer surgery. The timing of closure of the ileostomy remains debatable as it is believed that early closure (EC) may be beneficial to most patients than the standard practice of late closure (LC). This meta-analysis was performed to compare surgical outcomes in patients who underwent EC versus LC.

Methods Randomised controlled trials (RCT) which evaluated the effect of EC versus LC of ileostomy on surgical outcomes in rectal cancer patients was searched on PubMed, Web of Science, Embase and Cochrane Library. RCTs evaluating EC vs. LC of defunctioning ileostomies for rectal cancer patients were included. The primary outcome measures include overall morbidity, surgical complications, anastomotic dehiscence, and reoperation rates.

Results Five RCTs were included in this meta-analysis of 387 patients. The pooled estimate of the OR for overall morbidity (OR 1.80, 95% CI 0.97–3.31; $p=0.06$), reoperation (OR 2.57, 95% CI 0.72–9.14; $p=0.14$), and anastomotic leakage (OR 3.25, 95% CI 0.40–26.38; $p=0.27$) were not statistically significant. EC however resulted in a statistically significant increase in terms of surgical complications (OR 2.63, 95% CI 1.04–6.67; $p=0.04$). These studies had low to moderate levels of statistical heterogeneity.

Conclusion EC of defunctioning ileostomy in rectal cancer patients results in increased surgical complications compared to patients with LC. Caution must be undertaken in patients in whom an EC is performed.

Keywords Meta-analysis, Rectal cancer, Ileostomy, Early closure, Morbidity

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Introduction

A defunctioning ileostomy is commonly created to avert systemic sepsis associated with a tenuous anastomosis, particularly when the risk of anastomotic dehiscence is high [1]. One commonly encountered clinical scenario is a patient requiring a low colorectal anastomosis for rectal cancer following neoadjuvant therapy. In such cases, the ileostomy is left in situ for the duration of adjuvant chemotherapy and is only reversed five to six months following its creation [2]. In addition, between 15 and 25% of all supposedly temporary ileostomies never get reversed [3, 4].

Ileostomies are not without its complications. Following ileostomy creation, about 15% of patients require readmissions due to complications associated with the ileostomy. Surgery to reverse the ileostomy also poses a risk of anastomotic dehiscence and even mortality [5, 6]. The impact of temporary ileostomy on quality of life is also well documented, with patients reporting decreases in physical and role functioning [7].

In addition, with the increased adoption of total neoadjuvant therapy (TNT) in locally advanced rectal cancer where there is no further need for systemic treatment after surgery, there has been heightened interest on the safety and feasibility of early reversal of defunctioning ileostomies, especially since anastomotic dehiscence after rectal cancer surgery occurs in only about 10% of patients [8]. While existing systematic reviews and meta-analyses have examined the outcomes of patients who underwent distal colorectal resections after early and late ileostomy closure, both benign and malignant surgical indications were included in these studies. For example, in an earlier meta-analysis by Farag et al. [9], out of four randomised controlled trials, one trial included rectal firearm injuries while another considered both benign and malignant rectal lesions concurrently. There are good reasons to consider only rectal cancer patients as in this meta-analysis. The surgical option between a patient with rectal cancer and a patient with benign disease is markedly different as surgery in cancer requires a more aggressive lymphadenectomy. This therefore corresponds to increased complications and risks of surgery, therefore raising this pertinent question about whether an ileostomy needs to be maintained for a longer period of time.Taken together, the aim of this study is therefore to perform a meta-analysis of randomised controlled trials to determine the pooled potential for early versus late ileostomy reversal in low rectal cancer patients.

Methods

This meta-analysis was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement [10]. A PRISMA checklist [11] has also been included in Appendix A. The review protocol was registered on PROSPERO (ID: CRD42024541325).

Clinical trial number

Not applicable.

Search strategy

An electronic search was conducted on PubMed, Web of Science, Embase and Cochrane Library. There were no date or language restrictions. Full articles from systematic reviews and meta-analyses were also checked for potential articles. Medical subject headings (MeSH) and Emtree headings were used as appropriate. Headings and key words used in the searches included: “rectal neoplasms”, “rectal cancer”, “rectal tumor”, “proctectomy”, “rectum resection”, “defunctioning ileostomy”, “loop ileostomy”, “ileostomy”, “early reversal”, “early ileostomy reversal”, “ileostomy closure”, “loop ileostomy closure”, “loop ileostomy reversal”, and “ileostomy reversal”. All MeSH and Emtree terms were “exploded” to include subheadings. The truncation symbol (*) was also used as appropriate. The Boolean operator “OR” was used within concepts, while “AND” was used to link concepts. Conference abstracts found during the search were reviewed. Articles relating to relevant conference abstracts were searched for, and when none found, authors were contacted for their data. The search was last performed on 2 January 2024.

Study selection

Inclusion criteria for this meta-analysis included: (1) Randomised controlled trials evaluating early versus late closure (EC vs. LC) of defunctioning ileostomies; (2) Studies which had rectal cancer patients as their population; (3) Studies which evaluated overall morbidity, surgical complications, and anastomotic leakage as their main outcomes. Exclusion criteria included: (1) Publication types such as case reports, case series, letters to the editor, retrospective studies, non-randomised studies, systematic reviews, meta-analyses, guidelines, and conference abstracts; (2) Animal studies and other experimental studies not involving human subjects. The study selection process is demonstrated in Fig. 1. Via the PRISMA flowchart.

Data extraction

Relevant studies were imported into Endnote, following which duplicates were removed using a published de-duplication method. Titles and abstracts were then reviewed for eligibility by DKHC. This was followed by full text reviews of eligible articles by DKHC and JL. Disputes in article inclusion were resolved via discussion and consensus between the two authors. Data extraction was performed by DKHC. Data parameters extracted

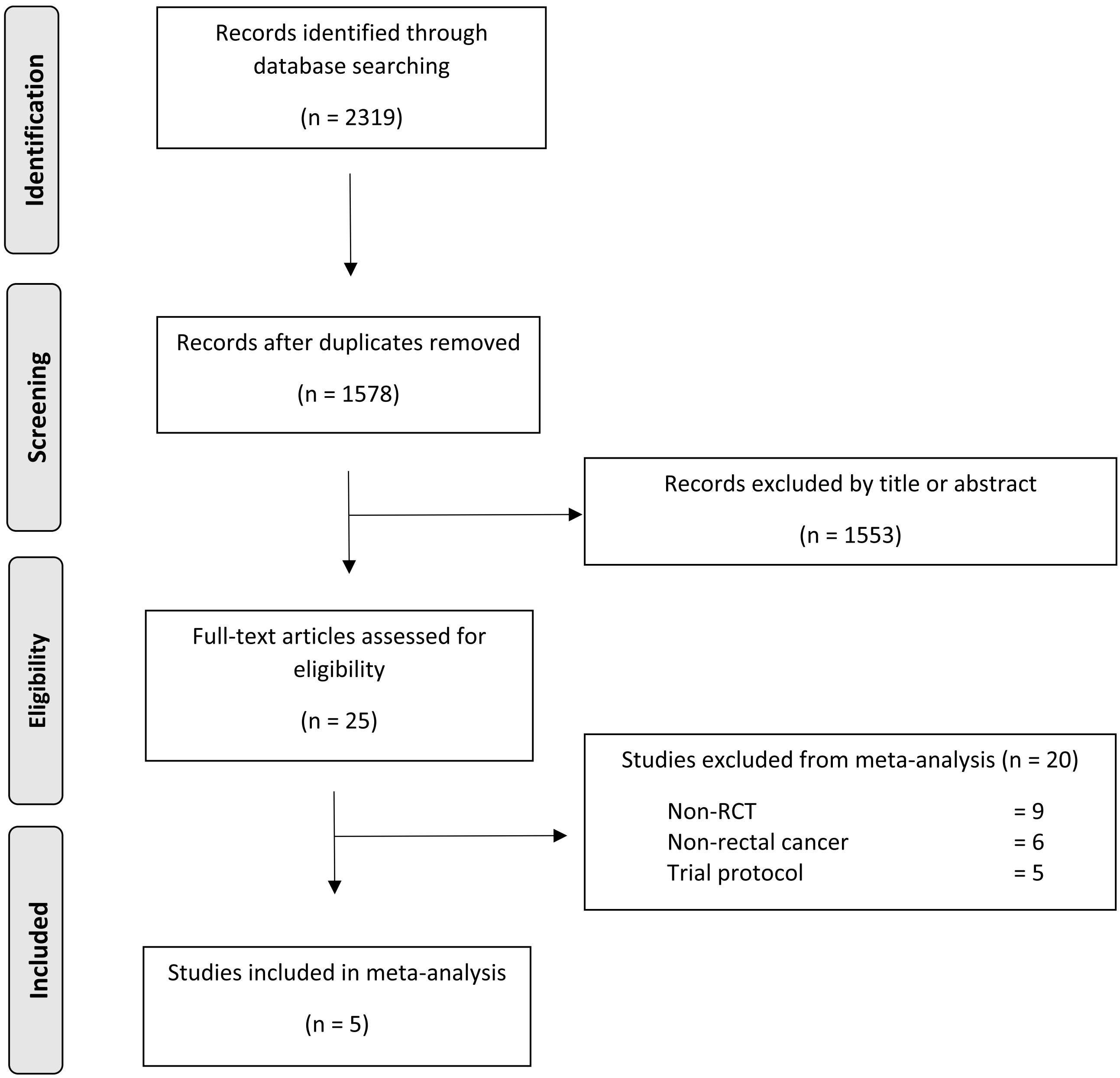

Fig. 1 PRISMA chart illustrating the search strategy, excluded records and records included in the quantitative analysis

included years which the RCT was conducted, country of study, study population, and population demographics, and definition of early reversal.

Outcome measures

Primary outcome measures evaluated the safety of early reversal of ileostomy compared to late reversal. These components were therefore overall morbidity (n), surgical complications (n), anastomotic dehiscence (n), and reoperation rates (n). Secondary outcome measures evaluated quality outcomes such as duration of surgery (min), length of stay (days), time to flatus (days) and time to normal oral intake (days). Anastomotic dehiscence was also considered a surgical complication but was analysed separately because it is the most feared complication after an anastomosis in colorectal surgery.

Study quality and risk of bias assessment

Assessment of risk of bias was performed concurrently by DKHC. The Cochrane risk of bias tool was utilised to determine of quality of RCTs [12]. A funnel plot describing the possibility of publication bias was performed, and Egger's test was used to quantitatively measure the risk of publication bias.

Data analysis

All primary and secondary outcomes were represented based on odds ratios (OR) or mean differences (MD) for dichotomous and continuous data respectively, with 95% confidence intervals (CI). A p-value of 0.05 was set as the statistical significance level. Studies which presented data as medians with either ranges or interquartile ranges were converted to mean and standard deviation based on Wan et al. [13]. A random-effects model based on the Mantel-Haenszel method was utilised following an evaluation of each study's clinical and methodological heterogeneity in their design, treatment population and interventions. Forest plots were generated for all outcomes, and statistical heterogeneity was assessed using the I^2 test with $I^2 > 50\%$ and $p < 0.05$ indicating substantial statistical heterogeneity. Sensitivity analyses was conducted using the leave-one-out approach to improve the study heterogeneity. Statistical analysis was conducted using Review Manager 5.3 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark). The funnel plot and Egger's test was performed using JASP 0.18.3 (JASP Team, Amsterdam, The Netherlands).

Results

Study selection

This search strategy across four databases returned 2379 studies. Following de-duplication, 1578 studies were analysed based on title and abstract. Twenty-five articles were analysed for full-text review. Twenty articles were excluded from the meta-analysis. Of these, nine articles were excluded as they were not RCTs, while six did not evaluate rectal cancer patients exclusively. Another five were excluded as they were trial protocols. Notably, among the articles in which six did not evaluate rectal cancer patients exclusively, two articles included patients which indeed had rectal cancer [14, 15]. In the case of Lasithiotakis at al., 12 out of a total of 36 patients underwent surgery for rectal cancer. Unfortunately, no subgroup analysis was performed for results from this trial which considered only the outcomes of patients with rectal cancer. In Alves et al., this much larger trial recruited 121 patients with rectal cancer, out of a total of 186 patients. As was the case with Lasithiotakis et al., there was no subgroup analysis and specific results relating to patients with rectal cancer cannot be determined. The corresponding authors were both contacted but there was no reply from either, hence the results have been excluded from this meta-analysis.

Trial protocols were however evaluated for their relevance to our meta-analysis, and three were deemed to be relevant. The clinicaltrials.gov identifier for these three protocols were NCT01865071 [16], NCT02609451 [17], and NCT03746353 [18]. None of these protocols had been updated in the past two years. Authors were emailed seeking further information regarding the trials but no replies were obtained. Finally, four RCTs were included in this meta-analysis, one of which was translated from Russian to English using Google Translate [19–23].

Study characteristics

The five RCTs included in this analysis involved a total of 387 patients, with 195 participants (50.4%) in the EC group, and 192 (49.6%) in the LC group. These five studies originated from four countries within Europe, and were all published between 2017 and 2021. The smallest study recruited 58 patients, while the largest had 112. None of the studies provided funding information for the conduct of their trials. All patients included in this study underwent a defunctioning ileostomy for rectal cancer. Patients who receive neoadjuvant therapy are at increased risk for anastomotic dehiscence. In this meta-analysis, the proportion of patients who received neoadjuvant therapy in the EC and LC groups were similar at 44.6% ($n = 87$) and 44.2% ($n = 85$) of patients respectively.

There was some heterogeneity regarding the definition of EC. In four out of the five studies, EC was defined as closure which occurred during the second week following primary cancer resection. In these three studies, early ileostomy reversal occurred between 8 and 14 days. In the study by Bausys et al., EC was defined as occurring within 30 days of primary cancer resection.

The trials centred around the complications between the EC and LC approach. Overall, surgical complications included bleeding, infection and anastomotic leakage. Reasons for reoperation included failed attempt at stoma closure [19], small bowel obstruction [19, 21, 22], volvulus [20], intra-abdominal bleeding [20], anastomotic leakage at either the ileal-ileal anastomosis or the colorectal anastomosis [22, 23].

Results from the Cochrane risk of bias tool can be found in Fig. 2. All studies utilised computer generated randomisation and concealment with opaque sealed envelopes except Gallyamov et al., which did not specify the concealment method and hence was judged to have uncertain risk of bias. Blinding of patient and surgeon was not possible due to the intervention performed, but this was not likely to affect performance bias. The most concerning aspect was the high risk of detection bias in two studies. In Gallyamov et al. and Klek et al., there was no discussion regarding how complications following ileostomy were captured. As many patients would have been discharged from hospital 30 days post ileostomy reversal, there was also no mention about whether patients had been contacted or reviewed in the outpatient clinic. These two studies were judged to be at high risk of bias. Attrition was minimal across all studies. Finally, only Danielsen et al. had published their protocol, and

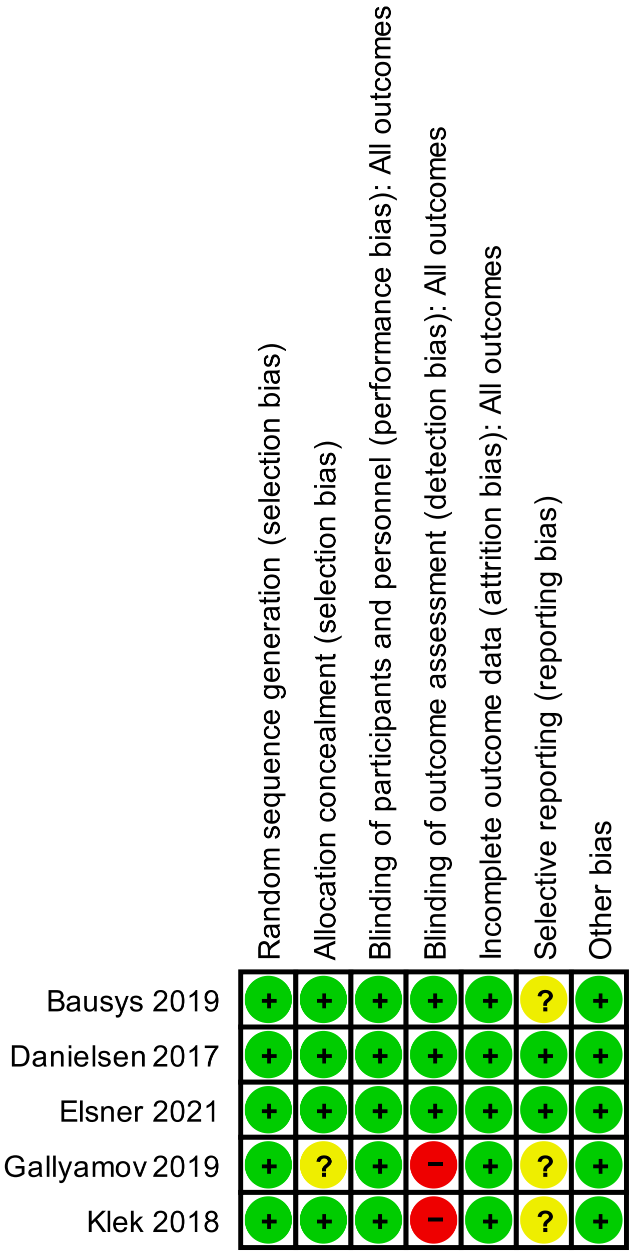

Fig. 2 Cochrane risk of bias tool for quality assessment in randomized controlled trials

therefore, published endpoints could be checked against a pre-established protocol. As such, only Danielsen et al. and Elsen et al. were judged to have low risk of reporting bias, while all other studies had uncertain risk. Overall, three studies had low risk of bias, while another two had moderate risk of bias. Table 1. Summarizes the characteristics of the included studies.

It is also important to note the implications of the study by Elsner et al. having been stopped earlier due to exceptionally high risks associated with the group which had early ileostomy reversal. This will be discussed in greater detail in the discussion section. However, briefly, the reasons that the trial was stopped were due to the significantly higher risk of reintervention and anastomotic leakage in the early closure group compared with late closure.

With regards to quality-of-life analysis, only Elsner et al. provided information on quality-of-life measurement. The authors used the Gastrointestinal Quality of Life index six weeks after anterior resection and notably found that there was no improvement in the quality of life after early reversal of ileostomy. This factor contributed to the earlier termination of the study as the higher complication risk did not bring about the purported benefit of an improvement in quality of life. As this was the only study which had considered quality of life, no meta-analysis was performed on this metric.

Primary study outcomes

The outcome data from the individual studies are summarised in Table 2.

Overall morbidity

This analysis included all five studies with 195 patients in the EC arm and 192 patients in the LC arm. Overall morbidity included both surgical and medication complications occurring outside the normal recovery process following surgery to reverse the ileostomy. The proportion of patients who suffered morbidity was 20.0% ($n = 39$) in the EC group and 12.0% ($n = 23$) in the LC group. Although not statistically significant, the odds of morbidity in the EC group was 1.82 (95% CI 0.97–3.31; $p = 0.06$). The studies had a low level of statistical heterogeneity, with an I^2 of 1% and p value of 0.40 (Fig. 3).

Surgical complications

This analysis also included all five studies. Surgical complications referred to complications specific to the operation, such as bleeding, wound infection, or small bowel obstruction occurring after ileostomy reversal. The proportion of patients with surgical morbidity was 11.3% ($n = 22$) in the EC group, and 3.6% ($n = 7$) in the LC group. This analysis was statistically significant, as the odds of surgical complications in the EC group was 2.63 (95% CI 1.04–6.67; $p = 0.04$). The studies had a low level of statistical heterogeneity, with an I^2 of 0% and p-value of 0.44 (Fig. 4).

Anastomotic dehiscence

Only three studies evaluated anastomotic dehiscence specifically (Danielsen et al., Bausys et al., and Elsner et al.) and were included in this analysis. There were 135 patients in the EC group and 129 in the LC group. The odds of anastomotic leak in the EC group was 3.75 (95% CI 0.40–26.38; $p = 0.27$) though this was not statistically significant. The studies had a low level of statistical heterogeneity, with an I^2 of 30% and p-value of 0.24 (Fig. 5).

Table 1 Study and patient characteristics

Original study	Duration of RCT	Country	Population, n	Age, median (range) or mean (SD), years	Gender proportion (M/F), n (%)	Timing of early ileostomy reversal	Timing of late ileostomy reversal	Actual time to reversal, median (range) or mean (SD), days	Clavien-Dindo ≥3, n (%)	Stage of cancer (0/1/2/3/4), n (%)	Neoadjuvant therapy administered, n (%)
Danielsen 2017	2011– 2015	Denmark	EC:55 LC: 57	EC: 67 (36– 82) LC: 67 (39– 81)	EC: 24/31 (43.6/56.4) LC: 36/21 (63.2/36.8)	8– 13 days after stoma creation	>12 weeks after stoma creation	EC: 11 (8-152) LC: 148 (64-665)	EC: 2/55, (3.6) LC: 4/57 (7.0)	EC: 0/12/21/18/3 (0/22/38/33/5) LC: 0/19/13/20/1 (0/33/23/35/2)	EC: 16 (29) LC: 16 (28)
Klek 2018	2016– 2017	Poland	EC: 29 LC: 29	EC: 55.7 (12.2) LC: 56.2 (12.5)	EC: 18/11 (62.1/37.9) LC: 16/13 (55.2/44.8)	14 days after stoma creation	30 days after completion of adjuvant chemotherapy	EC: 17.3 (1.5) LC: 278.6 (89.1)	EC: 1/29 (3.4) LC: 1/29 (3.4)	EC: 0/0/17/12/0 (0/0/58.6/41.4/0) LC: 0/0/17/12/0 (0/0/58.6/41.4/0)	EC: 29 (100) LC: 29 (100)
Gal-lyamov 2019	-	Russia	EC: 31 LC: 34	EC: 62 (32– 78) LC: 67 (35– 77)	EC: 14/17 (45.2/54/8) LC: 21/13 (61.8/38.2)	8– 13 days after stoma creation	>12weeks after stoma creation	EC: 11(8-21) LC: 148 (64-265)	EC: 1/31 (3.2) LC: 1/34 (2.9)	EC: 0/7/12/10/2 (0/22/38/33/5) LC: 0/12/8/13/1 (0/33/23/35/2)	EC: 9 (29) LC: 9 (28)
Bausys 2019	2011– 2017	Lithuania	EC: 43 LC: 38	EC: 65 (56–72)[a] LC: 66 (60– 70)	EC: 25/18 (58.1/41.9) LC: 18/25 (41.9/58.1)	30 days after stoma creation	90 days after stoma creation	EC: 34 (29-47)[a] LC: 92 (80-157)	EC: 5/43(11.6) LC 0/38	EC: 0/16/16/10/1 (0/37.2/37.2/23.3/2.3) LC: 0/14/11/12/1 (0/36.8/28.9/31.6/2.6)	EC: 20 (46.5) LC: 19 (50)
Elsner 2021	2007– 2014	Switzerland	EC: 37 LC: 34	EC: 67 (41– 88) LC: 67 (48– 87)	EC: 21/16 (57/43) LC: 26/8 (76/24)	2 weeks from the index anterior resection surgery	12 weeks from the index anterior resection surgery	EC: 15 (10– 134) LC: 89 (76– 128)	EC: 6/37 (16.2) LC: 0/37	EC: 4/11/9/11/2 (11/30/24/30/5) LC: 4/14/5/7/4 (12/41/15/20/12)	EC: 13 (35) LC: 12 (35)

[a]Interquartile range is presented in parenthesis instead of range

Table 2 Outcome data in eligible studies

Original study	Morbidity, n (%)	Surgical complications, n (%)	Anastomotic leak, n (%)	Reoperation, n (%)	Duration of surgery (min), median (range) or mean (SD)	Length of stay (days), median (range) or mean (SD)	Time till flatus (days), median (range) or mean (SD)	Time till diet (days), median (range) or mean (SD)
Danielsen 2017	EC: 4 (7.3) LC: 4 (7.0)	EC: 2 (3.6) LC: 1 (1.8)	EC: 0 LC: 1 (1.8)	EC: 2 (3.6) LC: 1 (1.8)	EC: 50 (17– 180) LC: 71 (31– 401)	EC; 4 (2– 27) LC: 4 (2– 28)	EC: 1 (0– 6) LC: 2 (0– 8)	EC: 1 (0– 23) LC: 2 (0– 20)
Klek 2018	EC: 3 (10.3) LC: 4 (13.8)	EC: 3 (10.3) LC: 3 (10.3)	EC: 0 LC: 0	EC: 1 (3.4) LC: 1(3.4)	EC: 83.2 (15.9) LC: 87.1 (21.7)	EC: 5 (4– 6)[a] LC: 5 (4– 5)	EC: 2 (1– 2)[a] LC: 2 (1– 2)	NR
Gallyamov 2019	EC: 2 (6.5) LC: 2 (5.9)	EC: 1 (3.4) LC 1 (3.4)	EC: 0 LC: 0	EC: 0 LC: 1 (3.4)	EC: 50 (27– 126) LC: 71 (31– 134)	EC: 4 (2– 21) LC: 4 (2– 28)	EC: 1 (0– 6) LC: 2 (0– 8)	EC: 1 (0– 8) LC: 2 (0– 20)
Bausys 2019	EC: 12 (27.9) LC: 3 (7.9)	EC: 10 (23.3) LC: 2 (5.3)	EC: 3 (7.0) LC: 0	EC: 4 (9.3) LC: 0	EC: 50 (40– 65) LC: 50 (40– 60)	EC: 7 (6– 9)[a] LC: 6 (6– 7)	NR	NR
Elsner 2021	EC: 18 (49) LC: 10 (29)	EC: 6(16) LC: 0	EC: 3 (8) LC: 0	EC: 6(16) LC: 0	EC: 130 (60– 240) LC: 110 (60– 257)	EC: 28 (17– 77) LC: 27 (17– 87)	EC: 2 (1– 5) LC: 2 (0– 4)	EC: 4 (1– 26) LC: 4 (2– 10)

[a] Interquartile range is presented in parenthesis instead of range

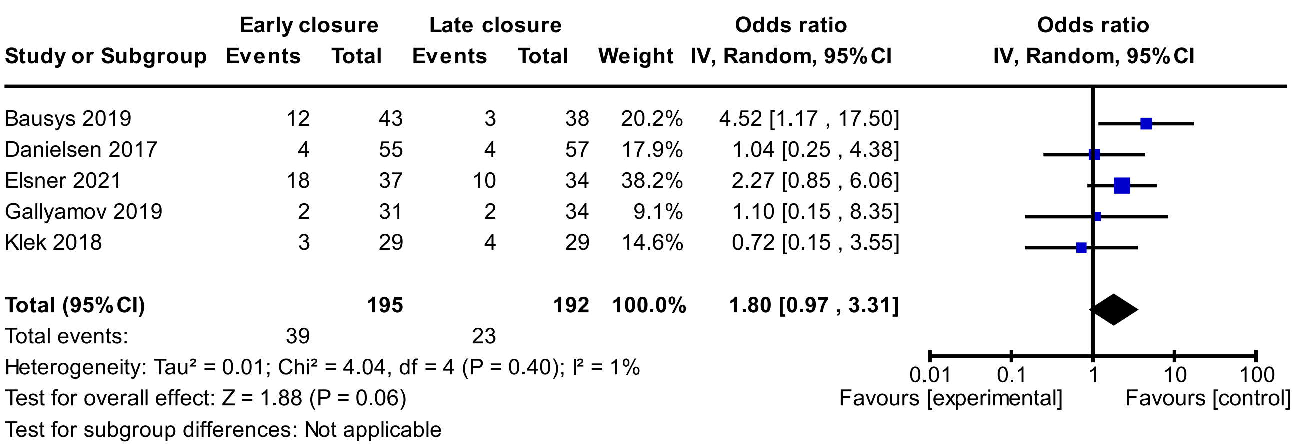

Fig. 3 Forest plot comparing overall morbidity rate between EC and LC

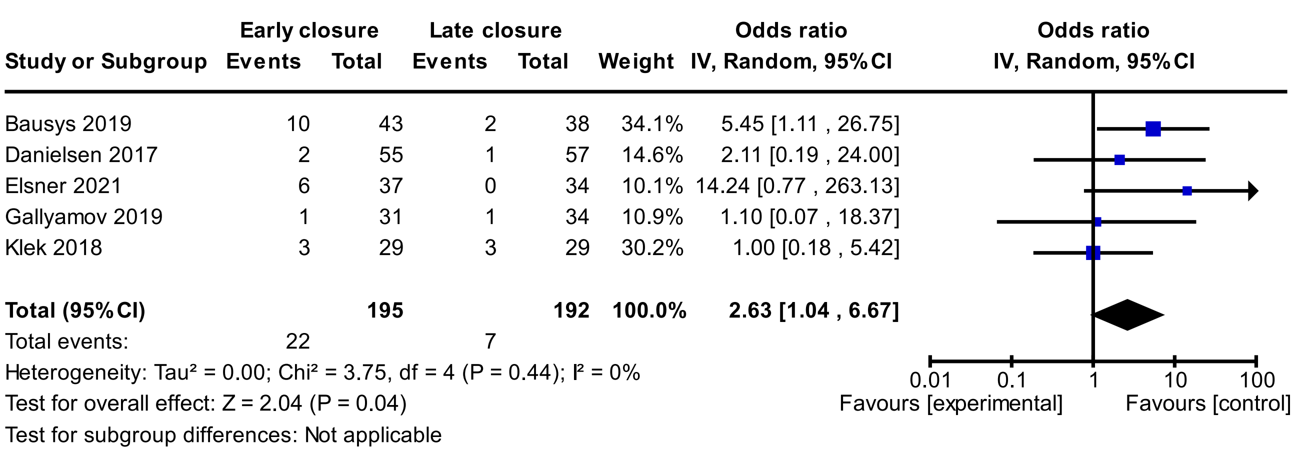

Fig. 4 Forest plot comparing post-operative surgical complications between EC and LC

Reoperation

All five articles were also evaluated for reoperation rates. The proportion of patients who were re-operated was 6.7% ($n=13$) in the EC group while it was 1.6% ($n=3$) in the LC group. The odds of reoperation were 2.57 (95% CI 0.72–9.14; $p=0.14$) and this was not statistically significant. The studies had a low level of statistical heterogeneity, with an I^2 of 0% and p-value of 0.42 (Fig. 6).

Secondary outcomes

All five studies were evaluated for duration of surgery, and length of hospital stay post ileostomy creation. For duration of surgery, the MD for EC was –11.90 (95% CI

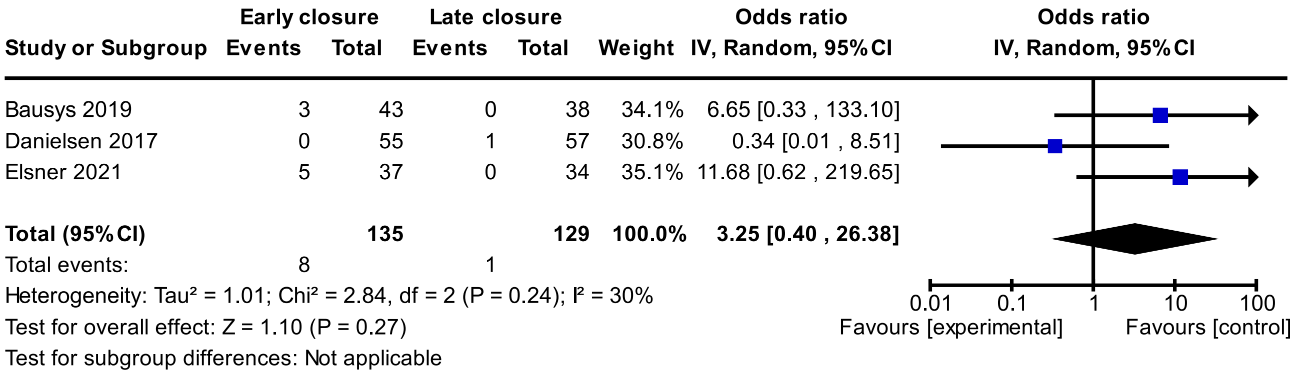

Fig. 5 Forest plot comparing anastomotic leak rates from ileostomy reversal between EC and LC

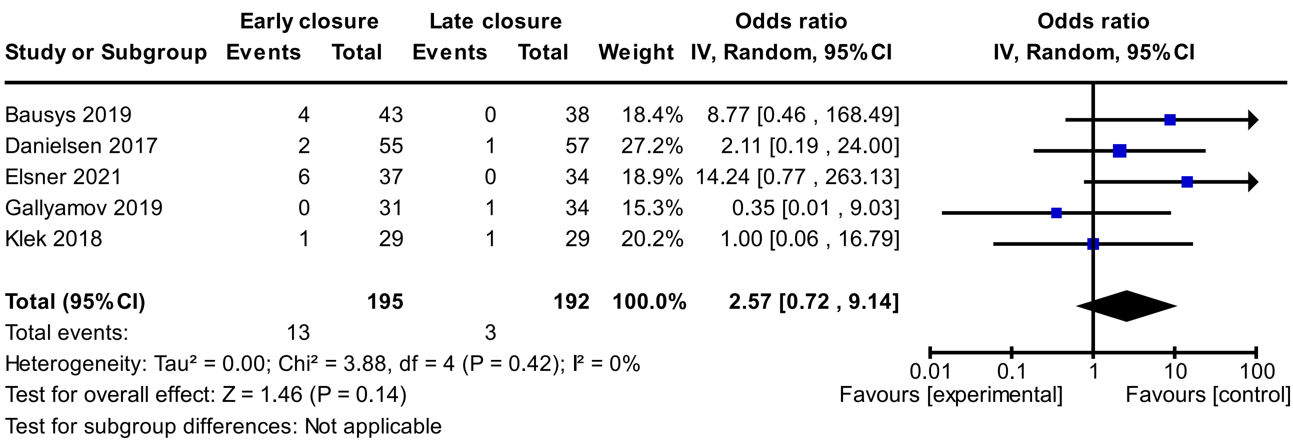

Fig. 6 Forest plot comparing re-operation rates between EC And LC

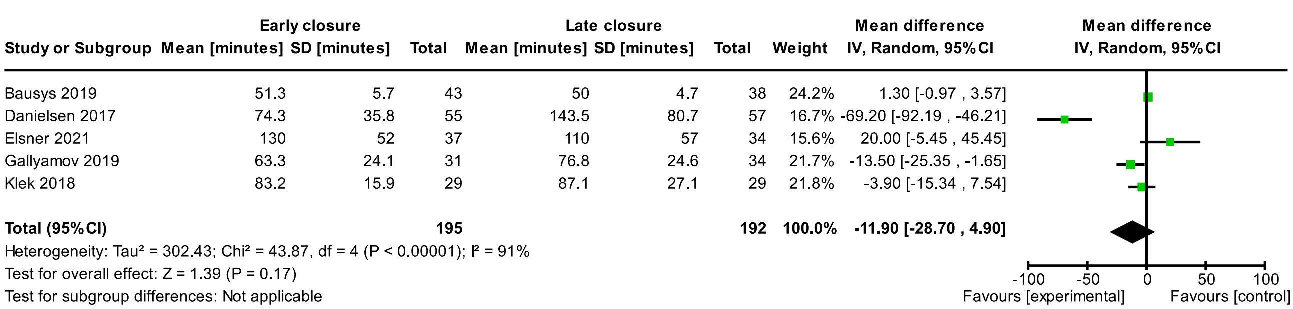

Fig. 7 Forest plot comparing duration of surgery between EC and LC

−28.70–4.90; $p=0.17$) min. There was however a high level of statistical heterogeneity with an I^2 of 91% and p-value of <0.01 (Fig. 7). Sensitivity analysis conducted through the exclusion of a single study with outlying results (Danielsen et al.) led to a pooled estimate of −3.79 (95% CI −12.05–4.46) which was also not statistically significant ($p=0.37$), but study heterogeneity improved ($Chi^2=6.62$; df = 2; $p=0.04$; $I^2=70\%$). For length of stay, the MD for EC was 0.43 (95% CI −0.21–1.07; $p=0.19$) days, and was not statistically significant also. There was a moderate level of statistical heterogeneity, with an I^2 of 24% and p-value of 0.26 (Fig. 8).

Four studies were evaluated for time to flatus. The MD for EC was − 0.44 (95% CI −0.99–0.11; $p=0.11$) days. There was a high level of statistical heterogeneity with an I^2 of 76% and p-value of <0.01 (Fig. 9). Three studies provided results for time to diet. The MD for EC was − 1.11 (95% CI −3.66–1.44 $p=0.39$) days and was not statistically significant. There was a high level of statistical heterogeneity, with an I^2 of 76% and p-value of <0.01 (Fig. 10).

Publication bias

We constructed a funnel plot based on overall morbidity to evaluate the risk of publication bias in this

Study or Subgroup	Early closure Mean [days]	Early closure SD [days]	Early closure Total	Late closure Mean [days]	Late closure SD [days]	Late closure Total	Weight	Mean difference IV, Random, 95% CI
Bausys 2019	7.3	2.3	43	6.3	0.8	38	40.2%	1.00 [0.27 , 1.73]
Danielsen 2017	9.3	5.5	55	9.5	5.7	57	8.6%	-0.20 [-2.27 , 1.87]
Elsner 2021	28	17	37	27	20	34	0.5%	1.00 [-7.67 , 9.67]
Gallyamov 2019	7.8	4.6	31	9.5	6.2	34	5.5%	-1.70 [-4.34 , 0.94]
Klek 2018	5	1.6	29	4.7	0.8	29	45.2%	0.30 [-0.35 , 0.95]
Total (95% CI)			**195**			**192**	**100.0%**	**0.43 [-0.21 , 1.07]**

Heterogeneity: Tau² = 0.13; Chi² = 5.27, df = 4 (P = 0.26); I² = 24%
Test for overall effect: Z = 1.32 (P = 0.19)
Test for subgroup differences: Not applicable

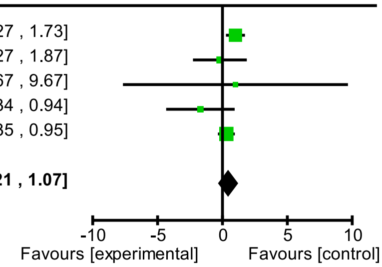

Fig. 8 Forest plot comparing length of stay between EC and LC

Study or Subgroup	Early closure Mean [days]	Early closure SD [days]	Early closure Total	Late closure Mean [days]	Late closure SD [days]	Late closure Total	Weight	Mean difference IV, Random, 95% CI
Danielsen 2017	2	1.3	55	3	1.7	57	25.1%	-1.00 [-1.56 , -0.44]
Elsner 2021	2	1	37	2	1	34	27.3%	0.00 [-0.47 , 0.47]
Gallyamov 2019	2	1.5	31	3	1.9	34	19.1%	-1.00 [-1.83 , -0.17]
Klek 2018	1.7	0.8	29	1.7	0.8	29	28.5%	0.00 [-0.41 , 0.41]
Total (95% CI)			**152**			**154**	**100.0%**	**-0.44 [-0.99 , 0.11]**

Heterogeneity: Tau² = 0.23; Chi² = 12.39, df = 3 (P = 0.006); I² = 76%
Test for overall effect: Z = 1.58 (P = 0.11)
Test for subgroup differences: Not applicable

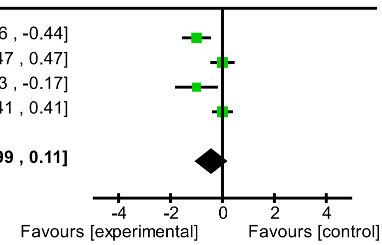

Fig. 9 Forest plot comparing time to flatus between EC And LC

Study or Subgroup	Early closure Mean [days]	Early closure SD [days]	Early closure Total	Late closure Mean [days]	Late closure SD [days]	Late closure Total	Weight	Mean difference IV, Random, 95% CI
Danielsen 2017	6.3	5	55	6	4.4	57	34.7%	0.30 [-1.45 , 2.05]
Elsner 2021	4	7	37	4	2	34	30.6%	0.00 [-2.35 , 2.35]
Gallyamov 2019	2.5	1.9	31	6	4.8	34	34.7%	-3.50 [-5.25 , -1.75]
Total (95% CI)			**123**			**125**	**100.0%**	**-1.11 [-3.66 , 1.44]**

Heterogeneity: Tau² = 4.09; Chi² = 10.48, df = 2 (P = 0.005); I² = 81%
Test for overall effect: Z = 0.85 (P = 0.39)
Test for subgroup differences: Not applicable

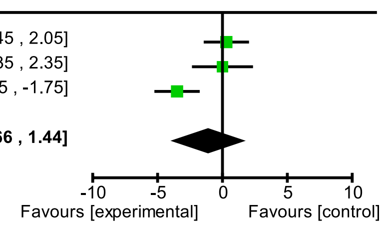

Fig. 10 Forest plot comparing time to diet between EC and LC

meta-analysis (Fig. 11). Egger's test was applied which revealed a *p*-value of 0.354, suggesting a low risk of publication bias.

Discussion

Our analysis demonstrates that EC of defunctioning ileostomy must be approached with caution. This analysis builds on one meta-analysis recently published by Podda et al. [24] analysing a number of parameters not previously included in the aforementioned meta-analysis. Here, we include analyses regarding a number of quality metrices such as length of stay, time to diet, time to flatus, as well as duration of surgery. Together, these two meta-analyses should be taken together, and provide a detailed overview of the pros and cons of the early closure technique.

The most recently concluded trial by Elsner et al. perhaps paints a cautionary tale with regards to the outcomes associated with early ileostomy reversal. EC was associated with statistically significant increased rates of surgical complications. While anastomotic leak rate, overall morbidity and rates of reoperation were not statistically significant, these were very close to approaching statistical significance. Surgeons must factor these potential complications when advising patients to consider EC for the purported benefits of reducing complications and worse quality of life whilst living with the ileostomy.

In the 5 RCTs that were included in this analysis, the studies by Danielsen et al., Gallyamov et al. and Klek et al. individually did not demonstrate any statistically significant increase in overall morbidity and surgical complications. Results from the studies by Bausys et al. and Elsner et al. were concerning as the EC group suffered from a high rate of postoperative complications. In fact, both studies were terminated early following interim analysis. On closer examination of both studies, Bausys et al. defined EC as closure occurring 30 days after stoma creation. The median time to ileostomy closure was however

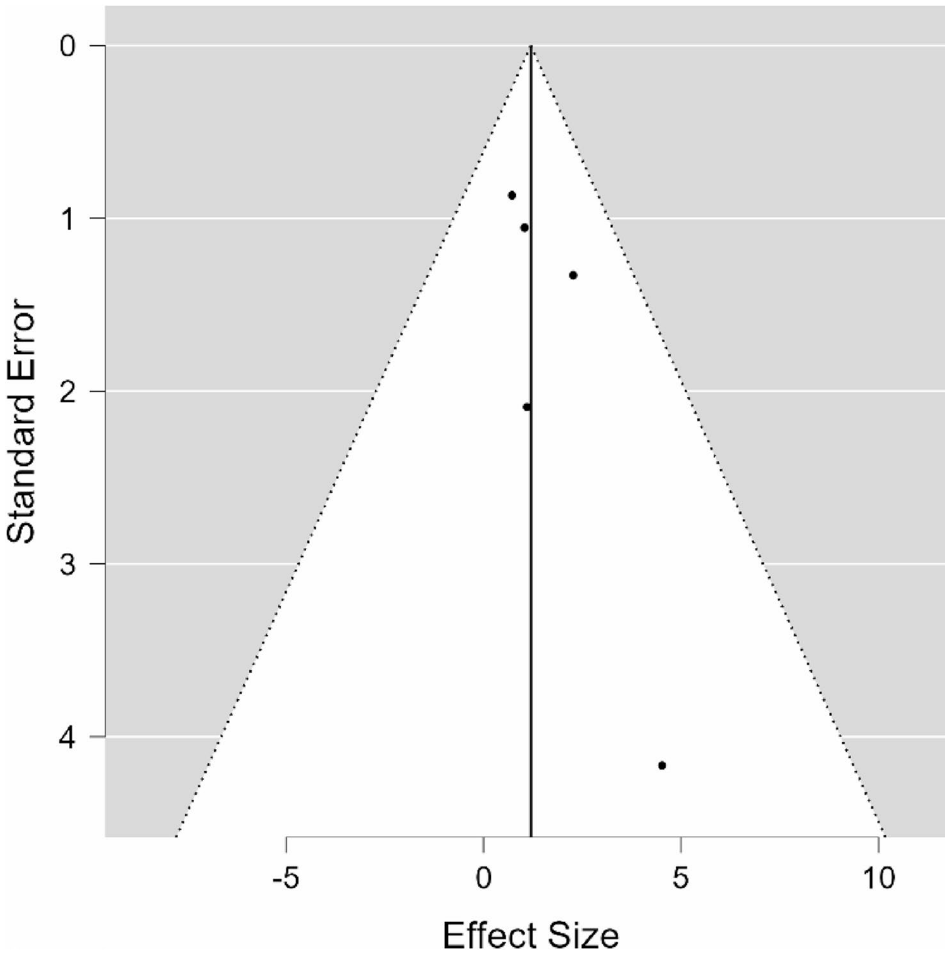

Fig. 11 Funnel plot for overall morbidity in the assessment of publication bias

34 days, range 29–47 days. This period is classically associated with the worst severity of abdominal adhesions and would likely have hampered ileostomy reversal. It remains puzzling as to why ileostomy reversal was attempted during this period and hence, not surprising that there was no reduction in the operative time compared to the other RCTs. Furthermore, 39.5% of operations in the EC group were reported to have "unexpected difficulties during surgery." This reason does not extend to the results from Elsner et al., as in this trial, the definition of EC was concordant with all the other studies. Yet, this study also experienced a significant rate of anastomotic leakage as well as re-operative intervention.

The trials conducted by Elsner et al. and Bausys et al. are both highly significant. These are two of the more recent studies, and both showed an exceptionally high risk associated with the EC group resulting in study termination. Specifically in the Elsner et al. study, there were three anastomotic leakages relating to the colorectal anastomosis and two anastomotic leakages associated with the ileostomy reversal, resulting in a total of five anastomotic leakages in total. The colorectal anastomotic leakages are highly significant. In the study, the authors had evaluated all anastomoses prior to reversal using digital palpation as well as contrast enema via stoma, and in some cases, with proctoscopy. That there were still colorectal anastomotic leakages highlights the significant difficulty associated with interrogating the joint at this early period. Moving forward, it would be ideal to definitively evaluate the surgical risks associated with EC with rigorous contemporary studies in prospective rectal cohorts.

Despite the higher surgical complications, which can range in extent of severity, surgeons also need to address the issues of living with a defunctioning ileostomy when it is no longer essential. The EASY trial by Danielsen et al. [19] was the only RCT in this meta-analysis which followed patients up for longer than 30-days post ileostomy reversal. By 12 months, there was a statistically significant decrease in the mean number of complications with an OR for EC of 0.42 (95% CI 0.32–0.57; $p < 0.0001$). The EASY trial also evaluated functional outcomes [25] but were not able to find a statistically significant difference in health-related quality of life (HRQOL) at 12 months following ileostomy reversal. This finding differs from other prospective trials, which demonstrated uncertainty whilst having the ileostomy, and improvements in global quality of life, physical functioning, social functioning, role-physical and energy-vitality scores only after the ileostomy was reversed [26, 27]. A cost-analysis of participants from the EASY trial however showed significant cost reduction associated with EC compared to LC [28].

Earlier meta-analyses which have interrogated a similar question have been performed [9, 24, 29]. These meta-analyses have however yielded different conclusions. One reason for this could be accounted for by our stringent criteria of only including rectal cancer patients in our meta-analysis. As discussed earlier, surgical decisions differ significantly in the case of cancer compared to other conditions which necessitate a diverting ileostomy. In the example of the meta-analysis by Farag et al. [9], two of the included trials recruited patients who had benign diagnoses and firearm injuries. In the other meta-analysis by Menahem et al. [29], both retrospective studies as well as non-randomised prospective studies made up half of the number of trials included for analysis. We believe that randomisation is of critical importance in determining the feasibility of EC vs. LC given that the clinical decision to reverse a stoma is likely to result in significant selection bias for both groups. Finally, in the study by Podda et al., [24], their meta-analysis included two studies which we had not included [14, 15], as we were not able to obtain subgroup analyses of rectal cancer patients in spite of contacting the authors. Nonetheless, these two studies accounted for the two earliest studies, both done more than 15 years ago, and could reasonably be excluded due to changes in contemporary practice. We believe these account for the differences in conclusion between our study and earlier ones.

Our meta-analysis therefore serves as a cautionary warning for the surgical community that EC of ileostomy in rectal cancer, while technically feasible and potentially cost-saving from an institutional perspective, can result in an increased risk of surgical complications. While other metrics such as anastomotic leak rate were not statistically significant, the results favoured towards an increased complication risk which cannot be simply ignored despite lack of statistical significance. We chose to include only rectal cancer patients in this review as any complication which occurs during this immediate post-reversal period may result in delays to chemotherapy delivery. Timely chemotherapy delivery is associated with improved overall survival [30]. In addition, neoadjuvant therapy, which about 50% of patients in both groups underwent, is an independent risk factor for anastomotic leakage at the colorectal anastomosis [31]. Surgeons concerned about the effects of systemic sepsis in the event of a colorectal anastomotic dehiscence might be inclined to keep the ileostomy for longer. Our results also suggest that further high-quality RCTs are required, as this could be the determining factor in a meta-analysis which ultimately statistically and clinically suggests that risks of EC are high.

Further consideration needs to be accorded to specific subgroups of patients who differ in their treatment regime for rectal cancer. One such group includes patients who may not have undergone any neoadjuvant therapy but require adjuvant therapy following histopathologic analysis of the resection specimen. In such patients, the morbidity which arises from EC could result in a delay of commencement of adjuvant therapy, therefore bringing about worse outcomes. Another group of patients have indeed received some form of neoadjuvant therapy. In such patients, it is well known that radiotherapy results in fibrosis which may make dissection in the pelvis more challenging [32], and therefore increase the risks of EC in such patients. Further studies will need to be done to characterise the specific risk of complications of EC arising from patients who have undergone neoadjuvant therapy.

Finally, we have the group of patients who undergo the contemporary regimes of TNT where no further chemotherapy is given to the patient after surgery [33]. In patients who have undergone TNT, up to 30% of patients may even obtain a pathological complete response [34]. In such patients who will not be receiving further chemotherapy after surgery, the role of the defunctioning ileostomy only applies to the initial healing period of the low anastomosis. Hence, patients may themselves advocate for an earlier reversal of the defunctioning ileostomy once this initial healing period is over. Even among patients not receiving TNT, the increased push towards the use of laparoscopic or robotic surgery has resulted in reduced length of stay post-surgery [35]. Patients may therefore not stay in hospital long enough for the ileostomy to be reversed in the same admission. Future trials could therefore study the possibility of stoma reversal at varying periods before the commencement of adjuvant chemotherapy.Ultimately, considering the findings of this meta-analysis that morbidity is increased in EC of defunctioning ileostomies, further research will need to be conducted to determine the precise time in which reversal of ileostomy is both as safe and as early as possible.

Limitations of this meta-analysis include the small number of RCTs performed, which precluded meaningful sensitivity analyses or meta-regression. Although the number of studies in this meta-analyses could have been increased by including non RCTs, we ultimately declined to do so as taking an RCT-only approach was more likely to demonstrate the highest available scientific rigour in this field of surgical research. We were also not able to conclusively comment on secondary outcomes due to the small number of studies and the large statistical heterogeneity between studies. This large statistical heterogeneity is likely due to most studies not having been powered to evaluate these outcomes. All studies utilised overall morbidity as the primary outcome to determine an appropriate sample size. Further RCTs need to be designed with standardisation of surgical technique, including an appraisal of the seniority of the surgeons performing the ileostomy reversal, and the use of hand-sewn versus stapled anastomoses [36], all of which have been shown to result in differences in surgical outcomes.

These limitations notwithstanding, the current research has demonstrated that EC in patients with a defunctioning ileostomy in the setting of an anterior resection should be undertaken with caution. Although pooled estimates for overall morbidity, surgical anastomotic dehiscence and reoperations were not found to be significant, the magnitude of increased risk as provided by the ORs was high. Future studies should seek to achieve a high level of scientific rigour using appropriate sample size estimation, particularly for low-prevalence but clinically significant outcomes such as anastomotic dehiscence or reoperation– especially in the control groups. We also encourage future trials to consider the importance of secondary outcomes related to health services delivery and post-closure quality of life, as these indicators will be necessary for long-term cost-effectiveness analyses of EC for the benefit of institutions. Ultimately, we encourage the surgical community to consider further trials of good quality to meet this pressing need, and to finally answer the dilemma surrounding the EC of defunctioning ileostomies.

Supplementary Information

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Supplementary Material 1.

Supplementary Material 2.

Authors' contributions

Dedrick Kok Hong Chan designed the study. Dedrick Kok Hong Chan performed the data searches and extracted the data. Dedrick Kok Hong Chan and Jerrald Lau performed validation and critical appraisal of the data. DKHC drafted the manuscript. Ker-Kan Tan provided supervision. Dedrick Kok Hong Chan, Jerrald Lau, Jarrod Kah-Hwee Tan, Bryan Buan, Kai-Yin Lee, Norman Sihan Lin, Ian Jse-Wei Tan, Jing-Yu Ng, Bettina Lieske, Wai-Kit Cheong, and Ker-Kan Tan reviewed, critiqued and edited the final version of the manuscript.

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Data availability

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

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Competing interests

The authors declare no competing interests.

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