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SYSTEMATIC REVIEW

Is early bowel resection better than medical therapy for ileocolonic Crohn's disease? A systematic review and meta-analysis

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Abstract

Aim: There is emerging evidence supporting early bowel resection (EBR) for ileocaecal Crohn's disease (CD) as an alternative to conventional escalation of medical therapy (MT). Here, we present a systematic review and meta-analysis of studies comparing the outcomes of EBR with those of MT in ileocolonic CD, with a focus on ileocaecal disease.

Methodology: The MEDLINE, Embase, CINAHL and Cochrane Central Register of Controlled Trials databases were searched for studies reporting the outcomes of EBR versus MT for ileocolonic CD. The Cochrane tools for assessment of risk of bias were used to assess the methodological quality of studies.

Results: Nine records (from 8 studies, with a total of 1867 patients) were included in the analysis. Six studies were observational and two were randomised controlled trials. There was a reduced need for drug therapy in the EBR arm. The rate of intestinal resection at 5 years was 7.8% in the EBR arm and 25.4% in the MT group with a pooled OR of 0.32 (95% CI 0.19, 0.54; $p < 0.0001$). The EBR group had a longer resection-free survival (HR 0.56, 95% CI 0.38, 0.83; $p = 0.004$). These outcomes were consistent in a subgroup analysis of patients with ileocaecal disease. Morbidity and quality of life scores were similar across the two groups.

Conclusion: EBR is associated with a more stable remission compared to initial MT for ileocolonic Crohn's disease. There is enough evidence to support EBR as an alternative to escalation of MT in selected patients with limited ileocaecal disease.

KEYWORDS
Crohn's disease, early bowel resection, ileocaecal disease, medical therapy

INTRODUCTION

Crohn's disease (CD) affects 276 per 100,000 people in the United Kingdom [1]. Ileocaecal disease (also known as L1 disease [2]) is the most common CD phenotype; at least one third of patients have isolated ileocaecal disease [3, 4]. Treatment usually involves initial medical therapy (MT), with steroids to induce remission, typically followed by immunosuppressors or biological agents such as infliximab to maintain remission. Surgery is typically reserved for disease refractory to MT and for complications (e.g., fibrostenosis or fistulae). The addition of multiple biologics to the therapeutic armamentarium over time has resulted in a tendency to use different drug

combinations to avoid surgery, the latter being considered the "last resort" by patients and clinicians. However, CD currently cannot be cured medically and nearly 80% of patients with ileocaecal CD eventually require surgery [5].

Surgery for inflammatory bowel disease (IBD) has evolved over the past two decades, with an increasing number of dedicated IBD units, a trend towards subspecialisation (from colorectal to highly specialised IBD surgeons) and increasing adoption of minimally invasive techniques and enhanced recovery protocols [6]. New surgical techniques may also reduce relapse after ileocaecal resection [7, 8]. While previously, patients and clinicians have viewed surgery as an option worth delaying to avoid significant morbidity, the risks with limited surgery and the negative impact on patients have now reduced.

There is a school of thought that considers that bowel resection for ileocaecal disease should not be the "last resort", as emerging evidence suggests improved outcomes with earlier surgery. A systematic review comparing early bowel resection (EBR) with initial MT for CD indicates early surgery is associated with reduced disease relapse [9]. We performed an updated systematic review and meta-analysis of studies comparing the outcomes of EBR with those of conventional MT in ileocolonic CD, with a focus on L1 disease, and incorporating more recently published evidence.

MATERIALS AND METHODS

The protocol for this systematic review was previously registered (PROSPERO, CRD42022307605). The review has been reported in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement and MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines [10, 11].

Search strategy

MEDLINE, Embase, CINAHL and Cochrane Central Register of Controlled Trials databases were searched from 1998 until 1st February 2022. Searches were limited to English language studies due to the lack of resources to support translation. Reference lists of primary studies and related reviews were hand-searched. The grey literature was searched through the OpenGrey database. Pilot searches revealed that restricting the search to ileocaecal CD would exclude relevant studies reporting outcomes in ileocolonic CD in general that nonetheless include a significant proportion of patients with L1 disease. Search terms were therefore expanded to include any ileocolonic CD. Appendix 1 contains detailed search strategies.

Eligibility criteria

Eligible studies were randomised trials, case–control, and prospective and retrospective cohort studies, reporting the outcomes of primary EBR for ileal or ileocolonic CD in adults (16 years or older), compared to either MT or late surgery (LS). Studies involving patients with CD affecting exclusively the upper gastrointestinal tract, colon or perianal region were excluded.

The definition of "early" bowel resection was accepted as surgery within a year of diagnosis of CD, including at the time of diagnosis, in observational studies, or as an alternative to escalation of MT in randomised trials, informed by experiences from pilot searches. Studies involving patients with prior bowel resection for IBD, or that made no distinction between bowel resection and other surgical procedures, or that reported only short-term postoperative outcomes were excluded. Conference proceedings were included if related full text articles were identified, or complete data obtained by contacting the corresponding author.

Outcomes

The primary outcomes were relapse rate (measured by the need for drug therapy and for surgery) and time to relapse. Data on factors influencing duration of treatment effect, morbidity (including stoma rates), mortality and quality of life were extracted where available.

Screening and data extraction

Two authors (NH and TG) independently screened the search results using the Rayyan web tool and agreed on studies warranting a full-text search [12]. NH and ZK independently extracted data from studies onto a predesigned proforma. Discrepancies during screening or data extraction were resolved through discussion. Where data were missing or unclear, corresponding authors were contacted for further information.

Risk of bias assessment

The Cochrane tool for assessment of risk of bias (ROB-2) was used to assess the methodological quality of randomised trials [13]; the ROBINS-I tool was used for nonrandomised studies [14]. Assessment was performed independently by two authors (NH and AGH) and disagreements resolved by consensus.

Data synthesis and analysis

Meta-analysis of data was performed if three or more studies reported an outcome using the same effect measure (or provided enough data for deduction of the effect measure), if the quality of the studies (based on the degree of bias in the evidence) permitted and if the studies were sufficiently homogeneous in terms of the direction of effect [15].

Results were pooled using the random-effects model. Event rates were expressed dichotomously, with the overall effect presented as pooled odds ratios (ORs). Where studies presented outcomes at different time points, outcomes were synthesised at a point at which outcomes could most consistently be estimated across studies. Time-to-event data was extracted using previously described methods [16] and presented as pooled hazard ratios (HRs). Analysis was performed using RevMan 5.4 [17]. Sensitivity analyses were conducted to determine if the robustness of results was impacted by exclusion of [1]: studies comparing outcomes of EBR with those of LS (as opposed to initial MT), or [2] studies at higher risk of bias. Where a quantitative approach was not feasible, a narrative description of the evidence, supported by structured tabulation or plots of odds ratios, has been presented. A subgroup analysis of outcomes for patients with L1 disease was performed.

Heterogeneity

The presence and degree of statistical heterogeneity between studies was quantified using the I^2 statistic. Generally, a value of 0%–40% signifies no important observed heterogeneity and > 50% represents substantial heterogeneity [15].

Quality of the evidence

The Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system was used to grade the certainty of the evidence for primary outcomes [18].

RESULTS

Search results

A total of 2320 records were identified from databases and through hand-searching. After removal of duplicates and exclusion of records based on the title and abstract, full-text searches were required for 42 records. Thirty-three were excluded with reasons (Figure 1). Nine records (from 8 studies, with a total of 1867 patients) were included in the final analysis.

Characteristics of included studies

Six studies were observational and retrospective [19–24]. Two were randomised controlled trials (RCTs): laparoscopic ileocaecal resection versus infliximab for terminal ileitis in CD (LIR!C) and the

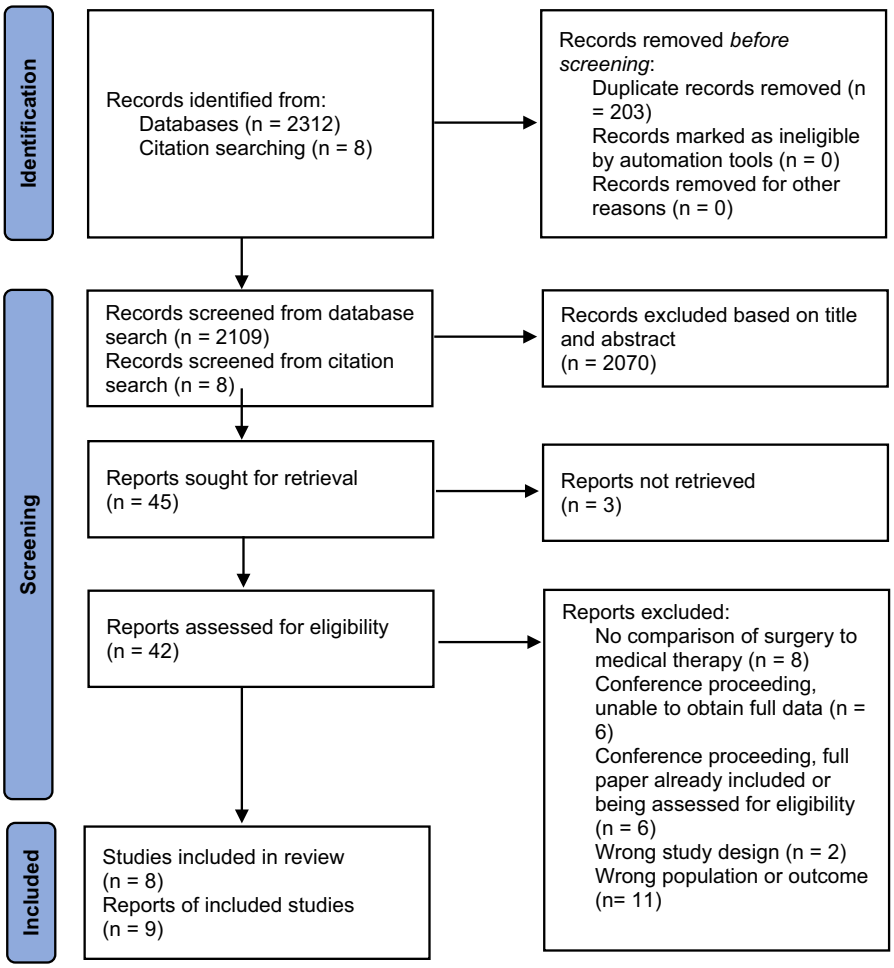

FIGURE 1 PRISMA flow chart showing inclusion and exclusion of searches.

Swedish Crohn's trial [25, 26]. A report of a 5-year retrospective review of the LIR!C RCT was included, resulting in nine studies [27]. Data were extracted from either of the two studies from the LIR!C trial (whichever reported on a more complete dataset), but not from both, for any given outcome.

The outcomes of EBR were compared with those of MT in five studies [20–22, 25, 26]. The other three included patients with a previous bowel resection for CD in both cohorts and compared the outcomes of EBR with those of LS. The definition of "early surgery", "late surgery" and inclusion criteria varied across studies, as shown in Table 1 which summarises characteristics of the studies.

Three studies included only patients with ileal or ileocaecal (L1) disease [19, 25, 26]. The others included patients with ileocolonic disease, two of which reported subgroup analyses of patients with L1 disease [22, 23]. Table 2 summarises the characteristics of patients in the included studies. Retrospective studies reported the need for intestinal resection (or repeat resection) and/or for medication as primary endpoints. The RCTs reported quality of life or disease activity as primary outcomes.

Risk of bias assessment

This is shown in Figures S1 and S2 (Appendix 2). Three observational studies were at serious risk [19, 20, 24], and one RCT was at high risk of bias [26].

Outcomes

Need for drug therapy

The differential requirement for steroids was reported as statistically significant in four studies [19, 21–23], for immunomodulators in two studies [19, 21], and for biologics in two studies [20, 24], all in favour of EBR (Table S1, Appendix 2). Immunomodulators were mainly administered prophylactically in the operative arm of the LIR!C trial; the remaining studies did not specify whether these were given as prophylaxis or treatment.

As the follow-up period over which outcomes were reported varied widely across studies (12 to a mean of 167.8 months), pooled estimates were not produced. Figure 2 shows a plot of the odds ratio of the need for medication in studies that reported overall proportions. A statistically significantly higher proportion of patients required no additional drug therapy during follow-up in the EBR arm in all three studies reporting this outcome (Figure 3) [20, 23, 27].

Need for surgical resection

Seven studies (1380 patients) provided sufficient data to estimate the rate of intestinal resection at 5 years. This was 7.8% (39/502) in the EBR arm and 25.4% (223/878) in the MT (or LS) group. The pooled OR was 0.32 (95% CI: 0.19, 0.54; $p < 0.0001$) (Figure 4). A low degree of heterogeneity was observed ($I^2 = 38\%$). This remained robust to sensitivity analyses excluding studies at high risk of bias, studies comparing EBR to LS (as opposed to MT), and studies with event rates <5. The overall quality of the evidence was moderate due to the risk of bias in individual studies.

Duration of treatment effect

The EBR group had a longer resection-free survival compared to the MT or LS group (Figure 5; HR 0.56, 95% CI: 0.38, 0.83; $p = 0.004$), based on data from five studies [19–22, 24]. A high degree of heterogeneity was observed ($I^2 = 69\%$). The heterogeneity disappeared when three studies were considered separately [19, 21, 24], the EBR arms of which consisted of patients that had "upfront" surgery for emergency presentations of CD.

Four studies reported the time to repeat resection following the first intestinal resection [19, 20, 22, 24]. This was longer in the EBR group (HR 0.65, 95% CI: 0.47, 0.91; $p = 0.01$). There was no associated heterogeneity ($I^2 = 0\%$) (Figure 6). The overall quality of the evidence, for both the time to first resection and the time to repeat resection, was moderate due to the risk of bias.

In the LIR!C trial, patients in the EBR group had a longer period without infliximab than did patients in the MT (infliximab) group without a resection (median 25.5 vs. 17.0 months, $p = 0.01$). Time without additional drug therapy was similar between the two groups (median 33 vs. 34 months respectively; $p = 0.521$); corresponding values for the EBR group versus the LS group were 14 months versus 1 month, respectively ($p < 0.001$) in the study by Kelm and colleagues [23].

Factors associated with duration of treatment effect

Three studies identified EBR as the only independent variable favourably influencing the duration of treatment effect based on their multivariable analyses. Aratari and colleagues reported a reduced need for steroids ($p = 0.02$) [19], Latella and colleagues a reduced need for intestinal resection ($p < 0.0001$) [21], and Golovics and colleagues a reduced probability of requiring a second resection ($p = 0.04$) [22]. One study reported late surgery ($p = 0.08$) and young age at surgery ($p = 0.001$) to be independently associated with a higher risk of biologic use [24]. Prophylactic immunomodulators were found to decrease the need for additional treatment in both arms of the LIR!C trial [27].

Morbidity and mortality

Where reported, anastomotic leak and stoma formation rates were similar between the two arms (Table 3). In one study, overall major morbidity occurred in 12 out of 207 (5.8%) patients, without

TABLE 1 Studies comparing the outcomes of early bowel resection and medical therapy (or delayed surgery) for ileocolic Crohn's disease.

First author (year of publication)	Type of study period studied duration of follow-up	Inclusion criteria	Comparators		Endpoints
			Early bowel resection	Medical therapy (MT) or late surgery (LS)	
Aratari (2007) [19]	Retrospective cohort Not specified Mean of 147 months (12–534)	Previous radical surgical resection for ileal CD (with or without right colon involvement)	Primary surgery performed at the time of diagnosis for an acute presentation of CD ($n = 83$)	Late surgery during the course of the disease ($n = 124$)	1. Clinical recurrence (need for steroids). 2. need for immunosuppressants, need for surgical resection
Latella (2009) [21]	Retrospective cohort 1980–2005 EBR Mean 167.8 months (12–468). MT 103.8 months (12–540)	Patients with a new diagnosis of CD	Primary surgery performed at the time of diagnosis for an acute presentation of CD (acute abdomen) ($n = 115$)	Initial medical therapy ($n = 375$)	1. Need for first intestinal resection since diagnosis. 2. Need for medical therapy
Golovics (2013) [22]	Retrospective cohort 1977–2008 Median 11.4 years	Patients with a new diagnosis of CD	Limited bowel resection within 1 year of diagnosis ($n = 63$)	Initial medical therapy during the first year of diagnosis ($n = 428$)	1. Disease course, drug exposure, need for surgery and reoperation rates
An (2016) [20]	Retrospective cohort 1995–2014 Median 67 months (range 31–114) for EBR group, 97 months (58–150) for MT	Patients with ileal or ileocolonic CD	Primary surgery at the time of diagnosis for acute presentation of CD, or surgery within 6 months of diagnosis of CD ($n = 42$)	At least 6 months of medical therapy ($n = 115$) "Deferred surgery" – subgroup who had surgery after 6 months ($n = 62$)	1. Need for surgical resection. 2. Number and duration of hospitalisations, need for medical therapy
Gerdin (2016) (Swedish Crohn's trial) [26]	RCT 1999–2007 1, 3, 5 years	Patients with TI or ileocaecal CD diagnosed not more than 1 year before inclusion and who had not received any prior treatment for CD	Open ileal or ileocaecal resection ($n = 18$)	Induction of remission with budesonide and treatment with azathioprine or 6MP ($n = 18$)	1. Crohn's disease activity index (CDAI) at 1, 3 and 5 years. 2. QoL measured using SF-36 questionnaire and a visual analogue scale (VAS)
Ponsioen (2017) (LIR!C trial) [25]	RCT May 2008 – Oct 2015 12 months (Ponsioen)	Active Crohn's disease of the TI, with at least 3 months of conventional therapy with steroids, thiopurines or methotrexate that failed	Laparoscopic ileocaecal resection ($n = 73$)	Infliximab (induction followed by maintenance regime) ($n = 70$)	1. Disease-specific quality of life (QoL) score assessed with IBD-Q. 2. General QoL score assessed with SF-36 questionnaire, days on sick leave, morbidity, body image and cosmesis, costs per QALY
Lee (2018) [24]	Retrospective cohort 1982 to 2008 Median 99 months (1–323) in EBR group; 105 months (2–277) in LS group	Patients with ileocolonic Crohn's disease with previous bowel resection	Bowel resection within 1 month prior to or after diagnosis of CD ($n = 120$)	Bowel resection at least 1 month after diagnosis ($n = 123$), also naïve to medical therapy	1. Medication use and reoperation rates
Stevens (2020) (Retrospective follow up of LIR!C trial) [27]	Retrospective cohort May 2008 – October 2015 Median 63.5 months (IQR 39–94.5)	Active Crohn's disease of the TI, with at least 3 months of conventional therapy with steroids, thiopurines or methotrexate that failed	Laparoscopic ileocaecal resection ($n = 69$)	Infliximab (induction followed by maintenance regime) ($n = 65$)	1. Need for surgery/ repeat surgery or anti-TNF therapy, duration of treatment effect, factors associated with duration of treatment effect
Kelm (2021) [23]	Retrospective cohort 2006–2017 2 years	Previous ileocaecal resection due to CD with terminal ileitis	Primary resection without previous MT ($n = 29$)	Resection following a period of MT ($n = 74$)	1. Need for anti-inflammatory or immunosuppressant within 2 years after surgery. 2. Time interval between resection and start of medication, escalation of medical therapy, need for additional resection

Abbreviations: CD, Crohn's disease; EBR, early bowel resection; IBD-Q, Inflammatory bowel disease questionnaire; IQR, interquartile range; LS, late surgery; MT, Medical therapy; QALY, quality-adjusted life year; RCT, randomised controlled trial; SF-36, 36 item short form survey; TI, terminal ileum.

TABLE 2 Characteristics of patients in included studies.

	Number of patients		Gender No. of male pts (%)		Smoker *n* (%)		Disease phenotype (no. with each phenotype)													
							Location								Behaviour					
							EBR				MT or LS				EBR			MT or LS		
Study	EBR	MT or LS	EBR	MT or LS	EBR	MT or LS	L1	L2	L3	L4	L1	L2	L3	L4	B1	B2	B3	B1	B2	B3
Aratari (2007) [19]	83	124	48 (58)	71 (57)	50 (60)	73 (59)	83	-	-	-	124	-	-	-	NR	NR	34	NR	NR	60
Latella (2009) [21]	115	375	66 (57)	225 (60)	38 (33)	122 (33)	85	2	25	3	204	52	109	10	3	89	23	151	178	40
Golovics (2013) [22]	63	428	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Propensity-matched cohort with L1 disease^	58	58	32 (55)	34 (59)	36 (62)	35 (60)	58	-	-	-	58	-	-	-	10	20	28	10	19	29
An (2016) [20]	42	115	22 (52)	50 (43)	15 (36)	43 (37)	28	NR	14	NR	25	NR	74	NR	3	17	22	38	26	41
Delayed surgery subgroup within MT group^		62		24 (39)		25 (40)					17		45					4	24	34
Gerdin (2016) [26]	15	18	7 (47)	9 (50)	5 (33)	5 (28)	15	-	-	-	18	-	-	-	NR	NR	-	NR	NR	-
Ponsioen (2017) [25]	73	70	26 (36)	21 (30)	21 (31)	30 (45)	73	-	-	-	70	-	-	-	73	-	-	70	-	-
Lee (2018) [24]	120	123	96 (80)	75 (61)	18 (15)	9 (7.3)	48	9	63	-	43	4	76	-	44	34	42	86	17	20
Stevens (2020) [27]¥	69	65	24 (35)	19 (29)	21 (30)	30 (46)	69	-	-	-	65	-	-	-	69	-	-	65	-	-
Kelm (2021) [23]	29	74	18 (62)	39 (53)	11 (38)	19 (26)	29	-	-	-	30	NR	NR	NR	NR	20	NR	NR	63	NR
Localised ileocaecal disease^	29	30	NR	NR	NR	NR	29	-	-	-	30	-	-	-	NR	20	NR	NR	25	NR
Total	**540**	**1327**																		

Abbreviations: ES, early bowel resection; LS, late surgery; MT, medical therapy; NR, not reported; −: not applicable.

Note: ^ subgroup analysis within an included study. ¥ retrospective follow up of study by Ponsioen et al.[25] Figures from ^ and ¥ have been excluded from the "total" figures.

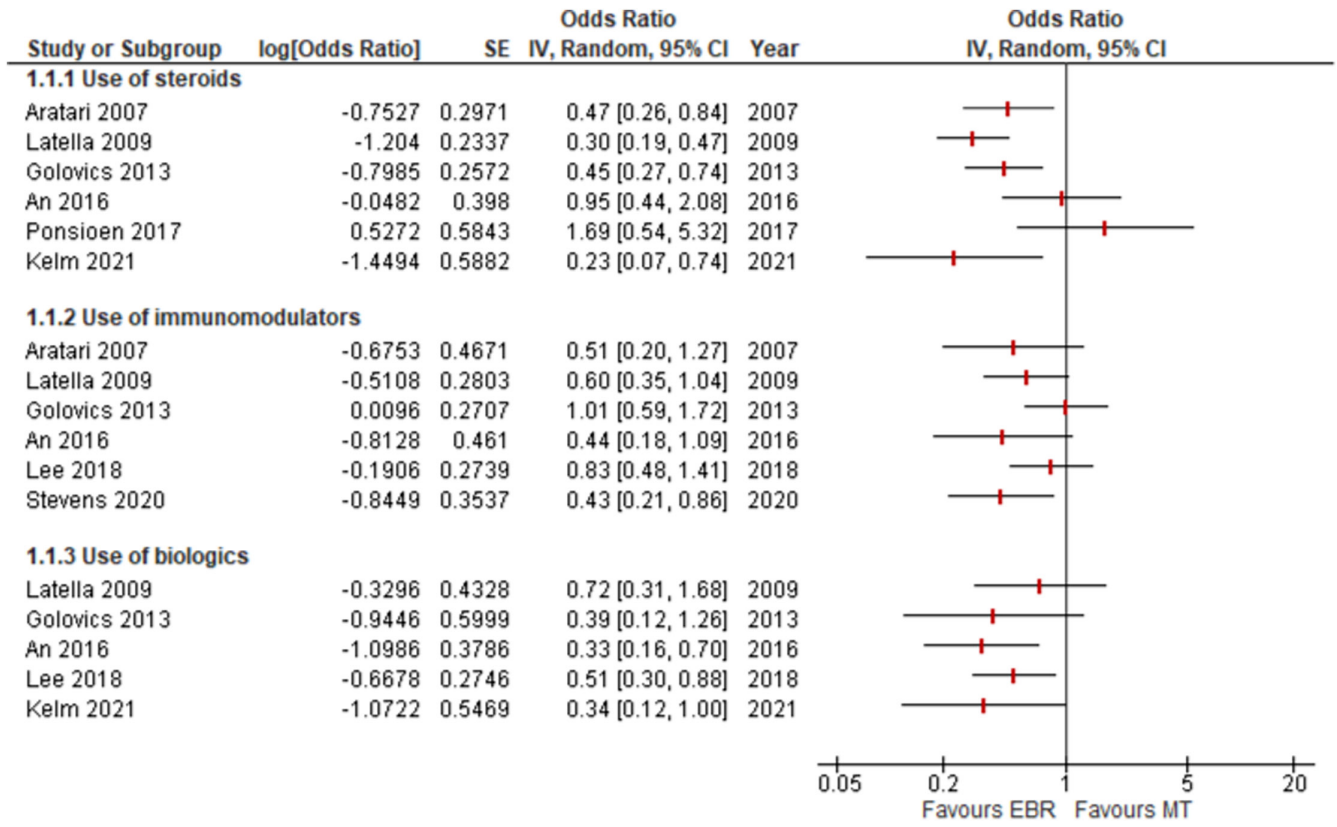

FIGURE 2 Overall need for medical therapy in EBR vs MT (or LS) cohorts. Statistical synthesis not performed as values reported for different follow-up periods. SE: standard error; IV: inverse variance; CI: confidence interval.

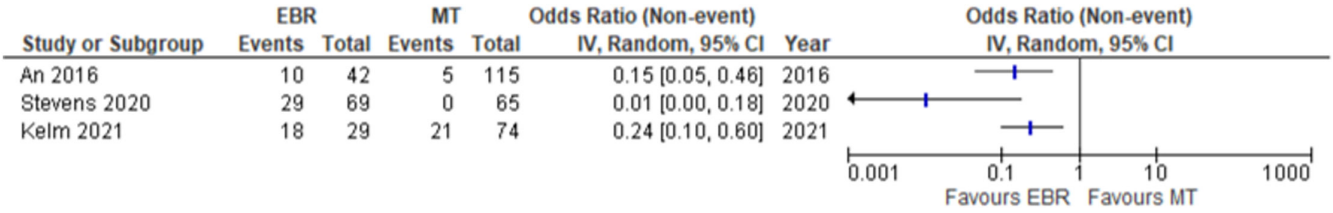

FIGURE 3 Drug-free remission in EBR vs MT (or LS) cohorts. Statistical synthesis not performed as values reported for different follow-up periods. IV: inverse variance; CI: confidence interval.

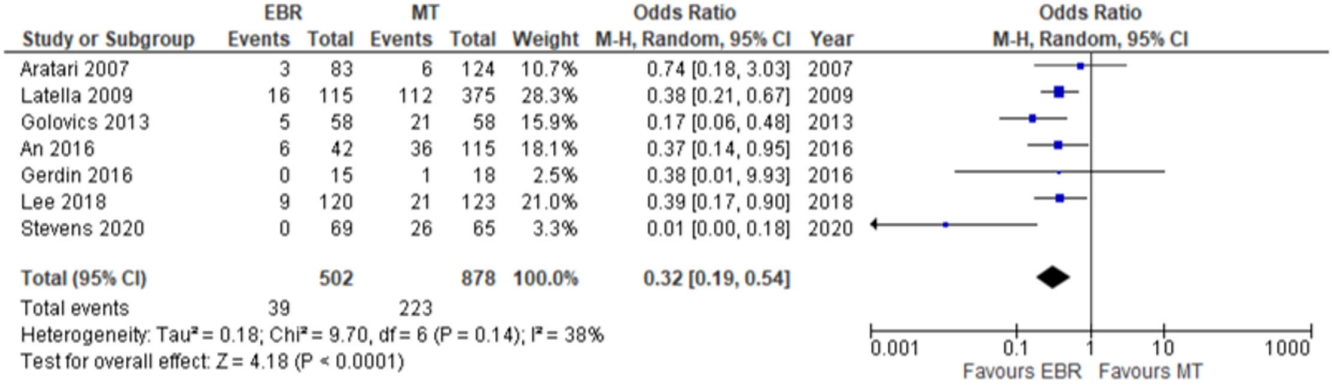

FIGURE 4 Forest plot of need for surgical resection at 5 years in EBR vs MT (or LS) cohorts. M-H: Mantel-Haenszel; CI: confidence interval.

significant difference between the two groups [19]. Three studies reported data on hospital admissions; Ponsioen and colleagues and Kelm and colleagues found the number of patients with unscheduled admissions and the median length of stay respectively to be similar in each arm [23, 25]. One study found a lower median number of hospital admissions in the EBR cohort (1 vs. 3; $p = 0.012$) [20]. Latella

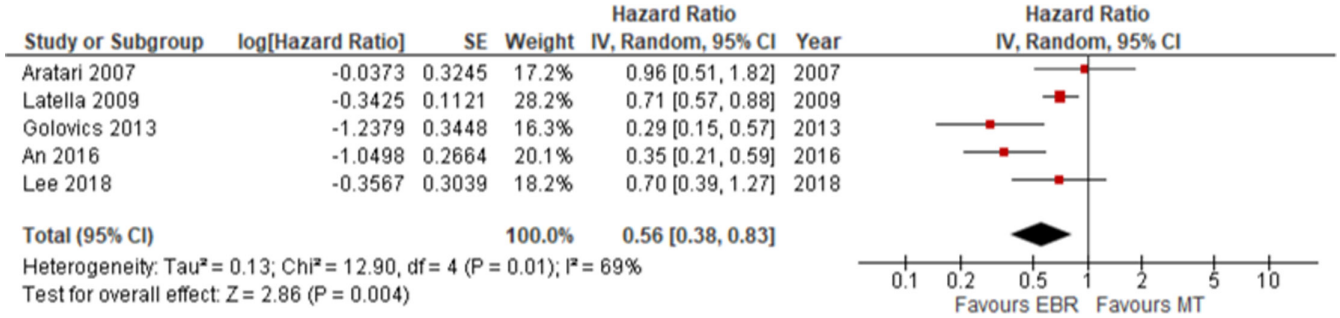

FIGURE 5 Time to first operation after initial surgical or medical therapy in EBR vs MT (or LS) cohorts. SE: standard error; IV: inverse variance; CI: confidence interval.

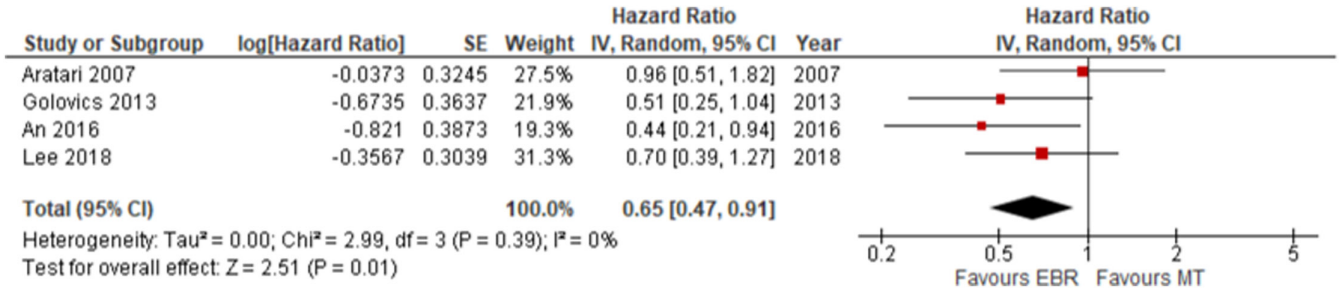

FIGURE 6 Time to second operation following index resection in EBR vs MT cohorts. SE: standard error; IV: inverse variance; CI: confidence interval.

TABLE 3 Rates of anastomotic leak and stoma formation

Outcome of interest	Study (author, year)	EBR, N/ total (%)	MT or LS, N/ total (%)	*p*-value if reported
Anastomotic leak	Gerdin (2016) [26]	0/15 (0)	1/18 (5.6)	NR
	Ponsioen (2017) [25]	3/73 (4.1)	0/70 (0)	NR
	Kelm (2021) [23]	2/29 (6.9)	6/74 (8.1)	NS
Stoma	An (2016) [20]	3/42 (7.1)	5/62 (8.1)	NS
	Gerdin (2016) [26]	0/15 (0)	1/18 (5.6)	NR
	Ponsioen (2017) [25]	3/73 (4.1)	1/70 (1.4)	NR
	Kelm (2021) [23]	2/29 (6.9)	4/74 (5.5)	NS

Abbreviations: NR, not reported; NS, reported as not significant; actual values not provided.

and colleagues found no statistically significant difference in mortality rates between the EBR and MT groups [21].

Quality of life

The RCTs measured this outcome [25, 26]. Overall scores were similar across the two arms at 1, 3 and 5 years in the Swedish trial, and at 1 year in the LIR!C trial (although the physical component of the SF-36 score (see Table 1) was significantly better in the EBR group).

Subgroup analysis of patients with L1 disease

Three studies only included patients with L1 disease [19, 25, 26]. Golovics and colleagues and Kelm and colleagues also included a propensity-matched cohort analysis and a subgroup analysis respectively of patients with ileal or ileocaecal disease [22, 23]. A pooled estimate for the outcome "need for surgery at 5 years" (Figure 7) remained in favour of EBR (HR 0.18; 95% CI: 0.04, 0.88; $p = 0.03$), albeit with a high degree of heterogeneity amongst the studies ($I^2 = 66\%$). The need for steroids was reported as statistically significantly lower in three studies [19, 21, 22], and a statistically significantly higher proportion of patients in the EBR group were in drug-free remission in two studies [23, 27] (Figures S3 and S4, Appendix 2).

DISCUSSION

Our key findings were that compared to conventional MT for ileocolonic CD, EBR is associated with a lower rate of bowel resection at 5 years, a longer period without resection or repeat resection and a

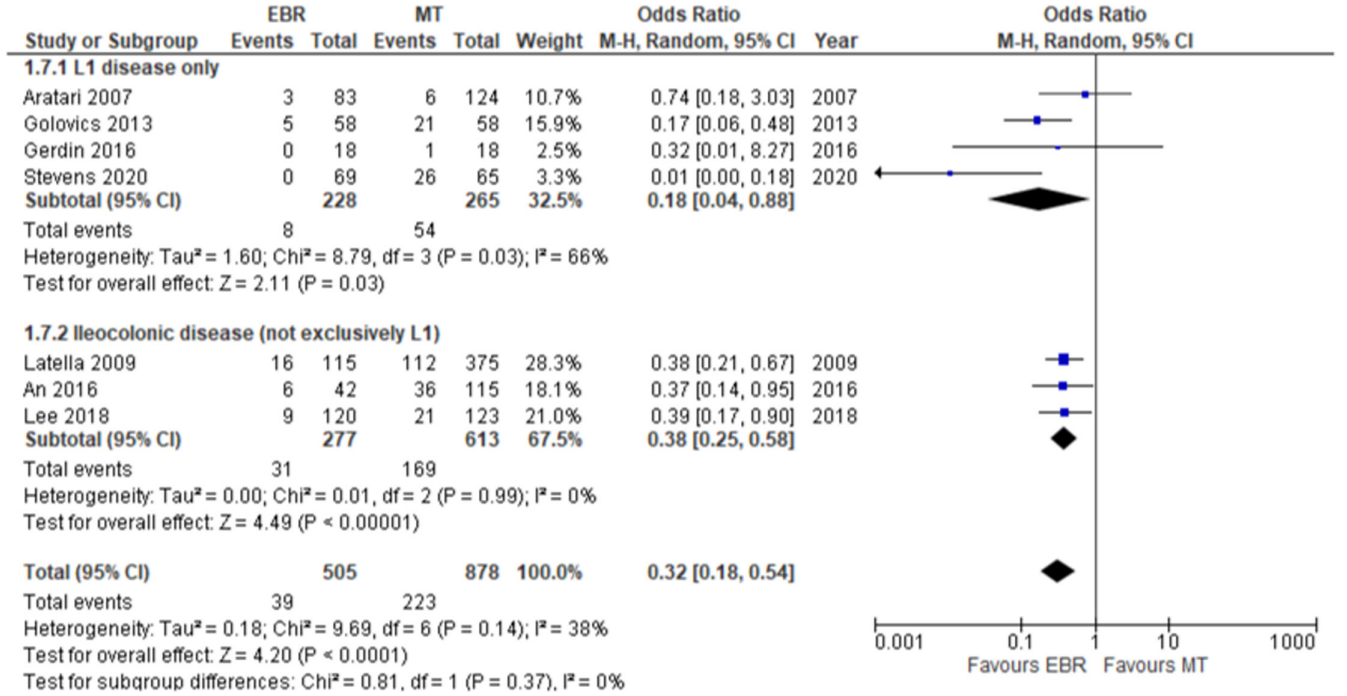

FIGURE 7 Subgroup analysis of patients with ileal or ileocaecal disease: forest plot of need for surgery at 5 years. M-H: Mantel-Haenszel; CI: confidence interval.

decreased need for drug therapy. Rates of morbidity were low, and similar between the two groups, as were quality of life scores. These findings are similar to those reported by Ryan and colleagues [9]. Current American, British, and European guidelines support consideration of EBR as an alternative to MT for localised CD, especially when localised to the terminal ileum [28–30]. In a separate analysis on health economics, patients in the surgical arm of the LIR!C trial incurred lower direct healthcare costs at 1 year and experienced more quality-adjusted life years compared to the infliximab group [31].

The mechanism by which early surgery leads to more stable remission is unclear. Resection removes the burden of mesenteric creeping fat (which may secrete proinflammatory mediators) and removes inflamed bowel with impaired barrier function that promotes chronic inflammation [32–34]. Ongoing inflammation in CD also causes cumulative bowel damage [35, 36], hence the move towards "top-down" and "treat-to-target" treatment approaches [37] that modify disease behaviour to prevent or slow down cumulative bowel damage [35, 38, 39]. Perhaps EBR achieves better disease control by reducing or eliminating disease burden and represents a more aggressive "top-down" strategy.

An RCT comparing laparoscopic resection combined with infliximab treatment (LaRIC) versus infliximab for terminal ileitis in CD is underway and may add to the evidence base. However, RCTs comparing these treatment modalities are difficult to implement. Investigators of the LIR!C trial and the Swedish Crohn's trial report difficulties in recruiting patients. The latter was prematurely terminated, as was the ESPRIT trial (Early Surgery versus Conservative Treatment in Patients with Ileocaecal Crohn's Disease; NCT02716454). When the treatment options (MT vs. surgery) are fundamentally different, there is often lack of equipoise and treatment choice is often preference-sensitive, affecting participant willingness to be randomised.

Additionally, it is difficult to define "early surgery" and establish an ideal point in the treatment pathway of ileocaecal CD to offer surgery and randomise patients. The LIR!C trial, as the only successfully completed RCT, recruited patients over 7.5 years [25]. This protracted recruitment period can affect external validity, especially if clinical practice changes during that time. For instance, there has been an increasing adoption of early pharmacological prophylaxis following ileocaecal resection over the past decade [29, 40, 41]. Evidence from the POCER trial has also led to more active postoperative endoscopic surveillance and treatment step-up for recurrence [42]. Trials evaluating the effect of radical mesenteric excision and the Kono-S anastomosis on postoperative recurrence are underway (NCT04578392, NCT04538638, NCT02631967 and the MEErKAT trial [43]). These techniques may further reduce the risk of disease recurrence after EBR for ileocaecal CD.

Despite emerging evidence supporting EBR, a paradigm shift in its favour is yet to occur in clinical practice. Possible reasons include reluctance to move away from accepted and established practice (i.e., MT), fear of surgery, and organisational factors such as the lack of local surgical expertise or facilities to enable multidisciplinary consultations for suitable patients. Future research should explore the patient and clinician perspective on, and barriers to implementation of, EBR in practice. There is also a need for more data on patient-reported outcome measures, including quality of life, to guide patient decision-making and standardise reporting of outcomes across clinical studies.

Our study has some limitations. Few studies, of variable methodological quality, have addressed this topic. Most are observational and retrospective, the majority of which had lengthy follow-up. While this allows measurement of long-term outcomes, the constant evolution of treatment strategies means that heterogeneity exists, affecting the certainty of the evidence. In the observational studies, the implementation of early surgery will have been dictated by clinical need, reflected by the more aggressive disease behaviour in their EBR groups (Table 2). Only the RCTs report outcomes of early surgery in "uncomplicated" inflammatory disease. Four studies included phenotypes other than L1 disease and the exact nature of the intestinal resection was not specified in all studies, making it difficult to appreciate the full efficacy of EBR for limited ileocaecal disease. However, two thirds of the patients included in the meta-analysis did have L1 disease. Outcome measures varied across the studies, and have been reported over different follow-up periods, precluding statistical synthesis of data for some outcomes.

Although synthesising data from studies of variable design and methodological quality is not ideal, given the limited number of studies and the difficulties in conducting trials in this area, it was important to produce a comprehensive overview of the literature to guide clinical practice. Our review addresses some limitations of the meta-analysis by Ryan and colleagues [9]. We included three additional studies, only included studies on ileocolonic disease (excluding the study on colonic disease included in their review [44]), presented a subgroup analysis of L1 disease, and statistically synthesised data only for outcomes that were consistently reported across studies in order to deal with the variation in reported outcomes and duration of follow-up across studies.

Despite the paucity of relevant studies within the literature, there is enough evidence to support EBR as a valid alternative to escalation of MT in selected patients with limited ileocaecal disease. EBR should be discussed with patients at an early stage to allow them to make an informed treatment choice.

AUTHOR CONTRIBUTIONS

NH: conceptualisation (supporting), development of methodology (lead), data curation (lead), analysis (lead), writing - original draft preparation. TG: development of methodology (supporting), data curation (supporting), analysis (supporting), writing – review and editing (equal). AGH: analysis (supporting), writing – review and editing (equal). ZK: analysis (supporting), writing – review and editing (equal). JLM: development of methodology (supporting), supervision (supporting), writing – review and editing (equal). LW: development of methodology (supporting), supervision (supporting), writing – review and editing (equal). SRB: conceptualisation (lead), development of methodology (supporting), supervision (lead), writing – review and editing (equal).

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CONFLICT OF INTEREST STATEMENT

The authors have no relevant financial or nonfinancial interests to disclose.

DATA AVAILABILITY STATEMENT

Data available on request from the authors

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