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Original Article

Temporary Faecal Diversion for Refractory Perianal and/or Distal Colonic Crohn's Disease in the Biologic Era: An Updated Systematic Review with Meta-analysis

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Abstract

Background and Aims: We evaluated short- and long-term outcomes of temporary faecal diversion [FD] for management of refractory Crohn's disease [CD], focusing on outcomes in the biologic era.

Methods: Through a systematic literature review until March 15, 2023, we identified 33 studies [19 conducted in the biologic era] that evaluated 1578 patients with perianal and/or distal colonic CD who underwent temporary FD [with intent of restoring bowel continuity] and reported long-term outcomes [primary outcome: successful restoration of bowel continuity, defined as remaining ostomy-free after reconnection at a minimum of 6 months after diversion or at the end of follow-up]. We calculated pooled rates (with 95% confidence interval [CI]) using random effects meta-analysis, and examined factors associated with successful restoration of bowel continuity.

Results: Overall, 61% patients [95% CI, 52-68%; 50% in biologic era] experienced clinical improvement after FD. Stoma takedown was attempted in 34% patients [28–41%; 37% in biologic era], 6–18 months after diversion. Among patients where bowel restoration was attempted, 63% patients [54–71%] had successful restoration of bowel continuity, and 26% [20–34%] required re-diversion. Overall, 21% patients [17–27%; 24% in biologic era] who underwent FD were successfully restored; 34% patients [30–39%; 31% in biologic era] required proctectomy with permanent ostomy. On meta-regression, post-diversion biologic use and absence of proctitis was associated with successful bowel restoration after temporary FD in contemporary studies.

Conclusion: In the biologic era, temporary FD for refractory perianal and/or distal colonic CD improves symptoms in half the patients, and bowel continuity can be successfully restored in a quarter of patients.

Key Words: Perianal fistula; surgery; ostomy; biologics

1. Introduction

Approximately one in five patients with Crohn's disease [CD] develop perianal disease within 10 years of CD diagnosis.[1] Approximately two-thirds of these patients require minor perianal surgery, with a smaller fraction requiring major abdominal surgery. In a subset of patients with refractory perianal disease and/or distal colonic CD, faecal diversion with a temporary ostomy may be effective in controlling symptoms. In a systematic review of 16 cohort studies with 556 patients who underwent faecal diversion for refractory perianal disease, Singh *et al.* observed high rates of early clinical response to faecal diversion [64%] but low rates of successful restoration of bowel continuity on long-term follow-up [17%].[2] However, most of these studies were conducted in the pre-biologic era, and even among studies in the biologic era, tumour necrosis factor alpha [TNF-α] antagonists were the only available advanced therapy.

Over the past decade, there have been significant advances in the medical management of CD with availability of novel therapies, including non-TNF target biologics and oral small molecule modulators/inhibitors, as well as novel treatment paradigms such as early advanced therapy, combination therapy, and treat to target. These advances have been accompanied by a decline in the cumulative risk of surgery in patients with CD.[3] However, it remains unclear if these advances have altered clinical outcomes in patients who undergo temporary faecal diversion for refractory perianal and/or distal CD. As there is significant morbidity with a permanent ostomy, including increased rates of depression and

reductions in quality of life, any change in these results would be important to identify so that surgeons and gastroenterologists can counsel patients appropriately.[4]

Hence, we conducted an updated systematic review with meta-analysis to evaluate short-and long-term outcomes of temporary faecal diversion for management of refractory perianal and/or distal colonic CD, with a specific focus on comparing outcomes between the pre- and post-biologic eras. Furthermore, we sought to identify factors associated with favourable outcome of temporary faecal diversion, through subgroup analyses, meta-regression, and qualitatively synthesising reported risk factors in individual studies.

2. Methods

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] standards and followed an a priori established protocol [available upon request].[5] The data underlying this article are available in the article and in its online version.

2.1. Selection criteria

We included cohort studies and case series in: [1] patients: paediatric and adult patients with established perianal CD and/or distal colonic CD; [2] intervention: who underwent temporary faecal diversion to treat CD [with intent to restore bowel continuity in the future]; and [3] outcome: with reported long-term outcomes [minimum follow-up, 6 months] following temporary faecal diversion, including rates of attempted and successful restoration of bowel continuity, re-diversion [in patients with attempted restoration], and rates of CD-related definitive surgery [colectomy with permanent end-ileostomy]. We excluded the following studies: [1] case-control or cross-sectional studies; [2] studies with insufficient follow-up on the fate of faecal diversion [ie, do not report proportion in whom takedown was attempted, etc.]; and [3] studies on CD recurrence after permanent ileostomy. In the case of multiple studies from the same cohort, we included the data from the most recent comprehensive report.

2.2. Search strategy

We conducted a comprehensive search of multiple electronic databases [OVID Medline and OVID EMBASE], updating our prior search[2] by including studies from July 15, 2015, to March 15, 2023, in children and adults using a combination of keywords and Medical Subject Headings [MeSH] terms: [ileostom* OR colostom* OR ileal OR stoma*] AND [faecal or fecal] OR [diversion* OR drain* OR divert* OR management] OR [perianal* or peri-anal*] AND [crohn* OR ibd OR inflammatory bowel disease*]. The title and abstract of studies identified in the search were reviewed by two authors independently [MJ, JM] to exclude studies that did not address the research question of interest, based on pre-specified inclusion and exclusion criteria. The full text of the remaining articles was examined to determine whether it contained relevant information. Bibliographies of the selected articles and review articles on the topic were manually searched for additional studies. A manual search of conference proceedings of major gastroenterology conferences [Digestive Disease Week, European Crohn's and Colitis Organszation annual meeting] between 2015 and 2021 was conducted to identify additional studies published only in the abstract form.

2.3. Data abstraction and risk of bias assessment

One investigator [MJ] abstracted data using a standardised data collection form: [1] study characteristics: primary author, time period of study/year of publication, geographical location, total number of patients, duration of follow-up after faecal diversion; [2] patient characteristics: age, sex, location of CD [perianal disease and/or colonic disease], duration of CD, prior surgeries; [3] treatment characteristics: biologic use prior to diversion [including TNFα antagonists, ustekinumab, vedolizumab, oral small molecule drugs], biologic use after diversion, type of diversion [ileostomy or colostomy, loop vs end]; and [4] outcome assessment: proportion of patients with clinical improvement, attempted restoration of bowel continuity after temporary diversion, successful restoration of bowel continuity, patients requiring re-diversion after attempted takedown, and patients requiring progression to proctocolectomy with end-ileostomy. A second investigator [JM] independently reviewed the abstracted data for accuracy and any discrepancies were addressed by a joint re-evaluation of the original article, in consultation with the senior investigator [SS]. The National Institute of health and Care Excellence [NICE] scale was used for critical assessment of the quality of each included study.[6]

2.4. Outcomes assessed

The primary outcome was pooled proportion of patients with successful restoration of bowel continuity [remaining ostomy-free without significant relapse of CD, at least 6 months after stoma takedown] after temporary faecal diversion for perianal and/or distal colonic CD. Secondary outcomes were: [1] proportion of patients with clinical improvement following faecal diversion [most often defined subjectively as symptomatic improvement, including decrease in fistula drainage for patients with perianal CD]; [2] proportion of patients in whom restoration of bowel continuity was performed [regardless of the eventual outcome]; and [3] proportion of patients needing additional surgery [re-diversion in case bowel continuity was restored or proctectomy with or without colectomy and end-ileostomy]. We compared differences in the rates of both primary and secondary outcomes in the pre-biologic era and biologic era [after 1998].

We performed subgroup analyses to examine potential sources of heterogeneity for two outcomes: short-term clinical improvement after diversion, and successful restoration of bowel continuity in the long term. These subgroups included: treatment era [patients who underwent diversion in the pre-biologic vs biologic era vs overlapping time period], geographical location [North America vs outside North America, given potential differences in treatment patterns and access to medications], and decade mid-point of cohort recruitment [before 1980 vs 1990s vs 2000s vs 2010s, to reflect evolving treatment approach]. To further examine sources of heterogeneity, we performed meta-regression, based proportion of patients on biologic prior to diversion, proportion of patients on biologic after diversion prior to takedown, proportion of patients diverted for refractory perianal disease alone, proportion undergoing ileostomy [vs colostomy], proportion undergoing loop ileostomy [vs end-ileostomy], mean age at diagnosis of CD, and mid-point of study cohort recruitment year. We also qualitatively synthesised demographic, clinical, and treatment-related factors associated with successful restoration of bowel continuity reported in individual studies.

2.5. Statistical analysis

We used the random effects model described by DerSimonian and Laird to calculate pooled rates [and 95% confidence interval] of clinical improvement with faecal diversion, rates of attempted and successful restoration of bowel continuity, and rates of needing proctectomy with or without colectomy and end-ileostomy post-diversion.[7] We assessed heterogeneity between study-specific estimates using the inconsistency index [I^2], and used cutoffs of 0% to 30%, 31% to 60%, 61% to 75%, and 76% to 100% to suggest minimal, moderate, substantial, and considerable heterogeneity.[8] Between-study sources of heterogeneity were investigated using subgroup analyses by stratifying original estimates according to study characteristics [as described above]. In this analysis, a *p*-value for differences between subgroups of <0.10 was considered statistically significant [ie, a value of p <0.10 suggests that stratifying based on that particular study characteristic partly explained the heterogeneity observed in the analysis]. We used random effects meta-regression models to evaluate the impact of baseline covariates on the calculated heterogeneity; since meta-regression has low statistical power, *p*-value ≤0.10 was considered statistically significant. Publication bias was assessed qualitatively using funnel plot asymmetry.[9] Meta-analyses were performed using StatsDirect version 3.3.4 [StatsDirect, Merseyside, UK] and meta-regression was performed using Comprehensive Meta-Analysis [CMA] version 3 [Biostat, Englewood, NJ, USA].

3. Results

We identified 4629 unique studies using our search strategy and 32 studies met our inclusion criteria.[10-42] We also included our own unpublished data from a single-centre, retrospective cohort, for a total of 33 studies in this meta-analysis. After full-text review, the primary reasons for exclusion were incomplete data on long-term outcomes after temporary diversion, specifically rates of restoration of bowel continuity, reporting recurrence rates after intended permanent ostomy formation, and studies that included patients with ulcerative colitis or patients who underwent ileostomy as part of a staged pouch formation procedure [ileal pouch-anal anastomosis]. Figure 1 shows the study selection flow chart.

3.1. Characteristics and quality of included studies

Table 1 shows the characteristics of the patients included in the studies. Ten studies were performed exclusively during the pre-biologic era [prior to 1998], 19 studies in the biologic era [ie, all patients operated and analysed after 1998], and four studies in the overlapping period [including patients before and after 1998]. Eighteen studies were performed in North America [including five paediatric studies] and 15 studies were performed outside of North America. Median follow-up in studies after temporary faecal diversion ranged from 9 to 135 months. Ileostomy for faecal diversion was performed more frequently than colostomy; 26 studies evaluated outcomes in patients with refractory perianal CD alone with/without colonic disease and seven studies with distal colonic disease. All included studies were retrospective, with most performed at single tertiary centres and three studies being multicentre. Supplementary Table 1 demonstrates the quality assessment of the included studies, using the National Institute of Health and Care Excellence [NICE] checklist: studies were at moderate risk of bias due to selection bias.

3.2. Outcomes after faecal diversion

3.2.1. Clinical response

Thirty studies [1242 patients] reported clinical response [most frequently defined subjectively as symptomatic improvement, including decrease in fistula drainage for patients with perianal CD] after faecal diversion. Each individual study's definition of clinical response is reported in Table 1. Clinical response was characterised within a few to 6 months after diversion was performed. On meta-analysis, 61% patients [95% CI, 52-68%]£ experienced improvement in symptoms after faecal diversion, with considerable heterogeneity [I^2 = 83%] [Figure 2]. In a subset of studies conducted in the biologic era, rate of initial clinical response was lower at 50% [95% CI, 42-59%] [Table 2]. There was no difference in clinical response after faecal diversion between studies performed within North America and outside North America [p = 0.27]. On meta-regression of studies conducted in the biologic era, pre-diversion use of biologics [p<0.01], use of loop ileostomy [vs end ileostomy] [p = 0.08] and advanced age at CD diagnosis [p = 0.04] were associated with lower rates of clinical response, whereas post-diversion use of biologics [p = 0.70] and diversion performed for perianal CD [p = 0.13] were not associated with improved clinical response.

3.2.2. Attempted restoration of bowel continuity

A total of 33 studies [1578 patients] reported rates of attempted restoration of bowel continuity after temporary faecal diversion. On meta-analysis, restoration of bowel continuity was attempted in 34% patients [95% CI, 28-41%], with considerable heterogeneity [I^2 = 83%] [Figure 3]; in other patients, restoration of bowel continuity was not attempted by the end of study follow-up, either due to inadequate clinical response to temporary diversion or patient preference. Stoma takedown was attempted on average between 6 and 18 months after faecal diversion. In studies conducted in the biologic era, rates of attempting restoration of bowel continuity were numerically higher (37% [95% CI, 28-47%]) than in the pre-biologic era [Table 2]. There was no difference in attempted restoration of bowel continuity seen between studies performed within North America and outside North America [*p*-value = 0.92]. On meta-regression of studies conducted in the biologic era, pre-diversion use of biologics [p = 0.07] and use of loop ileostomy [p = 0.09] were associated with higher rates of attempted restoration of bowel continuity, whereas faecal diversion for perianal CD [p = 0.38], post-diversion use of biologics [p = 0.19], and age at diagnosis [p = 0.60] were not associated with attempted restoration of bowel continuity.

3.2.3. Successful restoration of bowel continuity

A total fo 33 studies [1578 patients] reported rates of successful restoration of bowel continuity after temporary faecal diversion. Duration of follow-up after restoration of bowel continuity was inconsistently reported and was at least 6 months, and frequently several years; in six studies that reported follow-up after restoration of bowel continuity, median follow-up was 48 [range, 16–99] months. On meta-analysis, bowel continuity was successfully restored in 21% patients [95% CI, 17-27%] who underwent temporary faecal

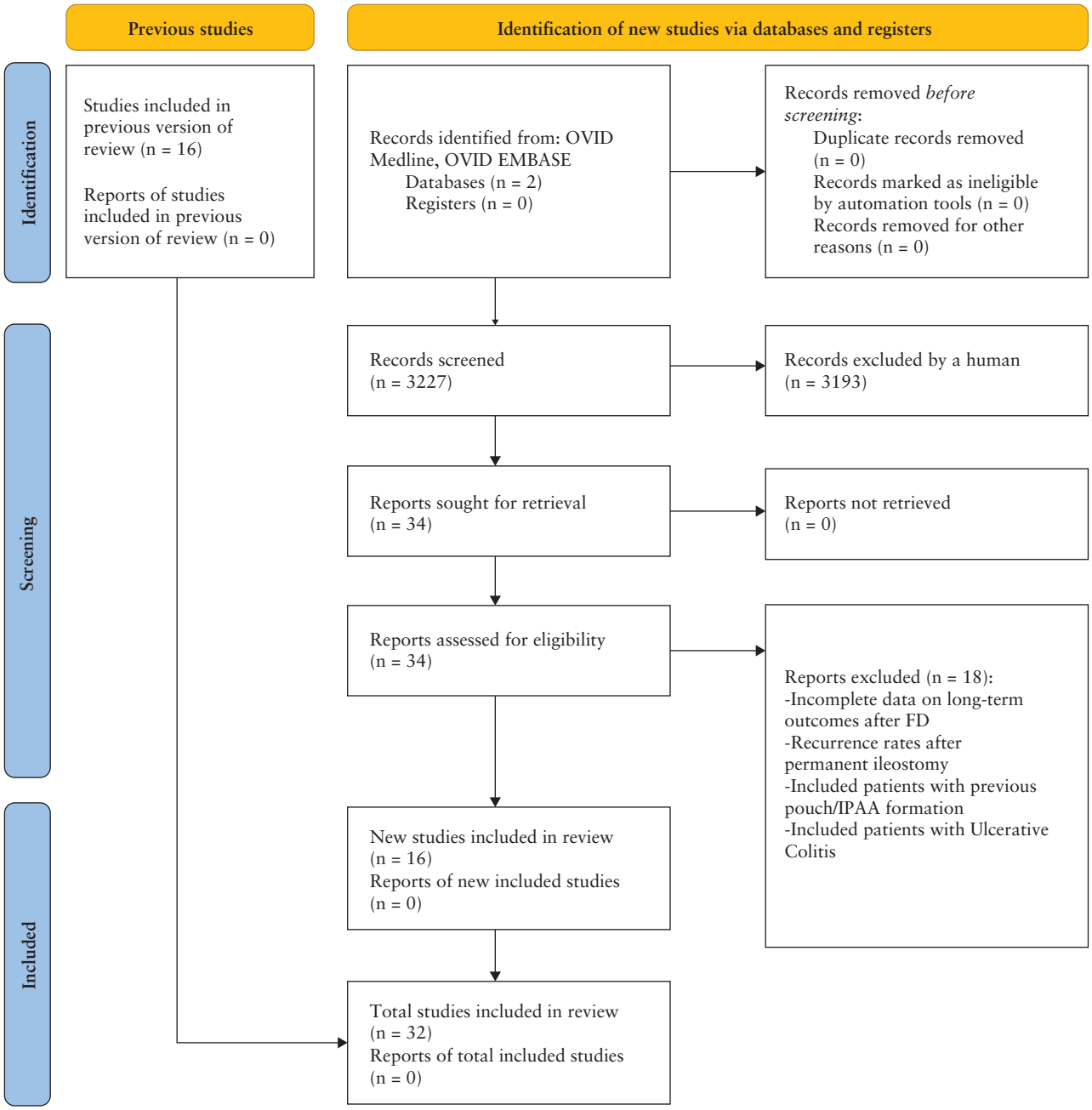

Figure 1 Study Selection Flowsheet

diversion, with considerable heterogeneity [I^2 = 77%], with higher rates in studies conducted in the biologic era (24% [95% CI, 17-31]) [Figure 4, Table 2]. Of patients in whom bowel restoration was attempted after temporary diversion, 63% patients [95% CI, 54-71%] underwent successful bowel restoration without relapse of CD, with substantial heterogeneity between studies [I^2 = 64%] [Supplementary Figure 1]. There was no difference in rates of successful restoration of bowel continuity after diversion, seen between studies performed within North America and outside North America [*p*-value = 0.27]. On meta-regression of studies conducted in the biologic era, pre-diversion [p <0.01] and post-diversion [p <0.01] use of biologics, and use of loop ileostomy [p = 0.03], were associated with higher rates of successful restoration of bowel continuity, whereas diversion performed for refractory perianal CD [p = 0.14] and advanced age [p = 0.28] were not associated with successful restoration of bowel continuity. Meta-regression by mid-point of study cohort recruitment also suggested higher rates of successful restoration of bowel continuity in recent time periods [p = 0.07].

3.2.4. Need for re-diversion after restoration of bowel continuity

Thirty studies [1545 patients] reported the rates of re-diversion after previously attempted restoration of bowel continuity. On meta-analysis, of patients in whom restoration of bowel continuity was performed, 26% patients [95% CI, 20-34%] required re-diversion without proctectomy for management of symptoms, with substantial heterogeneity [I^2 = 52%] [Supplementary Figure 2]. There was no difference in need for additional surgeries, including need for re-diversion

Table 1. Baseline characteristics and outcomes of faecal diversion for refractory distal Crohn's disease in studies included in the systematic review

Author, year of publication; location; time period	No. of patients undergoing FD; follow-up after FD	Indication for FD [perianal, colonic, or both]	Age at FD; sex distribution [M/F]	Type of ostomy [ileostomy or colostomy]	Pre-diversion/ post-diversion medications	Outcomes after FD			
						Clinical response; definition of clinical response	Restoration of bowel continuity [attempted, time to restoration, repeat FD]	Successful restoration of bowel continuity [total, definition, time after reconnection]	No attempt at restoration [continued diversion, proctocolectomy]
Pre-biologic era [all patients undergoing procedures before 1998]									
Oberhelman, 1967; Palo Alto, USA 1962–1967	13; 16m [3–24]	Perianal: 0 Colonic: 3 Both: 10	28y [12–58]; M/F: 7/6	Ileostomy: 13 [end-ileostomy: 13] Colostomy: 0	NR/NR	• Improved: 13/13 • Symptom improvement with weight gain and linear growth	• Attempted: 3/13 • Time to restoration: NR • Recurrence of CD, repeat FD: 0	• Successful: 3 • Remaining ostomy-free without major relapse • 16m [2-36]	• Continued diversion: 10/13 • Proctocolectomy: 0/13
McIlrath, 1971; Rochester, USA 1967–1970	13; 17m [4–43]	Perianal: 8 Colonic: 5 Both: 0	25y [16–55]; M/F: 5/8	Ileostomy: 9 Colostomy: 4	NR/NR	• Improved: 13/13 • Symptom improvement	• Attempted: 2/13 • Time to restoration: NR • Recurrence of CD, repeat FD: 1	• Successful: 1 • Remaining ostomy-free without recurrence • NR	• Continued diversion: 8/13 • Prococolectomy: 4/13
Harper, 1983; Oxford, UK 1960–1980	102 NR	Perianal: 11 Colonic: 73 Both: 18	27 [4–74]; M/F: 40/62	Ileostomy: 102 [split ileostomies] Colostomy: 0	NR/NR	• Improved: 95/102 • Symptom improvement	• Attempted: 61/102 • Time to restoration: 20m [1-61] • Recurrence of CD, repeat FD: 11	• Successful: 44 • Intestinal continuity remains intact • 62.5m [0-231]	• Continued diversion: 28/102 • Proctocolectomy: 30/102
Grant, 1985; Toronto, Canada; NR	12 NR	Perianal: 10 Colonic: 2 Both: 0	28 ± 7y; M/F: 3/9	Ileostomy: 12 [loop] Colostomy:0	Pre: 5-ASA: 6 Steroids: 9 Antibiotics: 8 Post: NR	• Improved: 7/12 • Symptom improvement	• Attempted: 2/12 • Time to restoration: NR • Recurrence of CD, repeat FD: 0	• Successful: 1 • NR • NR	• Continued diversion: 6/12 • Proctocolectomy: 5/12
Orkin, 1985; Rochester, USA 1970–1983	11 [total 42 patients with perianal CD, of whom 11 underwent temporary FD]; 94m [12–184]	Perianal: 11 Colonic: 0 Both: 0	16y; M/F: 29/13	Ileostomy: 11 [loop] Colostomy: NR	NR/NR	• Improved: 2/11 • Symptom improvement	• Attempted: 0/11 • Time to restoration: NR • Recurrence of CD, repeat FD: -	• Successful: - • NR • NR	• Continued diversion: 4/11 • Proctocolectomy: 7/11
Winslet, 1993; Birmingham, UK 1947–1986	44 108m [72–204]	Perianal: 8 Colonic: 36 Both: 0	36y [14–80] M/F: 20/24	Ileostomy: 40 [loop 35, split 5] Colostomy: 4 [loop]	NR/NR	• Improved: 31/44 • Symptom improvement, reduction in steroid use	• Attempted: 5 • Time to restoration: 16m [6-34] • Recurrence of CD, repeat FD: 0	• Successful: 4 • Intestinal continuity remains intact • 99m [21-153]	• Continued diversion: 24/44 • Proctocolectomy: 16/44

Table 1. Continued

Author, year of publication; location; time period	No. of patients undergoing FD; follow-up after FD	Indication for FD [perianal, colonic, or both]	Age at FD; sex distribution [M/F]	Type of ostomy [ileostomy or colostomy]	Pre-diversion/ post-diversion medications	Outcomes after FD			
						Clinical response; definition of clinical response	Restoration of bowel continuity [attempted, time to restoration, repeat FD]	Successful restoration of bowel continuity [total, definition, time after reconnection]	No attempt at restoration [continued diversion, proctocolectomy]
Edwards, 2000; Oxford, UK 1970–97	73 36m [2–204]	Perianal: 18 Colonic: 55 Both: 0	40y [19–87]; M/F: 40/33	Ileostomy: 68 [split: 48, loop 20] Colostomy: 5 [loop]	NR/NR	• Improved: 63/73 • Reduction or cessation of GI symptoms, off steroids and improved well-being; fistula closure data reported	• Attempted: 29/73 • Time to restoration: NR • Recurrence of CD, repeat FD: 4	• Successful: 13 • Intestinal continuity remains intact with good long-term function without disease relapse • NR	• Continued diversion: 38/73 • Proctocolectomy: 22/73
Yamamoto, 2000; Birmingham, UK 1970-97	31 103m [13-332]	Perianal: 11 Colonic: 0 Both: 20	29y [14-80]; M/F:14/17	Ileostomy:27 [Loop] Colostomy:4 [Loop]	NR/NR	• Improved: 25/31 • Resolution of perianal sepsis and active fistulae	• Attempted: 5/31 • Time to restoration: 41m [19-240] • Recurrence of CD, repeat FD: 2	• Successful: 3 • Intestinal continuity remains intact • 34m [19-231]	• Continued diversion: 5/31 • Proctocolectomy: 21/31
Regimbeau, 2001; Paris, France 1980-98	17 135m [12-328]	Perianal: 8 Colonic: 0 Both: 9	29 ± 9y; M/F: 6/11	Ileostomy:12 Colostomy:5	Pre: 5-ASA: 2 IM: 7 Steroids: 9 Post: NR	• Improved: 11/17 • Symptom resolution, with no evidence of active fistula on clinical examination or at operation	• Attempted: 11/17 • Time to restoration: 14m [3-52] • Recurrence of CD, repeat FD: 0	• Successful: 8 • Normal bowel continuity at end of follow-up • 90m [12-290]	• Continued diversion: 0/17 • Proctocolectomy: 9/17
Koganei, 2005; Yokohama, Japan 1993-2005	42 NR	Perianal: 0 Colonic: 9 Both: 33	NR; M/F:24/18	Ileostomy: 0 Colostomy: 42	Pre: 5-ASA: 42 IM: 17 Post: NR	• Improved: 31/42 • Symptom improvement and improvement in perianal lesions	• Attempted: 16/42 • Time to restoration: NR • Recurrence of CD, repeat FD: 15	• Successful: 4 • Restored intestinal continuity at end of follow-up • NR	• Continued diversion: 28/42 • Proctocolectomy: 10/42
Biologic era [all patients undergoing procedure after 1998]									
Rehg, 2009; Tampa, USA 2000-07	13 60m [21-110]	Perianal: 0 Colonic: 13 Both: 0	27y [10-59]; M/F: 2/11	Ileostomy: NR Colostomy: NR	NR/NR	• Improved: 11/13 • Symptom improvement with either decrease in drainage with minimal perianal pain or complete fistula closure without drainage	• Attempted: 6/13 • Time to restoration: NR • Recurrence of CD, repeat FD: 2	• Successful: 3 • Complete resolution of symptoms with remaining intestinal continuity • NR	• Continued diversion: 8/13 • Proctocolectomy: 2/13

Table 1. Continued

Author, year of publication; location; time period	No. of patients undergoing FD; follow-up after FD	Indication for FD [perianal, colonic, or both]	Age at FD; sex distribution [M/F]	Type of ostomy [ileostomy or colostomy]	Pre-diversion/ post-diversion medications	Outcomes after FD			
						Clinical response; definition of clinical response	Restoration of bowel continuity [attempted, time to restoration, repeat FD]	Successful restoration of bowel continuity [total, definition, time after reconnection]	No attempt at restoration [continued diversion, proctocolectomy]
Chernoguz, 2012; Cincinnati, USA 2006-2011 [abstract]	11 27m [4-61m]	Perianal: NR Colonic: NR Both: NR	15y [7-21]; M/F: NR	Ileostomy: 9 Colostomy: 2	Pre: NR Post: Anti-TNF: 5	• Improved: 8/11 • Symptom improvement	• Attempted: 8/11 • Time to restoration: 9.7m [3-15] • Recurrence of CD, repeat FD: 3	• Successful: 5 • Retained intestinal continuity without major recurrence or need for major surgery • NR	• Continued diversion: 4/11 • Proctocolectomy: 2/11
Kim, 2013; Weston, USA 2000-12 [abstract]	50 41m [4-126]	Perianal: 18 Colonic: 0 Both: 32	44y [18-87]; M/F:16/34	Ileostomy: NR Colostomy: NR	Pre: Anti-TNF and/or IM: 36 Post: NR	• Improved: 23/50 • Symptom improvement	• Attempted: 21/50 • Time to restoration: NR • Recurrence of CD, repeat FD: 1	• Successful: 16 • Remaining ostomy-free • NR	• Continued diversion: 24/50 • Proctocolectomy: 10/50
Marti–Gallostra, 2013; Oxford, UK 2003–11	76 48m [12–107]	Perianal: 45 Colonic: 22 Both: 9	34y [12–85]; M/F: 34/42	Ileostomy: 62 [loop 54, end 8] Colostomy: 14 [loop]	Pre: IM: 40 Anti-TNF: 57 [Ada:18, IFX: 39, Both: 5] >1 Anti-TNF:5 Post: NR	• Improved: 31/76 • Reduction in GI symptoms and improvement in well-being and reduction in inflammatory markers	• Attempted: 24 • Time to restoration: 16m [3-75] • Recurrence of CD, repeat FD: 4	• Successful: 20 • Reversal of diverting ostomy and intact continuity at end of follow-up • NR	• Continued diversion: 19/76 • Proctocolectomy: 35/76
Uzzan 2013; Clichy, France 2006–2012	3 NR	Perianal: 0 Colonic: 1 Both: 2	41y [28–50]; M/F: 1/2	Ileostomy:2 Colostomy:1	Pre: Anti-TNF: 1 Post: Anti-TNF: 3	• Improved: 2/3 • Symptom improvement and healed perianal lesions one exam	• Attempted: 1/3 • Time to restoration: 6m • Recurrence of CD, repeat FD: 1	• Successful: 0 • NR • NR	• Continued diversion: 0/3 • Proctocolectomy: 3/3
Mennigen 2015; Muenster, Germany 2003–2012	29 33m [3–103]	Perianal: 14 Colonic: 6 Both: 8	30y [18–76]; M/F: 15/14	Ileostomy:25 [loop] Colostomy:4 [loop]	Pre: 5-ASA: 3 IM: 21 Anti-TNF: 22 Steroids: 10 Post: Anti-TNF: 15 [4 naïve to therapy after diversion]	• Improved: 16/29 • Symptom improvement, with or without endoscopic evidence of healing of colonic inflammation	• Attempted: 19/29 • Time to restoration: 13m [2-90] • Recurrence of CD, repeat FD: 4	• Successful: 4 • Remain ostomy-free with stable course and without need for further definitive surgery • 21m [1-68]	• Continued diversion: 15/29 • Proctocolectomy: 10/29
Mathis, 2015; Multiple centres NR	70 64 ± 52m	NR	NR; M/F: 32/38	Ileostomy: NR Colostomy: NR	Pre: IM: 36 Anti-TNF: 27 Steroids: 31 Post: NR	• Improved: 45/70 • Symptom improvement, with reduced fistula drainage at examination	• Attempted: 26/70 • Time to restoration: NR • Recurrence of CD, repeat FD: 7	• Successful: 12 • NR • NR	• Continued diversion: 17/70 • Proctocolectomy: 27/70

Table 1. Continued

Author, year of publication; location; time period	No. of patients undergoing FD; follow-up after FD	Indication for FD [perianal, colonic, or both]	Age at FD; sex distribution [M/F]	Type of ostomy [ileostomy or colostomy]	Pre-diversion/ post-diversion medications	Outcomes after FD			
						Clinical response; definition of clinical response	Restoration of bowel continuity [attempted, time to restoration, repeat FD]	Successful restoration of bowel continuity [total, definition, time after reconnection]	No attempt at restoration [continued diversion, proctocolectomy]
Kuehn, 2015; Munich, Germany 2005–2014 [abstract]	19 NR	Perianal: 19 Colonic: 0 Both: 0	34y; M/F: NR	Ileostomy: NR Colostomy: NR	Pre: Steroids: 10 Post: NR	• Improved:5/19 • Symptom improvement	• Attempted: 5 • Median time to restoration: 12m • Recurrence of CD, repeat FD: NR	• Successful: 5 • NR • NR	• Continued diversion: 14/19 • Proctocolectomy: NR
Parisi, 2016; London, UK 2005–2015 [abstract]	45 60m	Perianal: 37 Colonic:8 Both: 0	NR; M/F: NR	Ileostomy: NR Colostomy: NR	NR/NR	• Improved: 8/45 • Symptom improvement	• Attempted: 8 • Time to restoration: NR • Recurrence of CD, repeat FD: 4	• Successful: 2 • Clinical remission and ostomy-free at time of end of follow-up • NR	• Continued diversion: 31/45 • Proctocolectomy: 12/45
Lodhia, 2016; Chicago, USA 2009–2014 [abstract]	23 [total cohort 39 patients, but excluded 16 with initial proctocolectomy] 36m	Perianal: 23 Colonic: 0 Both: 0	36y [18–64]; M/F:16/23	Ileostomy:23 Colostomy:0	Pre:NR Post: Anti-TNF: 10	• Improved: 7/23 • Symptom improvement	• Attempted: 7 • Time to restoration; NR • Recurrence of CD, repeat FD: 2	• Successful: 5 • Successful restoration of bowel continuity without the need for proctocolectomy • NR	• Continued diversion: 11/23 • Proctocolectomy: 7/23
Fahy, 2016; Rochester, USA 1998–2016 [abstract]	5 [total cohort 27, but excluded 22 due to initial colectomy with end-ileostomy] 45m	Perianal: 0 Colonic: 5 Both: 0	15y [3–18]; M/F: NR	Ileostomy:5 [loop] Colostomy:0	NR/NR	• Improved: 1/5 • Symptom improvement	• Attempted: 1 • Time to restoration: NR • Recurrence of CD, repeat FD: 1	• Successful: 0 • Intestinal continuity remains intact at end of follow-up • NR	• Continued diversion: 5/5 • Proctocolectomy: NR
Bafford, 2017; Baltimore, USA 2004–2014	30 24m	Perianal: 11 Colonic: 10 Both: 9	NR; M/F: 15/15	Ileostomy:16 Colostomy: 14	Pre: Anti-TNF: 28 >1 Anti-TNF: 17 IM: 11 Post: NR	• Improved: 12/30 • Symptom Improvement	• Attempted: 12/30 • Time to restoration: NR • Recurrence of CD, repeat FD: 1	• Successful: 11 • Successful fecal stream restoration without need for re-diversion • NR	• Continued diversion: 13/30 • Proctocolectomy: 6/30
Dharmaraj, 2017; Milwaukee, USA 2000–2014	28 27m [9.5–122]	Perianal: 7 Colonic: 21 Both: 0	13.9y [6.11–20.6] M/F: 8/20	Ileostomy: 21 Colostomy: 7	Pre: IM: 25 Anti-TNF: 25 Combination IM and anti-TNF: 18 Steroids: 27 Post: Anti-TNF: 22	• Improved: 23/28 • Symptom improvement	• Attempted: 14/28 • Time to restoration: 7m • Recurrence of CD, repeat FD: 3	• Successful: 11 • Remaining ostomy-free after restoration of intestinal continuity • NR	• Continued diversion: 17/28 • Proctocolectomy: 3/28

Table 1. Continued

Author, year of publication; location; time period	No. of patients undergoing FD; follow-up after FD	Indication for FD [perianal, colonic, or both]	Age at FD; sex distribution [M/F]	Type of ostomy [ileostomy or colostomy]	Pre-diversion/ post-diversion medications	Outcomes after FD			
						Clinical response; definition of clinical response	Restoration of bowel continuity [attempted, time to restoration, repeat FD]	Successful restoration of bowel continuity [total, definition, time after reconnection]	No attempt at restoration [continued diversion, proctocolectomy]
Maxwell, 2017; Philadelphia, USA 2000–14	10 40.8m [8–123.6]	Perianal: 0 Colonic: 9 Both: 1	8.9y [2.9–17.6] M/F:7/3	Ileostomy:10 [loop] Colostomy:0	Pre: IM: 5 Anti-TNF: 10 >1 Anti-TNF: 2 Steroids: 7 Combination therapy IM and Anti-TNF: 5 Post: IM: 1 Anti-TNF: 6 Vedo: 2 >1 Anti-TNF: 1 Steroids:2 Combination therapy: 2	• Improved: 3/10 • Symptom improvement	• Attempted: 3/10 • Time to restoration: 23m [5-35] • Recurrence of CD, repeat FD: NR	• Successful: 3 • Restoration of intestinal continuity and remaining ostomy-free at end of follow-up • NR	• Continued diversion: 3/10 • Proctocolectomy: 4/10
Hain, 2019; Clichy, France 2005–2017	65 49m [7–120]	Perianal disease: 10 Colonic: 0 Both: 55	36y [16–69] M/F:25/40	Ileostomy:52 [loop] Colostomy: 13 [loop]	Pre: Anti-TNF: 43 [IFX:22, Ada:21] Post: Anti-TNF: 54 [IFX:28, Ada:22 Certolizumab: 3, Golimumab:1] Vedo: 6 Ust: 13 IM: 2	• Improved: 43/65 • Primary healing of anoperineal CD	• Attempted: 43/65 • Time to restoration: 16m [2-87] • Recurrence of CD, repeat FD: 15	• Successful: 33 • Absence of fecal diversion at end of follow-up [last patient's visit] • NR	• Continued diversion: 15/65 • Proctocolectomy: 17/65
Lightner, 2021; Multicentre, USA 2000–2019	132 35m [IQR 11–75]	Perianal: 24 Colonic: 45 Both: 59	36y [IQR:25–49] M/F: 67/65	Ileostomy: = 132 [loop] Colostomy:0	Pre: IM: 55 Anti-TNF: 56 [Ada:28,IFX:16,Certolizumab:12] Vedo: 13 Ust: 13 Steroids: 59 Post: NR	• Improved: 57/132 • Symptom improvement or endoscopic response to diversion w/ improvement in mucosal inflammation	• Attempted: 25/132 • Time to restoration: NR • Recurrence of CD, repeat FD: 0	• Successful: 25 • Restoration of intestinal continuity and without need for re-diversion by end of follow-up • NR	• Continued diversion: 21/132 • Proctocolectomy: 50/132

Table 1. Continued

Author, year of publication; location; time period	No. of patients undergoing FD; follow-up after FD	Indication for FD [perianal, colonic, or both]	Age at FD; sex distribution [M/F]	Type of ostomy [ileostomy or colostomy]	Pre-diversion/ post-diversion medications	Outcomes after FD			
						Clinical response; definition of clinical response	Restoration of bowel continuity [attempted, time to restoration, repeat FD]	Successful restoration of bowel continuity [total, definition, time after reconnection]	No attempt at restoration [continued diversion, proctocolectomy]
McCurdy, 2021; Multicentre, Canada 1999–2020	68 [total cohort 82 patients, but 14 with initial proctectomy excluded]; 58m [IQR 20–122]	Perianal: 1 Colonic: 0 Both: 67	29y [IQR 21–40] M/F:43/39	Ileostomy:46Colostomy: 22	Pre: NR Post: Biologics: 44 Anti-TNF: [IFX:19, Ada: 16] Ust:4: Vedo:5	• Improved: 38/68 • Symptom improvement with fistula healing	• Attempted: 21/68 • Time to restoration: Majority within first year after FD • Recurrence of CD, repeat FD: 7	• Successful: 14 • Restoration of intestinal continuity and remaining ostomy-free • NR	• Continued diversion: 35/68 • Proctocolectomy: 15/68
Jew, 2021; San Diego, USA 2014–2021	12 NR	Perianal: 4 Colonic: 4 Both: 4	31y M/F: 6/6	Ileostomy: 8 Colostomy: 4	NR/NR	• Improved: 9/12 • Symptom improvement with or without endoscopic improvement	• Attempted: 9/12 • Time to restoration: NR • Recurrence of CD, repeat FD: 3	• Successful: 6 • Remaining ostomy-free without major disease recurrence at end of follow-up • NR	• Continued diversion: 2/12 • Proctocolectomy: 4/12
Kuroki, 2023; Yokohama, Japan 1999–2017	174 144m [20–358]	Perianal: 91 Colonic: 58 Both: 0	NR M/F: 118/56	Ileostomy: 82 Colostomy: 92	Pre: IM: 34 Biologics [not specified]: 39 Post: IM: 48 Biologics [not specified]: 56	• Improved: 129/174 • Symptom improvement	• Attempted: 15/174 • Time to restoration: NR • Recurrence of CD, repeat FD: 9	• Successful: 4 • Restoration of bowel continuity without major disease recurrence or need for re-diversion or major surgery at end of follow-up • NR	• Continued diversion: 99/174 • Proctocolectomy: 71
Overlapping pre-biologic and biologic era									
Hong, 2011; Melbourne, Australia 1990-2007	21 22m [4-121]	Perianal: 14 Colonic: 7 Both: 0	34y [21-67]; M/F: 1/20	Ileostomy:19 [Loop 17, End 2] Colostomy:2 [Loop]	Pre: Anti-TNF: 7 Post: Anti-TNF: 4	• Improved: 17/21 • Symptom improvement	• Attempted: 4/21 • Time to restoration: NR • Recurrence of CD, repeat FD: 0	• Successful: 1 • Restoration of intestinal continuity without need for re-diversion or permanent stoma • NR	• Continued diversion: 6/21 • Proctocolectomy: 11/21

Table 1. Continued

Author, year of publication; location; time period	No. of patients undergoing FD; follow-up after FD	Indication for FD [perianal, colonic, or both]	Age at FD; sex distribution [M/F]	Type of ostomy [ileostomy or colostomy]	Pre-diversion/ post-diversion medications	Outcomes after FD			
						Clinical response; definition of clinical response	Restoration of bowel continuity [attempted, time to restoration, repeat FD]	Successful restoration of bowel continuity [total, definition, time after reconnection]	No attempt at restoration [continued diversion, proctocolectomy]
Sauk 2014; Boston, USA 1991–2011	49 84m [12–264]	Perianal: 22 Colonic: 7 Both: 20	33y [12–63]; M/F: 10/39	Ileostomy: 28 [loop 13, end 15] Colostomy: 21 lLoop]	Pre: IM: 41 Anti-TNF: 35 >1 Anti-TNF: 20 Combination IM and anti-TNF: 17 Post: Anti-TNF: 35 Combination IM and anti-TNF: 11	• NR	• Attempted: 15/49 • Time to restoration: 12m • Recurrence of CD, repeat FD: 10	• Successful: 5 • Sustained restoration of bowel continuity at end of follow-up • NR	• Continued diversion:30/49 • Proctocolectomy: 14/49
Gu, 2015; Cleveland, USA 1994–2012	138 68m±54	Perianal: 119 Colonic: 11 Both: 6	36 ± 13y; M/F:50/88	Ileostomy: 130 Colostomy:8	Pre: Antibiotics:85 5-ASA:67 Steroids:92 IM: 73 Anti-TNF: 67 Post: Antibiotics: NR 5-ASA: NR Steroids: NR IM: NR Anti-TNF: 30	• NR	• Attempted: 37/138 • Time to restoration:9m [2-77] • Recurrence of CD, repeat FD: 7	• Successful: 30 • Absence of repeated stoma, symptom recurrence or patient intolerance of symptoms • NR	• Continued diversion: 40/138 • Proctocolectomy: 63/138
Ludewig, 2022; Jena, Germany 1973–2020	149 78m	Perianal: 5 Colonic: 55 Both: 70	34y; M/F: 73/76	Ileostomy: 92 l[loop 57, end 35] Colostomy: 57 [Loop 21, End 36]	Pre: Steroids: 76 IM: 39 Biologics [not specified]: 34 Post:	• NR • Symptom improvement	• Attempted: 73/149 • Time to restoration: 11.7m • Recurrence of CD, repeat FD: 17	• Successful: 56/149 • Stoma reversal without need for re-diversion or major surgery • NR	• Continued diversion: 110/149 • Proctocolectomy: NR

5-ASA, 5-aminosalicylates; Ada, Adalimumab; CD, Crohn's disease; F, female; FD, faecal diversion; IM, immunomodulators; IFX, infliximab; IQR, interquartile range; m, months; M, male; NR, not reported; SB, small bowel; TNF, tumour necrosis factor alpha; ust, ustekinumab; vedo, vedolizumab; y, years.

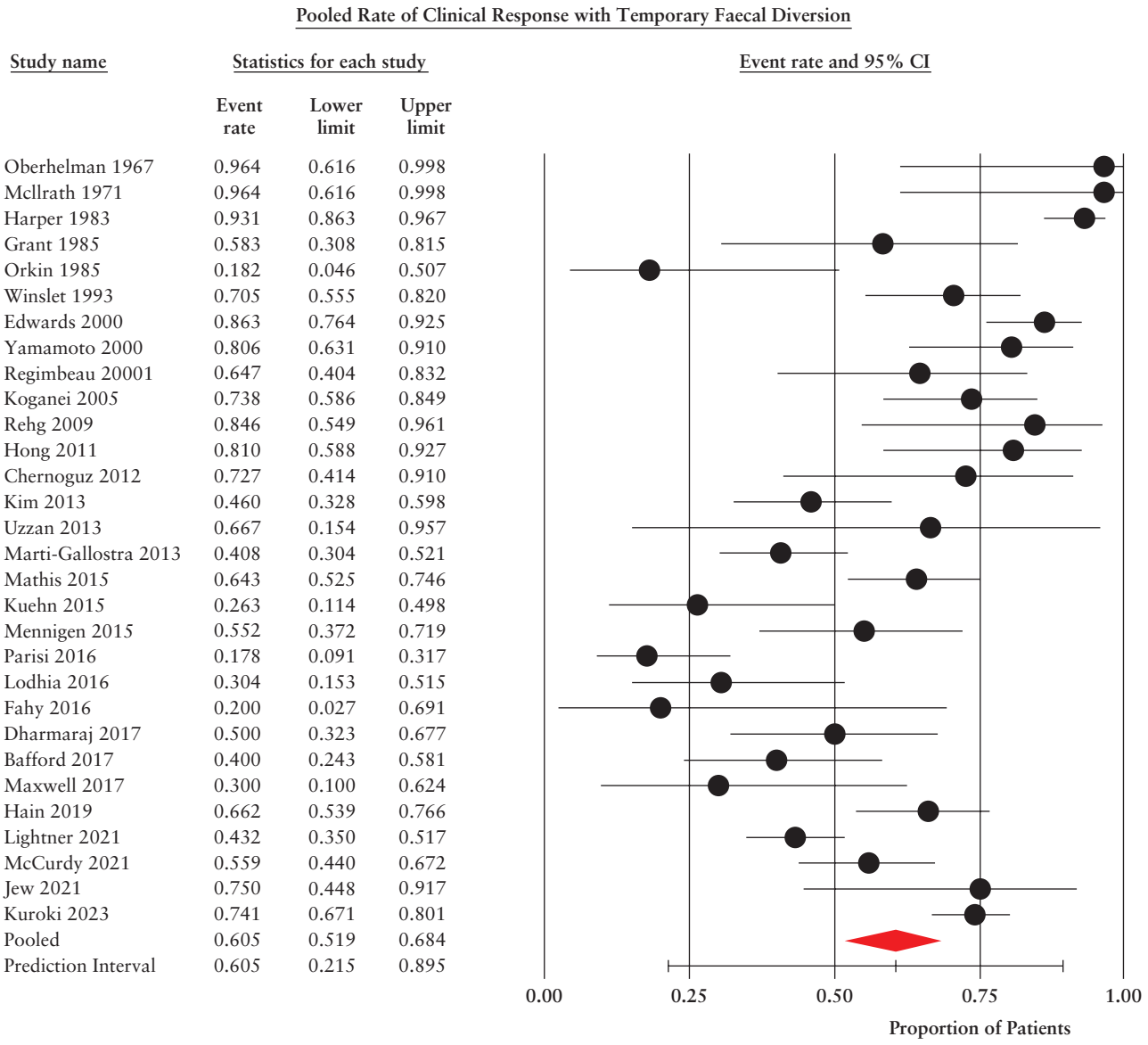

Figure 2 Pooled rate of short-term clinical response with temporary faecal diversion for perianal and/or distal colonic Crohn's disease

Table 2. Subgroup analysis based on era of study, for different outcomes. Results of the contemporary biologic era are presented in bold.

	Pre-biologic era [pooled rate, 95% CI]	Overlapping period between pre-biologic and biologic era [pooled rate, 95% CI]	Biologic era [pooled rate, 95% CI]	*p*-value
Short-term clinical improvement	**77% [64–86%]**	**81% [58–93%]**	**50% [42–59%]**	**0.001**
Attempted restoration of bowel continuity	29% [18–44%]	32% [20–47%]	**37% [28–47%]**	0.64
Successful restoration of bowel continuity	17% [9–29%]	19% [10–35%]	**24% [17–31%]**	0.59
Need for completion proctectomy	38% [29–49%]	41% [29–55%]	**31% [26–36%]**	0.18

CI, confidence interval.

after attempted bowel restoration, seen between pre-biologic, overlapping, and biologic eras [p = 0.76], nor between studies performed within North America and outside North America [p = 0.91].

3.2.5. Need for proctectomy with or without colectomy after temporary diversion

In all, 31 studies [1410 patients] reported rates of proctectomy with or without colectomy after temporary faecal diversion. On meta-analysis, 34% of patients [95% CI, 30-39%] ultimately required proctectomy with or without colectomy, either due to inadequate clinical response after temporary faecal diversion or to failure to successfully restore bowel continuity [Figure 5]. There was moderate heterogeneity between studies [I^2 = 59%]. There was no difference in need for proctectomy with or without colectomy seen between pre-biologic, overlapping, and biologic eras [p = 0.18], nor between studies performed within North America and outside North America [p = 0.10]. On meta-regression, no variable was associated with need for proctectomy after temporary faecal diversion.

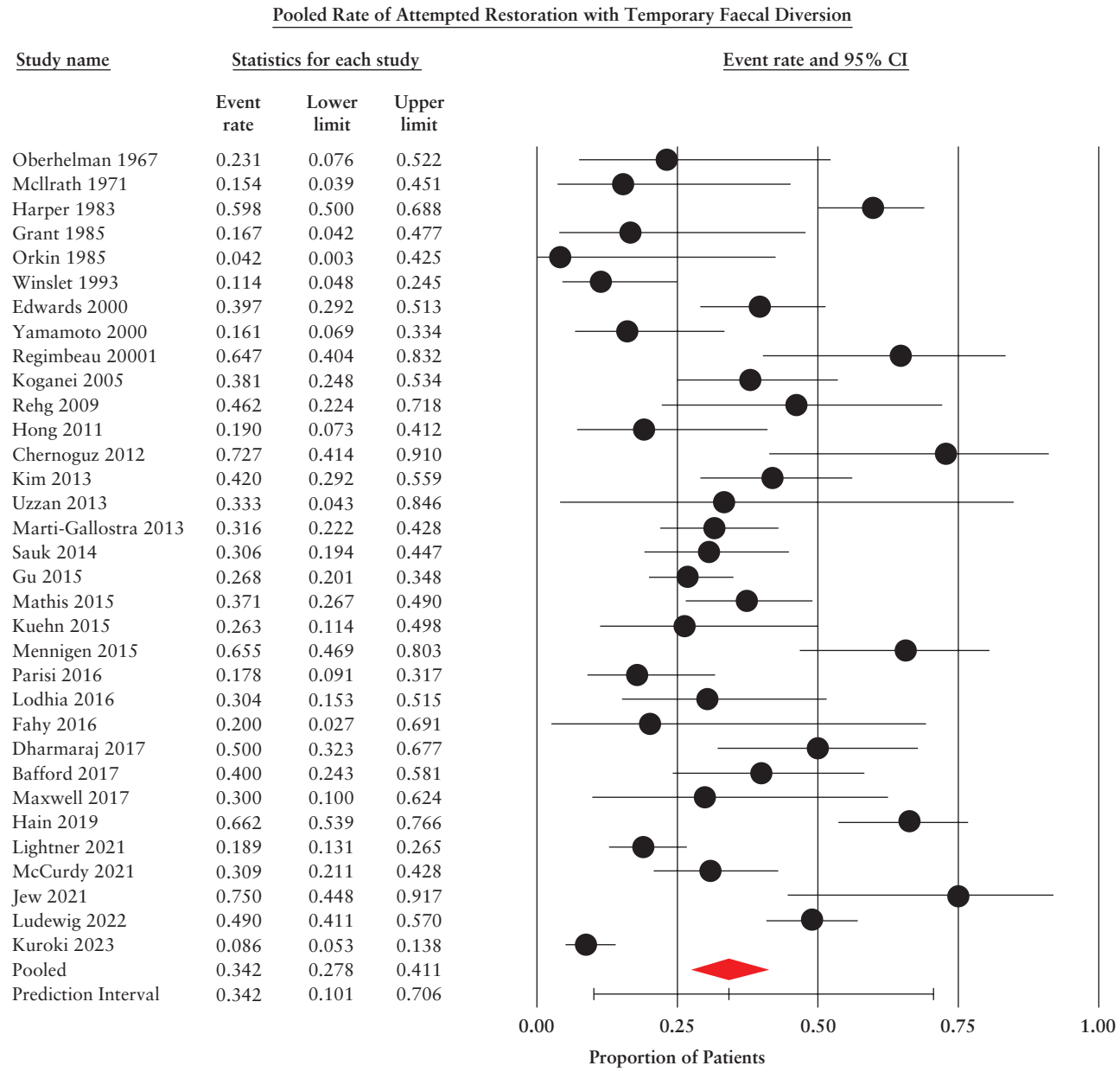

Figure 3 Pooled rate of attempted restoration of bowel continuity after temporary faecal diversion for perianal and/or distal colonic Crohn's disease

3.3. Qualitative analysis: factors associated with successful restoration of bowel continuity

Multiple studies examined factors associated with successful restoration of bowel continuity. Absence of rectal involvement and endoscopic improvement in the diverted colon were associated with restoration of bowel continuity in four studies. On multivariable analysis, Gu *et al.* observed that persistent rectal involvement was associated with a 7.5-fold higher risk of failure to achieve restoration.[19] On univariate analysis, Regimbeau *et al.* observed that 89% patients with rectal involvement required total proctectomy as compared with only 13% patients without rectal involvement.[31] Marti-Gallostra *et al.* observed that 44% patients with endoscopic improvement post-diversion were more likely to undergo stoma takedown compared with 8% patients who had persistent endoscopic activity.[26] Hain *et al.* observed that patients with active rectal disease were 4-fold more likely to require persistent stoma after faecal diversion.[20] Despite these associations, studies did not consistently identify an association between disease location and likelihood of successful restoration of bowel continuity. Among therapy-related factors, use of biologic agents [either before and/or after faecal diversion] was not associated with an increased rate of successful restoration of bowel continuity in five studies that analysed this factor, though on meta-regression, we observed higher rates of successful restoration of bowel continuity in studies with higher rates of pre-diversion and post-diversion use of biologics. One study identified the use of immunosuppressive agents prior to faecal diversion as a risk factor associated with failure of restoration of bowel continuity. Mathis and colleagues identified prior CD-related surgery as a risk factor for failure to restore bowel continuity,[12] and Gu *et al.* observed non-use of setons [compared with the use of setons prior to faecal diversion for management of perianal CD] as predictive of restoration of bowel

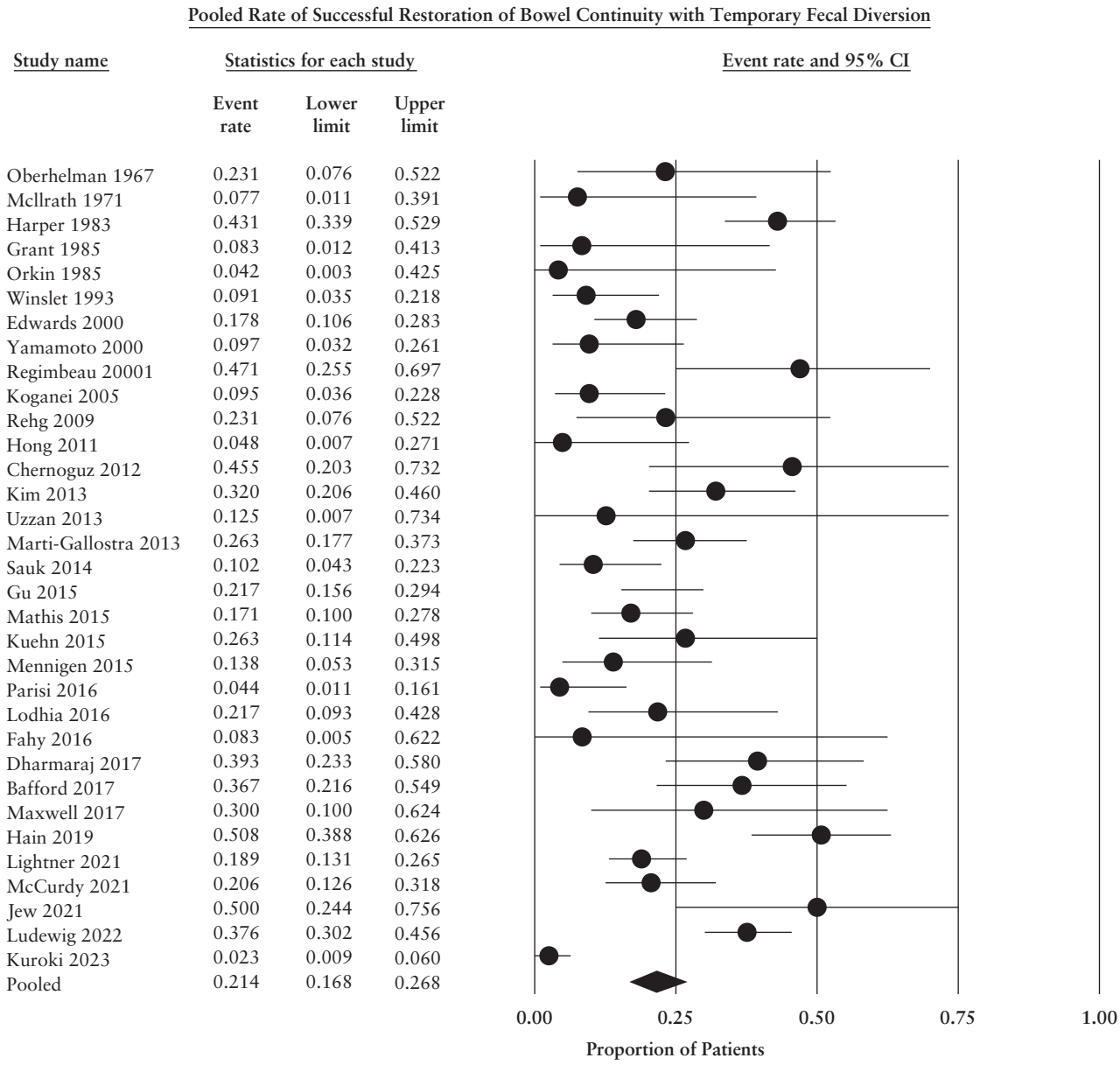

Figure 4 Pooled rate of successful restoration of bowel continuity of all patients who underwent temporary faecal diversion for perianal and/or distal colonic Crohn's disease

continuity, though it is unclear whether this was adjusted for baseline severity of perianal CD.[19] None of the other medical therapies, including 5-aminosalicylates or steroids, were associated with outcomes. No study identified any association between age, sex, smoking, indication for diversion, type of diverting stoma, duration of disease, disease activity score, or long-term outcomes after temporary faecal diversion.

4. Discussion

In this systematic review and meta-analysis of 33 cohort studies of 1578 patients who underwent temporary faecal diversion for refractory perianal and/or distal colonic luminal CD, we made several key observations. First, faecal diversion results in clinical improvement in 61% patients with refractory CD, with rates being lower [50%] in more contemporary studies in the biologic era. Second, although faecal diversion is often planned as a temporising measure for refractory disease, restoration of bowel continuity is successful in one in four patients who underwent temporary faecal diversion. Third, pre- and post-diversion use of biologics was associated with increasing rates of successful restoration of bowel continuity. In contrast, faecal diversion performed for refractory perianal CD and persistent proctitis after diversion were associated with failure to restore bowel continuity. These findings have important implications for clinical practice. We infer that temporary faecal diversion is a reasonable management strategy in a select group of patients with refractory perianal disease or disabling distal colonic disease, where disease is significantly affecting quality of life. Faecal diversion may improve symptoms in a significant proportion of patients, and ultimate stoma takedown will be successful in about one in four patients. In some instances, even if takedown is unsuccessful, having a temporary ostomy may improve a patient's acceptance of a permanent ostomy in the future should it be needed.

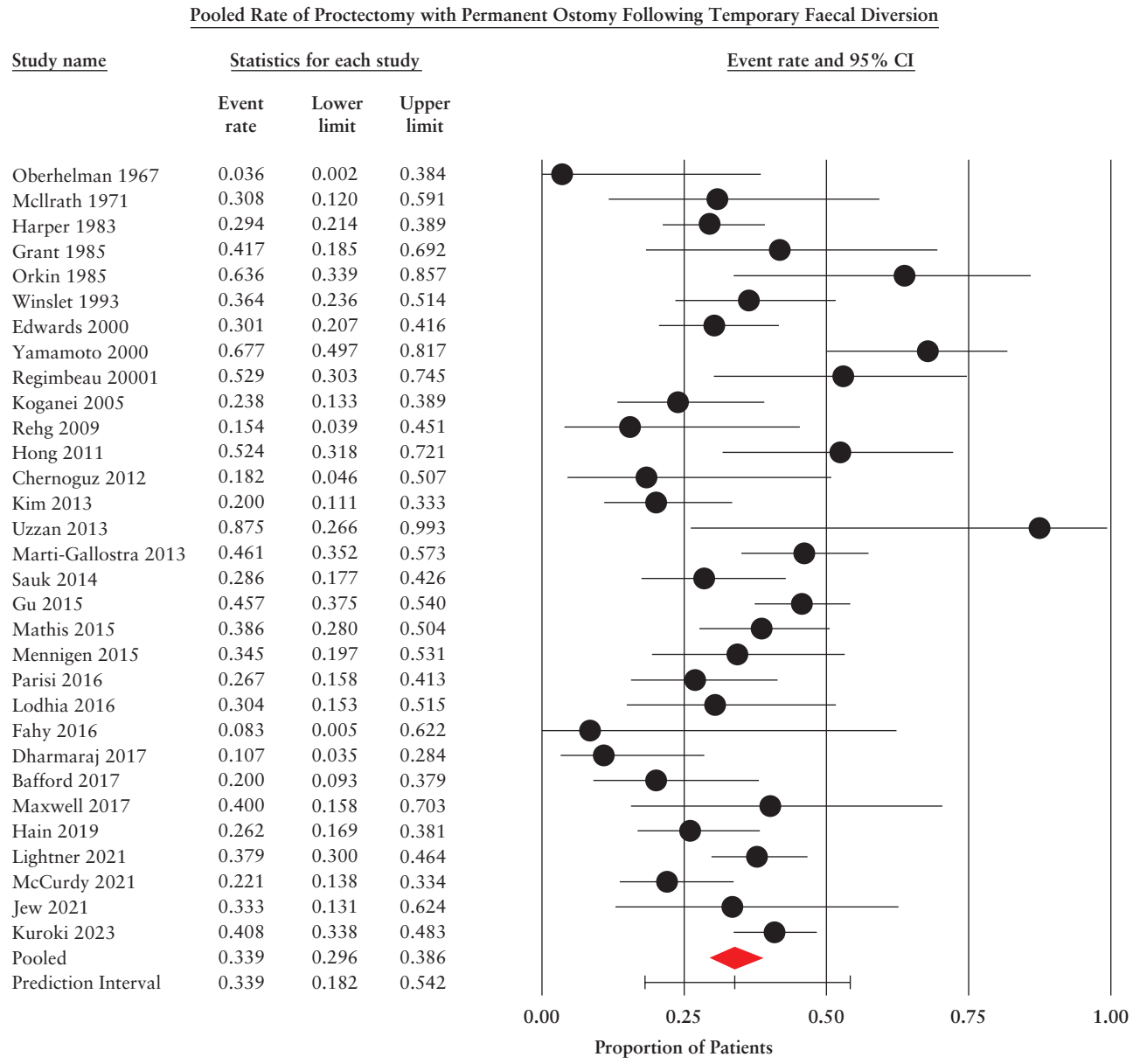

Figure 5 Pooled rate of proctectomy after temporary faecal diversion for perianal and/or distal colonic Crohn's disease

Whereas overall long-term success with temporary faecal diversion for refractory perianal and/or distal CD continues to be low, through this meta-analysis we were able to identify some signals that may help identify patients more likely to benefit from diversion with higher rates of successful restoration of bowel continuity. In a multicentre cohort study of 82 patients who under diversion for perianal CD, McCurdy and colleagues observed that whereas fistula-free survival was 21% after median follow-up of 4.9 years, use of biologics was independently associated with 68% lower risk of needing proctectomy and 3.1-times higher risk of being able to restore bowel continuity.[28] In another retrospective cohort study, Coscia *et al.* previously observed that patients treated in the biologic era were significantly less likely to require permanent ostomy after temporary faecal diversion, compared with patients who underwent diversion in the pre-biologic era [19% vs 61%].[43]

The majority of data regarding biologic use in this study refers to treatment with TNFα antagonists. Studies examining whether exposure to a new advanced therapy [to which patients were not exposed prior to faecal diversion] improves outcomes, with successful takedown, were rather limited. Hain and colleagues specifically evaluated post-faecal diversion biologic treatment; 7/13 [54%] patients who received ustekinumab post-diversion experienced successful stoma takedown, 2/6 [33%] patients who received vedolizumab post-diversion had stoma reversal.[20] These findings, as well as signals from our meta-analysis, suggest that potentially offering earlier faecal diversion prior to failure of all available biologic agents may result in improved chances at successful restoration of bowel continuity, and avoidance of proctocolectomy with permanent ostomy. This might be seen in a subset of patients with poor pharmacokinetics who are exposed to new biologic therapies after faecal diversion.

More data are needed on factors predictive of successful restoration of bowel continuity. In individual studies, which were small in size, presence of persistent rectal disease after diversion was consistently associated with poor rates of successful takedown. However, it is unclear what attempts were made to treat the diverted colon with advanced immunosuppressive therapies, either with medications to which the patient had been exposed prior to diversion, or newer therapies. It is also unclear whether medication-induced improvement in rectal disease prior to takedown will improve outcomes.

This systematic review provides contemporary estimates of outcomes after faecal diversion, but there are several limitations in our study. First, the meta-analysis consists of studies performed at tertiary referral centres with inherent selection bias for severe and refractory cases of CD. Second, all evidence is based on retrospective observational studies, and thus causal inference cannot be established. Third, there was substantial heterogeneity for most outcomes. This was partly explained through meta-regression, where use of biologics and indication for diversion were the most consistent sources of heterogeneity across outcomes. These factors could not explain all observed heterogeneity, and there are likely other unmeasured sources of heterogeneity such as variability in surgical and medical practice between institutions, including between paediatric and adult practices, variability in surgeon-related preferences, variability in defining refractory perianal CD, and varying availability of newer therapies. Additionally, there may be variability between the reasons for which patients may or may not choose to attempt reconnection, including some who may prefer to ultimately remain diverted due to improvement in their symptoms. Finally, factors associated with successful restoration of bowel continuity were not consistently reported and studied.

In conclusion, in a systematic review and meta-analysis of 33 cohort studies with 1578 patients, temporary faecal diversion results in early clinical response in about half the patients in the biologic era, and successful restoration of bowel continuity can be performed in a quarter of patients. Future studies examining early use of faecal diversion in high-risk patients with poor pharmacokinetics, and post-diversion use of effective biologics and small molecule drugs, and examining factors predictive of successful restoration of bowel continuity, are warranted to help better inform patients and providers. Ultimately, the inclusion of patients with ostomy in clinical trials is warranted to better understand the efficacy of novel therapies in these patients with high morbidity and disability due to refractory CD.[44]

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Conflicts of Interest

SS has received consulting fees from Takeda and Ethicon Surgical Robotics, and research support from the Crohn's and Colitis Foundation. VJ has received consulting/advisory board fees from AbbVie, Alimentiv Inc., Arena Pharmaceuticals, Asahi Kasei Pharma, Asieris, Astra Zeneca, Bristol Myers Squibb, Celltrion, Eli Lilly, Ferring, Flagship Pioneering, Fresenius Kabi, Galapagos, GlaxoSmithKline, Genentech, Gilead, Janssen, Merck, Mylan, Pandion, Pendopharm, Pfizer, Protagonist, Prometheus, Reistone Biopharma, Roche, Sandoz, Second Genome,Takeda, Teva, Topivert, Ventyx, Vividion, and speaker's fees from, Abbvie, Ferring, Galapagos, Janssen Pfizer Shire, Takeda, Fresenius Kabi. JM has received consulting/advisory board fees/speaker honoraria from Abbvie, BMS, Fresenius Kabi, Janssen, Pfizer, Takeda. SS's institution has received research grants from Pfizer and AbbVie; SS has received personal fees from Pfizer [for ad hoc grant review].

Author Contributions

Study concept and design: SS. Acquisition, analysis and interpretation of data: MJ, JM, SS. Drafting of the manuscript: MJ, JM. Critical revision of the manuscript for important intellectual content: SE, VJ, JDM, SS. Approval of the final manuscript: MJ, JM, SE, VJ, JDM, SS. Guarantor of article: SS.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

Data Availability Statement

The data underlying this article are available in the article and in its online supplementary material.

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