CURRENT STATUS REVIEWS

Meta-analysis of Postoperative Mortality and Morbidity After Total Abdominal Colectomy Versus Loop Ileostomy With Colonic Lavage for Fulminant *Clostridium Difficile* Colitis

Daniel Moritz Felsenreich, M.D.[1] • Mahir Gachabayov, M.D., Ph.D.[2] • Aram Rojas, M.D.[2]
Rifat Latifi, M.D.[2] • Roberto Bergamaschi, M.D., Ph.D.[2]

1 Division of General Surgery, Department of Surgery, Vienna Medical University, Vienna, Austria
2 Department of Surgery, Westchester Medical Center, New York Medical College, Valhalla, New York

BACKGROUND: Emergency surgery is often required for fulminant *Clostridium difficile* colitis. Total abdominal colectomy has been the treatment of choice despite high morbidity and mortality.

OBJECTIVE: The aim of this meta-analysis was to evaluate postoperative mortality and morbidity after total abdominal colectomy and loop ileostomy with colonic lavage in patients with fulminant *C difficile* colitis.

DATA SOURCES: Studies comparing total abdominal colectomy to loop ileostomy for fulminant *C difficile* colitis were identified by a systematic search of PubMed, Cochrane Library, MEDLINE, and CINAHL.

STUDY SELECTION: Relevant records were detected and screened using a cascade system (title, abstract, and/or full text article).

INTERVENTION(S): Total abdominal colectomy (rectal-sparing resection of the entire colon with end ileostomy) was compared to loop ileostomy (exteriorization of an ileal loop not far from the ileocecal junction for colonic lavage).

MAIN OUTCOMES MEASURES: This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Guidelines. Primary outcome was *postoperative mortality*, defined as death occurring within 30 days after the intervention. Secondary end points were the rates of ostomy reversal, deep venous thrombosis/embolism, surgical site infection, urinary tract infection, respiratory complications, reoperations, and adverse events. Mantel–Haenszel method with random-effects model was used for meta-analysis.

RESULTS: Five observational studies (3 cohort and 2 database analysis studies) totaling 3683 patients were included. Postoperative mortality rate was 31.3% after total abdominal colectomy and 26.2% after loop ileostomy (OR = 1.36 (95% CI, 0.83–2.24); $p = 0.22$; number needed to treat/harm = 20; $I^2 = 55\%$). Ostomy reversal rate was both statistically and clinically significantly higher after loop ileostomy as compared with total abdominal colectomy (80% vs 25%; OR = 0.08 (95% CI, 0.02–0.30); $p = 0.002$; number needed to treat/harm = 2) with low heterogeneity ($I^2 = 0\%$).

LIMITATIONS: A limitation is the observational nature of the included studies introducing an overall high risk of selection bias.

CONCLUSIONS: This meta-analysis suggests that loop ileostomy with colonic lavage for fulminant *C difficile* colitis may be associated with similar survival and decreased surgical site infection rates as compared with total abdominal colectomy. Although loop ileostomy with colonic lavage was associated with higher ostomy reversal

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML and PDF versions of this article on the journal's Web site (www.dcrjournal.com).

Funding/Support: None reported.

Financial Disclosure: None reported.

Correspondence: Daniel Moritz Felsenreich, M.D., Department of Surgery, Division of General Surgery, Vienna Medical University, Waehringer Guertel 18-20, 1090 Vienna, Austria. Email: moritz.felsenreich@meduniwien.ac.at

Dis Colon Rectum 2020; 63: 1317–1326
DOI: 10.1097/DCR.0000000000001764

rates, this finding was based on the data from only 2 studies.

KEY WORDS: *Clostridium difficile*; Loop ileostomy; Total abdominal colectomy.

Fulminant *Clostridium difficile* colitis (FCDC) is a serious condition requiring immediate intervention.[1–3] Total abdominal colectomy (TAC) has been the standard of care operation despite its associated high morbidity and mortality rates. In 2011, Neal et al[4] introduced loop ileostomy (LI) with intraoperative and postoperative colonic lavage as a new therapeutic approach for patients with FCDC. Although LI may have gained some popularity in the United States, surgeons in other parts of the world may perhaps not be quite as familiar with this procedure in the context of FCDC. Secondly, surgeons tend to choose procedures leading to source control. Lastly, LI may have its own physiologic or mechanical complications.[5]

The intention of a less invasive operation would be decreasing postoperative mortality while preserving the colon, as well as avoiding a permanent ileostomy, which is the case in 81% of the cases.[4] The question regarding whether LI with colonic lavage is a safe alternative to TAC for FCDC is still controversial.[6] LI with colonic lavage has been tested in animal studies[7] and practiced in small case series since the 1980s.[8,9] According to a Nationwide Inpatient Sample (NIS) study, an increasing number of US institutions have been performing LI with colonic lavage for FCDC since 2011.[10]

A major limitation of the currently available body of evidence is the feasibility of conducting adequately powered randomized controlled trials (RCTs). Massachusetts General Hospital prematurely terminated an RCT because the number of eligible patients markedly decreased since the inception of the study (clinicaltrials.gov, NCT01441271). Another RCT comparing TAC with LI with colonic lavage was also prematurely terminated because of slow accrual (clinicaltrials.gov, NCT02347280). It is well known that consenting acutely ill patients with a life-threatening condition to a random order design study is ethically and logistically challenging.[11] The aim of this meta-analysis was to evaluate postoperative mortality and morbidity after TAC and LI with colonic lavage in patients with FCDC.

MATERIALS AND METHODS

This meta-analysis was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions[12] and complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[13] and Meta-Analysis of Observational Studies in Epidemiology (MOOSE) guidelines.[14] After developing the protocol, this meta-analysis was registered in the International Prospective Register of Systematic Reviews (Prospero ID: CRD42020158502). Research (ie, literature search and data retrieval) and analysis, as well as the subsequent critical assessment, were carried out by 2 independent researchers (D.M.F. and M.G.); any differences arising during the process were discussed and resolved by the senior author (R.B.). The research question was formulated according to PICO framework as follows: (P) population: patients experiencing FCDC; (I) intervention: total colectomy; (C) comparator intervention: LI with on-table colonic lavage; and (O) outcomes: postoperative mortality, postoperative morbidity, and ostomy reversal rate.

Eligibility Criteria

The inclusion criterion was any observational or experimental comparative study comparing TAC with LI. Noncomparative descriptive studies, as well as studies comparing one of the interventions of interest with another irrelevant intervention, reviews, technical notes, and correspondence articles were not included.

Definitions

FCDC was defined as a severe progression disease requiring emergency surgery. *TAC* was defined as a rectal-sparing resection of the entire colon with end ileostomy. *LI* was defined as exteriorization of an ileal loop not far from the ileocecal junction for colonic lavage.

Postoperative mortality was defined as death occurring within 30 days after the intervention regardless of location. Ostomy reversal rate reflects the percentage of patients alive with reestablishment of intestinal continuity. Postoperative variables such as deep venous thrombosis (DVT)/embolism, surgical site infection (SSI), urinary tract infection (UTI), and respiratory complications were clinically diagnosed according to the Centers for Disease Control and Prevention National Nosocomial Infections Surveillance System.[4] Any additional operations carried out within the same hospital stay were defined as reoperations except stoma reversals.

End Points

The primary end point of this meta-analysis was postoperative mortality. The secondary end points included the rates of ostomy reversal, DVT/embolism, SSI, UTI, respiratory complications, and reoperations. In addition, a composite secondary end point of postoperative adverse events (DVT/embolism, SSI, UTI, and respiratory complications) was evaluated.

Search Strategy and Study Selection

The following meta-databases were systematically searched using the MeSH terms *Clostridium difficile*, *colectomy*, and *ileostomy* and connected with the operator *and*: PubMed, Cochrane Library, MEDLINE (Ovid), CINAHL, and Clinicaltrials.gov. The terms were chosen to be very general so as not to miss any suitable studies. Synonyms such as *pseudomembranous* were used to find additional studies. Relevant articles were thus detected, and the results of the search were screened using a cascade system (title, abstract, and/or full text article). By screening the references of included articles for additional publications, the search strategy's sensitivity was verified (see Supplement 1, Supplemental Digital Content, http://links.lww.com/DCR/B266).

Data Extraction and Quality Assessment

Data from the articles included in the present meta-analysis were collected using predefined Microsoft Excel (Microsoft, Redmond, WA) tables, and the validity of the studies was evaluated by 2 researchers independently (D.M.F. and M.G.). Collected data included author, year of publication, study design, sample size, inclusion and exclusion criteria, mortality, ostomy reversal rate, DVT/embolism, SSI, UTI, respiratory complications, and reoperations.

The quality assessment of the included studies was carried out by 2 researchers independently (F.D.M. and G.M.) using the Newcastle-Ottawa Quality Assessment Scale for Cohort Studies.[15] The scoring in the Newcastle-Ottawa Scale uses a "star system" in which a study is judged on 3 broad perspectives: the selection of the study groups, the comparability of the groups, and the ascertainment of either the exposure or outcome of interest for cohort studies. A study should reach 3 or 4 stars in selection domain, 1 or 2 stars in comparability domain, and 2 or 3 stars in outcomes domain to have a good quality. A study that reaches 2 stars in selection domain, 1 or 2 stars in comparability domain, and 2 or 3 stars in outcomes domain to have a fair quality. A study with 0 or 1 stars in selection domain, 0 stars in comparability domain, and 0 or 1 stars in outcomes domain to have a poor quality.

Statistical Analysis

The Mantel–Haenszel method of meta-analysis was used. ORs with 95% Cis were calculated for dichotomous variables. Among-study statistical heterogeneity was assessed using Cochran χ^2 and I^2. Between-study variance was assessed using τ^2 statistic when the I^2 was ≥50%.[16] Random-effects model was used for meta-analysis regardless of the extent of heterogeneity.

The results of the present meta-analysis were illustrated on forest plots. Absolute risk reduction and number needed to treat/harm (NNT) were calculated to assess clinical significance of the statistical findings. Funnel plot, Egger's test, and Begg and Mazumdar rank correlation tests were used to detect any publication bias (see Supplements 2 and 3, Supplemental Digital Content, http://links.lww.com/DCR/B266). Statistical significance was set at a *p* value of <0.05. RevMan (version 5.3; Nordic Cochrane Center, Cochrane Collaboration, Copenhagen, Denmark) and CMA Software (version 3; Biostat, Raritan, NJ) were used to perform statistical analysis.

RESULTS

Literature Search and Study Selection

Supplement 1 (see Supplemental Digital Content, http://links.lww.com/DCR/B266) shows the specifics of the search strategy, and the PRISMA flowchart (Fig. 1) presents the details of the study selection. Five databases were searched, which yielded 133 records. Two additional records were found at clinicaltrials.gov. A total of 110 records

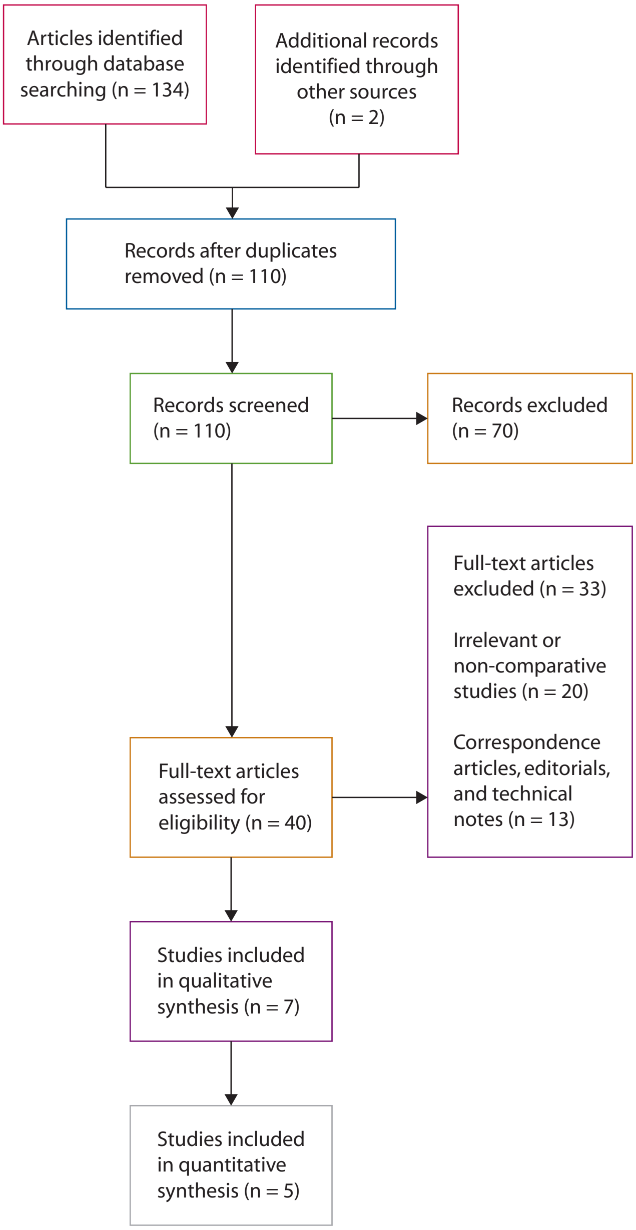

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram.

TABLE 1. Characteristics of the included studies

Author	*Publication*	*Design*	*Primary end point*	*Sample size (N = 3683)*	*No. of patients with TAC (N = 2950)*	*No. of patients with LI (N = 733)*
Fashandi et al. [17]	*Am J Surg* 2017	R (2011 – 2015)	30-d mortality	23	13	10
Ferrada et al. [18]	*J Trauma Acute Care Surg* 2017	R (2010 – 2014)	NA	98	77	21
Hall et al. [19]	*Am J Surg* 2019	R Database (ASC-NSQIP) (2011 – 2016)	NA	457	410	47
Juo et al. [10]	*JAMA Surg* 2019	R Database (NIS) (2011 – 2015)	In-hospital mortality	3 021	2 408	613
Neal et al. [4]	Ann Surg 2011	R (2009 – 2011)	Resolution of CD-associated disease	84	42	42

TAC = total abdominal colectomy; LI = loop ileostomy; R = retrospective; CD = *Clostridium difficile*; NA = not available; NIS = Nationwide Inpatient Sample; ASC-NSQIP = American College of Surgeons–National Surgical Quality Improvement Program.

were screened thru titles and abstracts. After excluding 70 nonrelevant articles, 40 articles were assessed for eligibility thru full text. Thirty-three articles (irrelevant or noncomparative studies, correspondence articles, editorials, and technical notes) were excluded; finally, 7 articles were included in qualitative data synthesis and, after excluding 2 reviews, 5 studies were included in the meta-analysis.

Description of Included Studies

Five studies comparing TAC with LI in patients with FCDC with 3683 patients in total (TAC: 2950, LI:733) were included in the present meta-analysis (Table 1).[4,10,17–19] The retrospective observational study by Neal et al[4] published in 2011 was the first of its kind and contains the initial description of LI. Additional retrospective observational studies were published in 2016 by Fashandi et al[17] and in 2017 by Ferrada et al,[18] the latter being a multicenter study including 10 centers. Finally, 2 retrospective database analyses, namely American College of Surgeons–National Surgical Quality Improvement Program (ASC-NSQIP) and NIS analyzed by Hall et al[19] (2018) and Juo et al[10] (2019), were included in the present meta-analysis. The primary outcome was postoperative mortality in 2 studies,[10,17] resolution of FCDC in 1 study,[4] and not reported in 2 studies.[18,19] The exclusion criteria defined by each individual study are listed in Table 2.

TABLE 2. Characteristics of the included studies

Author	*Inclusion criteria*	*Exclusion criteria*	*Definition of TAC*	*Definition of LI*
Fashandi et al 2017[17]	Surgical treatment for complicated CD infection	4 patients with TAC without CD infection	NA	LI with intraoperative colonic lavage polyethylene glycol 3350/electrolyte solution via the ileostomy and postoperative antegrade instillation of vancomycin flushes via the ileostomy
Ferrada et al 2017[18]	Surgical treatment for CD-associated disease	2 patients excluded that died in the OR	NA	LI with washout
Hall et al 2019 [19]	LI or TAC for CD infection	Patients with outlying age (>86 y), LOS (>55 d) and operative time (>262 min)	Rectal-sparing total colectomy with end ileostomy	NA
Juo et al 2019[10]	LI or TAC for FCDC	Patient with concomitant diagnoses of ulcerative colitis, Crohn's disease, ischemic colitis, cancer and lower GI hemorrhage	NA	NA
Neal et al 2011[4]	Severe complicated (fulminant) CD-associated disease	None	NA	LI with 8l of warmed polyethylene glycol 3350/electrolyte solution (Golytely; Braintree Laboratories) was infused into the colon via catheter and antegrade vancomycin

TAC = total abdominal colectomy; LI = loop ileostomy; R = retrospective; CD = *Clostridium difficile*; NA = not available; LOS = length of stay.

TABLE 3. Comparison of patient baseline characteristics in TAC vs LI

	Age, y		Sex, % women		Apache II score		Preoperative immunosuppression,%	
Author	TAC	LI	TAC	LI	TAC	LI	TAC	LI
Fashandi et al[17]	63.2[a] (R, 59.4–72.4)	59.7[a] (R, 56.4–63.4)	53.8%	70.0%	NA	NA	15.4%	20.0%
Ferrada et al[18]	65.0[a]	60.0[a]	40.2%	38.0%	16.5	22.0	NA	NA
Hall et al[19]	65.4 ± 14.2	64.8 ± 14.1	56.1%	68.1%	NA	NA	18.5%	22.8%
Juo et al[10]	68.4 ± 14.8	60.4 ± 16.6	58.8%	50.9%	NA	NA	NA	NA
Neal et al[4]	62.1 ± 14.0	65.3 ± 13.0	45.2%	45.2%	28.5	29.7	40.5%	45.2%

TAC = total abdominal colectomy; LI = loop ileostomy; R = range; NA = not available.
[a]SD was not reported.

Description of Study Populations and Interventions

All 3 studies and both database analyses (ASC-NSQIP and NIS) included in this meta-analysis were performed in the United States.[10,19] Baseline characteristics of the patients included in this meta-analysis are shown on Table 3. Most studies did not contain a detailed description of TAC. The only exception was the database analysis by Hall et al,[19] where TAC was defined as rectal-sparing total colectomy.

LI was characterized by Neal et al[4] as an LI with intraoperative colonic lavage using 8 L of warm polyethylene glycol (3350 per electrolyte) solution through the stoma followed by postoperative antegrade instillation of vancomycin flushes. Fashandi et al[17] described the same method. Ferrada et al[18] only stated having used LI with lavage. The remaining 2 studies did not describe LI in detail but referred to the original description by Neal et al.[4]

Quality Assessment

Random sequence generation and allocation concealment were not provided, because no RCTs were included in this meta-analysis. The risk of performance and detection bias was high in all studies, because blinding surgeons to the intervention and assessment of the outcome is impracticable and unethical. Reporting, attrition, and other bias risks were low in the studies included (Table 4).

Meta-analysis of Experimental and Observational Studies

All 5 studies were included in the current meta-analysis. The baseline characteristics in patients undergoing TAC versus LI are summarized in Table 3.

Postoperative Mortality

All included studies reported postoperative mortality (924 of 2950 in TAC vs 192 of 733 in LI), which was 31.3% after TAC and 26.2% after LI.[4,10,17–19] This difference was neither statistically nor clinically significant (OR = 1.36 (95% CI, 0.83–2.24); p = 0.22; NNT = 20). Statistical among-study heterogeneity was moderate (I^2 = 55%; τ^2 = 0.15; Fig. 2).

Ostomy Reversal Rate

Data on ostomy reversal rates were provided in 2 clinical studies only.[4,17] Ostomy reversal rate was both statisti-

TABLE 4. Quality assessment of included observational studies according to Newcastle–Ottawa score

	Selection[a]					Outcomes[c]			
Study	Representativeness of exposed cohort	Selection of nonexposed cohort	Ascertainment of exposure	Outcome not present at the start of study	Comparability[b]	Assessment of outcomes	Length of follow-up	Adequacy of follow-up	Overall score
Fashandi et al[17]	*	*	*	-	**	*	*	*	8 (good)
Ferrada et al[18]	*	*	*	-	**	*	-	*	7 (good)
Hall et al[19]	*	-	*	*	*	*	-	*	6 (good)
Juo et al[10]	*	-	*	*	*	*	-	*	6 (good)
Neal et al[4]	*	*	*	-	**	*	-	*	7 (good)

In Newcastle–Ottawa quality assessment form, a maximum of 1 star (*) for each item under selection and outcomes categories can be given; a maximum of 2 stars (**) can be given for comparability.
[a]Data evaluate the risk of selection bias.
[b]Data evaluate the risk of confounding factors.
[c]Data evaluate the risk of detection, attrition, and selective reporting bias.

Study or Subgroup	TAC Events	TAC Total	LI Events	LI Total	Weight	Odds Ratio M-H, Random, 95% CI
Fashandi 2017 [17]	3	13	3	10	6.0%	0.70 (0.11—4.54)
Ferrada 2017 [18]	26	77	5	21	13.5%	1.63 (0.54—4.95)
Hall 2019 [19]	125	410	17	47	25.0%	0.77 (0.41—1.45)
Juo 2019 [10]	749	2408	159	613	39.5%	1.29 (1.06—1.57)
Neal 2011 [4]	21	42	8	42	15.9%	4.25 (1.60—11.32)
Total (95% CI)		2950		733	100.0%	1.36 (0.83—2.24)
Total events	924		192			

Heterogeneity: $\tau^2 = 0.15$; $\chi^2 = 8.80$, df = 4 ($p = 0.07$); $I^2 = 55\%$
Test for overall effect: Z = 1.23 ($p = 0.22$)

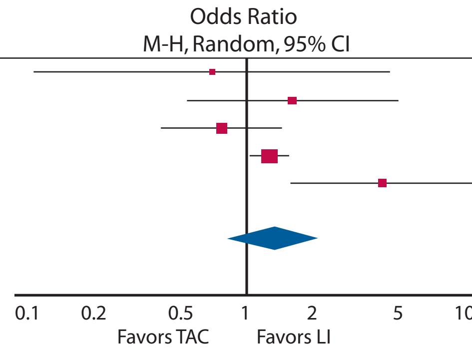

FIGURE 2. Meta-analysis of 30-day mortality: forest plot comparing the outcome in total abdominal colectomy (TAC) versus loop ileostomy (LI). df = degrees of freedom.

cally and clinically significantly lower after TAC with 25% (7/28) as compared to LI with 80% (20/25; (OR = 12.71 (95% CI, 3.35–48.24); $p = 0.00002$; NNT = 2) with low heterogeneity ($I^2 = 0\%$; Fig. 3).

DVT/Embolism Rate

Data on postoperative DVT or embolism as a postoperative complication were provided in 3 studies.[4,18,19] The rate was 7.6% (47/529) in TAC and 2.7% (3/110) in LI. This outcome was in favor of LI clinically; however, statistical significance was not achieved (OR = 2.65 (95% CI, 0.84–8.30); $p = 0.09$; NTT = 17) with low heterogeneity ($I^2 = 0\%$; Fig. 4).

SSI Rate

Another postoperative complication was SSI rate, which was provided in only 2 studies.[4,19] In total, 11.5% (52/452) had SSI in TAC and 4.5% (4/89) in LI. SSI rate was both statistically and clinically significantly in favor of LI (OR = 4.06 (95% CI, 1.30–12.70); $p = 0.02$; NTT = 15) with low heterogeneity ($I^2 = 0\%$; Fig. 5).

UTI Rate

UTI rate was reported in 2 studies.[4,17] UTI rate was 10.1% after TAC (12/119) and 7.9% (5/63) after LI. This difference was neither statistically nor clinically significant (OR = 1.23 (95% CI, 0.40–1.83); $p = 0.72$; NNT = 47). Statistical among-study heterogeneity was low ($I^2 = 0\%$; Fig. 6)

Respiratory Complication Rate

Data on respiratory complications including postoperative pneumonia were provided in 3 studies.[4,18,19] The rates were 38.2% (202/529) in TAC and 26.4% (29/110) in LI. No statistically significant difference was found (OR = 0.98 (95% CI, 0.58–1.63); $p = 0.93$). However, the difference was clinically significant favoring LI (absolute risk reduction = 0.12 (0.03–0.21); NNT = 9 (95% CI, 5–38)). Statistical heterogeneity among the studies was low ($I^2 = 0\%$; Fig. 7).

Reoperation Rate

All additional operations associated with TAC or LI (except for ostomy reversal procedures) were included in the reoperation rate. Three studies provided data on this secondary outcome.[4,18,19] Statistical among-study heterogeneity was low ($I^2 = 0\%$). The pooled reoperation rate (76/529 in TAC vs 15/110 in LI) was 14.4% after TAC and 13.6% after LI. This difference was neither statistically nor clinically significant (OR = 1.10 (95% CI, 0.56–2.15); $p = 0.78$; NNT = 137; Fig. 8).

Adverse Events

A composite secondary end point of postoperative adverse events (DVT/embolism, SSI, UTI, and respiratory complications) was evaluated as the majority of specific complications were reported in only 2 studies. Three studies provided data on this outcome.[4,18,19] The statistical among-study heterogeneity was low ($I^2 = 0\%$). The adverse

Study or Subgroup	TAC Events	TAC Total	LI Events	LI Total	Weight	Odds Ratio (Non-event) M-H, Random, 95% CI
Fashandi 2017 [17]	3	7	5	6	26.0%	6.67 (0.49—91.33)
Neal 2011 [4]	4	21	15	19	74.0%	15.94 (3.38—75.10)
Total (95% CI)		28		25	100.0%	12.71 (3.35—48.24)
Total events	7		20			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.32$, df = 1 ($p = 0.57$); $I^2 = 0\%$
Test for overall effect: Z = 3.74 ($p = 0.0002$)

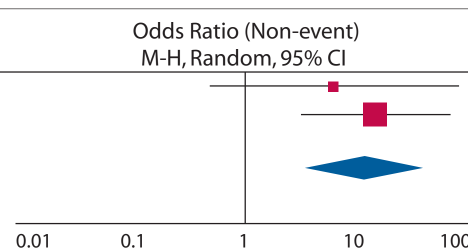

FIGURE 3. Meta-analysis of ostomy reversal rate: forest plot comparing the outcome in total abdominal colectomy (TAC) versus loop ileostomy (LI). df = degrees of freedom.

Study or Subgroup	TAC Events	TAC Total	LI Events	LI Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Ferrada 2017 [18]	5	77	0	21	14.8%	3.26 (0.17—61.38)
Hall 2019 [19]	39	410	2	47	66.3%	2.37 (0.55—10.13)
Neal 2011 [4]	3	42	1	42	18.9%	3.15 [0.94—31.62]
Total (95% CI)		529		110	100.0%	2.65 (0.84—8.30)
Total events	47		3			

Heterogeneity: $\chi^2 = 0.06$, df = 2 ($p = 0.97$); $I^2 = 0\%$
Test for overall effect: Z = 1.67 ($p = 0.09$)

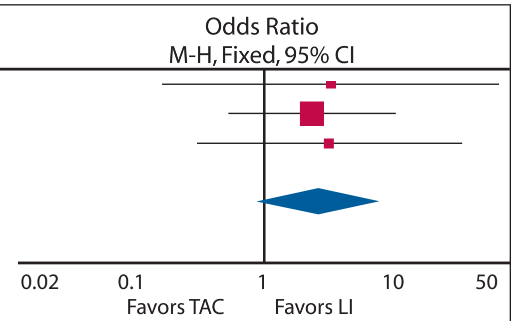

FIGURE 4. Meta-analysis of deep venous thrombosis/embolism: forest plot comparing the outcome in total abdominal colectomy (TAC) versus loop ileostomy (LI). df = degrees of freedom.

Study or Subgroup	TAC Events	TAC Total	LI Events	LI Total	Weight	Odds Ratio M-H, Random, 95% CI
Hall 2019 [19]	43	410	1	47	32.3%	5.39 (0.72—40.07)
Neal 2011 [4]	9	42	3	42	67.7%	3.55 (0.89—14.18)
Total (95% CI)		452		89	100.0%	4.06 (1.30—12.70)
Total events	52		4			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.12$, df = 1 ($p = 0.73$); $I^2 = 0\%$
Test for overall effect: Z = 2.41 ($p = 0.02$)

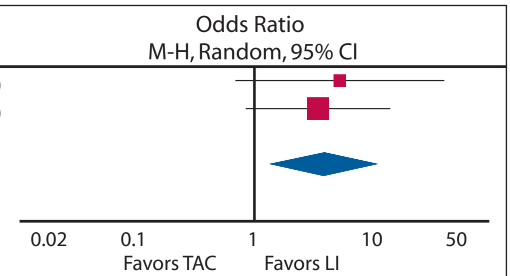

FIGURE 5. Meta-analysis of surgical site infection: forest plot comparing the outcome in total abdominal colectomy (TAC) versus loop ileostomy (LI). df = degrees of freedom.

Study or Subgroup	TAC Events	TAC Total	LI Events	LI Total	Weight	Odds Ratio M-H, Random, 95% CI
Ferrada 2017 [18]	8	77	2	21	47.9%	1.10 (0.22—5.62)
Neal 2011 [4]	4	42	3	42	52.1%	1.37 (0.40—6.53)
Total (95% CI)		119		63	100.0%	1.23 (0.40—3.81)
Total events	12		5			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.04$, df = 1 ($p = 0.85$); $I^2 = 0\%$
Test for overall effect: Z = 0.36 ($p = 0.72$)

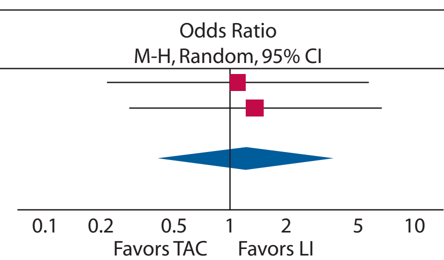

FIGURE 6. Meta-analysis of urinary tract infection: forest plot comparing the outcome in total abdominal colectomy (TAC) versus loop ileostomy (LI). df = degrees of freedom.

Study or Subgroup	TAC Events	TAC Total	LI Events	LI Total	Weight	Odds Ratio M-H, Random, 95% CI
Ferrada 2017 [18]	9	77	3	21	13.5%	0.79 (0.19—3.24)
Hall 2019 [19]	188	410	22	47	72.8%	0.96 (0.53—1.76)
Neal 2011 [4]	5	42	4	42	13.8%	1.28 [0.32—5.16]
Total (95% CI)		529		110	100.0%	0.98 (0.58—1.63)
Total events	202		29			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.23$, df = 4 ($p = 0.89$); $I^2 = 0\%$
Test for overall effect: Z = 0.09 ($p = 0.93$)

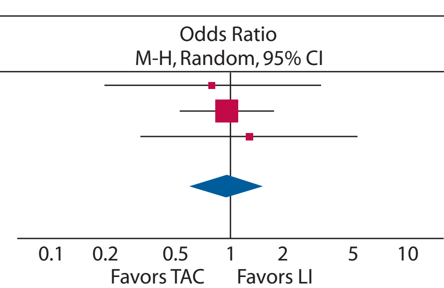

FIGURE 7. Meta-analysis of respiratory complications: forest plot comparing the outcome in total abdominal colectomy (TAC) versus loop ileostomy (LI). df = degrees of freedom.

event rates were 59.2% (313/529) in TAC and 37.3% in LI (41/110), with both statistically and clinically significantly difference in favor of LI (OR = 1.84 (95% CI, 1.16–2.92); $p = 0.01$; NNT = 5; Fig. 9).

Sensitivity Analysis and Publication Bias

A sensitivity analysis was performed by excluding studies with the highest risk of bias. This did not affect the findings.

A potential publication bias was evaluated by visual assessment of symmetry on the funnel plot of the primary end point (Fig. 10). Furthermore, Egger's test (t value = 0.23; $p = 0.83$) and Begg and Mazumdar rank correlation test ($p = 1.00$; see Supplements 2 and 3, Supplemental Digital Content, http://links.lww.com/DCR/B266) showed a low risk of publication bias.

Study or Subgroup	TAC Events	TAC Total	LI Events	LI Total	Weight	Odds Ratio M-H, Random, 95% CI
Ferrada 2017 [18]	29	77	9	21	46.6%	0.81 (0.30—2.15)
Hall 2019 [19]	43	410	4	47	38.9%	1.26 (0.43—3.68)
Neal 2011 [4]	4	42	2	42	14.5%	2.11 (0.36—12.17)
Total (95% CI)		529		110	100.0%	1.10 (0.56—2.15)
Total events	76		15			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.98$, df = 2 ($p = 0.61$); $I^2 = 0\%$
Test for overall effect: Z = 0.28 ($p = 0.78$)

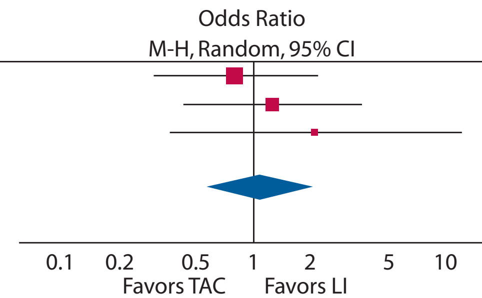

FIGURE 8. Meta-analysis of reoperations: forest plot comparing the outcome in total abdominal colectomy (TAC) versus loop ileostomy (LI). df = degrees of freedom.

DISCUSSION

Interpretation of the Results

This meta-analysis did not yield any statistically or clinically significant differences in postoperative mortality between TAC and LI. In fact, approximately one third of patients undergoing either procedure died. High mortality rates are expected in patients with FCDC because of severity of illness, as well as the extent of the operation, which counterbalances the intention of TAC to control the source. High postoperative mortality rates after LI with colonic lavage may be explained by the lack of source control, which may have resulted in death attributed to disease progression. Therefore, additional research focused on antimicrobial/antiseptic agents for colonic lavage and adjuvant medical therapy is required to further reduce the risk of disease progression and improve survival after LI. Although no statistical or clinical significances were found, we should be cautious in drawing any robust and clinically sound conclusions given the moderate statistical heterogeneity among the included studies.

The disadvantage of an invasive procedure such as TAC in critically ill patients is also demonstrated by its increased postoperative morbidity. Although statistical significance was achieved in 1 end point only, namely SSI rates, pooled rates of other end points (DVT/embolism, UTI, respiratory complications, reoperation) were also decreased in patients undergoing LI with colonic lavage. Although the difference in SSI rates makes sense, confounding factors may have contributed to different reporting of SSIs. Surgical incision necessary for emergency TAC is generally larger and does not become the stoma site as with LI. Evaluation of a composite secondary end point of overall adverse event rate showed a significantly decreased rate after LI. This finding should not be interpreted as lower overall postoperative morbidity because the composite end point does not include multiple systemic complications, as well as ileostomy-related physiologic and mechanical complications, including but not limited to dehydration, retraction, necrosis, and prolapse of the ileostomy. More detailed reporting of postoperative complication is recommended in future studies. As expected, the rates of ostomy reversal after LI with colonic lavage were higher than after TAC. Nonetheless, the risk for recurrent *C difficile* colitis after LI reversal is to be kept in mind.[20] The fact that only 2 studies reported ostomy reversal rates does not allow us to draw robust conclusions. LI reversal is an easier undertaking than ileorectostomy, creating bias in favor of LI. Notwithstanding that bias, the difference in stoma closure rate is based on 7 of 28 patients closed for TAC and 20 of 25 patients closed for LI or a total of only 53 patients reportedly undergoing closure. Hence, additional observational studies are required to confirm these findings.

Existing Evidence

Since the 1980s the incidence of *C difficile* colitis has been reported to have an increasing trend.[21] During the last 4 decades, mortality rates associated with FCDC have not changed and still account for one third of the patients.[22]

Study or Subgroup	TAC Events	TAC Total	LI Events	LI Total	Weight	Odds Ratio M-H, Random, 95% CI
Ferrada 2017 [18]	22	77	5	21	17.5%	1.28 (0.42—3.92)
Hall 2019 [19]	270	410	25	47	57.6%	1.70 (0.92—3.12)
Neal 2011 [4]	21	42	11	42	25.4%	2.84 (1.16—7.04)
Total (95% CI)		529		110	100.0%	1.84 (1.16—2.92)
Total events	313		41			

Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.30$, df = 4 ($P = 0.52$); $I^2 = 0\%$
Test for overall effect: Z = 2.59 ($P = 0.010$)

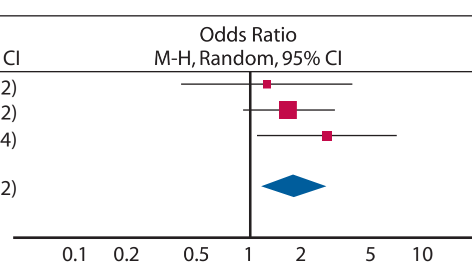

FIGURE 9. Meta-analysis of adverse events: forest plot comparing the outcome in total abdominal colectomy (TAC) versus loop ileostomy (LI). df = degrees of freedom.

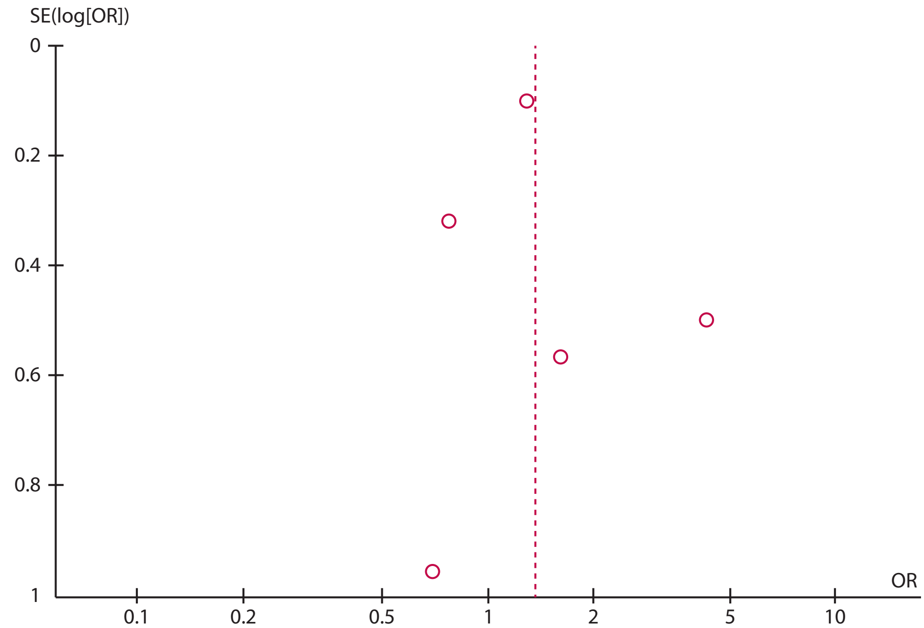

FIGURE 10. Funnel plot of the primary end point. This chart plots the SE of log OR relative to OR. The vertical dotted line shows the overall effect estimate of the primary end point, whereas the circles show effect estimates of the primary end point of each individual study.

Our findings are in line with those rates. Early diagnosis and immediate treatment for FCDC is crucial. In fact, an observational study including 183 patients with FCDC found a mortality rate of up to 80% in case of delay.[23] Although Olivas et al[24] expressed that LI with colonic lavage could be a safe alternative to TAC as early as in 2010 (based on a few historical animal studies and case reports), there are no summary design studies comparing TAC with LI for FCDC in the literature.

However, the literature does include 1 systematic review comparing TAC with surgical procedures other than LI (eg, segmental colon resection). The same review, which included 31 studies with 1433 patients, did not find any differences in mortality rates comparing TAC with non-TAC patients (OR = 0.87).[25] Another systematic review published in 2013 including 6 studies with 510 patients undergoing TAC or conservative management found a survival benefit in TAC patients (OR = 0.70).[26]

Strengths and Limitations

There are no previous meta-analyses comparing TAC to LI with colorectal lavage for FCDC in the literature. Rigorous literature search, compliance with the PRISMA and MOOSE guidelines, and assessment of clinical relevance of statistical findings are other strengths.

A major limitation of this meta-analysis is the observational nature of the included studies introducing an overall high risk of selection bias. Lack of RCTs comparing interventions of interest further contributes to the overall high risk of selection, performance, and detection biases. Another limitation is the lack of standardized definitions of interventions in addition to inconsistent reporting of relevant outcomes. Moreover, 2 of the included studies were based on administrated databases, such as NIS and ASC-NSQIP. Our inability to ensure that exclusively fulminant cases and all fulminant colitis patients were included in our meta-analysis may have introduced additional selection bias. Finally, data on the rates of recurrent *C difficile* colitis after LI reversal were not reported.

CONCLUSIONS

This meta-analysis suggests that LI with colonic lavage for FCDC may be associated with similar survival and decreased SSI rates as compared with TAC. Although LI with colonic lavage was associated with higher ostomy reversal rates, this finding was based on the data from only 2 studies.

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