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Transmural Inflammation, Ileitis, and Granulomas at the Time of Proctocolectomy in Patients with Ulcerative Colitis Do Not Predict Future Development of Pouchitis

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Pathology · Pouchitis · Ileal pouch-anal anastomosis · Histology

Abstract
Background: The most common complication following ileal pouch-anal anastomosis (IPAA) in patients with ulcerative colitis (UC) is pouchitis. Our study aimed to investigate the relationship between histopathologic findings of ileitis, granuloma, or transmural inflammation on the colectomy specimen of patients with clinically and endoscopically diagnosed UC and the development of pouchitis within the first 2 years after IPAA. ***Methods:*** We performed a retrospective cohort study evaluating patients undergoing colectomy with IPAA for UC between January 1, 2004 and December 31, 2016. Bivariate analyses were conducted to evaluate the relationship between clinical factors and the development of pouchitis. We performed multivariate logistic regression to evaluate the relationship between histologic, clinical, and demographic factors at the time of colectomy and subsequent development of pouchitis. ***Results:*** Among 626 patients, pouchitis occurred in 246 (39%). Patients with primary sclerosing cholangitis were more likely to develop pouchitis (adjusted odds ratio [aOR] 2.81, 95% confidence interval [CI] 1.02–7.72), as were patients with a family history of inflammatory bowel disease (aOR 1.75, 95% CI 1.11–2.77). Histologic findings of ileitis, granuloma, or transmural inflammation were not associated with an increased odds of developing pouchitis (aOR 0.70, 95% CI 0.45–1.08). ***Discussion/Conclusion:*** Patients with ileitis, granulomas, or transmural inflammation at the time of colectomy were not at greater risk for development of pouchitis in the 2 years after IPAA. These pathological findings should not preclude IPAA for UC.

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Introduction

Although proctocolectomy with ileal pouch-anal anastomosis (IPAA) is the most common restorative surgical procedure among patients with ulcerative colitis (UC) who require surgical therapy for refractory colitis or dysplasia-associated UC, the burden of inflammatory conditions after IPAA is well recognized [1, 2]. Up to 80% of patients will develop pouchitis at some point after IPAA [3, 4], and 10% will develop Crohn's-like disease of the pouch, despite a preoperative diagnosis of UC [5]. Despite their relatively high prevalence, there is a paucity of predictors of these complications.

Traditionally, the findings of transmural inflammation and a granuloma on gross pathology have been associated with a clinical diagnosis of Crohn's disease [6]. Thus, the identification of these findings at the time of total abdominal colectomy in a patient with UC might conceivably impact surgical planning, including the decision to pursue an IPAA or treatment strategies in the early postoperative setting. Prior studies have demonstrated an increased risk for pouchitis among patients with UC-associated ileitis (backwash ileitis) [7, 8] and ileitis on histopathology at the time of colectomy [9]. However, this relationship is not definitive as other studies have demonstrated no significant association [10–12]. Similarly, the relationship between histopathologic findings such as granuloma and subsequent pouch outcomes is not well defined [12]. Although end ileostomy in the setting of UC may also be associated with complications and variable effects on quality of life [13], we hypothesized that these histopathologic findings might increase the risk of early pouchitis. If such a relationship were demonstrated, we believed that the potential for worse pouch-related outcomes due to perioperative pathological findings could prompt a change in surgical planning, including the decision to pursue end ileostomy over IPAA. Given the lack of definitive data regarding the impact of histopathology at the time of colectomy and future outcomes after IPAA, we performed a retrospective cohort study to evaluate the relationship between the presence of ileitis, granuloma, or transmural inflammation on histopathology from colectomy specimens and the development of pouchitis within the first 2 years after IPAA among patients with UC.

Methods

Patient Selection

We identified 758 patients who underwent restorative proctocolectomy with IPAA for UC at the University of North Carolina at Chapel Hill (UNC) between January 1, 2004 and December 31, 2016. Of these, 626 (83%) met the inclusion criteria for the study. Patients were identified utilizing the Carolina Data Warehouse for Health (CDW-H), a central data repository that contains clinical and administrative data from electronic health records in the UNC Health system. Pertinent clinical, demographic, and laboratory data were extracted from the electronic medical record using a standardized case extraction form. Any patient older than 18 years who had undergone proctocolectomy with IPAA for clinically established UC at the UNC during the study period and had 2 years of complete follow-up after surgery was eligible for inclusion. The preoperative diagnosis of UC was based on available clinical, endoscopic, and pathological data prior to the time of colectomy and confirmed on the review of the medical record. Patients undergoing IPAA for UC during the study period without a full 2 years of follow-up after IPAA were excluded from the study. Additionally, patients with a preoperative diagnosis of Crohn's disease or IBD-unclassified (IBD-U) at the time of colectomy were excluded.

Outcomes of Interest

The primary outcome of interest was the development of pouchitis within the first 2 years after the final stage of IPAA surgery. At least 2 of 3 expert gastroenterologists (E.L.B., B.K., or H.H.H.) reviewed the charts of all 626 included patients to determine if the patient had a diagnosis of pouchitis within the first 2 years of IPAA. This diagnosis was based on clinical symptoms including frequency, urgency, abdominal pain, and a sense of malaise, as well as response to therapy. Pouchoscopy and/or biopsies were not required for a diagnosis of pouchitis. Any cases where a discrepancy existed between the reviewers were automatically re-reviewed with the assistance of a third reviewer to resolve the differences and make a final determination on the clinical diagnosis of pouchitis. The inter- and intra-rater reliability of the assessment of pouchitis were assessed using kappa statistics and intra-class coefficients as directed by the Landis and Koch [14] benchmarks (<0.00 poor, 0–0.2 slight, 0.21–0.40 fair, 0.41–0.60 moderate, 0.61–0.80 substantial, and 0.81–1.00 almost perfect). For inter-rater reliability, the kappa was 0.70 (95% confidence interval [CI] 0.64–0.76) indicating substantial agreement; for intra-rater reliability, the kappa was 0.86 (95% CI 0.76–0.96) indicating almost perfect agreement.

Covariates

The medical record of each patient was examined to extract demographic, clinical, and pathological factors that might be associated with the development of pouchitis, including preoperative factors such as disease extent and medications prior to colectomy and concomitant diagnoses such as primary sclerosing cholangitis (PSC). At our center, a modified 2-stage IPAA is defined as follows: a total abdominal colectomy with end ileostomy is completed in the first operation, and after a recovery interval, a second surgery is performed including completion proctectomy and IPAA (without a diverting loop ileostomy) [15]. A traditional 2-stage IPAA was defined as a total proctocolectomy IPAA with loop ileostomy followed by an ostomy takedown. We specifically evaluated the pathology report of each patient's colectomy specimen to document the presence of ileitis, granulomas, or transmural inflammation on the examination of the gross specimen removed at the time of colectomy. All pathological findings were confirmed by documentation of the presence of specific findings in pathological reporting. The stated absence of findings in the

Table 1. Demographics and clinical characteristics of patients undergoing proctocolectomy with IPAA between 2004 and 2016

	Patients undergoing IPAA (n = 626)	
	n	%
Age at surgery (median, IQR), years	40.6	29.5–52.5
Disease duration prior to surgery (median, IQR), years	6.08	2.18–14.2
Female sex	302	48
Race[a]		
White	545	11
Non-white	66	89
Hispanic	13	2
Family history of IBD	97	17
Indication for surgery		
Medically refractory colitis	494	79
Dysplasia or cancer	83	13
Other indication	49	8
Disease extent prior to surgery		
Proctitis	26	4
Left-sided colitis	173	29
Extensive colitis	388	66
Type of IPAA surgery		
1-Stage	116	19
2-Stage	224	36
Modified 2-stage[b]	234	37
3-Stage	51	8
Ileitis on pathology	105	17
Granuloma on pathology	26	4
Transmural inflammation on pathology	34	5
Abscess or pelvic sepsis after IPAA surgery	117	19
Evidence of an IPAA leak immediately after surgery	46	7
PSC	19	3
Medications prior to colectomy		
Systemic aminosalicylate	495	79
Topical aminosalicylate	302	48
Thiopurine	390	62
Methotrexate	67	11
Anti-TNF	321	51
Vedolizumab	17	3
Cyclosporine	26	4

Anti-TNF, anti-tumor necrosis factor alpha; IPAA, ileal pouch-anal anastomosis; IBD, inflammatory bowel disease; IQR, interquartile range; PSC, primary sclerosing cholangitis. [a] Race was missing or not reported for 15 patients. [b] Modified 2-stage IPAA: a total abdominal colectomy with end ileostomy is completed in the first operation, and after a recovery interval, a second surgery is performed including completion proctectomy and IPAA.

pathological report (lack of granuloma, ileitis, or transmural inflammation) was not required.

Statistical Analysis

Continuous variables were summarized using means and standard deviations and compared using the Wilcoxon rank-sum test. Categorical variables were expressed as proportions and compared using Fisher's exact and χ^2 testing, as appropriate. Bivariate and multivariable logistic regression models were utilized to evaluate the relationship between specific pathological findings at the time of colectomy (ileitis, granulomas, or transmural inflammation) and the development of pouchitis within the first 2 years after IPAA, controlling for potential confounders. All covariates included in the multivariable analyses were identified a priori based on suspected association with disease activity in UC preoperatively or the subsequent development of pouchitis after IPAA. All statistical analyses were performed using SAS (version 9.4) statistical software (SAS Institute, Cary, NC, USA). The study protocol was approved by the Institutional Review Board at the UNC.

Table 2. Univariate comparison of demographic and clinical characteristics of patients with and without pouchitis in the 2 years following an IPAA

	Patients without pouchitis (n = 380)		Patients with pouchitis (n = 246)		p value
	n	%	n	%	
Age at surgery (median, IQR), years	42.4	30.7–54.3	39.6	29.7–51.9	0.17
Disease duration prior to surgery (median, IQR)	5.73	2.18–15.3	6.21	2.21–13.1	0.93
Female sex	179	47	123	50	0.48
Race					
White	327	88	218	91	0.30
Non-white	44	12	22	9	
Hispanic	6	2	7	3	0.56
Family history of IBD	49	14	48	21	0.02
Indication for surgery					
Medically refractory colitis	297	78	197	80	
Dysplasia or cancer	55	15	28	11	0.50
Other indication	28	7	21	9	
Disease extent prior to surgery					
Proctitis	17	5	9	4	
Left-sided colitis	95	27	78	34	0.22
Extensive colitis	242	68	146	63	
Type of IPAA surgery					
1-Stage	75	20	41	17	
2-Stage	119	31	105	43	0.03
Modified 2-stage	155	41	79	32	
3-Stage	30	8	21	9	
Ileitis on pathology	70	18	35	14	0.17
Granuloma on pathology	18	5	8	3	0.36
Transmural inflammation on pathology	27	7	7	3	0.02
Abscess or pelvic sepsis after IPAA surgery	71	19	46	19	0.10
Evidence of an IPAA leak immediately after surgery	28	7	18	7	0.98
PSC	8	2	11	5	0.09
Medications prior to colectomy					
Systemic aminosalicylate	291	77	204	83	0.06
Topical aminosalicylate	175	46	127	52	0.17
Thiopurine	225	59	165	67	0.05
Methotrexate	43	11	24	10	0.53
Anti-TNF	196	52	125	51	0.85
Vedolizumab	7	2	10	4	0.10
Cyclosporine	12	3	14	6	0.12

Anti-TNF, anti-tumor necrosis factor alpha; IPAA, ileal pouch-anal anastomosis; IBD, inflammatory bowel disease; IQR, interquartile range; PSC, primary sclerosing cholangitis.

Results

Among 626 patients who underwent proctocolectomy with IPAA for UC, 246 (39%) developed pouchitis within the first 2 years after the final stage of IPAA surgery. Of the 626 patients, 302 (48%) were female, and the median age of patients at the time of IPAA was 40.6 years, interquartile range 29.5–52.5 years (shown in Table 1). The most common type of surgical procedure performed was a modified 2-stage IPAA (37%), although another 36% of patients underwent a traditional 2-stage IPAA. When evaluating the specific pathological findings of interest on the colectomy specimen, 17% of patients had ileitis, 4% had a granuloma or granulomas, and 5% had transmural inflammation.

Among patients developing pouchitis, the median time to development of pouchitis was 148 (interquartile range 75–320) days. When evaluating the clinical factors

Table 3. Unadjusted and adjusted odds of developing pouchitis among patients undergoing proctocolectomy with IPAA as a treatment of UC

	Unadjusted OR (95% CI)	aOR (95% CI)
Age at the time of surgery	1.01 (1.00–1.02)	1.01 (0.99–1.02)
PSC	2.18 (0.86–5.49)	2.81 (1.02–7.72)
Family history of IBD	1.70 (1.09–2.63)	1.75 (1.11–2.77)
Disease extent prior to surgery		
Proctitis	0.65 (0.27–1.53)	0.67 (0.28–1.64)
Left-sided colitis	Reference	Reference
Extensive colitis	0.74 (0.51–1.06)	0.78 (0.53–1.16)
Type of IPAA surgery		
1-Stage	0.62 (0.39–0.98)	0.61 (0.37–1.03)
2-Stage	Reference	Reference
Modified 2-stage	0.58 (0.40–0.84)	0.64 (0.42–0.97)
3-Stage	0.79 (0.43–1.47)	0.85 (0.43–1.69)
Ileitis, granuloma, or transmural[a]		
inflammation on pathology	0.59 (0.40–0.89)	0.70 (0.45–1.08)

CI, confidence interval; OR, odds ratio; aOR, adjusted OR; IPAA, ileal pouch-anal anastomosis; IBD, inflammatory bowel disease; UC, ulcerative colitis; PSC, primary sclerosing cholangitis. [a] Pathological findings evaluated as combined variable, given that each pathological finding was underpowered to include as an individual variable.

associated with the development of pouchitis, patients with pouchitis were more likely to undergo a traditional 2-stage IPAA than patients without pouchitis (43% vs. 31%) and were less likely to undergo a modified 2-stage IPAA (32% vs. 41%, shown in Table 2). There were no significant associations between preoperative medication use and development of pouchitis, including the preoperative use of biologics.

In bivariate analysis, patients with pouchitis were less likely to demonstrate transmural inflammation alone on gross pathology of their resected colon and rectum than patients without pouchitis (3% vs. 7%, $p = 0.02$). There were no significant differences in the proportion of patients with granulomas or ileitis on pathology when comparing patients who developed pouchitis compared to patients who did not develop pouchitis (3% vs. 5% and 14% vs. 18% respectively).

In the unadjusted analysis, the combined findings of ileitis, granuloma, or transmural inflammation on pathology at the time of colectomy were not associated with an increased risk of pouchitis and were in fact associated with a slight decreased risk of pouchitis (odds ratio [OR] 0.59, 95% CI 0.40–0.89, shown in Table 3). After adjustment for potential confounders however, this relationship was no longer significant (adjusted OR [aOR] 0.70, 95% CI 0.45–1.08). A concomitant diagnosis of PSC was associated with a significant increase in the odds of development of pouchitis (aOR 2.81, 95% CI 1.02–7.72) as was a family history of IBD (aOR 1.75, 95% CI 1.11–2.77). When evaluating the surgical procedure used, patients who underwent a modified 2-stage procedure were less likely to develop pouchitis than those undergoing a 2-stage procedure (aOR 0.64, 95% CI 0.42–0.97).

Discussion

In an analysis of 626 patients undergoing colectomy with IPAA for UC at our tertiary care referral center between 2004 and 2016, histopathologic findings of ileitis, granuloma, and transmural inflammation were not associated with the development of pouchitis within the first 2 years after IPAA. These findings have a clinical impact for gastroenterologists, surgeons, and patients, given the significant concern about the postoperative burden of inflammatory conditions of the pouch. Although almost 40% of patients developed pouchitis within the 2-year follow-up period, these pathological findings at the time of colectomy that might give providers pause in proceeding with restorative surgery were not predictive of future pouchitis. Despite a relatively small prevalence, well-recognized risk factors such as PSC [16, 17] were associated with future development of pouchitis.

Currently, a staged approach to restorative proctocolectomy with IPAA is preferred over a 1-stage operation in patients with active, therapy-refractory UC [1]. Although a 3-stage IPAA has several advantages including a decreased rate of pelvic sepsis and a decreased risk

for unplanned reoperations [1], the initial total abdominal colectomy also allows for the examination of the gross pathology from the resected specimen, which could influence decision-making if there were concerns regarding future inflammatory conditions of the pouch. Our study extends the results of a prior study from Cedars-Sinai Medical Center, which found that no single atypical histopathologic feature of UC (or combination of features) was associated with worse outcomes after IPAA in multivariate analysis [12]. However, the study from Cedars-Sinai Medical Center included only 153 patients, 22% of whom carried a preoperative diagnosis of indeterminate colitis. Although we attempted to identify those patients with clinically diagnosed UC prior to colectomy, the findings of transmural inflammation and (and more specifically granuloma) at the time of colectomy likely indicate a spectrum of disease, given that no prior indication of IBD-U existed in these patients. UC-associated or backwash ileitis, which was found in 17% of our patients at the time of colectomy, has been associated an increased risk of developing pouchitis or a higher incidence of pouchitis after IPAA in a number of small studies [7–9]; however, these results are not conclusive as a separate smaller study showed no relationship [10], and in a prospective study, backwash ileitis was not associated with the development of acute or chronic pouchitis after IPAA [18].

Other preoperative factors have been identified with an increased risk for pouchitis. PSC has been identified as a significant risk factor for the later development of pouchitis [7, 19–25], and some authors have speculated that PSC-related pouchitis may be a different phenotype from other idiopathic forms of pouchitis that develop after IPAA [26]. We also demonstrated a significantly increased risk of pouchitis in the first 2 years after surgery among patients with a positive family history of IBD, which has also been associated with an increased risk for development of Crohn's-like disease of the pouch [27]. Due to the relatively short follow-up, we cannot rule out that our positive association may result in an increased incidence of a Crohn's-like phenotype of pouch inflammation with a longer follow-up. A recent publication from the University of Chicago indicated that patients with preoperative use of anti-tumor necrosis factor alpha therapy were at an increased risk to develop pouchitis during a median follow-up of 62 months [28]. In our analysis, there was no relationship between preoperative biologic exposure and subsequent development of pouchitis.

Taken together, these findings suggest that in patients with clinically and endoscopically proven UC, the presence of ileitis, granulomas, or transmural inflammation on the resected colectomy specimen is not associated with increased risk for pouchitis. Thus, in patients with a planned staged IPAA, these histopathologic findings should not change the future plans for restorative surgery. Given that the presence of UC-associated ileitis and granuloma might be noted in the preoperative setting, including on biopsies from colonoscopy, these specific findings might also extend to pathological findings from preoperative evaluations and not the gross colectomy specimen. However, this remains a continued area of research.

Our study has multiple strengths including large sample size collected over a 13-year period of time from a tertiary care IBD referral center. However, our study has limitations. Our outcomes occurred in a single IBD center. Given that this was a retrospective study, we did not have accurate data regarding smoking or the presence of extraintestinal manifestations of UC at the time of colectomy, both of which have been evaluated as risk factors for pouchitis [29, 30]. We also did not evaluate the use of immunosuppressive or biologic therapies in the post-IPAA period, which could have influenced the development of pouch inflammation or other complications. Although we had a complete 2-year follow-up for all included patients, allowing us to evaluate the incidence of pouchitis within the first 2 years after IPAA as it related to specific clinical predictors, we do not have long-term data on these patients. Thus, we could not evaluate the relationship between these predictors and other potentially important but longer term outcomes such as Crohn's-like disease of the pouch and pouch failure. Finally, the overall rate of the pathological findings of interest was low, limiting the power to evaluate these pathological features individually in a multivariable analysis. However, no individual pathological factor was associated with an increased risk of pouchitis in bivariate comparison, and thus, by combining these high-risk factors, we were aiming to amplify any signal not detected by the small sample size of each individual factor.

In summary, among patients with UC undergoing restorative proctocolectomy with IPAA, histopathologic findings at the time of colectomy including ileitis, granuloma, and transmural inflammation were not associated with an increased risk for the development of pouchitis within the first 2 years after IPAA. These data provide reassurance that gastroenterologists, colorectal surgeons, and patients who encounter these findings on pathology at the time of the initial colectomy should not prevent further planned stages of restorative surgery in the form of an IPAA. Future studies should evaluate the impact of

these findings on long-term outcomes such as Crohn's-like disease of the pouch and pouch failure in the current biologic era.

Statement of Ethics

This study was a retrospective analysis and informed consent was not required on review of the study protocol by the Institutional Review Board at the UNC (18-1804). All study protocols and research were conducted ethically in accordance with the World Medical Association Declaration of Helsinki.

Conflict of Interest Statement

Edward L. Barnes has served as a consultant for AbbVie, Gilead, Pfizer, Takeda, and Target RWE. Bharati Kochar has served as a consultant for Pfizer. Michael D. Kappelman has served as a consultant for Abbvie, Takeda, Janssen, and Eli Lilly and has received research support from Abbvie and Janssen. Millie D. Long has served as a consultant for AbbVie, UCB, Takeda, Janssen, Pfizer, Salix, Valeant, and Target Pharmasolutions and has received research support from Pfizer and Takeda. Hans H. Herfarth has served as a consultant for Alivio, AMAG, Finch, Gilead, Lycera, Merck, Otsuka, Pfizer, PureTech, and Seres and research support from Pfizer and Artizan Biosciences. Joshua Hudson, Scott Eckilsen, Mark Koruda, and Robert S. Sandler have no relevant disclosures or conflicts of interest.

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Author Contributions

E.L.B. was involved in the study concept and design, data acquisition, statistical analysis, interpretation of the data, drafting of the manuscript, and critical revision of the manuscript. J.H., S.E., B.K., M.K., and H.H.H. were involved in the study concept and design, data acquisition, interpretation of the data, and critical revision of the manuscript. M.D.K., M.D.L., and R.S.S. were involved in the study concept and design, interpretation of the data, and critical revision of the manuscript.

Data Availability Statement

Raw data and analytic methods may be available by contacting the corresponding author at edward_barnes@med.unc.edu.

References

1 Barnes EL, Lightner AL, Regueiro M. Perioperative and postoperative management of patients with Crohn's disease and ulcerative colitis. Clin Gastroenterol Hepatol. 2020;18(6):1356–66.
2 Le Berre C, Ananthakrishnan AN, Danese S, Singh S, Peyrin-Biroulet L. Ulcerative colitis and Crohn's disease have similar burden and goals for treatment. Clin Gastroenterol Hepatol. 2020;18(1):14–23.
3 Barnes EL, Herfarth HH, Sandler RS, Chen W, Jaeger E, Nguyen VM, et al. Pouch-related symptoms and quality of life in patients with ileal pouch-anal anastomosis. Inflamm Bowel Dis. 2017;23(7):1218–24.
4 Lightner AL, Mathis KL, Dozois EJ, Hahnsloser D, Loftus EV Jr, Raffals LE, et al. Results at up to 30 years after ileal pouch-anal anastomosis for chronic ulcerative colitis. Inflamm Bowel Dis. 2017;23(5):781–90.
5 Barnes EL, Kochar B, Jessup HR, Herfarth HH. The incidence and definition of Crohn's disease of the pouch: a systematic review and meta-analysis. Inflamm Bowel Dis. 2019;25(9):1474–80.
6 Torres J, Mehandru S, Colombel JF, Peyrin-Biroulet L. Crohn's disease. Lancet. 2017;389(10080):1741–55.
7 Abdelrazeq AS, Kandiyil N, Botterill ID, Lund JN, Reynolds JR, Holdsworth PJ, et al. Predictors for acute and chronic pouchitis following restorative proctocolectomy for ulcerative colitis. Colorectal Dis. 2008;10(8):805–13.
8 Kroesen AJ, Dullat S, Schulzke JD, Fromm M, Buhr HJ. Permanently increased mucosal permeability in patients with backwash ileitis after ileoanal pouch for ulcerative colitis. Scand J Gastroenterol. 2008;43(6):704–11.
9 Schmidt CM, Lazenby AJ, Hendrickson RJ, Sitzmann JV. Preoperative terminal ileal and colonic resection histopathology predicts risk of pouchitis in patients after ileoanal pull-through procedure. Ann Surg. 1998;227(5):654–5; discussion 63–5.
10 Gustavsson S, Weiland LH, Kelly KA. Relationship of backwash ileitis to ileal pouchitis after ileal pouch-anal anastomosis. Dis Colon Rectum. 1987;30(1):25–8.
11 Arrossi AV, Kariv Y, Bronner MP, Hammel J, Remzi FH, Fazio VW, et al. Backwash ileitis does not affect pouch outcome in patients with ulcerative colitis with restorative proctocolectomy. Clin Gastroenterol Hepatol. 2011;9(11):981–8.
12 Nasseri Y, Melmed G, Wang HL, Targan S, Fleshner P. Rigorous histopathological assessment of the colectomy specimen in patients with inflammatory bowel disease unclassified does not predict outcome after ileal pouch-anal anastomosis. Am J Gastroenterol. 2010;105(1):155–61.
13 Baker DM, Folan AM, Lee MJ, Jones GL, Brown SR, Lobo AJ. A systematic review and meta-analysis of outcomes after elective surgery for ulcerative colitis. Colorectal Dis. 2021;23(1):18–33.
14 Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33(1):159–74.
15 Samples J, Evans K, Chaumont N, Strassle P, Sadiq T, Koruda M. Variant two-stage ileal pouch-anal anastomosis: an innovative and effective alternative to standard resection in ulcerative colitis. J Am Coll Surg. 2017;224(4):557–63.
16 Quinn KP, Raffals LE. An update on the medical management of inflammatory pouch complications. Am J Gastroenterol. 2020;115(9):1439–50.
17 Shen B. Pouchitis: what every gastroenterologist needs to know. Clin Gastroenterol Hepatol. 2013;11(12):1538–49.

18 White E, Melmed GY, Vasiliauskas EA, Dubinsky M, Berel D, Targan SR, et al. A prospective analysis of clinical variables, serologic factors, and outcome of ileal pouch-anal anastomosis in patients with backwash ileitis. Dis Colon Rectum. 2010;53(7):987–94.
19 Block M, Jørgensen KK, Oresland T, Lindholm E, Grzyb K, Cvancarova M, et al. Colectomy for patients with ulcerative colitis and primary sclerosing cholangitis – what next? J Crohns Colitis. 2014;8(5):421–30.
20 Dafnis G. Early and late surgical outcomes of ileal pouch-anal anastomosis within a defined population in Sweden. Eur J Gastroenterol Hepatol. 2016;28(7):842–9.
21 Lepisto A, Karkkainen P, Jarvinen HJ. Prevalence of primary sclerosing cholangitis in ulcerative colitis patients undergoing proctocolectomy and ileal pouch-anal anastomosis. Inflamm Bowel Dis. 2008;14(6):775–9.
22 Pavlides M, Cleland J, Rahman M, Christian A, Doyle J, Gaunt R, et al. Outcomes after ileal pouch anal anastomosis in patients with primary sclerosing cholangitis. J Crohns Colitis. 2014;8(7):662–70.
23 Penna C, Dozois R, Tremaine W, Sandborn W, LaRusso N, Schleck C, et al. Pouchitis after ileal pouch-anal anastomosis for ulcerative colitis occurs with increased frequency in patients with associated primary sclerosing cholangitis. Gut. 1996;38(2):234–9.
24 Wasmuth HH, Tranø G, Endreseth BH, Wibe A, Rydning A, Myrvold HE. Primary sclerosing cholangitis and extraintestinal manifestations in patients with ulcerative colitis and ileal pouch-anal anastomosis. J Gastrointest Surg. 2010;14(7):1099–104.
25 Barnes EL, Holubar SD, Herfarth HH. Systematic review and meta-analysis of outcomes after ileal pouch-anal anastomosis in primary sclerosing cholangitis and ulcerative colitis. J Crohns Colitis. 2021;15(8):1272–8.
26 Quinn KP, Lightner AL, Faubion WA, Raffals LE. A comprehensive approach to pouch disorders. Inflamm Bowel Dis. 2019;25(3):460–71.
27 Shen B, Remzi FH, Hammel JP, Lashner BA, Bevins CL, Lavery IC, et al. Family history of Crohn's disease is associated with an increased risk for Crohn's disease of the pouch. Inflamm Bowel Dis. 2009;15(2):163–70.
28 Bertucci Zoccali M, Hyman NH, Skowron KB, Rubin M, Cannon LM, Hurst RD, et al. Exposure to anti-tumor necrosis factor medications increases the incidence of pouchitis after restorative proctocolectomy in patients with ulcerative colitis. Dis Colon Rectum. 2019;62(11):1344–51.
29 Kani HT, Ramai D, Caniglia E, Hudesman D, Axelrad J, Nicholson J, et al. Systematic review with meta-analysis: a history of smoking is not associated with a higher risk of pouchitis. Aliment Pharmacol Ther. 2020;52(7):1117–24.
30 Hata K, Okada S, Shinagawa T, Toshiaki T, Kawai K, Nozawa H. Meta-analysis of the association of extraintestinal manifestations with the development of pouchitis in patients with ulcerative colitis. BJS open. 2019;3(4):436–44.