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Preoperative Use of Multiple Advanced Therapies Is Not Associated With Endoscopic Inflammatory Pouch Diseases

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Background: Patients with an ileal pouch-anal anastomosis (IPAA) can experience pouch inflammation postoperatively. The use of antitumor necrosis factor (anti-TNF) biologics may be associated with pouch inflammation, but limited data exist on the impact of multiple advanced therapies on development of subsequent pouch inflammation. The aim of this study was to assess for an association between preoperative use of multiple advanced therapies and risk of endoscopically detected inflammatory pouch diseases (EIPDs).

Methods: We performed a retrospective analysis of ulcerative colitis (UC) and indeterminate colitis (IBDU) patients who underwent an IPAA at a quaternary care center from January 2015 to December 2019. Patients were grouped based on number and type of preoperative drug exposures. The primary outcome was EIPD within 5 years of IPAA.

Results: Two hundred ninety-eight patients were included in this analysis. Most of these patients had UC (95.0%) and demonstrated pancolonic disease distribution (86.1%). The majority of patients were male (57.4%) and underwent surgery for medically refractory disease (79.2%). The overall median age at surgery was 38.6 years. Preoperatively, 68 patients were biologic/small molecule-naïve, 125 received anti-TNF agents only, and 105 received non-anti-TNF agents only or multiple classes. Ninety-one patients developed EIPD. There was no significant association between type ($P = .38$) or number ($P = .58$) of exposures and EIPD, but older individuals had a lower risk of EIPD ($P = .001$; hazard ratio, 0.972; 95% confidence interval, 0.956-0.989).

Conclusion: Development of EIPD was not associated with number or type of preoperative advanced therapies.

Key Words: pouchitis, IPAA, biologics, cuffitis, IBD

Introduction

Nearly 10% to 20% of patients with ulcerative colitis (UC) do not respond adequately to medical therapies and require surgical management of their disease.[1] A common surgical approach for medically refractory UC is a total proctocolectomy followed by creation of an ileal pouch-anal anastomosis (IPAA) to restore intestinal continuity.[1] Greater than 90% of patients report satisfaction with having undergone IPAA, and the quality of life in these patients is comparable to that of a healthy reference population.[2,3] However, patients commonly experience inflammatory conditions of the pouch such as pouchitis, cuffitis, or Crohn's disease–like phenotype of the pouch.[4] It is reported that over 60% of patients experience pouchitis acutely, which leads to decreased quality of life, and 20% develop chronic pouchitis, necessitating immunosuppressive agents and increasing the risk of pouch failure.[5–8]

Prior studies have suggested that medically refractory disease prior to IPAA creation and pancolonic disease distribution may predict risk of future pouch inflammation.[5,8,9] However, data are conflicted as to whether the necessity for preoperative treatment with antitumor necrosis factor (anti-TNF) biologic agents may convey additional risk of inflammatory pouch conditions postoperatively.[10–12] Additionally, specific endoscopic phenotypes of ileal pouches have been shown to predict short- (eg, acute pouchitis) and long-term (eg, pouch failure) ileal pouch outcomes, emphasizing that endoscopic activity is an informative tool in predicting the clinical course of one's pouch function even in the absence of clinical symptoms.[11,13]

In the last decade, numerous non-anti-TNF biologic agents and small molecule therapies have been approved for treatment of UC including monoclonal antibodies targeted against $\alpha_4\beta_7$ integrin, anti-interleukin (IL)-12/23, and small molecules that inhibit Janus kinases (JAK).[14] Although previous studies have investigated anti-TNF biologic agents and the development of postoperative ileal pouch inflammation, the potential impact of newer advanced therapies conferring additional

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Key Messages

- Inflammation of the ileal pouch is common among patients who undergo IPAA, and it has been suggested that preoperative exposures to biologic and small molecule agents may confer an increased risk of inflammatory pouch conditions.
- This study demonstrates that endoscopic inflammation of the ileal pouch is neither associated with number nor type of preoperative advanced therapies.
- Monitoring for inflammatory pouch diseases should not intensify based on the type or number of prior advanced therapies but rather symptoms or signs of inflammation.

risk for subsequent pouch dysfunction has not been studied. With an increasing number of medical therapies with varying mechanisms of action currently approved for the management of ulcerative colitis, it is unknown whether continued medical management in the face of medically refractory disease is associated with post-operative pouch inflammatory disorders or whether advanced therapies result in higher rates of inflammatory pouch disease.

The aim of the current study was to fill the current knowledge gaps by determining whether the number and type of advanced therapies utilized preoperatively influence the risk of developing endoscopic pouch inflammation following IPAA creation. A retrospective cohort study of patients with either ulcerative colitis or indeterminate colitis who received an IPAA and had follow-up at a quaternary care ileal pouch center was performed with the hypothesis that treatment with multiple advanced therapies may be associated with an increased incidence of pouchitis and other inflammatory pouch conditions following IPAA creation.

Methods

Study Design

This was a retrospective cohort study of patients with either ulcerative colitis or indeterminate colitis who received an ileal pouch-anal anastomosis at a tertiary care center from January 2015 to December 2019. To be included in this study, patients needed to be 18 years or older at time of colectomy, have a diagnosis of either ulcerative colitis or indeterminate colitis leading to either a 2- or 3-stage creation of an IPAA, have ≥18 months of follow-up time after loop ileostomy closure, and have ≥1 pouchoscopy after the perioperative period, which was defined as 6 months following loop ileostomy takedown. Exclusion criteria for this study were diagnoses of Crohn's disease or non-IBD diseases (eg, familial adenomatous polyposis) leading to colectomy. Diagnoses of IBD were determined through International Classification of Disease (ICD) coding and verified through review of clinician notes, endoscopic findings, and pathology specimens from the individual colectomies. In cases in which there was ambiguity in determining whether an individual had a diagnosis of ulcerative colitis or Crohn's disease based on clinical features, preoperative endoscopic findings, and colectomy pathology, a diagnosis of indeterminate colitis was assigned to the patient.

Patient characteristics including demographics, disease distribution (defined by clinician notes, prior endoscopies, and pathology at time of colectomy), extraintestinal manifestations, surgical details (number of operations, technical approach, perioperative complications), and endoscopies (pouchoscopies) were recorded in a secure electronic database. Anti-TNF biologic agents considered in this study included infliximab, adalimumab, golimumab, certolizumab, and biosimilars. Non-anti-TNF biologics included in this study were vedolizumab, ustekinumab, and natalizumab. Tofacitinib was the only small molecule considered in this study. Due to the study time period, upadacitinib and ozanimod were not included. Preoperative exposure to these therapeutic agents was determined through review of the medical record and defined as at least 1 confirmed receipt of infusion or prescription of the medication recorded in provider documentation. If a provider documented that a patient was prescribed but did not receive a medication prior to colectomy, the patient was recorded as not having an exposure to that medication. Immunomodulators including 6-mercaptopurine, azathioprine, and methotrexate were considered separately from advanced therapies for the purposes of this study.

The protocol for this study was reviewed by the institutional IRB, and all procedures set forth in the Declaration of Helsinki were followed.

Outcome Measures

The primary outcome for this study was development of endoscopic inflammatory pouch diseases within 5 years of IPAA, which was a composite of the following: (1) endoscopic pouch disease activity index (PDAI) score >5 if available[15]; (2) diffuse pouch inflammation noted on pouchoscopy; (3) mucosal breaks proximal to the pouch-anal anastomosis; and (4) development of pouch strictures (body, inlet, or prepouch) or fistulas. Patients were considered to have met the composite outcome if they developed one or more of the individual outcomes. Pouch inflammation was recorded by a single researcher (J.C.P.) through review of endoscopic record notes. Diffuse pouch inflammation for the purposes of this study was defined as inflammation (erythema, induration, edema, and/or mucosal breaks) observed in all of the following locations: the pouch body, pouch inlet, and the pouch afferent limb/pre-pouch ileum. Mucosal breaks included erosions, ulcerations, or aphthae noted on endoscopy that were not limited solely to anastomotic lines with the aim of excluding ulcerative findings suggestive of ischemic causes or surgical complications. Secondary outcomes included development of individual components of the composite outcome, inflammation in the pre-pouch ileum, and development of cuffitis. Cuffitis was defined as endoscopic inflammation of the rectal cuff noted by the endoscopist in one or more pouchoscopies following loop ileostomy closure.

Statistics

Data were described using median and interquartile range (IQR) for non-normal continuous variables and frequency (percentage) for categorical variables. When appropriate, the Shapiro-Wilk test was used to determine the normality of the continuous variable. Analysis of variance (ANOVA) and Kruskal-Wallis tests were used to assess differences in continuous variables, and the χ^2 test and Fisher exact test were used to compare categorical variables as appropriate.

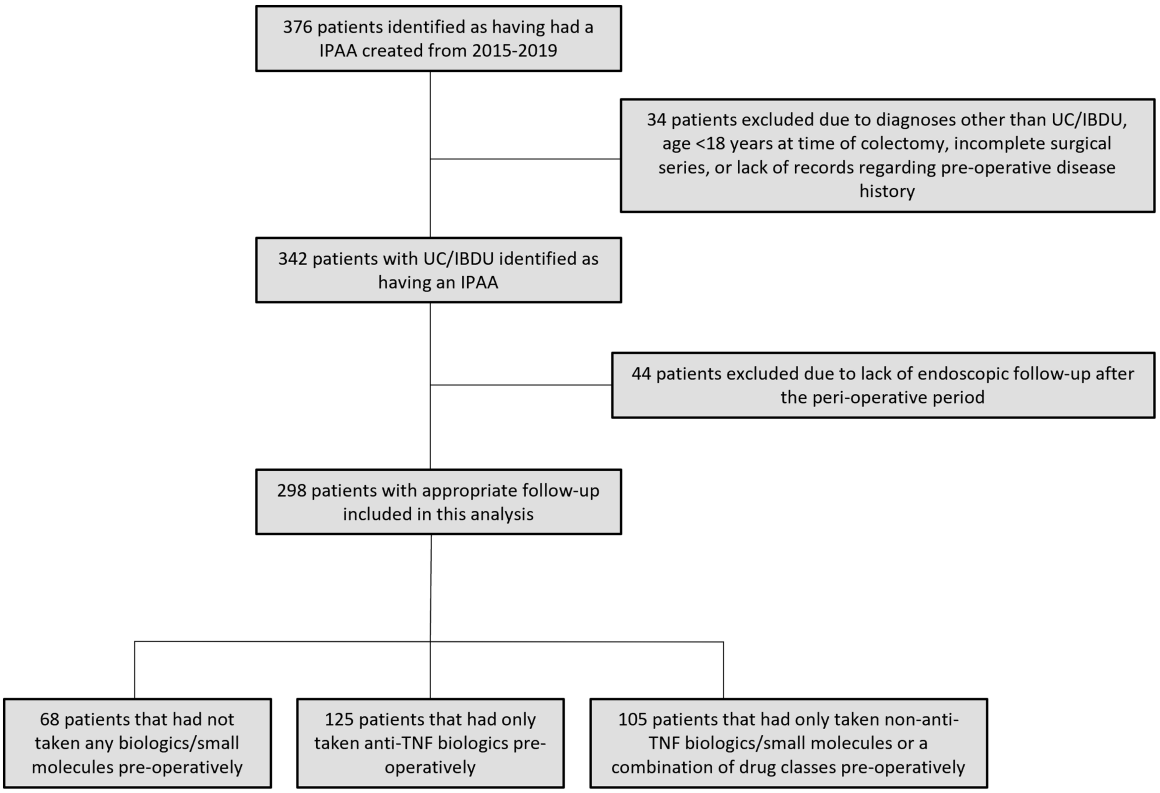

Figure 1. Consort diagram depicting the patient sample and those who met the criteria for inclusion in this analysis.

Patients were grouped based on number (0 vs 1 vs >1) and type (none vs anti-TNF only vs non-anti-TNF only or combination of classes) of advanced therapies utilized prior to colectomy. Univariate Cox proportional hazards models were fit to assess the association between each risk factor and outcomes. After identifying possible confounders through univariate analysis, multivariable Cox proportional hazards models were used to assess the association between biologics group and outcomes with adjustment of these confounders. Both number and type of advanced therapy groupings were considered in the univariate analyses, but due to collinearity among these 2 classifications, only the type of advanced therapy exposure was included in the multivariable models. Confounders with rare event or complete separation were excluded from the multivariable model. The multivariate imputation by chained equation (MICE) was utilized in this study to account for missing data and construct a complete dataset. The *P* values from type 3 test were provided to show overall significance for multilevel categorical variables. For the analyses, a Kaplan-Meier survival curve with 95% confidence intervals (CIs) was constructed. The scaled Schoenfeld residual were checked for proportional hazard assumptions. Statistical analysis was performed using R (version 3.6.2; Vienna, Austria) and SAS (version 9.4; Cary, NC) software, and *P* values <0.05 were considered statistically significant.

Results

Patient Characteristics

Three hundred forty-two patients were identified that had an ileal pouch created between 2015 and 2019. Forty-four of these patients were excluded due to not having greater than or equal to eighteen months of follow-up time after loop ileostomy closure and/or greater than or equal to one pouchoscopy after the perioperative period. Thus, the remaining 298 patients were included for the study analysis (Figure 1). Demographics of the patient cohort are presented in Table 1. The majority of patients were male (57.4%), White (91.9%) and demonstrated pancolonic disease distribution prior to colectomy (86.1%). Medically refractory disease was the most common indication for surgery (79.2%), followed by dysplasia/adenoma (14.4%), and toxic megacolon (3.4%). The median age of patients in this study was 38.6 years, with a median disease duration prior to colectomy of 6.6 years. Two hundred eighty-three patients were diagnosed with ulcerative colitis, and 15 were diagnosed with indeterminate colitis. The overall median follow-up time for the patient cohort was 24.9 (13.2-40.6) months. Seven hundred ninety-three individual pouchoscopy exams from colorectal surgery office visits and gastroenterology were reviewed for the follow-up period. The overall median number of pouchoscopies was 2, with an interquartile range of 1 to 3. Pouch excisions and redos were uncommon during the follow-up period, with 5.4% of patients having a pouch excision and 1% of patients undergoing a pouch redo. There was no significant difference among exposure groups for the absolute occurrence of pouch excision ($P = .7595$) and pouch redo ($P = .4529$), and these findings are shown in Table 1.

Sixty-eight (22.8%) patients received no advanced therapies prior to colectomy, 88 (29.5%) patients received a single therapy, and 142 (47.7%) patients received more than 1 advanced therapy for the management of ulcerative colitis or indeterminate colitis. Considering the type of exposures, 125 (41.9%) patients solely received anti-TNF agents

Table 1. Characteristics of patient cohort.

	Overall (%)	No Biologics or Small Molecules (%)	Anti-TNF only (%)	Non-Anti-TNF or Combination (%)	P
N	**298**	**68**	**125**	**105**	
Number of preoperative therapies					<0.001
0	68 (22.8)	68 (100)	0 (0)	0 (0)	
1	88 (29.5)	0 (0)	83 (66.4)	5 (4.8)	
2+	142 (47.7)	0 (0)	42 (33.6)	100 (95.2)	
IBD Subtype					0.176
Ulcerative colitis	283 (95.0)	64 (94.1)	116 (92.8)	103 (98.1)	
Indeterminate colitis	15 (5.0)	4 (5.9)	9 (7.2)	2 (1.9)	
Sex (male)	171 (57.4)	38 (55.9)	69 (55.2)	64 (61.0)	0.653
Race					0.306
Asian	7 (2.3)	1 (1.5)	4 (3.2)	2 (1.9)	
Black/African American	7 (2.3)	2 (2.9)	3 (2.4)	2 (1.9)	
White	274 (91.9)	61 (89.7)	112 (89.6)	101 (96.2)	
More than one race	7 (2.3)	2 (2.9)	5 (4.0)	0 (0)	
Unknown/not reported	3 (1.0)	2 (2.9)	1 (0.8)	0 (0)	
Age at time of colectomy (years; IQR)	38.6 (27.3-54.9)	48.1 (30.1-56.5)	37.7 (26.3-52.5)	35.5 (25.7-57.0)	0.020
IBD duration ≥ 1 year prior to colectomy	270 (90.6)	57 (83.8)	112 (89.6)	101 (95.1)	0.022
Indication for surgery					<0.001
Dysplasia/adenoma	43 (14.4)	25 (36.8)	12 (9.6)	6 (5.7)	
Medically refractory disease	236 (79.2)	35 (51.5)	104 (83.2)	97 (92.4)	
Toxic megacolon	10 (3.4)	4 (5.9)	5 (4.0)	1 (1.0)	
Other	9 (3.0)	4 (5.9)	4 (3.2)	1 (1.0)	
UC distribution					0.068
Proctitis	4 (1.4)	1 (1.6)	2 (1.7)	1 (1.0)	
Left-sided colitis	35 (12.5)	13 (20.6)	8 (7.0)	14 (13.6)	
Pancolitis	242 (86.1)	49 (77.8)	105 (91.3)	88 (85.4)	
History of EIMs	105 (35.2)	18 (26.5)	49 (39.2)	38 (36.2)	0.203
Preoperative smoker	12 (4.0)	1 (1.5)	9 (7.2)	2 (1.9)	0.082
Preoperative C. difficile	85 (28.6)	8 (11.8)	37 (29.8)	40 (38.1)	<0.001
Preoperative BMI					0.0154
<18.5 (underweight)	24 (8.1)	0 (0)	12 (9.6)	12 (11.4)	
18.5-25 (normal weight)	145 (48.7)	30 (44.1)	62 (49.6)	53 (50.4)	
25-30 (overweight)	79 (26.5)	21 (30.9)	27 (21.6)	31 (29.5)	
30-35 (Class 1 Obesity)	39 (13.1)	14 (20.6)	18 (14.4)	7 (6.7)	
>35 (Class 2/3 Obesity)	10 (3.4)	3 (4.4)	6 (4.8)	1 (1.0)	
Three Stage IPAA	239 (80.2)	45 (66.2)	100 (80.0)	94 (89.5)	<0.001
Colectomy Technique					0.277
Pure laparoscopic	242 (81.8)	52 (76.5)	99 (80.5)	91 (86.7)	
Open	44 (14.9)	14 (20.6)	20 (16.3)	10 (9.5)	
Laparoscopic to open	8 (2.7)	1 (1.5)	3 (2.4)	4 (3.8)	
Robotic	2 (0.7)	1 (1.5)	1 (0.8)	0 (0)	
Readmission within 30 days of IPAA	66 (22.1)	14 (20.6)	30 (24.0)	22 (21.0)	0.8059
Infectious complication within 30 days of IPAA	36 (12.8)	8 (11.8)	17 (13.6)	11 (10.5)	0.766
Preoperative corticosteroids	282 (94.6)	60 (88.2)	120 (96.0)	102 (97.1)	0.027
Preoperative immunomodulators	136 (45.6)	19 (27.9)	56 (44.8)	61 (58.1)	<0.001

Table 1. Continued

	Overall (%)	No Biologics or Small Molecules (%)	Anti-TNF only (%)	Non-Anti-TNF or Combination (%)	P
N	298	68	125	105	
Preoperative PSC	17 (5.7)	2 (2.9)_	7 (5.6)	8 (7.6)	0.4310
Backwash Ileitis	60 (20.1)	16 (23.5)	23 (18.4)	21 (20.0)	0.6968
Pouch Excision	16 (5.4)	3 (4.4)	6 (4.8)	7 (6.7)	0.7595
Pouch Re-Do	3 (1)	1 (0.3)	2 (0.7)	0 (0)	0.4529

(Supplemental Table 1), with infliximab alone being the most common (39.2%), followed by infliximab and adalimumab (26.4%), and adalimumab alone (23.2%). One hundred five (35.2%) patients received either a non-anti-TNF agent alone or greater than 1 class of advanced therapies (Supplemental Table 1). In this group, 3 or more therapies was the most common (44.8%), followed by vedolizumab and infliximab (25.7%) and vedolizumab and adalimumab (18.1%). The remainder (22.8%) consisted of the 68 patients that were naïve to biologics and small molecule treatment. Patients that had not been preoperatively exposed to any advanced were more likely to undergo colectomy for an indication of dysplasia compared with individuals trialed on anti-TNF advanced therapies or non-anti-TNF advanced therapies/combination of classes, which were more likely to undergo colectomy for medically refractory disease (Table 1). Median follow-up times were 31.9 (15.3-43.4) months, 25.7 (13.5-45.0) months, and 21.0 (12.3-36.2) months for no exposures, anti-TNF only, and combination or non-anti-TNF only groups, respectively.

Development of Endoscopic Inflammatory Pouch Diseases

In total, 91 patients (26.6%) developed the primary outcome of endoscopic inflammatory pouch diseases during the study period. On univariate analysis, neither number (P = .58) nor type (P = .38) of preoperative advanced therapy exposure was associated with increased risk of the primary outcome (Figures 2 and 3). The results of the univariate analysis are presented in Supplemental Table 2, which shows that older age at time of colectomy and readmission within 30 days of pouch creation were associated with a decreased risk of endoscopically detected inflammatory pouch disorders. However, adjusting for confounders showed that type of advanced therapy exposure did not have a significant association with the primary outcome (P = .59). The multivariable analysis results are presented in Table 2 and demonstrate reduced risk age at time of colectomy (hazard ratio [HR] = 0.972; 95% CI, 0.956-0.989; P = .001) and readmission within 30 days of pouch creation (HR = 0.53; 95% CI, 0.28-0.998; P = .042) have significant associations with EIPD when controlling for other variables. Pelvic sepsis and volume imbalances/dehydration were found to be the most common causes of readmission within 30 days of IPAA, with less common indications including wound/skin infections, endocrine disturbances, vascular indications, abdominal/rectal pain, early signs of pouchitis and/or cuffitis, and other causes (Supplemental Table 3).

Development of Strictures and/or Fistulas

Twenty-one patients (7.0%) developed pouch strictures and/or fistulas during the follow-up period, and patients with indeterminate colitis had a higher risk of these findings on univariate analysis compared with patients with ulcerative colitis (HR = 4.44; 95% CI, 1.30-15.17; P = .017). Results of the univariate analysis are presented in Supplemental Table 4. On multivariable analysis (Table 3), age was associated with a lower risk of development of strictures and fistulas (HR = 0.93; 95% CI, 0.89-0.98; P = .005), but type of advanced therapy exposure was not significantly associated with this outcome (P = .85). Additionally, having a body mass index (BMI) less than 18.5 was associated with a higher risk of stricture/fistula development compared with individuals with a normal BMI preoperatively (HR = 3.48; 95% CI, 1.06-11.36; P = .039).

Development of Mucosal Breaks Proximal to the Pouch-anal Anastomosis

During the follow-up period, 80 patients (26.8%) developed mucosal breaks not limited to anastomotic lines. On univariate analysis (Supplemental Table 5), older age at time of colectomy was associated with a decreased risk of the outcome. The multivariable analysis (Supplemental Table 6) likewise showed reduced risk in older individuals (HR = 0.976; 95% CI, 0.959-0.994; P = .008). Neither univariate (P = .71) nor multivariable analysis (P = .95) showed a significant association between type of preoperative therapy exposure and risk of developing the mucosal breaks outside of anastomotic lines.

Inflammation in the Pre-pouch Ileum

Inflammation localized specifically to the pre-pouch ileum (afferent limb) was noted in 47 (15.8%) individuals during the study follow-up period. On univariate analysis, open colectomy and older age had a lower risk of inflammation localized to this site (Supplemental Table 7). The univariate analysis suggested that having an open colectomy was associated with a decreased risk of pre-pouch inflammation compared with individuals that had a laparoscopic converted to open colectomy (HR = 0.18; 95% CI, 0.03-0.94; P = .042). However, given the much lower number of individuals having undergone the latter technique, the effect size is likely derived from the small sample size and would have limited the utility of including this variable in the multivariable analysis. Thus, this variable was solely included in the univariate analysis. Another finding in the univariate analysis was that being underweight at the time of colectomy was associated with an increased risk of pre-pouch inflammation (HR = 3.31; 95% CI, 1.36-8.06; P =

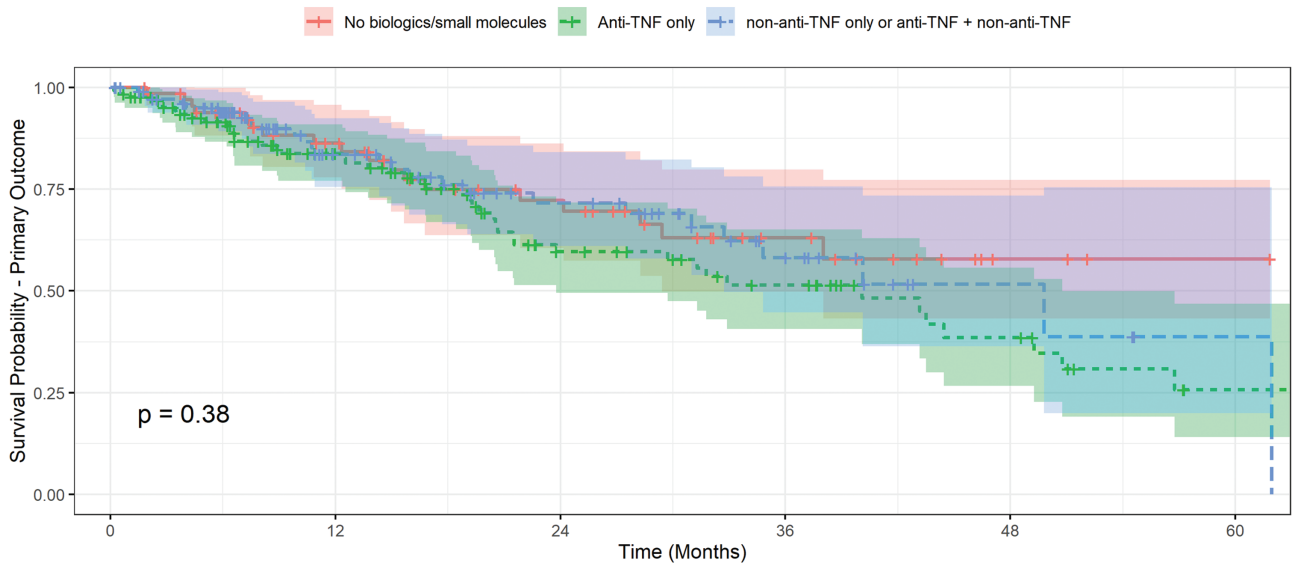

Figure 2. Kaplan-Meier curve for curve for development of EIPD based on number of preoperative advanced therapies.

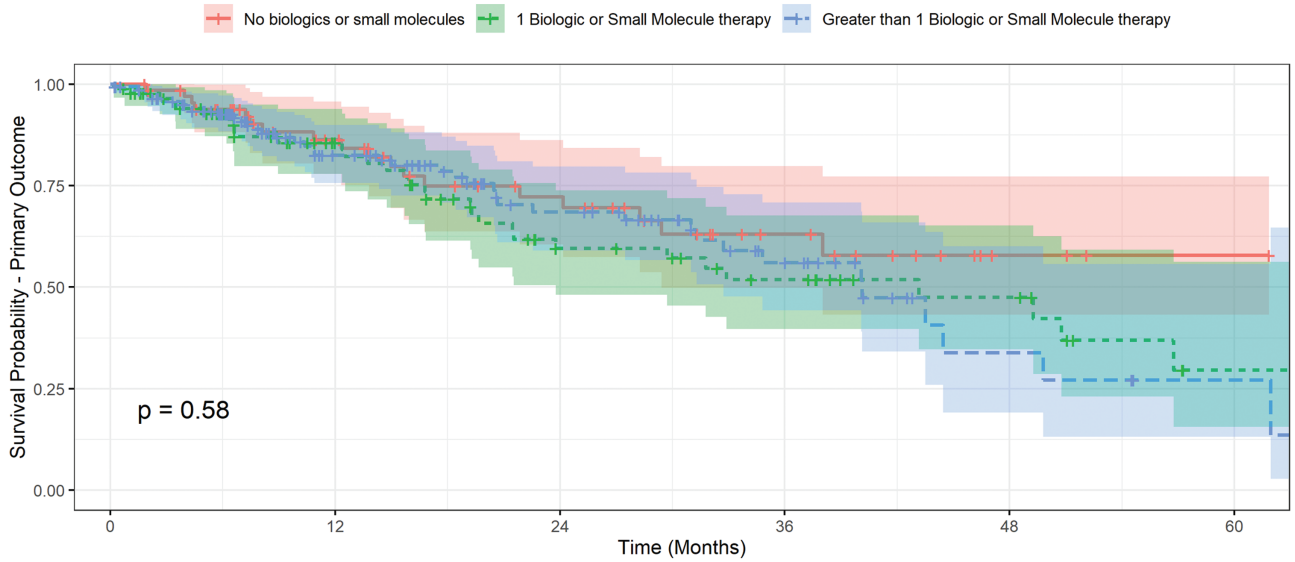

Figure 3. Kaplan-Meier curve for curve for development of EIPD based on type of preoperative advanced therapies.

.008). The multivariable analysis (Supplemental Table 8) demonstrated a similar result, with older individuals having a lower risk of inflammation at this site when controlling for disease duration (HR = 0.970; 95% CI, 0.947-0.994; *P* = .014) and that underweight individuals have a higher risk of pre-pouch inflammation (HR = 2.76; 95% CI, 1.10-6.94; *P* = .030).

Development of Cuffitis

A total of 112 patients developed endoscopic inflammation of the rectal cuff on 1 or more pouchoscopy during this study's follow-up period. On univariate analysis (Supplemental Table 9), individuals with a disease duration of ≥1 year and older individuals had a lower risk of developing cuffitis. On multivariable analysis (Table 4), a similar trend was noted for individuals with disease duration of ≥1 year (HR = 0.45; 95% CI, 0.26-0.78; *P* = .004), but there was not a significant association between age and cuffitis (*P* = .087). Multivariable analyses also demonstrated that individuals that had received anti-TNF biologics prior to their colectomy (HR = 1.78; 95% CI, 1.04-3.05; *P* = .035) had a higher risk of developing cuffitis postoperatively. The BMI category was not found to be significantly associated with risk of cuffitis (*P* = .12), but there was a general trend noted in that the higher BMI categories had higher risk ratios of developing cuffitis compared with normal weight patients.

Discussion

In this study, 26.6% of patients with an ileal pouch developed endoscopically detected inflammatory pouch disorders. Preoperative use multiple advanced therapies was not associated with an increased risk of endoscopic inflammatory pouch diseases such as pouchitis. To our knowledge, this

Table 2. Multivariable analysis on time to development of the primary outcome.

Variable	N	Events N (%)	Cox Multivariate Hazard Ratio (95% CI)	Cox Multivariate Wald *P*	Cox Multivariate Likelihood Ratio *P*
Type of drug exposure					0.59
No biologics/small molecules	67	18 (27)	1.00 (REF)		
Anti-TNF only	125	47 (38)	1.09 (0.59, 2.02)	0.79	
Non-anti-TNF or combination	106	26 (25)	0.84 (0.43,1.61)	0.59	
Preoperative BMI					0.77
Underweight (< 18.5)	25	11 (44)	1.25 (0.63, 2.48)	0.53	
Normal Weight (18.5-25)	145	46 (32)	1.00 (REF)		
Overweight (25-30)	79	21 (27)	0.90 (0.52, 1.57)	0.72	
Class 1 Obesity (30-35)	39	9 (23)	0.75 (0.35, 1.60)	0.45	
Class 2/3 Obesity (>35)	10	4 (40)	1.42 (0.49, 4.14)	0.52	
Sex					0.54
Female	127	41 (32)	1.00 (REF)		
Male	171	50 (29)	1.15 (0.74,1.78)	0.54	
Duration of IBD prior to colectomy					0.44
<1 year	28	8 (29)	1.00 (REF)		
≥1 year	270	83 (31)	1.36 (0.62,2.97)	0.44	
UC Distribution					0.46
Pancolitis	263	82 (31)	1.07 (0.52,3.67)		
Proctitis/left-sided colitis	35	9 (26)	1.00 (REF)	0.46	
IBD Subtype					0.46
Ulcerative colitis	283	86 (30)	1.00 (REF)		
Indeterminate colitis	15	5 (33)	1.43 (0.55,3.67)	0.46	
Preoperative smoker	12	3 (25)	0.73 (0.22,2.43)	0.61	0.61
History of EIMs	104	32 (31)	1.18 (0.74, 1.88)	0.48	0.48
Readmission within 30 days of IPAA	66	13 (20)	0.53 (0.28,0.98)	**0.042**	**0.042**
Age at colectomy	298	91 (31)	0.972 (0.956,0.989)	**0.001**	**0.001**

study is the first to explore the impact of non-anti-TNF biologic agents and small molecules in the context of subsequent postoperative pouch inflammation. These results suggest that older age had a slight protective effect for several inflammatory diseases including diffuse pouch inflammation, development of strictures and fistulas, and mucosal breaks proximal to the pouch-anal anastomosis.

Cuffitis was more likely in individuals that used anti-TNF biologic drugs preoperatively and individuals that had a shorter disease duration prior to colectomy. Although not statistically significant, there appeared to be a trend of a positive correlation with BMI group and risk of cuffitis in that the groups with higher BMIs had a higher hazard ratio compared with normal weight and underweight patients, and this may stem from individuals with larger BMIs potentially having longer rectal cuffs. In contrast, having a BMI less than 18.5 was significantly associated with an increased risk of stricture/fistula formulation and inflammation in the pre-pouch compared with normal weight individuals. Recent studies have shown that poor nutritional status prior to surgery for patients with ulcerative colitis and Crohn's disease may predispose individuals to perioperative complication such as infections, and these risks of malnutrition may extend to the specific findings noted in this study.[16,17]

Similar to older age, readmission following IPAA was associated with a decreased risk of diffuse pouch inflammation, with individuals who were readmitted within 30 days of IPAA having a lower risk of subsequent EIPD. Common reasons for readmissions for IPAA patients typically include small bowel obstruction, pelvic sepsis, dehydration, and venous thromboembolism.[18] However, the specific indications for readmission were not included in our current analyses. These findings warrant further investigation to evaluate which factors may have conferred a impacted this association.

There is variability among prior studies as to whether anti-TNF biologics are associated with increased risk of clinical pouchitis and endoscopic inflammation of the pouch following IPAA.[10–12,19] The findings of this study suggest that use of anti-TNF drugs (alone or in combination with non-anti-TNF biologics and small molecules) was not associated with increased risk of pouch inflammation, but rather an increased risk of cuffitis. This finding resembles that of recent studies that have also suggested that preoperative anti-TNF use is not associated with increased risk of pouchitis.[12] There are a few reasons that likely underly variation among studies. First, other studies that investigated similar endoscopic outcomes were conducted with longer follow-up times of approximately 10 years.[11] Although longer follow-up times are

Table 3. Multivariable analysis on time to development of strictures/fistulas

Variable	N	Events N (%)	Cox Multivariate Hazard Ratio (95% CI)	Cox Multivariate Wald *P*	Cox Multivariate Likelihood Ratio *P*
Type of drug exposure					0.85
No biologics/small molecules	67	5 (7)	1.00 (REF)		
Anti-TNF only	125	9 (7)	0.43 (0.13,1.45)	0.17	
Non-anti-TNF or combination	106	7 (7)	0.55 (0.15,2.00)	0.37	
Preoperative BMI					
Underweight (< 18.5)	25	5 (20)	3.48 (1.06,11.36)	0.039	
Normal Weight (18.5-25)	145	9 (6)	1.00 (REF)		0.23
Overweight (25-30)	79	6 (8)	2.30 (0.73,7.23)	0.15	
Class 1 Obesity (30-35)	39	0 (0)	NA	0.99	
Class 2/3 Obesity (>35)	10	1 (10)	3.33 (0.36,30.76)	0.29	
Sex					0.31
Female	127	12 (9)	1.00 (REF)		
Male	171	9 (5)	0.63 (0.25,1.55)	0.31	
Duration of IBD prior to colectomy					0.81
<1 year	28	2 (7)	1.00 (REF)		
≥1 year	270	19 (7)	1.20 (0.26,5.57)	0.81	
Age at colectomy	298	21 (7)	0.93 (0.89,0.98)	0.005	**0.005**

optimal in capturing long-term outcomes, the recency of the introduction of non-anti-TNF advanced therapies limited the follow-up time available for this study. Second, other studies that have suggested an association of pouch inflammation with preoperative anti-TNF use explored clinical factors such as diagnostic coding and use of antibiotics as markers for pouchitis.[10] Studies have shown there may be discordance in terms of clinical symptoms of endoscopic intestinal inflammation in IBD patients, which may also explain differences in study outcomes.[20] Lastly, overlap of clinical symptoms among pouchitis, cuffitis, and irritable pouch syndrome may introduce uncertainty and lead to misdiagnoses in some cases.[21]

In terms of clinical implications, these findings suggest that endoscopic inflammation of the ileal pouch following IPAA is common, with 26.6% of patients in this study meeting the outcome of EIPD for the study period. Prior studies have shown that specific pouch diseases including diffuse pouch inflammation are associated with the long-term risk of pouch failure, requiring pouch excision.[11] Likewise, Kayal et al (2019) found that mucosal breaks in asymptomatic ileal pouch patients were associated with an increased risk of acute pouch, further emphasizing the clinical relevance of specific endoscopic findings on which our study was based.[13] Overall, our findings regarding EIPD are similar to other studies which have also found that early pouchitis is common among patients after IPAA.[22] Additionally, trialing multiple advanced therapies prior to IPAA does not yield additional risk of pouch inflammation postoperatively. Thus, there is not a greater need to monitor for inflammatory pouch disorders in individuals that had received multiple advanced therapies preoperatively compared with individuals who received 0 or 1 preoperative advanced therapies.

This study carries a few limitations that need to be considered in the context of its findings. First, this study was conducted at a single center, which conveys limitations related to surgical technique, institutional follow-up practices, inconsistent reporting of rectal cuff length on pouchoscopy reports, and possible selection bias for patients who undergo endoscopy due to symptoms rather than for general screening purposes. For example, the standard surgical approach for IPAA at this institution is a stapled anastomosis rather than hand-sewn, so the vast majority of patients in this study (98.7%) had a stapled anastomosis, limiting the ability to generalize these findings to all techniques. Likewise, a minority of pouchoscopies from our center for this study described rectal cuff length, a potentially informative piece of information to better understand the findings related to cuffitis. Follow-up schedules also likely vary by institution. Our institution's standard approach is to perform an initial pouchoscopy at 6 months following loop ileostomy closure and then at the discretion of the clinical provider, which typically is either annually or biannually. In our cohort, the overall follow-up time was limited with a median time of 19.9 months, and the development of strictures and fistulas was uncommon in this early follow-up period. This constraint is primarily due to the newer classes of advanced therapies only becoming approved in the last decade; therefore, the patient cohort of individuals who received multiple classes of these drugs is limited to patients in recent years. However, even though being conducted at a single center carries these limitations, our patient cohort was geographically diverse and received care at a large ileal pouch center in the United States, from which nearly 800 individual pouchoscopies were evaluated for this analysis. It is plausible that long-term pouch outcomes may likewise be affected by the variables described in these results, so future studies should build on this investigation by exploring pouch outcomes for patients from different institutions over longer follow-up times.

Another limitation is that given the recency of approval of the newer advanced therapies, patients toward the end of our

Table 4. Multivariable analysis on time to development of cuffitis.

Variable	N	Events N (%)	Cox Multivariate Hazard Ratio (95% CI)	Cox Multivariate Wald *P*	Cox Multivariate Likelihood Ratio *P*
Type of drug exposure					0.073
No biologics/small molecules	67	22 (33)	1.00 (REF)		
Anti-TNF only	125	54 (43)	1.88 (1.09,3.24)	0.023	
Non-anti-TNF or combination	106	36 (34)	1.68 (0.94,3.02)	0.081	
Preoperative BMI					0.12
Underweight (< 18.5)	25	9 (38)	1.00 (REF)	0.29	
Normal Weight (18.5-25)	79	48 (33)	0.67 (0.32,1.41)		
Overweight (25-30)	79	33 (42)	1.50 (0.94,2.38)	0.087	
Class 1 Obesity (30-35)	39	16 (41)	1.59 (0.84,2.99)	0.15	
Class 2/3 Obesity (>35)	10	6 (60)	2.03 (0.82,5.01)	0.12	
Sex					0.92
Female	127	50 (39)	1.00 (REF)		
Male	171	62 (36)	1.02 (0.69,1.51)	0.92	
Duration of IBD prior to colectomy					**0.002**
<1 year	28	16 (57)	1.00 (REF)		
≥1 year	270	96 (38)	0.40 (0.23,0.72)	0.002	
UC Distribution					0.92
Proctitis/left-sided colitis	35	12 (34)	1.00 (REF)		
Pancolitis	263	100 (38)	0.97 (0.51,1.82)	0.92	
IBD Subtype					0.77
Ulcerative colitis	283	108 (38)	1.00 (REF)		
Indeterminate colitis	15	4 (27)	0.86 (0.31,2.37)	0.77	
Preoperative smoker	12	3 (25)	0.53 (0.16,1.70)	0.29	0.29
History of EIMs	104	37 (36)	0.80 (0.53,1.22)	0.30	0.30
Age at colectomy	298	112 (38)	0.9861 (0.9717,1.0007)	0.063	0.063

study period were more likely to have received the non-anti-TNF agents; but this was not explicitly investigated in our analysis. A final limitation is that this study solely considered endoscopic outcomes, which have been shown to have variable reliability among endoscopists and may not translate directly to one's clinical status.[20,23] To address the subjectivity of individual endoscopists interpretation of pouchoscopies, objective findings including presence of mucosal breaks and site-specific inflammation were included for the analysis based on the established literature.[11,13] Future studies should expand on this work by correlating the histologic and clinical aspects of pouch health with endoscopic outcomes to better understand the risk of multiple advanced therapies preoperatively.

In summary, this study found that preoperative treatment with multiple advanced therapies is not associated with subsequent risk of inflammatory conditions of the ileal pouch and that older individuals may have a lower risk of EIPD. The implication of these findings is that the decision to trial multiple advanced therapies prior to surgery does not appear to impact future risk of inflammatory pouch disorders. Future directions to expand on these findings include investigating longer-term pouch outcomes, considering the impact of the recency and duration of exposure to specific advanced therapies, conducting analyses related to the absolute occurrences of the outcomes, investigating the impact of newly approved biologic and small molecule agents, and correlating clinical outcomes with endoscopic findings.

Supplementary Data

Supplementary data is available at *Inflammatory Bowel Diseases* online.

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References

1. Magro F, Gionchetti P, Eliakim R, et al.; European Crohn's and Colitis Organisation [ECCO]. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. part 1: definitions, diagnosis, extra-intestinal manifestations, pregnancy, cancer surveillance, surgery, and ileo-anal pouch disorders. *J Crohns Colitis*. 2017;11(6):649-670. doi:10.1093/ECCO-JCC/JJX008
2. Carcamo L, Miranda P, Zúñiga A, et al. Ileal pouch-anal anastomosis in ulcerative colitis: outcomes, functional results, and quality of life in patients with more than 10-year follow-up. doi:10.1007/s00384-020-03529-7
3. Heikens JT, De Vries J, Goos MRE, Oostvogel HJ, Gooszen HG, Van Laarhoven CJHM. Quality of life and health status before and after ileal pouch–anal anastomosis for ulcerative colitis. *Br J Surg*. 2012;99(2):263-269. doi:10.1002/BJS.7711
4. Shen B, Kochhar GS, Kariv R, et al. Diagnosis and classification of ileal pouch disorders: consensus guidelines from the International Ileal Pouch Consortium. *Lancet Gastroenterol Hepatol*. 2021;6(10):826-849. doi:10.1016/S2468-1253(21)00101-1
5. Kayal M, Plietz M, Rizvi A, et al. Inflammatory pouch conditions are common after ileal pouch anal anastomosis in ulcerative colitis patients. *Inflamm Bowel Dis*. 2020;26(7):1079-1086. doi:10.1093/IBD/IZZ227
6. Vw F, Rp K, Fh R, et al. Ileal pouch anal anastomosis: analysis of outcome and quality of life in 3707 patients. *Ann Surg*. 2013;257(4):191-194. doi:10.1097/SLA.0B013E31827D99A2
7. Barnes EL, Herfarth HH, Sandler RS, et al. Pouch-related symptoms and quality of life in patients with ileal pouch-anal anastomosis. *Inflamm Bowel Dis*. 2017;23(7):1218-1224. doi:10.1097/MIB.0000000000001119
8. Hashavia E, Dotan I, Rabau M, Klausner JM, Halpern Z, Tulchinsky H. Risk factors for chronic pouchitis after ileal pouch-anal anastomosis: a prospective cohort study. *Colorectal Dis*. 2012;14(11):1365-1371. doi:10.1111/J.1463-1318.2012.02993.X
9. Kmeid M, Arker SH, Petchers A, et al. Appendiceal inflammation in colectomy is independently correlated with early pouchitis following ileal pouch anal anastomosis in ulcerative colitis and indeterminate colitis. *Ann Diagn Pathol*. 2021;55(5):151838. doi:10.1016/J.ANNDIAGPATH.2021.151838
10. El B, Hh H, Md K, et al. Incidence, risk factors, and outcomes of pouchitis and pouch-related complications in patients with ulcerative colitis. *Clin Gastroenterol Hepatol*. 2021;19(8):1583-1591.e4. doi:10.1016/J.CGH.2020.06.035
11. Akiyama S, Ollech JE, Rai V, et al. Endoscopic phenotype of the J pouch in patients with inflammatory bowel disease: a new classification for pouch outcomes. *Clin Gastroenterol Hepatol*. 2022;20(2):293-302.e9. doi:10.1016/J.CGH.2021.02.010
12. Barnes EL, Allin KH, Iversen AT, Herfarth HH, Jess T. increasing incidence of pouchitis between 1996 and 2018: a population-based danish cohort study. *Clin Gastroenterol Hepatol*. 2022;21:(1):192-199. doi:10.1016/J.CGH.2022.04.015
13. Kayal M, Plietz M, Radcliffe M, et al. Endoscopic activity in asymptomatic patients with an ileal pouch is associated with an increased risk of pouchitis. *Aliment Pharmacol Ther*. 2019;50(11-12):1189-1194. doi:10.1111/APT.15505
14. Lasa JS, Olivera PA, Danese S, Peyrin-Biroulet L. Efficacy and safety of biologics and small molecule drugs for patients with moderate-to-severe ulcerative colitis: a systematic review and network meta-analysis. *Lancet Gastroenterol Hepatol*. 2022;7(2):161-170. doi:10.1016/S2468-1253(21)00377-0
15. Sandborn WJ, Tremaine WJ, Batts KP, Pemberton JH, Phillips SF. Pouchitis after ileal pouch-anal anastomosis: a Pouchitis Disease Activity Index. *Mayo Clin Proc*. 1994;69(5):409-415. doi:10.1016/S0025-6196(12)61634-6
16. Okita Y, Araki T, Okugawa Y, et al. The prognostic nutritional index for postoperative infectious complication in patients with ulcerative colitis undergoing proctectomy with ileal pouch-anal anastomosis following subtotal colectomy. *J Anus Rectum Colon*. 2019;3(2):91-97. doi:10.23922/JARC.2018-032
17. Zhu Y, Zhou W, Qi W, et al. Body mass index is a practical preoperative nutritional index for postoperative infectious complications after intestinal resection in patients with Crohn's disease. *Medicine (Baltimore)*. 2017;96(23):e7113. doi:10.1097/MD.0000000000007113
18. Mckenna NP, Mathis KL, Khasawneh M, et al. Thirty-Day Hospital Readmission After Restorative Proctocolectomy and Ileal Pouch Anal Anastomosis for Chronic Ulcerative Colitis at a High-Volume Center. doi:10.1007/s11605-017-3542-7
19. Zoccali MB, Hyman NH, Skowron KB, 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):1344-1351. doi:10.1097/DCR.0000000000001467
20. Ma C, Sandborn WJ, D'haens GR, et al. Discordance between patient-reported outcomes and endoscopic inflammation in mild-to-moderate ulcerative colitis. *Clin Gastroenterol Hepatol*. 2020;18(8):1760-1768.e1. doi:10.1016/J.CGH.2019.09.021
21. Zezos P, Saibil F. Inflammatory pouch disease: the spectrum of pouchitis. *World Journal of Gastroenterology: WJG*. 2015;21(29):8739. doi:10.3748/WJG.V21.I29.8739
22. Kayal M, Kohler D, Plietz M, et al. Early pouchitis is associated with Crohn's disease-like pouch inflammation in patients with ulcerative colitis. *Inflamm Bowel Dis*. 2022;28(12):1821-1825. doi:10.1093/IBD/IZAC012
23. Samaan MA, Shen B, Mosli MH, et al. Reliability among central readers in the evaluation of endoscopic disease activity in pouchitis. *Gastrointest Endosc*. 2018;88(2):360-369.e2. doi:10.1016/J.GIE.2018.04.2330