


Extensive Colitis and Smoking Are Associated With Postoperative Complications Within 30 Days of Ileal Pouch–Anal Anastomosis

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Background: Our understanding of outcomes after proctocolectomy with ileal pouch–anal anastomosis (IPAA) for ulcerative colitis (UC) is largely based on analyses of selected populations. We created a state-level registry to evaluate the epidemiology of IPAA surgery and pouch-related outcomes across the major healthcare systems performing these surgeries in our state.

Methods: We created a retrospective cohort of all patients undergoing restorative proctocolectomy with IPAA for UC at 1 of 4 centers between January 1, 2018, and December 31, 2020. The primary outcomes of this study were the rate of complications and all-cause readmissions within the first 30 days of the final stage of IPAA surgery.

Results: During the study period, 177 patients underwent IPAA surgery with 66 (37%) experiencing a complication within 30 days. After adjusting for the number of stages in IPAA surgery, patients with extensive UC (odds ratio, 3.61; 95% confidence interval, 1.39–9.33) and current or former smokers (odds ratio, 2.98; 95% confidence interval, 1.38–6.45) were more likely to experience a complication. Among all patients, 57 (32%) required readmission within 30 days. The most common reasons for readmission were ileus/small bowel obstruction (22%), peripouch abscess (19%), and dehydration (16%).

Conclusion: In this first state-level examination of the epidemiology of IPAA for UC, we demonstrated that the complication rate after IPAA for UC was 37%, with one-third of patients being readmitted within 30 days. Extensive disease at the time of colectomy appears to be an indicator of more severe disease and may portend a worse prognosis after IPAA.

Key Words: pouchitis, ileal pouch–anal anastomosis, J-pouch, readmission, outcomes research

Introduction

Despite an increasing number of available therapies for the treatment of ulcerative colitis (UC), approximately 15% of patients will require a colectomy within the first 10 years of diagnosis.¹ In cases of medically refractory UC or UC-related dysplasia, restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA) remains the surgical therapy of choice for most patients.² However, this procedure is not without complications, with a traditional estimated morbidity of 30%³ as well as long-term complications including pouchitis and other inflammatory conditions of the pouch.^{2,4,5}

Much of our understanding of the natural history, epidemiology, and outcomes after IPAA surgery for UC has been generated from single-center studies or examinations of selected populations.^{3,6–12} Although these have been informative and have shaped practice decisions in many cases, questions have been raised regarding both the generalizability of these results and the need for more multicenter evaluations.¹³ Given the fact that perioperative complications after IPAA may lead to readmission rates that are 2 to 3 times higher than those of other colorectal surgeries^{10,14} recent efforts from the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) have used a prospective multicenter design to evaluate readmission

Key Messages**WHAT IS ALREADY KNOWN**

- Ileal pouch–anal anastomosis for ulcerative colitis is associated with short- and long-term complications. Much of our understanding of these complications has been generated from selected populations.

WHAT IS NEW HERE

- We created a state-level database allowing us to study the epidemiology and outcomes after ileal pouch–anal anastomosis surgery among patients in North Carolina. We demonstrated comparable complication rates to prior studies, with extensive colitis and smoking status being associated with increased risk of 30-day complications after ileal pouch–anal anastomosis.

HOW CAN THIS STUDY HELP PATIENT CARE

- This cohort provides a novel method of studying outcomes after ileal pouch–anal anastomosis for ulcerative colitis. By studying outcomes among all patients undergoing ileal pouch–anal anastomosis at the state level, we can begin to understand trends in both the natural history and healthcare utilization patterns across a large catchment area and identify at-risk patients who may benefit from tailored approaches to surgery and early intervention after surgery.

rates, indications for readmissions, and potential risk factors for readmissions.¹³ In these analyses, 32.9% of patients were readmitted within 30 days of IPAA surgery, with the leading diagnoses for readmission being infectious complications, dehydration, and venous thromboembolic events (VTEs). These immediate postoperative complications can have detrimental long-term effects as well, with pelvic sepsis and anastomotic leak increasing the long-term risk for pouch failure.

In the North Carolina Pouch Project, we sought to create a state-level registry for the evaluation of outcomes after successful restorative proctocolectomy with IPAA for UC. By evaluating the majority of patients undergoing IPAA for UC in North Carolina during the study period, the primary objective of this study was to evaluate the incidence of 30-day complications as well as 30-day readmission rates after the final stage of IPAA surgery. Our specific interest in this study was evaluating outcomes after restoration of fecal flow through the pouch, which constitutes the most elemental assessment for clinical function and structural integrity of the pouch formation. However we also evaluated complications following pouch creation among patients undergoing classical 2- or 3-stage IPAA surgeries.

Methods**Patient Selection**

We evaluated 177 patients who underwent restorative proctocolectomy with IPAA for UC at 4 tertiary care referral inflammatory bowel disease (IBD) centers in North Carolina between January 1, 2018, and December 31, 2020. The 4 centers (Atrium Health Charlotte, Atrium Health Wake Forest Baptist, Duke Health, and University of North Carolina Health) have a catchment area that covers the majority of

the state of North Carolina. Additionally, colorectal surgeons from other large health systems in the state were consulted to identify the number of IPAA performed outside of these 4 centers, with an estimated <10 surgeries performed per year outside of these 4 centers/health systems.

Within each healthcare center or system, patients were identified using a standard method of data collection with a case report form that was agreed upon by all study investigators prior to study initiation. Using this standardized case report form, pertinent clinical, demographic, and laboratory data were extracted from the electronic medical record and entered into a central REDCap (Research Electronic Data Capture) data tool, hosted at the University of North Carolina at Chapel Hill.

Patients were eligible for inclusion in this study based on the following criteria: (1) age ≥ 18 years of age, (2) documented proctocolectomy with IPAA for UC at 1 of the 4 participating centers or health systems during the study period, and (3) at least 30 days of follow-up after surgery. A preoperative diagnosis of UC was confirmed via review of the medical record. Patients < 18 years of age at the time of surgery and those patients with a preoperative diagnosis of Crohn's disease or indeterminate colitis at the time of colectomy were excluded.

Outcomes of Interest

The primary outcome of interest was the development of any of the following specific complications within the first 30 days after the final stage of IPAA surgery, evaluated individually and as a composite outcome: *Clostridioides difficile* infection, peripouch abscess, pelvic sepsis, postoperative leak, other surgical site or wound infection, ileus, VTEs, or urinary tract infection. The need for reoperation within the 30 days postoperative was also evaluated as an initial complication. As a secondary outcome, we evaluated the incidence of all-cause readmissions within the first 30 days of the final stage of IPAA surgery, and noted the primary diagnosis documented at the time of readmission. Given our interest in evaluating outcomes after restoration of fecal flow through the pouch as the ultimate assessment of clinical function and structural integrity of the pouch, the final stage of IPAA surgery was chosen for all initial analyses. However, given the potential for complications after the initial stages of pouch-related surgery, for any patient undergoing a classical 2-stage or 3-stage procedure, we also evaluated outcomes in the 30-days after pouch creation (without the re-establishment of fecal flow) in a secondary analysis.

Covariates

The medical record of each patient was examined to collect demographic variables that may affect perioperative morbidity and the course after IPAA including age and sex, as well as clinical factors including a history of primary sclerosing cholangitis,¹⁵⁻¹⁷ smoking status,^{18,19} the use of nonsteroidal anti-inflammatory drugs,^{16,18} the indication for colectomy,²⁰ disease extent of UC prior to colectomy,^{9,18,21} the stage of IPAA,²² and therapy prior to colectomy. Disease extent of UC at the time of colectomy was also evaluated using the Montreal classification, defining extensive colitis, left-sided colitis, and proctitis as inflammation extending beyond the splenic flexure, distal to the splenic flexure, and affecting the rectum only, respectively.^{23,24} When evaluating the stages of IPAA surgery,

a modified 2-stage IPAA was defined in the following manner: in the first operation, a total abdominal colectomy with end ileostomy is completed; after a recovery interval, a second surgery is performed including completion proctectomy and IPAA without a defunctioning loop ileostomy.^{25,26}

Statistical Analysis

Descriptive statistics were used to summarize baseline demographic and available clinical characteristics among patients undergoing IPAA for UC. Continuous variables were reported as median with interquartile range while categorical variables were reported as raw values with percentages. Continuous variables were compared using Wilcoxon rank sum testing given the assumption of non-normal distribution, while categorical variables were compared using Fisher exact and chi-square testing as appropriate. Multivariable logistic regression was used to evaluate the odds of developing specific complications in the first 30 days after IPAA, adjusting for potential confounders. All potential confounders were evaluated for inclusion, with the final multivariable models constructed initially via backward elimination strategy and the inclusion of previously identified or suspected risk factors for pouchitis. For all analyses, 2-sided *P* values of .05 or less were considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute).

Ethics

The study was approved by the Institutional Review Board of the University of North Carolina at Chapel Hill and all participating centers.

Results

Among 177 patients evaluated after the final stage of IPAA for UC with re-establishment of fecal flow between January 1, 2018, and December 31, 2020, 66 (37%; 95% confidence interval [CI], 30%-44%) experienced a complication within the first 30 days after surgery. The most common complications experienced by patients undergoing IPAA for UC included ileus (19%), abscess (15%), and leak (10%) (Table 1).

Complications Within 30 Days of the Final Stage of IPAA Surgery

When comparing demographics and clinical characteristics among patients who developed a complication within 30

days of surgery and those who did not, patients who developed a complication were more likely to have extensive colitis (84% vs 70%; *P* = .003) and were more likely to be current smokers (5% vs 1%) or former smokers (39% vs 21%) (*P* = .006) (Table 2). A significant difference was also noted in the number of stages involved in IPAA surgery, with patients experiencing a complication being more likely to have undergone a modified 2-stage procedure (45%) or 2-stage procedure (29%) and less likely to have undergone a 3-stage procedure (26%) compared with patients not experiencing a complication (*P* = .018). Although no significant difference was noted when evaluating body mass index (BMI) categories overall, when comparing obese patients (BMI >30 kg/m²) with all other patients, obese patients were significantly more likely to experience a complication in the 30 days after surgery (53% vs 34%; *P* = .036).

Medication use did not appear to impact complications after IPAA for UC. In an evaluation of IBD-specific medication use in the 30 days prior to the final stage of IPAA, there were no significant associations between steroid, biologic, or small molecule use and postoperative complications in the 30 days after IPAA (Table 3). Additionally, in an evaluation of IBD-specific medication use in the 90 days prior to colectomy, there were no significant associations between IBD-specific medication use prior to colectomy and post-IPAA complications (Supplemental Table 1).

In a multivariable analysis, a significant association was again demonstrated between extensive colitis and complications (odds ratio [OR], 3.61; 95% CI, 1.39-9.33) (Table 4). Additionally, patients who were current or former smokers were more likely to experience a complication within the first 30 days of the final stage of IPAA surgery than never smokers (OR, 2.98; 95% CI, 1.38-6.45). In multivariable analysis, there was no association between stages involved in IPAA surgery and complications or obesity at the time of IPAA.

Readmissions Within 30 Days of Final Stage of IPAA Surgery

Among the 177 patients evaluated after the last stage of IPAA surgery and re-establishment of fecal flow, 57 (32%; 95% CI, 25%-40%) were readmitted within the first 30 days of the final stage of IPAA surgery. When evaluating the primary indications for readmission, peripouch abscess (19%), dehydration (16%), ileus (11%), and small bowel obstruction (11%) were the most common indications for readmission (Supplemental Table 2). There were no significant associations between clinical or demographic risk factors and readmission identified on univariate or multivariable analysis.

Outcomes Within the 30 Days of Pouch Creation Among Patients Undergoing 2- and 3-Stage Surgeries

A total of 107 patients underwent 2- or 3-stage IPAA surgeries. Among these patients, 30% (95% CI, 21%-38%) experienced a complication within the first 30 days of pouch creation. The most common complications included ileus (16%), peripouch abscess (11%), and a leak (6%). Six percent required unplanned reoperation in the 30 days after pouch creation. In an evaluation of clinical and demographic factors associated with complications in the 30 days after pouch creation, only smoking status (67% current smokers vs 48% prior smokers

Table 1. Complications within 30 days of the final stage of ileal pouch-anal anastomosis surgery for ulcerative colitis (n = 66).

Abscess	27 (41)
<i>Clostridioides difficile</i> infection	1 (2)
Ileus	34 (52)
Leak	18 (27)
Pelvic sepsis	11 (17)
Other surgical infection	4 (6)
Need for reoperation	15 (23)
Urinary tract infection	3 (5)
Venous thromboembolic event	5 (8)

Table 2. Comparison of demographic and clinical characteristics among patients who experienced a complication within 30 days of the final stage of IPAA surgery for ulcerative colitis and patients who did not.

	No complications within 30 d (n = 111)	Complications within 30 d (n = 66)	P value
Female	47 (42)	26 (39)	.700
Race/ethnicity			.198
Black or African American	6 (5)	8 (12)	
Hispanic	4 (4)	1 (2)	.417
White	95 (86)	55 (83)	
Other	10 (9)	3 (5)	
Age at IPAA, y	38.2 (27.6-55.0)	43.4 (32.4-50.6)	.298
Body mass index at time of IPAA			.156
Underweight	4 (4)	4 (6)	
Normal	51 (48)	24 (38)	
Overweight	35 (33)	18 (28)	
Obese	16 (15)	18 (28)	
Disease extent prior to surgery ^a			.003
Proctitis	1 (1)	4 (7)	
Left-sided	28 (29)	5 (9)	
Extensive colitis	67 (70)	48 (84)	
Indication for surgery			.866
Medically refractory colitis	85 (77)	54 (82)	
Dysplasia/colorectal cancer	10 (9)	4 (6)	
Other	12 (11)	6 (9)	
Medically refractory disease and dysplasia/colorectal cancer	3 (3)	2 (3)	
Number of stages in surgery			.018
1	6 (5)	0 (0)	
2	24 (22)	19 (29)	
Modified 2	34 (31)	30 (45)	
3	47 (42)	17 (26)	
Delayed pouch creation ^b	81 (77)	47 (71)	.384
Time between colectomy and final stage of surgery, d ^c	138 (57-259)	134 (69-239)	.883
Smoking status at the time of colectomy			.006
Current	1 (1)	3 (5)	
Former	23 (21)	23 (39)	
Never	86 (78)	37 (56)	
Primary sclerosing cholangitis	8 (7)	4 (6)	.769
Extraintestinal manifestations of IBD	109 (98)	63 (95)	.287
Pathology findings at the time of colectomy			
Granulomas	5 (5)	2 (3)	1.000
Ileitis	17 (15)	10 (15)	.978
Transmural inflammation	12 (11)	11 (17)	.263
NSAIDs at the time of IPAA	27 (25)	22 (34)	.211
Therapy in 30 d prior to final stage of IPAA surgery			
Oral steroids	20 (18)	13 (20)	.745
Topical steroids	3 (3)	3 (5)	.500
Oral aminosalicylate	6 (5)	5 (8)	.556
Topical aminosalicylate	3 (3)	2 (3)	1.000
Thiopurine (azathioprine or mercaptopurine)	2 (2)	1 (2)	1.000
Methotrexate	1 (1)	0 (0)	1.000

Table 2. Continued

	No complications within 30 d (n = 111)	Complications within 30 d (n = 66)	P value
Tofacitinib	4 (4)	2 (3)	1.000
Anti-TNF monotherapy	3 (3)	2 (3)	1.000
Ustekinumab	1 (1)	0 (0)	1.000
Vedolizumab	1 (1)	1 (2)	1.000

Values are n (%) or median (interquartile range).

Abbreviations: anti-TNF, anti-tumor necrosis factor α ; IBD, inflammatory bowel disease; IPAA, ileal pouch–anal anastomosis; NSAID, nonsteroidal anti-inflammatory drug.

^aDisease extent at the time of surgery unknown for 24 patients.

^bDelayed pouch creation defined as a modified 2-stage or 3-stage approach to IPAA.

^cTime between colectomy and final stage of surgery evaluated among all patients with a 2-stage, modified 2-stage1 or 3-stage approach to IPAA.

vs 23% nonsmokers; $P = .021$) was significantly associated with an increased risk for complications. There was no difference in the rate of complications when comparing open, laparoscopic, and robotic techniques for pouch creation (33% vs 31% vs 22%; $P = .617$). Additionally, 26 (24%) patients required readmission within the 30 days following pouch creation, with peripouch abscess (26%), dehydration (15%), and abdominal or pelvic pain (15%) being the most common indications for readmission.

Discussion

In this evaluation of 177 patients undergoing IPAA for UC at 4 tertiary care referral centers or health systems in North Carolina, the rate of complications was 37% within the first 30 days of IPAA surgery, with an associated readmission rate of 32%. This cohort represents a state-level database of patients undergoing IPAA surgery for UC during a 3-year period and provides a novel method of studying outcomes after IPAA. In studying outcomes among all patients undergoing IPAA at the state level, we can begin to understand trends in both the natural history and healthcare utilization patterns across a large catchment area, and ultimately identify opportunities for earlier intervention to improve the care of patients with IBD undergoing surgery.

The 30-day complication and readmission rates that we identified in this study are comparable to prior single-center and more importantly multicenter cohort reports in recent years. In an evaluation of the ACS-NSQIP data, McKenna et al¹³ evaluated readmission rates among 3401 patients undergoing IPAA. In this evaluation, 32% of patients were readmitted within the first 30 days of IPAA surgery, with the most common indications for readmission being infectious complications, dehydration, and VTEs. Given that McKenna et al analyzed outcomes at the time of pouch creation in patients undergoing 2- and 3-stage procedures, this proportion of complications was very similar to our 30% complication rate in the same population analyzed in a secondary analysis. Prior evaluations of both single-center evaluations and selected populations demonstrated complication rates similar to ours,²⁷⁻³¹ with the most common complications being peripouch abscesses, anastomotic leaks, pelvic sepsis, and ileus. Differences in a staged approach to IPAA surgery have previously been demonstrated, with delayed pouch creation being associated with decreased rates of multiple complications.²² In this analysis, our primary objective was to evaluate those complications that occurred after

restoration of continuity in IPAA surgery; however, similar complications and indications for readmissions were also demonstrated in the 30 days after pouch creation among those patients undergoing classical 2- or 3-stage procedures. Given that peripouch abscess was the most common complication and reason for readmission, comparing our rate of this specific complication with the prior literature is important. Although relatively similar to other populations overall,³⁰⁻³² this rate was higher than in a recently published single-center cohort comparing staged approaches to IPAA.³² In our analysis, the highest rate of peripouch abscess was noted among patients undergoing a modified 2-stage IPAA, which may also indicate an increased risk for complication using this technique as compared with a classical 3-stage approach.

In our analyses, current and former smoking was associated with an increased risk of complications within the first 30 days after IPAA surgery and in the 30 days after pouch creation, in a subset of the population. Although smoking has been viewed as having potentially protective effects in the natural history of UC,³³ the association between smoking and worse perioperative outcomes, especially in IBD-related surgeries,³³⁻³⁵ is well recognized. In particular, smoking has been associated with increased risk for 30-day outcomes such as surgical site infections after stoma reversal in at least 1 evaluation from the ACS-NSQIP database.³⁶ These findings would suggest that continued counseling regarding the need for smoking cessation is warranted in patients with UC undergoing surgery, and that patients who are current smokers (or who have recently quit smoking) should be closely monitored in the perioperative period.

Extensive colitis is typically recognized as a more severe phenotype of UC, and thus a stronger argument may be present to pursue a delayed pouch creation. Even though the majority of patients in our study had a delayed approach to pouch creation, the association between extensive colitis and increased risk for post-IPAA complications remained. Other potential markers of disease severity such as therapies utilized at the time of colectomy (and immediately pre-IPAA surgery) did not seem to impact the rate of complications, consistent with recent large evaluations such as PUCINI (Prospective Cohort of Ulcerative Colitis and Crohn's Disease Patients Undergoing Surgery to Identify Risk Factors for Post-Operative Infection) study.³⁷ Given that the disease extent at the time of surgery is not a modifiable risk factor, patients with extensive disease will likely require increased attention

Table 3. Medications used in the 30 days prior to the final stage of ileal pouch–anal anastomosis surgery.

	No complications within 30 d (n = 111)	Complications within 30 d (n = 66)	P value
Oral steroids	20 (18)	13 (20)	.745
Topical steroids	3 (3)	3 (5)	.500
Oral aminosalicylate	6 (5)	5 (8)	.556
Topical aminosalicylate	3 (3)	2 (3)	1.000
Thiopurine (azathioprine or mercaptopurine)	2 (2)	1 (2)	1.000
Methotrexate	1 (1)	0 (0)	1.000
Tofacitinib	4 (4)	2 (3)	1.000
Anti-TNF monotherapy	3 (3)	2 (3)	1.000
Ustekinumab	1 (1)	0 (0)	1.000
Vedolizumab	1 (1)	1 (2)	1.000

Values are n (%).

Abbreviation: anti-TNF, anti-tumor necrosis factor α .

Table 4. Odds of developing a complication within the first 30 days of ileal pouch–anal anastomosis surgery for ulcerative colitis after adjusting for potential risk factors.

	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)
Disease extent		
Proctitis/left-sided disease	Reference	Reference
Extensive colitis	2.31 (1.00-5.32)	3.61 (1.39-9.33)
Number of stages in IPAA surgery ^a		
2	Reference	Reference
Modified 2	1.12 (0.51-2.42)	1.28 (0.52-3.20)
3	0.46 (0.20-1.04)	0.53 (0.20-1.42)
Smoking status at time of IPAA		
Never	Reference	Reference
Current or former	2.81 (1.45-5.46)	2.98 (1.38-6.47)
Body mass index at time of IPAA		
<30 kg/m ²	Reference	Reference
30 kg/m ² or greater (obese)	2.23 (1.04-4.75)	1.93 (0.78-4.77)

Abbreviations: CI, confidence interval; IPAA, ileal pouch–anal anastomosis.

^aPatients with a 1-stage approach to IPAA not included in model due to <10 events.

in the perioperative period and recognition of a potentially increased risk for complications. In our analysis, obese patients also demonstrated a significant increase in risk of complications within the 30 days after the final stage of IPAA surgery, a risk factor for short- and long-term complications after IPAA previously demonstrated in multiple studies.^{27,38} Although not significant in the multivariable analysis, continued emphasis on preoperative counseling regarding the risks of obesity on potential adverse outcomes after IPAA surgery will be critical, as the lack of significance in multivariable analysis may have been influenced by the smaller sample size of obese patients in our study population and unmeasured influences such as an intentional decision by surgeons to avoid pouch creation in obese patients.

Strengths of this study include a standardized method of data collection as well as the large catchment area represented within a state-level registry created to study outcomes after IPAA. Our study has limitations. All centers represented in this study are tertiary care referral centers, and thus IBD-related surgeries occurring at these centers may occur in more advanced disease states or urgent/

emergent settings. Additionally, given that these are referral centers, there is a possibility that patients may seek care outside of the 4 health systems represented in the 30 days postoperatively for urgent/emergent complications, which would lead to underreporting of 30-day complication and/or readmission rates. Due to the retrospective nature of the study, we are not able to account for patients who underwent the initial stages of planned IPAA surgery but due to complications or technical difficulties never achieved re-establishment of fecal flow. We are also not able to evaluate potential confounding factors that may have affected the choice of surgery (classical 2-stage vs modified 2-stage vs 3-stage). Although this was designed as a state-level database and other colorectal surgeons in the state of North Carolina were queried regarding IPAA volume, we recognize that some patients undergoing IPAA surgery in our state are not represented as estimated in the methods. The study period represented also overlaps with the beginning of the COVID-19 pandemic, and the impact of the COVID-19 pandemic on surgery rates and/or complications was not specifically analyzed in this study.

Conclusions

Among 177 patients undergoing IPAA for UC in the state of North Carolina over a 3-year period, we identified a complication rate of 37% and a readmission rate of 32%. These estimates are similar to prior single and multicenter cohort studies, and are informative in the setting of the epidemiology and natural history after IPAA at the state level, in a novel approach to studying outcomes after IPAA surgery. This data source offers both new information regarding immediate postoperative outcomes, as well as the infrastructure for future longitudinal studies of important outcomes such as pouchitis, chronic inflammatory conditions of the pouch, and healthcare utilization patterns after IPAA surgery.

Supplementary data

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

Author Contribution

E.L.B. designed the study, was responsible for study supervision and data maintenance, performed all data analysis, wrote the first draft of the manuscript and participated in revising the manuscript. S.E., A.C., K.M., P.P., J.D., and M.D. participated in the study design, were responsible for data acquisition and data maintenance, and revised the manuscript. J.A., A.B., R.B., J.S.H., and H.H.H. participated in the study design, were responsible for study supervision, and revised the manuscript. R.R. and T.S.S. participated in the study design, were responsible for study supervision, and revised the manuscript. All authors agree with the final version of the manuscript and are accountable for the work presented.

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Conflict of Interest

E.L.B. has served as a consultant for AbbVie, Lilly, and Target RWE. H.H.H. has served as a consultant for Alivio, AMAG, BMS, ExeGI Finch, Gilead, Janssen, Lycera, Merck, Otsuka, Pfizer, PureTech, and Seres; and received research support from Pfizer and Artizan Biosciences. All other authors have no relevant disclosures.

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