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Use of Biologic Medications Does Not Increase Postoperative Complications among Patients with Ulcerative Colitis Undergoing Colectomy: A Retrospective Cohort Analysis of Privately Insured Patients

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Abstract

BACKGROUND: Existing studies on the effects of biologic medications on surgical complications among ulcerative colitis patients have mixed results. Because biologics may hinder response to infections and wound healing, preoperative exposure may increase postoperative complications.

OBJECTIVE: Evaluate associations between biologic exposure within six months preceding colectomy or proctocolectomy and postoperative complications among ulcerative colitis patients.

DESIGN: Retrospective cohort study with multivariate regression analysis following coarsened exact matching.

SETTING: A large commercial insurance claims database (2003-2016).

PATIENTS: A total of 1,794 ulcerative colitis patients underwent total abdominal colectomy with end ileostomy, total proctocolectomy with end ileostomy, or total proctocolectomy with ileal pouch anal anastomosis. 22% were exposed to biologics in the six months preceding surgery.

MAIN OUTCOMES MEASURES: Healthcare utilization (length of stay, unplanned reoperation/procedure, emergency department visit, or readmission) and complications (infectious, hernia or wound disruption, thromboembolic, or cardiopulmonary) within 30 postoperative days.

RESULTS: Exposure to biologic medications was associated with shorter surgical hospitalization (7 vs. 8 days, $p < 0.001$), but otherwise was not associated with differences in healthcare utilization or postoperative complications. Patients who underwent total proctocolectomy with ileal pouch anal anastomosis had higher odds of infectious complications compared to those who underwent total abdominal colectomy with end ileostomy (aOR 2.2, 95% CI [1.5-3.0], $p < 0.001$) but had lower odds of cardiopulmonary complications (aOR 0.4, 95% CI [0.3-0.6], $p < 0.001$).

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LIMITATIONS: Analysis of private insurance database claims data may not represent uninsured or government-insured patients and may be limited by coding accuracy. Matched cohorts differed in age and Charlson comorbidity index, which could be influential even after multivariate adjustments.

CONCLUSION: Biologic exposure among ulcerative colitis patients is not associated with higher odds of postoperative complications or healthcare resource utilization. These data, in combination with clinical judgment and patient preferences, may aid in complex decision-making regarding operative timing, operation type, and perioperative medication management. See Video Abstract.

Abstract

Estudios existentes sobre los efectos de medicamentos biológicos, en complicaciones quirúrgicas, en pacientes con colitis ulcerativa, presentan resultados mixtos. Debido a que los productos biológicos pueden retrasar la respuesta a las infecciones y curación de heridas, su exposición preoperatoria pueden aumentar las complicaciones postoperatorias.

Evaluar las asociaciones entre la exposición biológica dentro de los seis meses anteriores a la colectomía o proctocolectomía y las complicaciones postoperatorias entre los pacientes con colitis ulcerativa.

Estudio de cohorte retrospectivo con análisis de regresión multivariante después de una coincidencia exacta aproximada.

Una gran base de datos de reclamaciones de seguros comerciales (2003-2016).

Un total de 1.794 pacientes con colitis ulcerativa, se sometieron a colectomía abdominal total con ileostomía terminal, proctocolectomía total con ileostomía terminal o proctocolectomía total con anastomosis anal y bolsa ileal. 22% estuvieron expuestos a productos biológicos, seis meses antes de la cirugía.

Utilización de la atención médica (duración de la estadía, reoperación o procedimiento no planificado, visita al servicio de urgencias o reingreso) y complicaciones (infecciosas, hernias o dehiscencias de heridas, tromboembólicas o cardiopulmonares) dentro de los 30 días postoperatorios.

La exposición a medicamentos biológicos se asoció con una hospitalización quirúrgica más corta (7 frente a 8 días, $p < 0.001$), pero por lo demás, no se asoció con diferencias en la utilización de la atención médica o complicaciones postoperatorias. Los pacientes que se sometieron a proctocolectomía total con anastomosis anal y bolsa ileal, tuvieron mayores probabilidades de complicaciones infecciosas, en comparación con aquellos que se sometieron a colectomía abdominal total con ileostomía final (aOR 2.2, IC 95% [1.5-3.0], $p < 0.001$) pero tuvieron menores probabilidades de complicaciones cardiopulmonares (aOR 0.4, IC 95% [0.3-0.6], $p < 0.001$).

El análisis de los datos de reclamaciones, de la base de datos de los seguros privados, puede no representar a pacientes no asegurados o asegurados por el gobierno, y puede estar limitado por la precisión de la codificación. Las cohortes emparejadas diferían en la edad y el índice de comorbilidad de Charlson, lo que podría influir incluso después de ajustes multivariados.

La exposición biológica entre los pacientes con colitis ulcerativa, no se asocia con mayores probabilidades de complicaciones postoperatorias, o a la utilización de recursos sanitarios. Estos datos, en combinación con el juicio clínico y las preferencias del paciente, pueden ayudar en la

toma de decisiones complejas con respecto al momento quirúrgico, el tipo de operación y el manejo de la medicación perioperatoria. Consulte Video Resumen.

Keywords

Biologic medications; Colectomy; Inflammatory bowel disease; Postoperative complications; TNF-alpha inhibitor; Ulcerative colitis

INTRODUCTION

Management of ulcerative colitis (UC) increasingly involves the use of biologic medications to induce and maintain disease remission. The biologic medications most commonly used to treat UC are monoclonal antibodies inhibiting tumor necrosis factor alpha (TNFa) activity, such as adalimumab, infliximab, and golimumab. More recently, antibodies to integrin alpha 4/beta 7 (vedolizumab)—which prevent T-cell homing to the gut—are also being used. Despite the introduction of these new therapies, a significant proportion of patients with UC must undergo colectomy for severe disease refractory to treatment, intolerance of medical therapy, or neoplasia.¹ Postoperative complications are frequent among this population, ranging from 10-65%.²

Given the effect of biologic medications on the immune system, there has been concern for increased risk of infectious and wound-healing complications after surgery for patients on biologics. However, results are mixed regarding the effects of biologic medications on postoperative complications. Initial studies showed that UC patients taking TNFa inhibitors are more likely to suffer from complications after surgery.³ Several studies have compared postsurgical outcomes in the “pre-biologic era” to those in the “biologic era” and found an increase in postsurgical complications in the era in which biologics are more commonly prescribed.^{4,5} However, meta-analyses,^{6–8} an insurance claims database⁹ and large retrospective studies¹⁰ have shown no effect on infectious complications and mixed results on overall complications. The risk of postoperative complications appear to be similar for patients taking vedolizumab compared to those on TNFa inhibitors.^{11,12} The discrepant findings on the effects of biologics on postoperative complications have spurred debate on the management of perioperative biologic medications, timing of major operations in relation to the most recent dose of biologic medications, and type of operation to perform in the setting of recent biologic therapy exposure.^{8,13} Thus, understanding the association between biologics and postoperative complications is critical for surgical decision-making and providing optimal patient care.

To address this question on a broader scale, we used an insurance claims database to evaluate a large cohort of patients with UC who underwent definitive surgical management for their disease (total colectomy or total proctocolectomy). The primary outcome of this study was the risk of postoperative complications in patients exposed to biologic medications in the six months prior to surgery, compared to those who were not exposed to biologics. The secondary outcome was postoperative healthcare resource utilization in surgical patients exposed to biologic medications preoperatively, compared to those who were not.

METHODS

Data Source

We used the Optum Clinformatics® Data Mart administrative health claims database to evaluate a retrospective cohort of patients with UC who underwent surgery. Optum Clinformatics® Data Mart is a national private insurance claims database with deidentified inpatient, outpatient, and pharmaceutical claims previously used to evaluate surgical outcomes^{14–16} as well as medications in inflammatory diseases.^{17–19} Each year, data from approximately 15 million members of a national managed care company affiliated with Optum are included. Data include demographic characteristics, encounter data (inpatient and outpatient encounters and associated procedures/surgeries), and pharmaceutical data (medications prescribed, days supply, and dose). The Stanford University Institutional Review Board determined that this project did not meet the definition of human subjects research and exempted it from further review.

Study Population

We identified patients with UC, aged 12+ years, who underwent total colectomy or proctocolectomy from 2003–2016. A diagnosis of IBD was defined as 2 distinct outpatient or inpatient claims for either Crohn's disease or ulcerative colitis. Patients with IBD were considered to have UC if 80% or more of their distinct IBD-related encounter codes were for UC²⁰ (Supplementary Table 1). We then selected patients with an inpatient claim for colectomy. Colectomy was grouped by total abdominal colectomy (TAC) with end ileostomy, total proctocolectomy (TPC) with end ileostomy, or TPC with ileal pouch anal anastomosis (IPAA) based on ICD or CPT codes, as shown in Supplementary Table 2. Patients <12 years of age at time of surgery were excluded due to the low likelihood of surgical treatment for UC in this population. We included patients with continuous enrollment for at least six months prior to surgery to provide sufficient enrollment time to ascertain preoperative risk factors and 30 days following surgery to evaluate postoperative healthcare utilization and 30-day complications.

Outcomes

Our primary outcomes of interest were 30-day complications categorized in four domains: infectious, hernia or wound disruption, thromboembolic, or cardiopulmonary (Supplementary Table 3). We specifically modeled infectious and hernia/wound disruption complications because inhibition of T-cell action by biologic medications has previously been implicated in causing these complications.^{21–23} UC patients are at higher risk for thromboembolic events due to their chronic inflammatory state, so we additionally modeled the effect of biologics on thromboembolic complications. Lastly, we evaluated cardiopulmonary complications, hypothesized to be unrelated to biologic exposure. Secondary outcomes were healthcare utilization within 30 days after surgery including: length of hospital stay, unplanned procedure or reoperation, emergency department visit, and readmission (Supplementary Table 3).

To determine postoperative complications, we extracted all diagnosis and procedure codes for each patient in the 30 days after surgery. Two authors (KR and CK) classified each code

as either not a complication or as an infectious, hernia/wound disruption, thromboembolic, or cardiopulmonary complication. Complications not falling in those categories, such as bleeding, were grouped as “any complication.” The goal of this approach was to capture the actual complication burden experienced by patients rather than limiting the analysis to a predetermined set of complication codes. If a patient had a previously documented complication code within the six months preceding surgery, that code was not classified as a postoperative complication for that patient (e.g. postoperative ventral hernia was not counted as a complication if ventral hernia was present on claims within six months before surgery). Unplanned procedures and operations occurring within 30 days after the index operation were identified using procedure and anesthesia codes.

Variable Classification

The primary independent variable of interest was biologic prescription in the six months preceding surgery. Biologic medications have long half-lives, and typical dosing intervals range from two to eight weeks. To determine the study definition of biologic exposure timing, we conducted analyses comparing multiple definitions: 1) exposure to biologics within six months prior to surgery, 2) exposure within 30 days prior to surgery, and 3) exposure within three half-lives of the given biologic therapy prescribed. We found minimal differences in the demographic and clinical characteristics of resulting patient cohorts from these definitions. Thus, we chose to include patients exposed to biologic medications within six months prior to surgery to fully capture exposure to biologics with longer half-lives. By looking only at 30-day exposure, the effects of longer half-life biologics would be inappropriately assigned to the non-exposed group. Patients were classified as having received a biologic medication based on presence of Healthcare Common Procedure Coding System J-codes (procedure codes) or pharmaceutical claims for infliximab, adalimumab, golimumab, vedolizumab, certolizumab, ustekinumab, and natalizumab. Steroid prescriptions for prednisone, prednisolone, methylprednisolone or hydrocortisone in the six months preceding surgery were also evaluated. The Charlson Comorbidity Index (CCI)²⁴ was calculated over a six-month preoperative period.

Statistical Analysis

Patient characteristics were compared between surgery groups using χ^2 tests for categorical variables and independent sample t-tests for continuous variables.

We applied a many-to-one coarsened exact matching (CEM) approach to minimize treatment selection bias for patients receiving biologics in this retrospective observational study. CEM is a monotonic imbalance bounding method that prunes observations, creating balanced treatment and control groups within the matched observations.²⁵ While the more common approach of propensity score matching can still produce large imbalance through complete randomization, CEM eradicates this imbalance through full blocking.²⁶ Matched covariates included: age, sex, malnutrition (263.x, E44.x), diabetes (250.x, E08.x-E11.x, E13.x), obesity (278.x, E66.x), and anemia (280.x-285.x, D50.x-D53.x, D55.x-D63.x). Selected matching characteristics were thought likely to be related to disease severity and also to affect postoperative complications in the IBD population.

We calculated multivariate logistic regression models using CEM-derived weights to compare matched biologic and non-biologic cohorts. Covariates included age group (12-18 years, 19-45 years, 46-65 years, and >65 years), sex, CCI (0, 1, 2+), region (Northeast, Midwest, South, West), race (White, African-American, Hispanic/Latino, Asian), steroids, net worth range (<\$25,000, \$25,000-\$149,000, \$150,000-\$249,000, \$250,000-\$499,000, and \$500,000), and surgery type. Respective referent groups include 12-18 years, female, CCI of 0, Northeast region, White race, no steroid exposure, <\$25,000, and total abdominal colectomy with end ileostomy. Missing data were considered a separate category within each variable. Patients with missing region were excluded from the analysis due to the small population size within the matched cohort (n=4) and lack of outcome occurrences in this small group. Statistical significance was defined as $\alpha=0.05$. All statistical analyses were completed using Stata v14.2 (College Station, TX).

RESULTS

We identified 175,191 patients with a diagnosis of UC between 2003 and 2016. 3,328 of those patients (2%) underwent total colectomy or proctocolectomy. After many-to-one coarsened exact matching, 1,794 patients were included in regression analysis (Figure 1). Most patients exposed to biologic medications in the six months before surgery were prescribed TNFa inhibitors [infliximab (n=248, 62%) adalimumab (n=122, 30%), golimumab (n=20, 5%), and certolizumab (n=20, 5%)]. Few were prescribed an integrin $\alpha 4\beta 7$ inhibitor (vedolizumab (n=9, 2%)). No patients in this cohort were taking ustekinumab (interleukin-12/23 inhibitor) or natalizumab (integrin $\alpha 4\beta 7$ inhibitor). Sixteen patients (4%) were prescribed two biologics in the six months before surgery, and one (0.3%) was prescribed three biologics within six months before surgery. We found minimal differences in the cohorts when we looked at biologic exposure in the six months, 30 days, or three half-lives (for each given medications) before surgery; we used the cohort with biologic exposure within six months of surgery so as not to miss exposure to biologics with longer half-lives. Although medication adjustments are often made within the 30 days before surgery, the 8-25 day half-life of these biologics means that they could still be exerting effects even months after the last dose is administered.

In the pre-matching cohort, the biologic-exposed group was considerably younger than the non-exposed group (43 ± 16 years vs. 54 ± 18 years, $p < 0.001$, Supplementary Table 4). After matching, the imbalance was minimized with consideration for maintaining adequate sample size. The group of patients excluded after coarsened exact matching were generally an older, sicker group than the matched group (CEM matched age 48.1 ± 16.5 , CCI 1.5 ± 2.4 vs. unmatched age 66.8 ± 17.4 , CCI 3.3 ± 3.0 , $p < 0.001$ for both). However, even after matching, the biologic-exposed cohort was still younger than the non-exposed cohort (44 ± 15 vs. 48 ± 15 years, $p = 0.03$) but differences had been minimized without overly sacrificing sample size. The matched, biologic-exposed group had a lower CCI (0.8 ± 1.5 vs. 1.7 ± 2.5 , $p < 0.001$) and had higher level of educational attainment ($p < 0.001$) than patients not exposed to biologics. Patients in the biologic-exposed group were more likely to have also been exposed to steroids in the six months preceding surgery (82% vs. 51%, $p < 0.001$). The biologic-exposed group was more likely to have undergone IPAA (44% vs. 29% in the non-

exposed group), whereas the non-exposed group was more likely to have undergone TAC with end ileostomy (54% vs. 41% in the biologic-exposed group, $p<0.001$) (Table 1).

Healthcare utilization was evaluated by length of hospital stay, unplanned reoperation or procedure, emergency department visit, or readmission within 30 days after surgery. The biologic-exposed group had a shorter median length of hospital stay (7 vs. 8 days, $p<0.001$). There were no statistically significant differences in other healthcare utilization parameters between patients with and without preoperative biologic exposure (Table 2). There were no statistically significant differences in utilization outcomes by biologic exposure or steroid exposure after adjusting for covariates in multivariate regression (Table 3). However, operations involving total proctocolectomy were associated with higher odds of emergency department visits compared to TAC: TPC with end ileostomy had an aOR of 1.9 [1.1-3.1] ($p=0.02$), and TPC with IPAA had an aOR of 3.0 [2.1-4.3] ($p<0.001$). IPAA was also associated with higher odds of readmission within 30 days postoperatively (aOR 1.3 [1.1-1.6], $p=0.02$) compared to TAC.

Twenty-one percent of patients experienced at least one complication within 30 days of surgery. In bivariate analysis, biologic exposure was not associated with a change in the rate of complications (Table 4). In multivariate analysis, the odds of infectious, hernia or wound disruption, thromboembolic, and cardiopulmonary complications did not differ significantly between biologic-exposed and non-exposed groups (Table 5). Patients with preoperative steroid exposure had higher odds of cardiopulmonary complications (aOR 1.4 [1.0-2.0], $p=0.05$) compared to those without steroid exposure. Patients who underwent TPC with IPAA had twice the odds of developing postoperative infectious complications (aOR 2.2 [1.5-3.0], $p<0.001$) compared to those who underwent TAC with end ileostomy. Infectious complications were twice as common after proctocolectomy with IPAA (14%) compared to TAC with end ileostomy (7%); 10% of patients who underwent TPC with end ileostomy experienced an infectious complication. Proctocolectomy patients had lower odds of cardiopulmonary complications: those undergoing TPC with end ileostomy had an aOR of 0.6 [0.4-0.9] ($p=0.03$), and IPAA had an aOR of 0.4 [0.3-0.6] ($p<0.001$) compared to those undergoing TAC. Cardiopulmonary complications were nearly twice as common following total abdominal colectomy (14%) than after proctocolectomy (TPC with end ileostomy: 9%; TPC with IPAA: 6%).

Given the difference in infectious complications based on type of surgery, we wanted to look further at the effect of biologics on complication by surgery type. Neither biologics nor steroids affected odds of complications for patients undergoing TAC or TPC with end ileostomy. Among patients who had TPC with IPAA, biologic exposed patients had lower odds of infectious complications (aOR 0.5 [0.3-0.9], $p=0.03$). The higher odds of infectious complications in this surgery group were attributable to the patients who had not been exposed to biologic medications before surgery. However, the TPC with IPAA group that had been exposed to steroids had higher odds of both thromboembolic (aOR 3.2 [1.1-9.3], $p=0.03$) and cardiopulmonary complications (aOR 4.6 [1.6-13.0], $p=0.004$). Taken together, these data show that the higher odds of cardiopulmonary complications seen among all patients exposed to steroids is largely due to those who had TPC with IPAA. While the odds of cardiopulmonary complications are highest among patients undergoing TAC with end

ileostomy, there was no difference in odds whether or not this group was exposed to biologic medications or steroids.

DISCUSSION

This is one of the largest studies to assess postoperative complications among UC patients exposed or not exposed to biologic medications. We found no difference in postoperative complications after total colectomy or proctocolectomy whether or not patients were prescribed biologic medications if the surgery included end ileostomy. Patients who had TPC with IPAA had double the odds of an infectious complication compared to patients who got an end ileostomy. However, for patients who underwent TPC with IPAA, biologic exposure was associated with lower odds of infectious complications. Exposure to biologic medications also did not result in more unplanned reoperations, emergency department visits, or readmissions.

This study reinforces prior work showing that TPC with IPAA is more prone to infectious complications.¹⁰ Of the three operations performed for UC, IPAA is the only one involving the formation of anastomoses, which may be the reason behind the highest risk of infection. The higher odds of emergency department visits and readmissions in the IPAA group is likely due to the higher risk of infectious complications, in addition to the higher risk for dehydration from a more proximal loop ileostomy. Interestingly, among the IPAA group, having received preoperative biologic medications was associated with lower odds of infectious complications in our study. This could be due to better disease control in the biologic-exposed group. Kulaylat et al similarly looked at complications after IPAA among UC patients using a different insurance claims database. In their cohort, anti-TNF therapy did not affect the rates of fistula, abscess, sepsis/bacteremia/pneumonia, or wound debridement/dehiscence. The differences with our findings are potentially due to their study having evaluated codes for specific complications as opposed to our approach of evaluating all postoperative claims codes to determine complication rates. Our methodology allows for more broadly detecting infectious complications such as anastomotic leak, a limitation they acknowledge in their work.⁹

When looking at all UC patients regardless of surgery type, steroid exposure was associated with higher odds of cardiopulmonary complications. The odds were highest among patients undergoing TAC with end ileostomy. Although the odds of cardiopulmonary complications were lowest in the IPAA group, even among IPAA patients steroid exposure was associated with a nearly five-fold higher odds of cardiopulmonary complications compared to non-exposed IPAA patients. Steroid-exposed IPAA patients also had three-fold higher odds of thromboembolic events compared to non-steroid exposed IPAA patients. This suggests that physicians should have an increased concern for cardiopulmonary complications when operating on steroid-exposed UC patients, regardless of surgery performed, and for thromboembolic events after IPAA surgery. The prophylactic anticoagulation status for these patients is unknown, but certainly could play a role in these findings.

The effects of biologic medications on perioperative outcomes differ between Crohn's disease and ulcerative colitis. Studies in CD more consistently show an increased risk of

postoperative infectious and non-infectious complications after biologic-exposure.^{7,27,28} While we do not know why biologics have more of a detrimental effect on postoperative complications in CD, it may be because colectomy in UC is curative of IBD, but patients with CD still have IBD after surgery. In UC, results of prior studies regarding the effects of biologic medications on postoperative complications are mixed, but the evidence increasingly shows no effects on infectious complications.^{6–10} In contrast to other large series that show an increase in complications during the “biologic era,” our work directly evaluated complications and biologic-exposure on a per patient basis. We suspect that patients compared by era may differ in other meaningful ways such as more advanced disease severity when undergoing operation in the “biologic era” compared to the “pre-biologic era.” Our study design allows for direct attribution of complications to a patient exposed or not-exposed to biologics. It was unexpected to have lower odds of infectious and wound complications among the steroid-exposed group. Using this claims database, we were unable to evaluate the dose of steroid, but most (81%) of steroid exposed patients were on prednisone. Using a different insurance claims database, no effect of steroids on infectious complications has previously been shown.⁹ We suspect this is a limitation of using claims database in that steroid exposure chronicity and dose could not be determined. Patients may have been on low dose prednisone or short-term steroids and thus had minimal impact on infectious complications.

This study has several limitations. The outcomes reported here are from a privately insured population, and thus may not be generalizable to uninsured or government-insured patients. In using an insurance claims database, administrative inaccuracies in billing codes can affect the integrity of the data and selection bias from clinical decision making cannot be eliminated. It is possible that pharmaceutical claims do not reflect actual drug use, as not all patients who fill a prescription use the medications as prescribed. However, work by Tkacz et al show that, for rheumatoid arthritis, anti-TNFa adherence is high.¹⁷ Although we matched for anemia and malnutrition as markers of disease severity, these parameters are unlikely to fully represent disease severity. We are also unable to account for whether surgeries were elective or emergent. In the matching, we chose to minimize imbalance while maintaining sample size. After matching, the biologic-exposed group was younger and had a lower CCI than the non-exposed group. To account for the remaining imbalance between cohorts, we used multivariate regression to adjust for age and CCI. Despite adjustments, we acknowledge that these cohort differences may be important markers of residual confounding and could be influential. As this study was one of the first exploratory observational studies of UC complications in a large private-payer claims database, p-values were not adjusted for multiple comparisons in consideration of the balance between type I and type II error risk. Although testing multiple outcomes without p-value adjustment increases the risk of type I errors, or false positive results, the alternative, adjusting p-values for multiple comparisons, would increase the risk of type II errors (false negative results), thereby missing potentially important findings.^{29–31} Our work supports that of others that biologics may not increase risk of infectious postoperative complications in ulcerative colitis. We hope this work will spur further research to investigate even more granular clinical data which may be difficult to study through insurance claims.

CONCLUSION

Our study provides further evidence that preoperative exposure to biologic medications is not associated with more healthcare utilization or with increased postoperative complications in ulcerative colitis patients undergoing curative surgery. These findings may aid patients with ulcerative colitis and their physicians through the complex decision-making process to determine timing and type of operation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:
Cohort flow diagram.

Table 1:

Patient characteristics of matched biologic and non-biologic-exposed groups.

Patient Characteristics	Total n=1,794	Preoperative Biologic Exposure n=401 (22.4%)	No Biologic Exposure n=1,393 (77.6%)	p-value
Age, Years (mean $\pm$ SD) *	48.1 $\pm$ 16.5	44.0 $\pm$ 15.1	48.2 $\pm$ 15.4	0.034
Female Sex, n (%) *	811 (45.2)	186 (46.3)	625 (44.9)	0.659
Malnutrition, n (%) *	306 (17.1)	76 (18.9)	230 (16.5)	0.252
Diabetes, n (%) *	238 (13.3)	47 (11.7)	191 (13.7)	0.171
Obesity, n (%) *	151 (8.4)	38 (9.5)	109 (7.8)	0.208
Anemia, n (%) *	1,461 (81.4)	322 (80.3)	1,139 (81.7)	0.506
Race, n (%)				0.356
White	1,406 (78.4)	324 (80.8)	1,082 (77.7)	
Black/ African American	112 (6.2)	24 (6.0)	88 (6.3)	
Hispanic or Latino	103 (5.7)	24 (6.0)	79 (5.7)	
Asian	36 (2.0)	8 (2.0)	28 (2.0)	
Unknown	137 (7.6)	21 (5.2)	116 (8.3)	
Geographic Region, n (%)				0.330
Northeast	201 (11.2)	42 (10.5)	159 (11.4)	
Midwest	534 (29.8)	107 (26.7)	427 (30.7)	
South	761 (42.4)	184 (45.9)	577 (41.4)	
West	294 (16.4)	68 (17.0)	226 (16.2)	
Unknown	4 (0.2)	1 (0.2)	4 (0.3)	
Charlson Comorbidity Index (mean $\pm$ SD)	1.5 $\pm$ 2.4	0.8 $\pm$ 1.5	1.7 $\pm$ 2.5	<0.001
Net Worth, n (%)				0.213
<\$25K	170 (9.5)	48 (12.0)	122 (8.8)	
\$25K-\$149K	358 (20.0)	80 (20.0)	278 (20.0)	
\$150K-\$249K	247 (13.8)	52 (13.0)	195 (14.0)	
\$250K-\$499K	420 (23.4)	94 (23.4)	326 (23.4)	
>\$500K	360 (20.1)	85 (21.2)	275 (19.7)	
Unknown	239 (13.3)	42 (10.5)	197 (14.1)	
Education, n (%)				<0.001
Less than 12 th Grade	12 (0.7)	1 (0.3)	11 (0.8)	
High School Diploma	407 (22.7)	75 (18.7)	332 (23.8)	
Less than Bachelor's	958 (53.4)	226 (56.4)	732 (52.6)	
At least Bachelor's Degree	358 (20.0)	95 (23.7)	263 (18.9)	
Unknown	59 (3.3)	4 (1.0)	55 (4.0)	
Steroids, n (%)	1,033 (57.6)	329 (82.0)	704 (50.5)	<0.001
Surgery Type, n (%) **				<0.001
TAC with end ileostomy	918 (51.2)	164 (40.9)	754 (54.1)	
TPC with end ileostomy	291 (16.2)	62 (15.5)	229 (16.4)	
TPC with IPAA	585 (32.6)	175 (43.6)	410 (29.4)	

* Groups matched based on age, sex, anemia, malnutrition, obesity, and diabetes

** TAC: total abdominal colectomy, TPC: total proctocolectomy, IPAA: ileal pouch anal anastomosis

Table 2:

Healthcare utilization of matched biologic and non-biologic-exposed groups.

	n (%)	Total n= 1,794	Preoperative Biologic Exposure n= 401 (22.4%)	No Biologic Exposure n= 1,393 (77.6%)	p-value
Hospital Length of Stay, Days, median (IQR)		8 (5, 14)	7 (5, 12)	8 (6, 15)	<0.001
Unplanned Procedure or Reoperation, n (%)		188 (10.5)	39 (9.7)	149 (10.7)	0.576
Emergency Department Visit, n (%)		163 (9.1)	44 (11.0)	119 (8.5)	0.136
Readmission, n (%)		461 (25.7)	100 (24.9)	361 (25.9)	0.693

IQR: Interquartile range

Table 3:

Multivariate regression results of healthcare utilization, by pre-operative biologic exposure, pre-operative steroid exposure, and operation type.

Independent Variables	Unplanned Procedure or Reoperation		Emergency Department Visits		Readmission	
	aOR [95% CI]	p-value	aOR [95% CI]	p-value	aOR [95% CI]	p-value
No Biologic Exposure	Referent					
Biologic Exposure	1.2 [0.8, 1.7]	0.47	1.0 [0.7, 1.5]	0.83	1.0 [0.7, 1.3]	0.92
No Steroid Exposure	Referent					
Steroid Exposure	0.8 [0.6, 1.2]	0.27	1.1 [0.8, 1.6]	0.63	1.1 [0.8, 1.3]	0.63
Surgery Type						
<i>TAC with end ileostomy</i>	Referent					
<i>TPC with end ileostomy</i>	0.6 [0.4, 1.1]	0.09	1.9 [1.1, 3.1]	0.02	0.8 [0.6, 1.2]	0.34
<i>TPC with IPAA</i>	0.9 [0.6, 1.2]	0.38	3.0 [2.1, 4.3]	<0.001	1.3 [1.1, 1.6]	0.02

* aOR: Odds Ratio adjusted for age, sex, Charlson Comorbidity Index, region, race, and net worth. CI: confidence interval.

Table 4:

Postoperative complications of matched biologic and non-biologic-exposed groups.

n (%)	Total n= 1,794	Preoperative Biologic Exposure n= 401 (22.4%)	No Biologic Exposure n= 1,393 (77.6%)	p-value
Infectious	176 (9.8)	39 (9.7)	137 (9.8)	0.095
Hernia or Wound Disruption	124 (6.9)	29 (7.2)	95 (6.8)	0.774
Thromboembolic	84 (4.7)	18 (4.5)	66 (4.7)	0.835
Cardiopulmonary	190 (10.6)	36 (9.0)	154 (11.1)	0.233
Any Complication*	383 (21.4)	77 (19.2)	306 (22.0)	0.234

Categories are not mutually exclusive; patients could have more than complication.

Table 5:

Multivariate regression results of postoperative complications in the matched cohort, by preoperative biologic exposure, preoperative steroid exposure, and operation type.

Pre-operative and Operative Characteristics	Infectious Complication		Hernia or Wound Disruption		Thromboembolic Complication		Cardiopulmonary Complication	
	aOR [95% CI]	p-value	aOR [95% CI]	p-value	aOR [95% CI]	p-value	aOR [95% CI]	p-value
No Biologic Exposure Biologic Exposure	Referent 0.9 [0.6, 1.3]	0.437	1.2 [0.7, 1.8]	0.534	0.9 [0.5, 1.5]	0.619	0.9 [0.6, 1.3]	0.482
No Steroid Exposure Steroid Exposure	Referent 0.9 [0.7, 1.3]	0.657	1.1 [0.7, 1.6]	0.708	1.4 [0.8, 2.3]	0.253	1.4 [1.0, 2.0]	0.05
Surgery Type <i>TAC with end ileostomy</i> <i>TPC with end ileostomy</i> <i>TPC with IPAA</i>	Referent 1.3 [0.8, 2.1] 2.2 [1.5, 3.0]	0.356 <0.001	0.7 [0.4, 1.3] 0.7 [0.5, 1.1]	0.247 0.169	1.0 [0.5, 2.1] 1.2 [0.7, 2.0]	0.912 0.485	0.6 [0.4, 0.9] 0.4 [0.3, 0.6]	0.03 <0.001
TAC with end ileostomy <i>No Biologic Exposure (n=754)</i> <i>Biologic Exposure (n=164)</i>	Referent 1.4 [0.7, 2.6]	0.34	1.0 [0.5, 2.0]	0.99	0.9 [0.3, 2.2]	0.76	0.6 [0.4, 1.1]	0.13
<i>No Steroid Exposure (n=418)</i> <i>Steroid Exposure (n=500)</i>	Referent 0.9 [0.5, 1.6]	0.71	0.8 [0.5, 1.5]	0.51	0.7 [0.4, 1.6]	0.43	1.1 [0.7, 1.7]	0.71
TPC with end ileostomy <i>No Biologic Exposure (n=229)</i> <i>Biologic Exposure (n=62)</i>	Referent 1.1 [0.4, 3.3]	0.88	3.0 [0.9, 10.0]	0.08	1.7 [0.4, 7.4]	0.47	2.1 [0.7, 6.2]	0.18
<i>No Steroid Exposure (n=129)</i> <i>Steroid Exposure (n=162)</i>	Referent 0.5 [0.2, 1.3]	0.16	4.1 [0.9, 18.5]	0.06	1.9 [0.4, 8.7]	0.39	1.4 [0.4, 4.1]	0.60
TPC with IPAA <i>No Biologic Exposure (n=410)</i> <i>Biologic Exposure (n=175)</i>	Referent 0.5 [0.3, 0.9]	0.03	1.2 [0.5, 2.7]	0.66	0.7 [0.3, 1.6]	0.39	0.9 [0.4, 2.1]	0.89
<i>No Steroid Exposure (n=214)</i> <i>Steroid Exposure (n=371)</i>	Referent 1.1 [0.7, 1.8]	0.72	1.1 [0.5, 2.3]	0.88	3.2 [1.1, 9.3]	0.03	4.6 [1.6, 13.0]	0.004

aOR: Odds Ratio adjusted for age, sex, Charlson Comorbidity Index, region, race and net worth. CI: confidence interval