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Research Article

Smoking is not an Independent Risk Factor for Surgery in Patients with Crohn's Disease on Biologic Therapy

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Short Title: Smoking & surgery in Crohn's Disease

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Abstract
Introduction: The development and course of inflammatory bowel disease (IBD) appears to be influenced by environmental factors. Particularly, smoking has been shown to assume a harmful role in Crohn's disease (CD) and a protective role in ulcerative colitis (UC). This study aims to examine the effect of smoking on need for surgery in patients with moderate to severe Crohn's disease (CD) receiving biologic therapy.
Methods: Retrospective study of adult patients with CD at a University Medical Center over a 20-year period.
Results: A total of 251 patients were included (mean age 36.0 ± 15.0; 70.1% males; current, former, and non-smokers: 44.2%,11.6%, and 43.8%, respectively). Mean duration on biologics was 5.0 ± 3.1 years (>2/3 received anti-TNFs, followed by ustekinumab in 25.9%) and a third of patients (29.5%) received more than one biologic. Disease-related surgeries (abdominal, perianal or both) occurred in 97 patients (38.6%): 50 patients had surgeries prior to starting biologics only, 41 had some surgeries after, and 6 had insufficient information. There was no significant difference in surgeries between ever-smokers (current or previous) vs. non-smokers in the overall study group. On logistic regression, the odds of having any CD surgery were higher in patients with longer disease duration (OR = 1.05, 95% CI = 1.01, 1.09) and in those receiving more than one biologic (OR = 2.31, 95% CI = 1.16, 4.59). However, among patients who had surgery prior to biologic therapy, smokers were more likely to have perianal surgery compared to non-smokers (OR = 10.6, 95% CI = 2.0, 57.4; p=0.006).
Conclusion: In biologic-naive CD patients requiring surgery, smoking is an independent predictor of perianal surgery. Smoking, however, is not an independent risk factor for surgery in this cohort after starting biologics. The risk of surgery in those patients is primarily associated with disease duration and the use of more than one biologic.

Introduction

Inflammatory Bowel Disease (IBD) is a life-long disease characterized by chronic inflammation of the gastrointestinal (GI) tract. It is divided into two different disease phenotypes: Crohn's disease (CD) and ulcerative colitis (UC) [1]. Despite similarities in symptomatology, these two diseases may differ in histology, location, and extent of involvement. The pathogenesis of IBD has long been studied, and the leading hypothesis posits a multifactorial model of etiology including a complex interplay between genetic susceptibility, environmental triggers, microbiota dysbiosis, and dysregulation of the immune system [1,2]. Several environmental elements seem to interact with the aforementioned factors, playing either a protective or a harmful role. Diet, for example, can be on either end of the spectrum [3]. A high-fiber diet has been shown to be inversely correlated with either CD or UC [3], while a diet high in fats has been linked with an increased risk of developing both CD and UC [2]. Furthermore, increased stress levels, a sedentary lifestyle, and decreased sleep have been associated with IBD [3]. Although all these different factors have similar patterns of association with both CD and UC, smoking has a distinct interaction with these two diseases. In specific, it has been associated with a detrimental effect on the development and course of CD [4, 5] compared to a possible beneficial effect on the progression of UC [4]. In fact, many studies have confirmed these associations. Upon examining the association between smoking and IBD in a group of 95 adults with CD and UC, it was shown that smokers with CD had more severe disease, hospitalizations, surgeries, as well as increased risk of recurrence post-surgery [6]. Further, smoking was shown to complicate the course of disease in CD patients with more frequent disease flare-up, higher rates of recurrence after surgery, and an increased chance of requiring a second surgery [5]. Interestingly, smoking cessation was shown to be beneficial in CD patients that also smoke [5]. In addition, it has been suggested that smokers have reduced response to anti-TNF therapy and may have lower concentrations of the drug in their blood when compared to non-smokers [7,12] and that smokers have higher levels of anti-TNF antibodies than non-smokers [7]. This association between smoking and clinical outcomes and response to biologic therapy has, however, been recently challenged, and several studies have shown little or no effect of smoking on disease outcomes or response to treatment in the era of biologics [13-15]. Indeed, a large multicenter study has confirmed this notion that smoking status has a limited effect on the prevalence of perianal disease and need for surgery in patients with CD [16]. It is worth noting that in the aforementioned study, the use of biologics and immunosuppressive agents was more prevalent is smokers. However, the results of this study were not replicable when the analysis was performed on a larger population by the same research group [17]. Therefore, whether, as has been suggested, the use of biologics neutralizes the detrimental effect on the natural course of CD [15], remains unanswered, mainly because of the paucity of studies that have specifically looked at the timing and type of CD-related surgeries in relationship to tobacco use (current, former, or never) and biologic exposure. This retrospective study aims to investigate the relationship between smoking and the course of disease in CD patients who received biologic therapy at a tertiary care medical center in Lebanon.

Materials and Methods

This is a retrospective study performed at the American University of Beirut Medical Center using the electronic health records system. The study was conducted after Institutional Review Board approval. Patients included were adults known to have moderate to severe Crohn's disease receiving biologic therapy for their disease. Patients who were less than 18 or did not receive any biologic therapy were excluded. Similarly, patients who were lost to follow up with insufficient data in their medical records were excluded. Demographic variables and smoking status were collected. Variables pertaining to disease characteristics as well as therapy plan and management were obtained, namely years since diagnosis, family history of IBD, current and prior biologics, use of immunomodulators, and number of hospitalizations, infusions, and surgeries if applicable. Details concerning surgeries were reviewed, including type of surgery (abdominal, perianal, or both) and their temporal relationship (before or after) to initiation of biologics.

Statistical analysis

For descriptive and inferential statistics, SPSS for windows version 25 was used (IBM, SPSS Inc. Chicago, IL, USA). Mean age, mean years since diagnosis, and mean number of hospitalizations, transfusions, and surgeries were obtained along with their standard deviations. Re-categorization of the smoking status was done to include it as a binary variable in further analysis; a group of current or previous smokers and another group of nonsmokers. For the bivariate analysis, since the analysis only included categorical variables, a chi-square analysis was performed, and for cases where chi-square analysis was not applicable, Fisher's exact test was performed. Survival curves of time until surgery between non-smokers and smokers were compared using Kaplan-Meier estimates with log-rank test over the follow-up time (follow-up start time was the year of starting biologics until last clinical follow-up). In addition, multivariable regressions models (binary logistic regression and Cox regression) were done to delineate the relation between smoking and risk of surgery and perianal surgery in our study sample.

Results

A total of 251 patients were included, and patient characteristics are shown in Table 1. More than two thirds were males (70.1%), with a mean age of 36.0 ± 15.0. Most were current or non-smokers (44.2% and 43.8% respectively), while 11.6% were former smokers. Patients receiving anti-TNF therapy (infliximab or adalimumab) constituted more than two-thirds of our population, while 25.9% of patients received ustekinumab. Around two-thirds of patients received only one biologic. A total of 97 patients (38.6%) had prior surgeries related to their disease, almost half of which had abdominal surgeries only, while the rest had perianal surgeries. When evaluating the effect of smoking on disease course, no significant difference was observed in terms of hospitalizations, transfusions, and surgeries done between the group of ever-smokers (current or previous) and the group of non-smokers (shown in Table 2). Figure 1 shows the Kaplan-Meier survival curves for CD-related surgery in the two study cohorts. However, among patients who had surgery, a significant difference was noted between ever-smokers and non-smokers in terms of the type of surgery; the former group were more likely to have perianal surgery done than the latter ($\chi 2$ (1) =5.471, p=0.019). This conclusion held true for patients who had all their surgeries performed prior to starting biologics as well, but not to those who had surgeries after ($\chi 2$ (1) =7.065, p=0.008 vs. $\chi 2$ (1) =0.210, p=0.647) (shown in Table 2).

To better understand the actual effect of smoking on surgery, multivariable regressions were done. First, the odds of having any type of surgery among the whole sample were higher in patients with longer disease duration (OR = 1.048, 95% CI = 1.007, 1.089) and in patients who received more than one biologic (OR = 2.31, 95% CI = 1.163, 4.593) (shown in Table 3). Cox regression was performed on the whole sample to check factors affecting having surgery after starting biologics while accounting for time at risk (shown in Table 4). The only significant variable was receiving more than one biologic therapy (HR = 3.589, 95%CI = 1.733, 7.429). When the regression analysis was performed on patients who underwent all their surgeries prior to starting biologic therapy, smoking was observed as a significant independent predictor for perianal surgery (OR = 10.58, 95% CI = 1.950, 57.388) (shown in Table 5). This effect of smoking was however not observed among patients who had their surgeries after starting biologic therapy (shown in table 6).

Discussion

Smoking is a known risk factor for the development of Crohn's disease and for worse clinical outcomes among patients who have the disease. Smoking has been associated with increased frequency of disease flares [1,2-4], increased need for a first- or second-time surgery [1], and earlier age at which the first surgery was required [5]. Further, several studies have shown that smoking is a risk factor for recurrence of the disease after surgery and for recurrence of fistula [6]. In one study, smokers had nearly double the chance of recurrence compared to non-smokers [7]. Therefore, in the literature, there is ample evidence regarding the deleterious effects of smoking in the general population of patients with Crohn's disease. However, to the best of our knowledge, this study is the first of its kind to assess whether the impact of smoking on Crohn's disease outcomes remains significant among a specific subset of patients with Crohn's disease, namely patients with moderate

to severe disease who receive biologic therapy. Interestingly, our study shows that among this subset of patients, there was no significant difference in the number of Crohn's-related hospitalizations, need for transfusions, and need for any Crohn's-related surgery between ever-smokers (former and current smokers) and never-smokers. This suggests that the untoward effect of smoking on disease-related outcomes in CD becomes less significant once biologics are started. The only factor that showed a significant difference between the two groups was the type of surgery, with perianal surgeries being more common among ever-smokers. Smoking status was not associated with the need for perianal surgery in the whole study cohort. However, in patients who only underwent Crohn's-related surgery prior to starting biologics, ever-smokers were significantly more likely to require perianal surgery compared to never smokers (OR = 10.577, 95% CI = 1.950, 57.388).

Our study also found that among the population of patients with Crohn's disease taking biologics, only the number of years since diagnosis, and the use of more than one biologic over the course of the disease were associated with an increased probability of undergoing any Crohn's-related surgery. In this context, we found no significant correlation between the use of anti-TNF agents and any Crohn's-related surgery (p-value= 0.129) (shown in Table 3), indicating that there was no significant difference between the use of anti-TNF versus other biologic agents when it comes to surgery-free survival. With the limited number of head-to-head randomized controlled trials comparing different biologics in Crohn's disease, meta-analyses of existing trials and real-world observational studies, such as this study, can provide some insight regarding the presence or absence of superiority between the available agents [9]. However, one factor that our study did not include in the analysis was the duration of taking the medications, which could play an important differentiating role. In fact, a recent Swedish register-based cohort study showed a significantly higher risk of surgery in patients who stopped anti-TNF therapy before 12 months when compared to those who received anti-TNF drugs for more than 12 months [10].

In addition, among the general population of our study, we found that the only factor that was significantly correlated with an increased probability for perianal surgery was requiring the use of immunomodulators, especially methotrexate. This is probably because patients with perianal disease are more likely to be treated with combination of biologic agent (especially anti-TNFs) plus an immunomodulator. These results are in-line with those of a large study that included several gastroenterology centers across Australia and New Zealand, which also found that patients who required immunosuppressive medications were significantly more likely to have perianal disease [11]. However, our study did not find a significant correlation between years since diagnosis and the risk for perianal surgery specifically, although this factor was correlated with the overall risk for any Crohn's-related surgery. This comes in contrast to previous studies that have concluded a positive correlation between younger age at diagnosis and the incidence of perianal disease [12, 18]. The difference could be due to the fact that one of these studies included pediatric patients only [12], while our study, although did not have an age restriction, had a mean age (± SD) of participants of 36.0 (± 15 years).

Our study has several limitations. These include the retrospective nature of the design and the fact that participants' information was collected from medical records, which do not always specify the chronological sequence of events. This indicates that this study was not able to stratify the factors and outcomes chronologically, so that we could not always ascertain that the measured outcomes occurred after the risk factors that they are being crossed against in the analyses. We tried to ameliorate this limitation by classifying surgeries as done before or after the initiation of biologics. Another problem arises from the fact that several patients included in the study had medical charts dating before the introduction of the electronic health records system "EPIC" at our center, which means that a significant amount of data had to be collected from hand-written charts that are inherently difficult to interpret. Finally, smoking status is included in the medical charts as a qualitative measure rather than a quantitative one, and the exact time of smoking cessation is generally not available. Accordingly, we could not specify clear cutoffs for the classification of participants as smokers, former smokers, or non-smokers as well as the number of cigarettes per day, duration of smoking history, and time since smoking cessation.

In conclusion, our study shows that smoking is a risk factor for perianal surgery in patients with CD who are naïve to biologic therapy. Smoking is, however, not a significant risk factor for surgery in CD patients receiving biologic therapy, and such therapy appears to overcome the detrimental effect of smoking on the course of CD. This notwithstanding, given the detrimental effects of smoking on health in general, all patients with CD should be encouraged to stop smoking independent of therapy.

Statement of Ethics

Study approval statement: This study was approved by the Institutional Review Board of the American University of Beirut (IRB ID: BIO-2021-0134).

Consent to participate statement: No informed consent was needed due to the retrospective nature of the study, and as approved by the Institutional Review Board of the America University of Beirut (IRB ID: BIO-2021-0134).

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Ala I. Sharara: Study idea, design and supervision; interpretation of data; review of literature; drafting of the manuscript. Guarantor of the study.

Saleem Halablab, Christian Sadaka, Hassan Slika, Ayman Alrazim, Nour Adra, Manar Shmais: data collection and analysis, review of literature; drafting of the manuscript.

Wissam Ghusn: study idea, literature review, drafting and reviewing manuscript.

Ayman Alrazim: data analysis, regulatory administration, review of the manuscript.

Data Availability Statement

All data were collected and analyzed as presented in this paper. The data is available upon request from the corresponding author to whom further enquiries regarding the data may be directed.

References

1. To N, Gracie DJ, Ford AC. Systematic review with meta-analysis: the adverse effects of tobacco smoking on the natural history of Crohn's disease. Aliment Pharmacol Ther. 2016;43:549-61.
2. Schreiner P, Neurath MF, Ng SC, El-Omar EM, Sharara AI, Kobayashi T, at al. Inflamm Intest Dis 2019 Aug;4(3):79-96
3. Breuer-Katschinski BD, Hollander N, Goebell H. Effect of cigarette smoking on the course of Crohn's disease. Eur J Gastroenterol Hepatol. 1996;8:225-8.
4. Mahid SS, Minor KS, Soto RE, Hornung CA, Galandiuk S. Smoking and inflammatory bowel disease: a meta-analysis. Mayo Clin Proc. 2006;81:1462-71.
5. Majewska K, Rusinowski C, Jabłońska B, Gołka D, Mrowiec S. Retrospective study of surgical outcomes in 60 patients with Crohn disease from a single center in Poland. Med Sci Monit. 2022;28:e934463.
6. Wood T, Truong A, Mujukian A, Zaghiyan K, Fleshner P. Increasing experience with the LIFT procedure in Crohn's disease patients with complex anal fistula. Tech Coloproctol. 2022;26:205-12.
7. Yang KM, Yu CS, Lee JL, Kim CW, Yoon YS, Park IJ, et al. Risk factors for postoperative recurrence after primary bowel resection in patients with Crohn's disease. World J Gastroenterol. 2017;23:7016-24.
8. Lee S, Kuenzig ME, Ricciuto A, Zhang Z, Shim HH, Panaccione R, et al. Smoking may reduce the effectiveness of anti-TNF therapies to induce clinical response and remission in Crohn's disease: a systematic review and meta-analysis. J Crohns Colitis. 2021;15:74-87.
9. Singh S, Murad MH, Fumery M, Sedano R, Jairath V, Panaccione R, et al. Comparative efficacy and safety of biologic therapies for moderate-to-severe Crohn's disease: a systematic review and network meta-analysis. Lancet Gastroenterol Hepatol. 2021;6:1002-14.
10. Eberhardson M, Myrelid P, Söderling JK, Ekbom A; SWIBREG Study Group, Everhov ÅH, Hedin CRH , et al. Tumour necrosis factor inhibitors in Crohn's disease and the effect on surgery rates. Colorectal Dis. 2022;24:470-83.
11. Lawrance IC, Murray K, Batman B, Gearry RB, Grafton R, Krishnaprasad K, et al. Crohn's disease and smoking: is it ever too late to quit? J Crohns Colitis. 2013;7:e665-71.
12. Brückner A, Werkstetter KJ, de Laffolie J, Wendt C, Prell C, Weidenhausen T, et al. Incidence and risk factors for perianal disease in pediatric crohn disease patients followed in CEDATA-GPGE registry. J Pediatr Gastroenterol Nutr. 2018;66:73-8.
13. Zabana Y, Garcia-Planella E, Van Domselaar M, Mañosa M, Gordillo J, López San Román A, et al. Does active smoking really influence the course of Crohn's disease? A retrospective observational study. J Crohns Colitis. 2013;7:280-5.
14. Fefferman DS, Lodhavia PJ, Alsahli M, Falchuk KR, Peppercorn MA, Shah SA, et al. Smoking and immunomodulators do not influence the response or duration of response to infliximab in Crohn's disease. Inflamm Bowel Dis. 2004;10:346-51.
15. Savarino E, Bodini G, Savarino V. Letter: biologics are effective in neutralising the detrimental effect of smoking on the natural course of Crohn's disease. Aliment Pharmacol Ther. 2016;43:1245.
16. Nunes T, Etchevers MJ, Merino O, Gallego S, García-Sánchez V, Marín-Jiménez I, et al. Does smoking influence Crohn's disease in the biologic era? The TABACROHN study. Inflamm Bowel Dis. 2013;19:23-9.
17. Nunes T, Etchevers MJ, Domènech E, García-Sánchez V, Ber Y, Peñalva M, et al. Smoking does influence disease behaviour and impacts the need for therapy in Crohn's disease in the biologic era. Aliment Pharmacol Ther. 2013;38:752-60.
18. Tan V, Thia KT, Tay WL, et al. Perianal complications in an Asian Crohn’s disease cohort. Gastroenterology. 2012;142:255-6.

Figure Legend

Fig. 1. Kaplan-Meier survival curves for CD-related surgery in the two study cohorts
Blue line: not smoker
Red line: smoker (current or previous)
Log-rank P = 0.362

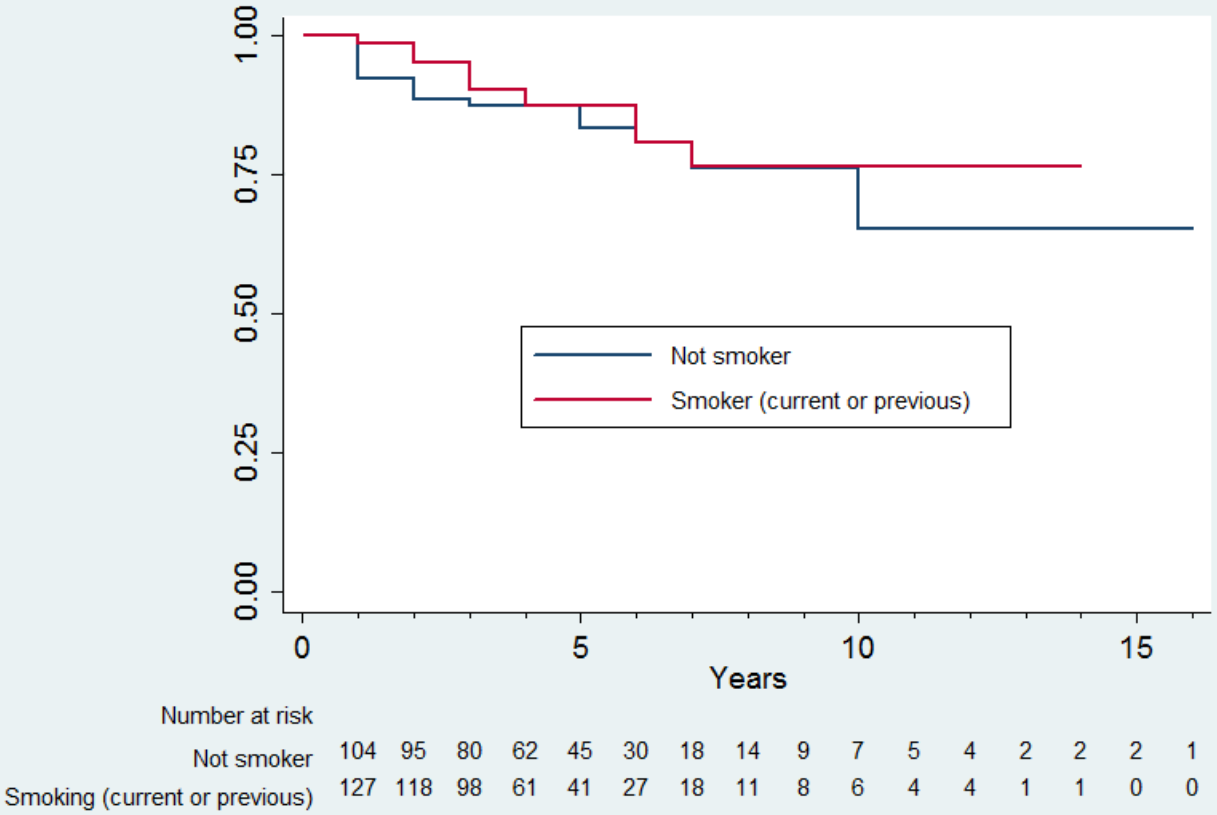

Table1. Descriptive characteristics of the patient population (N=251).

Sex	Male	176 (70.1)
	Female	75 (29.9)
Mean age		35.95 ± 14.98
Smoking status	Active smoker	111 (44.2)
	Former smoker	29 (11.6)
	Non-smoker	110 (43.8)
Mean years since diagnosis		7.80 ± 7.52
Mean years on biologics		5.03 ± 3.11
Biologics	Adalimumab	103 (41.0)
	Infliximab	73 (29.1)
	Ustekinumab	65 (25.9)
	Vedolizumab	10 (4.0)
Took only one biologic		
Number of biologics taken	Only one	170 (67.7)
	More than one	74 (29.5)
Immunomodulators	Azathioprine	64 (25.5)
	Methotrexate	36 (14.3)
Family history of IBD	No	125 (49.8)
	Yes	36 (14.3)
Hospitalizations	No	168 (66.9)
	Yes	83 (33.1)
Mean number of hospitalizations		0.76 ± 1.82
Transfusion	No	244 (97.2)
	Yes	7 (2.8)
Mean number of transfusions		0.03 ± 0.20
Surgeries	No	154 (61.4)
	Yes	97 (38.6)
Type of surgery (n=97)	Abdominal	47 (48.5)
	Perianal	38 (39.2)
	Both	12 (12.4)
Mean number of surgeries		0.64 ± 1.23
Surgery timeline with reference to biologic therapy (n=97)	All surgeries before	50 (51.5)
	Some surgeries after	41 (42.3)
	Unknown	6 (6.2)
Smoking status for patients who underwent surgery	Active smoker	41 (42.3)
	Former smoker	13 (13.4)
	Non-smoker	43 (44.3)

IBD: Inflammatory Bowel Disease

Table 2. Bivariate analysis by smoking status.

Variable		Non-smoker	Current or previous smoker	Total	P-Value
Hospitalizations	No	72 (65.5)	96 (68.6)	168 (67.2)	0.602
	Yes	38 (34.5)	44 (31.4)	82 (32.8)	
Transfusions	No	107 (97.3)	136 (97.1)	243 (97.2)	0.631[a]
	Yes	3 (2.7)	4 (2.9)	7 (2.8)	
Surgeries	No	67 (60.9)	86 (61.4)	152 (61.2)	0.933
	Yes	43 (39.1)	54 (38.6)	99 (38.8)	
Type of surgery	Abdominal	26 (60.5)	21 (38.9)	47 (48.5)	**0.004**
	Perianal	9 (20.9)	29 (53.7)	38 (39.2)	
	Both	8 (18.6)	4 (7.4)	12 (12.4)	
Any perianal surgery among patients who had surgery (n=97)	No	27 (62.8)	21 (38.9)	48 (49.5)	0.019
	Yes	16 (37.2)	33 (61.1)	49 (50.5)	
Any perianal surgery in patients with all surgeries before biologics (n=50)	No	15 (75.0)	11 (36.7)	26 (52.0)	0.008
	Yes	5 (25.0)	19 (63.3)	24 (48.0)	
Any perianal surgery in patients with surgeries after biologics (n=41)	No	12 (54.5)	9 (47.4)	21 (51.2)	0.647
	Yes	10 (45.5)	10 (52.6)	20 (48.8)	
Surgery done after starting biologics	No	87 (79.8)	116 (85.9)	203 (83.2)	0.204
	Yes	22 (20.2)	19 (14.1)	41 (16.8)	
History of surgery prior to biologics	No	86 (78.9)	101 (74.8)	187 (76.6)	0.453
	Yes	23 (21.1)	34 (25.2)	57 (23.4)	

[a]*Using Fisher's exact test*

Table 3. Binary logistic regression for odds of surgery.

Variables		Adj. OR (95% CI)		P-value
Sex	Male	1		
	Female	0.697	(0.380, 1.279)	0.244
Age	<30 years			
	>30 years	1.259	(0.710, 2.233)	0.431
Years since diagnosis		1.048	(1.007, 1.089)	**0.020**
Smoking status	Non-smoker			
	Current or previous	0.896	(0.513, 1.564)	0.699
Use of biologics	Only one biologic			
	>1 biologic	2.311	(1.163, 4.593)	**0.017**
Use of anti-TNF	Yes			
	No	0.567	(0.273, 1.179)	0.129
Immunomodulators	None			
	Azathioprine	1.731	(0.906, 3.306)	0.097
	Methotrexate	1.403	(0.631, 3.119)	0.406

TNF: tumor necrosis factor; OR: odds ratio

Table 4. Multivariable Cox Regression analysis of factors associated with requiring any surgery after starting biologics among all patients.

Variables		HR (95% CI)		P-value
Sex	Male	1		
	Female	0.831	(0.406, 1.704)	0.614
Age	<30 years	1		
	>30 years	1.094	(0.55, 2.174)	0.798
Years since diagnosis		1.022	(0.974, 1.072)	0.379
Smoking status	Not smoker	1		
	Current or previous	0.645	(0.33, 1.261)	0.2
Use of biologics	Only one biologic	1		
	>1 biologic	3.589	(1.733, 7.429)	**0.001**
Use of anti-TNF	Yes	1		
	No	0.501	(0.22, 1.143)	0.1
Immunomodulators	None	1		0.273
	AZA	1.700	(0.832, 3.473)	0.145
	MTX	0.879	(0.282, 2.735)	0.824
History of surgery prior to biologics	No	1		
	Yes	0.714	(0.308, 1.657)	0.433

TNF: tumor necrosis factor; AZA: azathioprine; MTX: methotrexate; HR: hazard ratio

Table 5. Binary logistic regression: odds for any perianal surgery among patients who underwent all surgeries before starting biologics.

Variables		Adj. OR (95% CI)		P-value
Sex	Male	1		
	Female	1.492	(0.225, 9.907)	0.679
Age	<30 years	1		
	>30 years	1.330	(0.247, 7.162)	0.740
Years since diagnosis		0.928	(0.792, 1.087)	0.353
Smoking status	Not smoker	1		
	Current or previous	10.577	(1.950, 57.388)	**0.006**
Use of biologics	Only one biologic	1		
	More than one	0.969	(0.110, 8.508)	0.977
Use of Anti-TNF	Yes	1		
	No	0.115	(0.013, 1.019)	0.052
Immunomodulators	None	1		
	AZA	1.646	(0.274, 9.907)	0.586
	MTX	13.902	(1.217, 158.779)	**0.034**

TNF: tumor necrosis factor; AZA: azathioprine; MTX: methotrexate; OR: odds ratio

Table 6. Multivariable Cox Regression analysis of factors associated with perianal surgery after starting biologics among all patients.

Variables		HR (95% CI)		P-value
Sex	Male	1		
	Female	0.677	(0.218, 2.102)	0.500
Age	<30 years	1		
	>30 years	0.646	(0.238, 1.759)	0.393
Years since diagnosis		1.037	(0.975, 1.102)	0.252
Smoking status	Not smoker	1		
	Current or previous	0.671	(0.256, 1.76)	0.417
Use of biologics	Only one biologic	1		
	>1 biologic	2.342	(0.809, 6.781)	0.117
Use of anti-TNF	Yes	1		
	No	0.528	(0.153, 1.819)	0.311
Immunomodulators	None	1		
	AZA	1.073	(0.372, 3.091)	0.896
	MTX	0.544	(0.109, 2.723)	0.458
History of perianal surgery prior to biologics	No	1		
	Yes	3.035	(0.886, 10.394)	0.077

TNF: tumor necrosis factor