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## **Incidence of and risk factors for colorectal strictures in ulcerative colitis: a multicenter study**

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PAL, LG and SS wrote the article. LPB conceived the study. FD, PN, SD, CB, AL, ICU, SS, and LPB critically revised the manuscript. All authors approved the final version of the manuscript.

### **Conflict of interest**

PA Laurain declares no conflict of interest. L Guillo declares no conflict of interest. F D'Amico declares no conflict of interest. P Netter declares no conflict of interest. S Danese has served as a speaker, consultant and advisory board member for Schering- Plough, AbbVie, MSD, UCB Pharma, Ferring, Cellerix, Millenium Takeda, Nycomed, Pharmacosmos, Actelion, Alphawasserman, Genentech, Grunenthal, Pfizer, Astra Zeneca, Novo Nordisk, Cosmo Pharmaceuticals, Vifor and Johnson & Johnson, Nikkiso Europe GMBH, Theravance. C Baumann declares no conflict of interest. A Luc declares no conflict of interest. I Clerc-Urmes declares no conflict of interest. S Spyros declares no conflict of interest. L Peyrin-Biroulet has served as a speaker, consultant and advisory board member for Merck, Abbvie, Janssen, Genentech, Mitsubishi, Ferring, Norgine, Tillots, Vifor, Hospira/Pfizer, Celltrion, Takeda, Biogaran, Boehringer-Ingelheim, Lilly, HAC- Pharma, Index Pharmaceuticals, Amgen, Sandoz, Forward Pharma GmbH, Celgene, Biogen, Lycera, Samsung Bioepis, Theravance.

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## **Abstract (255 words)**

**Background and aims:** Ulcerative colitis (UC) is increasingly recognized as a progressive disease and patients with long-standing disease can develop colorectal stricture. Few data about its incidence in UC are available, while risk factors for colorectal strictures in UC remain to be determined. We assessed the incidence of and risk factors for developing colorectal strictures in a large UC population.

**Methods:** All adult patients followed at Nancy University hospital and at the centre hospitalier de Luxembourg for UC, between January 2004 and July 2019, were eligible for inclusion in this multicenter retrospective cohort study.

**Results:** A total of 439 patients with UC were included. Median follow-up duration was 9.6 years. Incidence of colorectal stricture was 3.6%. The cumulative probability of developing this complication was 1% at 5 years and 2.3% at 10 years. Median age at stricture diagnosis was 47.9 years [41.0; 63.0], and median time from UC diagnosis to onset of stricture was 11.5 years [5; 15.3]. Montreal A3 classification (age > 40 years) ( $p=0.008$ ) and steroids use (HR=4.1, CI 95% 1.1-16.1) were independent risk factors for stricture, whereas 5-ASA-treated patients carried a lower risk (HR=0.3, CI 95% 0.1-0.9). Dysplasia was found in 6 patients with strictures (42.9%) and among them 5 developed a colorectal cancer (33.3%).

**Conclusion:** Patients with Montreal A3 classification have a higher risk for strictures, while use of steroids and 5-ASA are predictive factors for this complication by increasing and reducing the risk, respectively. These factors should be assessed in daily clinical practice to prevent stricture occurrence in these patients.

**Keywords:** Inflammatory bowel disease, ulcerative colitis, stricture, risk factors

## **What You Need to Know**

### **Background**

Ulcerative colitis is a progressive disease and patients with long-standing disease can develop colorectal strictures.

### **Findings**

Patients with Montreal A3 classification have a higher risk for strictures, while use of steroids and 5-ASA are predictive factors for this complication.

### **Implications for patient care**

Physicians should assess and pay attention to these factors in daily practice in order to prevent stricture occurrence in these patients.

## **Introduction**

Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) (1). It is characterized by a mucosal inflammation, which starts in the rectum and can extend to proximal segments of the colon, (1) and it is increasingly recognized as a progressive disease (2–4). UC shares several similarities with Crohn's disease (CD) in terms of disease complications, postoperative complications, economic burden, and disability with a significant impact on patients' lives (4). As for CD, UC can also lead to cumulative bowel damage due to recurrent inflammatory events (3,4). On the other hand, UC has a dynamic natural history with disease extension changing over time (1,2,5). In long-standing disease, patients can develop structural and functional complications such as colonic dysmotility, giant pseudopolyposis, impaired permeability, anorectal incontinence, and colorectal strictures (2,4). Thus, it is imperative to assess destructive and progressive UC nature in order to act at an early stage of disease and to prevent any complications (2,4).

The stricture is a narrowing of the gut lumen and is considered clinically relevant when it leads to intestinal blockage and upstream dilation (6). The colorectal stricture is a challenging condition to treat and it is a topic of particular relevance as dysplasia or cancer can be detected in patients with strictures (7,8). Indeed, in a multicenter retrospective study including 12,013 IBD patients undergoing surgery for colonic strictures, dysplasia or cancer were found in 2.4% of CD cases and up to 10% of UC patients (9). Although it is a well-described complication, its physiopathology remains unclear (10). It is likely that repeated cycles of damage and healing of the bowel wall due to chronic inflammation lead to gut fibrosis under regulation of cytokines and growth factors (11–13). In addition, muscular hypertrophy and thickening of the muscularis mucosae could also play a role in stricture occurrence (2,10). A better understanding of natural history of this complication may allow us to support the need for an earlier and more aggressive treatment strategy (2). Surprisingly, there are only a few single-center retrospective cohort studies addressing this issue (14–18).

To date, risk factors for strictures in UC patients are unknown. In addition, most studies on this topic have been published for several decades: two in 1960s (16,18), two in the 1990s (15,17), and one in 2011 (14).

We assessed the incidence of and risk factors for developing colorectal strictures in UC patients in a large multicenter cohort study.

## **Methods**

### *Study design and study population*

This multicenter retrospective cohort study included all adult patients (age  $\geq 18$  years) with confirmed diagnosis of UC followed at the Nancy University hospital and at the Centre hospitalier de Luxembourg between January 2004 and July 2019. Patients who underwent at least one colonoscopy and two follow-up visits were eligible for inclusion. Exclusion criteria were a confirmed diagnosis of CD and patients with unclassified colitis. The UC diagnosis was based on the combination of clinical symptoms and endoscopic, radiologic, and histological criteria according to the European Crohn's and Colitis Organization (ECCO) guidelines (19). A stricture was defined as a localized and persistent narrowing of the colorectal lumen based on endoscopy, excluding obvious polypoid lesions and anastomotic strictures (1,12,13,18). Strictures were distinguished in benign or malignant on the basis of histopathologic reports of endoscopic biopsies or surgery. This study was approved by the local ethical committees (Commission Nationale de l'Informatique et des Libertés, number 1,404,720 for Nancy, and Comité national d'éthique de recherche number 202001/02 for Luxembourg) and was conducted according to local regulations.

### *Data collection*

Three investigators (PAL, SS, and LG) reviewed patients' medical records collecting the following data for each patient: date of birth, date of UC diagnosis, age at diagnosis



according to the Montreal classification (20), family history of IBD, smoking status (non-smoker, former smoker, or active smoker), history of stricture, history of appendectomy and colectomy, disease extent with the cumulative Montreal classification (20), previous IBD medical treatments prior to the stricture diagnosis or the end of follow-up for patients without stricture (including start and end date of therapy), date of the last follow-up. Moreover, the following characteristics were recorded when strictures were identified: date of diagnosis, location, length, surmountable by endoscopy, need for colectomy, and association with dysplasia or colorectal cancer.

### *Statistical Analysis*

Categorical variables were described by numbers and percentages, while continuous variables by median and interquartile range [Q1; Q3]. Patients' characteristics were compared between the two involved centers using Chi square and Fisher's test as appropriate. Survival curves were built using the Kaplan-Meier method. Bivariable and multivariable Cox proportional hazards models were performed to identify predictive factors for colorectal strictures in UC. Variables with a p-value < 0.2 in the bivariable Cox model were eligible for the multivariable model. A stepwise selection procedure was applied to retain significant factors. The significant threshold was fixed at 5%. All analyses were performed using SAS® software version 9.4 (SAS Institute, Cary, NC, USA).

## **Results**

### *Patients' characteristics*

After careful review of medical records, a total of 439 patients with UC were included (Table 1). Among them, 232 were women (52.8%) and the median age at UC diagnosis was 31 years [Q1=23; Q3=43]. Based on the Montreal classification, 27 patients (6.2%) were diagnosed before 17 years (A1), 274 patients (62.4%) between 17 and 40 years (A2), and 138

patients (31.4%) after 40 years (A3). Most patients had a pancolitis (E3) (225, 51.3%), while proctitis (E1) and left-sided colitis (E2) were diagnosed in a lower percentage of cases (65, 14.8% and 149, 33.9%, respectively). The median follow-up duration was 9.6 years [5.2; 15.1]. History of tobacco use was found in 135 patients (30.8%), while 45 subjects (10.3%) were active smokers at last news. Only a few patients underwent appendectomy (25/270, 10.7%) or had a family history of IBD (29/439, 6.6%). The most commonly administered drugs were 5-aminosalicylic acid (5-ASA) (403/439, 91.8%), steroids (283/439, 64.5%), anti-tumor necrosis factor  $\alpha$  agents (TNF $\alpha$ ) (247/439, 56.3%), immunosuppressant agents (thiopurine and methotrexate) (113/249, 25.7%), and vedolizumab (91/439, 20.7%). Finally, the colectomy rate in our series was 14.1% (62/439).

#### *Incidence and characteristics of colorectal strictures*

Colorectal strictures were detected in 16 patients in our cohort (3.6%). Characteristics of patients with strictures are summarized in Table 2. Half of the patients were women (8, 50%). Median age at UC diagnosis was 41 years [23.7; 53.0], while median age at stricture diagnosis was 47.9 years [41.0; 65.0]. The median time from UC diagnosis to stricture onset was 11.5 years [5; 15.3] with a median follow-up duration of 11.8 years [5.3; 15.8]. Most patients were over 40 years old (9/16, 56.3%), while subjects aged 17 to 40 (6/16, 37.5%) or younger than 17 (1/16, 6.2 %) were found in a smaller percentage of cases. More than half of subjects had an extensive disease (9/16, 56.3%), while left-sided UC (6/16, 37.5%) and proctitis (1/16, 6.2 %) were less frequent. Two patients (12.5%) were active smokers and 7 were former smokers (43.8%). No subject had family history of IBD and none underwent appendectomy. Regarding treatment, 13 patients were treated with steroids (81.3%), 12 received 5-ASA (75%), 10 anti-TNF agents (62.5%) 4 immunosuppressants (25%), and 4 vedolizumab (25%) prior to the stricture diagnosis. 8 strictures (50%) were surmountable by the endoscope. The most frequent stricture location was the left colon (7, 43.8%), followed by

rectum (5, 31.2%) and right colon (4, 25%). The median length of the strictures was 25 mm [10; 50] and the strictures were surmountable by the endoscope in 50% of cases. Dysplasia was found in 6 patients (42.9 %) and among them 5 developed a colorectal cancer (83.3%). Finally, the colectomy rate in patients with strictures was 75% (12/16). The Kaplan-Meier curve of survival estimate is provided in Figure 1. The probability of developing colorectal strictures was 1% at 5 years and 2.3% at 10 years, respectively.

### *Risk factors for colorectal strictures*

In the bivariate analysis (*Table 3*), the Montreal A3 classification was associated with a higher risk of strictures ( $p=0.0104$ ) compared to Montreal A2 and A1. In addition, patients with a previous exposure to steroids had a higher risk of strictures compared to non-users ( $HR=2.51$ , CI 95% 0.71-8.82). Conversely, 5-ASA users had a lower risk of strictures than non-users ( $HR=0.30$ , CI 95% 0.10-0.93). No significant association was found between strictures and smoking status, family history of IBD, appendectomy, disease extension, and previous exposure to anti-TNF agents, immunosuppressants, or vedolizumab. Of note, no significant correlation was found between age at diagnosis, exposure to 5-ASA, and steroids (*Supplementary Table 1*). In the multivariate analysis, the Montreal A3 classification ( $p=0.008$ ) and use of steroids ( $HR=4.1$ , CI 95% 1.1-16.1;  $p=0.042$ ) were found to be independent risk factors for strictures, while 5-ASA treatment was associated with a lower risk for stricture occurrence ( $HR=0.3$ , CI 95% 0.1-0.9;  $p=0.029$ ) (*Table 4*).

## **Discussion**

Strictures are challenging complications occurring in UC patients with long-standing disease (2,4,14). We investigated data from 439 patients with UC followed at the Nancy University hospital and at the Centre hospitalier de Luxembourg to identify any risk factors for colorectal strictures. Strictures were found in 16 patients accounting for an incidence rate

of 3.6% during a follow-up period of about ten years. Importantly, two single-center cohort studies published in 1960s found an incidence of 6.3% (18) and 11.2% (16). On the other hand, single-center cohort studies, published in 1990s and 2011, showed incidence rates of 1.5% (14), 3.2% (17), and 5%, respectively (15). Our findings are in line with the most recent data, suggesting a decrease in the stricture incidence over time. This downward trend could be explained with the development of new effective biological drugs and ambitious therapeutic strategies (e.g. top-down strategy) based on early treatment of patients(4). However, our work did not succeed to find a significant association with the use of biologics and the reduction of stricture occurrence. Recently, a multicenter cohort study by Xu et al. (7) reported a higher percentage of stenosis in UC patients (14.2%). However, this has some limitations. Only 246 patients were included, which is substantially lower compared to other studies addressing this topic (from 465 to 1156) (14–18) and surprisingly low for such study period (1986 to 2018), especially in Asia. Moreover, patients were referred from several centers, but they were all treated at the same center. Finally, all included patients underwent medical treatment or surgery, meaning that patients referred to their center for colectomy were included, which is a major bias likely explaining this high percentage of stricture. The different results between studies could be explained by the operator-dependent heterogeneity of the stricture definition. In fact, stricture is generally defined as a localized and persistent narrowing of the gut lumen(1,12,13,18), but this narrowing is a subjective criterion and is based on physician's opinion. Moreover, no validated approach is available to identify strictures. Regarding dysplasia and colorectal cancer, we found rates of 42.9% and 33.3% in patients with strictures, respectively. These data were significantly higher compared to previous literature data. A single-center study by Gumaste et al. reported a lower rate of malignancy in UC patients with strictures (24%) (15). Similarly, a recent multicenter study confirmed that cancer was diagnosed in one quarter of UC patients with strictures (25.7%) (7). In another retrospective study including IBD patients undergoing surgery for colonic strictures, dysplasia

and cancer were both detected in 10% of UC patients (9). Disease duration and presence of stenosis are proven risk factors for the development of colorectal neoplasia in UC patients. However, it is not yet well defined whether there is a direct proportionality between type of stenosis (stratified according to length and upstream dilation) or disease duration and risk of neoplasia(21). It is reasonable to hypothesize that a long-lasting disease is associated with a greater exposure to an inflammatory stimulus, thus resulting in a greater potential of developing malignancy. The association between long-standing disease and risk for colorectal stricture has been supported in several studies (2,4,7,14). The median time from UC diagnosis to stricture onset was 11.5 years [5; 15.3] in our cohort, while previous studies reported a median time of stricture onset ranging from 13.3 years (17), to 15.6 years (14). Of note, no study investigated the association between age at diagnosis and stricture occurrence. We report for the first time that the Montreal A3 classification is associated with a higher risk of colorectal stricture compared to Montreal A2 and A1 ( $p=0.008$ ). This finding could be due to current IBD management strategies, which generally involve more aggressive behavior in younger patients. Young patients have less comorbidities and are more frequently treated with biologics, combination with immunosuppressant agents, and surgery as rescue therapy(22). In addition, in the past decades, treatment paradigms have shifted from a conventional "step-up" approach to a "top-down" early intervention (23,24). The target of this new strategy is to stop chronic inflammation which leads to bowel damage. It has also been suggested that inflammatory strictures can be reversible after optimal medical treatment (10,12). Interestingly, a case report showed that a rectal stricture returned to normal after starting treatment, supporting the early biological therapy introduction (25). To date, there is no validated tool to quantitative assess the strictures in UC population (2,4). Conversely, a score called Lémann index(26) has been validated in CD patients to evaluate bowel damage. It is desirable that also in the UC setting, a tool is soon developed to characterize stenosis and predict the risk of disease progression. UC patients are exposed to a higher risk of surgery.

The colectomy rate in our cohort was of 14.1%, which is in line with literature data. Indeed, a recent systematic review showed that the 5- and 10-year cumulative risk of colectomy was about 10-15% (5). Similarly, a 5-years follow-up population-based European study including 717 UC patients, reported that 6% of patients underwent colectomy (27). Finally, a systematic review revealed that patients with pancolitis at diagnosis had a 10-year cumulative colectomy rate of 19% (28). Interestingly, three quarters of patients with strictures underwent colectomy in our study, highlighting the increased need for surgery in this condition. This is likely due to the high proportion of subjects with dysplasia and colorectal cancer in our cohort since surgery is the main therapeutic option in this situation. Furthermore, steroid use was associated with a higher risk for stricture (HR=4.1, CI 95% 1.1-16.1; p=0.042), while patients treated with 5-ASA had a lower risk for stricture occurrence (HR=0.3, CI 95% 0.1-0.9; p=0.029). Therapeutic management in UC is based on severity, extent, and pattern of disease (20). Systemic steroids are recommended in patients with moderate to severe disease or acute severe UC (19). Conversely, 5-ASA is recommended in mild to moderate disease (19). For this reason, it is likely that treatment with steroids or 5-ASA is not a risk factor for colorectal strictures, but rather represent a predictor of disease severity. To the best of our knowledge, this study showed for the first time an increased risk for colorectal stricture in Montreal A3 patients. Other relevant strengths of our work were the multicenter design, the large sample size, and the long follow-up duration. On the other hand, there were also some limitations including the retrospective study design and the lack of assessment disease activity and severity. In addition, our sample size may have limited the ability to highlight other factors.

In conclusion, an incidence rate of stricture of 3.6% was found in our cohort. The cumulative probability of developing this complication was 1% at 5 years and 2.3% at 10 years. Montreal A3 classification was identified as an independent risk factor for colorectal strictures in UC. The use of steroids and 5-ASA were predictive factors for this complication by increasing and reducing the risk, respectively. Physicians should pay attention to these

factors in daily practice in order to ensure the best therapeutic approach. Further studies are needed to evaluate whether treatment with biologics is associated with a lower risk for strictures and whether an earlier intervention may prevent or reverse this complication.

**Table 1: Patients characteristics**

	N	%/median	Q1	Q3
<b>Gender</b>				
Female	232	52.8%		
<b>Median age at UC diagnosis (years)</b>	439	31	23	43
<b>Montreal A</b>				
A1: ≤16 years	27	6.2%		
A2: 17-39 years	274	62.4%		
A3: ≥40 years	138	31.4%		
<b>Montreal E</b>				
E1 (proctitis)	65	14.8%		
E2 (left-sided colitis)	149	33.9%		
E3 (pancolitis)	225	51.3%		
<b>Median follow-up (years)</b>	439	9.6	5.2	15.1
<b>Smoking</b>				
Active smoker	45	10.3%		
Former smoker	90	20.5%		
Non-smoker	304	69.2%		
<b>Family history of IBD</b>	29	6.6%		
<b>Appendectomy</b>	25	10.7%		
<b>Colectomy</b>	62	14.1%		
<b>IBD treatments</b>				
5-ASA	403	91.8%		
Steroids	283	64.5%		
Immunosuppressant (thiopurine, methotrexate)	113	25.7%		
Anti-TNF	247	56.3%		
VDZ	91	20.7%		

Anti-TNF, anti-tumor necrosis factor; IBD, inflammatory bowel disease; N, number; Q, quartile; VDZ, vedolizumab; 5-ASA, 5-aminosalicylic acid;



**Table 2: Patients with stricture characteristics**

	N	%/median	Q1	Q3
<b>Gender</b>				
Female	8	50		
<b>Median age at UC diagnosis (years)</b>	16	41	23.7	53.0
<b>Montreal A</b>				
A1: ≤16 years	1	6.3%		
A2: 17-39 years	6	37.5%		
A3: ≥40 years	9	56.3%		
<b>Montreal E</b>				
E1 (proctitis)	1	6.2%		
E2 (left-sided colitis)	6	37.5%		
E3 (pancolitis)	9	56.3%		
<b>Median Follow-up (years)</b>	16	11.8	5.3	15.8
<b>Smoking</b>				
Active smoker	2	12.5%		
Former smoker	5	31.3%		
Non-smoker	9	56.3%		
<b>Family history of IBD</b>	0	0%		
<b>Appendectomy</b>	0	0%		
<b>Colectomy</b>	12	75%		
<b>IBD treatments</b>				
5-ASA	12	75%		
Steroids	13	81.3%		
Immunosuppressant	4	25%		
Anti-TNF	10	62.5%		
VDZ	4	25%		
<b>Median age at stricture diagnosis (years)</b>	16	47.9	41.0	65.0
<b>Median duration onset of stricture (years)</b>	16	11.5	5	15.3
<b>Location of stricture</b>				
Rectum	5	31.2%		
Left colon	7	43.8%		
Right colon	4	25%		
<b>Stricture length (mm)</b>	16	25	10	50
<b>Associated with dysplasia</b>	6	42.9%		
<b>Associated with colorectal cancer</b>	5	33.3%		

Anti-TNF, anti-tumor necrosis factor; IBD, inflammatory bowel disease; N, number; Q, quartile; VDZ, vedolizumab; 5-ASA, 5-aminosalicylic acid;

**Table 3: Factors associated with stricture occurrence (bivariate analysis)**

	<b>Total population (N)</b>	<b>Stricture n (%)</b>	<b>Hazard ratio</b>	<b>CI 95%</b>	<b>p-value</b>
<b>Total n of patients</b>	439	16 (3.6%)			
<b>Gender</b>					0.908
Male	207	8 (3.9%)	1		
Female	232	8 (3.4%)	0.9	(0.4 - 2.5)	
<b>Montreal A</b>					0.010
A3: ≥40 years	27	9 (6.5%)	1		
A2: 17-39 years	138	6 (2.2%)	0.2	(0.1 - 0.6)	
A1: ≤16 years	274	1 (3.7%)	0.3	(0.1 - 2.4)	
<b>Montreal E</b>					0.643
E1 (proctitis)	65	1 (1.5%)	1		
E2 (left-sided colitis)	149	6 (4%)	2.8	(0.3 - 22.9)	
E3 (pancolitis)	225	9 (4%)	2.5	(0.3 - 19.7)	
<b>Smoking</b>					0.491
Non-smoker	304	9 (3%)	1		
Former smoker	90	5 (5.6%)	1.9	(0.6 - 5.8)	
Active smoker	45	2 (4.4%)	1.5	(0.3 - 7.0)	
<b>Family history of IBD</b>					0.996
No	241	5 (2.1%)	1		
Yes	29	0 (0%)	0	0	
<b>Appendectomy</b>					0.993
No	414	16 (3.9%)	1		
Yes	25	0 (0%)	0	0	
<b>IBD treatments</b>					
<b>5-ASA</b>					0.037
No	36	4 (11.1%)	1		
Yes	403	12 (3%)	0.3	(0.1 - 0.9)	
<b>Steroids</b>					0.152
No	156	3 (1.9%)	1		
Yes	283	13 (4.6%)	2.5	(0.7 - 8.8)	
<b>Immunosuppressant</b>					0.644
No	326	12 (3.7%)	1		
Yes	113	4 (3.5%)	0.8	(0.3 - 2.4)	
<b>Anti-TNF</b>					0.228
No	192	6 (3.1%)	1		
Yes	247	10 (4.1%)	1.9	(0.7 - 5.5)	
<b>VDZ</b>					0.289
No	348	12 (3.5%)	1		
Yes	91	4 (4.4%)	1.9	(0.6 - 5.9)	

Anti-TNF, anti-tumor necrosis factor; CI, confidence interval; IBD, inflammatory bowel disease; N, number; VDZ, vedolizumab; 5-ASA, 5-aminosalicylic acid

**Table 4: Factors associated with stricture occurrence (multivariate analysis)**

	<b>Total population (N)</b>	<b>Stricture n (%)</b>	<b>Hazard ratio</b>	<b>CI 95%</b>	<b>p-value</b>
<b>Total n of patients</b>	439	16 (3.6%)			
<b>Montreal A</b>					
A3: $\geq 40$ years	138	9 (6.5%)	1		
A2: 17-39 years	274	6 (2.2%)	0.2	(0.1 - 0.6)	0.008
A1: $\leq 16$ years	27	1 (3.7%)	0.1	(0.1 - 1.5)	
<b>IBD treatments</b>					
<b>5-ASA</b>					
No	36	4 (11%)	1		0.029
Yes	403	12 (3%)	0.3	(0.1 - 0.9)	
<b>Steroids</b>					
No	156	3 (1.9%)	1		0.042
Yes	283	13 (4.6%)	4.1	(1.1 - 16.1)	

Anti-TNF, anti-tumor necrosis factor; CI, confidence interval; IBD, inflammatory bowel disease; N, number; VDZ, vedolizumab; 5-ASA, 5-aminosalicylic acid

## Figures legends

**Figure 1: The Kaplan-Meier curve of estimate survival**

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