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Impact of co-existent celiac disease on phenotype and natural history of Inflammatory Bowel Diseases

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Abstract

Introduction—Inflammatory bowel disease (IBD) and celiac disease are the two most common immune-mediated gastrointestinal diseases. There is limited knowledge regarding the course of IBD in those with co-existing celiac disease. We conducted this study to determine whether patients with co-existing celiac disease present a unique phenotype of IBD and to examine the

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frequency of co-occurrence of celiac disease and IBD in comparison to other autoimmune disorders.

Methods—This was a case-control study performed at two tertiary referral centers. Cases comprised of patients with known diagnoses of celiac disease and IBD. Two random IBD controls without celiac disease were selected for each case after matching for IBD type. Disease phenotype and natural history for both CD and UC were noted from medical record review, and were compared between IBD patients with and without celiac disease.

Results—We identified a total of 51 patients with IBD [22 ulcerative colitis (UC), 1 indeterminate colitis, 28 Crohn's disease (CD)] and celiac disease. There was no significant difference in the age, gender, or ethnicity between celiac-IBD and controls. Pancolitis was more common in celiac-UC patients as compared to controls (odds ratio 3.30, 95% confidence interval 1.05–21.50). There was also a trend towards increased use of immunomodulators among celiac-UC patients than in non-celiac UC controls (OR 2.83, CI 95% 0.95 – 8.48). No phenotypic differences were found in celiac-CD patients. There were no significant differences in IBD-related medication usage, hospitalizations, or surgeries.

Conclusion—Patients with UC and celiac disease were more likely to have pancolitis and had a trend towards greater use of immunomodulators. Co-existing celiac disease did not influence natural history of CD.

Keywords

celiac disease; Crohn's disease; ulcerative colitis; sprue

INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease (CD) are the two predominant forms of inflammatory bowel diseases (IBD). They often have their onset during young adulthood and have a relapsing-remitting course, requiring the use of immunomodulator or biological therapies, hospitalizations and surgery^{1, 2}. However, there is significant heterogeneity in the natural history with some patients having mild disease, but others developing early penetrating complications, requiring multiple hospitalizations and surgeries^{1, 2}. There is growing interest in identifying subgroups of IBD patients at higher risk of adverse outcomes. Clinical markers of aggressive disease include younger age of onset, need for steroids at diagnosis and perianal disease³. In addition, genetics and serologic markers have shown promise in similarly predicting aggressive disease^{4–7}. For example, variants in the NOD2 alleles predict fibrostenotic small bowel CD and the need for early surgery in such patients⁴. Antibodies directed against luminal microbial antigens have also shown significant potential in predicting aggressive disease^{5, 6}. Patients with higher titers of antimicrobial antibodies (ASCA, OmpC, CBir1) have a greater likelihood of small bowel disease, penetrating complications, and need for surgery in CD^{8, 9}.

Celiac disease is an autoimmune response to the protein fractions of gluten and affects up to 1% of the North American population^{10–13}. Its manifestations can be protean and often resemble IBD including symptoms of abdominal pain, diarrhea, and associated iron deficiency anemia^{14, 15}. While the genetic basis of IBD is still incompletely understood, there is considerable overlap in genetic risk loci between CD and celiac disease. For example, *PTPN2*, *IL18RAP*, *TAGAP*, and *PUS10* have all demonstrated genome-wide association with both CD and celiac disease¹⁶. The only studies examining co-occurrence of the two are limited to case-reports or small case-series describing the outcomes of patients with co-existing celiac disease and IBD^{17–28}. Whether the shared genetic risk between both diseases predisposes to a more aggressive phenotype of IBD has not been examined

previously. Also, whether the association between antibodies to luminal microbial antigens and severe disease also extends to antibodies against luminal dietary antigens (i.e. gluten) has also not been studied previously.

Consequently, we performed this study with the following objectives: 1) to explore whether patients with both celiac disease and IBD represent a distinct disease phenotype; 2) to examine the prevalence of celiac disease in IBD patients, and IBD in those with celiac disease; and 3) to compare the frequency of occurrence of celiac disease among various autoimmune diseases.

METHODS

Study Population

This was a retrospective study including patients from two tertiary referral hospitals – Massachusetts General Hospital (MGH) and Brigham and Women's Hospital (BWH) – which serve over 3 million patients in the Greater Boston area. Both hospitals also serve a large number of patients from neighboring states in the Northeastern United States. We adopted a case-control design. Potential cases and controls were identified through a query of the Partners Healthcare Research Practice Data Registry (RPDR), an electronic database of all patients seen at MGH, BWH, and affiliated institutions within the Partners Healthcare system. The RPDR is a centralized clinical data repository and query system initiated in 1996. It is automatically and continuously populated with patient data from a variety of data sources including billing, encounter scheduling, medications, laboratory, radiology, endoscopy, and surgery databases. For diseases and procedures, encounters have been coded with International Classification of Diseases, 9th edition (ICD-9-CM) codes since the inception of RPDR. The case population comprised of all patients with a confirmed diagnosis of IBD [ulcerative colitis (UC) or Crohn's disease (CD)] who also had been diagnosed with celiac disease. This was performed by first performing broad searches using ICD-9-CM codes for CD (ICD-9-CM 555.x) or UC (ICD-9-CM 556.x) in combination with a diagnosis code for celiac disease (ICD-9-CM 579.0) or abnormal celiac serology testing (anti-tissue transglutaminase IgG or IgA, anti-endomysial antibody, or anti-gliadin antibody). A chart review of the electronic medical records was then performed for every potential case identified to confirm the diagnoses of coexisting IBD and celiac disease using standard clinical, radiographic, endoscopic and histological criteria. For celiac disease, this included an abnormal serologic test and duodenal histology demonstrating some degree of villous atrophy where available and if the patient had not been previously started on a gluten free diet. A diagnosis of CD or UC required presence of typical symptoms of at least 3 months duration in combination with compatible endoscopic (or radiologic findings) findings and histology demonstrating chronic inflammation. Patients with microscopic colitis were excluded from the study. All potential patients received at least one diagnosis code for CD, UC, or celiac disease after 1996. To identify controls, the RPDR was queried for a set of random controls with a diagnosis of IBD alone without a co-existing ICD-9-CM code for celiac disease. For each case we identified 2 randomly selected controls from this population through computer-generated random numbers, matched on IBD type (CD or UC or indeterminate colitis), after further confirming absence of co-existing celiac disease through chart review.

Study Variables and Outcomes

Demographic and disease variables were obtained from electronic medical records and included age, gender, ethnicity, age at diagnosis and duration of IBD, and type of disease (CD versus UC). The Montreal Classification was used to categorize disease behavior (inflammatory, stricturing, or penetrating) and location (ileal, colonic, ileocolonic) in CD²⁹.

Upper GI involvement and perianal disease formed non-mutually exclusive categories of disease location and behavior. Disease extent in UC was classified as extensive (beyond splenic flexure) or limited colitis. We also recorded information on current and prior (ever use) use of therapy compared to never use including 5-ASA, oral corticosteroid (prednisone and budesonide), immunomodulator (IMM) (methotrexate, azathioprine, and 6-mercaptopurine) and biologic therapy (infliximab, adalimumab, certolizumab pegol, and natalizumab). Smoking status was classified into ever or never smoking based on history. Within the cohort of patients with celiac disease, information was obtained on how we were able to confirm the diagnosis of celiac disease (serology, endoscopy, biopsy, or established clinical history alone). We also assessed whether the patient had ever followed a gluten-free diet through references to such adherence within the electronic medical record. Additional information extracted from the medical record included history of IBD-related hospitalizations and surgeries, presence of another autoimmune disease in addition to IBD or celiac disease.

Disease Prevalence

To examine the relative prevalence of celiac disease among CD, UC, and other autoimmune diseases, we queried the RPDR for the proportion of patients with each of several immune-mediated diseases who also had a co-existing ICD-9-CM code for celiac disease (supplementary table 1).

Primary Outcomes and Statistical Analysis

Our primary comparisons were of disease phenotype (extent, behavior) and natural history (need for surgery and hospitalizations) between celiac-IBD cases and non-celiac controls. Data were analyzed using Stata 11.0 (StataCorp, College Station, TX). Continuous variables were summarized with means and standard deviations while categorical variables were described using proportions. The *t*-test was used to compare continuous variables. Categorical variables were compared using the chi-square test with the use of the Fisher's exact test when appropriate. Multivariate logistic regression analysis was used to determine the independent association of our outcomes of interest for celiac disease, adjusting for potential confounders. All *p*-values < 0.05 were considered statistically significant.

The study was approved by the Partners Healthcare Institutional Review Board.

RESULTS

Study Population

A total of 51 IBD patients with celiac disease and 102 IBD controls without celiac disease were included in our study. The years of IBD diagnosis ranged from 1966–2012. Figure 1 presents the methods of confirmation of celiac disease diagnosis. In nearly half of the patients, we could confirm diagnosis by review of both serology and biopsy results whereas one-quarter of the patients had an established clinical history and confirmed diagnosis of celiac disease from a non-Partners institution without details regarding their actual testing available in our EMR (*n* = 12, 23.5%). In patients diagnosed with serology alone, all had elevated anti-tissue transglutaminase antibodies and anti-endomysial antibodies. Among those diagnosed with serology and biopsy, three patients had positive anti-endomysial antibodies alone, two had positive anti-gliadin antibodies alone (anti-tissue transglutaminase not checked in these five patients). The rest all had positive anti-tissue transglutaminase IgA, most in combination with elevated anti-endomysial antibodies when these were checked. For two patients, only a notation that serology was positive was available in the medical record without specifying the type of serologic marker. A majority (92.2%) of the celiac-IBD patients reported following a gluten-free diet either continuously or intermittently.

Table 1 compares the characteristics of the celiac-IBD cases and non-celiac IBD controls. The mean age at IBD diagnosis (27.3 versus 28.7 years, $P = 0.65$) and gender distribution (58.8% versus 57.8% female, $P = 0.91$) were similar between the 2 groups, while the mean duration of disease was slightly shorter in the celiac-IBD group. There was a numerical higher proportion of other autoimmune diseases amongst the celiac-IBD group (23.5%) as compared to non-celiac controls (12.8%, $P = 0.09$).

Phenotype differences between celiac-IBD cases and non-celiac IBD controls

As seen in Table 1, presence of pancolitis was more common in celiac-UC patients as compared to non-celiac UC controls (63.2% versus 35.9%, odds ratio (OR) 3.30, 95% confidence interval (CI) 1.05 – 10.39). We conducted a sensitivity analysis to determine if the phenotypic differences also applied to the cohort of celiac-UC patients whose celiac diagnostic test results could directly be confirmed within our EMR through review of both serology and histology. Within this group, there was a similarly increased prevalence of the pancolitis phenotype as compared to the non-celiac UC controls (75.0% versus 35.9%, OR 5.8, 95% CI 1.55 – 21.50). There was no difference in the age of diagnosis between celiac-UC compared to non-celiac UC controls.

In contrast, for CD, we did not find any difference in disease behavior (inflammatory, structuring, or fistulizing) between the two groups (Table 1). Disease location was also similar between the celiac-CD cases and non-celiac CD controls in respect to the terminal ileum, colon, and ileocolon ($P = 0.48$). Additionally, the rates of upper GI tract (16.7% versus 9.3%, $P = 0.45$) or perianal (8.3% versus 22.2%, $P = 0.21$) involvement in the celiac-CD patients as compared to the non-celiac group were similar. Patients in the celiac-IBD group were significantly less likely to be ever-smokers than non-celiac IBD controls (26.7% vs. 45.1%, OR 0.44, 95% CI 0.21 – 0.95). The increased likelihood of ever-smoking among the control group persisted when compared to celiac-IBD patients whose celiac disease diagnostic test information was available in our EMR (24.2% vs. 45.1%, OR 0.39, 95% CI 0.16 – 0.95).

Outcomes in celiac-IBD compared to non-celiac IBD controls

As seen in Table 2, there was a trend towards increased use of immunomodulators among celiac-UC patients than in non-celiac UC controls (45.5% versus 22.7%, OR 2.83, CI 95% 0.95 – 8.48). There was no notable difference in immunomodulator use between celiac-CD patients compared to the non-celiac CD controls. The presence of co-existing celiac disease also did not influence the usage rate of 5-ASAs, oral corticosteroids, or biologics among Crohn's or UC patients (Table 2). There were no differences in IBD-related hospitalizations or surgeries between cases and controls.

Clustering of celiac, IBD, and other autoimmune diseases

We examined the prevalence of celiac disease among all patients with a diagnosis code for CD or UC. We found a prevalence of celiac disease among CD and UC of 1.27% and 1.04%, respectively within the Partners Healthcare system, which is similar to the prevalence estimates of celiac disease among the general North American population¹⁰. In contrast, the prevalence of CD or UC among those with a diagnosis code for celiac disease in the Partners Healthcare system was significantly greater at 4.0% and 3.2%, respectively, suggesting that while patients with IBD may not be at a higher risk for celiac disease, those with underlying celiac disease may be much more likely to have CD or UC. The prevalence of a diagnosis code for celiac disease was much less common in those with other autoimmune diseases including rheumatoid arthritis (0.54%), Systemic Lupus Erythematosus (SLE) (0.84%), psoriasis (0.52%), type 1 diabetes (0.69%) or multiple sclerosis (0.26%) (Figure 2).

DISCUSSION

Inflammatory bowel disease (Crohn's disease and ulcerative colitis) and celiac disease are the two most common immune-mediated gastrointestinal diseases and share common genetic risk variants^{30, 31}. However, there have been few prior studies that have examined the association between the two diseases; and in particular, clinical outcomes of IBD in the presence of co-existing celiac disease have not been previously well-characterized.

Our data show that patients who have both celiac disease and UC are more likely to have pancolitis as opposed to more limited colonic inflammation despite having a shorter duration of UC disease than our non-celiac UC controls. This is similar to a few previous studies that have examined other co-existing autoimmune diseases in UC. For example, UC patients with primary sclerosing cholangitis (PSC) are similarly more likely to have pancolitis as opposed to patients with isolated UC.^{25, 32} A prior case series of IBD patients with celiac disease similarly found 4/5 patients with UC and celiac disease to have pancolitis.²⁸ Thus, patient with UC and co-existing celiac disease or PSC may represent a unique autoimmune-related phenotype of UC. However, further studies with other concomitant autoimmune diseases would be essential to define this further. We also identified a trend towards increased use of immunomodulators among the celiac-UC cohort. However, there was no significant difference in other IBD medications, hospitalizations or surgeries. These findings differ from some of the small early case reports that postulated that patients with a combination of UC and celiac disease were more likely to have severe disease requiring colectomy.²⁸ However, as the study by Yang et al. was also from a referral center but had no non-celiac UC controls for comparison, it is difficult to estimate if the rate of colectomy in that exceeded that in non-celiac UC patients.

We also did not find any effect of co-existing celiac disease in influencing disease phenotype or natural history in CD. A previously published review of 8 cases found that CD manifested in atypical locations when in conjunction with a celiac disease diagnosis, however our study shows no significant difference in CD location in the presence of celiac disease.²⁷ The lack of significant differences in the clinical outcomes of patients with celiac disease and Crohn's disease may argue against an effect of the shared risk loci between CD and celiac disease in influencing the natural history of disease. It may also be indicative that the association between immunological response seen against luminal microbial antigens and severe disease may not extend to dietary antigens such as gliadin.

An interesting observation was that patients in the celiac-IBD group were less likely to have been ever-smokers than controls which is consistent with previously published studies have also found lower smoking rates in patients diagnosed with celiac disease and have suggested a protective role of cigarette smoking.³³ Smoking has similarly been found to have a protective effect on UC and PSC, again highlighting the possibility of a common link in the pathogenesis of these immune-mediated diseases. Our celiac-IBD patients were more likely to be afflicted with other autoimmune diseases than non-celiac IBD controls, highlighting the shared genetic susceptibility many of these patients may have. Indeed, shared genetic risk loci have been described between celiac disease and CD, Type I diabetes, and rheumatoid arthritis.^{16, 34, 35}

An important finding from our study is that while the prevalence of celiac disease in IBD patients within the Partners database was similar to what was expected in the general North American Caucasian population¹⁰; the prevalence of IBD among those with celiac disease was considerably higher than would be expected in the general population as has been reported previously.^{19, 24, 28} This suggests that in patients with celiac disease, particularly in those with non-response to gluten free diet, one should consider work up for possible

underlying inflammatory bowel disease as this may exist concurrently in such patients. There is limited data to compare prevalence of celiac disease among other autoimmune diseases. We found a lower prevalence of celiac disease in Type I diabetics than has been reported elsewhere (0.7% vs. 4–9%).³⁶ The true prevalence of the co-morbidity of celiac disease with other autoimmune disorders such as RA and SLE has not been previously well-established^{37, 38} and merits further analysis in larger validated disease cohorts, and where possible with prospective structured screening for celiac disease. Ludvigsson *et al.* recently identified a three-fold increase in risk for SLE among those with biopsy proven celiac disease³⁹. There are a few potential explanations for the potentially higher frequency of celiac disease among IBD compared to other autoimmune diseases. First, this could represent an ascertainment bias. As celiac disease and IBD are both managed commonly by gastroenterologists, there may be a lower threshold to obtain celiac serology testing or endoscopic biopsies in such patients compared to those managed by non-gastroenterologist physicians. Secondly, the higher frequency of celiac disease among IBD compared to other autoimmune diseases could also be consequent to the greater degree of genetic overlap between celiac disease and IBD than that observed with other diseases. The higher prevalence of IBD in those with celiac disease but not celiac disease in those with IBD may be due to the multifactorial etiopathogenesis of both diseases in that the development of disease requires a combination of environmental and genetic influences, and shared genes contribute a differential fraction of the disease risk for both diseases.

We believe there are a few clinical implications to our findings. First, reassuringly we did not identify a more aggressive phenotype of disease in those with co-existing celiac disease and IBD. Consequently, we do not suggest any need to modify current practice patterns in the management of IBD in this cohort of patients with the exception of recognizing the higher frequency of pancolitis among celiac-UC patients. Secondly, recognizing a possible higher prevalence of IBD among those with celiac disease, celiac disease patients with persistent gastrointestinal symptoms despite a gluten free diet should also potentially trigger evaluation for underlying IBD (in addition to standard practice of evaluating for inadvertent gluten ingestion as well as underlying refractory celiac disease or lymphoma).

There are a few limitations to our study. First, referral bias is possible in studies at large tertiary centers. However such bias is unlikely to affect our results because both the case and controls groups were taken from the same pool of patients in the Partners database. As with any retrospective study, the level of past documentation affects completeness and quality of data collected. In our study, due to gaps in data, we were not able to consistently determine whether IBD or celiac disease was diagnosed first, or the symptoms/signs that led to diagnosis of celiac disease. It is possible that the order in which a patient is afflicted with the diseases may have some effect on outcome and further investigation is warranted in this area. Due to the retrospective nature of the study, it was not possible to obtain serologic testing for all of the included patients; therefore there is a possibility that some patients in our control group have “silent” or asymptomatic celiac disease.⁴⁰ However, given the expected prevalence of this being less than 1%, it is unlikely to have influenced our results. Finally, we also acknowledge the possibility of false positive findings due to simultaneous comparison of multiple patient characteristics and outcomes. As this is an exploratory study with limited prior literature in this area, we did not correct for multiple hypothesis testing within the context of this study. Consideration for this should be given in larger cohorts further characterizing and confirming the phenotype of celiac-IBD patients.

In summary, to our knowledge, this is the first case-control study examining clinical outcomes of patients with concurrent diagnoses of celiac disease and IBD to non-celiac IBD controls. While patients with celiac disease and UC may be more likely to have pancolitis, it is not clear that having the two diseases simultaneously leads to worse outcomes. However,

while celiac disease is not more common in those with CD or UC, co-existing IBD seems to occur more commonly in patients with celiac disease.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What is known?

- Celiac disease and inflammatory bowel diseases are common immune mediated diseases of the gastrointestinal tract
- Celiac disease occurs in 1% of the North American population
- Whether co-existence of IBD and celiac disease represents an unique disease phenotype is unknown

What is new here?

- Ulcerative colitis (UC) patients with co-existing celiac disease have a higher frequency of pancolitis than non-celiac UC controls
- UC-celiac patients also had a trend towards greater use of immunomodulators
- Co-existing celiac disease did not influence phenotype or natural history of Crohn's disease

Figure 1.

Method of ascertainment of celiac disease diagnosis

* Serologic tests for celiac disease included anti-tissue transglutaminase (IgA or IgG), anti-endomysial, or anti-gliadin antibodies

Figure 2.
Prevalence of celiac disease among patients with various autoimmune diseases within the Partners Healthcare system

Table 1

Comparison of characteristics of patients with inflammatory bowel disease with and without celiac disease

Characteristic	Celiac-IBD (<i>n</i> = 51) [<i>N</i> (%)]	Non-Celiac IBD Controls (<i>n</i> = 102) [<i>N</i> (%)]	<i>P</i> - value
Mean age (in years) [mean (SD)]	38.6 (19.5)	43.2 (21.9)	0.21
No. of women	30 (58.8)	59 (57.8)	0.91
IBD Type			
Crohn's disease	28 (54.9)	57 (55.9)	1.0
Ulcerative Colitis	22 (43.1)	23 (44.1)	
Indeterminate Colitis	1 (2.0)	0 (0)	
Age at diagnosis (in years) [mean (SD)]	27.3 (15.5)	28.7 (17.2)	0.65
Duration of disease (in years) [mean (SD)]	10.5 (10.2)	14.0 (12.4)	0.10
Crohn's Disease Location			0.48
Terminal Ileum	8 (33.3)	15 (27.8)	
Colon	7 (29.2)	11 (20.4)	
Ileocolon	9 (37.5)	28 (51.9)	
Upper GI Crohn's Disease	4 (16.7)	5 (9.3)	0.45
Perianal Crohn's Disease	2 (8.33)	12 (22.2)	0.21
Crohn's Disease Behavior			
Inflammatory	18 (75.0)	38 (70.4)	0.92
Strictureing	2 (8.3)	5 (9.3)	
Fistulizing	4 (16.7)	11 (20.4)	
Ulcerative Colitis Extent			
Limited colitis	7 (36.8)	25 (64.1)	0.05
Pancolitis	12 (63.2)	14 (35.9)	
5-ASA Ever Use	45 (90.0)	89 (87.3)	0.79
Corticosteroid Ever Use	39 (76.5)	76 (75.3)	0.87
Immunomodulator Ever Use	28 (54.9)	44 (43.6)	0.19
Biologics Ever Use	14 (27.5)	25 (24.8)	0.72
IBD-related hospitalization	17 (33.3)	39 (38.2)	0.55
IBD-related surgery	11 (21.6)	28 (27.5)	0.43
Other autoimmune diseases	12 (23.5)	13 (12.8)	0.09
Ever Smoker	12 (26.7)	46 (45.1)	0.035

Table 2
Comparison of Characteristics of patients with Inflammatory Bowel Disease Patients With and Without Celiac Disease, by IBD-Type

Characteristic	Celiac-CD (n = 28) [N(%)]	Non-Celiac CD (n = 57) [N(%)]	P-value	Celiac-UC (n = 22) [N(%)]	Non-Celiac UC (n = 23) [N(%)]	P-value
Number of women	17 (60.7)	30 (52.6)	0.48	13 (59.1)	29 (64.4)	0.67
Age at diagnosis (in years) [mean (SD)]	27.2 (13.8)	26.0 (15.4)	0.73	28.4 (17.7)	32.0 (18.9)	0.46
Duration of disease (in years) [mean (SD)]	11.2 (11.6)	11.7 (12.1)	0.88	10.1 (8.4)	16.8 (12.2)	0.03
Ever Smoker	7 (28.0)	27 (47.4)	0.10	5 (26.3)	19 (42.2)	0.27
5-ASA Ever Use	23 (85.2)	50 (87.7)	0.74	21 (95.5)	39 (86.7)	0.41
Corticosteroid Ever Use	20 (71.4)	42 (73.7)	0.82	18 (81.8)	34 (77.3)	0.76
Immunomodulator Ever Use	18 (64.3)	34 (39.7)	0.68	10 (45.5)	10 (22.7)	0.058
Biologics Ever Use	9 (32.1)	19 (33.3)	0.91	5 (22.7)	6 (13.6)	0.48
IBD-related Hospitalization	12 (42.9)	24 (42.1)	0.95	5 (22.7)	15 (33.3)	0.41
IBD-related surgery	8 (28.6)	21 (36.8)	0.45	3 (13.6)	7 (15.6)	1.00
Other autoimmune diseases	7 (25.0)	8 (14.0)	0.21	5 (22.7)	5 (11.1)	0.28