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Impact of Concomitant Prescriptions and Lifestyle Factors on the Initial Course of Newly Diagnosed Inflammatory Bowel Disease

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Keywords
Ulcerative colitis · Crohn's disease · Proton pump inhibitor · Alcohol · Smoking

Abstract
Introduction: There is a close relationship between the relapse of inflammatory bowel disease (IBD) and lifestyle factors, including concomitant medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), antithrombotic drugs, smoking status, and alcohol consumption. However, solid evidence is limited regarding the risk factors at diagnosis and initial disease course. This study aimed to explore the impact of concomitant prescriptions and lifestyle factors in patients with newly diagnosed IBD using a large-scale real-world database. ***Methods:*** This is a retrospective inception cohort study using the insurance claims database. Newly diagnosed patients with UC and CD were enrolled between January 2005 and May 2020. Concomitant prescriptions and lifestyle factors were assessed for new biologics use, surgery, and hospitalization during the first year. ***Results:*** In total, 6,743 patients with UC and 1,000 patients with CD were enrolled. Proton pump inhibitors, antithrombotics, antibiotics, and NSAIDs were identified as associated factors for both biologics use and hospitalization in UC patients (all $p < 0.01$), and antithrombotics were identified as associated factors for both biologics use and hospitalization in CD patients (all $p < 0.01$) in multivariable analyses. Interestingly, smoking was protective against hospitalization in UC patients ($p < 0.01$) but not in CD patients ($p = 0.997$), analyzed by univariate analysis. Alcohol consumption was protective against hospitalization outcomes in UC patients ($p = 0.02$) but not in CD patients ($p = 0.27$), analyzed by univariate analysis. ***Conclusion:*** Immediate attention should be paid to concomitant medications at diagnosis because they may have impact on the initial course of IBD.

Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory disease characterized by repeated relapses and remissions [1]. IBD has become a global burden and patients may have a lower quality of life owing to relapse, hospitalization, and surgery [2]. Especially, a poor initial course of disease may have a negative impact not only on the patient's quality of life but also on the long-term prognosis and thus early disease modification may help improve disease outcomes [3].

Patients may present with multiple comorbidities that require medical treatment. However, concomitant

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prescriptions such as nonsteroidal anti-inflammatory drugs (NSAIDs) [4] and antithrombotics [5] could be risk factors for IBD relapse, and antibiotics are known to increase the risk of *Clostridioides difficile* infection [6]. In contrast, there is no evidence regarding whether antihypertensive, antidiabetic, or antihyperlipidemic drug could influence the course of IBD. Recently, it has been reported that regular use of proton pump inhibitors (PPIs) may increase the risk of IBD [7] and may reduce the efficacy of infliximab [8]. However, these analyses are not fully controlled for various confounders, and solid evidence especially about the prescriptions at the time of IBD diagnosis is scarce.

There is also a close relationship between lifestyle factors and relapse of IBD [9]. For example, previous reports have shown that smoking is a risk factor for relapse of Crohn's disease (CD) [10]. In contrast, current smokers have a milder disease course, fewer surgeries, and the need for immunosuppression in cases of ulcerative colitis (UC) [10]. Alcohol has been reported to exacerbate abdominal pain in patients with CD [11], but there is no consensus on whether these habits at diagnosis have an immediate impact on the initial disease course [12]. This study aimed to explore the impact of concomitant prescriptions and lifestyle factors at diagnosis on the initial disease course in patients with newly diagnosed IBD using a large-scale real-world database.

Methods

Study Design

This is an observational retrospective inception cohort study aimed at detecting the risk factors for poor outcomes in patients with newly diagnosed IBD using the Japanese medical insurance claims database with health checkup results.

Setting and Inclusion Criteria

Japan has a universal health insurance system, and this study used the Japan Medical Data Center (JMDC) database [13]. Between January 2005 and May 2020, patients who met the criteria that were specifically validated in previous studies for UC and CD [14, 15] without any previous records of these disease codes were enrolled. In detail, CD is a patient with a diagnosis code of K50 confirmed by the Tenth Revision of the International Statistical Classification (ICD-10), but no confirmed ICD-10 diagnosis code for UC or Behçet's disease in the same month and a confirmed CD prescription code in the same month as the diagnosis code. For UC, it is a patient with a confirmed diagnosis of UC with a systemic treatment code for UC or UC procedure codes such as leukocyte apheresis or granulocyte-monocyte apheresis or a surgery code such as total colorectal resection with the use of antidiarrheal agents, excluding a confirmed primary diagnosis of CD or Behçet's disease. The index date was defined as the time when the patients first met the inclusion criteria, from which point the patients were followed up for 1 year unless the following three outcomes occurred: new biologics, surgery, and hospitalization (online suppl. Fig. 1; for all online suppl. material, see https://doi.org/10.1159/000541984).

Study Group and Outcome

The primary outcome was defined as the initiation of new biologics. The biologics included infliximab, adalimumab, golimumab, ustekinumab, vedolizumab, and tofacitinib. The secondary outcomes were IBD-related surgery (defined as the procedure codes for UC or CD) and IBD-related hospitalization (defined by ICD-10 code for UC or CD as the primary discharge diagnosis) (online suppl. Table 1). The outcomes were compared between the outcome and non-outcome groups. Each outcome was separately analyzed.

Variables

Information on sex, age, disease type, and prior history of surgery (online suppl. Table 1) up to 1 year before inclusion; use of steroids, biologics, or immunomodulators; concomitant prescriptions for other diseases that have been prescribed for more than 3 months in 1 year after enrollment; and a questionnaire for health checkups regarding smoking status and alcohol consumption in the year before and after enrollment was collected. The results of post-outcome health checkups were not collected.

Disease type was defined by the ICD-10 codes from the database as extent, course, and severity of disease, steroid-refractory, steroid-dependent, extraintestinal manifestations, postoperative status in patients with UC, and location and behavior in patients with CD (online suppl. Table 2). A questionnaire was used to record whether patients were current smokers (smoking more than 100 cigarettes in total, more than 6 months of smoking, or smoking in the last month) and whether they were categorized as having less than 20 g of ethanol equivalent per day. Concomitant prescriptions were defined as steroids, probiotics, histamine-2 receptor antagonists (H2RAs), PPI, insulin, oral antidiabetics, antithrombotic, antihypertensive, antilipidemic drug, antibiotics, or NSAIDs using Anatomical Therapeutic Chemical (ATC) codes (online suppl. Table 2). The Charlson Comorbidity Index (CCI) [16] was extracted based on disease codes

listed in the claims data in the year prior to enrollment. The CCI [16] assigns a morbidity score associated with mortality risk based on chart review. The score is calculated from 19 medical conditions, considering the varying morbidity levels among patients. Given that the CCI was low (defined as 0) for most patients, only the low or non-low index was used for CCI.

Statistical Analysis

All statistical analyses were performed using R version 4.0.5 (the R Foundation for Statistical Computing Platform). Continuous variables were expressed as the mean and standard deviation. Categorical variables were expressed as numbers and percentages (%). In univariate analyses, differences between the two groups mentioned in the Study Group and Outcome section were tested using Welch's *t* tests for continuous variables and binary variables and chi-square tests for categorical variables with three or more values. A p value <0.05 was considered statistically significant. The explanatory variables for the multivariable logistic regression analysis were predetermined as the background factors, the factors for which $p < 0.1$ were obtained by the univariate analyses previously mentioned, and CCI to adjust for the risk of comorbidities. Current smoking and alcohol consumption were not included in the multivariate analysis because missing data were expected from patients who did not undergo a health checkup. We calculated the odds ratios and 95% confidence intervals, as estimates for the relative risk of the composite outcome with one of the above exposures, using logistic regression models. The sample size included all patients enrolled in the current database using the inclusion criteria.

Results

The baseline characteristics of each cohort are presented in Table 1. There were 6,743 patients with UC, aged 39.6 ± 12.9 years and 64.2% male, enrolled in this study. There were 1,000 patients with CD, aged 33.2 ± 14.2 years, and 78.6% were male. During the first year after diagnosis, 299 (4.4%), 42 (0.6%), and 940 (13.9%) UC patients required biologics, surgery, and hospitalization, respectively. Conversely, 470 (47.0%), 110 (11.0%), and 397 (39.7%) patients with CD required biologics, surgery, and hospitalization, respectively. Due to a small number of surgery outcomes, which only enabled univariate analysis, we presented the analysis for surgery in online supplementary Table 3. However, multivariate analysis was not conducted due to the small number of surgery events.

Clinical Characteristics and Concomitant Medications

The results of univariable analysis for biologics use outcomes of UC and CD are shown in Table 2. A younger age of onset was associated with the need for biologics in both UC and CD. The baseline use of steroids, antithrombotics, and antibiotics was also associated with the need for biologics in both UC and CD. Interestingly, the use of probiotics, H2RAs, PPIs, and NSAIDs was associated with the need for biologics only in UC patients, while antihyperlipidemic drugs were associated only with CD.

The results of the univariate analysis for hospitalization outcomes are shown in Table 3. Younger age of onset and use of steroids, PPIs, antithrombotics, antibiotics, and NSAIDs were associated with hospitalization in both UC and CD. Probiotics, H2RAs, insulins, oral antidiabetics, antihypertensives, and antihyperlipidemic drugs were associated with hospitalization only in UC. No other possible factors associated with hospitalization were found in CD.

The results of the multivariate analysis for UC patients are shown in Table 4. Younger age of onset (biologics: OR = 0.98, 95% CI: 0.98, 0.99, $p < 0.001$; hospitalization: OR = 0.99, 95% CI: 0.98, 0.99, $p < 0.001$), steroids (biologics: OR = 7.16, 95% CI: 5.31, 9.65, $p < 0.001$; hospitalization: OR = 3.92, 95% CI: 3.18, 4.81, $p < 0.001$), PPIs (biologics: OR = 2.18, 95% CI: 1.59, 2.99, $p < 0.001$; hospitalization: OR = 1.91, 95% CI: 1.52, 2.38, $p < 0.001$), antithrombotics (biologics: OR = 2.28, 95% CI: 1.45, 3.57, $p < 0.001$; hospitalization: OR = 5.13, 95% CI: 3.59, 7.34, $p < 0.001$), antibiotics (biologics: OR = 1.61, 95% CI: 1.21, 2.15, $p < 0.001$; hospitalization: OR = 2.25, 95% CI: 1.87, 2.72, $p < 0.001$), and NSAIDs (biologics: OR = 2.61, 95% CI: 1.83, 3.71, $p < 0.001$; hospitalization: OR = 1.61, 95% CI: 1.25, 2.08, $p < 0.001$) were associated with both biologics use and hospitalization in UC. Probiotics (OR = 2.87, 95% CI: 1.81, 4.54, $p < 0.001$) and H2RAs (OR = 1.49, 95% CI: 1.13, 1.97, $p = 0.005$) were associated only with hospitalization in UC.

The multivariate analysis for CD patients indicates that steroids (biologics: OR = 1.95, 95% CI: 1.33, 2.87, $p < 0.001$; hospitalization: OR = 1.56, 95% CI: 1.04, 2.35, $p = 0.032$) and antithrombotics (biologics: OR = 2.32, 95% CI: 1.18, 4.56, $p = 0.0014$; hospitalization: OR = 5.98, 95% CI: 2.67, 13.39, $p < 0.001$) were associated with both biologics use and hospitalization (Table 5). In addition, PPIs (OR = 1.63, 95% CI: 1.14, 2.33, $p = 0.008$) and antibiotics (OR = 1.79, 95% CI: 1.25, 2.57, $p = 0.002$) remained significant for CD-related hospitalization.

Table 1. Baseline characteristics

	UC (*n* = 6,743)	CD (*n* = 1,000)
Age (mean±SD), years	39.6±12.9	33.2±14.2
Male, *n* (%)	4,330 (64.2)	786 (78.6)
Code of disease type for UC, *n* (%)		
Pancolitis	551 (8.2)	
Intermittent or chronic active	27 (0.4)	
Fulminant colitis	7 (0.1)	
Severe colitis	90 (1.3)	
Steroid refractory	5 (0.1)	
Steroid dependent	11 (0.2)	
Code of disease type for CD, *n* (%)		
Ileal or ileocolonic		290 (29.0)
Peri-anal		256 (25.6)
Upper		14 (1.4)
Stricturing or penetrating		82 (8.2)
Biologics or immunomodulator use, *n* (%)	225 (3.3)	314 (31.4)
Cytoapheresis, *n* (%)	138 (2.0)	
Postoperative code for UC, *n* (%)		
Colostomy status	24 (0.4)	
Postoperative UC	22 (0.3)	
Total colectomy	12 (0.2)	
Prior history of surgery for CD, *n* (%)		
All		193 (19.3)
Intestine		64 (6.4)
Peri-anal		133 (13.3)

SD, standard deviation; UC, ulcerative colitis; CD, Crohn's disease.

Current Smoking and Alcohol Consumption

The data from the health checkup questionnaires were available for approximately half of the patients. Smoking status data before and after enrollment (diagnosis) were available for 3,509 and 3,582 UC patients and for 373 and 394 CD patients, respectively. Alcohol consumption data before and after enrollment were available for 3,170 and 3,261 UC patients and for 329 and 360 CD patients, respectively. Many missing values were thus observed. The statistical analysis was performed only univariate analysis, as described.

Neither smoking status nor alcohol consumption before enrollment was associated with the needs for biologics and IBD-related hospitalization. In contrast, smoking in the first year after enrollment was protective against hospitalization in UC with 59 (15.2%) and 668 (20.9%) in the hospitalization and non-hospitalization groups, respectively (p = 0004). However, smoking in the first year after enrollment was not protective against hospitalization in CD; there were 34 (26.2%) and 69 (26.1%) patients in the hospitalization and non-hospitalization groups, respectively (p = 0.997). Alcohol consumption after enrollment was protective against hospitalization outcomes in UC, with 34 (9.6%) and 395 (13.6%) patients in the hospitalization and non-hospitalization groups, respectively (p = 0.019). Conversely, alcohol consumption after enrollment was not protective against hospitalization outcomes in CD, with 8 (6.7%) and 24 (10.0%) patients in the hospitalization and non-hospitalization groups, respectively (p = 0.267).

Discussion

This study is the first large-scale claims database study to examine the association of concomitant prescriptions and lifestyle factors with the initial disease course of newly diagnosed IBD patients. The summary of this study is shown in Table 6. In short, baseline use of antithrombotics, antibiotics, PPI, and NSAIDs has been shown to be associated with poor initial disease course in both UC and CD patients, whereas H2RA, insulin, oral antidiabetics,

Table 2. Univariable analysis for biologics use outcome

	UC			CD		
	outcome (n = 299)	non-outcome (n = 6,444)	p value	outcome (n = 470)	non-outcome (n = 530)	p value
Age (mean ± SD), years	37.0±15.6	39.8±12.8	0.003	29.9±13.3	36.1±14.3	<0.001
Male, n (%)	178 (59.5)	4,152 (64.4)	0.093	386 (82.1)	400 (75.5)	0.010
Prior history of surgery for CD, n (%)						
Intestine				35 (7.4)	29 (5.5)	0.207
Peri-anal				81 (17.2)	52 (9.8)	<0.001
CCI = low, n (%)	280 (93.6)	6,133 (95.2)	0.004	449 (95.5)	506 (95.5)	0.171
Prescriptions, n (%)						
Steroids	168 (56.2)	585 (9.1)	<0.001	86 (18.3)	55 (10.4)	<0.001
Probiotics	11 (3.7)	96 (1.5)	0.048	17 (3.6)	14 (2.6)	0.379
H2RA	48 (16.1)	312 (4.8)	<0.001	46 (9.8)	43 (8.1)	0.356
PPI	117 (39.1)	553 (8.6)	<0.001	96 (20.4)	97 (18.3)	0.397
Insulin	4 (1.3)	19 (0.3)	0.120	1 (0.2)	3 (0.6)	0.365
Oral antidiabetics	7 (2.3)	136 (2.1)	0.797	10 (2.1)	14 (2.6)	0.594
Antithrombotic	36 (12.0)	155 (2.4)	<0.001	30 (6.4)	15 (2.8)	0.008
Antihypertensives	29 (9.7)	557 (8.6)	0.547	26 (5.5)	43 (8.1)	0.104
Antihyperlipidemic	19 (6.4)	434 (6.7)	0.793	14 (3.0)	31 (5.8)	0.026
Antibiotics	107 (35.8)	799 (12.4)	<0.001	94 (20.0)	80 (15.1)	0.043
NSAIDs	60 (20.1)	401 (6.2)	<0.001	36 (7.7)	53 (10.0)	0.192

SD, standard deviation; CD, Crohn's disease; CCI, Charlson Comorbidity Index; H2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor; NSAIDs, nonsteroidal anti-inflammatory drugs; UC, ulcerative colitis.

antihypertensive, antilipidemic drug, and probiotics were not. Although various factors have been shown to have an association with each outcome, factors identified for both outcomes in common are quite likely to be true risks for the unfavorable course of disease.

In general, a claims database only reflects insured individuals, but JMDC is Japan's largest epidemiological database utilizing the universal health insurance system and contains claims data for up to 9.4 million individuals, or approximately 13.4% of the Japanese population [13]. Komoto et al. [17] reported 28,179 new cases of UC in Japan during the 5-year period from 2004 to 2009, while Yoshida et al. [18] reported an incidence of CD of 0.51/100,000 in 1990. Thus, in the current study, with a 15-year enrollment period, the number of newly onset UC and CD patients during the same period is estimated to be about 80,000 and 10,000, respectively. We have identified 6,743 patients with UC and 1,000 patients with CD, which accounts for 8–10% of the total number. This allowed us to minimize the potential bias and adjust confounding factors, which was essential to examine the influence of multiple factors including prescriptions. Chiba et al. [19] reported 6,083 new UC cases and 1,615 CD cases from 1995 to 2000. They counted new-onset IBD based on the IBD registry of the Ministry of Health, Labour and Welfare in Japan, which differs from the extraction method used in this study. The extraction method required that the diagnostic criteria be met in that study, while a combination of disease name and prescription was required in the present study. As a result, the present study enrolled 6,743 UC cases and 1,000 CD cases, which is fewer CD cases than previously reported. This gap may suggest that there are more untreated patients with CD than with UC. In this study, biologics were used in as many as 470 (47%) of the total 1,000 cases. According to Hirai et al. [20] in Japan, 61.1% of patients were prescribed first-line biologics within 6 months of initial diagnosis of CD. This report used the receipt data as in the present study but with different case extraction criteria. Furthermore, Hirayama et al. [21] reported that the use of biologics as initial treatment was more than 50% in patients with onset between 2006 and 2020. This report used real-world data collected through a multicenter, prospective patients registry, which differs from the present study. Since these previous reports using these different methods also showed similarly high rates of

Table 3. Univariate analysis for hospitalization outcome

	UC			CD		
	outcome (n = 940)	non-outcome (n = 5,803)	p value	outcome (n = 397)	non-outcome (n = 603)	p value
Age (mean ± SD), years	38.1±15.7	39.9±12.4	0.001	30.8±14.5	34.8±13.8	<0.001
Male, n (%)	556 (59.1)	3,774 (65.0)	0.001	314 (79.1)	472 (78.3)	0.757
Prior history of surgery for CD, n (%)						
Intestine				33 (8.3)	31 (5.1)	0.056
Peri-anal				54 (13.6)	79 (13.1)	0.820
CCI = low, n (%)	891 (94.8)	5,522 (95.2)	0.312	381 (96.0)	574 (95.2)	0.299
Prescriptions, n (%)						
Steroids	338 (36.0)	415 (7.2)	<0.001	79 (19.9)	62 (10.3)	<0.001
Probiotics	45 (4.8)	62 (1.1)	<0.001	17 (4.3)	14 (2.3)	0.099
H2RA	120 (12.8)	240 (4.1)	<0.001	44 (11.1)	45 (7.5)	0.058
PPI	262 (27.9)	408 (7.0)	<0.001	100 (25.2)	93 (15.4)	<0.001
Insulin	10 (1.1)	13 (0.2)	0.014	3 (0.8)	1 (0.2)	0.206
Oral antidiabetics	34 (3.6)	109 (1.9)	0.006	12 (3.0)	12 (2.0)	0.317
Antithrombotic	108 (11.5)	83 (1.4)	<0.001	37 (9.3)	8 (1.3)	<0.001
Antihypertensives	116 (12.3)	470 (8.1)	<0.001	33 (8.3)	36 (6.0)	0.166
Antihyperlipidemic	80 (8.5)	373 (6.4)	0.031	18 (4.5)	27 (4.5)	0.967
Antibiotics	301 (32.0)	605 (10.4)	<0.001	101 (25.4)	73 (12.1)	<0.001
NSAIDs	137 (14.6)	324 (5.6)	<0.001	45 (11.3)	44 (7.3)	0.035

SD, standard deviation; CD, Crohn's disease; CCI, Charlson Comorbidity Index; H2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor; NSAIDs, nonsteroidal anti-inflammatory drugs; UC, ulcerative colitis.

Table 4. Multivariable analysis for biologics and hospitalization outcome of ulcerative colitis

	Biologics	p value	Hospitalization	p value
	OR (95% CI)		OR (95% CI)	
Age	0.984 (0.975–0.993)	<0.001	0.985 (0.979–0.991)	<0.001
Male	0.832 (0.643–1.077)	0.162	0.758 (0.647–0.886)	<0.001
Biologics or immunomodulator use	N/A		1.738 (1.251–2.415)	<0.001
CCI = low	0.753 (0.448–1.265)	0.284	0.973 (0.688–1.376)	0.877
Prescriptions				
Steroids	7.159 (5.312–9.649)	<0.001	3.915 (3.181–4.813)	<0.001
Probiotics	1.000 (0.491–2.038)	1.000	2.868 (1.813–4.538)	<0.001
H2RA	1.414 (0.958–2.088)	0.081	1.489 (1.125–1.971)	0.005
PPI	2.180 (1.589–2.991)	<0.001	1.905 (1.522–2.383)	<0.001
Insulin	N/A		1.808 (0.636–5.140)	0.266
Oral antidiabetics	N/A		1.493 (0.907–2.458)	0.115
Antithrombotic	2.276 (1.451–3.570)	<0.001	5.130 (3.588–7.335)	<0.001
Antihypertensives	N/A		1.153 (0.862–1.543)	0.336
Antihyperlipidemic	N/A		0.898 (0.646–1.247)	0.520
Antibiotics	1.610 (1.207–2.149)	<0.001	2.254 (1.868–2.720)	<0.001
NSAIDs	2.609 (1.833–3.714)	<0.001	1.612 (1.249–2.081)	<0.001

CCI, Charlson Comorbidity Index; H2RA, histamine-2 receptor antagonist; PPI, proton pomp inhibitor; NSAIDs, nonsteroidal anti-inflammatory drugs; N/A, not applicable.

Table 5. Multivariable analysis for biologics and hospitalization outcome of Crohn's disease

	Biologics	*p* value	Hospitalization	*p* value
	OR (95% CI)		OR (95% CI)	
Age	0.970 (0.961–0.980)	<0.001	0.975 (0.965–0.985)	<0.001
Male	1.343 (0.972–1.854)	0.074	0.976 (0.965–1.361)	0.884
Biologics or immunomodulator use	N/A		0.985 (0.738–1.314)	0.918
CCI = low	0.992 (0.530–1.854)	0.979	1.195 (0.614–2.324)	0.600
Prescriptions				
Steroids	1.951 (1.328–2.866)	<0.001	1.562 (1.039–2.348)	0.032
Probiotics	N/A		1.709 (0.780–3.741)	0.180
H2RA	N/A		1.150 (0.704–1.878)	0.577
PPI	N/A		1.627 (1.135–2.332)	0.008
Insulin	N/A		N/A	
Oral antidiabetics	N/A		N/A	
Antithrombotic	2.324 (1.184–4.563)	0.014	5.980 (2.671–13.390)	<0.001
Antihypertensives	N/A		N/A	
Antihyperlipidemic	0.662 (0.331–1.326)	0.245	N/A	
Antibiotics	1.157 (0.818–1.639)	0.410	1.793 (1.249–2.574)	0.002
NSAIDs	N/A		1.453 (0.896–2.356)	0.130

CCI, Charlson Comorbidity Index; H2RA, histamine-2 receptor antagonist; PPI, proton pomp inhibitor; NSAIDs, nonsteroidal anti-inflammatory drugs; N/A, not applicable.

Table 6. Summary of the results of this study

Odds ratio (99% CI)	UC		CD	
	biologics	hospitalization	biologics	hospitalization
Antithrombotic	2.28 (1.45–3.57)	5.13 (3.59–7.34)	2.32 (1.18–4.56)	5.98 (2.67–13.39)
Antibiotics	1.61 (1.21–2.15)	2.25 (1.87–2.72)	ns	1.79 (1.25–2.57)
PPI	2.18 (1.59–2.99)	1.91 (1.52–2.38)	N/A	1.63 (1.14–2.33)
NSAIDs	2.61 (1.83–3.71)	1.61 (1.25–2.08)	N/A	ns
H2RA	ns	1.49 (1.13–1.97)	N/A	ns
Probiotics	ns	2.87 (1.81–4.54)	N/A	ns
Smoking		↓		
Alcohol		↓		

↓, protective association in univariate analysis; H2RA, histamine-2 receptor antagonist; N/A, not applicable; ns, not significant; NSAIDs, nonsteroidal anti-inflammatory drugs; PPI, proton pomp inhibitor; UC, ulcerative colitis; CD, Crohn's disease.

biologics use in CD, it is not surprising that many biologics were used in the present study, and these results may reflect actual clinical practice in Japan.

Importantly, the JMDC database allows to analyze the prescription data even if patients receive prescriptions from multiple medical providers. Another interesting feature of the JMDC database includes datasets from health checkups, and its usefulness has been reported in various diseases including IBD [22]. Its questionnaire data are less prone to recall and information biases because the information was collected prospectively for health checkups, not for research purposes.

We have shown that NSAIDs and antithrombotics may increase relapse of IBD, consistent with the previous reports [5, 23]. Although a recent study suggested that the association between NSAIDs and IBD exacerbation might be secondary to residual bias [24], our study highlighted its potential harm to the initial course of IBD when used for more than 3 months. However, in this study, ATC codes were used to define the drug types, but detailed extraction of each drug type was not possible. In other words, antithrombotics include warfarin and direct oral anticoagulants (DOACs) as well as aspirin, and NSAIDs include cyclooxygenase-2 (COX-2) inhibitors. DOACs have been previously shown to be associated with IBD relapse, [5] while COX-2 inhibitors are controversial for IBD relapse [25]. This study, which includes DOACs and warfarin as antithrombotic agents and COX-2 inhibitors as NSAIDs, cannot assess their detailed effects on IBD exacerbations for each drug. Antibiotics and probiotics were also associated with both biologics and hospitalization. The use of antibiotics was previously reported to be associated with a lower risk of relapse in CD and to have no association with relapse in UC [26]. In contrast, antibiotic use may increase *Clostridioides difficile* infection in IBD patients, which is a known risk factor for subsequent treatment escalation, hospitalization, and surgery [6]. There are few reports of probiotics being useful [27], especially in CD, with respect to remission induction and maintenance. There are some reports of remission induction for UC but few reports of maintenance. It has also been suggested that the effect of probiotics on IBD may differ depending on the bacterial strain, but in this study, ATC codes were used to define the probiotics, making it difficult to extract detailed strains, and therefore, it is possible that the probiotics were not associated with each outcome.

In the United States, PPIs are among the top ten most commonly used drugs, with sales of USD 4.6 billion [28]. Interestingly, we found that PPIs influence outcomes in both UC and CD. In univariate analysis, PPIs were identified as an associated factor for surgical and hospitalization outcomes in CD and for all outcomes in UC. Lu et al. [8] showed in a meta-analysis of five randomized controlled trials of infliximab treatment those on concomitant PPIs were less likely to achieve remission; however, the patients in these randomized controlled trials may differ from the real-world patient population. Choden et al. [29] have shown that PPIs were associated with worse clinical outcomes in IBD patients using claims database analysis in the United States, and Juillerat et al. [30] have also shown that the use of PPIs and H2RAs might contribute to an increase in hospitalization and surgery for IBD. The results of these studies are similar to the present study. On the contrary, Singh et al. [31] have shown that PPIs are not related to IBD worsening. However, this study also failed to rule out possible confounding of steroids, antithrombotics, or NSAIDs. Steroids, antithrombotics, and NSAIDs are known risk factors for upper gastrointestinal complications such as bleedings [32], and PPIs may be used to prevent them [33]. In this study, a multivariate analysis including these drugs was performed to eliminate confounding factors, and PPIs remained significant in increasing biologics use in UC and hospitalization in both UC and CD, confirming that PPIs are an independent risk factor for worsening of the initial course of IBD.

Although the detailed mechanism for the influence of PPIs on IBD has not yet been clarified, it is known that PPIs suppress gastric acidity and increase intragastric pH, thereby decreasing the diversity of the gut microbiota. Lu et al. [8] have reported that PPIs alter the immune cell function and promote gut dysbiosis, leading to a decrease in the remission rate of infliximab treatment. Xia et al. [7] reported that PPI may impair intestinal barrier function due to dysbiosis. However, another anti-acid, H2RA, was not identified as an associated factor in this study. Although H2RAs may affect the gut microbiota in the same manner, PPIs may alter the composition of the gut microbiota more significantly than H2RA [34], which may explain the difference between PPI and H2RA in the impact on the clinical course of IBD.

Smoking has been reported to be a risk factor for therapy intensification, surgery, and postoperative relapse in CD [4, 35] and is inversely correlated with disease severity in UC [4]. A previous study reported that alcohol may cause abdominal symptoms in CD [9] although it has no effect on disease exacerbation [11]. On the other hand, it has been reported that moderate alcohol consumption, especially that of red wine, does not exacerbate IBD but lowers faecal calprotectin [36]. In the Japanese population, current smoking and habitual drinkers are associated with a lower risk of developing UC [37]. There are no reports of alcohol consumption regarding disease exacerbation of IBD, but smoking has been reported as a risk factor for relapse of postoperative CD [38]. Unfortunately, multivariate analysis of smoking status and alcohol consumption was not possible because of missing data. In other words, it is important to note that this study did not adjust for confounding factors such as concomitant medications (antithrombotics, PPIs, etc.) and age, as discussed earlier in this study. Smoking status was not detected as a risk factor for worse outcomes in CD in this study, which is inconsistent with previous reports. This might be because of the short period of time (1 year

after onset) and incomplete control of confounding factors. However, it was also interesting to note that these findings were not detected in the pre-diagnosis health checkup results, indicating the importance of monitoring lifestyle factors after IBD diagnosis.

This study has several limitations. First, the patient profile of the JMDC database may have had a small number of patients over the age of 65 and female patients due to its nature [13]. According to Murakami et al. [39], the male-to-female ratios of UC and CD in Japan were 1.24 and 2.40, respectively, while they were 1.79 and 3.67 in this study. However, we believe that these factors were adjusted by a multivariate analysis using a sufficient sample size. Second, although the inclusion criteria were previously validated [14, 15], other disease codes may not have been accurately extracted. In addition, the lack of information on disease activity is also the limitation of this study. Indications for biological therapy are related to disease activity. However, clinical, serological, and endoscopic activity of IBD was not collected in the receipt database used in this study and cannot be assessed. Third, although several risk factors were identified in this retrospective cohort study, it is unclear whether interventions reducing these risk factors could improve the course of IBD. Further prospective studies are warranted to determine whether these risk factors are amendable. In addition, the observational period varied depending on the occurrence of the outcome; therefore, the outcome group had a shorter observation period than the non-outcome group, and the chance of exposure to risk factors was shorter, thus reducing the effect of the risk factor. In other words, the effect of risk factors, such as PPIs, might have been underestimated in the outcome group, although it was statistically significant. However, it is important to note that this may overestimate the effect of protective findings such as smoking status and alcohol consumption.

In conclusion, in this large-scale real-world observational study, we explored the associated factors for poor outcomes in patients with newly diagnosed IBD. In addition to known concomitant prescriptions, PPIs were shown to be associated with worse outcomes in both UC and CD patients. Especially for IBD patients with the associated factors identified in this study, the disease course for IBD should be closely monitored because of the potential risk of relapse.

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Statement of Ethics

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. The Research Ethics Committee of Kitasato University Kitasato Institute Hospital approved the study protocol and all the necessary documents (Approval No. 20069). Since the data had already been recorded and anonymized, the Research Ethics Committee of Kitasato University Kitasato Institute Hospital waived the requirement for informed consent.

Conflict of Interest Statement

H.M. has received research grants from Japan Foundation for Takeda Pharmaceutical, Applied Enzymology. Under a contract between Kyoto University and Takeda Pharmaceutical Company Limited, fees for consulting with H.Y. were paid to Kyoto University, which are not related to this work. T.K. has received honorariums from AbbVie, Alfresa Pharma, Jansen Pharma, Takeda, Mitsubishi Tanabe Pharma, Phizer, and Mochida, received research grants from Nippon Kayaku and EA Pharma, received scholarship grants from Otsuka Holdings, JIMRO, EA Parma, AbbVie, Zeria, Alfresa Pharma, Mochida Pharmaceutical, Miyarisan Pharmaceutical, and Kyorin Pharmaceutical. These are not related to this work. T.N. and K.N. declare no conflicts of interest associated with this manuscript.

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Author Contributions

Conceptualization and methodology: Hiromu Morikubo, Takayoshi Nagahama, Katsuhiko Nagai, Hajime Yamazaki, and Taku Kobayashi. Data curation: Hiromu Morikubo and Katsuhiko Nagai. Formal analysis and investigation: Hiromu Morikubo, Katsuhiko Nagai, Hajime Yamazaki, and Taku Kobayashi. Original draft preparation: Hiromu Morikubo and Taku Kobayashi. Review and editing: all authors. All authors have seen and approved the final report.

Data Availability Statement

The data that support the findings of this study are not publicly available due to restriction of their containing information that was used under license for this study but are available from the corresponding author (T.K.) upon reasonable request.

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