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Effects of COVID-19 vaccines on patient-reported outcomes in patients with inflammatory bowel disease: a multicenter survey study in Korea

Jung Hyun Ji[1]*, Seung Hwan Shin[2]*, Yong Eun Park[3], Jihye Park[1], Jae Jun Park[1], Jae Hee Cheon[1], Tae Il Kim[1], Sang-Bum Kang[4], Sang Hyoung Park[2], Soo Jung Park[1], IBD Research Group of the Korean Association for the Study of Intestinal Diseases (KASID)

[1]*Department of Internal Medicine and Institute of Gastroenterology, Severance Hospital, Yonsei University College of Medicine, Seoul;* [2]*Division of Gastroenterology, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul;* [3]*Division of Gastroenterology, Department of Internal Medicine, Inje University Haeundae Paik Hospital, Inje University College of Medicine, Busan;* [4]*Division of Gastroenterology, Department of Internal Medicine, Daejeon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Daejeon, Korea*

Background/Aims: The impact of vaccination on inflammatory bowel disease (IBD) patients is still unknown, and no studies have assessed the changes in patient-reported outcomes (PROs) after vaccination in patients with IBD. Therefore, in this study, we investigated the impact of vaccines on the PROs of patients with IBD. **Methods:** We conducted a questionnaire survey of patients with IBD who visited outpatient clinics at 4 specialized IBD clinics of referral university hospitals from April 2022 to June 2022. A total of 309 IBD patients were included in the study. Patient information was collected from a questionnaire and their medical records, including laboratory findings, were reviewed retrospectively. Risk factors associated with an increase in PROs after COVID-19 vaccination were analyzed using logistic regression analyses. In addition, we assessed whether there were differences in variables by vaccine order using the linear mixed model. **Results:** In multivariate analysis, young age (<40 years) and ulcerative colitis (UC) were found to be independent risk factors for aggravation of PROs in patients with IBD. In all patients, platelet count significantly increased with continued vaccination in multiple pairwise comparisons. In UC patients, PROs such as the short health scale, UC-abdominal signs and symptoms, and UC-bowel signs and symptoms were aggravated significantly with continued vaccination. There was no significant increase in the variables of patients with Crohn's disease. **Conclusions:** Therefore, there may be a need to counsel patients with IBD younger than 40 years of age, and patients with UC before they receive COVID-19 vaccinations. **(Intest Res, Published online)**

Key Words: Inflammatory bowel disease; COVID-19 vaccination; Patient-reported outcome measures

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Correspondence to Soo Jung Park, Department of Internal Medicine and Institute of Gastroenterology, Severance Hospital, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea. Tel: +82-2-2228-5201, fax: +82-2-393-6884, E-mail: SJPARK@yuhs.ac

Co-Correspondence to Sang Hyoung Park, Division of Gastroenterology, Department of Internal Medicine, Asan Medical Center, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea. Tel: +82-2-3010-5768, Fax: +82-2-476-0824, E-mail: umdalpin@hanmail.net

Co-Correspondence to Sang-Bum Kang, Division of Gastroenterology, Department of Internal Medicine, Daejeon St. Mary's Hospital, 64 Daeheung-ro, Jung-gu, Daejeon 34943, Korea. Tel: +82-42-220-9824, Fax: +82-42-252-6807, E-mail: sangucsd@gmail.com

*These authors contributed equally to this study as first authors.

INTRODUCTION

Coronavirus disease (COVID-19) is an infectious disease caused by the novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; formerly called 2019-nCoV) and was first identified in Wuhan, China. Globally, as of October 18, 2022, there have been 622,389,418 confirmed COVID-19 cases, including 6,548,492 deaths, reported to the World Health Organization (WHO).[1]

Since the onset of the COVID-19 pandemic, various types of

vaccines have been developed to prevent the spread of COVID-19 worldwide.[2] According to recent large-scale studies, vaccination has been effective in reducing hospitalizations, progression to severe disease, and deaths.[3] Moreover, it has been effective in preventing both asymptomatic and symptomatic infections.[3] However, as patients with inflammatory bowel disease (IBD) have been excluded from large-scale clinical studies on COVID-19 vaccines, the impact of vaccination on IBD patients is still unknown.

As IBD is a chronic inflammatory immune-mediated intestinal disease, there have been concerns that vaccination might impair the immune system of the intestinal mucosa, leading to an IBD flare. Prior studies have assessed the exacerbation of IBD after vaccination against various pathogens, such as influenza, zoster, and pneumococcus, but there is no evidence that these vaccinations induce IBD flares.[4-6] However, little is known about whether COVID-19 vaccination affects the exacerbation of IBD.

Patient-reported outcomes (PROs) have been increasingly regarded as crucial outcome measures in IBD-related studies, with the recent recognition of the importance of direct impacts on patients, beyond its effects on disease activity.[7] PROs emphasize the experiences that patients had with the disease, including thoughts, impressions, perceptions, and attitudes.[8] With the recent development of guidelines for the Food and Drug Administration (FDA) PROs, greater attention is being paid to the role and importance of PRO in healthcare.[9] However, there have been no studies assessing changes in PROs after vaccination in patients with IBD.

Therefore, in this study, we investigated the impact of COVID-19 vaccines on the PROs of patients with IBD.

METHODS

1. Patients

We conducted a questionnaire survey of patients with IBD who visited 4 specialized outpatient IBD clinics of referral university hospitals from April 2022 to June 2022. Patients who were previously diagnosed with IBD by gastroenterologists at these hospitals and currently undergoing outpatient follow-up observations, were older than 18 years of age, had received at least one dose of COVID-19 vaccination between March 2021 and June 2022, and were clinically inactive for IBD were included in this study. Clinically inactive was defined as no change in medication, including the dose for IBD treatment, without complaints of distinct symptoms within 1 year before the first vaccination.[10,11]

We excluded patients who had intestinal Behçet's disease, ulcerative colitis (UC) with a partial Mayo score (pMayo) ≥5, or Crohn's disease (CD) with a Crohn's Disease Activity Index (CDAI) ≥220. A survey was conducted with 320 patients, and 11 patients were excluded according to the above criteria. Finally, a total of 309 patients were enrolled in this study (Fig. 1).

The study protocol was approved by the institutional review of each participating center, including Severance Hospital (IRB No. 4-2021-1062), Asan Medical Center (IRB No. 2021-1872),

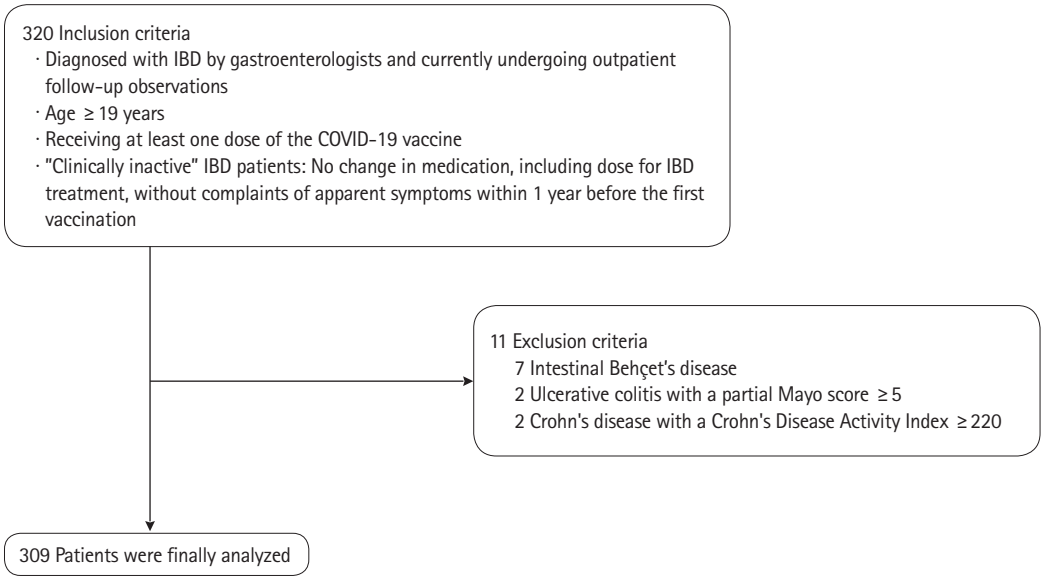

Fig. 1. Study flowchart. IBD, inflammatory bowel disease; COVID-19, coronavirus disease.

and Daejeon St. Mary's Hospital (IRB No. DC22QIDI0024), and conformed to the ethical guidelines of the 1975 Helsinki Declaration. All study participants provided written informed consent prior to study enrollment.

2. Variables from the Survey and Medical Records

The following information was collected from the questionnaire: age, sex, IBD type, smoking history, family history, COVID-19 vaccination history, COVID-19 infection history, adverse events after vaccination, self-imposed cessation of IBD medications, and scores of PROs. Family history ascertained whether the patients with IBD had first-degree relatives who had IBD. The COVID-19 vaccination history included the type of vaccination by order and date of vaccination. Self-imposed cessation of IBD medications was defined as the cessation of IBD-related medications owing to adverse events after vaccination, although the drug was not discontinued. The following PROs were investigated: UC PROs signs and symptoms (UC-PRO/SS), CD PROs signs and symptoms (CD-PRO/SS), and the short health scale (SHS). Each PRO was obtained within 3 months before the first dose of the vaccine and within 3 months after each dose.

The patients were vaccinated with 5 types of vaccines. The AstraZeneca, Janssen, and Novavax vaccines are viral vector vaccines that are similar to conventional viral vaccines. Moderna and Pfizer are new types of mRNA vaccines. All the 5 vaccines were inactivated.

The following medical records were obtained within 3 months prior to the first dose of the vaccine and within 3 months after each dose: the degree of physicians' global assessment, CDAI scores for CD patients, pMayo scores for UC patients, levels of hemoglobin, white blood cell count, lymphocyte count, platelet count, albumin, C-reactive protein, fecal calprotectin, and platelet-to-lymphocyte ratio.

3. Patient-Reported Outcomes

UC-PRO/SS, CD-PRO/SS were developed to standardize the quantification of gastrointestinal signs and symptoms in patients with UC and CD using direct reports from patient ratings. These are the first symptom measures of UC and CD to meet the U.S. FDA PRO guidelines.[12,13] The UC-PRO/SS measure includes 2 scales: bowel signs and symptoms (UC-PRO/SS(B), range: 0–28), which includes 6 items; and abdominal symptoms (UC-PRO/SS(A), range: 0–12), which includes 3 items, each scored separately.[12] The CD-PRO/SS measure includes 2 scales: bowel signs and symptoms (CD-PRO/SS(B), range: 0–16), which includes 3 items; and abdominal symptoms (CD-PRO/SS(A), range: 0–12), which includes 3 items, each scored separately.[13] Each scale of UC and CD showed evidence of adequate reliability, reproducibility, and validity, including moderate-to-high correlations with the pMayo and Inflammatory Bowel Disease Questionnaire score for UC and moderate correlations with the Inflammatory Bowel Disease Questionnaire score for CD.[12,13]

In this study, the primary endpoint was an increase in PRO scores after COVID-19 vaccination. This was defined as an increase by 4 or more in the UC-PRO/SS or the CD-PRO/SS scores after vaccination when compared to the baseline.

SHS is a simple, 4-part visual analog scale questionnaire designed to assess the impact of IBD on health-related quality of life.[14,15] The 4 dimensions include symptom burden, social function, disease-related worry, and sense of general well-being. The scores for each dimension range from 0 to 100.[14,15] In previous studies, patients with IBD in relapse scored higher on each of the 4 SHS questions than patients in remission. Each of the 4 SHS scores was associated with the results of their corresponding health dimension obtained with the other health-related quality of life questionnaires.[16,17] This score was validated in different languages for a variety of IBD patients.[16-18]

4. Statistical Analysis

All numerical values are expressed as means ± standard deviations or numbers (percentages). Continuous variables were compared using the Student *t*-test or Mann-Whitney *U*-test, and categorical variables were compared using the chi-square test or Fisher exact test. Risk factors associated with an increase in PROs after COVID-19 vaccination in each patient group for IBD, UC, and CD were analyzed using logistic regression analysis. Odds ratios (OR) and 95% confidence intervals (CI) were calculated to estimate the effects of variables. In addition, we assessed whether there were differences in variables by vaccine order using multiple pairwise comparisons, especially the linear mixed model. Bonferroni correction was used to avoid the possibility of obtaining false positive results. Statistical significance was set at $P<0.05$. All statistical analyses were performed using IBM SPSS Statistics version 28.0 (IBM Corp., Armonk, NY, USA).

RESULTS

1. Baseline Characteristics

The baseline characteristics of the patients are summarized in Table 1. In total, 47.9% (n=148) of patients had UC and 52.1%

Table 1. Baseline Clinical Characteristics of Patients

Characteristic	Total (n = 309)	UC (n = 148)	CD (n = 161)	*P*-value
Demographic variable				
Age (yr)	40.80 ± 14.30	46.40 ± 15.31	35.65 ± 11.08	< 0.001
Sex				0.082
Male	199 (64.4)	88 (59.5)	111 (68.9)	
Female	110 (35.6)	60 (40.5)	50 (31.1)	
Smoking	24 (7.8)	13 (8.8)	11 (6.8)	0.522
Family history[a]	31 (10.0)	17 (11.5)	14 (8.7)	0.415
Vaccination				
1st	309 (100)			
AstraZeneca	49 (15.9)	37 (25.0)	12 (7.5)	
Pfizer	198 (64.1)	86 (58.1)	112 (69.6)	
Moderna	53 (17.2)	22 (14.9)	31 (19.3)	
Janssen	8 (2.6)	2 (1.3)	6 (3.7)	
Novavax	1 (0.3)	1 (0.7)	0	
2nd	307 (99.4)			
AstraZeneca	32 (10.4)	26 (17.8)	6 (3.7)	
Pfizer	213 (69.4)	96 (65.8)	117 (72.7)	
Moderna	56 (18.2)	22 (15.1)	34 (21.1)	
Janssen	5 (1.6)	1 (0.7)	4 (2.5)	
Novavax	1 (0.3)	1 (0.7)	0	
3rd	251 (81.2)			
AstraZeneca	2 (0.8)	2 (1.6)	0	
Pfizer	181 (72.1)	88 (71.5)	93 (72.7)	
Moderna	67 (26.7)	32 (26.0)	35 (27.3)	
Janssen	0	0	0	
Novavax	1 (0.4)	1 (0.8)	0	
COVID-19 infection	121 (39.2)	54 (3.65)	67 (41.6)	0.356
Self-imposed cessation of medication	27 (8.8)	10 (6.8)	17 (10.6)	0.252
Booster vaccination	251 (81.2)	123 (83.1)	128 (79.5)	0.418
Scores of PRO range				
SHS (0–40)[b]	7.36 ± 7.08	6.65 ± 7.01	8.01 ± 7.10	0.092
PRO/SS(A), IBD (0–12)[c]	2.55 ± 2.25	2.05 ± 1.97	3.01 ± 2.40	< 0.001
UC-PRO/SS(B) (0–28)[c]	-	4.57 ± 3.21	-	
pMayo (0–9)	-	0.94 ± 0.94	-	
CD-PRO/SS(B) (0–16)[c]	-	-	3.01 ± 2.40	
CDAI (0-400)	-	-	74.04 ± 52.52	
Laboratory variable				
Hemoglobin (g/dL)	13.74 ± 1.71	13.82 ± 1.70	13.68 ± 1.72	0.529
WBC count (/μL)	6,174 ± 1,802	6,344 ± 1,842	6,043 ± 1,766	0.192
Platelet count ($\times 10^3$/μL)	263.70 ± 71.84	259.95 ± 80.23	266.60 ± 64.77	0.469
Albumin (g/dL)	4.42 ± 0.40	4.56 ± 0.32	4.31 ± 0.43	< 0.001

(Continued to the next page)

Table 1. Continued

Characteristic	Total (n = 309)	UC (n = 148)	CD (n = 161)	*P*-value
C-reactive protein (mg/dL)	0.30 ± 0.78	0.21 ± 0.45	0.36 ± 0.96	0.125
Lymphocyte count (/μL)[d]	2,154 ± 1,006	2,781 ± 1,118	1,807 ± 742	< 0.001
Platelet-to-lymphocyte ratio[d]	146.14 ± 82.01	100.24 ± 49.83	171.59 ± 85.40	< 0.001
Fecal calprotectin (μg/g)[d]	513.19 ± 891.67	369.33 ± 601.81	622.53 ± 1,051	0.084

Data are presented as means ± standard deviations or numbers (%).
[a]A patient with IBD among first-degree relatives was defined as having a family history.
[b]SHS is a simple, 4-part visual analog scale questionnaire that is designed to assess the impact of IBD on health-related quality of life. Total SHS scores correlated with total Inflammatory Bowel Disease Questionnaire scores in both CD and UC. There was a stepwise increase in SHS scores with increasing disease activity in both CD and UC groups. Reliability was confirmed using test-retest correlations.[14,15]
[c]PROs signs and symptoms of ulcerative colitis and CD (UC-PRO/SS, CD-PRO/SS) were developed to standardize the quantification of gastrointestinal signs and symptoms of patients with IBD including ulcerative colitis and CD through direct reports from patient ratings. These are the first symptom measures of UC and CD to meet U.S. Food and Drug Administration PRO guidelines.[12,13]
[d]The following variables, due to missing values, resulted in differing counts of the total number of patients: lymphocyte count and platelet-to-lymphocyte ratio (total n = 157, UC n = 56, CD n = 101), fecal calprotectin (total n = 132, UC n = 57, CD n = 75).
UC, ulcerative colitis; CD, Crohn's disease; COVID-19, coronavirus disease; PRO, patient-reported outcome; SHS, short health scale; PRO/SS(A), patient-reported outcome signs and symptoms (abdominal symptoms); PRO/SS(B), patient-reported outcome signs and symptoms (bowel signs and symptoms); IBD, inflammatory bowel disease; pMayo, partial Mayo score; CDAI, Crohn's Disease Activity Index; WBC, white blood cell.

(n = 161) had CD. The mean patient age was 40.8 years, and 64.4% (n = 199) of the patients were male. Seven point eight percent of the patients had a smoking history, and 31.0% had a family history.

All the patients included in this study received their first vaccination: 64.1% with Pfizer (n = 198); 17.2% with Moderna (n = 53); 15.9% with AstraZeneca (n = 49); 2.6% with Janssen (n = 8), and 0.3% with Novavax (n = 1). A total of 307 (99.4%) patients received a second vaccine: 69.4% with Pfizer (n = 213), 18.2% with Moderna (n = 56), 10.4% with AstraZeneca (n = 32), 1.6% with Janssen (n = 5), and 0.3% with Novavax (n = 1). A total of 251 (81.2%) patients received a booster vaccine: 72.1% with Pfizer (n = 181), 26.7% with Moderna (n = 67), 0.8% with AstraZeneca (n = 2) and 0.4% with Novavax (n = 1). The number of patients with a history of COVID-19 was 121 (39.2%). Although the medications should not be discontinued, the proportion of patients who self-suspended IBD-related medications owing to adverse effects after vaccination was 8.8% (n = 27). The baseline means were as follows: SHS was 7.36 ± 7.08, CD-PRO/SS(A) was 3.01 ± 2.40, UC-PRO/SS(A) was 2.05 ± 1.97, CD-PRO/SS(B) was 3.01 ± 2.40, and UC-PRO/SS(B) was 4.57 ± 3.21. The mean pMayo score of patients with UC was 0.94 ± 0.94, and the mean CDAI score of patients with CD was 74.04 ± 52.52.

2. Adverse Events after Vaccination

The characteristics of the adverse events after vaccination are summarized in Tables 2 and 3. After vaccination, the proportion of patients who experienced adverse events was 78.3% (n = 242/309), 80.1% (n = 246/307), and 74.5% (n = 187/251) after the 1st, 2nd, and 3rd inoculation, respectively. The most common adverse events after vaccination were injection site pain and redness (1st, 47.6%; 2nd, 45.0%; 3rd, 40.6%), fatigue (1st, 34.3%; 2nd, 31.9%; 3rd, 27.9%), fever (1st, 25.0%; 2nd, 21.5%; 3rd, 19.9%), and general myalgia (1st, 21.7%; 2nd, 16.9%;

Table 2. Incidence of Adverse Events after COVID-19 Vaccination

Adverse events	Vaccination		
	1st (n = 309)	2nd (n = 307)	3rd (n = 251)
No adverse events	67 (21.7)	61 (19.9)	64 (25.5)
Injection site pain, redness	147 (47.6)	138 (45.0)	102 (40.6)
Injection site swelling	31 (10.0)	34 (11.1)	25 (10.0)
Fever	77 (25.0)	66 (21.5)	50 (19.9)
Fatigue	106 (34.3)	98 (31.9)	70 (27.9)
Headache	45 (14.6)	45 (14.7)	35 (13.9)
Chill	44 (14.2)	43 (14.0)	34 (13.5)
General myalgia	67 (21.7)	52 (16.9)	48 (19.1)
Arthralgia	15 (4.9)	13 (4.2)	8 (3.2)
Nausea, vomiting	2 (0.6)	3 (1.0)	1 (0.4)
Lymphadenopathy	0	1 (0.3)	1 (0.4)
Anaphylaxis	0	1 (0.3)	1 (0.4)
Others	18 (5.8)	24 (7.8)	18 (7.2)

Values are presented as numbers (%). Patients were allowed to multi check the corresponding adverse events on the questionnaire.
COVID-19, coronavirus disease.

Table 3. Comparison of the Baseline Clinical Characteristics of Total Patients (n = 309) with and without Aggravated PROs after Vaccination

Characteristic	Patients with aggravated PROs after vaccination (n = 34)[a]	Patients without aggravated PROs after vaccination (n = 275)	*P*-value
Demographic variable			
Age (yr)	36.00 ± 9.58	41.39 ± 14.68	0.006
Age < 40 yr	25 (73.5)	132 (48.0)	0.005
Sex			0.271
Male	19 (55.9)	180 (65.5)	
Female	15 (44.1)	95 (34.5)	
Smoking	3 (8.8)	21 (7.6)	0.737
Family history[b]	3 (8.8)	28 (10.2)	0.804
COVID-19 infection	17 (50.0)	171 (62.2)	0.170
Self-imposed cessation of medication	3 (8.8)	24 (8.8)	1.000
Types of diseases			0.176
UC	20 (58.8)	128 (46.5)	
CD	14 (41.2)	147 (53.5)	
Type of vaccines (mRNA vs. viral-vector)			
1st vaccine; mRNA	26 (76.5)	225 (81.8)	0.451
2nd vaccine; mRNA	31 (91.2)	240 (87.3)	0.513
3rd vaccine; mRNA	33 (97.1)	275 (99.3)	0.214
Booster vaccination	25 (73.5)	226 (82.2)	0.223
Scores of PRO range			
SHS (0–40)[c]	7.59 ± 6.54	7.33 ± 7.15	0.840
PRO/SS(A) IBD (0–12)[d]	2.21 ± 1.89	2.59 ± 2.29	0.345
Laboratory variable			
Hemoglobin, (g/dL)	13.22 ± 2.32	13.79 ± 1.64	0.147
WBC count (/μL)	6,208 ± 2,246	6,171 ± 1,761	0.928
Platelet count ($\times 10^3$/μL)	314.38 ± 107.32	259.06 ± 66.09	0.030
Albumin (g/dL)	4.50 ± 0.41	4.40 ± 0.40	0.302
C-reactive protein (mg/dL)	0.22 ± 0.21	0.31 ± 0.82	0.663
Lymphocyte count (/μL)[e]	2,122 ± 974	2,157 ± 1,012	0.912
Platelet-to-lymphocyte ratio[e]	162.23 ± 63.92	144.93 ± 83.27	0.502
Fecal calprotectin (μg/g)[e]	918.29 ± 997.88	472.68 ± 874.64	0.099

Values are presented as mean ± standard deviation or number (%).
[a]PROs were defined as aggravated when PRO/SS(A) of UC and CD ≥ 4 or PRO/SS(B) of UC and CD ≥ 4.
[b]If there was a patient with IBD among the first-degree relatives, it was defined as having a family history.
[c]SHS is a simple, 4-part visual analog scale questionnaire that is designed to assess the impact of IBD on health-related quality of life. Total SHS scores correlated with total Inflammatory Bowel Disease Questionnaire scores in both CD and UC. There was a stepwise increase in SHS scores with increasing disease activity in both CD and UC groups. Reliability was confirmed using test-retest correlations.[14,15]
[d]PROs signs and symptoms of UC and CD (UC-PRO/SS, CD-PRO/SS) were developed to standardize the quantification of gastrointestinal signs and symptoms of patients with IBD including UC and CD through direct reports from patient ratings. These are the first symptom measures of UC and CD to meet U.S. Food and Drug Administration PRO guidelines.[12,13]
[e]The following variables, due to missing values, resulted in differing counts of the total number of patients: lymphocyte count and platelet-to-lymphocyte ratio (patients with aggravated PROs after vaccination n = 11, patients without aggravated PROs after vaccination n = 146), fecal calprotectin (patients with aggravated PROs after vaccination n = 12, patients without aggravated PROs after vaccination n = 120).
PRO, patient-reported outcome; COVID-19, coronavirus disease; UC, ulcerative colitis; CD, Crohn's disease; mRNA, messenger RNA; SHS, short health scale; PRO/SS(A), patient-reported outcome signs and symptoms (abdominal symptoms); PRO/SS(B), patient-reported outcome signs and symptoms (bowel signs and symptoms); IBD, inflammatory bowel disease; WBC, white blood cells.

Table 4. Comparison of the Baseline Clinical Characteristics of Patients with UC (n = 148) with and without Aggravated PROs after Vaccination

Characteristic	Patients with aggravated PROs after vaccination (n = 20)[a]	Patients without aggravated PROs after vaccination (n = 128)	*P*-value
Demographic variable			
Age (yr)	38.05 ± 10.00	47.70 ± 15.60	0.001
Age < 40 yr	13 (65.0)	36 (28.1)	0.001
Sex			0.958
Male	12 (60.0)	76 (59.4)	
Female	8 (40.0)	52 (40.6)	
Smoking	3 (15.0)	10 (7.8)	0.386
Family history[b]	0	17 (13.3)	0.129
COVID-19 infection	8 (40.0)	46 (35.9)	0.726
Self-imposed cessation of medication	1 (5.0)	9 (7.0)	0.736
Type of vaccines (mRNA vs. viral-vector)			
1st vaccine; mRNA	15 (75.0)	93 (72.7)	0.826
2nd vaccine; mRNA	19 (95.0)	101 (78.9)	0.124
3rd vaccine; mRNA	19 (95.0)	128 (98.4)	0.355
Booster vaccination	15 (75.0)	108 (84.4)	0.336
Scores of PRO range			
SHS (0–40)[c]	6.40 ± 6.75	6.69 ± 7.08	0.865
UC-PRO/SS(A) (0–12)[d]	1.90 ± 1.92	2.08 ± 1.99	0.709
UC-PRO/SS(B) (0–28)[d]	5.05 ± 3.43	4.50 ± 3.18	0.478
pMayo (0–9)	0.91 ± 0.54	0.95 ± 0.97	0.838
Laboratory variable			
Hemoglobin (g/dL)	13.31 ± 2.83	13.87 ± 1.56	0.551
WBC count (/μL)	6,424 ± 2,642	6,336 ± 1,759	0.886
Platelet count ($\times 10^3$/μL)	335.50 ± 122.38	252.32 ± 71.26	0.001
Albumin (g/dL)	4.62 ± 0.29	4.55 ± 0.32	0.502
C-reactive protein (mg/dL)	0.18 ± 0.18	0.21 ± 0.47	0.816
Lymphocyte count (/μL)[e]	2,561 ± 990	1,342 ± 1,362	0.086
Platelet-to-lymphocyte ratio[e]	149.78 ± 77.26	94.42 ± 46.03	0.038
Fecal calprotectin (μg/g)[e]	797.50 ± 1,051.31	299.42 ± 475.20	0.226

Values are presented as mean ± standard deviation or number (%).

[a]PROs were defined as aggravated when PRO/SS(A) of UC and CD ≥ 4 or PRO/SS(B) of UC and CD ≥ 4.

[b]If there was a patient with inflammatory bowel disease (IBD) among the first-degree relatives, it was defined as having a family history.

[c]SHS is a simple, 4-part visual analog scale questionnaire that is designed to assess the impact of IBD on health-related quality of life. Total SHS scores correlated with total Inflammatory Bowel Disease Questionnaire scores in both CD and UC. There was a stepwise increase in SHS scores with increasing disease activity in both CD and UC groups. Reliability was confirmed using test-retest correlations.[14,15]

[d]PROs signs and symptoms of UC and CD (UC-PRO/SS, CD-PRO/SS) were developed to standardize the quantification of gastrointestinal signs and symptoms of patients with IBD including UC and CD through direct reports from patient ratings. These are the first symptom measures of UC and CD to meet U.S. Food and Drug Administration PRO guidelines.[12,13]

[e]The following variables, due to missing values, resulted in differing counts of the total number of patients: lymphocyte count and platelet-to-lymphocyte ratio (patients with aggravated PROs after vaccination n = 4, patients without aggravated PROs after vaccination n = 52), fecal calprotectin (patients with aggravated PROs after vaccination n = 8, patients without aggravated PROs after vaccination n = 49).

UC, ulcerative colitis; PRO, patient-reported outcome; CD, Crohn's disease; COVID-19, coronavirus disease; mRNA, messenger RNA; SHS, short health scale; PRO/SS(A), patient-reported outcome signs and symptoms (abdominal symptoms); PRO/SS(B), patient-reported outcome signs and symptoms (bowel signs and symptoms); pMayo, partial Mayo score; WBC, white blood cells.

Table 5. Comparison of the Baseline Clinical Characteristics of Patients with CD (n = 161) with and without Aggravated PROs after Vaccination

Characteristic	Patients with aggravated PROs after vaccination (n = 14)[a]	Patients without aggravated PROs after vaccination (n = 147)	*P*-value
Demographic variable			
Age (yr)	33.07 ± 8.42	35.90 ± 11.29	0.363
Age < 40 yr	12 (85.7)	96 (65.3)	0.147
Sex			0.133
Male	7 (50.0)	43 (29.3)	
Female	7 (50.0)	104 (70.7)	
Smoking	0	11 (7.5)	0.601
Family history[b]	3 (21.4)	11 (7.5)	0.107
COVID-19 infection	9 (64.3)	58 (39.5)	0.072
Self-imposed cessation of medication	2 (14.3)	15 (10.2)	0.645
Type of vaccines (mRNA vs. viral-vector)			
1st vaccine; mRNA	11 (78.6)	132 (89.8)	0.194
2nd vaccine; mRNA	12 (85.7)	139 (94.6)	0.211
3rd vaccine; mRNA	14 (100)	147 (100)	
Booster vaccination	4 (28.6)	29 (19.7)	0.488
Scores of PRO range			
SHS (0–40)[c]	9.29 ± 6.07	7.88 ± 7.20	0.482
CD-PRO/SS(A) (0–12)[d]	3.57 ± 1.65	4.41 ± 2.42	0.554
CD-PRO/SS(B) (0–16)[d]	2.64 ± 1.82	3.04 ± 2.45	0.204
CDAI (0–400)	73.14 ± 50.29	74.11 ± 52.88	0.953
Laboratory variable			
Hemoglobin (g/dL)	13.15 ± 1.87	13.73 ± 1.71	0.283
WBC count (/μL)	6,012 ± 1,927	6,046 ± 1,760	0.951
Platelet count ($\times 10^3$/μL)	295.18 ± 93.30	264.19 ± 61.66	0.128
Albumin (g/dL)	4.40 ± 0.49	4.30 ± 0.43	0.478
C-reactive protein (mg/dL)	0.27 ± 0.23	0.37 ± 1.00	0.733
Lymphocyte count (/μL)	1,871 ± 942	1,802 ± 731	0.815
Platelet-to-lymphocyte ratio	169.34 ± 60.51	171.76 ± 87.21	0.943
Fecal calprotectin (μg/g)	169.34 ± 60.51	171.75 ± 87.21	0.603

Values are presented as mean ± standard deviation or number (%).
[a]PROs were defined as aggravated when PRO/SS(A) of UC and CD ≥ 4 or PRO/SS(B) of UC and CD ≥ 4.
[b]If there was a patient with inflammatory bowel disease (IBD) among the first-degree relatives, it was defined as having a family history.
[c]SHS is a simple, 4-part visual analog scale questionnaire that is designed to assess the impact of IBD on health-related quality of life. Total SHS scores correlated with total Inflammatory Bowel Disease Questionnaire scores in both CD and UC. There was a stepwise increase in SHS scores with increasing disease activity in both CD and UC groups. Reliability was confirmed using test-retest correlations.[14,15]
[d]PROs signs and symptoms of UC and CD (UC-PRO/SS, CD-PRO/SS) were developed to standardize the quantification of gastrointestinal signs and symptoms of patients with IBD including UC and CD through direct reports from patient ratings. These are the first symptom measures of UC and CD to meet U.S. Food and Drug Administration PRO guidelines.[12,13]
[e]The following variables, due to missing values, resulted in differing counts of the total number of patients: lymphocyte count and platelet-to-lymphocyte ratio (patients with aggravated PROs after vaccination n = 7, patients without aggravated PROs after vaccination n = 94), fecal calprotectin (patients with aggravated PROs after vaccination n = 3, patients without aggravated PROs after vaccination n = 61)
CD, Crohn's disease; PRO, patient-reported outcome; UC, ulcerative colitis; COVID-19, coronavirus disease; mRNA, messenger RNA; SHS, short health scale; PRO/SS(A), patient-reported outcome signs and symptoms (abdominal symptoms); PRO/SS(B), patient-reported outcome signs and symptoms (bowel signs and symptoms); CDAI, Crohn's Disease Activity Index; WBC, white blood cells.

Table 6. Factors Predicting Aggravating PROs[a] in Patients with Inflammatory Bowel Disease Who Were Vaccinated against COVID-19

	Multivariate analysis	
	P-value	OR (95% CI)
Total patients (n = 309)		
Age < 40 yr	0.001	4.255 (1.816–9.968)
UC	0.014	2.654 (1.216–5.794)
UC (n = 148)		
Age < 40 yr	0.003	8.667 (2.062–36.425)
CD (n = 161)		
Male sex	0.034	4.103 (1.115–15.104)

[a]PROs were defined as aggravated when PRO/SS(A) of UC and CD ≥ 4 or PRO/SS(B) of UC and CD ≥ 4.
PRO, patient-reported outcome; COVID-19, coronavirus disease; OR, odds ratio; CI, confidence interval; UC, ulcerative colitis; CD, Crohn's disease; PRO/SS(A), patient-reported outcome signs and symptoms (abdominal symptoms); PRO/SS(B), patient-reported outcome signs and symptoms (bowel signs and symptoms).

3rd, 19.1%). Anaphylaxis occurred twice in 1 patient after receiving AstraZeneca as the second vaccine and Pfizer as the third vaccine, and there were no deaths after vaccination.

3. Risk Factors Related to the Aggravation of PROs after Vaccination

We compared groups with and without aggravation of PROs after vaccination using univariate analysis (Tables 3-5). In all patients, age and platelet count were significantly associated with aggravation of PROs (Table 3). In addition, age, platelet count, and platelet-to-lymphocyte ratio significantly aggravated PROs in UC patients (Table 4). In contrast, risk factors that aggravated PROs were not found in the univariate analysis in CD patients (Table 5).

The independent risk factors, for the aggravation of PROs, in the multivariate analysis were: young age (less than 40 years) (OR, 4.255; 95% CI, 1.816–9.968) and UC (OR, 2.654; 95% CI, 1.216–5.794) in patients with IBD, young age (OR, 8.667; 95% CI, 2.062–36.425) in patients with UC, and male sex in patients with CD (OR, 4.103; 95% CI, 1.115–15.104) (Table 6).

4. Comparison of Serial Variables According to Vaccination Orders

We compared the serial PRO scores and laboratory data obtained at baseline and after each vaccination using multiple pairwise comparisons (Table 7). In all patients, the platelet count significantly increased with continued vaccination. In patients with UC, SHS, UC-PRO/SS(A), and UC-PRO/SS(B) were significantly aggravated with continued vaccination. Moreover, there was no significant increase in the number of CD patients. The variables that significantly increased as vaccination continued are plotted in Fig. 2.

DISCUSSION

Concerns regarding adverse events after vaccination were a key factor behind the reluctance of patients with chronic immune-mediated diseases to be vaccinated against COVID-19.[19] In this study, the incidence of adverse events after COVID-19 vaccination in patients with IBD was similar to that of a previous study with IBD patients and comparable to studies on the general population.[20-22]

Several clinical studies have evaluated IBD exacerbation after vaccination against various viral and bacterial pathogens. In one prospective observational study, among 67 IBD patients vaccinated with the recombinant herpes zoster vaccine, only 1 (1.5%) experienced an IBD flare after vaccination.[4] In another prospective observational study, disease exacerbation related to the influenza vaccine was reported in 2 patients (2.2%) out of 92 with CD receiving anti-TNF.[5] According to one study assessing the change in IBD activity after pneumococcal vaccination, 10 of 306 patients (3.3%; 7 patients with CD and 3 with UC) experienced an increase in IBD activity within the 2-month follow-up.[6] In one meta-analysis study, the pooled incidence was 2% (95% CI, 1%–4%) when analyzing 10 studies regarding the exacerbation of IBD patients after receiving influenza, pneumococcus, recombinant herpes zoster, and hepatitis B vaccines.[23] However, little is known about whether COVID-19 vaccinations exacerbate IBD.

In a recent large controlled retrospective study to determine whether the COVID-19 vaccination was associated with a flare of disease in patients with IBD, there were no substantive differences in disease outcomes between vaccinated and unvaccinated patients.[24] In this study, the baseline disease severity of patients with IBD was assessed based on laboratory variables such as C-reactive protein, erythrocyte sedimentation rate, platelets, hemoglobin, white blood count, and albumin.

The recent focus of IBD treatment has shifted to its prevention and management, targeting both clinical and endoscopic remission using a "treat-to-target" approach.[25] Along with clinical remission, endoscopic healing, and absence of disability, restoration of quality of life is considered the most important long-term achievable treatment target for patients with IBD.

Various PROs have been developed, validated, and utilized

Table 7. Comparison of the Serial PRO Scores and Laboratory Data by Vaccine Orders in Patients with IBD Vaccinated against COVID-19 Using a Linear Mixed Model

	P-value	Post-hoc analysis	
		P-value (Bonferroni)	Pairwise comparison
Total (n = 309)			
SHS[a]	0.074		
PRO/SS(A), IBD[b]	0.141		
Hemoglobin	0.820		
WBC count	0.862		
Lymphocyte count	0.459		
Platelet count	0.004	0.007 (baseline–3rd)	Baseline vs. 3rd (265.95 vs. 276.79)
		0.016 (1st–3rd)	1st vs. 3rd (265.84 vs. 276.79)
Albumin	0.323		
C-reactive protein	0.288		
Fecal calprotectin	0.945		
Platelet-to-lymphocyte ratio	0.596		
UC (n = 148)			
SHS[a]	0.041	0.040 (1st–3rd)	1st vs. 3rd (6.31 vs. 7.94)
UC-PRO/SS(A)[b]	0.007	0.045 (baseline–3rd)	Baseline vs. 3rd (2.05 vs. 2.56)
		0.014 (1st–3rd)	1st vs. 3rd (2.05 vs. 2.56)
		0.006 (2nd–3rd)	2nd vs. 3rd (2.12 vs. 2.56)
UC-PRO/SS(B)[b]	0.012	0.023 (1st–3rd)	1st vs. 3rd (4.49 vs. 5.42)
		0.009 (2nd–3rd)	2nd vs. 3rd (4.62 vs. 5.42)
pMayo	0.051		
Hemoglobin	0.257		
WBC count	0.494		
Lymphocyte count	0.951		
Platelet count	0.113		
Albumin	0.159		
C-reactive protein	0.234		
Fecal calprotectin	0.976		
Platelet-to-lymphocyte ratio	0.091		
CD (n = 161)			
SHS[a]	0.353		
CD-PRO/SS(A)[b]	0.848		
CD-PRO/SS(B)[b]	0.629		
CDAI	0.106		
Hemoglobin	0.981		
WBC count	0.650		
Lymphocyte count	0.218		
Platelet count	0.041	0.052 (1st–3rd)	
Albumin	0.771		
C-reactive protein	0.181		

(Continued to the next page)

Table 7. Continued

	P-value	Post-hoc analysis	
		P-value (Bonferroni)	Pairwise comparison
Fecal calprotectin	0.792		
Platelet-to-lymphocyte ratio	0.951		

[a]SHS is a simple, 4-part visual analog scale questionnaire that is designed to assess the impact of IBD on health-related quality of life. Total SHS scores correlated with total Inflammatory Bowel Disease Questionnaire scores in both CD and UC. There was a stepwise increase in SHS scores with increasing disease activity in both CD and UC groups. Reliability was confirmed using test-retest correlations.[14,15]

[b]PROs signs and symptoms of UC and CD (UC-PRO/SS, CD-PRO/SS) were developed to standardize the quantification of gastrointestinal signs and symptoms of patients with IBD including UC and CD through direct reports from patient ratings. These are the first symptom measures of UC and CD to meet U.S. Food and Drug Administration PRO guidelines.[12,13]

PRO, patient-reported outcome; IBD, inflammatory bowel disease; COVID-19, coronavirus disease; SHS, short health scale; PRO/SS(A), patient-reported outcome signs and symptoms (abdominal symptoms); PRO/SS(B), patient-reported outcome signs and symptoms (bowel signs and symptoms); WBC, white blood cell; UC, ulcerative colitis; pMayo, partial Mayo score; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index.

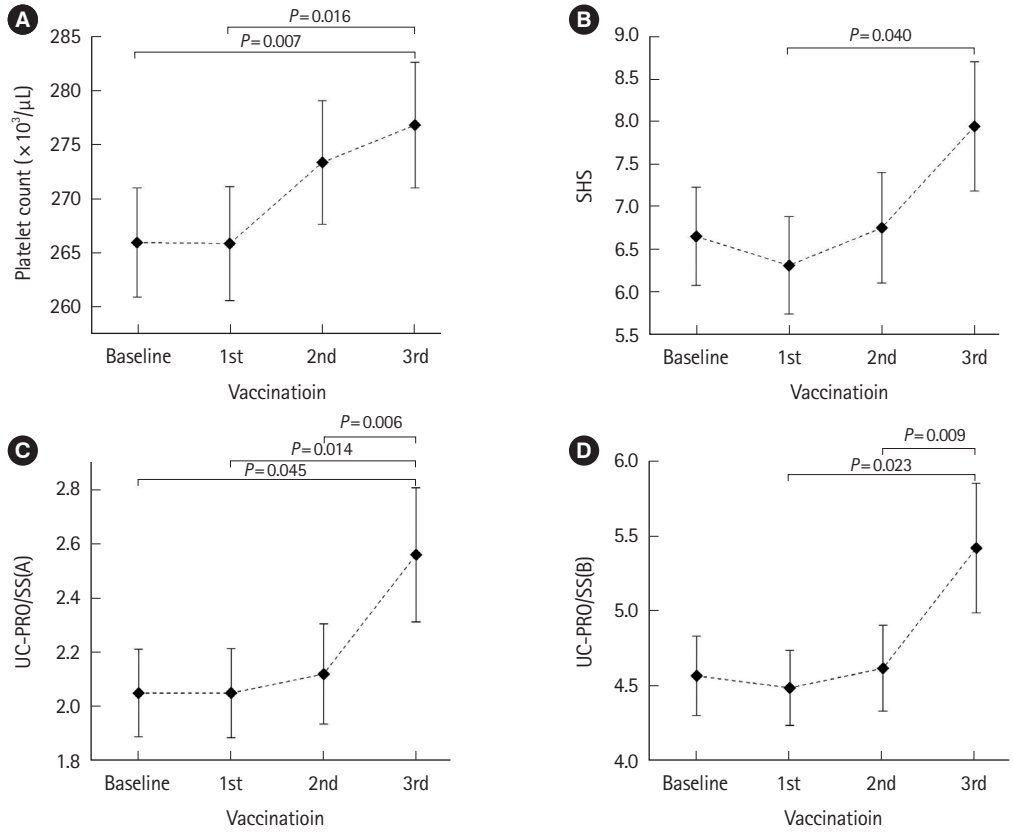

Fig. 2. The comparison of the serial patient-reported outcome scores and laboratory data by vaccine orders in the patients with inflammatory bowel disease vaccinated against COVID-19 using a linear mixed model: focusing on the variables evaluated as statistically significant. (A) In all patients, the platelet count significantly increased with continued vaccination. (B-D) In patients with ulcerative colitis (UC), SHS, UC-PRO/SS(A), UC-PRO/SS(B) were significantly aggravated with continued vaccination. SHS, short health scale; UC-PRO/SS(A), patient-reported outcomes signs and symptoms (abdominal symptoms) of UC; UC-PRO/SS(B), patient-reported outcomes signs and symptoms (bowel signs and symptoms) of UC; COVID-19, coronavirus disease.

in studies related to patients with IBD.[10] In this study, UC-PRO/SS and CD-PRO/SS, which met the U.S. FDA PRO guidelines for the first time, were used to assess disease aggravation.[12,13]

We found that UC is an independent risk factor for worsening PROs in patients with IBD. In addition, SHS, UC-PRO/SS(A), and UC-PRO/SS(B) were aggravated significantly with continued vaccination in patients with UC, whereas there

were no variables that increased risk significantly in patients with CD. Although the exact cause is not known, it could be due to the difference in pathophysiology between UC and CD.[26] The pathogenesis of IBD, including UC and CD, originates from a specific immunoinflammatory pathway, and it is known that T cells are one of the most important immune-related cells in this process.[26-28] However, T-cell profiles are disparate in UC and CD. T helper (Th) 1- and Th17-mediated immune responses are major processes in the pathophysiology of CD.[26] In contrast, atypical Th2 responses, mediated by natural killer T cells, are the main pathogenesis of UC.[27,28] Therefore, it can be speculated that the difference in T cell types involved in the pathogenesis of the 2 diseases causes a difference in the aggravation of PROs after vaccination. Translational research to precisely elucidate the mechanism of the influence of COVID-19 vaccination on the aggravation of PRO for UC is needed in the future.

In this study, young age was investigated as an independent risk factor for aggravating PROs in patients with IBD and UC. Recent studies have revealed that immunoglobulin G antibody titers against the SARS-CoV-2 spike protein and frequencies of neutralizing antibody titers after vaccination against COVID-19 were significantly higher in younger participants.[29] Therefore, it might be assumed that the elevated immune response in young patients influenced the aggravation of PROs in patients with IBD.

Male gender was identified as an independent risk factor for worsening PROs in patients with CD who received the COVID-19 vaccines in this study. In Asia, a higher prevalence of CD has been reported in males,[30] and there has been a report identifying males as the sole risk factor for the occurrence of complications in CD.[31] This suggests that in Asian IBD patients, autoimmune responses exacerbating CD activity might occur more prominently in males than females. Based on this, a cautious inference can be made that the immune response to COVID-19 vaccination might have a more significant impact on disease exacerbation in males compared to females. Molecular-level studies on gender-specific immune responses after COVID-19 vaccination in IBD patients should be conducted in the future.

Our study found that IBD patients with aggravated PROs after vaccination had significantly higher baseline platelet counts than those without; moreover, platelet counts increased significantly with continued vaccination. Several recent studies have reported that platelet abnormalities and increased platelet counts are observed in patients with IBD, suggesting that platelet activation is an important factor in the pathogenesis and severity of IBD.[32,33] Increased platelet counts have also been considered as biomarkers for assessing disease activity in IBD.[34,35] Therefore, the findings related to platelets in this study are in line with those of previous studies.

To the best of our knowledge, this is the first study to evaluate the risk factors for aggravating PROs after COVID-19 vaccination in patients with IBD. In this study, as the patients' PROs were investigated using a questionnaire survey, it was possible to comprehend the degree of disease exacerbation that the patients actually felt after vaccination. Moreover, 'clinically inactive' patients who did not complain of apparent symptoms and had not changed their medication, including the dose for IBD treatment, within 1 year before the first vaccination were included in this study. This strict inclusion criterion enabled accurate detection of the vaccine effect in patients with IBD. Third, a well-controlled group of patients in terms of vaccination was included in the study to minimize selection bias. The rate of one or more doses of COVID-19 vaccination in Korea was 87.2%, and the rate of 2 or more vaccinations was 86.4%,[36] which was much higher than the global rates of 63.9% and 29.2%, and the U.S. rates of 67.8% and 33.5%.[1] In addition, as patients were treated at 4 specialized IBD clinics in three large cities in Korea, patients were selected regionally without being concentrated in one region.

This study had several limitations. First, as the questionnaire survey was conducted during outpatient clinic visits, the results might have been influenced by recall bias. Second, the study enrolled 309 patients, a relatively small sample size. However, by including only patients defined as "clinically inactive" at the baseline through strict inclusion criteria, more accurate results were obtained despite the small sample. Third, due to limitations in sample size, patients who received all 5 types of COVID-19 vaccines were collectively analyzed. Future research should recruit more patients to assess the impact of each vaccine on IBDs. Fourth, the study did not investigate the types of medications taken by patients, suggesting a need for future research to explore if PROs' impact varies with medication type. Fifth, the study examined only baseline PROs before vaccination and PROs within 3 months after each vaccination, lacking data on whether the worsening of PROs persisted beyond the 3-month follow-up. Future research should examine disease exacerbation beyond 3 months post-vaccination. Sixth, information on patients' endoscopic inflammation was not collected, indicating a need for subsequent research to determine if PRO changes corre-

late with endoscopic inflammation. Lastly, the study focused solely on South Korean participants and was conducted at 4 tertiary referral hospitals in different regions (Seodaemun-gu, Seoul; Songpa-gu, Seoul; Haeundae-gu, Busan; Jung-gu, Daejeon), with no significant differences in patient group characteristics among these hospitals. Future research should explore potential demographic, ethnic, or regional factors affecting study results.

In conclusion, PROs in patients with IBD, especially UC, worsened after vaccination against COVID-19, with the exception of patients with CD. Moreover, young age and UC were found to be independent risk factors for aggravating PRO. Therefore, there may be a need to counsel patients with IBD younger than 40 years of age and patients with UC before they receive COVID-19 vaccinations.

ADDITIONAL INFORMATION

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Conflict of Interest

Park YE, Park J, and Cheon JH are editorial board members of the journal but were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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Not applicable.

Author Contributions

Conceptualization: Park YE, Kang SB, Park SH, Park SJ. Data curation: Ji JH, Shin SH, Park YE, Kang SB. Formal analysis: Ji JH, Shin SH. Investigation: Ji JH, Shin SH, Park YE, Kang SB, Park SH, Park SJ. Methodology: Ji JH, Park SJ. Project administration: Kang SB, Park SH, Park SJ. Resources: Kang SB, Park SH, Park SJ. Software: Ji JH, Park SJ. Supervision: Kang SB, Park SH, Park SJ. Validation: Park YE, Park J, Park JJ, Cheon JH, Kim TI, Kang SB, Park SH, Park SJ. Visualization: Ji JH. Writing - original draft: Ji JH. Writing - review & editing: Ji JH, Park SJ. Approval of final manuscript: all authors.

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ORCID

Ji JH https://orcid.org/0009-0001-0427-9411
Shin SH https://orcid.org/0000-0003-4131-1932
Park YE https://orcid.org/0000-0003-4274-8204
Park J https://orcid.org/0000-0002-5836-8735
Park JJ https://orcid.org/0000-0001-9974-1658
Cheon JH https://orcid.org/0000-0002-2282-8904
Kim TI https://orcid.org/0000-0003-4807-890X
Kang SB https://orcid.org/0000-0002-1946-7896
Park SH https://orcid.org/0000-0002-5366-5749
Park SJ https://orcid.org/0000-0003-0699-6809

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