

# SARS-CoV-2-inactivated vaccine hesitancy and the safety in inflammatory bowel disease patients: a single-center study

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## Abstract

**Background:** The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) vaccine is thought to be the most effective preventive method of controlling the coronavirus disease 2019 (COVID-19) epidemic. Some patients with immune-related diseases, including inflammatory bowel disease (IBD) patients, however, may hesitate to be vaccinated for various reasons. Although several guidelines recommend vaccinating all IBD patients with inactivated SARS-CoV-2 vaccines, there is still a lack of real-world data on the safety of inactivated SARS-CoV-2 vaccines and COVID-19 vaccination rate in IBD patients. In this study, we investigated the reasons for hesitancy in COVID-19 vaccination, the COVID-19 vaccination rate, and the safety of SARS-CoV-2-inactivated vaccination in patients with IBD.

**Methods:** This was a retrospective study. A total of 418 participants with IBD were enrolled to calculate the vaccination rates. A total of 232 patients with IBD who did not receive SARS-CoV-2 vaccination were recruited to investigate the reasons for hesitation. A follow-up survey of 151 IBD patients and 188 healthy participants who had received the SARS-CoV-2-inactivated vaccination was conducted to analyze adverse reactions.

**Results:** The COVID-19 vaccination rate was 49.3% and almost half of the participants were 'Concerned about the safety of the vaccine (such as adverse reactions) due to IBD'. After SARS-CoV-2 vaccination, adverse reactions were mild or moderate. The adverse reactions in the IBD and non-IBD populations were roughly the same, and IBD medications did not increase the risk of adverse reactions.

**Conclusion:** SARS-CoV-2-inactivated vaccination rates in IBD patients are still low and a significant proportion of patients are hesitant about the vaccine because of safety concerns. SARS-CoV-2-inactivated vaccination in patients with IBD appears to be safe.

**Keywords:** COVID-19, IBD, SARS-CoV-2-inactivated vaccination

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## Introduction

As of 19 November 2021, the number of coronavirus disease 2019 (COVID-19) cases recorded globally has exceeded 255 million and the number of deaths has exceeded 5.1 million.<sup>1</sup> The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) vaccine is thought to be the most effective preventive method for controlling the COVID-19 epidemic. Some patients with immune-related diseases, such as inflammatory bowel disease (IBD), however, may hesitate to be

vaccinated for various reasons, including concerns about the interaction between vaccines and IBD medications.<sup>2,3</sup> Several important types of vaccines include inactivated virus, live attenuated, viral-vector, nucleic acid, and protein-based vaccines.<sup>4,5</sup> Compared with other vaccines, inactivated vaccines are more widely recommended for IBD patients because of their higher safety profile<sup>3,6,7</sup> (a comparison of several types of vaccines is shown in Supplemental Table 1). To date, three inactivated SARS-CoV-2 vaccines

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**Table 1.** Participant characteristics of vaccinated IBD patients (N1) and unvaccinated IBD patients (N2).

	Vaccinated IBD patients (N1 = 206)	Unvaccinated IBD patients (N2 = 212)	$\chi^2$	p value
Diagnosis				
Crohn's disease	68.0% (140/206)	72.2% (153/212)	0.8828	0.3474
Ulcerative disease	26.2% (54/206)	23.6% (50/212)	0.3863	0.5343
Indeterminate colitis	5.8% (12/206)	4.2% (9/212)	0.5466	0.4597
Sex				
Male	56.3% (116/206)	63.2% (134/212)	2.0674	0.1505
Female	43.7% (90/206)	36.8% (78/212)	2.0674	0.1505
Age				
Mean ( SD)	36.7 (12.11)	33.9 (11.46)	NA	0.0139
Median (IQR)	34 (27–46)	31.5 (25–40)	NA	0.0116
Current IBD medications				
None	10.3% (20/206)	11.3% (23/212)	0.1472	0.7012
5-aminosalicylic acid	17.0% (43/206)	16.6% (28/212)	4.3547	0.0369
Glucocorticoid	1.4% (3/206)	2.0% (3/212)	0.0013	1
Immunosuppressant	19.4% (46/206)	21.8% (35/212)	2.2657	0.1323
Biologics	53.8% (88/206)	57.6% (137/212)	20.1695	<0.0001
Chinese traditional medicine	2.2% (6/206)	2.0% (3/212)	1.1121	0.3322
IBD, inflammatory bowel disease; IQR, interquartile range; SD, standard deviation.				

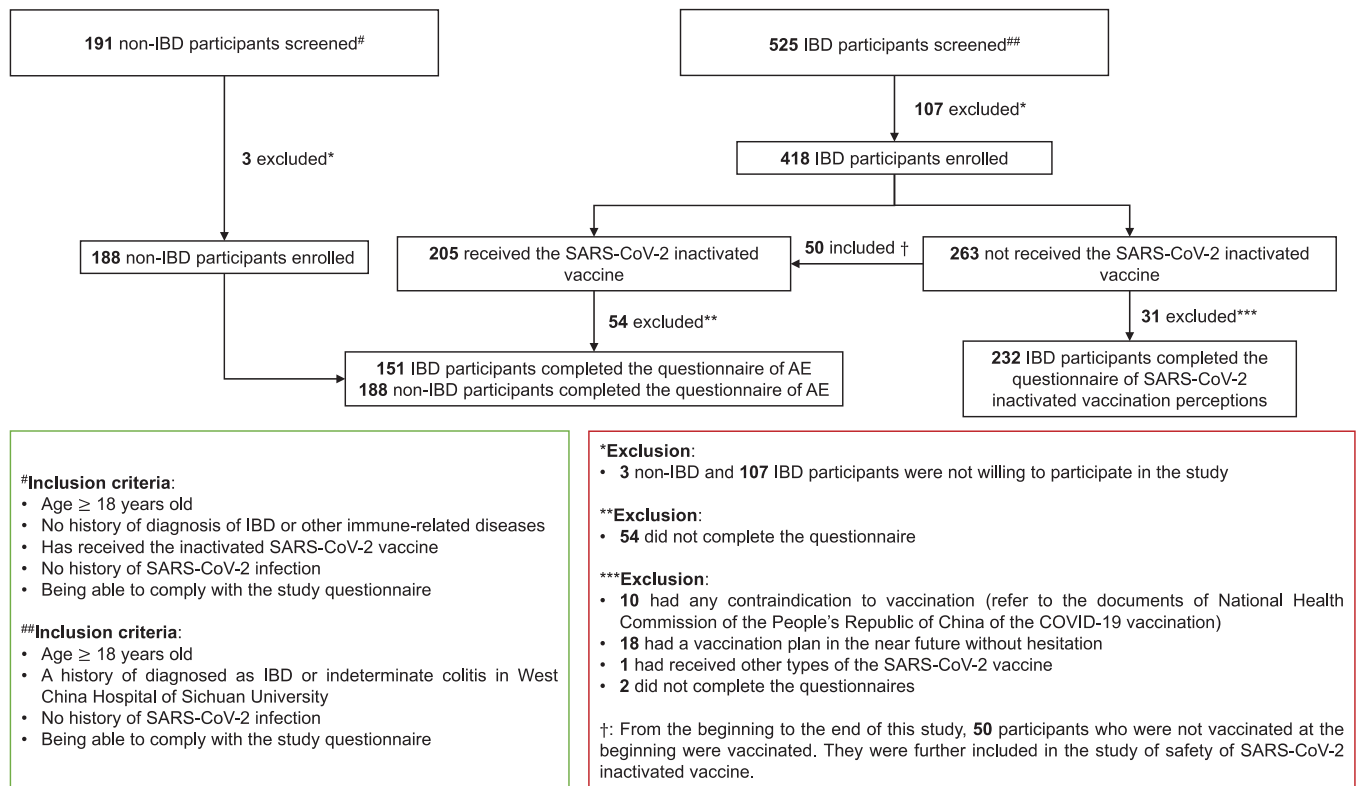
(BBIBP-CorV,<sup>8</sup> CoronaVac,<sup>9</sup> and COVIL0<sup>10</sup>) have been approved in China and other countries and regions worldwide. Although several guidelines recommend vaccinating all patients with IBD using preferentially inactivated SARS-CoV-2 vaccines, there is a paucity of direct data on their safety in this patient group.<sup>2,11–14</sup> In this study, we investigated SARS-CoV-2 vaccination hesitancy, SARS-CoV-2 vaccination status, and adverse event (AE) types and frequency after SARS-CoV-2-inactivated vaccine administration.

## Methods

### Study design and populations

This study utilized a retrospective design that followed the STROBE guidelines for reporting observational studies.<sup>15</sup> Patients with IBD or

IBD unclassified (IBDU) at the West China Hospital of Sichuan University, the largest IBD center in Southwest China, were included. In addition, healthy controls (HCs) were enrolled from the Health Physical Examination Center. The inclusion criteria for IBD patients were as follows: (1) age  $\geq$  18 years, (2) confirmed IBD/IBDU, (3) no history of SARS-CoV-2 infection, and (4) ability to complete the study questionnaire. The diagnosis of IBD was based on the 3rd European evidence-based consensus.<sup>16,17</sup> Eligible HCs were non-IBD patients aged  $\geq$  18 years who were not diagnosed with IBD or any other immune-related disorders and had no history of SARS-CoV-2 infection. Participants who did not complete the questionnaire were excluded from the study. A flowchart of the study design is shown in Figure 1.



**Figure 1.** Study profile.

This study was approved by the academic committee of the West China Hospital of Sichuan University and informed consent was obtained from all participants.

### Data collection

We conducted a real-name survey using an online questionnaire and telephone follow-up from 7 January 2021 to 29 July 2021. Three components of data were collected: (1) the COVID-19 vaccination status of the IBD population, (2) the reasons why the IBD population hesitated to receive the COVID-19 vaccination, and (3) the type and frequency of AEs after SARS-CoV-2-inactivated vaccine administration.

*Component 1: the COVID-19 vaccination status of the IBD population.* The vaccination status of each participant was monitored until 29 July 2021, which was the last day of follow-up. Participants who received at least one dose of SARS-CoV-2-inactivated vaccines were counted as vaccinated.

*Component 2: the reasons why the IBD population hesitated to receive the COVID-19 vaccination.* When enrolled, participants who did not receive the COVID-19 vaccine were asked if they (1) would receive the vaccine as soon as possible without hesitation and (2) had vaccine hesitancy. Those who selected option (2) were asked why they hesitated to receive the vaccine.

*Component 3: the type and frequency of AEs after SARS-CoV-2-inactivated vaccine administration in IBD participants.* Participants who received at least one dose of SARS-CoV-2-inactivated vaccine (BBIBP-CorV,<sup>8</sup> CoronaVac,<sup>9</sup> or COVIL<sup>10</sup>) were defined as vaccinated. All vaccinated patients included in this component received follow-up phone calls/questionnaires at 7 and 28 days after vaccination. The participants who received the SARS-CoV-2-inactivated vaccines were surveyed regarding the type and frequency of the AEs that occurred within 7 and 28 days after the first or second doses of inactivated SARS-CoV-2 vaccine (the grading scale is provided in Supplemental Tables 2 and 3, refer to the documents of the China Food

**Table 2.** Participant characteristics of IBD participants who have COVID-19 vaccination hesitancy.

	IBD (N = 232)
Diagnosis	
Crohn's disease	77.6% (180/232)
Ulcerative disease	22.4% (52/232)
Sex	
Male	61.2% (142/232)
Female	38.8% (90/232)
Age	
Mean (SD)	34.23 (11.33)
Median (IQR)	32 (25–42)
Current IBD medications	
None	11.6% (27/232)
5-aminosalicylic acid	12.9% (30/232)
Glucocorticoid	2.2% (5/232)
Immunosuppressant	18.1% (42/232)
Biologics	59.1% (137/232)
Chinese traditional medicine	1.7% (4/232)
Reasons for COVID-19 vaccination hesitancy	
Concerned about the safety of vaccine (such as AE) due or not due to IBD	47.4% (110/232)
Concerned the vaccine will aggravate IBD	36.2% (84/232)
Concerned about the effectiveness of vaccine due or not due to IBD	4.3% (10/232)
Concerned about the interaction between vaccine and IBD medication	34.1% (79/232)
Do not think vaccination is necessary	4.7% (11/232)
The attending physician did not advice IBD patients to receive the vaccines	7.8% (18/232)
Just 'watch-and-wait'	0.9% (2/232)
AE, adverse event; COVID-19, coronavirus disease 2019; IBD, inflammatory bowel disease; IQR, interquartile ranges.	

and Drug Administration for the classification of AEs<sup>18</sup>). The incidence of adverse reactions was compared between patients with IBD and HCs.

#### Statistical analysis

Continuous variables were presented as median values with interquartile ranges (IQRs), while categorical variables were presented as percentages.

Student's *t* test, Mann–Whitney *U* test, and chi-square test were performed to compare the participant characteristics between the two populations. Chi-square, Fisher's exact test, or Pearson's chi-square test were used to compare the differences in local AEs, systemic AEs, and overall AEs between the two groups. Univariate analysis was used to calculate odds ratios (ORs) of predictors (such as 'IBD', 'Crohn's disease',

**Table 3.** Participant characteristics of those who had SARS-CoV-2-inactivated vaccination.

	IBD (N = 151)	HC (N = 188)	$\chi^2$	p value
Diagnosis				
Crohn's disease	64.9% (98/151)	NA	NA	NA
Ulcerative disease	29.8% (45/151)	NA	NA	NA
Indeterminate colitis	5.3% (8/151)	NA	NA	NA
Sex				
Male	53.0% (80/151)	50.5% (95/188)	0.201	0.6539
Female	47.0% (71/151)	49.5% (93/188)	0.201	0.6539
Age				
Mean (SD)	36.25 (11.21)	35.62 (11.54)		0.6107
Median (IQR)	34 (27–45)	32 (24–46)		0.3782
Vaccine type				
BBIBP-CorV	41.1% (62/151)	45.7% (86/188)	0.7473	0.3873
CoronaVac	58.3% (88/151)	52.7% (99/188)	1.0688	0.3012
COVILO	0.7% (1/151)	1.6% (3/188)	0.6258	0.6318
Current IBD medications				
None	7.9% (12/151)	NA	NA	NA
5-aminosalicylic acid	21.9% (33/151)	NA	NA	NA
Glucocorticoid	1.3% (2/151)	NA	NA	NA
Immunosuppressant	25.8% (39/151)	NA	NA	NA
Biologics	41.1% (62/151)	NA	NA	NA
Chinese traditional medicine	4.6% (7/151)	NA	NA	NA
HC, healthy control; IBD, inflammatory bowel disease; IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; SD, standard deviation.				

'ulcerative disease', sex, vaccine type, and type of IBD medication) associated with AEs following SARS-CoV-2-inactivated vaccination. The statistical software used was R version 3.5.3. A *p* value <0.05 was considered statistically significant.

## Results

### COVID-19 vaccination status in IBD population

There were 212 participants with IBD who did not receive the COVID-19 vaccine and 206 IBD participants who received at least one dose of the

SARS-CoV-2 vaccine (205 received inactivated vaccines and one used recombinant vaccines). The SARS-CoV-2 vaccination rate was 49.3% in the IBD population. The characteristics of all 418 enrolled IBD participants are shown in Supplemental Table 4 and there was no significant difference between all 418 enrolled IBD participants and 344 IBD patients who completed further questionnaires (Supplemental Table 4).

In this component, the characteristics of vaccinated and unvaccinated IBD patients were also

compared. As shown in Table 1, the unvaccinated IBD patients were significantly younger than the vaccinated IBD patients. The median age was 34 (IQR = 27–46) years for vaccinated IBD patients and 31.5 (IQR = 25–40) years for unvaccinated IBD patients. Compared with vaccinated IBD patients, a significantly higher proportion of unvaccinated IBD patients used biologics (57.6% versus 53.8%,  $p < 0.0001$ ), whereas fewer used 5-aminosalicylic acid (5-ASA) as an IBD medication (16.6% versus 17.0%,  $p = 0.0369$ ). In addition, vaccination coverage in IBD patients was independent of sex and disease type.

#### *Reasons of SARS-CoV-2 vaccination hesitancy in IBD patients*

There were 263 IBD patients who did not receive the SARS-CoV-2-inactivated vaccine, 232 completed the survey, and 31 were excluded (10 had contraindications to vaccination, 18 had a vaccination plan in the near future without hesitation, one had received other types of the COVID-19 vaccine, and two did not complete the questionnaire). The former included 168 (77.6%) patients with Crohn's disease (CD) and 49 (22.4%) with ulcerative colitis (UC). The median patient age was 32 (IQR = 25–42) years. The patients' characteristics are presented in Table 2.

The most common reason for SARS-CoV-2 vaccination hesitancy was 'Concerned about the safety of vaccines (such as AE) due to IBD' (47.4%). A total of 36.2% of participants selected 'Concerned vaccine will aggravate IBD', approximately one-third (34.1%) of the participants selected 'Concerned about the interaction between the vaccine and IBD medication', and 4.3% of participants selected 'Concerned about the effectiveness of vaccine because or not because of IBD' (Table 2). In addition, 7.8% of patients selected 'The attending physician did not advise IBD patients to receive the vaccines'.

Fifty IBD participants hesitated at the beginning but received SARS-CoV-2 vaccines by the end of the follow-up period. The main reason for the change in mind was the recommendation by attending doctors.

#### *Safety analysis of SARS-CoV-2-inactivated vaccination among the IBD population and non-IBD population*

A total of 151 patients with IBD and 188 HCs who had received SARS-CoV-2-inactivated vaccination were enrolled in this component of the study. Of the former, 62 received BBIBP-CorV (41.1%), 88 received CoronaVac (58.3%), and one received COVILO (0.7%). Of the latter, 68 received BBIBP-CorV (45.7%), 99 received CoronaVac (52.7%), and three received COVILO (1.6%). The median age was 34 (IQR = 27–45) years for patients with IBD and 32 (IQR = 24–46) years for HCs. There was no statistically significant difference in sex, age, or vaccine type between IBD patients and HCs (Table 3).

All AEs, including injection-site and systemic AEs, were mild (grade 1) or moderate (grade 2) in severity. In IBD vaccine recipients, 90 of 151 (59.6%) had mild or moderate AEs within 7 days of inactivated vaccine administration compared with 112 (59.6%) of 188 vaccine recipients without IBD [odds ratio (OR) = 1.023; 95% confidence interval (CI) = 0.662–1.583]. There was no statistically significant difference between the two groups ( $p = 0.9957$ ) (Table 4).

The most common injection-site adverse reaction in both groups was 'pain', occurring in 81 (53.6%) of 151 IBD participants, compared with 97 (51.6%) of 188 recipients without IBD. There was no statistically significant difference in injection-site AEs ('pain', 'redness', and 'swelling') within 7 days of administration between the groups ( $p_1 = 0.7076$ ,  $p_2 = 1$ ,  $p_3 = 0.4747$ ).

In both groups, the most common systemic AE after either vaccination was 'fatigue', reported in 28 (18.5%) of 151 IBD recipients, compared with 37 (19.7%) of 188 non-IBD recipients; there was no statistically significant difference between the two groups ( $p = 0.7914$ ). Similarly, there was no statistically significant difference regarding other systemic AEs, including 'vomiting', 'diarrhea', 'fever', 'headache', and 'new or worsened joint pain', between the two groups. Regarding 'new or worsened muscle pain', the overall and grade 1 incidences were not significantly different between the two groups. The incidence of grade 2 AEs was significantly lower ( $p = 0.0098$ ) in patients with IBD.

**Table 4.** Adverse reactions and AEs after SARS-CoV-2-inactivated vaccinations.

	IBD (N = 151)	HC (N = 188)	$\chi^2$	p value
All adverse reactions within 7 days				
Any	59.6% (90/151)	59.6% (112/188)	<0.0001	0.9958
Injection-site adverse reactions within 7 days				
Pain	53.6% (81/151)	51.6% (97/188)	0.1407	0.7076
Grade 1	48.3% (73/151)	46.3% (87/188)	0.1437	0.7047
Grade 2	5.3% (8/151)	5.3% (10/188)	<0.0001	0.9931
Redness	2.6% (4/151)	3.2% (6/188)	0.0861	>0.9999
Grade 1	2.6% (4/151)	3.2% (6/188)	0.0861	>0.9999
Grade 2	0	0	–	–
Swelling	6.0% (9/151)	4.3% (8/188)	0.5110	0.4747
Grade 1	6.0% (9/151)	4.3% (8/188)	0.5110	0.4747
Grade 2	0	0	–	–
Systemic adverse reactions within 7 days				
Vomiting	1.3% (2/151)	0.5% (1/188)	0.5997	0.5876
Grade 1	1.3% (2/151)	0.5% (1/188)	0.5997	0.5876
Grade 2	0	0	–	–
Diarrhea	5.3% (8/151)	1.6% (3/188)	3.6560	0.0681
Grade 1	4.6% (7/151)	1.6% (3/188)	2.7033	0.1167
Grade 2	0.7% (1/151)	0	1.2487	0.4454
Fever	0.7% (1/151)	0.5% (1/188)	0.0243	>0.9999
Grade 1	0.7% (1/151)	0.5% (1/188)	0.0243	>0.9999
Grade 2	0	0	–	–
Headache	4.0% (6/151)	5.3% (10/188)	0.3372	0.5615
Grade 1	3.3% (5/151)	5.3% (10/188)	0.7983	0.3716
Grade 2	0.7% (1/151)	0	1.2487	0.4454
Fatigue	18.5% (28/151)	19.7% (37/188)	0.0700	0.7914
Grade 1	16.6% (25/151)	16.0% (30/188)	0.0221	0.8818
Grade 2	2.0% (3/151)	3.7% (7/188)	0.8822	0.5214
Chills	0.7% (1/151)	0	1.2487	0.4454
Grade 1	0.7% (1/151)	0	1.2487	0.4454

*(Continued)*



**Table 4.** (Continued)

	IBD (N = 151)	HC (N = 188)	$\chi^2$	p value
Grade 2	0	0	–	–
New or worsened muscle pain	9.3% (14/151)	14.4% (27/188)	2.0408	0.1531
Grade 1	9.3% (14/151)	10.1% (19/188)	0.0664	0.7966
Grade 2	0	4.3% (8/188)	6.5808	0.0098
New or worsened joint pain	2.6% (4/151)	2.1% (4/188)	0.0988	>0.9999
Grade 1	2.6% (4/151)	1.6% (3/188)	0.4594	0.7044
Grade 2	0	0.5% (1/188)	0.8056	>0.9999
Other suspected AEs within 28 days <sup>a</sup>	1.3% (2/151)	0	2.5048	0.1977

AEs, adverse events; HC, healthy control; IBD, inflammatory bowel disease; SARS-CoV-2, severe acute respiratory syndrome coronavirus-2; UC, ulcerative colitis.

Missing variable values were caused by an insufficient number of observations in the participants.

<sup>a</sup>Two UC patients had a recurrence of diarrhea within 7–28 days after vaccination. This will be described in detail in the 'Results' section.

Subgroup analysis revealed no differences in AEs after SARS-CoV-2-inactivated vaccine administration between patients with and without CD (68.9% *versus* 59.0%, OR = 1.538, 95% CI = 0.781–3.029). Different treatment regimens had no influence on the adverse reaction profile in IBD patients (5-ASA 16.7% *versus* 29.5%, OR = 0.478, 95%, CI = 0.219–1.043; glucocorticoid 1.1% *versus* 1.6%, OR = 0.674, 95% CI = 0.041–10.988; immunosuppressant 28.9% *versus* 21.3%, OR = 1.500, 95% CI = 0.699–3.219; biologics 42.2% *versus* 39.3%, OR = 1.127, 95% CI = 0.581–2.185). Finally, the AE profile of IBD patients was not related to sex, age, or vaccine type (Table 5).

#### *Two UC patients experienced relapse within 7–28 days after vaccination*

Two patients relapsed within 7–28 days of vaccination. In the first patient (female, 33 years old), stool frequency increased slightly within 7 days (2–3 times/day) after the first dose of the inactivated vaccine. Ten days after the second inoculation, stool frequency increased to 15–20 times/day with pus and blood. Detailed questioning regarding mesalazine (5-ASA) compliance, however, revealed dosing medication irregularities over several years and discontinuation of 5-ASA long before vaccination. The patient's condition improved after restarting 5-ASA.

The second patient (female, 42 years old) reported a slight increase in stool frequency 7 days after the first dose of the inactivated vaccine, up to 2–3 times/day, possibly related to increased peach consumption. Twenty-five days after the first inoculation, pus and blood began to appear in the stool and the frequency increased to 6–7 times/day. Her symptoms worsened after increasing her mesalazine (5-ASA) dose.

#### **Discussion**

During the COVID-19 outbreak, IBD patients are strongly recommended to be vaccinated by the International Organization for the Study of IBD because it is considered to be the most effective method of controlling the epidemic.<sup>11</sup> Existing phase III studies of SARS-CoV-2 vaccines, however, did not include patients with IBD. Thus, scruples remain for IBD patients to receive the COVID-19 vaccine, which represents concerns regarding AEs, weakens the efficacy of IBD medications, and aggravates the disease. To our knowledge, no previous study has investigated the safety of SARS-CoV-2-inactivated vaccination in patients with IBD.

Our study shows that the coverage of at least one dose of COVID-19 vaccination was 49.3% (206/419) in the adult IBD population at our center by the end of 29 July 2021. A survey from



**Table 5.** Subgroup analysis of IBD patients with or without adverse reactions after SARS-CoV-2-inactivated vaccination.

Variable	With adverse reactions (N = 90)	Without adverse reactions (N = 61)	OR (95% CI)	$\chi^2$	p value
Diagnosis					
Crohn's disease	68.9% (62/90)	59.0% (36/61)	1.538 (0.781–3.029)	1.5556	0.2123
Ulcerative disease	25.6% (23/90)	36.1% (22/61)	0.609 (0.301–1.232)	1.9197	0.1659
Indeterminate colitis	5.6% (5/90)	0.5% (3/61)	1.137 (0.262–4.945)	0.0295	>0.9999
Sex					
Male	51.1% (46/90)	55.7% (34/61)	0.830 (0.432–1.595)	0.3124	0.5762
Female	48.9% (44/90)	44.3% (27/61)	1.205 (0.627–2.314)	0.3124	0.5762
Age					
Mean (SD)	35.59 (11.21)	37.23 (11.54)	NA	NA	0.4009
Median (IQR)	34 (27–41)	37 (27–48)	NA	NA	0.5450
Vaccine type					
BBIBP-CorV	40.0% (36/90)	42.6% (26/61)	0.897 (0.464–1.736)	0.1034	0.7478
CoronaVac	58.9% (53/90)	57.4% (35/61)	1.064 (0.551–2.056)	0.0342	0.8533
COVIL0	0.4% (1/90)	0	–	0.6823	>0.9999
Current IBD medications					
5-aminosalicylic acid	16.7% (15/90)	29.5% (18/61)	0.478 (0.219–1.043)	3.5106	0.061
Glucocorticoid	1.1% (1/90)	1.6% (1/61)	0.674 (0.041–10.988)	0.0776	>0.9999
Immunosuppressant	28.9% (26/90)	21.3% (13/61)	1.500 (0.699–3.219)	1.0897	0.2965
Biologics	42.2% (38/90)	39.3% (24/61)	1.127 (0.581–2.185)	0.1244	0.7243
Ustekinumab	0	4.5% (1/22)	–	1.848	0.3548
Vedolizumab	5% (2/40)	9.1% (2/22)	0.526 (0.069–4.021)	0.3936	0.6104
Adalimumab	35% (14/40)	40.9% (9/22)	0.778 (0.267–2.267)	0.2124	0.6449
Infliximab	60% (24/40)	45.5% (10/22)	1.800 (0.629–5.148)	1.2125	0.2708
CI, confidence interval; IBD, inflammatory bowel disease; IQR, interquartile range; OR, odds ratio; SD, standard deviation. Missing variable values for COVIL0 were caused by an insufficient number of observations in the participants.					

Europe showed that, as of July 2021, 79.6% of IBD patients had received at least one dose of the SARS-CoV-2 vaccine and the vaccination rate was much higher than that in our center.<sup>19</sup> As of 29 July 2021, China has reported more than 1.6 billion COVID-19 vaccinations, and the vaccination rate in Beijing has exceeded 95%, indicating that the vaccination rate in the IBD population is much lower than that in the general population.<sup>20</sup>

In our study, we found that IBD patients on biologics might prefer to avoid COVID-19 vaccinations, while patients on 5-ASA were more inclined to be vaccinated. In addition, the younger age of unvaccinated IBD patients compared with vaccinated patients is of particular concern. A study in the United Kingdom also pointed to a higher level of vaccine hesitancy in younger age groups, highlighting the possibility that female patients of

childbearing age may be hesitant about the vaccine.<sup>21</sup> Furthermore, larger studies on the long-term safety of the vaccine in diverse IBD populations are needed. Above all, vaccination rates in the IBD population need to be improved, especially in the younger age group on biologics. To further explore the reason why IBD patients hesitated to receive the COVID-19 vaccination, we conducted a questionnaire survey and the results showed that the most common reason for SARS-CoV-2 vaccination hesitancy was 'Concerned about the safety of vaccine (such as AE) because or not because IBD' (47.4%) in IBD participants. The data of 'reasons for COVID-19 vaccination hesitancy' from two recent surveys in the United States showed results similar to those of our study.<sup>22,23</sup> These studies revealed that the most common reasons for SARS-CoV-2 vaccination hesitancy were also associated with vaccine safety. In addition, a recent survey showed that approximately 70% of patients with IBD wanted to obtain data on vaccine safety.<sup>22</sup> Thus, data on the safety of SARS-CoV-2 vaccination in the real world are urgently required.

In our study, the most common AE after SARS-CoV-2 vaccination in participants with IBD was injection-site pain, which agrees with previous studies on SARS-CoV-2-inactivated vaccines, including BBIBP-CorV,<sup>8</sup> CoronaVac,<sup>9</sup> and COVILLO.<sup>10</sup> Furthermore, the incidence of AEs in IBD patients was similar to that in non-IBD populations, without serious AEs (grade 3 or 4). Moreover, we found no differences in AEs after vaccination between IBD patients with and without 5-aminosalicylic acid/glucocorticoid/immunosuppressant/biologic use. Previous studies on other vaccine types have also indicated that inactivated vaccines are safe for patients receiving immunosuppressants. Our data further support the safety of SARS-CoV-2-inactivated vaccines in patients with IBD, regardless of their treatment regimen.<sup>6,24,25</sup>

UC relapse was reported in two patients post-vaccination, but a causal relationship could not be established, as serious medication compliance issues were noted in the first case and poor dietary habits in the second. Currently, there are no reports of IBD recurrence and/or worsening of other immune-related diseases (such as systemic lupus erythematosus) caused by COVID-19 vaccines. Studies with larger sample sizes are required

to establish a causal relationship between UC relapse and COVID-19 vaccination.

Fifty participants with IBD who hesitated to be inoculated received SARS-CoV-2 vaccines while the study was ongoing. The reason for the change in mind was the recommendations of their attending physicians, clearly underlining the important role of physicians in improving vaccination rates. Our findings are in accordance with previous reports in which only two of 56 IBD patients declined vaccination after the recommendation of a dedicated physician.<sup>26</sup> Our study and others emphasize the indisputable role of IBD physicians as key influencers in improving COVID-19 vaccination rates, and that physician education must focus on providing answers to hesitant patients.<sup>2,27,28</sup>

The study limitations include (1) the small sample size, (2) lack of ethnic diversity, (3) potential recall bias, and (4) different individual pain sensitivities. Thus, a multicenter study with a larger sample size may provide additional evidence. In conclusion, the inoculation of IBD patients with SARS-CoV-2-inactivated vaccines is safe, with an AE profile that is not different from that encountered in a healthy general population.<sup>3</sup> The IBD type and/or treatment regimen does not increase the risk of AEs.

### Ethics approval and consent to participate

This study was approved by the Ethics Committee of West China Hospital of Sichuan University and carried out in accordance with the Helsinki Declaration. The purpose and methods of the study were explained to all participants. Written informed consent was obtained from each participant prior to enrollment.

### Consent for publication

The contents of the paper and the opinions expressed within are those of the authors, and it was the decision of the authors to submit the manuscript for publication.

### Author contribution(s)

**Yubin Cao:** Data curation; Formal analysis; Investigation; Methodology; Project administration; Writing – original draft; Writing – review & editing.

**Jiaming Feng:** Data curation; Investigation; Writing – review & editing.

**Shihao Duan:** Investigation; Writing – review & editing.

**Yi Yang:** Investigation; Writing – review & editing.

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#### Availability of data and materials

Correspondence and requests for materials should be addressed to YZ.

#### Supplemental material

Supplemental material for this article is available online.

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