

## Research Article

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# Factors influencing vaccination against SARS-CoV-2 among patients with inflammatory bowel disease

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**Keywords:** Inflammatory bowel disease; SARS-CoV-2 vaccination; Logistic regression analyses.

**Abbreviations:** IBD: Inflammatory bowel disease; UC: Ulcerative colitis; CD: Crohn's disease; TNF- $\alpha$ : Anti-tumor necrosis factor- $\alpha$ ; COVID-19, coronavirus disease in 2019; WHO: World Health Organization; ARDS: Acute respiratory distress syndrome; IOIBD: International Organization for the Study of Inflammatory Bowel Diseases; SD: Standard deviations.

## Introduction

Inflammatory bowel disease (IBD), comprising Crohn's Disease (CD) and ulcerative colitis (UC), is a typical immune-mediated inflammatory disease, estimated to affect 620000 people in the UK, and its incidence continues to increase globally [1]. As the same with other immune-mediated inflammatory diseases, patients with IBD may require immunosuppressive drugs, such as high-dose corticosteroids ( $\geq 20$  mg prednisolone or equivalent), immunomodulators (thiopurines, methotrexate), biologicals (Infliximab, vedolizumab or ustekinumab), and small-mole-

## Abstract

**Background:** Vaccination against SARS-CoV-2 is a major public health challenge and vaccination coverage is still unsatisfactory, especially for patients with inflammatory bowel disease (IBD). To improve vaccination adherence, it is very important to know current SARS-CoV-2 vaccination rate.

**Methods:** An online interview questionnaire concerning SARS-CoV-2 vaccination rate was designed, univariate and multivariate logistic regression analyses were performed.

**Results:** Among 157 patients with IBD who responded to the survey, 37 patients (63.8%) with Ulcerative Colitis (UC) and 44 patients (44.4%) with Crohn's Disease (CD) had already received SARS-CoV-2 vaccination. After univariate logistic regression analyses, UC patients and anti-tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) were respectively significantly associated with getting and not getting SARS-CoV-2 vaccination in IBD group. After multivariate logistic regression analyses, above factors were insignificant. In subgroup analysis, especially in UC group, age  $\geq 50$  years, mesalamine and anti-TNF- $\alpha$  were significantly associated with not getting SARS-CoV-2 vaccination after multivariate logistic regression analyses.

**Conclusions:** Half of the patients with IBD had been vaccinated against SARS-CoV-2 in real world, it is essential that gastroenterologists are appropriately updated information of the SARS-CoV-2 vaccination to provide clear guidance to patients with IBD, especially for UC patients with age  $\geq 50$  years, using mesalamine and anti-TNF- $\alpha$ .

cule inhibitors of signaling (tofacitinib), which could leave them susceptible to infection [2].

The outbreak of coronavirus disease in 2019 (COVID-19) was declared to be a Public Health Emergency of International Concern on 30 January 2020, and a pandemic on 11 March 2020 by the World Health Organization (WHO) [3]. The COVID-19 pandemic is caused by a novel RNA coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [4]. SARS-CoV-2 can cause not only mild-to-moderate symptoms, but also life-threatening pneumonia, acute respiratory distress

syndrome (ARDS), multi-organ failure driven by hyper-inflammation and a cytokine storm syndrome or even death [5,6]. It is reported that 80% of SARS-CoV-2 patients may have only mild-to-moderate symptoms, while 20% may develop above serious manifestations [7]. As the time went by, the COVID-19 pandemic has always been a threatening to global public health and has already disrupted the world economy and normal life as well. Short of effective treatment, the most important way is to control the spread of SARS-CoV-2 from person to person, including series of mitigation measures such as wearing masks, travel restrictions, avoiding gatherings and home quarantine [8, 9], all these ways are inconvenient and constraining for people's normal life. Now with more and more people infected and deaths, it seems that the addition of SARS-CoV-2 vaccine holds the best hope for pandemic control and is likely to be especially important for those patients in high-risk, such as those with pre-existing health conditions [10].

A statement from International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) was recently released using the Delphi method, the group's consensus clearly stated that SARS-CoV-2 vaccination was safe and the ideal timing for vaccination was as early as possible for IBD patients [11]. Concurring with this, both D' Amico et al and the British Society of Gastroenterology IBD section and IBD Clinical Research Group position statement claimed that the advantages to SARS-CoV-2 vaccination outweigh the possible disadvantages from vaccinating IBD patients and that unbiased and consistent advice from doctors should be provided to patients to perish vaccine hesitancy [12,13]. Moreover, all cited sources emphasize that the most pivotal concern in IBD patients is vaccine effectiveness rather than safety, and patients should grasp every opportunity of vaccination to reach the highest possible vaccination rate [11,13]. However, IBD patients still may be hesitated by several unknown factors about SARS-CoV-2 vaccination such as long-term safety, efficacy and potential outcome during immunosuppression.

Recently, Rahul S. Dalal et al reported intention to receive SARS-CoV-2 vaccination in two adult IBD populations (local and social media) [14]. This study identified a relatively high rate of SARS-CoV-2 vaccination intent (80.6% for local and 61.1% for social media participants). Bénédicte Caron et al also reported a survey about the acceptance of SARS-CoV-2 vaccination among IBD patients, only 57 patients (54.8%) had intent to receive the SARS-CoV-2 vaccine [15].

Most surveys were only about acceptance of SARS-CoV-2 vaccination among IBD patients, not actual vaccination. Researches about SARS-CoV-2 vaccination rate of IBD patients in real world were very less. In this study, we aimed to identify actual SARS-CoV-2 vaccination among IBD patients followed at our IBD center.

## Materials and methods

### Study participants

The survey was implemented in routine practice and conducted from June 1<sup>st</sup> to July 15<sup>th</sup>, 2021. 157 patients with a proven diagnosis of IBD ever followed at Zhujiang Hospital of South Medical University were included. Each Patient voluntarily completed a self-administered, structured, electronic questionnaire

in our IBD we-chat group. Demographic data, medical history, knowledge, operation history, SARS-CoV-2 vaccination and perceptions of SARS-CoV-2 vaccination were collected. When some information was missed, we would complete it by telephone follow-up. The present study was approved by ethical committees of Zhujiang Hospital of South Medical University conforming to the ethical guidelines of the 1975 Declaration of Helsinki, informed consent was obtained from each patient included in this study.

### Data collection

We developed and administered an electronic-based survey instrument. The questionnaire was developed focusing on the most frequent questions asked about SARS-CoV-2 vaccination by IBD patients during daily practice. The questionnaire mainly consisted of multiple-choice questions and was designed to explore the following:

- Characteristics of patients: age, gender, education background, type and duration of disease, age at diagnosis, history of surgery and current medical treatment.
- SARS-CoV-2 vaccination status, vaccination time, perception about vaccination, reason of not getting SARS-CoV-2 vaccination.

### Analysis

We analyzed the results of different questions from both electronic questionnaire and telephone follow-up. The data was expressed as numbers (%) for qualitative data and as the means  $\pm$  standard deviations (SD) for quantitative data. Univariate logistic regression was used to select the factors influencing vaccination ( $P < 0.1$ ), Multivariate logistic regression was used to analyze the variables that are significant in univariate analysis and those that are considered clinically meaningful ( $P < 0.05$ ).

## Results

### Study population

During the study period, a total of 157 patients with IBD were included, 58 patients (36.9%) had UC, and 99 patients (63.1%) had CD. The characteristics of the study population were listed in Table 1. The mean age of UC at study inclusions was 47 years old (SD=16.9), CD was 32 years old (SD=10.7). 35 patients with UC (60.3%) were male, 67 patients with CD (67.7%) were male. The median duration of UC was 3.7 years (SD=4.4), CD was 4 years (SD=3.7). The majority of the patients with UC were treated with 5-ASA in 70.7%, anti-tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) in 8.6%, no any drugs in 20.7%. The majority of the patients with CD were treated with anti-TNF- $\alpha$  in 53.5%, immunosuppressant in 28.3%, ustekinumab in 2% and no any drugs in 16.2%. The level of education in most patients was below high school in UC (34.5%) and bachelor's degree in CD (47.5%).

### SARS-CoV-2 vaccination perceptions

37 patients (63.8%) with UC and 44 patients (44.4%) with CD had already received the SARS-CoV-2 vaccine. Among patients with UC who did not get SARS-CoV-2 vaccine (Table 2): 42.9% of patients were afraid of disease exacerbation, 9.5% of patients were afraid of severe adverse reaction, 9.5% of patients thought they were not suitable because of cancer or history

of allergic reaction. Among patients with CD who did not get SARS-CoV-2 vaccine (Table 2): 54.5% of patients were afraid of disease exacerbation, 25.5% of patients were afraid of severe adverse reaction, 23.6% of patients believed that long-term effects of vaccines were unknown, 7.3% of patients refused to get SARS-CoV-2 vaccine because of pregnancy or breast feeding.

After univariate logistic regression analyses (Table 3), UC patients (OR, 2.2; 95% confidence interval [CI], 1.13-4.29) were significantly associated with getting SARS-CoV-2 vaccine in IBD group. Anti-TNF- $\alpha$  treatment (OR, 0.41; 95% CI, 0.21-0.81) was significantly associated with not getting SARS-CoV-2 vaccine. After multivariate logistic regression analyses, above factors were insignificant.

In subgroup analysis, especially in UC group (Table 4), age  $\geq 50$  years (OR, 0.21; 95% CI, 0.056-0.74), mesalamine (OR, 0.11; 95% CI, 0.018-.65) and anti-TNF- $\alpha$  (OR, 0.094; 95% CI, 0.011-0.78) were significantly associated with not getting SARS-CoV-2 vaccine after multivariate logistic regression analyses. However, After univariate logistic regression analyses in CD group (Table 5), only Bachelor's or more advanced degree (OR, 2.63; 95% CI, 1.16-5.95) was significantly associated with getting SARS-CoV-2 vaccine.

**Table 1:** Patient characteristics.

Characteristics	UC(58)	CD(99)
Male gender, n(%)	35(60.3)	67(67.7)
Mean age, y(SD)	47(16.9)	32(10.7)
Age (y) at diagnosis, n(%)		
$\leq 16$	0	13(13.1)
17-40	24(41.4)	73(73.7)
$>40$	34(58.6)	13(13.1)
Level of education		
Below high school	20(34.5)	27(27.3)
High school degree	18 (31.0)	23(23.2)
Bachelor's degree	19 (32.8)	47(47.5)
Master's degree	1(1.7)	2(2.0)
Mean time since diagnosis, y(SD)	3.7(4.4)	4(3.7)
History of intestinal resection, n(%)	2(3.4)	31(31.3)
Current treatment, n(%)		
None	12(20.7)	16(16.2)
5-ASA	41(70.7)	9(9.1)
Immunosuppressant	0 (0)	28(28.3)
Anti-TNF	5(8.6)	53(53.5)
Vedolizumab	1(1.7)	0(0)
Ustekinumab	1(1.7)	2(2.0)
Chinese medicine	1(1.7)	
Corticosteroids	1(1.7)	2(2.0)
Mixed	5(8.6)	10(10.1)
SARS-CoV-2 vaccination, n(%)	37(63.8)	44(44.4)

5-ASA: 5-aminosalicylates; SD: standard deviation; TNF: tumor necrosis factor; y: years

**Table 2:** Negative attitudes toward SARS-CoV-2 vaccination.

	UC(21)	CD(55)
Main reasons for not intending to get SARS-CoV-2 vaccine, n(%)		
Delayed pregnancy or breast feeding	0	4(7.3)
Cancer or allergic constitution	2(9.5)	0
Disease exacerbation	9(42.9)	30(54.5)
Adverse reaction	2(9.5)	14(25.5)
Effect of vaccination	0	13(23.6)
Not free	2(9.5)	5(9.1)
Younger than 18 or older than 59	6(28.6)	8(14.5)

**Table 3:** Logistic regression of factors associated with intention to receive SARS-CoV-2 vaccine among IBD patients.

Predictor	Univariable OR (95% CI)	Multivariable OR (95% CI)
Male	1.17(0.61-2.25)	
Age $\geq 50$ y	0.73(0.34-1.58)	
Bachelor's or more advanced degree	1.67(0.88-3.14)	
Ulcerative colitis	2.20(1.13-4.29) <sup>a</sup>	1.68(0.81-3.48)
IBD duration $\geq 10$ y	0.51(0.14-1.83)	
Symptoms		
Abdominal pain	1.29(0.63-2.68)	
Frequency of stools $>3$	1.44(0.39-5.32)	
Abnormal stool property	1.42(0.67-3.02)	
Current treatment		
Mesalamine	1.15(0.59-2.26)	
Corticosteroids	0.000	
Azathioprine or thalidomide	1.10(0.49-2.50)	
Anti-TNF	0.41(0.21-0.81) <sup>a</sup>	0.51(0.25-1.06)
Vedolizumab and ustekinumab	0.94(0.13-6.82)	
2 prior biologic exposures	0.77(0.22-2.63)	
Operation history	0.86(0.43-1.73)	

**Note:** CI: confidence interval; IBD: inflammatory bowel disease; OR: odds ratio. <sup>a</sup>P $<.10$  on univariable analysis. Only these variables were candidates for multivariable analysis. <sup>b</sup>P $<.05$  on multivariable analysis.

## Discussion

Studies about IBD population to be vaccinated against SARS-CoV-2 are lacking. We investigated data from 157 patients with IBD followed at the Zhujiang Hospital of South Medical University to identify their status of SARS-CoV-2 vaccination. Almost half of the patients had already received SARS-CoV-2 vaccine. The reasons of not getting SARS-CoV-2 vaccine were constituted by the concern about disease exacerbation, risk of adverse reaction to vaccine, and the unknown long-term safety. We analyzed IBD group and found that patients with UC were more likely to get SARS-CoV-2 vaccine, Anti-TNF- $\alpha$  treatment could be an obstacle of vaccination in IBD patients. After subgroup analysis of UC group, we further found age  $\geq 50$  years and drug therapy (mesalamine, anti-TNF- $\alpha$ ) influencing patients' vaccination. Referring to age's issue, the results may be not so accurate, because early vaccination was forbidden for age younger than 18 or older than 59, but now age is not the issue, even children

**Table 4:** Logistic regression of factors associated with intention to receive SARS-CoV-2 vaccine among UC patients.

Predictor	Univariable OR (95% CI)	Multivariable OR(95% CI)
Male	0.66(0.22-2.00)	
Age ≥50 y		0.21(0.056-0.74) <sup>b</sup>
Bachelor's or more advanced degree	1.08(0.35-3.36)	
IBD duration ≥10 y	0.34(0.052-2.24)	
Symptoms		
Abdominal pain	1.66(0.39-7.07)	
Frequency of stools >3	0.54(0.071-4.17)	
Abnormal stool property	1.66(0.40-7.07)	
Current treatment		
Mesalamine	0.27(0.068-1.10) <sup>a</sup>	0.11(0.018-.65) <sup>b</sup>
Corticosteroids	0	
Azathioprine or thalidomide	1.10(0.49-2.50)	
Anti-TNF	0.41(0.21-0.81) <sup>a</sup>	0.094(0.011-0.78) <sup>b</sup>
Vedolizumab or ustekinumab	0	
2 prior biologic exposures	0.56(0.033-9.37)	
Operation history	0	

**Note:** CI: confidence interval; IBD: inflammatory bowel disease; OR: odds ratio. <sup>a</sup>P<.10 on univariable analysis. Only these variables were candidates for multivariable analysis. <sup>b</sup>P<.05 on multivariable analysis.

**Table 5:** Logistic regression of factors associated with intention to receive SARS-CoV-2 vaccine among CD patients.

Predictor	Univariable OR (95% CI)	Multivariable OR (95% CI)
Male	1.85(0.77-4.44)	
Age ≥50 y	0.60(0.14-2.54)	
Bachelor's or more advanced degree	2.63(1.16-5.95) <sup>a</sup>	
IBD duration ≥10 y	0.61(0.11-3.48)	
Symptoms		
Abdominal pain	1.37(0.57-3.29)	
Frequency of stools >3	2.65(0.46-15.19)	
Abnormal stool property	1.50(0.61-3.74)	
Current treatment		
Mesalamine	1.0(0.25-3.97)	
Corticosteroids	0	
Azathioprine or thalidomide	1.67(0.69-4.03)	
Anti-TNF	0.60(0.27-1.33)	
Vedolizumab and ustekinumab	0	
2 prior biologic exposures	0.56(0.033-9.37)	
Operation history	1.60(0.71-3.58)	

**Note:** CI: Confidence interval; IBD: Inflammatory bowel disease; OR: odds ratio. <sup>a</sup>P<.10 on univariable analysis. Only these variables were candidates for multivariable analysis. <sup>b</sup>P<.05 on multivariable analysis.

can get the vaccine. Drug therapy (mesalamine, anti-TNF- $\alpha$ ) was another factor influencing vaccination, some patients may be concerned about safety and efficacy of vaccine, so there is an urgent need for doctors to appropriately update on efficacy and safety of the SARS-CoV-2 vaccine and provide specific and professional recommendations for people with IBD, improving their attitude towards vaccination and minimizing their skepticism and confusion. As for there were less patients using vedolizumab or ustekinumab, the results could not reflect the reliable concern among these patients.

This study's strength includes recruitment of 2 populations including UC and CD with distinct vaccination behaviors and timely distribution of surveys. Although there were articles assessing IBD patients concerns and intentions regarding SARS-CoV-2 vaccination, but the results were all about plans of vaccination among IBD patients. However, our study showed real world vaccination situation, almost half of all patients had already got vaccine. Furthermore, we explored factors influencing vaccination to know patients concern in order to help them better. We also need to highlight some limitations of the present study. Limitations include response bias inherent to our survey and this study included a smaller group, therefore, the results could not represent the national IBD population of vaccination situation.

### Conclusion

The SARS-CoV-2 pandemic has presented several significant challenges including the willingness to be vaccinated against SARS-CoV-2. There is a need and responsibility to highlight and emphasize the benefits of SARS-CoV-2 vaccination, including targeting outreach and educational interventions which can reflect on strengthening trust in SARS-CoV-2 vaccines among the population, especially for UC patients with age ≥50 years, using mesalamine and anti-TNF- $\alpha$ .

### Declarations

**Authors' contributions:** Study concept and design: Meiling Sun, Xinying Wang; acquisition of data: Miaomiao Ma, Shao-heng Zhang; analysis and interpretation of data: Meiling Sun, Miaomiao Ma; drafting of the manuscript: Meiling Sun, Xiaoduan Zhuang; critical revision of the manuscript for important intellectual content: Meiling Sun; All authors had full access to all the data and had final responsibility for the decision to submit for publication.

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