

COVID-19 Vaccination Willingness and Hesitancy in Patients With Inflammatory Bowel Diseases: Analysis of Determinants in a National Survey of the Italian IBD Patients' Association

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Introduction

The coronavirus disease 2019 (COVID-19) pandemic has not finished yet, and the most promising option towards its ending is widespread vaccination.

Because patients with inflammatory bowel diseases (IBDs), namely Crohn's disease (CD) and ulcerative colitis (UC), often require immune-modifying treatment, which might increase the risk of opportunistic infection,¹ their vaccination history for several infectious diseases is routinely checked, and when inadequate, vaccination is performed at diagnosis or ideally before immune suppressive treatment is started.¹ However, IBD patients were not found to be at an increased risk of developing COVID-19 or of experiencing a more severe disease course.²

Vaccine hesitancy is defined by the World Health Organization (WHO) Strategic Advisory Group of Experts on Immunization Working Group on Vaccine Hesitancy as a "delay in acceptance or refusal of vaccination despite avail-

ability of vaccination services."³ Indeed, even before the COVID-19 pandemic, vaccine uptake was declining worldwide, and vaccine hesitancy was recognized by the WHO as being one of the 10 threats to global health. Because of the urgent need to achieve adequate COVID-19 vaccination coverage worldwide, hesitancy towards COVID-19 vaccines is a potential threat to safety of patients with IBD.

The aim of our study was to assess COVID-19 vaccine willingness and hesitancy in Italian IBD patients, to investigate their reasons, and to identify the determinants of these attitudes, including attitude to previous vaccinations, lifestyle, health-related behaviors, and sociodemographic characteristics.

Italy began its COVID-19 vaccination campaign at the end of December 2020. Since February 20, 2021, the campaign was extended to the general public, targeting the priority groups. Since March 2021, vaccination has been offered to those at very high risk of becoming severely ill with

COVID-19, followed by the general population according to age and comorbidities. At the time of the survey, the European Medicines Agency (EMA) and the Italian Agency approved 4 vaccines against COVID-19: BNT162b2 (Pfizer/BioNTech, New York, NY, US), mRNA-1273 (Moderna, Cambridge, MA, US), and AZD1222 (AstraZeneca, Cambridge, UK).

METHODS

Between February 10 and February 19, 2021, the Italian IBD patients' association (*Associazione Nazionale per le Malattie Infiammatorie Croniche dell'Intestino Onlus*, also known as AMICI) distributed an anonymous online questionnaire to their adult members through mailing lists and on social media platforms. The questionnaire consists of an adapted version of a previously validated questionnaire on vaccine hesitancy and is divided into 3 sections seeking information on: (1) sociodemographic characteristics, lifestyle, and IBD characteristics, (2) attitude towards vaccinations in general, and (3) attitude toward COVID-19 vaccines and information about the new vaccines. The questionnaire is reported in the [supplementary material](#).

Depending on whether they gave a positive or negative response to the question "Would you accept vaccination against COVID-19 tomorrow?" patients were defined as willing or hesitant. Among the hesitant patients, those refusing vaccination were defined as respondents who expressed a negative response to the following question: "If you answered no, would you eventually accept it in the future when more data are available?" Hesitant patients were asked about their reasons and whether their IBD influenced their decision.

Statistical Analysis

Absolute and relative frequencies were calculated for the categorical (qualitative) variables, and quantitative variables were summarized by their means (standard deviations). The differences in the categorical variables for hesitancy or refusal and between before and after the intervention were analyzed using χ^2 tests (Mantel-Haenszel) and Student *t* test for the means. All variables found to have a statistically significant association with vaccination hesitancy/refusal in the univariate analysis were included in a multivariate backward stepwise logistic regression model. All variables with a *P* value $\leq .20$ were selected in the multivariate model, to guarantee a more conservative approach. The crude odds ratio (crude OR) and the adjusted OR (AdjOR) with 95% confidence intervals (CIs) were also calculated in the logistic regression model. The level of significance chosen for the multivariate logistic regression analysis was .05 (2-tailed). We entered all the information into a database created with EpiInfo 3.5.4 (Centers for Disease Control and Prevention, Atlanta, GA, USA). All the data were analyzed using the statistical software package Stata/MP 12.1 (StataCorp LP, College Station, TX, USA).

RESULTS

Overall, 1252 IBD patients filled in the survey; 1021 patients completed the online survey out of 4039 email addresses to whom it was sent, with an overall response rate of 25.3%. A total of 231 patients filled in the questionnaire after having become aware of it through AMICI social networks. Respondents lived in each of the 20 Italian regions.

The sociodemographic details, disease characteristics, and lifestyle habits of IBD patients who filled in the questionnaire are described in [Table S1 of the supplementary material online](#). To summarize, 729 (58.2%) were women, median age was 48 (interquartile range 37–58), 852 (68.2%) were married or cohabiting, and 474 (37.8%) were graduated. Patients with Crohn's disease and ulcerative colitis were numerically almost identical, 1091 (87.1%) were diagnosed for >5 years, 475 (37.9%) had a previous IBD-related surgery, half of the patients were off-therapy or treated with mesalamine, and the other half were treated with an immunosuppressive drug.

Among the respondents, 877 (70.0%) declared they were informed about COVID-19 vaccines. Of the 1252 IBD patients who filled in the survey, 1005 (80.3%) were willing to be vaccinated, 222 (17.7%) were hesitant; among the hesitant patients 33 (14.9%) were refusing with a total refusal rate of 2.64%. Twenty-five patients (2%) did not give an answer to this specific question ([Figure 1](#)). Among the patients willing to be vaccinated, 78.2% (786) thought that their IBD was a valid reason for priority vaccination. Among the 222 hesitant patients, the main reasons (more than 1 could be indicated) for their attitude were as follows: fear of adverse effects in 160 respondents, concerns about too fast vaccine development in 145 respondents, and a belief that vaccines were not effective for preventing COVID-19 in 29 respondents; 23 patients stated their hesitancy was motivated by previous SARS-CoV-2 infection, and 13 claimed they were not worried about COVID-19. Four patients did not give any reasons at all ([Figure 1](#)). A total of 109 hesitant patients (49.1%) answered that their hesitancy was influenced by their IBD.

Regarding vaccines in general, 92.2% (1154) answered that they intended to be vaccinated again in the future.

As regards the perceived risk of SARS-CoV-2 infection, 54.5% (682) of the respondents thought they had a higher risk of COVID-19 because of their IBD and 31.8% (398) because of their current IBD treatment. Considering the perceived severity of the novel coronavirus disease, 69.0% (894) thought they

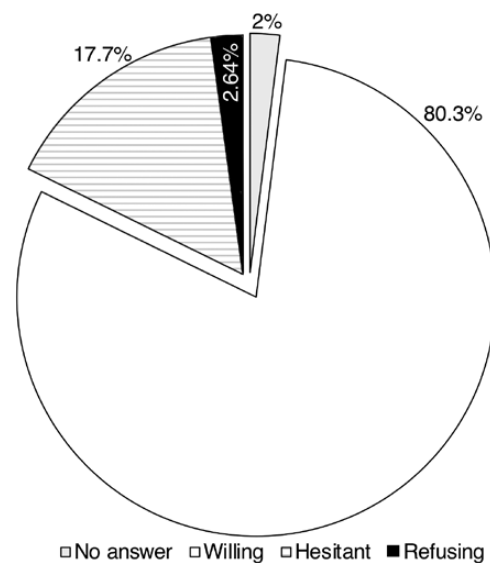


Figure 1. Willingness, hesitancy and refusal of IBD patients to receive a COVID-19 vaccine and their reasons

would have more severe COVID-19 because of IBD and 35.6% (446) because of their ongoing IBD treatment.

The crude and adjusted OR analysis of sociodemographic, lifestyle, and clinical characteristics and knowledge, attitudes, and perception about COVID-19 in general are described in (Table 1). The AdjOR showed significant positive associations between willingness and a positive attitude to vaccination (17.6; 95% CI, 11.4–27.2), male gender (1.68; 95% CI, 1.16–2.43), graduation degree at University (1.48; 95% CI, 1.03–2.13), perceived higher risk of COVID-19 because of IBD (1.47; 95% CI, 1.05–2.08), and alcohol intake (1.69; 95% CI, 1.16–2.45) and showed a significant negative association with positive attitudes to complementary and alternative medicine (CAM; 0.58; 95% CI, 0.36–0.92) (Table 1). Age, analyzed as a continuous variable, was not associated with vaccine willingness ($P = 0.82$).

Discussion

The beginning of COVID-19 vaccination campaigns worldwide has prompted the main medical organizations focused on IBD to comment on the lack of contraindications to the use of available COVID-19 vaccines in IBD patients.⁴ However, the reasons for IBD patient hesitancy to COVID-19 vaccines are less known. Regarding vaccinations in IBD patients, a recent systematic review has shown a low acceptance rate, ranging between 11% and 54%.⁵

In the present study, we report that more than 4 in 5 (80.3%) IBD patients were ready to be vaccinated. In our study, determinants associated with COVID-19 vaccination willingness at the multivariate analysis were adherence to previous vaccinations, a perceived higher risk of COVID-19

Table 1. Crude OR and adjusted OR (AdjOR) association analysis of sociodemographic, lifestyle and clinical characteristics, knowledge, attitudes, and perception about COVID-19, and general willingness to be vaccinated against COVID-19.

	Crude OR	95% CI	P	AdjOR	95% CI	P
Age in years (continuous variable)	1.09	(0.89–1.27)	.82			
Gender						
Female	Ref		<.01	Ref		<.01
Male	1.49	(1.11–2.01)		1.68	(1.16–2.43)	
Marital status						
Single/divorced/widowed	Ref		.36			
Married or cohabiting	1.06	(0.78–1.43)				
Number of family members						
≤2 Members	Ref		.21			
>3 Members	1.13	(0.82–1.51)				
Children under 10 years of age						
No	Ref		.38			
Yes	0.92	(0.62–1.37)				
Educational level						
Undergraduate	Ref		.07	Ref		<.05
Graduate (University)	1.31	(0.97–1.77)		1.48	(1.03–2.13)	
Healthcare professional						
No	Ref		.46			
Yes	1.03	(0.66–1.59)				
Smoking habit						
No	Ref		.14	Ref		.62
Yes	0.84	(0.62–1.15)		1.01	(0.69–1.45)	
Alcohol intake						
No	Ref		<.05	Ref		<.01
Yes	1.56	(1.15–2.11)		1.69	(1.16–2.45)	
Healthy lifestyle						
No	Ref		.21			
Yes	1.14	(0.86–1.52)				
Vegetarian or vegan diet						
No	Ref		<.05	Ref		.61
Yes	0.43	(0.22–0.83)		0.79	(0.33–1.90)	
Positive attitude to CAM						
No	Ref		<.001	Ref		<.05
Yes	0.44	(0.31–0.64)		0.58	(0.36–0.92)	
Disease type						
Crohn’s disease	0.92	(0.85–1.06)				

Table 1. Continued

	Crude OR	95% CI	P	AdjOR	95% CI	P
Ulcerative colitis	Ref		.87			
Undetermined colitis	0.78	(0.56–1.42)				
Disease duration						
<5 Years	Ref		.26			
>5 Years	1.18	(0.89–1.62)				
Therapy						
No one/mesalamine	Ref		.22			
Immunosuppressive drug	1.12	(0.84–1.50)				
Adherence to therapy recommended for IBD						
No/not at all	Ref		<.001	Ref		.10
Yes	1.88	(1.28–2.74)		1.48	(0.92–2.38)	
Previous negative experience (personal, family members, relatives) with vaccination						
No	Ref		<.001	Ref		.45
Yes	0.26	(0.18–0.36)		0.93	(0.78–1.11)	
Attitudes regarding vaccination						
Negative	Ref		<.001	Ref		<.001
Positive	16.6	(11.1–24.8)		17.6	(11.4–27.2)	
Perceived higher risk of contracting COVID-19 because of IBD						
No	Ref		<.05	Ref		<.05
Yes	1.43	(1.08–1.92)		1.47	(1.05–2.08)	
Perceived higher risk of contracting COVID-19 because of IBD treatment						
No	Ref		.29			
Yes	1.10	(0.80–1.51)				

Abbreviations: CAM, complementary and alternative medicine; IBD, inflammatory bowel disease.

due to IBD, male gender, graduation degree, and alcohol intake. Adherence to previous vaccinations had the highest AdjOR, indicating that patients with a positive attitude towards vaccines in general were also positive towards COVID-19 vaccines. The high uptake of general vaccinations among Italian IBD patients could be the result of a widespread Italian physicians effort in recommending vaccinations among their patients, as reported in a recent IG-IBD survey.⁶

We observed a predictable positive association between vaccine willingness and a perceived higher risk of COVID-19 because of IBD; similarly, the association with male gender could be motivated by the known higher risk of morbidity and mortality in men. A similar positive association with a higher level of education has been already reported.^{7,8} A positive attitude to CAM showed a significant negative association with willingness towards COVID-19 vaccines, as reported in other studies.⁹ Unexpectedly, we found a positive association with alcohol intake. To our knowledge this association has not previously been reported. We categorize alcohol intake both as self-reported social alcohol consumption (97.9%) and as self-reported excessive consumption (2.1%). A possible explanation is that social alcohol consumers may be more willing to be vaccinated so they can resume their usual social activities that have been limited by the COVID-19 pandemic.

The most common reasons for COVID-19 vaccine hesitancy were the fear of adverse events and concerns about a perceived too-fast development. It is of note that half of the hesitant patients stated that their reasons were influenced by IBD. In contrast, among patients willing to be vaccinated

when vaccines become available, 78.2% thought that their IBD was a valid reason for priority vaccination.

A survey in US IBD patients, carried out from December 2020 to January 2021, has shown an acceptance rate of COVID-19 vaccination ranging between 60% and 80%. The authors observed that age ≥ 50 years, having a bachelor's degree, white race, self-reported COVID-19 infection, and current biologic therapy were associated with a positive attitude towards vaccination.⁸

Possible limits of our study include (1) a potential selection bias as those well-disposed towards vaccines may have been more likely to fill out the questionnaire, (2) members of patients' associations may have greater compliance with medical recommendations, (3) the web-based nature could have selected younger subjects or those more familiar with information technology, (4) possible differences among COVID-19 vaccines, and (5) the lack of a control group; to partially overcome this last limitation, we could take into account the hesitancy rate (34.8%, refusal rate of 17.6%) of a large Italian cohort that answered a web-based COVID-19 vaccine hesitancy survey during the same period,⁷ but comparisons should be extrapolated with caution.

Nevertheless, our study has many strengths. Our questionnaire was sent to a large national cohort of IBD patients, whereas previous data were obtained from a single center.⁸ Our questionnaire has provided the first national published data on COVID-19 vaccine acceptance among Italian and European IBD patients.

In conclusion, the speed with which COVID-19 vaccines have been developed and the lack of data on long-term safety may have raised doubts in patients and reduced vaccine ac-

ceptance.¹⁰ In our study, most IBD patients would accept COVID-19 vaccines, although 1 in every 5 respondents is hesitant or would currently refuse vaccination.

COVID-19 vaccination for the general population has been proceeding in many European countries. In the meantime, IBD specialists are still called upon in conducting a campaign to convince their patients to get vaccinated.

The results of this survey may be helpful for physicians (including IBD specialists and general practitioners), researchers, and patients' associations activists seeking to develop specific interventions to address hesitancy.

Supplementary Data

Supplementary data is available at *Inflammatory Bowel Diseases* online.

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Author's Contributions

A.C. contributed to the conceptualization, writing, review, and editing.

D.N. contributed to the analysis of data, writing, review, and editing.

F.S.C. contributed to the writing, review, and editing.

M.A., A.A., F.B., F.F., F.M., G.M., A.O., L.P., S.R., F.R., A.T. contributed to the review and editing.

S.L. contributed to the data acquisition, review and editing.

C.C. contributed to the conceptualization, analysis of data, writing, review and editing, supervision.

M.V. contributed to the conceptualization, review and editing.

F.C. contributed to the conceptualization, writing, review and editing, supervision.

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Conflicts of Interest

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Data Availability

The data underlying this article will be shared upon reasonable request to the corresponding author.

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