Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Correspondence

Therapeutic adherence recorded in the outpatient follow-up of inflammatory bowel diseases in a referral center: Damages of COVID-19☆

Dear Editor,

Since the first case of human Severe Acute Respiratory Syndrome COronaVirus 2 (SARS-Cov-2) infection in December 2019 in Wuhan (China) and the subsequent pandemic, a major concern in gastroenterology has been to adopt strategies to defend patients with chronic digestive diseases, as Inflammatory Bowel Diseases (IBD), because of the higher risk of COVID-19 in patients with pre-existing medical conditions [1]. A non-negligible number of IBD patients still have major concerns that IBD-related therapy might facilitate SARS-Cov-2 infection and COVID-19 [2]. Several studies have, moreover, already raised the issue of IBD-related therapeutic adherence in the COVID-19 pandemic, but with conflicting results [3–6]. In developing a strategy to improve therapeutic adherence of IBD patients, it is probably necessary to study which subgroups of them are affected by a higher rate of non-adherence in this pandemic period and which are at higher risk of non-adherence to adopt personalized tools not to lose those patients who are inclined to stop therapy [7]. Patients who independently discontinue or modify a treatment against medical advice may be, in fact, at risk of developing complications or flare-ups of IBD or exacerbation of relative extra-intestinal manifestations. In our IBD referral center, at the Hepato-gastroenterology Unit of the University of Campania “Luigi Vanvitelli”, we found several findings worthy, in our opinion, of attention during the period between February 2021 and February 2022.

We, in detail, during outpatient visits, anonymously administered the Medication Adherence Rating Scale with a self-reported 5-statement Likert questionnaire (MARS-5) [8] considering a score of 20 or greater as a cut-off to define “adherent” patients [9] to our cohort of 270 patients (see Table 1) already diagnosed with IBD [10] followed by us on an outpatient basis. We also asked patients what their main COVID-19-related fears were in the management of their IBD as well as we checked whether patients had experienced our IBD center of delays or cancellations of follow-up visits. Our overall recorded therapeutic non-adherence rate was 32.8% (69/210). Several subpopulations, in our setting, showed, moreover, significantly higher therapeutic non-adherence: females ($p < 0.001$), younger patients ($p < 0.001$) as well as, consequentially, those with a lower age at diagnosis of IBD ($p = 0.002$). Our most adherent patients had higher levels of education ($p = 0.003$). An additional finding, we noted was a greater predominance of non-adherent patients in the subgroup of those who had prior SARS-Cov-2 infection ($p < 0.001$), and we identified the latter as a predictor of treatment nonadherence in our group in the multivariate logistic regression model (OR 7.822; 95% CI 3.385 - 18.07, $p < 0.001$). Whether previous SARS-Cov-2 infection affects the rate of adherence to therapy is not known. Our data suggest that prior

Table 1
Clinical-demographic characteristics of the sample.

Parameter	Adherent* (*N* = 141, 67.14%)	Non-adherent* (*N* = 69, 32.8%)	p**
Gender			
Male	91 (64.5%)	23 (33.3%)	**< 0.001**
Female	50 (35.5%)	46 (66.7%)	
Age	48 (33 – 63)	38 (28 – 46)	**< 0.001**
Age at IBD diagnosis	31 (21 – 48)	25 (19 – 37.5)	**0.002**
BMI	24.3 (21 – 26.8)	24.3 (21.4 – 27.2)	0.861
IBD			
Crohn's disease	65 (46.1%)	28 (40.6%)	0.464
Ulcerative colitis	76 (53.9%)	41 (59.4%)	
IBD Disease Activity			
Active	49 (34.8%)	32 (46.4%)	0.207
Remission	92 (65.2%)	37 (53.6%)	
Biologic therapy	109 (77.3%)	53 (76.8%)	0.9
Education			
Elementary school	3 (2.1%)	–	**0.003**
Middle school	32 (22.7%)	28 (40.6%)	
High school	83 (58.9%)	28 (40.6%)	
Bachelor's Degree	4 (2.8%)	8 (11.6%)	
Master's Degree	19 (13.5%)	5 (7.2%)	
Job			
Unemployed	51 (36.2%)	30 (43.5%)	0.131
Employee	38 (27%)	22 (31.9%)	
Entrepreneur	3 (2.1%)	–	
Freelancer	15 (10.6%)	3 (4.3%)	
Worker	18 (12.8%)	12 (17.4%)	
Student	16 (11.3%)	2 (2.9%)	
Smoking status			
Smoker	28 (19.9%)	14 (20.3%)	
Non-smoker	68 (48.2%)	46 (66.7%)	
Past smoker	45 (31.9%)	9 (13%)	0.057
Alcohol consumption			
Yes	13 (9.2%)	2 (2.9%)	
No	128 (90.8%)	67 (97.1%)	0.712
Comorbidity			
Diabetes mellitus	21 (14.9%)	–	0.314
Hypertension	26 (18.4%)	7 (10.1%)	
Chronic renal failure	9 (6.3%)	–	
Urolithiasis	3 (2.1%)	3 (4.3%)	
COPD	3 (2.1%)	3 (4.3%)	
Dyslipidemia	29 (20.6%)	4 (5.8%)	
Bronchial asthma	–	3 (4.3%)	
Previous SARS-Cov-2 infection	9 (6.4%)	24 (34.8%)	**< 0.001**
Past hospitalization for COVID-19 (yes)	3 (2.1%)	–	0.552
Visit delays (yes)	35 (24.8%)	25 (36.2%)	0.104
Visit cancellations (yes)	25 (17.7%)	20 (29%)	0.074

(*continued on next page*)

Abbreviations: COVID-19, ***Co****ronavirus****D****isease 19*.

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Table 1 (*continued*)

Parameter	Adherent* (*N* = 141, 67.14%)	Non-adherent* (*N* = 69, 32.8%)	p**
COVID-19 vaccination (yes)	132 (93.6%)	66 (95.7%)	0.755
Flu Vaccination (yes)	67 (47.5%)	14 (20.3%)	**< 0.001**

Data are expressed either as numerosity (percent of total) or as median (interquartile range).

* The distinction between adherent and nonadherent patients was made based on the 20-point cut-off of the MARS-5 questionnaire.

** *Mann-Whitney U test, Kruskal-Wallis test, or chi-squared test were used according to the type of variable.* **Acronyms. COVID-19**: COronaVIrus Disease 19; **IBD**: Inflammatory Bowel Disease, COPD: Chronic Obstructive Pulmonary Disease.

SARS-Cov-2 infection is a significant predictor of non-adherence to therapy. We hypothesize that patients previously infected, feel that they are at higher risk of being infected again because of IBD-related therapy.

In addition, we observed that the majority (64.2%) of patients had a pandemic-related relevant concern and that a non-negligible proportion of patients believed that they were at greater risk of severe COVID-19 than the rest of the population or yet were at least in doubt of it, while only a small minority of patients (27.1%) thought that IBD did not play this role in SARS-Cov-2 infection. About the latter concern, adherent patients were significantly more concerned than non-adherent ones ($p = 0.039$). Table 2 summarizes all major COVID-19 patient concerns related to IBD management.

Moreover, it is our opinion that patients need to be reassured even by primary care about the management of their chronic condition in the COVID-19 setting. While most of our patients (65.7%) felt reassured and adequately informed by their gastroenterologist this did not seem to apply to the general practitioner. 61.4% of them felt not to be adequately informed and or reassured by their family doctors. Therefore, efforts should be made to increase the level of attention that general practitioners should pay to their patients with chronic disorders in this pandemic era. Based on our data, the use of telemedicine should be encouraged as a system for regaining therapeutic adherence. Most of our patients preferred, not by chance, telemedicine as an alternative first-choice follow-up tool.

We also evaluated the attitude of our IBD patients toward the COVID-19 vaccine. A small number of them declared to be skeptical about receiving the vaccine, either for fear of major adverse events (28.6%) or because they did not consider it effective (15.7%). Also, 28.5% of patients stated that they did not want to undergo any further doses of the COVID-19 vaccine, beyond the third one, mostly because they had the feeling that vaccination might worsen their underlying disease or interfere with the efficacy of therapy or because they were afraid of a higher incidence of vaccine-related adverse events. However, we did not observe any difference in vaccine acceptance rate between adherent or non-adherent IBD patients.

We also examined what reasons led patients to be reluctant to undergo additional doses of the COVID-19 vaccine. We investigated, in our questionnaire, what reason might have driven them to this decision. 18 (8.6%) stated that they did not consider the vac-

Table 2
Survey results related to COVID-19-related fears.

Question	No	Yes	Maybe	Not particularly	Just a little bit	Fairly	Very much	Extremely	P*
How concerned do you feel about the COVID-19 pandemic?	–	–	–	30 (14.3%)	45 (21.4%)	87 (41.4%)	45 (21.4%)	3 (1.4%)	0.828
Do you think that you are at increased risk for COVID-19 of greater severity?	57 (27.1%)	87 (41.4%)	66 (31.4%)	–	–	–	–	–	**0.039**
Do you think you have been adequately informed by your general practitioner about how to protect your health from COVID-19?	81 (38.6%)	99 (47.1%)	30 (14.3%)	–	–	–	–	–	0.903
Do you think you have been adequately informed by your gastroenterologist about how to protect your health from COVID-19?	45 (21.4%)	138 (65.7%)	27 (12.9%)	–	–	–	–	–	0.939
Have you reduced your social activity more than the limits of widespread regulations?	84 (40%)	126 (60%)	–	–	–	–	–	–	0.18
How much have you cut back on your social activity?	–	–	–	30 (14.3%)	48 (22.9%)	96 (45.7%)	27 (12.9%)	9 (4.3%)	0.383
Do you think COVID-19, even if mild, may interfere with the therapy you are currently taking for IBD?	75 (35.7%)	51 (24.3%)	84 (40%)	–	–	–	–	–	0.853
Are you afraid to go to the hospital for checkups because of the possibility of contracting COVID-19?	129 (61.4%)	81 (38.6%)	–	–	–	–	–	–	0.177
Have you ever refused to go to the hospital for checkups for fear of contracting COVID-19?	201 (95.7%)	9 (4.3%)	–	–	–	–	–	–	0.721
Have you put off COVID-19 vaccination for fear of vaccine adverse events?	183 (87.1%)	27 (12.9%)	-	–	–	–	–	–	0.274
Did you cancel your COVID-19 vaccination for fear of vaccine adverse events?	201 (95.7%)	9 (4.3%)	–	–	–	–	–	–	0.062
Do you think IBD patients are at increased risk for vaccine adverse events?	150 (71.4%)	60 (28.6%)	–	–	–	–	–	–	0.257
Do you think the vaccine is effective in preventing COVID-19 in IBD?	33 (15.7%)	177 (84.3%)	–	–	–	–	–	–	0.688
Do you think you would do additional doses beyond the third dose of the COVID-19 vaccine should it be required?	60 (28.5%)	150 (71.4%)	–	–	–	–	–	–	0.714

Data are expressed as numerosity (percentage of total).

* The p-value is calculated by testing whether the distribution of responses was statistically different between adherent and non-adherent patients on specific therapy for their inflammatory bowel disease (*Mann-Whitney U test*). *The distinction between adherent and nonadherent patients was made based on the 20-point cut-off of the MARS-5 questionnaire.***Acronyms. COVID-19**: COronaVIrus Disease 19; **IBD**: Inflammatory Bowel Disease.

cine safe for IBD, 27 (12.9%) were afraid of interference of the vaccine with their IBD medication, 6 (2.9%) were afraid of not having enough immune defenses, 6 (2.9%) declared to have had adverse events with previous doses and finally, 3 (1.4%) did not consider the vaccine an effective tool. About this concern of additional doses of the COVID-19 vaccine, there was no difference between adherent and non-adherent patients ($p = 0.714$). Clearly, as a limitation of our data, our sample size should be enlarged to strengthen these conclusions and increase their external validity. In conclusion, in the pandemic setting, there is a substantial number of IBD patients with low adherence to therapy. Identifying predictors of non-adherence to therapy might help increase the adherence to therapy in this clinical setting.

Declaration of Competing Interest

None declared.

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Raffaele Pellegrino
Department of Precision Medicine, University of Campania "Luigi Vanvitelli", Via Luigi de Crecchio, 80138, Naples, Italy

Gianluca Pellino, Francesco Selvaggi
Department of Advanced Medical and Surgical Sciences, University of Campania "Luigi Vanvitelli", Via Luigi de Crecchio, 80138, Naples, Italy

Alessandro Federico, Marco Romano, Antonietta Gerarda Gravina*
Department of Precision Medicine, University of Campania "Luigi Vanvitelli", Via Luigi de Crecchio, 80138, Naples, Italy

*Corresponding author.
E-mail address: antoniettagerarda.gravina@unicampania.it (A.G. Gravina)