

Impact of COVID-19 pandemic on the healthcare and psychosocial well-being of patients with inflammatory bowel disease

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Abstract

COVID-19 pandemic has resulted in unprecedented disruptions to several aspects of gastroenterology healthcare services worldwide. In particular, patients with inflammatory bowel disease (IBD) represent a sensitive population that must retain access to healthcare services to avoid potential disease exacerbation under the continuous threat of viral infection. Emerging evidence also highlights the severe impact on these patients' mental well-being, leading to a constant cycle of stress/depression and disease activity relapse. In an effort to circumvent these healthcare challenges in a newly-shaped environment, physicians implemented telemedicine consultative care programs as a novel alternative follow-up method highly favored by the patients. The situation is still far from perfect, since a large proportion of patients are lost to follow up and/or lose adherence to their medication, especially when the exact timeframe or optimal strategy for the post-COVID era remains to be defined. Cancellation of elective endoscopic procedures has led to a significant decline of new IBD diagnoses. This review summarizes the data on the global impact of COVID-19 on IBD patients' healthcare and their psychosocial status.

Keywords COVID-19, inflammatory bowel disease, impact, well-being

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Introduction

Starting from Wuhan city in Hubei province, China, the novel coronavirus SARS-CoV-2 rapidly spread all around the world, leading to a global health crisis, with millions of cases and deaths. During this period, 6242 patients with inflammatory bowel disease (IBD) have been entered into the SECURE-IBD database (until 8 June 2021), of whom 15% needed hospitalization and 2% lost their lives [1]. The IBD community worldwide had to face up to these unprecedented circumstances, while maintaining the quality of IBD care standards [2]. Telemedicine replaced face-to-face visits, elective endoscopy and surgical procedures were temporarily postponed, and strict hospital protocols were adopted in an effort to interrupt virus transmission [2,3].

There is unanimity among the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) [4], the European Crohn's and Colitis Organization (ECCO) [2], the American Gastroenterology Association (AGA) [5] and the Hellenic Study Group for Inflammatory Bowel Diseases (EOMIFNE) [6] that IBD patients are not facing a higher risk of SARS-CoV-2 infection compared to the general population. On the contrary, some might even develop less severe forms when infected [7]. Initially, evidence suggested a greater probability of hospitalization among patients receiving prednisolone,

azathioprine, infliximab or adalimumab, compared to other IBD patients [6]. However, negative COVID-19 outcomes have only been associated with active IBD, older age, presence of comorbidities and high doses of corticosteroids, but not with other IBD treatments [8]. Therefore, patients should remain adherent to their medication to avoid an IBD flare that may require steroid therapy or hospitalization, both of which are related to a higher risk of an unfavorable COVID-19 outcome compared to the known risks of IBD therapies [5].

All IBD patients are strongly recommended to get vaccinated against SARS-CoV-2 as soon as possible [9]. All available vaccines are considered equally safe and effective for IBD patients; however, vaccine efficacy may be decreased in those receiving systemic corticosteroids. As far as patients under biological treatment are concerned, the only recommendation is to avoid receiving the vaccine on the same day as an infusion/subcutaneous dose, to avoid misinterpretation in case an adverse event occurs [10].

IBD is a chronic disease requiring tight control of activity, close monitoring of treatment, and a patient-oriented approach focusing on their physical and psychological well-being. Compared to non-IBD peers, they have a greater likelihood of developing depression and anxiety disorders [11], especially in the case of active disease [12]. The COVID-19 pandemic has exacerbated the problem, since individuals in self-isolation or under quarantine measures are more likely to develop mental health problems such as depression and anxiety [13]. This review presents the available evidence about the impact of the COVID-19 pandemic on IBD patients' healthcare and their psychosocial well-being.

Methodology

The Medline database was searched for eligible studies up to 12 May 2021, using the MeSH terms: ((2019 Novel Coronavirus Disease) OR (2019 Novel Coronavirus Infection) OR (2019nCoV Disease) OR (2019-nCoV Infection) OR (COVID-19 Pandemic) OR (COVID-19 Virus Disease) OR (COVID-19 Virus Infection) OR (COVID19) OR (Coronavirus Disease 2019) OR (Coronavirus Disease-19) OR (SARS Coronavirus 2 Infection) OR (SARS-CoV-2 Infection)) AND ((Inflammatory Bowel Disease) OR (Crohn's Disease) OR (Crohn's Enteritis) OR (Ulcerative Colitis)). All types of studies published in the English language, referring to humans and providing numerical data, were considered eligible for inclusion, while studies in any other language, non-human, *ex vivo* or pilot studies, editorials, narrative or systematic reviews and case reports/series were excluded from this review. After the exclusion of duplicates and articles deemed irrelevant to the study's aim, 24 original studies are discussed [14-37]. Their characteristics are summarized in Table 1.

Impact of COVID-19 on IBD healthcare

During the COVID pandemic all IBD units had to remodel their everyday clinical practice, affecting the quality

of healthcare services provided to their patients. Guidelines were immediately developed by ECCO [2], BSG [3], IOIBD [4], AGA [5] and EOMIFNE [6] to provide actual guidance regarding the management of IBD patients during the COVID pandemic. However, findings from surveys around the world reveal significant diversity. Most of them were conducted via electronically distributed questionnaires, aiming to evaluate various outcomes such as disease activity, presence of symptoms, adherence to medication, psychological condition, possible worries of the patient, and familiarization with telemedicine.

For the purposes of this review, the impact of the COVID-19 pandemic on IBD patients' healthcare is presented in terms of direct and indirect outcomes. Direct outcomes include flare-ups, hospitalizations and emergent surgeries, while indirect outcomes include treatment discontinuation, delay in infusion of biological agents, and loss of patient follow up, namely outcomes that could lead to IBD exacerbation and need for intervention.

As presented in Table 2, there is significant variance among the direct outcomes reported across different surveys. Flare-up rates fluctuate between 0.5 and 56%, emergent surgeries between 0.2 and 17.9%, and hospitalization rates between 0.78 and 15.8%. That is also the case for indirect outcomes, where treatment discontinuation varies between 3.73 and 28%, and delay of infusions from 1.3-69.6%. The main reason for these outcomes is patients' choice to stop their treatment or delay their infusion due to fear of COVID-19 contamination, especially in healthcare settings. Moreover, 1 of 4 patients have been lost to follow up (range 4-38.7%).

An observational study performed in Spain aimed to evaluate the impact of COVID-19 on an IBD unit's activity, comparing data to those from the previous year [20]. Sixty-four (76.19%) of the elective endoscopies and all scheduled surgeries were suspended. This led 9.4% of patients to experience a flare of IBD symptoms in the first 2 months of lockdown, compared to 6.9% the previous year (2.5% increase, $P=0.18$). Loss of follow up increased from 3.6% to 5.1%, and adherence to medication decreased from 99.5% to 94.9% ($P<0.05$). In particular, the discontinuation of biological treatment was almost 8-fold (from 0.5% to 3.73%, $P<0.05$).

As expected, patients who discontinued medication on their own initiative faced an increased risk for adverse outcomes. In a study from China, where guidance through telemedicine was provided, 107/386 (28%) of the patients reported treatment discontinuation and 108/386 (28%) experienced a flare-up [15]. Among those stopping their treatment, 57% (61/107) eventually required hospitalization and 4.7% (5/107) needed surgical treatment. Hospitalization rates were clearly and significantly higher among patients who discontinued their medication (57% vs. 0.78-15.8%).

It is noteworthy that adherence to the different categories of medication may be variable. An online survey from the United Kingdom [21] showed that the most frequently discontinued medications were oral steroids (43.9%). Immunomodulators were discontinued by 11.2% of the patients, 1 of 3 against a physician's recommendation. Contrariwise, adherence to biological agents remained high, since 99% of them continued their use. Between March and August 2020, 36.6% reported a flare of IBD symptoms. Almost

Table 1 Characteristics of included studies

Study author [ref.]	Country	Study period	Population, n (CD/UC)	Population characteristics	Methodology	Main outcomes
Yu <i>et al</i> [14]	China	02/2020	102 (46/56)	M: 66.7% Median age 34 years	Electronic survey	5/102 (4.9%) discontinued Tx 27/102 (26.5%) ↑ disease activity
Chen <i>et al</i> [15]	China	01-03/2020	386 (311/75)	M: 70.5% Mean age 32.8±6.8 years	Patient record, telephone follow up and questionnaire	107/386 (27.7%) discontinued Tx 17 UC and 91 CD pts experienced a flare
Lan <i>et al</i> [16]	China	01-03/2020	78 (64/6)	Patients undergoing IBD-related surgeries 61.5% elective surgery, 12 (15.4%) emergency surgery, 18 postponed	Anonymous online survey	7/18 (38.9%) ↑ symptoms 2/12 (11.1%) emergency surgery due to postponed surgery
Tian <i>et al</i> [17]	China	First wave of COVID-19	239 (71/151)	M: 54.81% 66.5% 5-ASA, 2.5% corticosteroids 14.2% immunosuppression, 17.6% biological Tx	Questionnaires	51 (21.34%) IBD flare 52 (21.76%) changed Tx 41/239 (17%) delay infusion
Chen <i>et al</i> [18]	China	01-04/2020	2277 (1639/555)	M: 61%	Anonymous online questionnaires	585/2277 (25.7%) had a flare 533/2277 (23.4%) discontinued Tx 791/2277 (34.74%) loss of follow up 443/2277 (39%) income ↓
Bai <i>et al</i> [19]	China	01-02/2020	125 (45/58)	M: 61.6% Median age 39 years	Questionnaires through emails, mobile communication applications and text messaging	18/125 (14.4%) exacerbation
El Hajra <i>et al</i> [20]	Spain	03-05/2020	510 (303/199)	85.49% inactive patients 9.41% IBD flare	Comparison between 2020 and 2019	2020 vs. 2019 IBD flare: 9.4% vs. 6.9% Loss of follow up: 5.1% vs. 3.6% Adherence to Tx: 94.9% vs. 99.5% Biological Tx discontinuation: 3.73% vs. 0.5%

(Contd...)

Table 1 (Continued)

Study author [ref.]	Country	Study period	Population, n (CD/UC)	Population characteristics	Methodology	Main outcomes
Harris <i>et al</i> [21]	UK	03-08/2020	685 (443/221)	M: 42% 26.3% immunomodulators, 28.5% on biological/ small molecules, 16.5% dual immunosuppression, 6% oral steroids	Electronically distributed questionnaires	251 (36.64%) had a flare 104 (15.2%) emergent surgery 127 (19%) cancelled outpatient appointment 363/685 (52.99%) negative impact on psychological well-being
Goodday <i>et al</i> [22]	UK, USA	04-06/2020	243 CD	86% United Kingdom 10% United States	Anonymous distributed survey through international gastroenterology clinics and networks	24% relative↑ in active symptoms compared to pre-COVID-19 period (P<0.001) 118/243 (48.6%) due to stress
Grunert <i>et al</i> [23]	Germany	04/2020	415 (215/192)	M: 45.3% 46.8% biological agents, 34.5% 5-ASA, 23.9% anti-TNF	Matched (4:1) anonymous survey of 415 IBD patients and 116 control participants	IBD patients significantly more affected by the COVID-19 pandemic than non-IBD peers, but generally remained adherent to medication
Foteinogiannopoulou <i>et al</i> [24]	Greece	03-04/2020	78	64 infusions	IBD unit experience report	58/64 (90.6%) received their infusion on time
Turner <i>et al</i> [25]	China, South Korea, Portugal	01-03/2020	446	7 children with IBD infected with SARS-CoV-2	Electronic reporting system	Pediatric IBD patients should not stop their medication or delay infusions
Viola A <i>et al</i> [26]	Italy	01-07/2020	689 (369/320)	247 patients IV biologics, 217 SC biologics, 225 oral Tx	Hospital records during lockdown compared with the respective period in 2019	Endoscopies↓85% compared to 2019
Rizello <i>et al</i> [27]	Italy	03-06/2020	1158 (695/463)	M: 55.6% 56.7% on remission	23 MCQ anonymous survey	204 (17.6%) ↑ symptoms: 102 (8.8%) discontinued Tx 244 (21.1%) delayed infusions
Zhang <i>et al</i> [28]	China	12/2019-02/2020	505 (354/126)	84 patients at consultation 56 patients on anti-TNF infusions	Observational study on healthcare and medication use Electronic questionnaire survey about telemedicine acceptance	39/56 (69.6%) delayed infusion Physicians using telemedicine↑by 18.9% compared with the pre-outbreak period (p<0.001)

(Contd...)

Table 1 (Continued)

Study author [ref.]	Country	Study period	Population, n (CD/UC)	Population characteristics	Methodology	Main outcomes
Saibeni <i>et al</i> [29]	Italy	04/2020 and 06/2020	NR	52.4% in northern Italy 85.7% in public hospitals, 54.7% in academic hospitals	Web-based online survey	>70% of follow up and 5% of first visits by virtual clinics 14% delay in infusions>70% of endoscopies cancelled
Scalaferrri <i>et al</i> [30]	Italy	03-04/2020	1451 (784/522)	M: 58% Mean age 44 years 27% infliximab, 31% adalimumab	Observational prospective study	222/1451 (15.33%) delayed infusions due to patients' choice
Costantino <i>et al</i> [31]	Italy	NR	100 (75/25)	M: 69% Mean age 41 years	Questionnaire about patients' trust in telemedicine	95% of patients using telemedicine trust this method of follow up
Allocca <i>et al</i> [32]	Italy	First wave of COVID-19	725	700 patients already on IV or SC 25 patients started infusions during the study	IBD unit experience report	350% ↑ of contacts in helpline after changes in the restriction rules
Iborra <i>et al</i> [33]	Spain	03-04/2020	234 (178/52)	Database: M: 53%, 117 IV and 117 SC Tx Telephone survey: 155 (77 IV, 78 SC)	Cross-sectional observational study	Database: 12/117 (10.26%) and 5/117 (5.13%) delayed IV and SC agents Phone survey: 26/155 (17%) postponed Tx (50% fear of going to the hospital)
Clough <i>et al</i> [34]	UK	05/2020	107	55.7% of patients attended infusion during survey period	Questionnaire	80.2% consider IBD unit's measures to prevent COVID to be adequate
Schlabit <i>et al</i> [35]	Germany	04-07/2020	1199	M: 23 Mean age 41.3 years	40-item web-based questionnaire on disease-related experiences and concerns	38.7% of appointments cancelled 6.9% Tx discontinuation 71% considered telemedicine as acceptable
Trindade <i>et al</i> [36]	Portugal	04/2020	124	M: 14.52% Mean age 40 years 75.8% immunosuppressants, biologics or corticosteroids	Online questionnaire	87/124 (70.1%) reported anxiety and 60/124 (48.3%) depression symptoms
Feitosa <i>et al</i> [37]	Brazil	05/2020	570 (179/46)	M: 53.3% Mean age 41.3 years	Cross-sectional study by personalized questionnaire	64.9% self-quarantined 80.2% depression, 58.2% anxiety/ fear of death

CD, Crohn's disease; UC, ulcerative colitis; IFX, infliximab; IV, intravenous; SC, subcutaneous; NR, not reported; Tx, treatment; M, male; MCQ, multiple choice questions; TNF, tumor necrosis factor; IBD, inflammatory bowel disease; 5-ASA, 5-aminosalicylate

Table 2 Effects of COVID-19 pandemic on IBD patients' healthcare

Study author [ref.]	Direct outcomes, n/N (%)			Indirect outcomes			
	Flare-up	Emergent surgery	Hospitalization	Treatment discontinuation, n/N (%)	Reason for discontinuation	Delayed infusions, n/N (%)	Loss of follow up, n/N (%)
Yu <i>et al</i> [14]	27/102 (26.5)	NR	NR	5/102 (4.9)	medication UA	NR	NR
Chen <i>et al</i> [15]	108/386 (28)	5/386 (1.3)	61/386 (15.8)	107/386 (28)	87% traffic restrictions 13% PC	NR	NR
Lan <i>et al</i> [16]	NR	14/78 (17.95)	NR	NR	NR	NR	NR
Tian <i>et al</i> [17]	51/239 (21.3)	NR	NR	61/239 (25.5)	16.4% medication UA 16.4% PC	41/239 (17)	NR
Chen <i>et al</i> [18]	585/2277 (25.7)	23/2277 (1)	137/2277 (6)	533/2277 (23.4)	28% physicians/ facilities UA	151/533 (28) infusion UA	791/2277 (34.74)
Bai <i>et al</i> [19]	18/125 (14.4)	NR	NR	NR	NR	NR	25/150 (16.67)
El Hajra <i>et al</i> [20]	48/510 (9.4)	1/510 (0.2)	12/510 (2.35)	26/510 (5.1) 19/510 (3.73) biological agents	73.08% PC	NR	26/510 (5.1)
Harris <i>et al</i> [21]	251/685 (36.64)	NR	NR	104/685 (15.18)	26% PC	18/629 (2.9)	2015/2700 (74.63)
Goodday <i>et al</i> [22]	136/243 (56)	NR	NR	NR	NR	NR	NR
Grunert <i>et al</i> [23]	21/415 (0.5)	NR	NR	15/415 (3.6)	PC	NR	NR
Foteinogiannopoulou <i>et al</i> [24]	4/67 (5.97)	NR	10/67 (14.92)	3/67 (3.4)	PC	4/64 (6.3)	11/78 (14.1)
Turner <i>et al</i> [25]	14/66 (21.2) China 3/13 (23) Korea	NR	10/66 (15.2) China	2/233 (0.9) China	PC	66/233 (28) China 13/272 (4.8) Korea	NR
Viola A <i>et al</i> [26]	28/689 (4.06)	NR	6/689 (0.87)	45/689 (6.53)	PC	38/247 (15)	NR
Rizello <i>et al</i> [27]	204/1158 (17.6)	NR	9/1158 (0.78)	102/1158 (8.8)	PC	244/1158 (21.1)	NR
Zhang <i>et al</i> [28]	14/84 (16.7) 5/39 (12.8)	4/84 (4.76)	7/84 (8.33)	NR	NR	39/56 (69.6)	NR
Saibeni <i>et al</i> [29]	NR	NR	NR	NR	NR	~663/4733 (14)	~800/3984 (20)
Scaldfarri <i>et al</i> [30]	NR	NR	NR	NR	15.33% PC	233/1451 (16.06)	NR
Allocca <i>et al</i> [32]	NR	NR	NR	NR	NR	9/700 (1.3) 3/25 (12) of new infusions	1/25 (4) of new infusions
Iborra <i>et al</i> [33]	NR	NR	NR	NR	PC	12/117 (10.26) IV 6/117 (5.13) SC agents	NR
Clough <i>et al</i> [34]	NR	NR	NR	20/212 (9.4)	NR	NR	NR

(Contd...)

Table 2 (Continued)

Study author [ref.]	Direct outcomes, n/N (%)			Indirect outcomes			
	Flare-up	Emergent surgery	Hospitalization	Treatment discontinuation, n/N (%)	Reason for discontinuation	Delayed infusions, n/N (%)	Loss of follow up, n/N (%)
Schlabitz <i>et al</i> [35]	NR	NR	NR	83/1199 (6.9)	NR	NR	464/1199 (38.7)
Trindade <i>et al</i> [36]	NR	NR	NR	5/124 (4.03)	PC	NR	NR
Feitosa <i>et al</i> [37]	NR	NR	NR	64/225 (28.4)	PC	NR	NR

NR, not reported, PC, patient choice, UA, unavailability, IV, intravenous, SC, subcutaneous

half of them contacted neither their general practitioner nor the IBD helpline and self-managed their symptoms.

A retrospective study conducted in the Netherlands used the nationwide registry of histo- and cytopathology researchers to compare the number of IBD-related procedures between 2020 and 2019 [38]. Overall, 14.2% fewer IBD-related procedures were performed between February and August 2020. More specifically, at the peak of the pandemic (April) the decline was almost 60%, while 125 fewer new diagnoses and 214 fewer low-grade dysplasia diagnoses were established, corresponding to reductions of 6.5% and 25.5%, respectively, compared to the previous year. Notably, no decline in high grade dysplasia or colorectal cancer was recorded.

Apart from the direct and indirect outcomes mentioned above, all aspects of IBD patients' healthcare were also disrupted. A questionnaire survey conducted by phone in Brazil to estimate the impact of the pandemic on IBD follow up and on patients' well-being [37] showed that medical therapy was discontinued by 28.4% of the patients, with fear of infection being the main reason. In addition, 83% missed at least one medical appointment, 45.5% missed their laboratory test, while 17% did not have any access to medical prescriptions or skipped their endoscopy.

Impact of COVID-19 on psychosocial well-being of IBD patients

There are many surveys featuring the negative impact of lockdown combined with the fear of SARS-CoV-2 infection on the psychosocial well-being of patients with IBD. For the purposes of this review, psychological outcomes have been divided into reported "negative mood", depression and anxiety (Table 3). A point that deserves attention is the fact that, in the majority of the studies (n=5/6), establishment of a mood disorder was not achieved via implementation of a validated questionnaire, but based on a simple report by the patient evaluated through scales created by the authors themselves; thus, all results should be interpreted cautiously. Only the study by Trindade *et al* [36] used a validated instrument, the Hospital Anxiety and Depression Scale (HADS), specifically designed to address anxiety and depression as 2 separate subscales. Similarly, the validated Short Inflammatory Bowel Disease Questionnaire (SIBDQ) was used to assess the

significant aspect of Health-Related Quality of Life (HRQoL) in the study by Yu *et al* [14]. As shown in Table 3, reports about "negative mood" varied between 0.5 and 52.99%, while regarding depression and anxiety the respective percentages ranged from 52.4-58.2% and 2.98-80%. Stress and depression may lead to IBD exacerbation, while flares can be followed by depression and anxiety, leading to a self-perpetuating cycle [12]. This is corroborated by a survey from the UK, focusing on stress-related consequences of the pandemic in patients with Crohn's disease [22]. A total of 136 (56%) patients reported symptoms of disease activity. There was a 24% relative increase in active symptoms during the lockdown compared with the previous months. "Increased stress and/or feeling of being overwhelmed" (118/236) was reported as the cardinal reason for the change. Among those reporting stress at the time of the survey, the relative increase in active symptoms was even more pronounced (42%). Despite the fact that IBD patients face no greater risk of SARS-CoV-2 infection [2-5], they seem to be more afraid than their non-IBD peers, since 38.2% of them admitted to leaving the house less frequently than their flat mates [23]. Findings from a similar survey [36] demonstrated that people in isolation had more symptoms of depression, but fewer symptoms of anxiety, because of the low fear of getting infected. According to the same survey, IBD patients reported that the pandemic had a negative or an extremely negative impact on their quality of life (42.8% and 10.2%, respectively). This impact was worse among younger adults. Almost half of the patients reported insomnia, reduced daily activity and productivity, as well as sexual dysfunction [37].

Data comparing the psychosocial status of IBD patients between the pre- and during-COVID-19 periods remain scant and heterogeneous. Harris *et al* [21] documented a significant increase in overall stress between the 2 eras (mean stress score pre-lockdown 4.0 vs. 5.5 during lockdown). Moreover, a history of anxiety or depression correlated with greater stress scores pre-lockdown (P=0.0005), during lockdown (P=0.0005) and concerns about a "second wave" (P=0.008). In another study, the proportion of respondents feeling "stressed" or "very stressed" was significantly higher during the COVID-19 period compared to the pre-COVID-19 era (n=122/236, 52% vs. n=73/236, 31%) [22]. More importantly, not only were these higher stress levels identified as the reason for a change in symptoms from pre- to during COVID-19, but also the

Table 3 Psychological impact of COVID-19 pandemic on IBD patients

Study author [ref.]	Psychosocial impact		
	Negative mood, n/N (%)	Depression, n/N (%)	Anxiety, n/N (%)
Yu <i>et al</i> [14]	7/102 (6.86)	NR	NR
Harris <i>et al</i> [21]	363/685 (52.99)	NR	NR
Goodday <i>et al</i> [22]	118/236 (0.5)	NR	NR
Grunert <i>et al</i> [23]	159/415 (38.2) leave house less frequently than peers	NR	NR
Foteinogiannopoulou <i>et al</i> [24]	NR	NR	2/67 (2.98) needed psychiatric medication
Trindade <i>et al</i> [36]	NR	65/124 (52.41)	62/124 (50)
Feitosa <i>et al</i> [37]	NR	131/225 (58.2)	180/225 (80)

NR, not reported

percentage increase in active symptoms was more pronounced among those reporting current stress (42%, n=122, P<0.0001).

Emergence of telemedicine

The doctor-patient relationship has been always the cornerstone of IBD patient healthcare. Clinical visits were the most common manner of follow up. However, the urgent need for telemedicine during the COVID-19 pandemic probably introduced long-term changes in medical practice. Findings of a tertiary referral center for IBD in Italy, which has largely embraced telemedicine, especially video-consultations, suggested that 95% of their patients using telemedicine trusted this method of follow up [31]. Another survey revealed that, although 65.8% of patients preferred face-to-face visits during flares, 67.3% of them preferred telephone follow up at remission in the post-COVID era [21]. Regarding gastrointestinal physicians, the majority (72.0%) agree that telemedicine should partly replace clinic visits in the future [28].

Discussion

The healthcare environment of IBD patients has been greatly affected by the COVID-19 pandemic. Although telemedicine rapidly emerged to replace clinical visits, it cannot fully take their place. Many visits were postponed around the world without being replaced by virtual meetings, especially in the case of first visits, rather than follow ups. The greatest limitation of the studies conducted in this COVID-19 era is that a significant number of patients did not participate in the online surveys. It is possible that people who did not participate in the surveys might have had risky behavior, such as non-adherence to medications [39]. Hence, the actual impact of the pandemic may be even larger in the real world setting, and studies seem to underestimate it. To make things even more ambiguous, one should take into account that the pandemic is not over yet and the optimal strategy for restarting remains unknown. Thus, the consequences will not be fully

understood until later. Another limitation is associated with the heterogeneity in methods, aims and patient cohorts among the aforementioned studies. As a result, the data are not easily comparable, warranting further and more detailed studies.

A third limitation concerns the number of deaths due to disease exacerbation, which were excluded from the strict/direct outcomes, since the studies were conducted mostly via questionnaires and not using hospital medical files. Moreover, reported flare-ups were mostly based on patients' symptoms and were not confirmed by either endoscopy or laboratory findings. Notably, symptoms like diarrhea, even increased fecal calprotectin (FC) levels, have been associated not only with IBD flare but also with COVID-19 disease [40].

Indeed, diarrhea represents a common symptom of COVID-19 infection, and for almost 10% of non-IBD patients can be the only symptom, without respiratory involvement [41]. These patients are at risk for a severe COVID-19 disease outcome, probably because of the delay in diagnosis. This percentage is even higher among IBD patients, according to a recent systematic review [42].

FC, a stool marker extremely useful in the differential diagnosis of an IBD flare-up, has been suggested as a home-based test for remote monitoring during the pandemic. However, there are indications that FC can be elevated in COVID-19 positive patients, especially among those with symptoms of diarrhea [40]. This is in line with the findings of a systematic review, according to which more than half of SARS-CoV-2 positive patients with gastrointestinal symptoms had elevated FC [43]. This means that the use of FC as a tool during the follow up of IBD patients is problematic during the pandemic, especially in the discrimination between COVID-19 infection and an IBD flare.

Another important issue is postponed endoscopies. Endoscopic procedures are an integral part of IBD surveillance, especially in monitoring therapy efficacy and screening for dysplasia or cancer [44]. Long waiting lists in the post-pandemic era will bring the need for specific prioritization. Experts recommend [45] that, during the first 3-6 months after lockdown, priority should be given to mild or moderate flares, subacute bowel obstruction, new IBD diagnosis with abnormal biochemical test, and surveillance for colorectal cancer and

postoperative recurrences. All patients should be tested for COVID before the procedure. Capsule endoscopy (CE) could find a breeding ground in the post COVID era [46]. CE could play an important role in Crohn's disease activity monitoring before and after the escalation of treatment, as it provides an alternative evaluation method that will offload the pressure from endoscopy departments.

Fear of SARS-CoV-2 infection in healthcare settings is one of the main reasons for non-adherence to medication during the pandemic. However, adherence to biological treatment was already a major issue even before the pandemic. A systematic review in 2013 reported that pooled adherence to anti-tumor necrosis factor (TNF) was 82.6% (83% for adalimumab and 71% for infliximab) [47]. As a result of anti-TNF discontinuation, 55% of patients with Crohn's disease or ulcerative colitis relapse after 32 and 18 months, respectively [48]. Hence, the effects of treatment discontinuation on patient health during the COVID era will be best evaluated in the near future. On the other hand, delays in the management of IBD patients due to limited access to the healthcare system will also have a huge impact on their overall well-being. A recent study estimated that a 3-month delay in cancer surgery, due to focusing on COVID-19 care, reduces the benefit in life-years gained of all COVID-19 care by 19% [49].

Hence, in light of the community's uncertainty—despite the vaccination—about when we will fully return to normality, there are some issues that needed to be directly addressed. Firstly, IBD units should actively ensure that patients will not delay their infusions. Phone calls 1 or 2 days earlier than the infusion could play a key role in patient adherence. Moreover, medical staff should be familiar with telemedicine. Home care nurses could play a crucial role in this direction by roughly assessing IBD patients well-being, carrying out blood tests and collecting FC samples. Lastly, effective and frequent communication between doctor and patient is the steppingstone for patients to express their worries or practical problems. Of course, they should be strongly advised to remain adherent to their medication, get vaccinated and apply hygiene measures, but at the same time to exercise, keep up with their hobbies and close friends if possible, so they can preserve their physical and mental well-being. From the clinician's point of view, all appropriate measures that should be implemented to optimize IBD patients' management (assessment according to severity of IBD and concurrent underlying COVID-19 infection, as well as prevention of infection transmission and management of non-COVID IBD patients) are thoroughly summarized within currently available guidelines [4,5]. Rather than focusing on efforts to address this topic, our review adds to the existing literature by identifying gaps in current knowledge, discussing important flaws of study design, and contextualizing the benefit of existing studies for everyday clinical practice.

Concluding remarks

The COVID-19 pandemic has negatively affected the quality of healthcare of IBD patients. Despite the widespread use of telemedicine, a large proportion of patients have been

lost to follow up, while others failed to remain adherent to their medication. A pronounced decline in new IBD diagnoses has also been reported. Moreover, the pandemic has had a detrimental psychological impact on IBD patients, leading to a self-perpetuating cycle of stress/depression and disease activity. Telemedicine has been gaining ground as a possible alternative follow-up method in IBD remission, accepted both by patients and physicians.

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