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2019 novel coronavirus disease (COVID-19) in patients with inflammatory bowel diseases

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Summary

Background: Data on patients with inflammatory bowel diseases (IBD) who have had 2019 novel coronavirus (SARS-CoV-2) disease (COVID-19) are needed.

Aims: To report the clinical characteristics, including gastrointestinal symptoms, of COVID-19 in IBD patients, and to assess the risk of COVID-19 in IBD.

Methods: This case series included consecutive IBD patients with laboratory-confirmed COVID-19. Age-adjusted cumulative incidences were compared with the general population in the Madrid region.

Results: Through April 8, 12 of 1918 IBD patients were diagnosed with COVID-19. The average age was 52 years, 75% of the patients were female and 58.3% had Crohn's disease. Seven patients (58%) were on maintenance treatment with immunomodulators/biologics, of these four with combined therapy (33%). Eight patients (66%) required hospitalisation (one intensive care unit admission, and two deaths), and four patients were isolated at home. Nine patients had diarrhoea ranging between 4 and 10 loose stools per day (mean 5.4, SD 1.6). In five patients (42%) diarrhoea was a presenting symptom. In two patients, diarrhoea was the only symptom at debut. Cumulative incidence of COVID-19 was 6.2 per 1000 IBD patients. IBD patients had a lower adjusted incidence ratio of COVID-19 (OR 0.74, 95% CI 0.70-0.77; $P < 0.001$), and a similar associated mortality ratio (OR 0.95, 95% CI: 0.84-1.06; $P = 0.36$), compared with the general population.

Conclusions: IBD patients do not have an increased risk of COVID-19 and associated mortality compared with the general population. In many IBD patients, diarrhoea was a presenting symptom, and sometimes, was the only symptom at onset of COVID-19.

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1 | INTRODUCTION

The World Health Organization (WHO) recently declared 2019 novel coronavirus disease (COVID-19) outbreak as a pandemic of international concern.[1] Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the novel coronavirus causing COVID-19, has spread rapidly throughout the world since it was first identified in Wuhan in December 2019.[2] Currently, Spain has one of the highest number of confirmed COVID-19 cases worldwide, with Madrid being the most affected region.

Elderly individuals and those with other chronic underlying conditions have more severe disease and a higher mortality rate when infected with SARS-CoV-2.[3,4] Inflammatory bowel diseases (IBD) are chronic, immune-mediated inflammatory diseases affecting people of all ages. A high percentage of IBD patients require immunosuppressive therapies for inducing and maintaining remission. These patients may have a greater risk of acquisition or progression of serious viral infections, including COVID-19.[5] However, the initial available evidence suggests that IBD patients do not have an increased risk of contracting SARS-CoV-2 infection or development of COVID-19, since no patients have been reported to be infected with SARS-CoV-2 in IBD centres in China.[6] Moreover, a recent study reported that none of the patients with IBD followed at a tertiary referral centre in Italy developed COVID-19.[7]

To date, there are limited data on patients with IBD who have had COVID-19. Therefore, there is a need for studies assessing the risk and clinical characteristics of the disease in IBD. The objective of this case series was to describe the clinical characteristics, including gastrointestinal (GI) symptoms, of COVID-19 among IBD patients followed at an IBD Unit. We also aimed to assess the risk of developing COVID-19 and the associated mortality in patients with IBD and compare it with that of the general population.

2 | MATERIALS AND METHODS

This was a single-centre, observational case-series study evaluating the incidence and clinical characteristics of laboratory-confirmed COVID-19 cases among IBD patients followed at a large IBD Unit in the Madrid region (IBD Unit of Hospital Clínico San Carlos, Madrid). Eligible patients included men or women with an established diagnosis of IBD. The study population comprised all consecutive IBD patients with confirmed diagnosis of SARS-CoV-2 infection by a positive result on real-time reverse transcriptase polymerase chain reaction (RT-PCR)-approved assays of nasopharyngeal swab samples. We included both hospitalised patients and out-patients with mild symptoms isolated at home according to recommendations. Patients with symptoms suggestive of COVID-19 without a positive RT-PCR were excluded. The study was approved by the hospital's Ethics Committee. Specific verbal informed consent was obtained for all out-patients and for hospitalised patients if possible.

Baseline demographic and clinical characteristics, as well as treatments for IBD, were extracted for the overall IBD population and for COVID-19 cases from the prospectively maintained database ENEIDA (Table 1). Clinical, laboratory and radiological findings, and treatment and outcome data of in-patients were extracted from electronic medical records using a standardised data collection form. For hospitalised patients, severity was assessed at admission by two validated pneumonia scoring indices (CURB-65 and Pneumonia

TABLE 1 Demographic and clinical characteristics of the overall population of inflammatory bowel disease patients (N = 1918)

Characteristic	Value
Sex, male, n (%)	997 (52.0)
Age (y), mean (SD)	50 (14)
Disease, n (%)	
CD	920 (48.0)
UC	998 (52.0)
Disease duration (y), median (IQR)	11 (8-18)
CD Localisation, n (%)	
L1	321 (34.9)
L2	168 (18.4)
L3	430 (46.7)
CD behaviour, n (%)	
B1	585 (63.6)
B2	78 (8.5)
B3	257 (27.9)
UC extension, n (%)	
E1	192 (19.2)
E2	452 (45.2)
E3	354 (35.5)
IMM treatment, n (%)	559 (29.1)
Azathioprine, n (%)	353 (63.1)
Mercaptopurine, n (%)	105 (18.8)
Methotrexate, n (%)	90 (16.1)
Tofacitinib*, n (%)	6 (1.1)
Tacrolimus, n (%)	2 (0.3)
Mycophenolate, n (%)	3 (0.5)
Biological treatment, n (%)	301 (15.7)
Infliximab, n (%)	110 (36.5)
Adalimumab, n (%)	119 (39.5)
Golimumab, n (%)	31 (10.3)
Vedolizumab, n (%)	18 (6.0)
Ustekinumab, n (%)	23 (7.6)
Biological + IMM treatment, n (%)	157 (8.2)
IMM alone, n (%)	402 (20.9)
Biologics alone n (%)	144 (7.5)

Disease location (L): L1 terminal ileum, L2 colon, L3 ileocolon, L4 upper gastrointestinal tract; Disease behaviour (B): B1 nonstricturing nonpenetrating; B2 stricturing, B3 penetrating. IMM: immunomodulator; Tofacitinib* is a JAKinase inhibitor not similar to conventional IMM.

Abbreviations: IQR, interquartile range; Montreal classification' of Crohn's disease (CD); SD, standard deviation; UC, ulcerative colitis.

Severity Index [PSI]).[8] Clinical symptoms from out-patients were obtained by the principal investigator by direct telephone contact. We evaluated the activity of IBD through validated indexes: Harvey-Bradshaw index (HBI) for Crohn's disease (CD) and Partial Mayo score (PMS) for ulcerative colitis (UC). We specifically assessed GI symptoms. We defined diarrhoea as passing loose stools (Bristol stool scale 6 or 7) ≥4 per day for at least three consecutive days. For hospitalised patients, we evaluated whether the onset diarrhoea occurred before or after start of COVID-19 therapies.

2.1 | Statistical analysis

Study variables were summarised descriptively using numbers and percentages for discrete variables and the mean and standard deviation (SD) or median and interquartile range (IQR) as appropriate for continuous variables. Cumulative incidence of COVID-19 in IBD was obtained by dividing cases by the overall population of IBD patients included in the database. For the same time period, the cumulative incidence of laboratory-confirmed SARS-CoV-2 infection and associated mortality in the general population of Madrid was extracted [Coordination Centre for Sanitary Alerts and Emergencies from Spain. Update 70. Coronavirus disease (COVID-19), April 8, 2020 (https://www.mscbs.gob.es/profesionales/saludPublica/ccayes/alertasActual/nCov-China/documentos/Actualizacion_70_COVID-19.pdf)]. Age-sex standardised incidence and mortality rates of COVID-19 in the IBD population were obtained with the direct method using the general population of Madrid as standard. We compared standardised incidence and mortality rates between the IBD population and the general population. Results were presented as odds ratios (OR) and their 95% confidence intervals (CI). Statistical analyses were done using the EPIDAT 3.1 software.

2.2 | Systematic literature search

We performed a systematic search of the PubMed database through to April 30, 2020 to find full-text case reports or case series using the following search strategy: ("SARS-CoV-2" OR "COVID-19") AND ("IBD" OR "inflammatory bowel diseases" OR "Crohn's disease" OR "ulcerative colitis").

3 | RESULTS

Through April 8, 12 patients out of 1.918 IBD patients included in the database had a laboratory-confirmed diagnosis of COVID-19. Baseline demographic and clinical characteristics, as well as concomitant treatments for IBD, are shown in Table 2. The mean age of the patients was 52 years (SD 16), 75% of the patients were female and 58.3% had a diagnosis of CD. Median duration of IBD was 17 years (IQR 10-22). Median interval between onset of symptoms and RT-PCR confirmation of infection was 5 days (IQR 4-8). Five patients had at least one underlying comorbidity. Eight patients required hospitalisation due to moderate-to-severe disease (one of them required mechanical ventilation and ICU admission and two died). Four patients with mild disease were isolated at home. Dates of onset of symptoms and laboratory confirmation, clinical and radiological findings, treatments for COVID-19 and outcomes are summarised in Table 3. Two patients (16.6%) had nausea/vomiting. Nine patients (75%) had diarrhoea ranging between 4 and 10 loose stools per day (mean 5.4, SD 1.6). In most patients, diarrhoea was watery, no bloody and not associated with abdominal pain. In five patients (41.6%), diarrhoea was a presenting symptom, and the only symptom at debut in two patients. Diarrhoea at onset accounted for most of the IBD activity score as evaluated by HBI or PMS (Table 2). In the remaining four patients, diarrhoea occurred after admission and initiation of hydroxychloroquine alone or together with lopinavir/ritonavir, and was self-limiting after drug discontinuation. All in-patients with diarrhoea had negative results in stool culture and test for *Clostridium difficile*.

On admission, bilateral abnormalities on chest radiography or computed tomography (CT) were detected in all but one hospitalised patients. The majority of patients showed lymphopenia and had elevated C-reactive protein, fibrinogen lactate dehydrogenase, ferritin and D-dimer levels (Table S1). We had less than 20% of missing laboratory data. To avoid duplications, certain characteristics of some cases were addressed in the discussion.

3.1 | Incidence of SARS-CoV-2 infection in IBD patients

Through April 8, 2020, cumulative incidence of laboratory-confirmed COVID-19 in the general population of Madrid was 6.6 cases per 1.000 (43.877 reported cases among an overall population of 6,663 million), with a mortality rate of 0.9 deaths per 1000 (5.800 deaths). In the same period, the crude incidence rate of COVID-19 was 6.2 cases per 1000 patients with IBD, and the age-adjusted rate was 4.9 cases per 1000 (95% CI 1.9-7.8). Patients with IBD had a significantly lower standardised risk of COVID-19 compared with the general population (OR 0.74, 95% CI 0.70-0.77; $P < 0.001$). For the IBD population, the crude mortality rate was 1 death per 1000 patients, and the age-adjusted mortality rate was 0.82 per 1000 (95% CI -0.3-2). There were no significant differences in the standardised mortality risk between IBD patients and the general population (OR 0.95, 95% CI: 0.84-1.06; $P = 0.36$). Given the distribution of populations, adjustment for sex did not affect standardised incidence and mortality rates. The case fatality rate for IBD cases with COVID-19 was 16.7%, and the case fatality rate for COVID-19 in the general population was 13.2%, with no significant differences (OR 1.31, 95% CI: 0.29-6.00, $P = 0.72$).

4 | DISCUSSION

This study is the first report of a case series of SARS-CoV-2 infection in adult IBD patients. The risk of COVID-19 and associated mortality

TABLE 2 Baseline characteristics and treatments of inflammatory bowel diseases patients with 2019 novel coronavirus disease

Case number	Sex	Age	IBD	CD 'Montreal' phenotype	UC extension	Disease duration (years)	Harvey-Bradshaw index (CD)	Partial Mayo score (UC)	Treatment for IBD	Comorbidities
1	M	76	CD	A3L1B1	—	13	2	—	Azathioprine	Hypertension Diabetes Chronic LD
2	M	76	UC	—	Left-sided	11	—	6	Mesalazine	CV disease Diabetes Chronic LD
3	M	53	UC	—	Left-sided	18	—	0	Azathioprine Mesalazine	NO
4	F	53	CD	A2L3B3p	—	26	2	—	Adalimumab	Hypertension
5	F	51	UC	—	Extensive	21	—	0	Mesalazine	Hypertension
6	F	47	CD	A2L3B3	—	26	4	—	NO	Chronic kidney disease
7	F	72	UC	—	Left-sided	19	—	0	Mesalazine	NO
8	F	51	UC	—	Extensive	5	—	3	Golimumab Methotrexate	NO
9	F	44	CD	A2L3B3	—	12	6	—	Adalimumab Methotrexate	NO
10	F	42	CD	A2L1B1	—	16	10	—	NO	NO
11	F	20	CD	A1L1B1p	—	7	2	—	Ustekinumab Mercaptopurine	NO
12	F	43	CD	A2L1B1	—	9	12	—	Vedolizumab Methotrexate	NO

Abbreviations: 'Montreal classification' of Crohn's disease (CD); B2 stricturing, B3 penetrating. UC, ulcerative colitis. CV, cardiovascular; Disease behaviour (B): B1 nonstricturing nonpenetrating; Disease location (L): L1 terminal ileum, L2 colon, L3 ileocolon, L4 upper gastrointestinal tract; IBD, inflammatory bowel diseases; LD, liver disease.

in patients with IBD were significantly lower than that of the general population in the same region. Although patients reported common symptoms already described for COVID-19, of note was the high rate of diarrhoea, which was sometimes the only symptom at onset.

With the results of the systematic literature search, we identified 24 articles. Eighteen were reviews, editorials, guidances or animal models and were excluded, and six articles were analysed (Material S1: PRISMA flowchart). The first study, evaluating initial evidence emerging from China, notes that no patients with IBD have been reported to be infected with SARS-CoV-2 in the IBD Elite Union, or in the three largest tertiary IBD centres in Wuhan.[6] The second study reported that among 522 IBD patients followed in a tertiary centre at Bergamo, the province with the highest rate of infection worldwide, no case of COVID-19 was diagnosed.[7] The third study reported a single case of COVID-19 occurring in an adult patient with UC.[9] The fourth study reported eight children with IBD who had mild SARS-CoV-2 infection among the 102 sites affiliated with the Paediatric IBD Porto group of ESPGHAN.[10] Two recent studies reported two other cases of COVID-19 in patients with IBD.[11,12] Through April 8, 457 IBD patients with COVID-19 were included in the SECURE-IBD worldwide reporting database (https://covidibd.org/). This database gives no information about incidence rates or clinical symptoms of COVID-19.

In this case cases series including 12 patients, we assessed the risk and the clinical characteristics, including GI symptoms, of COVID-19 in patients with IBD. The data included in our database allowed us to report an incidence of COVID-19 of 6.2 per 1000 patients with IBD. Given our small sample size and the high impact that missed cases of COVID could have, we believe that the finding of a lower standardised risk of developing COVID-19 in IBD should be treated with caution. The study shows that, despite the high use of immunosuppressive drugs in this population, patients with IBD do not have a higher risk of developing COVID-19 and associated mortality than the general population of the region. One of the possible explanations for this observation may be the correct adherence of this population to protection measures. Clinical characteristics, laboratory and radiological findings of COVID-19 among IBD patients were in line with reported evidence for the general population.[2-4,13] Regarding outcomes, the high case fatality rate in our cohort was not significantly different from that of the general population in the region. We consider that both rates were highly biased by the inclusion of more serious cases, while asymptomatic or mild cases remained isolated at home without testing for infection.

The most important finding of the study was the high rate of diarrhoea as a presenting symptom among IBD patients with COVID-19 compared with the previously reported data from

TABLE 3 Clinical characteristics, treatments and outcomes of inflammatory bowel diseases patients with 2019 novel coronavirus disease

Case number	Sex	Age	Onset of symptoms	Date of + PCR	Common symptoms	GI symptoms	CURB-65 PSI	Rx findings	Complications	Therapies for COVID-19	Outcomes
1	M	76	March 18	March 24	Fever, cough, dyspnoea	No	CURB-65: 2 PSI: I	Bilateral pneumonia	NO	Hydroxychloroquine Antibiotics[b]	Hospitalised discharged
2	M	76	March 6	March 17	Fever, dyspnoea	Diarrhoea	CURB-65: 2 PSI: I	Bilateral pneumonia	Acute KF Haemodialysis ARDS	Hydroxychloroquine Antibiotics[b]	Hospitalised death
3	M	53	March 13	March 17	Fever, myalgia, headache, sore throat	No	CURB-65: 2 PSI: IV	Bilateral pneumonia	ARDS ICU care Invasive ventilation	Hydroxychloroquine Lopinavir/ritonavir Antibiotics[b]	Hospitalised Discharged
4	F	53	March 16	March 27	Fever, cough, myalgia, ageusia	Diarrhoea[a]	CURB-65: 0 PSI: I	Bilateral pneumonia	NO	Hydroxychloroquine Lopinavir/ritonavir Antibiotics[b]	Hospitalised Discharged
5	F	51	March 16	March 25	Cough, dyspnoea, myalgia, sore throat	Diarrhoea[a]	CURB-65: 0 PSI: I	Bilateral pneumonia	NO	Hydroxychloroquine Antibiotics[b]	Hospitalised Discharged
6	F	47	April 1	April 2	Fever, fatigue	Diarrhoea[a] Nausea/ vomiting	CURB-65: 2 PSI: I	Bilateral ground-glass opacities (CT)	Pyelonephritis Haemodialysis	Hydroxychloroquine Antibiotics[b]	Hospitalised Discharged
7	F	72	March 15	March 17	Fever, cough, dyspnoea	Diarrhoea[a]	CURB-65: 2 PSI: I	Bilateral pneumonia	ARDS	Hydroxychloroquine Lopinavir/ritonavir	Hospitalised Death
8	F	51	March 30	April 3	Fever, cough, sore throat, fatigue, headache	Diarrhoea	CURB-65: 0 PSI: I	Unilateral pneumonia	NO	Hydroxychloroquine Lopinavir/ritonavir	Hospitalised
9	F	44	March 17	March 20	Myalgia, fatigue, headache, A+A	Diarrhoea	ND	ND	NO	NO	Out-patient Isolated at home
10	F	43	March 15	March 20	Fever, cough, sore throat, myalgia, dyspnoea, A+A	Diarrhoea	ND	ND	NO	NO	Out-patient Isolated at home
11	F	20	March 11	March 12	Fever, myalgia, fatigue, A+A	NO	ND	ND	NO	NO	Out-patient Isolated at home
12	F	43	March 21	April 2	NO	Diarrhoea, nausea/ vomiting	ND	ND	NO	NO	Out-patient Isolated at home

Abbreviations: Acute respiratory distress syndrome; AKF, acute kidney failure; ARDS, acute respiratory distress syndrome; GI, gastrointestinal; ICU, Intensive care Unit; ND, not done; PSI, Pneumonia Severity Index; RT-PCR, real-time polymerase chain reaction.

Common COVID-19 symptoms included: fever, cough, sore throat, myalgia, fatigue, expectoration, headache and dyspnoea. A+A, ageusia + anosmia. Gastrointestinal symptoms (GI): nausea, vomiting, diarrhoea and abdominal pain. Diarrhoea[a], onset of diarrhoea after starting COVID-19 therapies. CT, computed tomography. Antibiotics[b] for associated bacterial infections.

Wuhan and later case series for the general population.[2,3,13-19] In five patients, diarrhoea was a presenting symptom, and the only symptom at onset in patients 2 and 12. The presence and severity of diarrhoea were the main contributors to the score on HBI or PMS. Therefore, diarrhoea caused by infection could lead to misdiagnosis of an IBD flare, and inappropriate initiation of treatment that may include corticosteroids. Patient 2, a 76-year-old man diagnosed with UC and with severe comorbidities debuted 7 days before admission with watery diarrhoea causing acute kidney failure. After admission, treatment with haemodialysis and IV methylprednisolone 40 mg/day was started. Two days later, fever up to 38.8° and dyspnoea developed, and he was diagnosed with COVID-19 with bilateral pneumonia and fatal outcome. Patient 12, a 42-year-old female diagnosed with CD, debuted with diarrhoea and nausea/vomiting suggestive of acute gastroenteritis and ciprofloxacin was started. On day 10, watery diarrhoea persisted. Despite not having any common symptoms of COVID-19 and motivated by cumulative experience from the prior cases, we decided to test for

SARS-CoV-2 infection by RT-PCR assays of nasopharyngeal swab and stool samples; both were positive.

In the largest COVID-19 case series, diarrhoea was uncommon (rate 3.8%), which suggests a difference in viral tropism as compared with SARS-CoV and MERS-CoV.[2] Several other case series have reported rates of diarrhoea ranging between 2% and 12.9%.[3,13-19]. In a recent study, diarrhoea was a presenting symptom in 37.1% of patients with COVID-19.[20] A single case of SARS-CoV-2 induced diarrhoea as presenting symptom has been reported.[21] It has been suggested that the increase in GI symptoms in the later phase of this pandemic could be motivated by the possible mutation of the virus towards greater transmissibility, decreased virulence and multi-organ infection.[14]

Like prior coronavirus SARS-CoV and MERS-CoV, SARS-CoV-2 had a high tropism for the GI tract. [22-24] Spike (S) protein of SARS-CoV-2 had a high affinity for angiotensin-converting enzyme 2 (ACE2), abundantly expressed in GI cells, and this enzyme is thought to be responsible for the viral invasion of human cells.[24,25] ACE2 is overexpressed in the inflamed GI tract of IBD patients,[26] with significantly higher expression in CD than in UC.[27] These findings could explain the high rate of GI symptoms in IBD patients with COVID-19 observed in our study. Importantly, SARS-CoV-2 has been identified by RT-PCR in stools samples in over half the patients in the general population, suggesting transmission by a faecal-oral route.[28,29] Moreover, more than 20% of patients remained positive for viral RNA in stool samples after testing negative in respiratory samples, highlighting the importance of faecal tests to control spread.[29] Consequently, gastrointestinal physicians and other healthcare workers treating suspected COVID-19 patients with diarrhoea but without common symptoms would be at increased risk of infection and should take additional protective measures. GI endoscopy centres should be aware of the risk that colonoscopy poses for cross-contamination.[14]

In a large study, thiopurines but not biologics were associated with serious viral infections related to EBV, CMV, VZV and HSV infection.[5] A meta-analysis of clinical trial data including 4135 patients given anti-tumour necrosis factor (TNF) therapy found that the relative risk of developing an opportunistic infection, including severe viral infections, was significantly increased in the anti-TNF arm.[30] However, the International Organization for the study of Inflammatory Bowel Disease (IOIBD) and the AGA Clinical Practice Update recommended to continue with mesalazine, immunosuppressants, biologics and JAK-inhibitors for IBD patients during the SARS-CoV-2 pandemic, since inflammation itself may be a risk factor for acquiring COVID-19.[31,32] Overall, our study support this recommendation given that 36.6% of patients followed at our IBD Unit were receiving immunosuppressants and/or biologics (8.2% with combination therapy) and the incidence of COVID-19 was not increased compared with the general population. Once patients have, however, developed COVID-19, IOIBD and AGA recommended to stop these therapies.[31,32]

In our study, seven patients (58.3%) were on maintenance treatment with immunosuppressants and/or biologics (four with combined therapy [33%], two with thiopurines alone [16.6%] and one with anti-TNF alone [8.3%]). Although the proportion of patients receiving combined immunosuppressive and biological treatment was numerically higher than that of the overall cohort of patients with IBD, the small sample size does not allow us to draw any conclusions. In all but one patients, these therapies were temporarily stopped during infection.

Available observational data suggest that corticosteroids increased mortality and secondary infection rates in influenza, impaired clearance of SARS-CoV and MERS-CoV and led to complications in survivors, and so their use is not recommended to treat COVID-19 lung injury.[33] Therefore, given the lack of effectiveness and possible harm, routine corticosteroids should be avoided unless they are indicated for another reason, according to WHO interim guidance.[34] Only patient 2 received corticosteroids before diagnosis of SARS-CoV-2 infection in the belief diarrhoea was motivated by a severe UC flare causing acute kidney failure.

In view of the above, we recommend testing all IBD patients presenting diarrhoea for SARS-CoV-2 infection during the outbreak. Doing so will allow us to discriminate an IBD flare from diarrhoea due to SARS-CoV-2 infection and avoid inappropriate use of corticosteroids or other therapies that may favour the progression of COVID-19. In addition, this strategy helps contain the spread of the SARS-CoV-2 infection by detecting and isolating cases without common symptoms of COVID-19. Besides, faecal tests before discharging or ending isolation of patients with SARS-CoV-2 infection can further help reduce cross-contamination.

This study had several limitations. First, the incidence of COVID-19 in our cohort of IBD patients is probably underestimated. Following the instructions of the health authorities, some IBD patients with common symptoms of SARS-CoV-2 infection remain isolated in their homes without being tested for viral RNA. These patients were not included as cases. Given the same approach is taken for the general population, this limitation is unlikely to have a major impact on the comparison of incidences. Second, it cannot be ruled out that we missed cases of COVID-19 among the IBD population. To obviate this drawback, on April 8, 2020, an anonymous cross-search was carried out among patients followed at the Unit and the positive results of RT-PCR in our hospital. This strategy identified patient 7 of our case series. Third, the small sample size prevents us from using logistic regression models to assess risk factors for the acquisition or progression of COVID-19. We consider it particularly important to evaluate the association between corticosteroids and immunosuppressive/biological treatment and COVID-19 through large multicentre studies.

In conclusion, although 37% of IBD patients were receiving monotherapy or combination therapy with immunosuppressive drugs, the incidence of COVID-19 and associated mortality was not increased in this population. In many IBD patients, diarrhoea was a presenting symptom and sometimes the only symptom at onset of COVID-19. Diarrhoea can be misinterpreted as an IBD flare, potentially leading to inappropriate corticosteroid treatment which may contribute to COVID-19 progression. Therefore, we recommend

testing all IBD patients presenting diarrhoea for SARS-CoV-2 infection during the outbreak. Moreover, this strategy may help contain the spread of the infection, including transmission by a faecal-oral route.

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AUTHORSHIP

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Author contributions: CT designed the study, collected and analysed the data and wrote the paper. IS collected and monitored data and treated the patients. CA and NM collected data and treated the patients. DO extracted data from database, performed statistical analysis and designed Table 1. ER contributed with critical revision of the manuscript. All authors read and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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